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CONTENTS

An Epidemiological Aspect of Lung Cancer
—Increase in mortality and anti-smoking measures—

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Abstract: The number of lung cancer deaths in Japan, 39,053 for men and 14,671 for women in 2000, increased by a factor of 10.7 for men and by a factor of 9.6 for women over the past 40 years. When the influence of the rapid growth of the aged population is excluded from the analysis, age-adjusted death rates indicate that the increase slowed down after 1990 and began to decrease after 1995 both for men and for women. Lung cancer mortality increased among persons aged 80 or more, as well as in the <60 age group, while it peaked and then decreased in the 60- to 79-year-old age group. The trends observed in the 60- to 79-year-old age group might be due to the decrease in the prevalence of smoking after 1970. The trends among persons under 60 seem to reflect the recent downward shift in the age of smoking initiation. In Japan, about 70% and 15–25% of male and female lung cancer cases, respectively, are attributable to smoking. Reducing the prevalence of smoking is the most effective means of limiting lung cancer deaths. Every possible anti-smoking measure should be promoted.

Key words: Lung cancer; Mortality; Smoking; Relative risk

Introduction

Recent international data for lung cancer mortality show complex variations, increasing in some countries and decreasing in others. The data from Japan also indicate different trends in different age groups. This paper outlines the trends in lung cancer deaths in Japan in relation to the changes in the prevalence of smoking.

Trends in Lung Cancer Deaths and Crude Death Rates

The number of lung cancer deaths in Japan has been increasing consistently since 1960 both for males and for females. According to Vital Statistics by the Ministry of Health, Labour and Welfare, lung cancer killed 39,053 men and 14,671 women in 2000. These numbers

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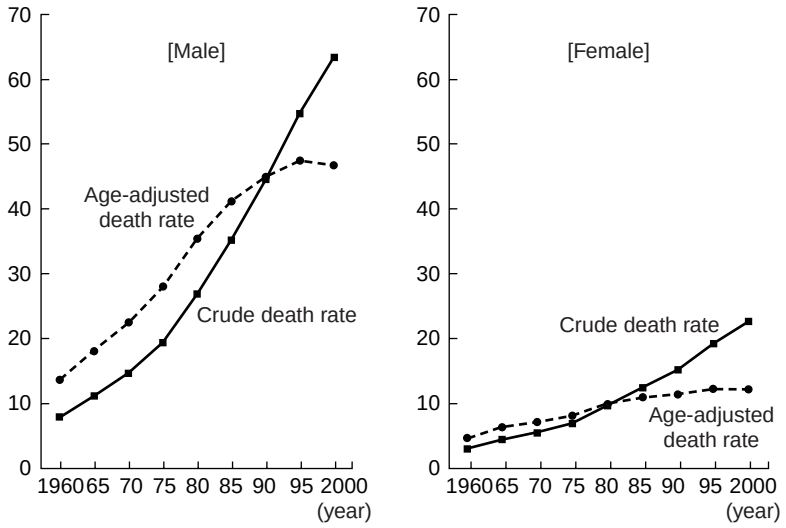

Fig. 1 Yearly tends in crude and age-adjusted death rates from lung cancer (per 100,000 population) in Japan (1960–2000)
(Source: Vital Statistics, Ministry of Health and Welfare)

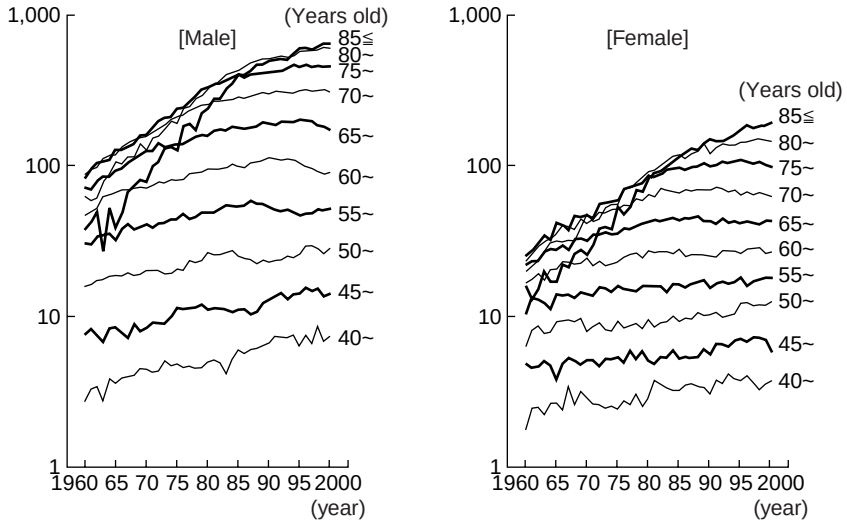

Fig. 2 Yearly tends in age-specific death rate from lung cancer (per 100,000 population) in Japan (1960–2000)
(Source: Vital Statistics, Ministry of Health and Welfare)

increased by a factor of 10.7 for males and by a factor of 9.6 for females over the past 40 years. The corresponding crude death rates from lung cancer (total number of lung cancer deaths per 100,000 Japanese) increased from 7.9 and 3.2 in 1960 to 63.5 and 22.9 in 2000 by factors of 8.0 and 7.2 for males and females, respectively (Fig. 1).

Trends in Age-Adjusted and Age-Specific Death Rates

The increase in the number of lung cancer deaths reflects the strong influence of the rapid

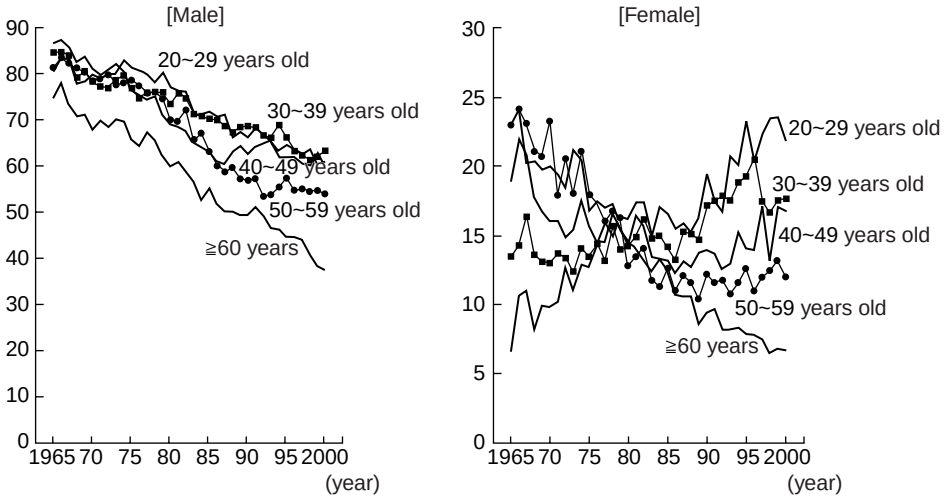

Fig. 3 Yearly trends in age-specific prevalence of smoking (%) in Japan (1965–2000)
(Source: Japan Tobacco and Salt Public Corporation and Japan Tobacco Corporation)

growth of the aged population. When this influence is excluded from the analysis, age-adjusted death rates (weighted average of age-specific death rates from lung cancer based on the model Japanese population as of 1985) indicate that the increase slowed down after 1990 and decreased after 1995 both for men and for women (Fig. 1).

The trends in age-specific death rates from lung cancer show a distinct decreasing tendency among males in the 60- to 69-year-old age group after 1990. A similar decreasing tendency is also evident among females in the 70- to 79-year-old age group (Fig. 2). Because lung cancer deaths are concentrated in the 60- to 79-year-old stratum, the trends in this age group have a strong influence on the overall trends in age-adjusted death rates.

Trends in the Prevalence of Smoking

An important factor contributing to the decrease in lung cancer cases in the 60- to 79-year-old age group is the decrease in the percentage of male smokers in Japan, which dropped from the peak of 83.7% in 1966 to 53.5% in 2000 (according to the surveys conducted by the Japan Tobacco and Salt Public Corporation and Japan Tobacco Corporation) (Fig. 3). Other contributing factors include people's preference for low-tar filtered cigarettes and the widespread availability of improved diagnosis of lung cancer. Smoking among women aged over 50 has also been decreasing since 1970.

Many developed countries recording successful reduction in the prevalence of smoking, including the U.K. and the U.S.A., have been showing decreases in lung cancer death rates. These decreases have been more remarkable in younger age groups.

Trends in Lung Cancer Death Rate in the <60 Age Group

In contrast, Japan has been recording an increase in lung cancer death rate in the <60 age group both for males and for females (Fig. 2). This increase may be related to the slowdown of the decrease in the prevalence of smoking among males younger than 60, the increase in the prevalence of smoking among 20- to 29-year-old females, and the shift to earlier ages of smoking initiation among both males and females. It is necessary to continue careful monitoring of the lung cancer death rate.

Relation between Lung Cancer and Smoking

Smoking is the most influential risk factor for lung cancer. The relative lung cancer risk due to smoking (lung cancer risk in smokers as compared with non-smokers) in Japan has been reported to range between 4 and 5 for males and between 2 and 3 for females. These values are relatively small in comparison with the corresponding values in Western countries.[1)]

This observation might be due to several factors: smoking was not popular in Japan until relatively recent times; there was a shortage of tobacco during and after World War II; non-filter cigarettes were used only for a short period; the age of smoking initiation is relatively late; there may be dietary factors (e.g., low fat intake) attenuating the effect of smoking; and there may be genetic factors lowering the sensitivity to smoking. Although the relative risk is lower than that observed in Western countries, the population attributable risk of smoking (the percentage of lung cancer attributable to smoking) is reported to be 70% for males and 15–25% for females in Japan, indicating that smoking is overwhelmingly more important than other risk factors.

Conclusion

After 1990, lung cancer mortality in Japan increased among males and females aged 80 or more, as well as in the <60 age group, while it peaked and then decreased in the 60- to 79-year-old age group. The trends observed in the 60- to 79-year-old age group might be due to the decrease in the prevalence of smoking after 1970. The trends among persons under 60 seem to reflect the recent downward shift in the age of smoking initiation.

About 70% and 15–25% of male and female lung cancer cases, respectively, are attributable to smoking in Japan. Reducing the prevalence of smoking is the most effective means of limiting lung cancer deaths. All anti-smoking measures should be promoted.

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Progress in Lung Cancer Screening
—CT screening and the diagnosis of small lung cancers—

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Abstract: Several case-control studies on lung cancer screening conducted in Japan reported that the current screening method contributes to the reduction of the risk of lung cancer death. However, the effectiveness has not been established, since randomized controlled trials (RTCs) in other countries did not confirm the effectiveness of screening in reducing lung cancer death rates. Because further improvement of accuracy is not expected using chest X-rays, studies were conducted to evaluate the possibility of low-dose helical CT as a new method of lung cancer screening. The results indicate that CT screening achieves a higher detection rate and detects a larger number of early-stage lung cancers. An advantage in survival rate was also reported. A cohort study is ongoing in Japan to evaluate the effectiveness of CT screening in reducing lung cancer deaths. While the widespread use of CT screening improved the detection of small lung cancers, diagnosis still requires thoracoscopic or open lung biopsy. It is necessary to develop low-invasive methods for the diagnosis of small lung cancers.

Key words: Lung cancer screening; Low-dose helical CT; Case-control study; Cohort study; Small lung cancer

Introduction

Lung cancer screening is conventionally performed using radiography of the chest. These methods have largely reached the limit of technical progress. There is a consensus that detection of early-stage lesions is difficult even using double reading and comparative reading protocols to improve diagnostic performance. Chest CT is superior to conventional radiography in density resolution, and it avoids the problem of blind spots caused by the overlapping of structures such as the heart, diaphragm, and bones in radiography. Despite these advantages in lesion detection, chest CT has not been used in screening because of the problems of exposure dose and long scanning time.

In 1990, a system was developed in which the

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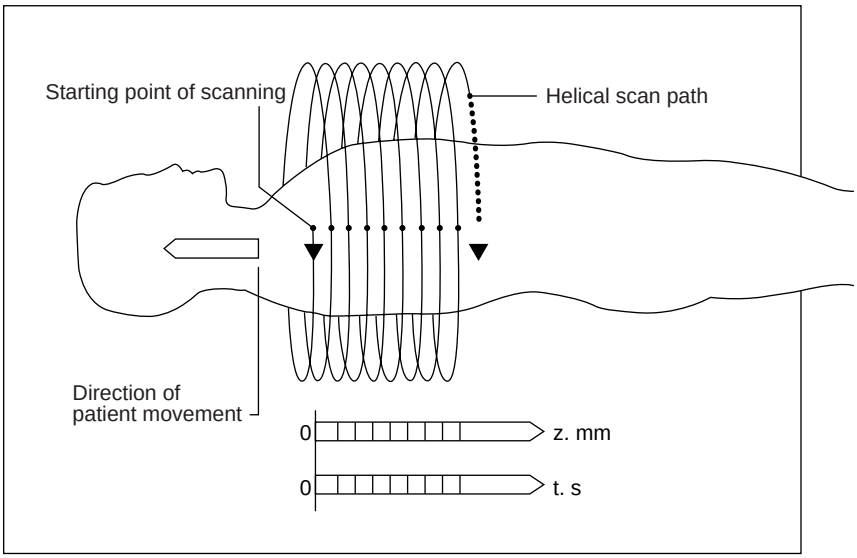

Fig. 1 Schematic diagram of helical CT[1)]
t, s: time in seconds, z: section position

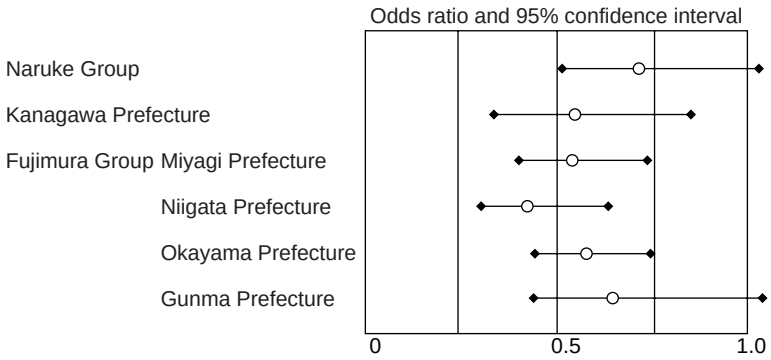

Fig. 2 Reduction of death rate in case-control studies in Japan[9–13)]
(Adjustment by smoking)

X-ray tube moves continuously along a spiral during the acquisition of projection data (Fig. 1).[1)] This technique shortened the time required for scanning. In the chest region, imaging of the whole lungs can now be performed with a 15-second breath hold, and this method is considered suitable for use in screening. With respect to exposure dose, satisfactory diagnostic performance is obtained when the current is reduced from the conventional value of 150 mA to 50 mA. Many facilities are now examining the possibility of lung cancer screening using low-dose high-speed helical CT (CT screening).[2)]

Present State of Lung Cancer Screening

Indirect chest radiography has been used in Japan since before World War II, initially for tuberculosis screening. The focus of screening shifted from tuberculosis to lung cancer, reflecting the changes in the prevailing disease profile. This procedure was covered by the Elderly Health Law in 1987, and standardized

Table 1 Results of CT Screening

	Initial screening				Repeated screening			
	N	Number of detection of lung cancer (%)	Stage I cases (%)	Mean tumor diameter (mm)	N	Number of detection of lung cancer (%)	Stage I cases (%)	Mean tumor diameter (mm)
Nagano Prefecture[a)15)]	5,483	23 (0.42)	23 (100)	15.1	8,303	37	32 (86)	—
Anti-Lung Cancer Association[b)16)]	1,611	14 (0.87)	11 (79)	19.8	7,897	22	18 (82)	14.6
ELCAP[c)17,18)]	1,000	27 (2.7)	23 (85)	—	1,184	7	5 (71)	8[d)]

a) Initial screening: 1996, yearly repeated screening: 1997 and 1998.
b) Initial screening 1993–1998, repeated screening at half-year intervals: 1994–1998.
c) Repeated screening at intervals of several months.
d) Median of tumor diameter.

screening protocols were defined in "The Manual of Mass Screening for Lung Cancer" and "The Manual of Clinic-based Lung Cancer Screening Program" to promote lung cancer screening.[3,4)]

Later, the subsidies for cancer screening were placed into the framework of the general revenue (to be covered by a portion of national tax revenue allocated to local governments) in fiscal 1998, and cancer screening became a non-mandatory service conducted by municipalities.

