TABLE 1. Summary of patients' brain lesions types[a]

	Glioma	Chronic Epilepsy	AVM	Meningioma	Cavernous malformation	Cerebral ischemia	Total
fMRI with VG + MEG	44	39	18	6	4	6	117
fMRI with A/C	41	34	15	6	4	6	106
Amytal test	42	29	16	6	4	0	97
Final analyses	39	26	12	6	4	0	87

[a] AVM, arteriovenous malformation; fMRI, functional magnetic resonance imaging; VG, verb generation task; MEG, magnetoencephalography; A/C, abstract/concrete categorization task.

nature of the word. During interval periods, patients passively viewed random dots of destructured *Kana* letters that were controlled to have the same luminance as the stimuli to eliminate primary visual responses.

Before scanning, all patients had a brief practice time, and the fMRI examinations were repeated for each task to confirm the reproducibility. After data acquisition, a motion detection program (MEDx; Medical Numerics, Sterling, VA) discarded fMRI sessions containing motion artifacts exceeding 25% of the pixel size. A Gaussian spatial filter (6 mm in half width) was applied, and functional activation maps were calculated by estimating the Z-scores between the rest and activation periods using Dr. View (Asahi Kasei, Tokyo, Japan). Pixels with Z-scores higher than 2.2 ($P < 0.05$) were considered to indicate real activation and were used for mapping. Image distortion of fMRI was corrected by maximizing the mutual information of the fMRI data sets and three-dimensional T1-weighted MRI (3D-MRI) scans of the patient's brain (morphing compensation). The result from each fMRI session was co-registered with the 3D-MRI by the Affine transformation (5). After total number of the activated pixels in the IFG and MEG were automatically counted, a patient was considered to have unilateral language dominance when hemispheric pixels of one hemisphere counted less than 70% of the other hemisphere. Otherwise, the language dominance was considered bilateral.

Language MEG

The MEG signals were recorded with a 204-channel biomagnetometer (VectorView; Neuromag, Helsinki, Finland) in a magnetically shielded room. To confirm the reproducibility, we acquired two data sets for each task by repeating the MEG recording on two different days. One hundred fifty nouns consisting of three *Kana* letters were visually presented with a 300-millisecond exposure time with interstimuli intervals ranging from 2800 to 3200 milliseconds. Patients were instructed to judge whether or not the presented word was "abstract" or "concrete" based on the nature of the word and to push a button with the index or middle finger (*Kana* reading task). Each epoch consisted of a 500-millisecond prestimulus baseline and a stimulus followed by a 1500-millisecond analysis period. Epochs with a reaction time exceeding 1200 milliseconds and MEG examinations with a successful task performance less than 70% were discarded.

One hundred fifty epochs of the magnetic signals were averaged and digitally filtered between 0.1 to 30 Hz. Significant MEG deflections were visually identified based on the square root mean fields of more than 10 sensors in the frontotemporal (FT) or temporo-occipital (TO) regions. Locations and dipole moments of equivalent current dipoles were calculated every 2 milliseconds from 250 to 600 milliseconds after the stimulus onsets using the single equivalent dipole and sphere head models. Only those dipoles of which the measured and the calculated field distributions showed a correlation value of more than 0.85 and confidence volumes less than 1000 mm^3 were used. To confirm the calculated results, the same MEG time sections were analyzed using a current density map (low-resolution tomography; LORETA, Curry, Neuroscan, and Compumedics USA, El Paso, TX). The coordinates of the MEG system were transformed into anatomic 3D-MRI scans by identifying external anatomic fiduciary markers (nasion, left/right preauricular points), and estimated dipoles were superimposed onto the 3D-MRI scans.

Dipoles located in the temporal region, including the STG, MTG, SmG, and FuG, were manually counted. A patient was considered to have unilateral language dominance when hemispheric dipoles of one hemisphere counted less than 70% of the other hemisphere. Otherwise, the language dominance was considered bilateral.

Determination of Language Dominance using fMRI and MEG

On the basis of the results of language fMRI and MEG, we determined language dominance for each patient. When the semantic activation in one side of the IFG and MFG was wider than that of the other side during the language fMRI tasks, a patient was considered to have unilateral dominance for the expressive language function. When one side of the temporal region included more MEG dipoles than the other during the language MEG task, we determined that a patient had laterality of the receptive language function.

The Wada Test

All patients received injections of amobarbital (100 mg in a 10% solution, Amytal; Eli Lilly and Co., Indianapolis, IN) through a catheter placed in the internal car otid artery. Language testing was performed during the observation period of maximal amobarbital action as indicated by contralateral

brachial plegia. Patients were given the following tasks in the following order and up to four points were given, depending on the severity of the language disturbance: 0, no response; 1, meaningless utterance; 2, incorrect repetition or paraphasia; 3, self-correction; and 4, unimpaired.

The tasks were as follows:

1) Spontaneous counting. Patients were instructed to count, starting immediately before the amobarbital administration and continuously until the next task was given. If the patient could continue to count even after brachial plegia appeared, obvious speech arrest and no impairment indicate 0 and 4 points, respectively.
2) Letter reading. Patients were instructed to read aloud seven words consisting of three or four *Kana* letters. The maximum score was 28 points (seven items × four points).
3) Naming. Patients were asked to name aloud the five objects presented pictorially. The maximum score was 20 points (five items × four points).
4) Auditory comprehension. Patients were asked to carry out three simple tasks such as blinking eyes, opening the mouth, and raising the unparalyzed arm. The maximum score was 12 points (three items × four points).
5) Pointing objects. Patients were shown a picture with a set of four objects and were instructed to point to one chosen by the investigator (*e.g.*, "Point to the cat."). The maximum score was 16 points (four items × four points).