The efficacy of lung cancer screening has not been established, since randomized controlled trials (RCTs) in other countries evaluating lung cancer screening did not confirm the effectiveness in decreasing lung cancer death rates.[5–8)] Six case-control studies have been conducted in Japan (Fig. 2).[9–13)] Sobue *et al.* reported that the estimated 0.72 reduction in the risk of death was indicative of the efficacy of screening, although the value was not statistically significant.[9)] Okamoto *et al.* reported a significant decrease in the risk of lung cancer death in their report on clinic-based screening.[10)] The case-control studies conducted in 4 districts (Miyagi, Gunma, Niigata, and Okayama) by the Fujimura Group (The Study Group for "Evaluation of the Efficacy of Mass Screening Program for Lung Cancer") revealed statistically significant decreases in the risk of lung cancer death in 3 districts, while the result in the other district was nearly significant.[11–13)] Based on these results, it was concluded that the current method of lung cancer screening contributes to the reduction of the risk of lung cancer death, provided that appropriate accuracy management is performed.[11)]

Lung Cancer Screening Using Low-Dose Helical CT

It is generally acknowledged that lung cancer screening using chest X-ray has little room for further improvement of diagnostic accuracy. As discussed above, the development of low-dose helical CT made it possible to shorten scanning time and reduce exposure dose, and this technique has been evaluated as a new method of lung cancer screening.[1,2)]

The development of CT units for lung cancer screening started in 1990 in Japan. Preliminary evaluation was conducted to establish the basic design concept and to perform risk, benefit, and cost analyses. Following these efforts, CT

screening came to be practiced widely.[14] An initial screening study covering 5,483 inhabitants of Nagano prefecture detected 23 cases of lung cancer with a detection rate of 0.42%, and all cases were stage I (Table 1).[15] The results of initial screening conducted by the Anti-Lung Cancer Association (ALCA), a membership organization conducting lung cancer screening in high-risk groups in Tokyo, and the Early Lung Cancer Action Project (ELCAP) in the U.S.A. indicated detection rates of 0.87% and 2.7%, respectively, and the percentage of stage I cases was 79% and 85%, respectively (Table 1).[16–18] CT screening showed detection rates that were 4 to 8 times as high as that of the chest X-ray conducted simultaneously.[15–17] A summation of the data from 8 facilities performing over 1,000 cases of CT screening reproducibly demonstrated the superiority of this method: detection rate was 0.36% and the percentage of stage I cases was 79%.[19] Sobue *et al.* also reported excellent results in which the 5-year survival of the lung cancer patients detected by initial screening and repeated screening was 76.2% and 64.9%, respectively.[16]

However, a problem associated with CT screening is the high percentage of cases requiring diagnostic workup.[15–17,20] The high rate of false-positive cases means a large number of persons receiving unnecessary workup, and we need to address this problem in view of the aggressiveness of diagnostic examination, the psychological burden on the patients, and the increase in medical expenditure. Future improvement is expected to take place through the preparation of interpretation standards and guidelines for small lung cancers, training and experience of evaluating physicians, and the introduction of comparative reading systems.[15,20,21]

Survival rates are confounded with 4 types of biases: (1) length bias, (2) self-selection bias, (3) lead time bias, and (4) overdiagnosis bias. The overdiagnosis bias (the fact that some of the cancers detected by screening do not lead to the death of the patient) presents a major problem in the case of CT screening, because this technique is characterized by high detection rates and a high percentage of adenocarcinomas among detected lung cancers. As a result, some of the patients incorrectly diagnosed as having lung cancer undergo unnecessary treatment.

Although CT screening is expected to improve survival rates, evaluation based on survival rates is not appropriate for evaluation of the effectiveness of CT screening in decreasing lung cancer death rates. The group for "the study on the identification of groups with high cancer prevalence and the early diagnosis and treatment to improve prognosis" (leader: Takaichiro Suzuki) was organized under Health Science Research Grants for Medical Frontier Strategy Research for the purpose of conducting cohort studies to evaluate the efficacy of CT screening. It is necessary to confirm the efficacy in reducing lung cancer death rates before using this method for lung cancer screening in the general population.

Diagnosis of Small Lung Cancers

The widespread use of CT screening increased the detection of "small lung cancers" with diameters of 15 mm or less (Table 1). Most of these cancers are adenocarcinomas of peripheral origin. On high-resolution CT, small lung cancers appear as ground-glass opacities, solid opacities, or mixtures of these lesions, and they are characterized by the involvement of bronchi and blood vessels and air bronchograms (Fig. 3).[22,23] The observed characteristics of these lesions are considered to correlate with Noguchi's classification of small lung adenocarcinomas based on histopathological analysis.[22,24]

Although imaging diagnosis of small lung cancers is making progress, definitive diagnosis still requires pathological or cytological confirmation. Transbronchial or percutaneous lung biopsy under X-ray fluoroscopy guidance is not useful for the evaluation of opacities that are

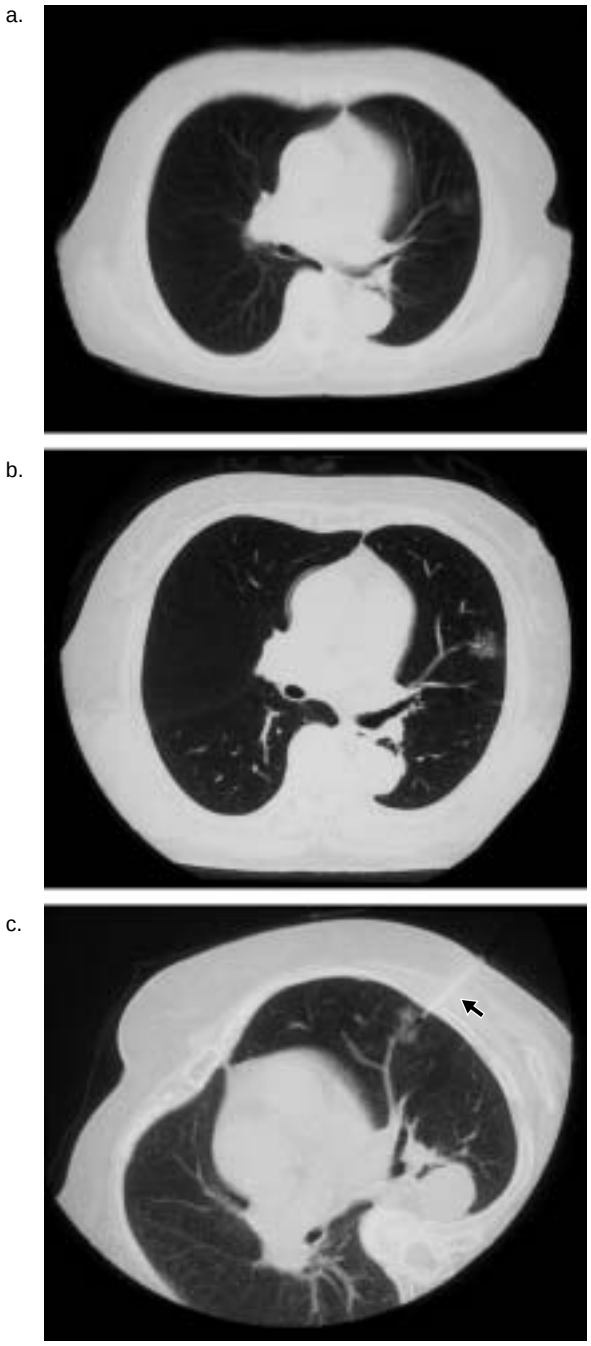

Fig. 3 Adenocarcinoma revealed by CT screening (lingular segment)
a. CT image at the time of CT screening: A ground-glass opacity is seen.
b. CT image at the time of workup: Radiolucent bronchi in addition to ground glass opacity.
c. CT-guided percutaneous lung biopsy: The arrow indicates biopsy needle.

not identified by chest X-ray. At present, diagnosis of small lung cancers is considered difficult. Suspected lung cancer lesions are generally examined by CT (fluoroscopy) guided transbronchial or percutaneous lung biopsy. If diagnosis is not given by these procedures, thoracoscopic or open lung biopsy is performed. In practice, surgical diagnosis is needed in many cases. Ten out of 14 cases (71%) of small lung cancers with diameters of 15 mm or less needed thoracoscopic or open lung biopsy for definitive diagnosis at our facility.[25] It is necessary to develop low-invasive methods for the diagnosis of small lung cancers.

On the other hand, nodular opacities lacking evidence of malignancy are followed up without invasive diagnosis. There are no guidelines stipulating the intervals and duration of follow-up. Aberle *et al.* proposed that nodular opacities smaller than 10 mm in diameter should be followed up at 3, 6, 12, and 24 months, while those with diameters of 10 mm or more should be diagnosed by biopsy.[26] It is necessary to establish appropriate guidelines for followup based on a sufficiently large number of cases.

Conclusion

Case-control studies in Japan suggest the effectiveness of lung cancer screening. However, the effectiveness has not been established, since randomized controlled trials in other countries did not confirm the efficacy in reducing lung cancer death rates. The development of low-dose helical CT made it possible to consider CT screening as a new method of lung cancer screening. This technique is promising in lung cancer screening because of its ability to detect early-stage lung cancers that have a good chance of cure. However, it is necessary to confirm the efficacy in reducing lung cancer death rates before using this method for lung cancer screening in the general population. Diagnosis of small lung cancers requires CT guided transbronchial or percutaneous lung biopsy in some cases and thoracoscopic or

open lung biopsy in others. Surgical diagnosis is needed in many cases. It is necessary to develop low-invasive methods for the diagnosis of small lung cancers.

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Basic Treatment Strategies for Lung Cancer

JMAJ 46(12): 532–536, 2003

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Abstract: Lung cancer is the leading cause of death from malignant diseases in Japan. Treatment of lung cancer should be selected appropriately according to clinical staging based on scientific evidence. Small cell lung cancer should be managed mainly with platinum-based chemotherapy, and the concurrent use of chemotherapy and radiotherapy is recommended for limited disease. Non-small cell lung cancer should be managed mainly by surgery for stage I and stage II, combined chemo-radiotherapy for stage III, and chemotherapy for stage IV. Chemotherapy is also suggested to be effective in relapsed cancer. The efficacy of these therapies has only been demonstrated in patients with favorable performance status (PS). Treatment lacking sufficient evidence of benefit should not be given to patients with poor PS. The use of newly developed agents, such as gefitinib and other molecular target drugs, must be considered cautiously in terms of applicability to individual patients. The development of better treatment methods needs to be based on evidence from clinical trials.

Key words: Lung cancer; Chemotherapy; Performance status; Evidence-based medicine

Introduction

Lung cancer is the leading cause of death from malignant diseases in Japan. Predictions indicate further increase in the prevalence of this disease. Clinicians have many opportunities to come in contact with patients with lung cancer, starting from the first visit of a patient presenting coughs and other symptoms to the process of definitive diagnosis and treatment.

This paper discusses the basic treatment strategies for lung cancer.[1,2] Please refer to other articles for detailed information concerning the treatment of various forms of lung cancer.

From the First Examination to Staging

Patients with lung cancer often present at a hospital complaining of nonspecific symptoms such as coughing, and are found to have abnormal shadows on chest X-ray. Care should be taken in the interpretation of chest X-ray

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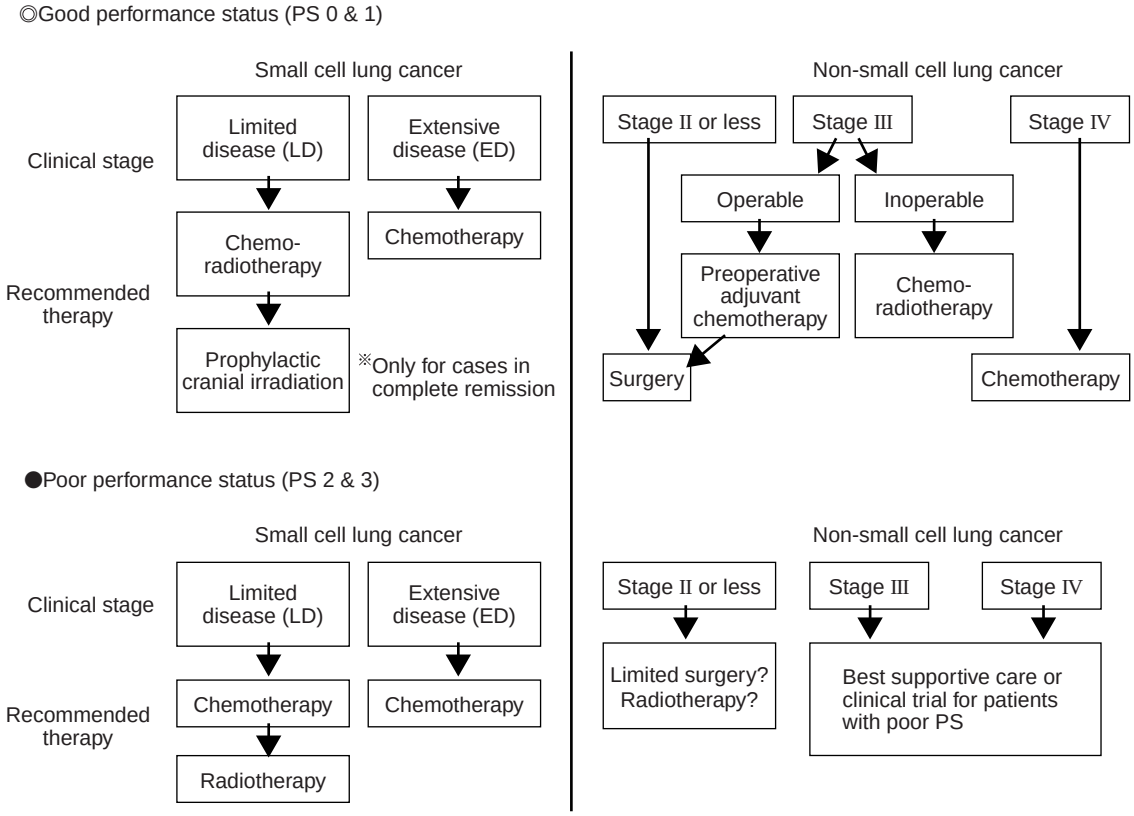

Fig. 1 Basic strategies for lung cancer treatment

images not to overlook lesions in the areas overlapping the shadows of the heart, blood vessels, and bones, as well as old tuberculosis foci.

In the next step, thoracic CT should be preformed to obtain more detailed information. In this case, use of a contrasting agent is recommended to facilitate the detection of mediastinal lymph node metastasis.

Once the location of lesions in the lungs has been identified, tumor tissues for histopathological examination are sampled using bronchoscopy, CT-guided biopsy, or other means. It should be noted that sputum cytology might provide a low-invasive method of diagnosis particularly suited to patients showing poor performance status (PS).

Understanding the PS of the patient is important in examining a patient with lung cancer. Because active treatment such as surgery and chemotherapy with antineoplastic agents places great physical and psychological burdens on the patient, such treatment for the patients with poor PS has to be often abandoned. If the patient presents problems requiring urgent action (e.g., severe pain, dyspnea due to tracheal stenosis, and neurological complications due to brain metastasis), symptomatic treatment for such problems should be given priority.

Selection of Appropriate Therapies According to Clinical Staging

Once the histopathological diagnosis of lung cancer has been established, detailed whole-body examinations (e.g., brain MRI, abdominal CT or abdominal echo, and bone scintigraphy) should be performed promptly to investigate possible distant metastases. Therapies are selected according to histopatho-

logical typing[3] and clinical staging (TNM classification[4]) as summarized below (see flow chart in Fig. 1).

1. Treatment of small cell lung cancer

Because small cell lung cancer is characterized by rapid progression and the propensity for distant metastasis, surgery is recommended only in the very early stage of the disease (stage I). On the other hand, chemotherapy and radiotherapy are important treatment for small cell lung cancer, because it responds to these therapies. Combined use of chemotherapy with cisplatin plus etoposide (PE) and radiotherapy is reported effective when the tumor is localized within the field of irradiation (limited disease; LD).[5] Addition of prophylactic cranial irradiation is recommended for patients showing complete remission on imaging diagnosis.[6]

However, small cell lung cancer showing systemic progression (extensive disease; ED) can be managed only by chemotherapy (although radiotherapy may be used to alleviate symptoms). While PE therapy has been the standard treatment for a long time, a comparative study conducted recently by the Japan Clinical Oncology Group (JCOG) suggested that the combination of cisplatin and irinotecan might be superior to PE therapy.[7]

2. Treatment of non-small cell lung cancer

Treatment of non-small cell lung cancer must be selected carefully according to different stages of the disease: cure by surgical treatment is expected in stages I and II; so-called multidisciplinary therapy consisting of combined chemo-radiotherapy with or without surgery is effective in stage III; and chemotherapy is used for elongation of survival in stage IV, where curative treatment is difficult.

The results of several clinical studies have suggested that resectable stage III cases benefit from preoperative chemotherapy. However, no consensus has been reached as to the type of appropriate antineoplastic agents and the propriety of the concurrent use of radiotherapy. These problems need to be clarified by clinical trials, and this will require collaboration among internal medicine, surgery, and radiology departments. See ASCO (American Society of Clinical Oncology) guidelines[8] for information concerning the treatment of unresectable non-small cell lung cancer.

A recent trend in the chemotherapy for advanced non-small cell lung cancer is the reports of efficacy of several regimens combining newly developed antineoplastic agents and platinum-based antineoplastic agents.[9] Although combinations of new antineoplastic agents (so-called non-platinum regimens) have been reported effective,[10] evaluation of such regimens is still considered insufficient at present. We should be cautious about the use of combinations of new drugs.[11]

3. Treatment for relapsed or refractory lung cancer

Both the patients with small cell lung cancer and non-small cell lung cancer are followed up at approximately monthly intervals. If progression of the tumor is observed after (or during) treatment, secondary treatment is indicated for patients having good PS. Relapsed small cell lung cancer is treated with several regimens such as CODE therapy[12] (chemotherapy with cisplatin, vincristine, doxorubicin, and etoposide), but no standard treatment has been established. This needs to be addressed in future study.

Docetaxel is reported effective in the treatment of relapsed non-small cell lung cancer.[13] Gefitinib (Iressa®), a new agent developed simultaneously in Japan and Europe, is showing successful results as a second-line treatment for non-small cell lung cancer patients who have been treated with platinum-based agents.

4. Treatment for patients with poor PS

As discussed above, active treatment may increase the risk of worsening the prognosis of patients with poor PS. Pain relief and other symptomatic treatments are usually considered

the best strategy for these patients (although chemotherapy may be attempted for untreated small cell lung cancer even in patients with poor PS, because such tumors often respond to chemotherapy).

The patients and their families may not be satisfied with the strategy of "doing nothing (against the cancer itself)," but the physicians should refrain from sharing such sentiment and discontinue treatment lacking scientific evidence and medical meaning (such as a chemotherapy regimen using aimlessly reduced doses).

Aimless administration of oral antineoplastic agents after surgery is unsupported by scientific evidence.[15] With these problems in mind, we should be very discreet in using oral antineoplastic agents, including gefitinib and other new additions to our arsenal.[16]

Conclusion

This paper outlines the basic strategies for lung cancer treatment.

Because the number of specialized oncologists is still small in Japan, generalist clinicians are engaged in the treatment of lung cancer, and many patients are receiving benefit from their services. In determining treatment strategies, physicians should sufficiently understand contemporary criterion standards and practice evidence-based medicine. Because no single method of therapy is sufficiently effective to ensure the success of lung cancer treatment, it is important to promote the development of better therapies through clinical trials and the collaboration between specialized cancer hospitals and community-based hospitals.

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Radiation Therapy in the Treatment of Lung Cancer

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Abstract: Although non-small cell lung cancer (NSCLC) has the potential for cure with surgical resection, unfortunately, less than 15% of all patients and less than 25% of those who present with intrathoracic localized disease are candidates for curative surgical resection. Elderly patients, even if they have resectable disease, often have medical contraindications to surgery, such as cardiovascular diseases and pulmonary dysfunction. For inoperable or unresectable NSCLC, radiation therapy (RT) is widely used as either curative or palliative treatment. There is increasing evidence that RT may improve the survival rate for patients with locally advanced unresectable NSCLC when combined with cisplatin-based chemotherapy or administered by altered fractionation. In limited-stage small cell lung cancer, the addition of thoracic RT and prophylactic cranial irradiation to systemic chemotherapy has also improved disease control. In patients with more advanced disease, RT has provided relief of symptoms. Newer radiotherapeutic methods are promising for increasing the dose targeted to the tumor while sparing healthy tissue. In addition, heavy ion charged particle therapy, brachytherapy, stereotactic irradiation, and multi-daily fractionation have shown promise in the treatment of lung cancer. Furthermore, there have been advances in the technology for treatment delivery, especially three-dimensional treatment planning systems, patient fixation tools, and respiratory synchronous system for RT.

Key words: Lung cancer; Radiotherapy; Chemotherapy

Introduction

Radiotherapy for lung cancer has been practiced as (1) curative treatment for unresectable non-small cell lung cancer (NSCLC); (2) preoperative and postoperative irradiation; (3) thoracic irradiation for small cell lung cancer (SCLC); (4) prophylactic cranial irradiation (PCI) for brain metastasis of SCLC; and (5) palliative treatment for respiratory symptoms,

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superior vena cava syndrome, and bone and brain metastases.[1,2] Although the treatment outcome is still poor, survival rates have been improved gradually through the development of radiotherapy techniques, as well as the advancement of combined chemoradiotherapy. This article discusses the role of radiotherapy in the treatment of lung cancer and reviews recent advances of radiotherapy, including combined therapies.

Curative Radiotherapy for Non-Small Cell Lung Cancer (NSCLC)

Curative radiotherapy is indicated for locally advanced NSCLC patients in the clinical stage of Bulky N2 IIIA and IIIB excluding the cases with malignant pleural effusion, as well as early-stage NSCLC in patients who are considered too old to be operable or who have other complications such as cardiopulmonary dysfunction.

1. Tumor size and local control

Because radiotherapy induces stochastic death of cancer cells according to the dose of radiation, the possibility of tumor control depends on the amount of cancer cells. In addition, larger tumors have higher proportions of hypoxic cells, which are less sensitive to radiation. Thus, patients with smaller tumors have a better chance of cure. It is generally considered that curative radiotherapy is indicated for tumors of sizes up to about 5 cm.[1,2] Using the standard fractionated irradiation of 2 Gy once daily, the dose needed for tumor control is 40 to 50 Gy for microscopic tumors and over 60 Gy for macroscopic residual tumors. The tumor control probability is 80% for T1 tumors at the dose level of 70 to 75 Gy, and 50% to 70% for T2 tumors with diameters of 5 cm or less at 75 Gy or more.[3]

2. Histological types and irradiation to nodal metastasis

Different histological types of lung cancer show different trends in lymph node metastasis. Observation in surgical cases indicates that squamous cell carcinoma metastasizes continuously from the pulmonary hilum to the mediastinum, while adenocarcinoma tends to spread discontinuously.[3] Some cases of squamous cell carcinoma have no distant metastasis even when there are mediastinal lymph node metastasis. On the other hand, mediastinal lymph node metastasis of adenocarcinoma and large cell carcinoma often accompanies distant metastasis. As a result, long-term survivors treated with radiotherapy include a high percentage of cases with squamous cell carcinoma, in which local control of disease has improved long-term survival. If the primary tumor is located in the upper lobe or the superior segment of the lower lobe, both the primary tumor and nodal metastasis can be irradiated within a relatively small field of irradiation. Better long-term survival can be expected in these cases as compared with cases having primary sites in other locations.

3. Combination with chemotherapy (chemoradiotherapy)

The standard treatment for unresectable locally advanced NSCLC now consists of combinations of radiotherapy and chemotherapy intended to control microscopic metastases and enhance the local effect of radiation.[4] The timing of the combined use of these therapies is crucially important in chemoradiotherapy. There are 3 different timings of the combined use: (1) sequential chemoradiotherapy in which neoadjuvant (induction) chemotherapy is followed by radiotherapy, (2) alternating chemoradiotherapy in which the two therapies are performed, and (3) concurrent chemoradiotherapy in which antineoplastic agents are used during radiotherapy. Sequential chemoradiotherapy is the least toxic and used widely in routine clinical practice. However, it has been reported that sequential chemoradiotherapy did not show clear benefit in the survival of patients with squamous cell carcinoma, although

it was effective in non-squamous cell carcinoma,[5] and it does not improve the overall rate of local relapse. For these reasons, the preference is moving towards concurrent chemoradiotherapy aiming at the improvement of local control rate.[4] Alternating chemoradiotherapy is not commonly used, since this protocol involves split course of radiotherapy. Chemoradiotherapy for elderly patients is still controversial because of the problems of toxicity.[5]

4. Advancement of radiotherapy techniques

The basic principle of radiotherapy is to improve the local control rate through administration of as large doses as possible to target lesions while limiting the effect on surrounding normal tissues within the limit of tolerance. Several irradiation methods have been developed to maximize dose concentration to lesions, including 3-dimensional conformal radiotherapy,[6] heavy ion (charged particle) therapy, stereotactic irradiation, and brachytherapy. Apart from brachytherapy, external radiotherapy methods are further reinforced by the development of techniques such as respiration synchronous irradiation and dynamic tracking systems, which counteract the respiratory movement of tumors. These techniques have been reported to achieve good local control of inoperable peripheral lung cancer in the early stage. While early-stage squamous cell carcinoma in the pulmonary hilum region is showing a tendency to increase, the most effective therapy for this cancer is endobronchial brachytherapy. This treatment is reported to achieve a cure rate of over 80%.[7]

While standard radiotherapy uses once daily fractionated irradiation at 1.8–2 Gy, 5 times per week, multi-daily fractionation may be performed for the purpose of expanding the difference between the effect on normal tissues and the therapeutic effect on tumors. The benefit of increasing doses in multi-daily fractionation is reported to be more marked in cases with squamous cell carcinoma.

Combination with Surgery

Because surgery and radiotherapy are both local therapies, a combination of these two modalities can be used only to a limited extent. The timing of combined use can be preoperative irradiation intended to improve resectability and prevent intraoperative metastasis and postoperative irradiation for the main purpose of controlling residual tumors and microscopic mediastinal lymph node metastasis. While the effectiveness of preoperative irradiation has not been reported except for the reports on Pancoast tumor, recent progress of chemotherapy has promoted clinical studies on the use of preoperative chemoradiotherapy. On the other hand, postoperative irradiation is generally considered to offer no benefit in survival, although it contributes to the improvement of the local control rate. However, radiotherapy after non-curative resection has been reported to achieve a 5-year survival rate of over 40%,[1] suggesting the significance of postoperative irradiation in cases with residual tumors. Future study is needed to evaluate postoperative mediastinal irradiation in patients with pN 2 to 3 tumors intended for control microscopic residual tumors.[8]

Radiotherapy for Small Cell Lung Cancer (SCLC)

1. Thoracic radiotherapy

While SCLC is more sensitive than NSCLC to both radiation and many antineoplastic

Note: LD refers to the lesions that are limited to the hemi-thorax, including the ipsilateral pulmonary hilum, the bilateral mediastinal lymph nodes and supraclavicular fossa (or ipsilateral pleural effusion). Advanced cases beyond the above-mentioned limits are referred to as ED (ipsilateral malignant pleural effusion is usually included in ED).

agents, it proliferates aggressively and the majority of patients show locally advanced disease or distant metastasis at the time of diagnosis. For this reason, clinical stages are generally classified into limited disease (LD) and extensive disease (ED).[Note)] Although SCLC is treated mainly with chemotherapy, standard therapy for LD disease includes the addition of thoracic irradiation to systemic chemotherapy, because it reduces local progression rate. The timing of radiotherapy is best when it is used concurrently with chemotherapy early after the beginning of treatment, and a 5-year survival rate of about 20% has been reported for LD cases.[9)] Recommended dose and fractionation is 45 Gy delivered as twice daily 1.5 Gy fractions over 3 weeks (accelerated hyperfractionation).

2. Prophylactic cranial irradiation (PCI)

Central nervous tissues are not sufficiently sensitive to the effect of chemotherapy because of the presence of the blood-brain barrier. Hence, prophylactic cranial irradiation PCI has long been used for the purpose of controlling microscopic brain metastases in the treatment of SCLC. Although PCI reduced the relapse rate of brain metastasis, few reports had documented the improvement of survival rate, and the propriety of this procedure is controversial. Recent results of meta-analysis, however, demonstrated that PCI also improves survival rate in patients showing clinically complete remission (CR) after initial treatment. As a result, PCI is gradually being incorporated into the standard therapy for patients showing CR after initial treatment. Recommended doses for PCI are 25 to 30 Gy in 10 to 15 fractions.[10)]

Palliative Radiotherapy

Even if extensively advanced stage of cancer prohibits the expectation of cure, patients with advanced cancer have multiple symptoms that impair function and quality of life. Various symptoms of lung cancer can be palliated by a slight reduction of the tumor volume in the infiltration sites causing symptoms. Hence, radiotherapy is also widely used as palliative treatment. Indications for palliative irradiation include (1) cancer pain, (2) symptoms due to tumor compression on organs, and (3) hemorrhage from tumors.[2)] More specifically, such treatment is considered for symptoms such as pain from chest wall infiltration and bone metastasis, disturbance of motor function and consciousness due to brain metastasis, superior vena cava syndrome, airway obstruction, and hemoptysis. All these symptoms are improved by irradiation in 80 to 95% of the patients. Doses of 20 Gy or less are sufficient for the purpose of relieving subjective symptoms. Unlike narcotics, irradiation for pain can achieve not only pain relief but also the control of metastatic foci. The ability of radiotherapy to facilitate rehabilitation of patients is an important advantage.