Performance in Tasks 1 and 3 were considered to reflect the expressive language capabilities (maximum score, 24 points); performance in Tasks 2, 4, and 5 reflected receptive language functions (maximum score, 56 points).

RESULTS

Handedness and the Wada Test

Ninety-one patients (80 right-, eight left-, and three bilateral-handers) successfully underwent the Wada test. Language dominance was left, right, and bilateral hemispheres in 81, six, and four patients, respectively. The language dominance of the right-handed patients was left in 75 patients (93.8%), right in two patients (2.5%), and bilateral in three patients (including one patient with dissociated expression and receptive functions [3.8%]), respectively. For left-handed patients, four patients showed left and four showed right dominance. For both-handed patients, two showed left dominance and one bilateral (dissociated). These results were similar to those of previous reports on language dominance (3, 4).

For further analysis, we subdivided the subjects into groups with chronic epilepsy and with non-epilepsy. In the epilepsy group (n = 29), left, right, and bilateral dominance was 24 (82.8%), three (10.3%), and two (6.9%), respectively. In the non-epilepsy group (n = 62), left, right, and bilateral dominance was 57 (91.6%), four (6.4%), and one (1.6%), respectively.

fMRI with the Verb Generation Task

The verb generation task was designed to locate the expressive language area by fMRI. Among 117 patients who underwent the verb generation task, 100 patients (84.6%) completed the task and provided useful fMRI data. The results showed that the dominant hemisphere for the expressive language function was left, right, and bilateral in 90, eight, and two patients, respectively. In the epilepsy group (n = 34), left, right, and bilateral dominance was 29 (85.2%), three (8.8%), and two (8.5%), respectively. In the non-epilepsy group (n = 66), left, right, and bilateral dominance was 61 (92.4%), five (7.6%), and zero (0%), respectively. The activated regions on fMRI mainly involved the IFG and MFG, the lateral precG, AG, and the supplementary motor area (SMA) (*Figs. 1* and *2*).

In some patients, activations were observed in bilateral hemispheres. Except for two patients who showed bilateral dominance, the activations in the non-dominant hemisphere were restricted to MFG and precG and smaller in size, so the pixels did not reach a cluster significance (maximum values of Z-score, <2.2 or <10 pixels).

Compared with successful results of the Wada test, the successful rate of fMRI with the verb generation task was 90.1%. Seven patients with aphasia or dementia failed to complete the task. Three glioma patients with marked surrounding, four patients with brain ischemia and three patients with large arteriovenous malformations failed to exhibit significant activations in the frontal lobe (*Fig. 3*). These incomplete results are accounted for by the reported disadvantage of fMRI that data may be affected by the pathological changes of cerebral circulation (7, 10, 15).

fMRI with the A/C Categorization Task

The A/C categorization task was designed to locate the receptive language area by fMRI. Among 106 patients who performed the A/C categorization task, 71 (67.0%) completed the task and provided useful fMRI data. Compared with the verb generation task, the A/C categorization task more often activated wider areas in bilateral hemispheres (*Fig. 2*). Activations generally involved the bilateral frontal lobes, including the IFG, MFG, and precG, with laterality. The superior temporal regions, such as the STG and SmG, demonstrated activation spots in only 45% (n = 32) of the investigated patients, and the side predominance was not apparent in most cases. The fMRI data of the A/C categorization task were considered unsuitable to determine the receptive language areas and were not used for the final analyses.

Language MEG Profiles and Dipole Locations

The *Kana* reading task was designed to locate the receptive language area by MEG. The language MEG was performed in 117 patients, of whom 99 (85.4%) completed the task and provided useful data (*Figs. 1* and *2*). Results showed that the dominant hemisphere for the receptive language function was left, right, and bilateral in 85, 11, and three patients, respectively. In the epilepsy group (n = 31), left, right, and bilateral dominance was 26 (83.9%), three (9.7%), and two (6.5%), respectively. In the non-epilepsy group (n = 68), left, right, and bilateral dominance was 59 (86.8%), eight (11.8%), and one (1.5%), respectively.

Dipole clusters of late deflections localized mainly in the superior temporal region (STG, MTG, and SmG), and 60% of investigated patients also showed dipoles in the inferior tempo-

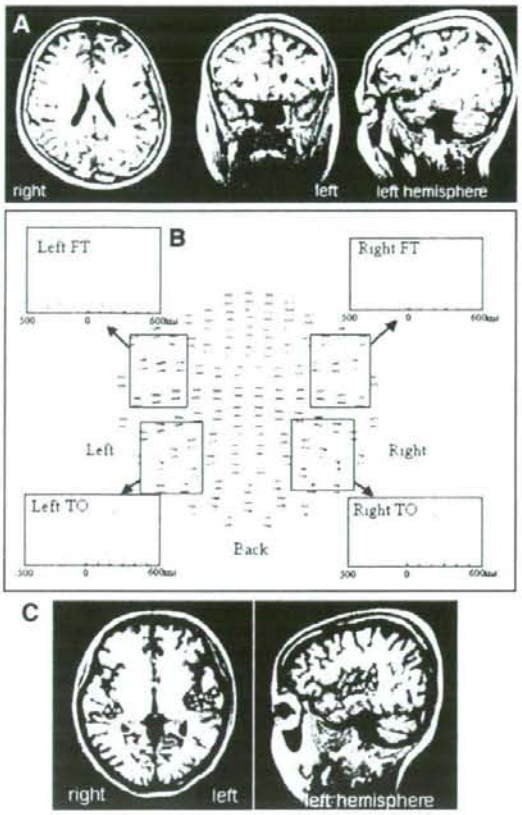


FIGURE 1. *A 24-year-old, right-handed man with epilepsy.* A, *fMRI with the verb generation task showing activations predominantly in the left IFG, MFG, PrecG, and parieto-occipital regions.* B, *square root mean field profiles of language MEG responses in the bilateral FT and TO regions. The left FT responses, peaking at 450 milliseconds, were markedly greater in amplitude than the right FT.* C, *source localization of the late deflections showing predominant dipole clusters (arrowheads) in the left superior temporal region. The left and right hemispheres contained 97 and 37 dipoles, respectively.*