Adverse Events Associated with Radiotherapy and Precautions[2)]

Because the effect of radiation on normal tissues is limited to the irradiated volume, radiotherapy usually does not cause significant systemic adverse reactions such as leukopenia, vomiting, and immunodeficiency, unless anticancer drugs are used concurrently. One of the acute reactions observed frequently during thoracic radiotherapy is radiation esophagitis associated with mediastinal irradiation. In some patients treated with multi-daily irradiation or the concurrent use of chemotherapy, radiation esophagitis may cause severe swallowing difficulty that would require interruption of treatment. In most patients, however, esophagitis is transient and resolves naturally after a few weeks from the completion of treatment. Alcohol ingestion during radiotherapy must be strictly prohibited.

Adverse reactions occurring after treatment include radiation pneumonitis and pulmonary fibrosis. Lung tissues receiving irradiation de-

velop inflammatory changes a few months after treatment and might eventually develop fibrosis. Although this condition is usually limited to the field of irradiation, serious pneumonitis extending beyond the radiation field may occur occasionally after chemoradiotherapy.

Among delayed adverse reactions after radiotherapy, the most important one that requires the greatest caution is the effect on the spinal cord. However, radiation myelopathy can be avoided if sufficient precautions are taken in the treatment plannings.

Conclusion

Radiotherapy plays important roles in the local control of lung cancer. Radiotherapy for inoperable or unresectable NSCLC provides a greater chance of cure when the tumor is smaller in diameter. The success of the treatment for locally advanced NSCLC depends on the locations of primary tumors and lymph node metastases. Recent advances of therapeutic techniques have enabled us to deliver large doses to the targets and improve local control rate. An important theme for future study is development of optimal regimens for the combined use of chemotherapy and radiotherapy aiming to improve local control rate and prevent distant metastases.

While clinical results of the treatment for SCLC has been improved substantially by the introduction of platinum agents, thoracic radiotherapy also plays a major role and PCI has been gradually incorporated into the standard therapy.

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Out-Patient Chemotherapy for Lung Cancer
—Principles and practice—

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Abstract: Recent emphasis on the importance of quality of life (QOL) has led to an increase in the demand for out-patient chemotherapy for lung cancer. Patients with no prospect of a cure, including patients with stage IV non-small cell lung cancer, those with relapsed cancer, and aged patients, can benefit from long-term outpatient chemotherapy at modest doses, which is expected to lengthen survival and help maintain QOL. Combinations of antineoplastic agents other than cisplatin, such as carboplatin, paclitaxel, docetaxel, irinotecan, gemcitabine, and vinorelbine, require shorter time for infusion, cause milder side effects such as nausea and vomiting, and can be controlled more easily on an out-patient basis. Attention has recently been directed to an oral antineoplastic agent gefitinib. Neutropenia caused by chemotherapy should be treated with G-CSF, and the patients showing febrile neutropenia should be hospitalized and treated with intravenous infusion of antibiotics. Oral serotonin antagonists are useful for preventing nausea and vomiting. Current problems include the facts that out-patient chemotherapy has not been assigned sufficient national health insurance reimbursement and that home care places burden on family members.

Key words: Cisplatin; Carboplatin; Paclitaxel; Docetaxel

Introduction

Recent emphasis on the importance of quality of life (QOL) in cancer treatment has led to an increase in the demand for out-patient chemotherapy for lung cancer.

Prognosis of lung cancer is generally poor. About one-half of patients die within a year. The time left for patients with no prospect of cure (relapsed cases and the patients with stage IV non-small cell lung cancer) must be respected as much as possible. If we want to conserve the social life and family life of the patients, chemotherapy is better conducted on an out-patient basis, as is the case in Western countries. Because many patients with lung cancer remain ambulant and retain the ability to eat until the terminal stages, out-patient care

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Table 1 Conditions for Performing Out-Patient Chemotherapy

(1) Conditions on the patient side
• The patient has self-motivation to fight the disease and informed consent can be obtained.
• Performance status is good.
• The patient lives near the hospital.
• It is desirable that the patient's family is cooperative.
(2) Conditions on the hospital side
• The hospital has the space for I.V. drip infusion and an efficient system for nursing.
• Patients showing sudden aggravation can be admitted.
• The data for blood counts are reported promptly.
(3) Content of chemotherapy
• Side effects can be controlled.
• Only a short time is needed for drip infusion.

is more suitable for them than for patients with other types of cancer. However, sufficient attention must be paid, some patients develop complications such as pneumonia, carcinomatous pleurisy, and brain metastasis, and their conditions may aggravate suddenly.

Criteria for Performing Chemotherapy at Out-Patient Clinics

Among patients with small cell lung cancer and stage IV non-small lung cancer who are indicated for chemotherapy, those satisfying the criteria listed in Table 1 may be treated with out-patient chemotherapy, no matter whether they have received prior treatment or not. However, hospitalized care is the more convenient form of treatment, if we intend to cure the patient through multidisciplinary treatment such as concurrent chemotherapy and radiotherapy for LD (limited disease) small cell lung cancer and that for stage III non-small cell lung cancer. The patient-side conditions for performing out-patient chemotherapy ((1) in Table 1) include good performance status (PS) and short distance from home to hospital (i.e., ambulance transportation is possible and the travel time is within 1.5 hours by car).

Outpatient chemotherapy is often requested by young patients who can visit the hospital by themselves and want to continue work during treatment. On the other hand, aged patients representing a large proportion of lung cancer patients are generally unsuitable for hospitalized active cancer therapies because of deterioration of the functions of various organs, and out-patient chemotherapy is recommended for these patients. This would also improve the prevention of senile dementia and depression. Moreover, chemotherapy has been reported effective in improving survival even in aged patients with non-small lung cancer.[1)]

As for the preparedness of hospitals ((2) in Table 1), we need space for the outpatient administration of drip infusion, because most antineoplastic agents are nowadays given by I.V. drip infusion. Our hospital has 44 beds in 6 rooms in a ward-type space called the daycare center,[2)] where outpatient chemotherapy and blood transfusion are performed. Drugs for injection are prepared promptly after the arrival of patients by pharmacists using the safety cabinet in the daycare center. The number of chemotherapy sessions performed here was 4,889 in 2001, and is increasing. Of this total, 1,156 sessions were given to patients of the Department of Pulmonary Medicine, mostly consisting of lung cancer patients.

Patients need to be hospitalized quickly after sudden aggravation or other emergencies. In our hospital, the introduction of a clinical path system and the increase in out-patient chemotherapy have shortened the mean length of hospitalization to about 16 days and accelerated the turnover of beds. Because of this improvement, we are able to arrange emergency hospitalization when needed.

Selection and Administration of Antineoplastic Agents

Out-patient chemotherapy does not differ from hospitalized chemotherapy in that the main purposes are the reduction/elimination of tumors and the elongation of survival. We

need procedures that can be performed in outpatient clinics without compromising the efficacy of treatment.

Cisplatin has come to be used for not only non-small cell lung cancer but also small cell lung cancer. It has been recently demonstrated that the combination of cisplatin and irinotecan is effective for ED (extensive disease) small cell lung cancer.[3] However, the administration of cisplatin at 60 to 80 mg/m^2 requires the use of large quantities of infusion to prevent renal damage, and accompanies severe side effects such as nausea and vomiting. For this reason, it is difficult to administer this regimen on an outpatient basis. A solution to this problem is the weekly administration of small divided doses of cisplatin (30 mg/m^2).[4] This regimen can be administered to out-patients because of its relatively mild side effects (mostly gastrointestinal) and high safety.

During the 1990s, a series of new antineoplastic agents were developed mainly targeted at non-small cell lung cancer. Combinations of these agents excluding cisplatin are effective as cisplatin-containing chemotherapy, and they are superior with respect to the control of side effects. As a result, regimens excluding cisplatin are now the mainstream outpatient chemotherapy.

For example, we are now using the combination of docetaxel (30 mg/m^2) or paclitaxel (110 mg/m^2) and carboplatin [based on Calvert's formula* with the AUC (area under the curve) target of 3] at half the normal dose. This treatment is given at 2-week intervals, if considered possible based on the monitoring of leukopenia and other side effects. Each course of drip infusion takes 2 to 4 hours. The use of Calvert's formula enables us to correct for the individual difference in the AUC of carboplatin and improve safety. In addition, bone marrow side effects of paclitaxel and docetaxel are less prominent when they are given in divided doses.[6] Thrombocytopenia due to carboplatin is also lower than expected.[7] Other side effects are also slight because of the low dose per session. This regimen can be administered safely using hospital visits at intervals of 1 to 2 weeks.

Other combinations such as vinorelbine plus gemcitabine and docetaxel plus gemcitabin[5] are also practiced. The administration of these regimens is simple and requires only a short time of I.V. drip infusion.

A tyrosine kinase inhibitor gefitinib (Iressa®)[8] was authorized in July 2002. In addition, the indications of TS-1 (TS-1®), a combination drug containing tegafur, are going to be expanded to include non-small cell lung cancer. Both these drugs are administered orally. Iressa® has been reported to show response rates of 6 to 19% in cases of previously treated non-small cell lung cancer.[8] The side effect profile of this agent is entirely different from that of conventional antineoplastic agents, and it hardly causes bone marrow suppression, nausea, vomiting, or alopecia. The use of oral agents eliminates the need for the space for outpatient I.V. infusion, facilitating the execution of outpatient chemotherapy.

Side Effects and Prevention of Medical Accidents

In our department (Department of Pulmonary Medicine, Saitama Cancer Center), the patients receiving chemotherapy usually visit the hospital at intervals of 1 to 2 weeks. At each visit, blood samples are collected and I.V. chemotherapy is given based on the measurement of blood counts. If neutropenia is noted, G-CSF is given according to the standards approved in the national health insurance system. When fever (38°C or higher) accompanies neutropenia, the patient is hospitalized, examined for causative bacteria, and treated

* Calvert's formula: carboplatin dose (mg/body) = target AUC × (GFR + 25), where GFR is usually based on the measured value of 24-hr creatinine clearance (Ccr).

with the combined use of G-CSF and I.V. antibiotics.[10)]

Even if neutropenia is not observed, signs of infection such as fever and purulent sputum should be responded to quickly, because lung cancer is often complicated with obstructive pneumonia or opportunistic infections, which are possibly fatal.

Oral serotonin antagonists were authorized several years ago, and this facilitated the control of nausea and vomiting due to chemotherapy on an out-patient basis. Although slight anorexia does not need special treatment, hydration is required when the condition is so severe that the patient is unable to drink water.

There are wide individual variations in the side effects of irinotecan, such as leukopenia and late-onset diarrhea, and these problems must be treated with the greatest care. Oral alkalization with control of defecation can be useful in preventing diarrhea.

Prevention of medical accidents is extremely important in busy out-patient clinics. First, errors in prescription and dispensing must be prevented through multiple checks by pharmacists and nurses. Care should be taken because shock may be caused infrequently by hypersensitive reaction to paclitaxel, docetaxel, other antineoplastic agents, and additives. The leakage of antineoplastic agents to the skin should be prevented by secure keeping of the I.V. route.[11)] If there is difficulty in keeping peripheral veins, use of an indwelling I.V. port is useful.

Sufficient informed consent must be obtained concerning the possibility of toxic death and the fact that alopecia is almost inevitable.

Problems of Out-Patient Chemotherapy and Solutions

Outpatient chemotherapy eliminates the cost of hospitalization and reduces the overall cost of medical care. However, hospitals are not able to allocate sufficient staff needed for out-patient chemotherapy, because appropriate reimbursement has not been assigned in the national health insurance system. Although the revision of medical fees in April 2002 allowed hospitals to add the cost of out-patient chemotherapy to their invoices, the unit price of 300 points per day is grossly insufficient. In addition, hospitals are required to be accredited through medical performance evaluation conducted by the Japan Council for Quality Health Care or other authorized organizations.

The self-motivation of the patients is an important factor in out-patient care. Patients should be given not only information on the diagnosis but also the details of their disease including prognosis, and written consent must be obtained. However, physicians and other medical staff are too busy to allow sufficient time for explanation to patients, and they may overlook details of the situation of patients because of the inability to collect information from the patients. In particular, it takes a long time to understand the patient's condition, the selection of treatment strategy, and obtaining informed consent at the time of the first introduction of chemotherapy. It is also necessary to take great care concerning possible side effects. At present, we are addressing these problems through educational hospitalization for about 1 week at the beginning of treatment.

Nurses and paramedical staff are playing important roles in the U.S. concerning the education of patients and the practice of I.V. infusion and other procedures. It is desired that Japan develop systems for the training of nurses specializing in chemotherapy and the division of roles to make the best use of the abilities of these nurses.

Another problem is the burden on the patients' families, which might be severe in the case of aged patients requiring assistance and patients who are not able to visit hospitals by themselves because of brain metastases or other complications. It is necessary to expand further the system for supporting home care.

Conclusion

Considering the QOL of patients with advanced lung cancer and the cost of medical care, it is rational to perform chemotherapy on an outpatient basis, as is the case in Western countries. Recent use of non-platinum antineoplastic agents and the drugs to prevent side effects has facilitated the practice of out-patient chemotherapy. A system for supporting home care, revision of medical fees, and improvement of the preparedness of hospitals for outpatient care are desired.

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Laser Therapy and Airway Stenting for Central-Type Lung Cancer

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Abstract: Endoscopic procedures such as laser therapy and airway stenting are attracting attention as therapeutic methods for the treatment or preservation of pulmonary functions in inoperable cases. Among types of lung cancer, the best candidates for photodynamic therapy (PDT) using low-power laser and photosensitizer are cases with central-type early stage lung cancer, and complete remission (CR) can be expected. CR was achieved in 86.4% of cases with endoscopic early-stage lung cancer treated with PDT. High-power laser therapy for advanced lung cancer is performed for the purpose of palliative opening of tracheobronchial lesions presenting stenosis and obstruction due to tumors. This procedure was effective in 81.0% of cases with obstructive advanced lung cancer treated with Nd-YAG laser vaporization. If re-stenosis after the reopening of bronchial lumen is a problem, airway stenting is effective for maintenance of bronchial lumen, producing dramatic improvement of dyspnea immediately after stenting. These various endoscopic procedures are minimally invasive methods based on the respect for and improvement of the patients' QOL.

Key words: Central-type lung cancer; Laser therapy; Photodynamic therapy (PDT); Airway stenting

Introduction

Lung cancer has a tendency to develop preferentially in aged people as well as other types of cancer. Although the development of diagnostic techniques has gradually improved the detection of early-stage lung cancer, many of the newly detected cases still have inoperable

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advanced cancer, and some cases of early-stage cancer are inoperable because of cardiopulmonary dysfunction due to high age. Endoscopic procedures such as laser therapy and airway stenting intended for the treatment or preservation of pulmonary functions in these inoperable cases are considered very important.

Low-Power Laser Therapy for Early-Stage Lung Cancer

Photodynamic therapy (PDT) for cancer using a combination of low-power laser irradiation and tumor selective photosensitizer was first applied clinically by Dougherty *et al.* in 1978 to the skin metastasis of breast cancer.[1] Since then, we have been studying the clinical application of the world's first endoscopic PDT in cooperation with them.[2,3] In Japan, PDT using a tumor selective photosensitizer Photofrin and excimer dye laser was covered by the national health insurance system in April 1996. Thereafter, the combination of Photofrin and YAG-OPO laser was included. The mechanism of the action of this PDT is considered to involve singlet oxygen, which is generated through photochemical reactions and causes degenerative necrosis of tumor cells.

1. Indications

The best candidates for PDT are cases with central-type lung cancer in the early stage. While the therapy is intended for complete remission (CR), this currently requires satisfaction of the following endoscopic conditions: (1) the peripheral margin of the lesion can be identified; (2) the lesion is located in a position that can be irradiated with laser easily; (3) the lesion is superficial with a major diameter of 1.0 cm or less; and (4) histological type is early superficial squamous cell carcinoma.

2. Therapeutic results of PDT

Laser irradiation is performed endoscopically 48 to 78 hours after the intravenous administration of 2.0 mg/kg of Photofrin (Fig. 1). The

Fig. 1 Treatment with PDT

irradiation energy is 100 to 200 J/cm^2, and energy levels in this range do not cause any heat degeneration or other adverse effect. The technique is referred to as "low-power" because of this fact. The duration of irradiation is usually 10 to 20 minutes.

CR was achieved in 165 out of 191 lesions (86.4%) of endoscopic early-stage lung cancer. The analysis of treatment results according to various factors is summarized in Table 1. Recurrence after CR was observed in 21 lesions (11.0%). Reasons hindering CR included the difficulty in identifying the peripheral margin of the lesion, infiltration of the lesion beyond bronchial cartilage, and the difficulty of laser irradiation due to the tangential orientation of the lesion to the laser beam direction. Recently, techniques such as fluorescence bronchoscopy and endobronchial ultrasonography are used for objective evaluation of the extent and depth of the lesion. The 5-year survival rate was 94.2% excluding deaths of other diseases and 68.3% including deaths of other diseases. Figure 2 presents a case treated with PDT.

3. Complications and precautions

The generation of necrotic substances during several days after PDT may cause obstructive pneumonia due to airway obstruction, and these substances must be removed bronchoscopically. The only major side effect of Photo-

Table 1 Results of PDT for Early-Stage Lung Cancer by Endoscopic Diagnosis (The 1st Department of Surgery, Tokyo Medical University)

Endoscopic diagnosis	No. of lesions	CR (rate)	PR	Recurrence after CR
Nodular	31	28 (90.3%)	3	1
Hypertrophic	149	128 (85.9%) (94.9%)*	21	19
Polyp	11	9 (81.8%)	2	1
Identification of peripheral				
• Possible	145	134 (92.4%) (98.1%)*	11	20
• Impossible	46	31 (67.4%)	15	1
Tumor size (cm)				
<0.5	58	55 (94.8%)	3	9
0.5≦ <1.0	78	74 (94.9%)	4	8
1.0≦ <2.0	31	25 (80.6%)	6	3
2.0≦	24	11 (45.8%)	13	1
	191	165 (86.4%)	26	21

*: 1cm or less in diameter. CR: complete remission, PR: partial remission.

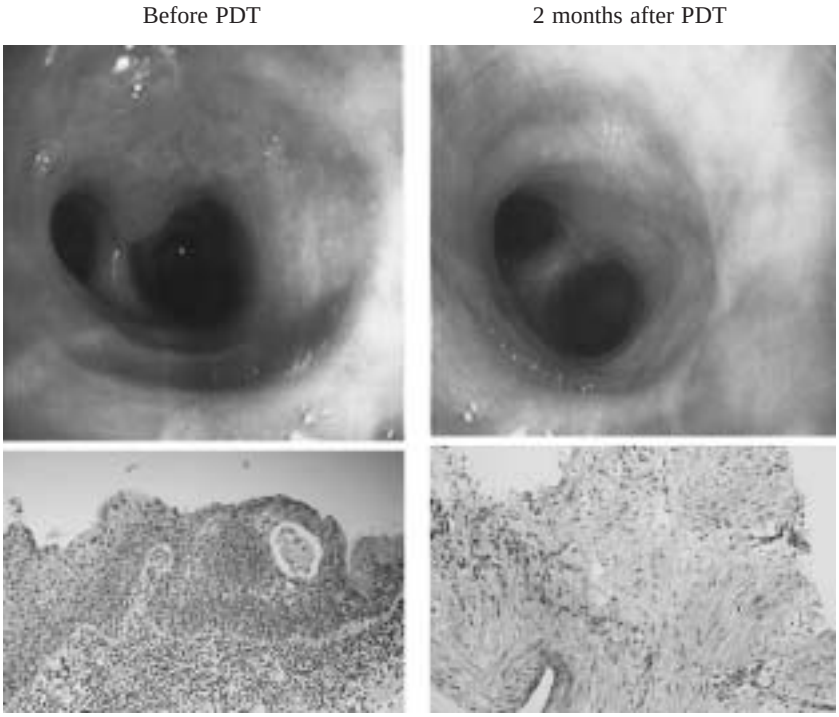


Fig. 2 A case in complete remission after PDT
A male, 77-year-old patient with nodular-type early-stage lung cancer in left B^{10}_{a+bc} bifurcation.
The patient was diagnosed as squamous cell carcinoma (carcinoma in situ) based on biopsy. Endoscopy performed 2 months after PDT revealed complete disappearance of tumor, and biopsy indicated CR.

frin is photosensitivity of the skin (sunburn). To prevent this effect, patients should avoid being exposed to direct sun light for about 2 weeks after dosing. Even if patients develop sunburn, it resolves with time in many cases.

High-Power Laser Therapy for Advanced Lung Cancer

The purpose of this therapy is to cauterize and vaporize tumors endoscopically using the high energy of the laser beam. Therefore, this procedure is indicated for tracheobronchial lesions developing stenosis or obstruction due to tumors.

1. Laser systems for vaporization

Nd-YAG (neodymium-yttrium-aluminum-garnet) laser system at the wavelength of 1,064 nm is used commonly. The Nd-YAG laser light is poorly absorbed by hemoglobin and water compared to the CO_2 laser, while it has high penetration into tissues. KTP/YAG laser and diode laser systems have also been developed recently. The KTP/YAG laser is a complex laser oscillation system that can switch freely between KTP laser (532 nm) suitable for incision and vaporization and Nd-YAG laser suitable for coagulation and hemostasis.

The diode laser has advantages of small size and stable output characteristics, and is maintenance-free. A small portable unit can operate with domestic 100-V power source, facilitating bedside treatment for patients that cannot be transported to the endoscopy room.

2. Indications

High-power laser vaporization of tumors is used in the role of local adjuvant therapy for radiotherapy, chemotherapy, and airway stenting. The main targets are tumors occurring in large airway in the range from the trachea to the entries to segmental bronchi. It is also indicated for emergency life-saving treatment in cases with serious ventilatory insufficiency due to tracheobronchial obstruction presenting a risk of asphyxia.[4] Palliative indications include atelectasis and obstructive pneumonia due to advanced cancer, preparation for stenting, and hemostasis for the bleeding from tumors.

3. Complications and precautions

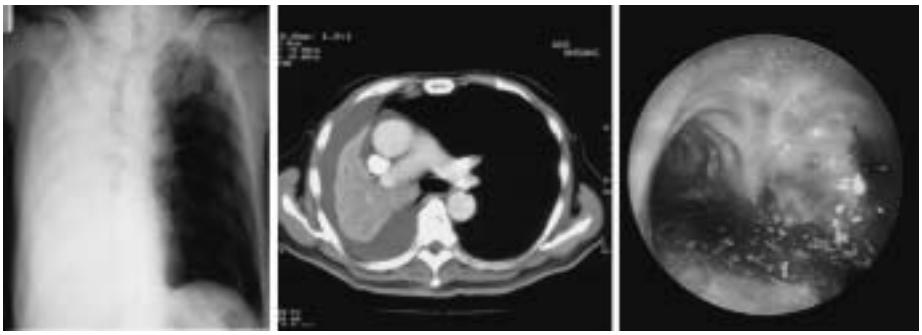
The process of tumor vaporization can damage surrounding normal tissues. Because of the risk of bronchial perforation, it is crucial to set the laser energy as low as 10 to 20 W to vaporize the margin of tumor. In particular, greatest care should be taken in irradiating a tumor where the peripheral bronchus is not identified. Considerable experience is required before performing accurate irradiation to lesions responding to the breathing and cough reflex of the patient.

Because the most dangerous complication is massive bleeding from blood vessel perforation, the operating physician must be fully acquainted with the anatomic location of blood vessels. Equipment for intubation, oxygen administration, etc. must always be provided at hand, so that it can be used when hemorrhage is not controlled by hemostatic irradiation and infusion of vasoconstrictors. Massive aspiration of the soot and smoke generated from the laser vaporization of tumors may cause serious respiratory insufficiency in the patient.

4. Therapeutic results

Nd-YAG laser vaporization was performed in 177 cases of obstructive advanced lung cancer at the 1st Department of Surgery, Tokyo Medical University. The result was considered effective if tumor diameter or obstruction was reduced by 50% or more, and ineffective if the reduction was less than 50%. Overall, 143 of 177 cases (81%) were evaluated as effective. As seen from the location occupied by tumors, the percentage of effective results was 93% (64/69) for lesions in the trachea or main bronchi and 73% (79/108) for lesions in lobar or segmental bronchi. Complications included massive hemorrhage in 10 cases (6%) and bronchial perforation in 4 cases (2.3%).[5]

Before stenting



After stenting

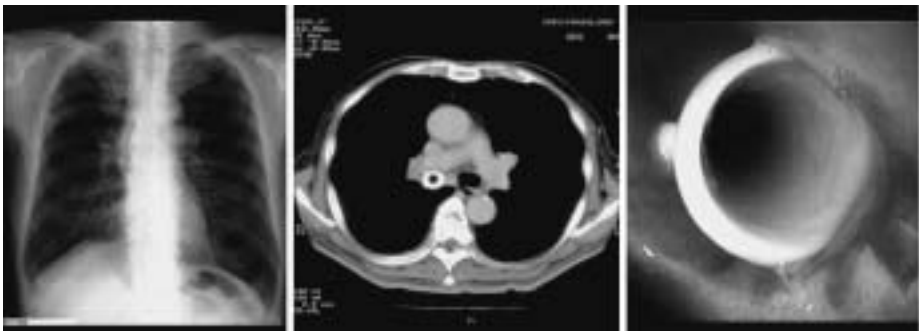


Fig. 3 A case of Dumon stent insertion

A case of complete atelectasis in the right lung (squamous cell carcinoma). A Dumon stent was inserted after the tumor obstructing the right main bronchus was cored out by the use of a rigid endoscope sheath. This procedure resulted in improvement of atelectasis and improvement of respiratory functions.

Stenting for Central Airway Obstruction[6)]

While Nd-YAG laser vaporization is effective as a palliative treatment for obstructive tracheobronchial lesions, re-stenosis occurring after the reopening of bronchial lumen presents a problem. In addition, this method is ineffective for stenosis by extrinsic compression due to outward tumor advancement beyond the tracheobronchial wall. Stenting is effective for maintaining airway in such cases. Dramatic improvement of dyspnea can be achieved immediately after stent insertion.

1. Various types of stents

Dumon Stent: This stent is made of silicone and has studs on the surface to prevent migration. Because barium is encapsulated in silicone, the stent can be identified under X-ray fluoroscopy. A Y-shaped stent is used for stenosis around the tracheal bifurcation. It is not affected by the problem of tumor ingrowth, is effective also for infiltrative stenosis, and can be removed. Figure 3 shows a case of Dumon stent insertion.

SEMS (self-expandable metallic stent): SEMS is the general term for a metallic stent that expands by the action of its own resilience (Z-stent, Ultraflex, and Wallstent). SEMS can be inserted easily via a flexible bronchoscope. The small volume before expansion means that the stent does not require elaborate pretreatment and can be inserted safely into highly stenotic sites. For this reason, it is often used for the purpose of emergency airway reopening.

Dynamic Stent: This is a composite Y-shaped stent made of silicone and metal. A horseshoe shaped stainless steel pieces are used in place of tracheal cartilage. The membranous portion is made solely of silicone to allow physiological movement of the stent. This mechanism was developed for the purpose of facilitating expectoration by coughing. This stent is used for long stenosis of the trachea and stenosis around the tracheal bifurcation.

2. Indications

Good candidates for airway stenting are cases with dyspnea showing no response to other therapies, 50% or more stenosis in central airway, preserved pulmonary function and blood flow in the peripheral area with stenosis, and a prognosis of 3 months or longer survival. Indications for malignant disease include (1) maintenance of bronchial lumen after dilation for infiltrative airway stenosis and obstructive lesions; (2) tracheobronchial malacia due to repeated laser vaporization; (3) stenosis by extrinsic compression of trachea and bronchi due to mediastinal lymph node metastasis, lymphoma, and mediastinal tumors; and (4) closing of esophagotracheal/bronchial fistula.

3. Therapeutic results

Colt and Dumon inserted 502 airway stents in 286 cases, and reported that mean duration of stent placement in cases with benign lesions was 14.2 months compared with 3.3 months in cases with malignant lesions.[7] Becker inserted 165 various types of stents in 95 cases, and reported a 2-year survival rate of 50% in cases of stenosis that developed after response to treatment, as well as records of patients who survived for 5 years without recurrence.[8] Bolliger *et al.* studied 31 cases of malignant disease and obtained a mean survival time of 4 to 6 months.[9] This survival exceeding 3 months suggested the efficacy of this technique. Improvement of dyspnea in 86 to 100% of cases has also been documented in many reports.

According to the report of Diaz-Jimnez, complications of airway stenting using Dumon stents included migration and displacement in 17.5%, granulation in 6.3%, and symptomatic retention of secretion in 6.3%.[10] Using Wallstent, Bolliger and Monier reported that they observed deviation and displacement in 12 to 15%, granulation in 15%, symptomatic retention of secretion in 19 to 38%, and re-stenosis in 36%.[11,12]

Conclusion

PDT is considered a very effective minimally invasive treatment for central-type early-stage lung cancer. At present, efforts are continuing for the development of novel photosensitizers that can be used for PDT with better accumulation to tumors, reduced side effect (sunburn), and longer excitation wavelengths improving tissue transmission. A chlorine-based agent called ME2906 (NPe6) is considered as the most promising second-generation photosensitizer after Photofrin. Compact diode laser system for PDT has also been developed in response to this newly development of photosensitizer with long excitation wavelength. It is certain that PDT using novel photosensitizers and diode laser systems will be in the main stream of clinical practice.[13]

High power laser vaporization and airway stenting are performed as local therapies for central airway stenosis caused by advanced cancer, and these procedures offer dramatic improvement of dyspneic symptoms.

These various endoscopic procedures are considered new therapeutic methods based on the respect for and improvement of the patients' QOL.

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New Evaluation Criteria for Response and Toxicity in Lung Cancer Treatment

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Abstract: Response Evaluation Criteria in Solid Tumors (RECIST) and the National Cancer Institute—Common Toxicity Criteria (NCI-CTC) Version 2.0 were prepared for the purpose of standardizing the evaluation criteria for response and toxicity of cancer treatment. Objective response evaluation in RECIST has been simplified from the method using bidimensional measurement (product of 2 diameters) in WHO Standards to the summation of unidimensional measurement (largest diameter). NCI-CTC Version 2.0 includes toxicities and categories that have been increased from 49 toxicities in 18 categories in the previous version to 279 toxicities in 24 categories. It also provides more appropriate toxicity evaluation by grading of associated toxicities.