ral region (FuG and inferior temporal gyrus). In 96 patients who showed unilateral language dominance, the total number of dipoles in the dominant versus non-dominant hemispheres was 124.1 ± 62.1 and 58 ± 30.9 (mean ± standard deviation), respectively. The ratio of the dipole number in the dominant hemisphere to the non-dominant hemisphere in each individual was 2.4 ± 1.7 (range, 1.43–14.4).

A typical result with all channels of MEG with the *Kana*-reading task is illustrated in *Figure 1*. Later deflections peaking at approximately 400 milliseconds were predominantly observed in the left FT. Bilateral TO regions demonstrated early deflections at approximately 200 milliseconds with short durations and little laterality. Estimated dipoles of the FT regions were densely accumulated in the left STG, MTG, and SmG (102 dipoles), whereas the right hemisphere showed fewer dipoles (54 dipoles) in the superior temporal region. This patient was thus determined to have receptive language dominance in the left temporal lobe.

The successful rate of language-MEG was 82.4%. Nine out of 39 epilepsy patients (23.1%) could not provide useful MEG data owing to artifacts from constant eye movements; the *Kana*-reading task was more difficult to complete than the verb generation task for patients with mental dysfunction. On the other hand, only one out of 18 AVM patients, owing to severe dyslexia, failed to provide useful MEG data, indicating that, in contrast to fMRI, MEG was not frequently affected by cerebral blood flow abnormalities (*Fig. 3*).

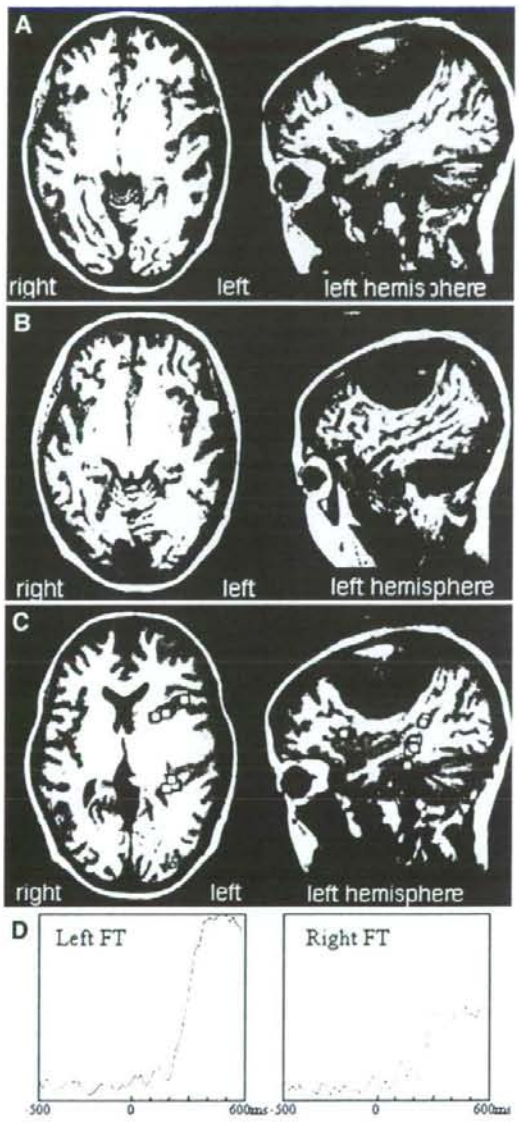
Combination of fMRI and MEG with Wada Test Verification

The verb generation task fMRI data depict expressive language areas well, but may be affected by cerebral blood flow abnormalities. The MEG results indicate receptive language areas well, but the task is rather complicated and may not be suited for patients with mental disorders. We sought to establish a non-invasive and reliable method to determine the laterality of language dominance by combining the advantages of these approaches. Furthermore, in terms of language functions, the results from fMRI and MEG can be integrated to locate expressive and receptive language areas and to provide reliable evidence whether or not there is dissociation. To verify the reliability of our method, 97 patients also underwent the Wada test.

Useful data from the method co-utilizing fMRI and MEG could be obtained from 87 out of 91 patients (95.6%). Remarkably, regarding language dominance, the results from the combination method matched the results of the Wada test in all 87 patients. Worth noting is that two patients (one with left temporal lobe epilepsy and the other with right insular astrocytoma) showed dissociated language areas using the combined method. The expressive language area was depicted in the left frontal lobe by fMRI, but the receptive language area was demonstrated in the right temporal lobe by MEG (*Fig. 4*). The Wada test results confirmed that both patients have language functions dissociated in the bilateral hemispheres. Among the 91 patients who underwent the Wada test, these were the only two patients in whom the Wada test detected dissociation of language functions.

In 12 epilepsy patients, the expressive and/or receptive language areas were electrophysiologically investigated via a subdural electrode implantation and the results were compared with those determined via the combined fMRI plus MEG method (*Fig. 5*). Out of eight patients who underwent cortical mapping for the expressive language area, all showed a speech arrest by electrical stimulation to the IFG and four to the MFG. All of the physiologically determined locations were confined within the areas depicted by the combined method. Out of six patients who received electrical stimuli to the temporal lobe,

four showed responses interpretable as impaired speech comprehension. In all such cases, the electrophysiologically determined location matched the area depicted by the combined method, although MEG-depicted receptive language areas covered relatively broad areas of the temporal lobe. The regions determined by the combined method were always broader, but had the border within the adjacent gyri of those determined by electrophysiological mapping.



ILLUSTRATIVE CASES

Patient 1

A 16-year-old, right-handed female patient had experienced transient numbness in her left upper extremity with a 2-month history. T1-weighted MRI scans demonstrated an extra-axial cystic lesion in the left frontal region. Although the lesion markedly compressed the frontal lobe, she had no impairment of language and motor functions. fMRI with the verb generation task demonstrated obvious activation in the left IFG and MFG shifted inferiorly by the lesion (*Fig. 2A*). The A/C categorization task activated a small area of the left IFG, but mainly the bilateral occipital lobes. Concerning MEG with the *Kana* reading task, RMS of the left FT was much higher than that of the right, and numbers of semantic dipoles were 117 and 30 in left and right hemispheres, respectively. The main dipole clusters were located in the left IFG and STG. The tumor was totally removed and histopathological diagnosis was meningioma.

Patient 2

A 24-year-old, right-handed male patient had a large AVM in the left frontal lobe. fMRI detected little activation in the IFG or MFG, although a part of the left angular gyrus was activated by the verb generation task (*Fig. 3A*). MEG, however, disclosed numerous dipole accumulations in the left superior temporal region. In the MEG examination, the left and right hemispheres contained 130 and 45 dipoles, respectively, suggesting left language dominance (*Fig. 3B*). Auditory comprehension and letter-reading were suppressed by administration of amobarbital into the left carotid artery, although motor language function was preserved. These findings suggested that the steal effect caused by the AVM partly interfered with functional brain mapping of fMRI and the Wada test. In this case, MEG was helpful to decide language dominance (*Fig. 3*).

Patient 3

A 32-year-old, right-handed man experienced amnesia for several minutes. T1-weighted MRI scans and brain computed tomographic scans disclosed a hypointense and hypodense mass in the right insular cortex involving the surrounding white matter. Computed tomographic scans performed 6 years earlier, however, revealed no abnormality. These findings suggested that a low-grade astrocytoma might

FIGURE 2. *A 16-year-old, right-handed female patient with a large meningioma in the left frontal region. The patient had no impairment of language or motor functions.* A, *fMRI with the verb generation task showed activations mainly in the left IFG and MFG that shifted inferiorly by the tumor.* B, *fMRI with the abstract/concrete categorization task demonstrated activations in the bilateral occipital regions in addition to small active spots in the left IFG.* C, *square root mean field profiles of language-MEG responses demonstrated that the left FT responses, peaking at 400 milliseconds, were markedly larger in amplitude than the right FT.* D, *source localization of the late deflections showed predominant dipole clusters in the left posterior temporal region. The left and right hemispheres contained 117 and 30 dipoles, respectively. The combined fMRI plus MEG method indicated left language dominance, which was confirmed by Wada test.*

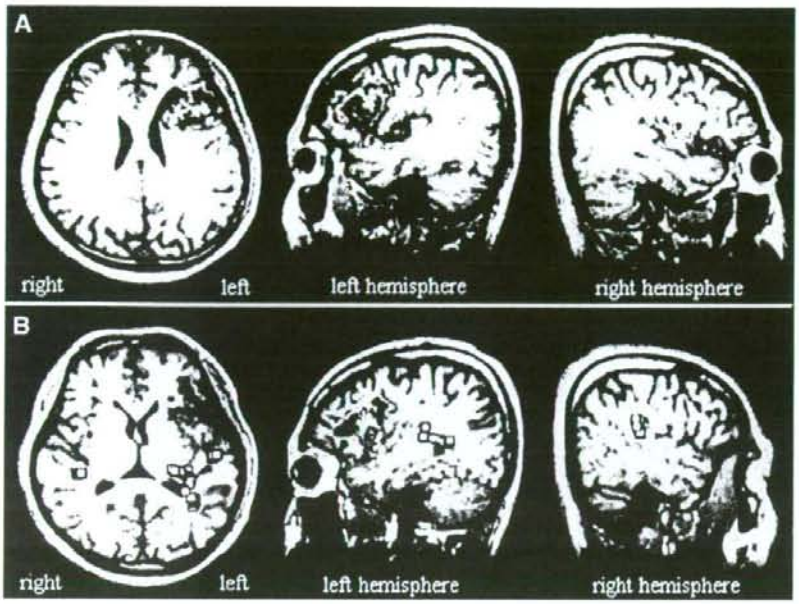


FIGURE 3. *A 24-year-old, right-handed man with a large AVM in the left frontal lobe.* A, *fMRI with the verb generation task showed little activation in the left frontal lobe where the AVM was located.* B, *source localization of the late FT and TO deflections on MEG showed predominant dipole clusters in the left posterior STG. The left and right hemispheres contained 123 and 51 dipoles, respectively.*

have slowly developed during the past 6 years. In the results of the verb generation task, the left hemisphere had obvious activations in the IFG, MFG, precG, and the angular gyrus, indicating that this patient had left dominance of motor-language functions (*Fig. 4A*). In contrast, estimated dipoles of the FT responses were concentrated in the posterior part of the right STG and MTG (138 dipoles) and another dipole cluster (64 dipoles) of the TO region was localized in the right FuG. The total dipole number of the left hemisphere (48 dipoles) did not reach even a quarter of that of the right hemisphere, suggesting right-sided dominance of temporal language functions (*Fig. 4*).