Key words: Response evaluation criteria; Toxicity evaluation criteria; RECIST; NCI-CTC Version 2.0

Introduction

The clinical effectiveness of various therapies for malignant tumors is measured in terms of objective response (tumor size reduction) assessed shortly after treatment and the assessment of long-term results, which include the time from treatment to relapse or progression and the survival time.

In 1979, the World Health Organization (WHO) published the "WHO Handbook for Reporting Results of Cancer Treatment"[1] stipulating the standards for summary reporting of objective response and long-term results (hereinafter called "WHO Standards"). The WHO Standards have been used internationally, and Japanese physicians are using the Japan Society of Clinical Oncology Clinical Response Evaluation Criteria for Chemotherapy in Solid Tumor[2] formulated based on the WHO Standards.

However, various problems in the WHO Standards have been pointed out, and various groups have modified the standards. To ensure international harmonization, a revised edition of the WHO Standards called the Response Evaluation Criteria in Solid Tumors (RECIST)[3] was prepared in 1999.

Because the usefulness of cancer chemotherapy is evaluated based on the comprehen-

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sive assessment of anti-tumor effects and toxicity, the evaluation of toxicity is as important as the evaluation of anti-tumor effects.

The method of toxicity evaluation in clinical trials has conventionally been based on the "WHO Criteria for the Evaluation of Side Effects",[1] National Cancer Institute — Common Toxicity Criteria (NCI-CTC), and other references. A revised version of NCI-CTC was prepared in 1998 in response to the need for internationally harmonized toxicity evaluation criteria based on the new GCP (Good Clinical Practice: Ministry of Health and Welfare Ordinance on Standards for the Implementation of Clinical Trials on Pharmaceutical Products). At present, this new NCI-CTC is used internationally as the criteria for toxicity evaluation.

This article explains the outline of RECIST and the features of the revised NCI-CTC (Version 2.0).

Outline of New Response Evaluation Criteria (RECIST)

1. Measurement of tumors[4]

While current WHO Standards use bidimensional measurement (the product of the length of the major axis and the longest diameter intersecting with it at right angles), the new RECIST uses unidimensional measurement because of the theoretical consideration that unidimensional measurement is in better proportion to the number of tumor cells than bidimensional measurement and because of the ease of measurement.

2. Definition of lesions measured as tumors at baseline

(1) Measurable lesions

These are defined as lesions that can be measured unidimensionally and have a longest diameter of 20 mm or more on conventional CT scan and 10 mm or more on helical CT scan. This definition includes only lesions with a length of the major axis at least twice as large as the slice thickness.

(2) Non-measurable lesions

These lesions include small lesions with a longest diameter of <20 mm on conventional CT and <10 mm on helical CT, as well as true non-measurable lesions [bone lesions, carcinomatous meningitis, ascites, pleural effusion, pericardial effusion, inflammatory breast lesions, lymphangitis (skin/lung), abdominal tumors that cannot be identified and traced by imaging techniques, and cystic lesions].

3. Methods of measurement

(1) Clinical measurement (external measurement)

Only superficial lesions, such as skin tumors and palpable lymph nodes, are considered measurable. In the case of skin lesions, it is recommended to use color photographs including a ruler to indicate lesion size.

(2) Chest X-ray

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

(3) CT and MRI

CT and MRI are the best currently available and reproducible methods for measuring target lesions selected for response assessment. Conventional CT and MRI in thoracic, abdominal, and pelvic regions should be performed with cuts of 10 mm or less in slice thickness. Helical CT in these regions should be performed using a 5 mm reconstruction algorithm. Head and neck tumors and those of extremities usually require specific protocols.

(4) Ultrasound

When the primary endpoint of the study is objective response evaluation, ultrasound should not be used to measure tumor lesions that are not directly measurable from the body surface. Ultrasound is, however, a possible alternative to clinical measurements of superficial palpable superficial nodules, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful for confirming the complete disappearance of superficial lesions.

(5) Endoscopy and laparoscopy

The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

(6) Tumor markers

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared. At present, studies are conducted to establish special criteria for the standardized use of PSA and CA-125 in clinical trials.

(7) Cytology and histology

Cytology and histology can be used to differentiate between CR (complete response) and PR (partial response) in rare cases such as germ cell tumors. In addition, cytology is needed in determining whether the overall evaluation should be PD (progressive disease) in the case that a measurable lesion was reduced or unchanged by treatment and appearance or increase of coelomic fluid was observed.

4. Objective response evaluation

(1) In objective response evaluation, tumors in all organs should be evaluated as a whole using the sum of their longest diameters, as contrasted to the evaluation based on the degree of response in each organ. If the protocol uses objective response as the primary end point, the study should include only the patients having measurable tumors at baseline.

(2) Documentation of target and non-target lesions at baseline

[Target lesions]: All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total should be identified as target lesions. Target lesions should be selected based on their longest diameter and their suitability for accurate repeated measurements. Objective response should be evaluated based on the sum of the longest diameter for all target lesions.

Table 1 Overall Response Evaluation

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	IR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR: complete response, PR: partial response,
IR: incomplete response, PD: progressive disease.
(Cited from Ref. 3: Therasse, P. *et al.*: New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000; 92: 205–216.)

[Non-target lesions]: All other lesions should be identified as non-target lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

(3) Criteria for objective response

(i) Evaluation of target lesions

Complete response (CR): Disappearance of all target lesions.

Partial response (PR): At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum of the longest diameter.

Progressive disease (PD): At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded.

Stable disease (SD): Neither CR nor PR.

(ii) Evaluation of non-target lesions

Complete response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete response (IR)/stable disease (SD): Persistence of one or more non-target

lesion(s) or/and maintenance of tumor marker level above the normal limits.

Progressive disease (PD): Unequivocal progression of non-target lesions.

(iii) Overall objective response

Overall response is evaluated based on the effect on target lesions and non-target lesions and the presence or absence of new lesions (Table 1).

(iv) Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression. In general, the patient's best response assignment will depend on the overall response and its duration.

(4) Duration of objective response

(i) Duration of CR: The duration of CR is measured from the time measurement criteria are met for CR until the date of recurrence (at least 4 weeks as defined in the study protocol).

(ii) Duration of PR: The duration of PR is measured from the time measurement criteria are met for PR until the date of disease progression (at least 4 weeks as defined in the study protocol).

(iii) Duration of SD: SD is measured from the start of the treatment until the criteria for disease progression are met (usually 6 to 8 weeks as defined in the study protocol). The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD.

Features of New Toxicity Criteria (NCI-CTC Version 2.0)

1. Increased number of toxicities

Toxicities are classified into pathophysiological categories or anatomical categories. The 24 categories (Table 2) and 279 toxicities are arranged in alphabetical order.

Table 2 Toxicity Categories of NCI-CTC (Version 2.0)

ALLERGY/IMMUNOLOGY
AUDITORY/HEARING
BLOOD/BONE MARROW
CARDIOVASCULAR (ARRHYTHMIA)
CARDIOVASCULAR (GENERAL)
COAGULATION
CONSTITUTIONAL SYMPTOMS
DERMATOLOGIC/SKIN
ENDOCRINE
GASTROINTESTINAL
HEMORRHAGE
HEPATIC
INFECTION/FEBRILE NEUTROPENIA
LYMPHATICS
METABOLIC/LABORATORY
MUSCULOSKELETAL
NEUROLOGY
OCULAR/VISUAL
PAIN
PULMONARY
RENAL/GENITOURINARY
SECONDORY MALIGNANCY
SEXUAL/REPRODUCTIVE FUNCTION
SYNDROMES

2. Important changes in Version 2.0

(1) Infection has been subdivided into 4 categories according to absolute neutrophil count (ANC): "febrile neutropenia" (fever of unknown origin without clinically or microbiologically documented infection) (ANC$<$1,000/mm^3, fever$\geqq$38.5°C), "infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia" (ANC$<$1,000/mm^3), "infection without neutropenia," and "infection with unknown ANC," and a new criterion "catheter-related infection" has been added.

(2) Associated toxicities should also be graded. Example: If toxicity "hemorrhage/bleeding with grade 3 or 4 thrombocytopenia" is noted, the criterion directs: "Also grade the site or type of hemorrhage/bleeding" and "Also consider Platelets, Hemoglobin, Transfusion-platelet, Transfusion-pRBCs."

(3) The grade-4 criterion for "platelets" has been revised from $<$25,000/mm^3 to $<$10,000/mm^3.

(4) Toxicity Module and Infection Module have

been included to be implemented when more detailed information is considered pertinent.

(5) Options covering special therapies (hematopoietic stem cell transplant and the RTOG/EORTC Late Radiation Morbidity Scoring Scheme) have been added.

(6) Toxicity from radiotherapy occurring within 90 days after the start of radiation therapy is graded according to CTC, while that occurring greater than 90 days after radiation therapy is graded according to the RTOG/EORTC Late Radiation Morbidity Scoring Scheme.

Conclusion

Objective response evaluation in RECIST has been simplified from the method using bidimensional measurement (product of 2 diameters) in WHO Standards to the summation of unidimensional measurement (largest diameter). RECIST has already been used in some clinical trials on lung cancer in Japan. In time, response evaluation criteria will be totally based on RECIST.

NCI-CTC Version 2.0 includes toxicities and categories that have been increased from 49 toxicities in 18 categories to 279 toxicities in 24 categories, and the ability for appropriate evaluation of toxicity has been improved. The Japanese translation by JCOG (2nd edition)[5] is now widely used in Japan.

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Palliative Care and Supportive Therapy for Lung Cancer Patients

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Abstract: Palliative medicine occupies an important position in cancer treatment. It is a specialty in cancer medicine ranking with surgery, radiotherapy, anticancer chemotherapy, and immunotherapy. Palliative medicine should be provided to patients throughout the whole process from the diagnosis of cancer to the terminal stage. In a wider sense, it also includes supportive therapy performed during treatment. The management of pain symptoms, which is a pillar of palliative medicine, requires a whole-person approach covering not only physical pain but also mental, social, and spiritual pain. In addition, treatment must be addressed to not only patients but also to their families. The end point of this approach is the improvement of Quality of Life (QOL) paying attention to prognosis. This article discusses the management of coughs, pain, dyspnea, and mental symptoms, which occur frequently; the management of brain metastasis, spinal cord compression, and hypercalcemia, which may develop suddenly and cause considerable deterioration of QOL; and the management of G-CSF-producing tumors and superior vena cava syndrome. Medication, radiotherapy, and mental support for these conditions are considered paying attention to the median survival period after the onset of symptoms.

Key words: Lung cancer; Palliative care; Symptom management; Supportive therapy

Introduction

Palliative care and supportive therapy are forms of comprehensive care addressing the patient as a whole person throughout the whole process of treatment. In Japan, Lung cancer is the leading cause of death from cancer. The median length of survival after the diagnosis of lung cancer is reported to be 11 months. In view of this fact, palliative care and supportive therapy must be introduced from the early days of treatment. Patients with lung cancer experience dyspnea and mental anxiety more strongly than patients with other types of

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cancer. Patients with lung cancer also experience frequent coughs during the early phase of treatment, pain from chest wall infiltration and bone metastasis during the middle phase, and dyspnea and mental symptoms during the terminal phase.

Management of Coughs

The explosive exhalation triggered by the cough reflex consumes as much as 2 kcal of energy each time. Persistent coughing causes sleep disorder, dyspnea, general malaise, pain, and anorexia, as well as it induces hemoptysis, pneumothorax, and other complications. This results in considerable deterioration of the patient's QOL.

(1) Treat the causes of coughs, if such an approach is possible. This may apply to wet coughs from heart failure, pleuritis carcinomatosa and infection and interstitial pneumonia as a complication of radiotherapy and anticancer chemotherapy.
(2) Sputum retention and wet coughs from a loss of ciliary movement caused by radiotherapy should be treated with expectorant and inhalation therapy combined with respiratory physical therapy for sputum removal.
(3) Suppression of coughs should be attempted, if coughs are not contributing to the clearing of airways and persistent. Use dextromethorphan, codeine phosphate, and other oral central antitussive and lidocaine, morphine hydrochloride, and other inhalations.
(4) Sufficient pain control should be practiced, because pain in the ribs and lumbar vertebrae prevent coughing and sputum removal, leading to a risk of complications such as pneumonia.
(5) When a patient starts coughing, ensure a comfortable body position and maintain appropriate moisture and temperature conditions.

Management of Pain

1. Bone metastasis

The median survival time for stage IV lung cancer with remote metastasis is 6 months. Bone metastasis is usually multifocal and treated with medication. A combination of morphine and nonsteroidal anti-inflammatory drugs (NSAIDs) is preferable to morphine alone. Medication is usually started with oral morphine 20 to 30 mg/day and control is achieved at 60 to 120 mg/day in many cases. Radiotherapy is effective for sudden breakthrough pain caused by body movement.

2. Pain from chest wall invasion and visceral metastasis

This pain usually responds to morphine.

3. Neurogenic pain such as Pancoast syndrome

Although morphine is used in combination with anticonvulsants, ketamine, antiarrhythmic drugs, and other adjuvant analgesic drugs, neurogenic pain is refractory.

Management of Dyspnea

In contrast to respiratory insufficiency documented by arterial blood gas analysis, dyspnea is a subjective feeling described as the "sensation of respiratory effort" and "discomfort in breathing." The term "dyspneic feeling" is sometimes used to clarify the distinction from respiratory insufficiency. Lung cancer more frequently causes dyspnea than other types of cancer[1]; over 90% of patients experience dyspnea before death.

1. Pathophysiology of dyspnea

The breathing center of the brain transmits respiratory effort signals to respiratory muscles in response to the mechanical stimuli from the stretch receptors of the lungs, muscle spindles and tendon spindles of intercostal muscles and the diaphragm, etc. Copies of respiratory effort

signals are considered to reach the dyspnea detection area of the cerebral cortex via alternative pathways to cause the "sensation of respiratory effort" and "discomfort in breathing" (motor command theory).

2. Causes and nature of dyspnea in terminal lung cancer patients

(1) Dyspnea due to the decrease in respiratory surface

This type of dyspnea is often severe and presents a marked decrease in arterial oxygen tension (PaO_2) and tachypnea. Sensation of effort is considered the main symptom. Typical causes are complications with lymphangitis carcinomatosa, pleuritis carcinomatosa, and pneumonia.

(2) Dyspnea due to airway obstruction

This type of dyspnea is severer than expected from blood gas values. Discomfort in breathing is considered the main symptom. In addition to tracheal stenosis, difficulty in expectoration, coughing, and wheezing may cause dyspnea in many cases.

(3) Psychogenic dyspnea

Dyspnea is associated with the immediate fear of death. This type of dyspnea often occurs at night, and may cause a vicious cycle of dyspnea/suffocation panic attacks.

3. Management principles

(1) Method of evaluation

Evaluation by the patients themselves is important for the control of symptoms. Commonly used evaluation scales are the Borg scale, visual analogue scale, face scale, and cancer dyspnoea scale.[2)]

(2) Oxygen therapy

While the administration of oxygen is effective in patients with hypoxemia, there are large individual variations in hypoxic respiration response and the placebo effect may be considerable.[3)] Arrangements should be made so that the patients can be freed from oxygen supplementation when they are at rest and experiencing less subjective symptoms, while they can use oxygen during physical activity.