During the Wada test, he stopped counting (0 out of 4 points; 0%) and failed to name objects (6 out of 20 points; 30%) after left intracarotid injection, whereas letter-reading (21 out of 28 points; 75%), auditory comprehension (12 out of 12 points, 100%), and pointing objects tasks (16 out of 16 points; 100%) were well preserved. In contrast, after right intracarotid injection, letter reading (13 out of 28 points; 45%), auditory comprehension (3 out of 12 point; 25%), and pointing objects (4 out of 16 points; 25%) tasks were markedly suppressed, although he continued to count correctly without speech blockade (4 out of 4 points; 100%) and could perform naming (17 out of 20 points; 85%). These findings suggested that language functions were distributed separately over the bilateral hemispheres, and the expressive and receptive language functions were dissociated in the left frontal and right temporal lobes, respectively. A striking fact was that the combination of fMRI and MEG predicted the special profiles of language functions noninvasively.

DISCUSSION

We demonstrated that our method using both fMRI with the verb generation task and MEG with the *Kana* reading task is highly reliable in determining the language dominance in patients with brain lesions. The accuracy of the dominance laterality was confirmed by a 100% match with the results from the Wada test. fMRI and MEG compensated each other's disadvantages. The tasks of fMRI were rather simple and could be accomplished even by patients with mental dysfunctions, whereas MEG results were seldom affected by cerebral blood flow abnormalities. Reliable data on language functions were also obtained by combining the advantageous features of fMRI and MEG. fMRI with the verb generation task well depicted the expressive language area as activations in the frontal lobe, most commonly in the IFG. MEG, on the other hand, showed dipole clusters predominantly in the superior temporal regions representing the receptive language area. In the epilepsy group, left and bilateral dominance were approximately 85% and more than 6%, respectively, whereas, in the non-epilepsy group, left and bilateral dominance were more than 90% and less than 2%, respectively. The combined method, including the Wada test, fMRI, and MEG, clearly demonstrated bilateral dominance is more often observed in the epilepsy group than in the non-epilepsy group.

In our study, two out of 87 patients analyzed (2.3%) were found to have dissociation of the expressive and receptive language functions by co-utilization of fMRI and MEG, verified by the Wada test, which best described the usefulness of our method in identifying the areas of the two language functions separately. In both cases, neither modality alone demonstrated the dissociation. Although several cases have been reported that dissociated language functions were found by fMRI, none of those was proven by the Wada test (2, 8, 21, 23). Our results show that neither fMRI nor MEG alone is sufficient to accurately locate the expressive and receptive language areas, and the combined use is the key to obtaining high reliability.

The results from electrophysiological investigation via a subdural electrode implantation in 12 patients further confirmed the accuracy of the present method. Pouratian et al. (22) reported that the sensitivity and specificity of language-fMRI

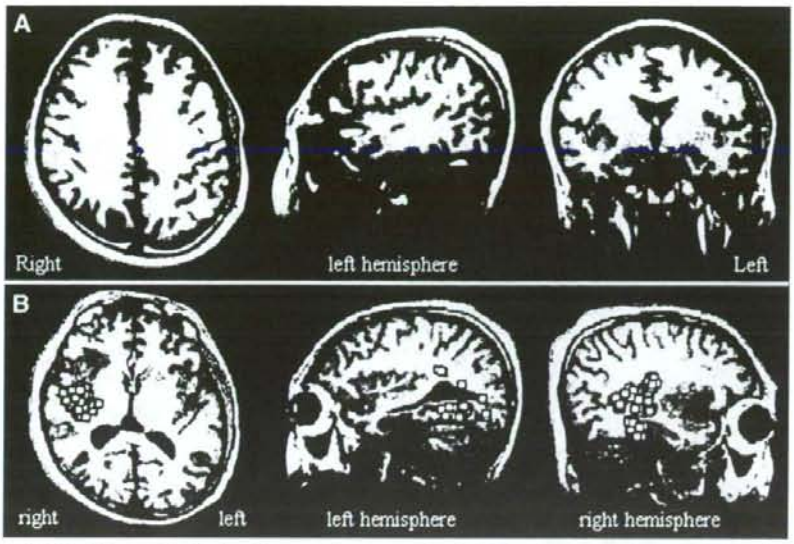
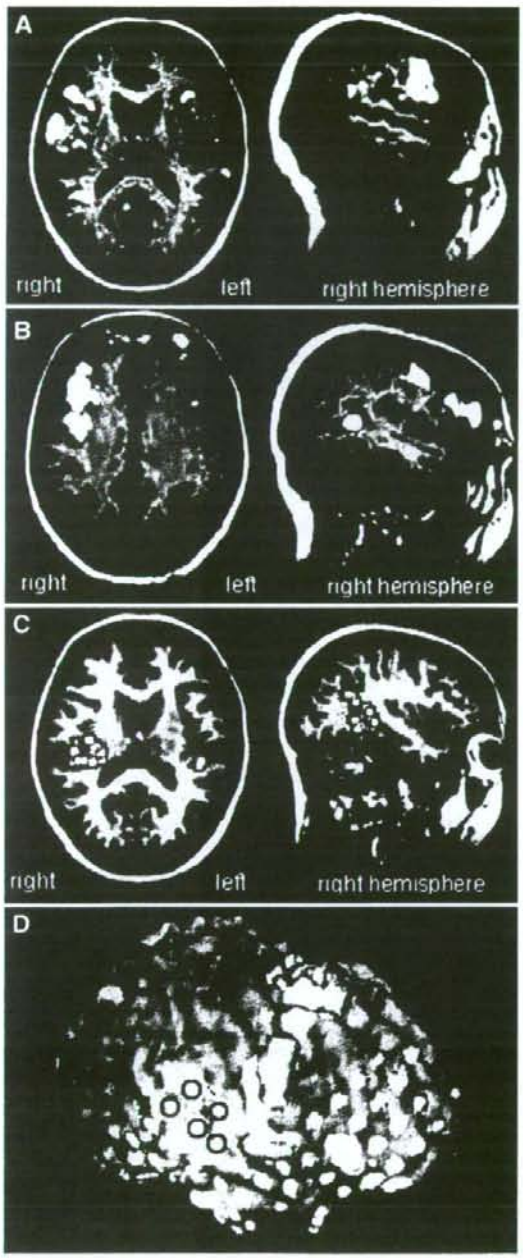


FIGURE 4. *A 32-year-old, right-handed man with astrocytoma in the right insular cortex and the surrounding white matter.* A, *fMRI with the verb generation task showed main activations in the IFG, MFG, precG, and AG, indicating left dominance of the expressive language function.* B, *in contrast to the fMRI results, source localization of the late FT deflections on MEG showed predominant dipole clusters in the right temporal lobe. The left and right hemispheres contained 48 and 202 dipoles, respectively. The combined fMRI plus MEG method thus indicated dissociated frontal motor and temporal receptive language functions. This result was confirmed by the Wada test. The patient showed impaired counting and object naming after amobarbitol injection into the left carotid artery. In contrast, letter reading, auditory comprehension and object pointing tasks were markedly suppressed, without counting impairment and speech blockade, after amobarbitol injection into the right carotid artery.*

were dependent on the task, lobe, and matching criterion. The sensitivity and specificity of fMRI activations during expressive linguistic tasks in the frontal lobe were found to be up to 100 and 66.7%, respectively, in the frontal lobe. FitzGerald et al. (6) reported that sensitivity and specificity for all multiple language tasks ranged from 81 to 53% (6). On the other hand, several groups have reported that the language map obtained from fMRI poorly matched the intraoperative electrical stimulation mapping (6, 25). In our study of language-fMRI, every electrical stimuli to the IFG, where the fMRI-activation was observed, caused speech arrest. However, the stimulation to MFG caused language-related symptoms in only half of patients. Although the sensitivity of fMRI might be high, there are still several issues of individual variability of fMRI activation and semantic tasks. The discrepancy can be partly accounted for by the fundamental differences in methodology such that the electrical stimulation directly blocks the specific language functions, whereas fMRI picks up all activated areas involved in the language tasks. Therefore, fMRI-based mapping largely depends on the design of the performing task. We tested two different tasks for fMRI and found the verb generation task better suited for language mapping than the A/C categorization task. The significance of activations depicted on fMRI is still under debate. Language-fMRI activations may be related to various semantic components of the task, including the will to retrieve verbal materials and the memory related to articulations. Despite that the A/C categorization task was designed to detect the receptive language area, activations in the temporoparietal region was less frequently observed than in the frontal region. Neural activities in the temporoparietal area are considered relatively scarce (25), and the discrepant activities of the frontal and temporoparietal regions may be owing to physiological variations of brain regions. Alternatively, the frontal and temporal lobes may have different oscillations (brain rhythms) of brain activity in response to verbal tasks, which are reflected in changes in neuronal currents and cerebral blood flow.

Our study demonstrated that dominance of the receptive language function could be accurately determined by MEG. For that purpose, we originally designed the task of three-letter word reading and silent categorization and used the dipoles calculated from late deflections to process the MEG results. It has been reported that cortical evoked potentials recorded by subdural electrodes showed responses at approximately 200 (early) and 400 (late) milliseconds in the left temporal lobe cortex after letter presentation (1, 17). The late potentials have been noted especially in tasks involving decisions based on visually presented words (13, 14). In this study, the sources of late responses (250–600 ms) were located mostly in the posterior temporal region, and the laterality of dipole clusters accurately reflected the receptive language dominance. It has been reported that dipoles in the superior temporal region showed an excellent agreement with an intraoperative electrical mapping (27). We also included dipoles in the FuG for language dominance determination based on our experience with a case in which an injury of FuG resulted in pure dyslexia (12). These contrivances in our method may have led to improvement in accuracy on language dominance determination over previous reports (20). Basic technical issues of the MEG investigation still remain. Eye movement artifacts were strong enough to distort the baseline of the MEG data. In our study,



we asked patients to keep gazing at the center of the screen during the semantic decision without blinking. As a result, artifacts were observed at later than 600 milliseconds after letter presentation and usually did not affect the early and late semantic responses. It is, however, important to prevent artifacts by monitoring eye movements and using rejection thresholds.

In conclusion, by co-utilizing fMRI and MEG, we established a method to determine language dominance with a high reliability. The fMRI activations with the verb generation task identified the expressive language area, whereas the language MEG dipoles located the receptive language areas. Our institution is now routinely using the combined technique to identify the language dominance. If it does not produce data on cerebral dominance, we additionally perform the Wada test before surgery. This non-invasive and repeatable method may be an effective alternative to the Wada test and may be useful in the management of patients with brain lesions.

Disclosure

This work was supported in part by the Japan Epilepsy Research Foundation, Takeda Promotion of Science Foundation, a grant-in-aid No.17591502 for scientific research from MEXT, a Research Grant of the Princess Takamatsu Cancer Research Fund, Terumo Promotion of Science Foundation, Brain Science foundation, and Grant-in-Aid No. 18020010 for Scientific Research on Priority Areas Integrative Brain Research from MEXT.