(3) Systemic administration of morphine

Opioids improve dyspnea via the mechanism of respiratory depression. In other words, they reduce the respiration rate and weaken the sensation of the need for respiratory effort. Opioids are effective in about 70% of cases.[4)] Oral morphine hydrochloride should be started from small doses. If no effect is seen after titration up to 30 mg/day, the patient is likely to be non-responsive.[5)] Dangerous respiratory depression can be avoided using sufficient precaution, because it is preceded by strong sleepiness. Drugs preventing nausea, vomiting, and constipation should be administered concurrently.

(4) Morphine inhalation

Morphine inhalation exerts direct effects of the suppression of airway secretion and coughing and relaxation of airway smooth muscles, as well as systemic effects after absorption. Advantages of this treatment include rapid action, low occurrence of systemic side effects, and ease of use allowing self-control by the patient. A 10 mg dose of morphine in physiological saline and inhalation is administered so that inhalation is completed within 5 minutes. The effect of this treatment comprises the effect of morphine, the effect of the inhalation of physiological saline, and psychological effect. This treatment is effective in about 40% of cases.[5)]

(5) Pleuritis carcinomatosa

This is the most frequent cause of dyspnea in patients with lung cancer. In cases with terminal lung cancer, pleurodesis is indicated only for cases in which the space between the visceral pleura and parietal pleura is eliminated by continuous drainage. Intermittent needle drainage at about 500 to 1,000 m*l* is preferred in many cases. Intermittent pleural drainage using IVH tube is suitable for cases requiring frequent discharge, and this method causes less pain.[6)]

(6) Respiratory physical therapy

(i) Extracorporeal assisted ventilation is a method of helping sufficient expiration

using compression of the lower part of the chest in time to expiration.[7] This method is effective for stopping the vicious cycle of respiratory panic attacks.

(ii) Squeezing operation is a method in which the operator places his hands on the chest of the patient with sputum retention and applies pressure toward the tracheal bifurcation along the direction of the movement of the ribs during expiraion.[7] This method is effective for releasing sputum from bronchi.

(7) Death rattle

Death rattle is caused by secretion in the lower pharynx. Hypoglossal administration of scopolamine hydrobromide (Hysco®) injection is effective for alleviating death rattle through suppression of airway secretion.

(8) Furosemide inhalation

Furosemide increases the activity of stretch receptors and decreases the activity of irritant receptors in the lungs,[8] and this alleviates dyspnea.[8,9] It is also reported to elongate the breath holding time needed for speech, swallowing, and defecation.[9] A 20 mg/A dose of furosemide in physiological saline is inhaled. This treatment does not cause significant side effect.

(9) Sedation

Dyspnea is a distressing symptom that is not easily controlled and involves direct risk of death. Dyspnea often triggers initiation of sedation. It such cases, patients need urgent establishment of palliative treatment, as well as better psychological support and communication. As a rule, sedation should be given with the consent of the patient. The therapy should start with intermittent shallow sedation using such agents as midazolam.

(10) Others

Opening of windows and breezes from an electric fan stimulate the trigeminal nerve on the face and directly improve dyspnea. Oxygen administration is also considered effective. In addition, application on the chest alleviates dyspnea through the action of cold receptors in the airway.

Management of Mental Symptoms

Patients with lung cancer experience fear and anxiety starting from when they undergo diagnostic examinations. These feelings develop into a concrete fear of death with the aggravation of dyspnea. At the same time, various experiences of loss cause depression. Depression is the most frequent mental burden experienced by patients with lung cancer. It has been pointed out that the patients tend not to complain about depression, and this condition is often neglected as being a natural reaction of cancer patients.

Akechi *et al.* claimed that 10 to 20% of depressed patients need therapeutic intervention, adjustment disorder as a form of slight depression should not be overlooked, patients should be asked specifically using questions such as "Have you felt gloomy or depressed for several days recently?." They also indicated that screening and diagnosis criteria for depression based on Hospital Anxiety and Depression Scale (HADS)[10] should be introduced.[11]

Management of Brain Metastasis

The median survival time of cases with brain metastasis is 3 to 5 months, and 1-year survival rate is about 10%. MRI should be used in deciding treatment strategy, because brain metastasis appearing as unifocal on CT can be multifocal on MRI. Because small cell lung cancer often accompanies meningeal metastasis, patients with this cancer require cranial irradiation including the base of skull at doses of 30 to 40 Gy. Localized solitary brain metastasis within 2 cm in diameter and consisting of no more than several lesions responds to gamma knife (stereotactic radiation therapy), which can offer good local control in a short time.

Management of Spinal Cord Compression

About 95% of cases with spinal cord compression are caused by the epidural infiltration of vertebral metastasis. Most patients presenting paralysis experience pain arising from the spinal cord or spinal roots several weeks or several months before onset of paralysis.

If vertebral metastasis is confirmed, close follow-up should be continued to avoid overlooking early symptoms and the patient should be informed of the nature of early symptoms. Rapid development of severe compression requires prompt treatment within a few hours. Even in the case of chronic compression, paralysis is inevitable unless radiotherapy is initiated within 2 or 3 days. Paralysis can be avoided in many cases in which treatment is started while the patients are ambulatory. On the other hand, only about one-half of patients presenting paresis and 10% of patients with paraplegia can restore the ability to walk.

Management of Hypercalcemia

Hypercalcemia accompanying cancer is caused by direct bone destruction due to bone metastasis and the increased calcium absorption from bones and uriniferous tubules mediated by parathyroid hormone-related peptide (PTH-RP) produced by cancer. Unless treated promptly, this condition is life threatening. The frequency of hypercalcemia in lung cancer is reported to be 12 to 35%, following breast cancer and multiple myeloma. This condition develops more frequently in cases with squamous cell carcinoma. The median survival time from the onset of this condition is about 1 month.

Major symptoms include nausea, anorexia, weakness, and sleepiness. Care must be taken not to confuse these symptoms with the terminal-stage symptoms of cancer. The standard treatment for moderate and severe cases is the intravenous drip infusion of pamidronate (Aredia®). Among the drugs used for cancer patients, thiazide, NSAIDs, and H_2 receptor antagonists require special attention, as they block calcium excretion.

Management of G-CSF-Producing Tumor

G-CSF (granulocyte colony-stimulating factor), which is mainly produced by large cell carcinoma, causes leukocytosis, fever (≧38°C), and general malaise without evident infection. The standard treatment for tumor fever is naproxen. When control becomes difficult, corticosteroid should be used in combination with naproxen.

Management of Superior Vena Cava Syndrome

About 70% of cases with superior vena cava syndrome are caused by lung cancer. This condition develops more frequently in cases with small cell carcinoma, which tend to develop mediastinal lymph node metastasis. Because this syndrome by itself is not life threatening and treatment strategies depend on histologic typing, histologic diagnosis should be established before treatment whenever possible. The standard initial treatments are chemotherapy or combined chemotherapy and radiotherapy in the case of small cell lung cancer and radiotherapy in the case of non-small cell lung cancer. Carboplatin is usually preferred to cisplatin, which requires large-volume infusion.

Conclusion

This article discusses the management of frequent symptoms in lung cancer, including coughs, pain, dyspnea, and depression, as well as the symptom management of complications, including brain metastasis, spinal cord compression, hypercalcemia, G-CSF-producing tumor, and superior vena cava syndrome. Medication, radiotherapy, and mental support for these

conditions are considered paying attention to the median survival time after the onset of symptoms.

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Diagnosis of Wrist Pain in Daily Practice

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Abstract: Recently, a significant progress has been made in the area of diagnostic imaging. It thus greatly contributes to making a diagnosis on wrist pain. However, detailed history taking, carefully observed physical findings, and accurate interpretation of plain x-ray images will probably become more important so that such methods can be truly utilized. Because the pain associated with wrist injury or disease is location-specific and characteristic in nature, the nature of the pain also has particularity. In this article, the procedure of diagnosis used by the author in his daily practice is discussed while focusing on the local specificity of wrist pain.

Key words: Wrist; Pain; Diagnostic imaging

Introduction

While there are various diseases that can cause wrist pain, they can be broadly categorized into those that are attributed to injuries and those that are not.

Since the pain associated with each injury and disease is location-specific and characteristic in nature, a physician will scarcely misdiagnose the condition if he takes patient history with this in mind, observes physical findings, and makes use of supplementary diagnostic methods. The procedure of diagnosis used by the author in his daily practice is herein discussed with an emphasis on the location specificity of wrist pain (Fig. 1).

History Taking

Accurate diagnosis begins with detailed history taking. When a patient comes with wrist pain, one must not fail to ask basic questions such as where in the wrist and since when the pain has existed, whether or not the pain is progressive, and whether there is any episode that might have caused the pain.

With injuries, one must ask the patient when and how the injury occurred, the position of the wrist at the time of injury, and the location and severity of the pain at the time of injury. When the patient has visited another physician for the injury, one must ask the content of treatment and obtain more information from the physician if necessary. Depending on the type of injury, x-ray images immediately fol-

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The Japanese text is a transcript of a lecture originally aired on December 6, 2001, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program “Special Course in Medicine”.

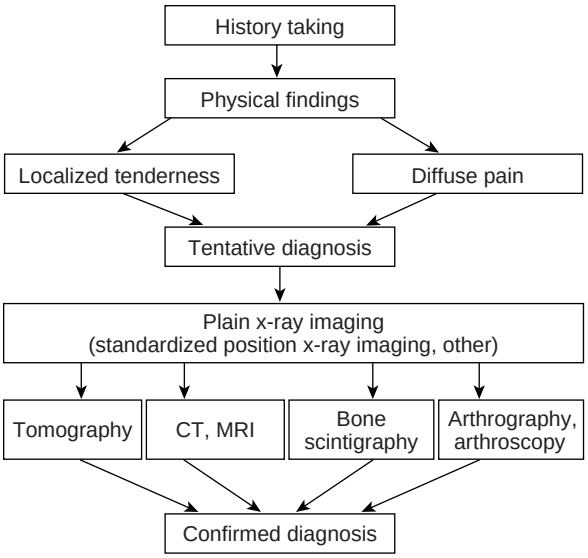
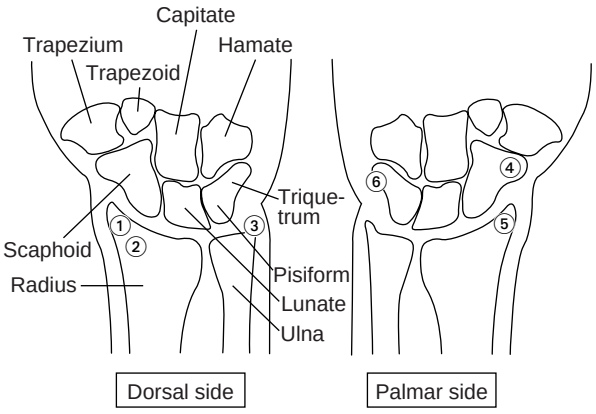


Fig. 1 Diagnostic procedure for wrist pain



Styloid process of radius ①, Lister's tubercle ②, and styloid process of ulna ③ are good landmarks on the dorsal side, and tubercle of scaphoid ④, styloid process of radius ⑤, and pisiform ⑥ are good landmarks on the palmar side. The palmar wrist crease approximately coincides with the midcarpal joint.

Fig. 2 Wrist landmarks

lowing the injury may be very useful in establishing treatment plans. If the injury was caused by a traffic accident, asking the details concerning the circumstance under which the injury occurred can help one to judge the severity of high-energy injuries. This is also the case with sports injuries.

During history taking, it is important to know that patients may not actively share information on a condition that he believes is completely unrelated to the wrist pain.

Physical Findings

Once one has comprehended the nature of the patient's complaint through history taking, he will usually observe physical findings. In seeing the patient, one should have the patient take off his clothes at least enough so that the entire upper limb can be observed. The author has had an experience of having difficulty arriving at a diagnosis of psoriatic arthritis of the wrist because he had been seeing the patient with his clothes on and did not notice the skin lesions.

Physical examination includes inspection, palpation, measurement of the range of motion, measurement of grasping/pinching power, and pain induction test. One is less likely to fail to discover something if he examines the entire wrist using a predetermined procedure. First, one should inspect the entire wrist to see if there is any redness or swelling. If a patient complains of wrist pain, identifying the location of tenderness can be particularly important and helpful during subsequent diagnostic imaging.

Landmarks that may guide one in identifying the location are shown in Fig. 2. Under the palmar wrist crease, which approximately coincides with the midcarpal joint, one can feel the tubercle of scaphoid on the radial side and the pisiform on the ulnar side.

Henceforth, diseases that accompany wrist pain will be discussed based on the location of tenderness in addition to the procedures of frequently used pain induction tests.

1. Dorsal side (Fig. 3)

(1) **Radial side**

De Quervain disease is suspected when there is tenderness in the first compartment of the extensor tendon. Having the patient fold his

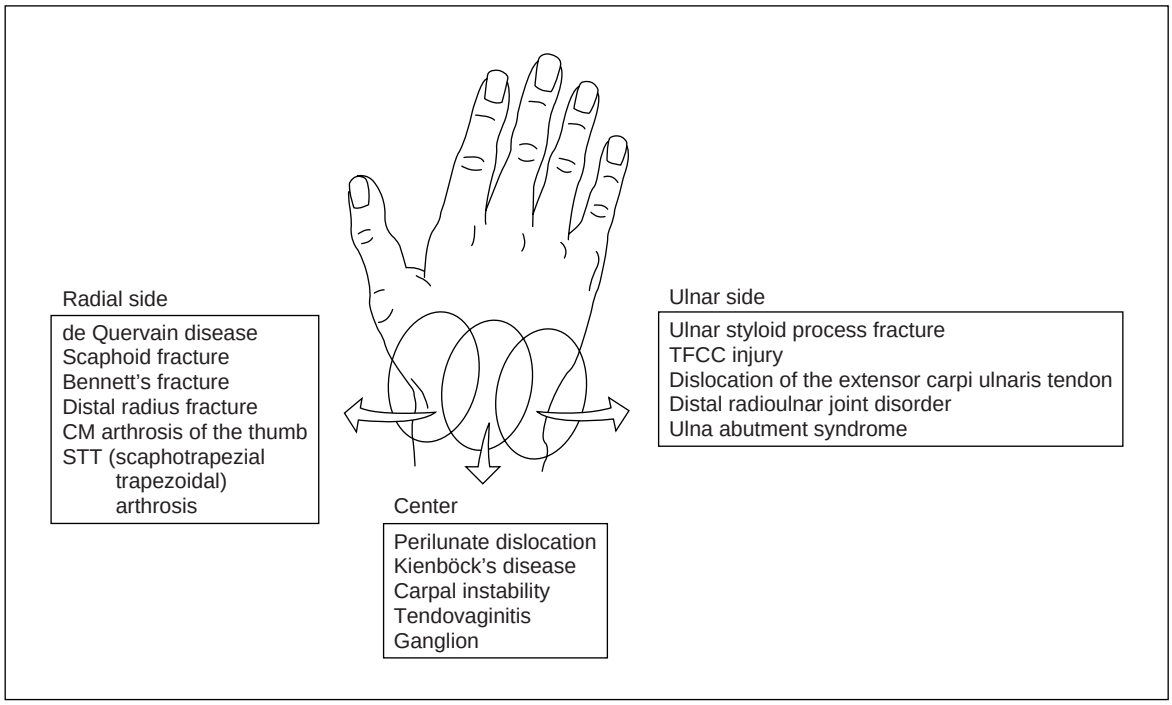


Fig. 3 Location of tenderness based on type of disease (dorsal side)

hand with his thumb inside (thumb in palm) and flex the wrist ulnar side causes acute pain in that location (Finkelstein test).