REFERENCES

1. Allison T, McCarthy G, Nobre A, Puce A, Belger A: Human extrastriate visual cortex and the perception of faces, words, numbers, and colors. **Cereb Cortex** 4:544–554, 1994.
2. Baciu MV, Watson JM, McDermott KB, Wetzel RD, Attarian H, Moran CJ, Ojemann JG: Functional MRI reveals an interhemispheric dissociation of frontal and temporal language regions in a patient with focal epilepsy. **Epilepsy Behav** 4:776–780, 2003.
3. Branch C, Milner B, Rasmussen T: Intracarotid sodium amytal for the lateralization of cerebral speech dominance: Observations in 123 patients. **J Neurosurg** 21:399–405, 1964.
4. Brazdil M, Zakopcan J, Kuba R, Fanfrdlova Z, Rektor I: Atypical hemispheric language dominance in left temporal lobe epilepsy as a result of the reorganization of language functions. **Epilepsy Behav** 4:414–419, 2003.
5. Chen HM, Varshney PK: Mutual information-based CT-MR brain image registration using generalized partial volume joint histogram estimation. **IEEE Trans Med Imaging** 22:1111–1119, 2003.

FIGURE 5. *A 40-year-old, left-handed woman with epilepsy. A, fMRI with the verb generation task showed activations predominantly in the right IFG and MFG. B, fMRI with the A/C categorization task demonstrated activations in the right MFG and the posterior STG. C, source localization of the late deflections on MEG showed predominant dipole clusters (*white squares*) in the right posterior temporal region. The left and right hemispheres showed 44 and 144 dipoles, respectively. D, three-dimensionally reconstructed MRI scans fused with activation of the verb generation-fMRI (*orange*) and dipoles of language-MEG (*blue*). After implantation of subdural electrodes (*gold*), cortical mapping was performed with 50Hz bipolar electrical stimulation. Stimulation with intensity of 7mA to the right IFG caused speech arrest (*white circles*), whereas stimulation to the posterior STG caused impairment of auditory comprehension and reading capability (*black circles*).*

6. FitzGerald DB, Cosgrove GR, Ronner S, Jiang H, Buchbinder BR, Belliveau JW, Rosen BR, Benson RR: Location of language in the cortex: A comparison between functional MR imaging and electrocortical stimulation. **AJNR Am J Neuroradiol** 18:1529–1539, 1997.
7. Holodny AI, Schulder M, Liu WC, Maldjian JA, Kalnin AJ: Decreased BOLD functional MR activation of the motor and sensory cortices adjacent to a glioblastoma multiforme: Implications for image-guided neurosurgery. **AJNR Am J Neuroradiol** 20:609–612, 1999.
8. Holodny AI, Schulder M, Ybasco A, Liu WC: Translocation of Broca's area to the contralateral hemisphere as the result of the growth of a left inferior frontal glioma. **J Comput Assist Tomogr** 26:941–943, 2002.
9. Janszky J, Ollech I, Jokeit H, Kontopoulou K, Mertens M, Pohlmann-Eden B, Ebner A, Woermann FG: Epileptic activity influences the lateralization of mesiotemporal fMRI activity. **Neurology** 63:1813–1817, 2004.
10. Kamada K, Houkin K, Iwasaki Y, Takeuchi F, Kuriki S, Mitsumori K, Sawamura Y: Rapid identification of the primary motor area by using magnetic resonance axonography. **J Neurosurg** 97:558–567, 2002.
11. Kamada K, Kober H, Saguer M, Moller M, Kaltenhauser M, Vieth J: Responses to silent Kanji reading of the native Japanese and German in task subtraction magnetoencephalography. **Brain Res Cogn Brain Res** 7:89–98, 1998.
12. Kamada K, Sawamura Y, Takeuchi F, Houkin K, Kawaguchi H, Iwasaki Y, Kuriki S: Gradual recovery from dyslexia and related serial magnetoencephalographic changes in the lexicosemantic centers after resection of a mesial temporal astrocytoma. Case report. **J Neurosurg** 100:1101–1106, 2004.
13. Kutas M, Hillyard SA: Reading senseless sentences: Brain potentials reflect semantic incongruity. **Science** 207:203–205, 1980.
14. Kutas M, Hillyard SA: Brain potentials during reading reflect word expectancy and semantic association. **Nature** 307:161–163, 1984.
15. Lehericy S, Biondi A, Sourour N, Vlaicu M, du Montcel ST, Cohen L, Vivas E, Capelle L, Faillot T, Casasco A, Le Bihan D, Marsault C: Arteriovenous brain malformations: Is functional MR imaging reliable for studying language reorganization in patients? Initial observations. **Radiology** 223:672–682, 2002.
16. Lehericy S, Cohen L, Bazin B, Samson S, Giacomini E, Rougetet R, Hertz-Pannier L, Le Bihan D, Marsault C, Baulac M: Functional MR evaluation of temporal and frontal language dominance compared with the Wada test. **Neurology** 54:1625–1633, 2000.
17. Nobre AC, Allison T, McCarthy G: Word recognition in the human inferior temporal lobe. **Nature** 372:260–263, 1994.
18. Oldfield RC: The assessment and analysis of handedness: The Edinburgh inventory. **Neuropsychologia** 9:97–113, 1971.
19. Papanicolaou AC, Simos PG, Breier JI, Zouridakis G, Willmore LJ, Wheless JW, Constantinou JE, Maggio WW, Gormley WB: Magnetoencephalographic mapping of the language-specific cortex. **J Neurosurg** 90:85–93, 1999.
20. Papanicolaou AC, Simos PG, Castillo EM, Breier JI, Sarkari S, Pataraia E, Billingsley RL, Buchanan S, Wheless J, Maggio V , Maggio WW: Magnetocephalography: A noninvasive alternative to the Wada procedure. **J Neurosurg** 100:867–876, 2004.
21. Petrovich NM, Holodny AI, Brennan CW, Gutin PH: Isolated translocation of Wernicke's area to the right hemisphere in a 62-year-man with a temporoparietal glioma. **AJNR Am J Neuroradiol** 25:130–133, 2004.
22. Pouratian N, Bookheimer SY, Rex DE, Martin NA, Toga AW: Utility of preoperative functional magnetic resonance imaging for identifying language cortices in patients with vascular malformations. **Neurosurg Focus** 13:E4, 2002.
23. Ries ML, Boop FA, Griebel ML, Zou P, Phillips NS, Johnson SC, Williams JP, Helton KJ, Ogg RJ: Functional MRI and Wada determination of language lateralization: A case of crossed dominance. **Epilepsia** 45:85–89, 2004.
24. Roux FE, Boulanouar K, Lotterie JA, Mejdoubi M, LeSage JP, Berry I: Language functional magnetic resonance imaging in preoperative assessment of language areas: Correlation with direct cortical stimulation. **Neurosurgery** 52:1335–1345, 2003.
25. Rutten GJ, Ramsey NF, van Rijen PC, Noordmans HJ, van Veelen CW: Development of a functional magnetic resonance imaging protocol for intraoperative localization of critical temporoparietal language areas. **Ann Neurol** 51:350–360, 2002.
26. Rutten GJ, Ramsey NF, van Rijen PC, van Veelen CW: Reproducibility of fMRI-determined language lateralization in individual subjects. **Brain Lang** 80:421–437, 2002.
27. Simos PG, Papanicolaou AC, Breier JI, Wheless JW, Constantinou JE, Gormley WB, Maggio WW: Localization of language-specific cortex by using magnetic source imaging and electrical stimulation mapping. **J Neurosurg** 91:787–796, 1999.
28. Woermann FG, Jokeit H, Luerding R, Freitag H, Schulz R, Guertler S, Okujava M, Wolf P, Tuxhorn I, Ebner A: Language lateralization by Wada test and fMRI in 100 patients with epilepsy. **Neurology** 61:699–701, 2003.
29. Yetkin FZ, Mueller WM, Morris GL, McAuliffe TL, Ulmer JL, Cox RW, Daniels DL, Haughton VM: Functional MR activation correlated with intraoperative cortical mapping. **AJNR Am J Neuroradiol** 18:1311–1315, 1997.