The scaphoid exists deep in the anatomical snuffbox, which is an area surrounded by the styloid process of radius and the extensor pollicis longus/brevis tendon. The snuffbox is more easily found when the thumb is extended, and the scaphoid bone can be easily felt by flexing the wrist ulnar side. Scaphoid fracture is suspected when there is localized swelling and tenderness in this location. When a teenager or a younger adult has wrist pain that occurred after a fall on the outstretched hand, multidirectional x-ray imaging of the scaphoid should be performed with the assumption that he might have scaphoid fracture. When a fracture line is observed in x-ray images at this time, one must be careful judging whether or not it is a fresh fracture. This is because patients with scaphoid pseudarthrosis can experience worsened symptoms following an injury.

Fractures such as Bennett's fracture or CM (carpometacarpal) arthrosis of the thumb may be suspected when there is tenderness in the carpometacarpal joint of the thumb distal to the scaphoid in the snuffbox.

Distal radius fracture can be suspected when there is pain in the entire wrist and tenderness in a wide area with a focus on the dorsal radial side of the wrist following the type of injury similar to that in the case of scaphoid fracture. It commonly occurs in the elderly, and swelling of the wrist and fork-shape deformity are observed in typical cases.

(2) **Center**

Kienböck's disease is a representative case in which localized tenderness is found in the center of the dorsal side of the wrist. Tenderness can be observed on the dorsal side even when the cyst on the lunate bone has begun to accompany pain. The lunate can be felt at the end of the Lister's tubercle. When there is superficial pain, tendovaginitis of the third compartment (extensor pollicis longus tendon) and fourth compartments (extensor digitorum

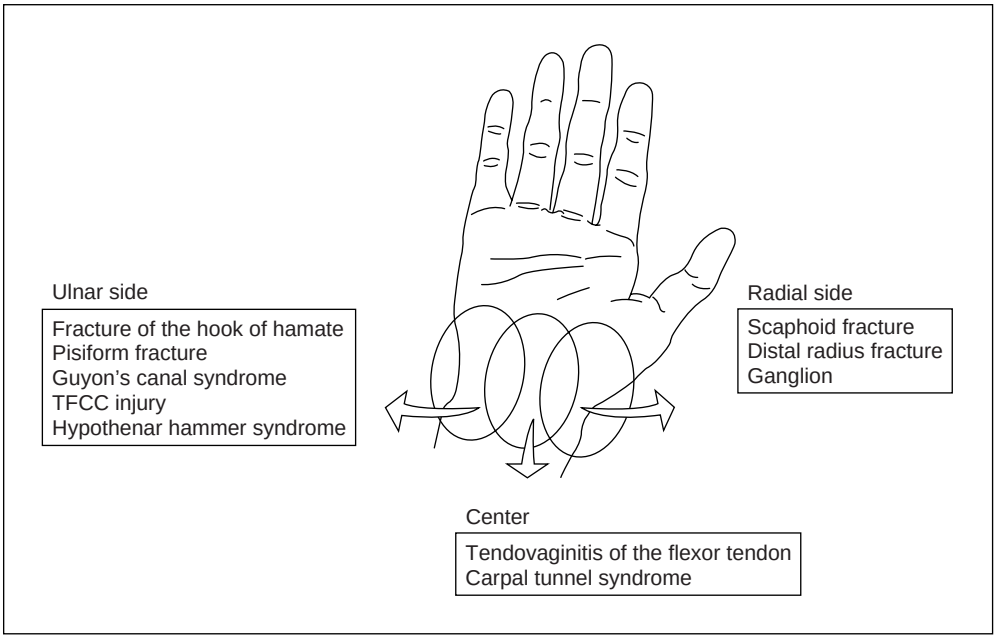


Fig. 4 Location of tenderness based on type of disease (palmar side)

tendon, extensor indicis proprius tendon) of the extensor tendon is occasionally noted, and "snow squeezing sound" can be heard when the location is pressed in typical cases.

It is common to find tenderness in this location even in scapholunate dissociation that is attributed to torn carpal ligament.

Ganglion on the dorsal side of the wrist often occurs in locations adjacent to the radius, scaphoid, and lunate.

(3) **Ulnar side**

Pain in the distal ulna can occur when there is the ulnar styloid process fracture, triangular fibrocartilage complex (TFCC) injury, distal radioulnar joint disorder, or dislocation of the extensor carpi ulnaris tendon. Swelling and tenderness in this location becomes marked in rheumatoid arthritis of the hand, since synovitis of the distal radioulnar joint is generally dominant. In the case of TFCC injury, friction sound may be heard during rotatory movement of the forearm. In the case of dislocation of the extensor carpi ulnaris tendon, dislocation of the tendon may be induced by supination of the forearm and ulnar flexion of the wrist.

2. Palmar side (Fig. 4)

(1) **Radial side**

Characteristic pain in this area is pain in the tubercle of the scaphoid bone. This finding is observed along with the aforementioned tenderness in the snuffbox when there is scaphoid fracture.

(2) **Center**

Lesions within the carpal tunnel, such as tendovaginitis of the flexor tendon and carpal tunnel syndrome, are usually present when there is pain in this area. One can induce pain by making the patient flex and extend his fingers when there is tendovaginitis of the flexor tendon. For carpal tunnel syndrome, one must take note of percussion pain along the median nerve (Tinel-like sign) and atrophy in the thenar muscle, and examine whether radiating pain in the median nerve area or worsening of abnormal sensation may occur when the patient is asked to keep his wrist in palmar flexion (Phalen's test).

(3) **Ulnar side**

Tenderness in the pisiform is found when there is pisiform fracture or Guyon's canal syn-

drome. The hook of hamate can be felt slightly distal to the pisiform on the radial side. Fracture of the hook of hamate should be suspected when there is localized pain in a location deeper than the pisiform bone.

Diagnostic Examination

Although diagnostic imaging technology, such as CT and MRI, has made great progress even in the field of orthopedic surgery, this does not mean that plain x-ray imaging has become less important as a supplementary diagnostic method in daily practice. Our overconfidence in new diagnostic technology must not cause us to neglect interpretation of plain x-ray images. Plain x-ray imaging is the most basic supplementary method for diagnosis of wrist pain, and special diagnostic imaging should be used purposefully when specific conditions need to be determined for treatment purposes or to verify conditions or diseases that cannot be detected by plain x-ray imaging.

1. Plain x-ray imaging

The basic wrist images are obtained from two directions: posterior to anterior (P-A) and lateral views. During imaging, place the wrist in a standardized position, treating forearm rotation and palmar dorsiflexion and radioulnar flexion of the wrist as the intermediate position. It is essential to always perform imaging under the same condition for the purpose of diagnosing abnormal alignment of carpal bones and determining whether there has been any change over time.

In daily practice, bilateral oblique positions are routinely added to the two directions for accurate diagnosis of fractures, because two directions are inadequate to determine the three-dimensional condition of the complicatedly shaped wrist, and fracture lines are sometimes verified for the first time by such four-directional imaging.

Special imaging positions and methods used for specific diseases and injuries are as follows.

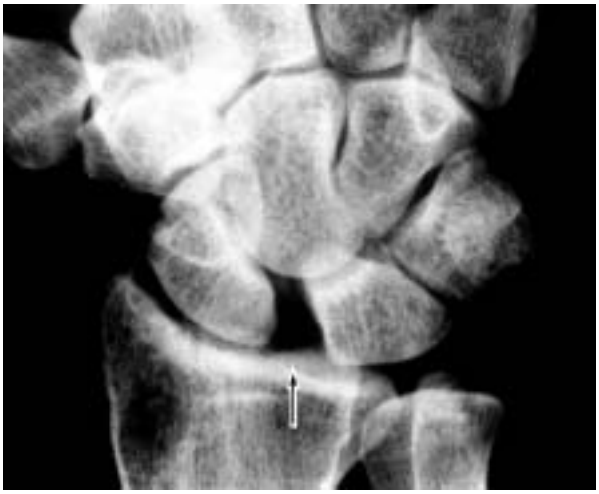


Fig. 5 Scapholunate dissociation

(1) **Carpal tunnel imaging**

Since carpal bones form an arch as a whole, it is difficult to determine the condition of the bones that form the inner wall of the carpal tunnel by conventional imaging. The hook of hamate, trapezium, and pisiform can be observed clearly when imaging is performed from a direction tangent to the carpal tunnel. This method is particularly useful for fracture of the hook of hamate. However, good images cannot be obtained unless dorsiflexion of the wrist is sufficient.

(2) **Front view of the scaphoid**

Scaphoid fracture is a type of fracture that is easily missed. This is partially attributed to the fact that the pain is relatively mild at the beginning compared with other types of fractures and also the fact that it is difficult to verify the fracture line due to overlapped carpal bones. A front view of scaphoid bone that is longitudinally parallel to the cassette and not overlapped with any other bone is needed. Therefore, P-A view of the fist is recommended for imaging.

(3) **Front view of the wrist with supination of the forearm**

Depending on the position, normal alignment of carpal bones can be maintained even

when syndesmosis is damaged. In such cases, it is necessary to perform stress imaging or imaging in a position that permits abnormality of carpal alignment to be clearly delineated. In the case of scapholunate dissociation, a greater dissociation can often be seen clearly in a front (A-P) view of the wrist with supination of the forearm or when axial pressure is applied in this position (Fig. 5).

2. Special diagnostic methods

(1) **Arthrography of the wrist**

Arthrography of the wrist is an effective method for diagnosis of ligament injury and TFCC injury of the wrist. The wrist cavity is categorized into three articular cavities that are each completely separated from another: radiocarpal joint, midcarpal joint, and distal radioulnar joint. Contrast medium is usually injected into the radiocarpal articular cavity for arthrography of the wrist. Although only the radiocarpal articular cavity is delineated by the medium in a normal wrist, contrast medium can occasionally leak into the pisotriquetral articular cavity. When contrast medium has leaked into the distal radioulnar joint, TFCC injury is suspected. However, this diagnostic method is particularly useful for the youth, because perforation of TFCC caused by abrasion is often seen as an age-related change.

(2) **CT**

Unlike conventional x-ray tomography, CT produces transverse images of the wrist. It can be an effective weapon against diseases that can be accurately diagnosed only by transverse images. For example, it is appropriate when the three-dimensional interrelationship of bone fragments need to be determined in the case of comminuted fracture of the distal radius or when the appropriateness of the distal radioulnar joint needs to be verified. Fracture of the hook of hamate can also be clearly delineated by CT even when wrist motion is limited (Fig. 6).

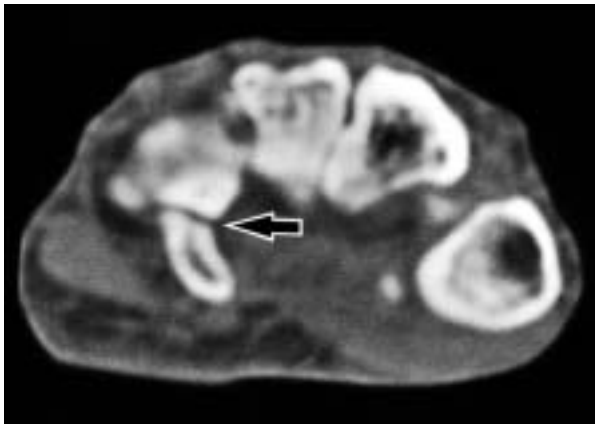


Fig. 6 Fracture of the hook of hamate (CT image)

(3) **MRI**

When it comes to diagnostic imaging of the wrist, MRI provides much more information than CT does. It is particularly useful for detecting tumors in the soft tissue, TFCC injury, and occult ganglion as well as evaluation of osteonecrosis in Kienböck's disease (Fig. 7).

(4) **Arthroscopy of the wrist**

While arthroscopy allows us to directly observe the synovial membrane, ligament, TFCC, and articular cartilage surface, it requires special equipment and technology, and it can be very stressful for the patient. Currently, arthroscopy is indicated primarily for TFCC injury, radiocarpal ligament and intercarpal ligament injuries, and cartilage damages of the radius and carpal bones. Partial resection of TFCC is conducted under the use of arthroscopy.

Bone scintigraphy, electromyogram, and angiography are also performed when necessary.

Special tests that are performed after plain x-ray tests should be used efficiently with the understanding of the merits of each test and with careful consideration of patients' stress and radiological exposure. Unnecessary tests may be avoided if priorities are carefully examined.

Conclusion

Recently, there has been a marked progress in the area of diagnostic imaging. However,

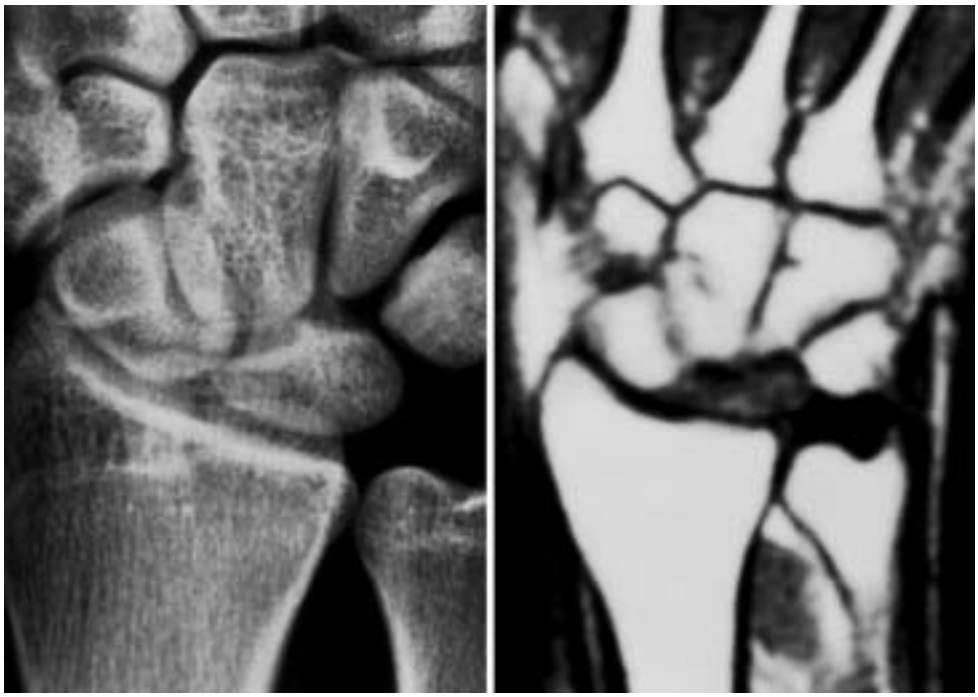


Fig. 7 Early-stage Kienböck's disease
Left: There is no clear abnormality in the plain x-ray image.
Right: The lunate bone is seen as a black box in the MRI image (T1-enhanced), suggesting osteonecrosis.

detailed history taking, carefully observed physical findings, and appropriate plain x-ray images will probably become more important so that such methods can be truly utilized. It is not the type of test we can perform but the ability to determine the type of test we need that is important to arrive at a diagnosis.

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