COMMENTS

This is an interesting article evaluating the complementary features of functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) to assess language lateralization in 87 patients. Whereas any test of language lateralization is suspect if 100% correlation is found, the authors have carefully described their techniques and the analysis of results. It is quite apparent that fMRI with verb generation tasks is best at activating anterior language areas, whereas abstract versus concrete naming tasks can be less robust. This is a good article and a large experience worthy of publication.

G. Rees Cosgrove
Burlington, Massachusetts

The authors have applied fMRI and MEG techniques to localize speech function in a large number of patients with different brain lesions. They were able to supplement the two noninvasive tests with the Wada test in 80% of the patients. They were able to obtain useful data with the co-utilization of fMRI and MEG in 95.6% of the patients and found a somewhat surprisingly good match with the results of the Wada test in 100% of those. In the results section, the authors discuss a few differences to the localization of language areas by electrophysiological means. They point out the fact that atypical language dominance or bilateral language representation is more frequent in patients with chronic epilepsy than in those without epilepsy. This is an important fact not known to many neurosurgeons who are not ordinarily involved with epilepsy cases. The results of this study make it more likely that, in the future, the invasive Wada test procedure might be abolished in those institutions at which MEG is available. This constitutes a notable limitation of this noninvasive technique. If fMRI is used alone, the success rate for obtaining useful data is 84.6% for word generation tasks and only 67% for the abstract/concrete categorization task. This is quite an interesting study and the results are very promising; however, the limitations are not economical. A number of patients cannot complete all the tasks necessary for fMRI study, and MEG studies can be disturbed by eye movement artifacts. We look forward to other reports confirming these promising results.

Johannes Schramm
Bonn, Germany

The authors present some very interesting data in the realm of functional imaging to determine cerebral dominance for language. Currently, the standard modality for determining cerebral dominance is the venerable Wada test. In this study, the authors use both MEG and fMRI to determine language dominance based on activation in the inferior frontal gyrus and middle frontal gyrus using fMRI and dipole moments reflecting or indicating receptive language fields in the temporal lobe. As expected, they had some difficulty with the fMRI data owing to the underlying deficit in the patient, which suggests that fMRI is not always as good as one might expect in terms of determin-

ing cerebral dominance using a verb generation silent language task. We know that fMRI is not a good choice for defining receptive language fields that correspond to intraoperative stimulation mapping. However, when fMRI was used together with MEG, the authors were able to demonstrate 100% concordance with data from the Wada test. Thus, this is a very important study indicating that, in the near future, it may be possible to bypass the Wada test with these two powerful functional imaging modalities. That being said, not every institution is going to be able to obtain both of these functional tests. Therefore, it is unlikely that this strategy is going to replace Wada tests completely. Yet, this is a very important line of investigation and a novel observation that points out the frailties of functional imaging for cerebral dominance localization and the potential power when the different functional tests are combined.

Mitchel S. Berger
San Francisco, California

Portrait of James Figg (1695–1734), by William Hogarth, (1697–1764). Acknowledged in Britain as the "Father of Boxing," Figg popularized the sport with teaching and exhibitions and, following victories over all the other British contenders, declared himself "heavyweight champion of England" in 1719.

Radiotherapy and Oncology 80 (2006) 93–97
www.thegreenjournal.com

Treatment of lung damage

Retrospective analysis of steroid therapy for radiation-induced lung injury in lung cancer patients

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Abstract

***Purpose*: To disclose characteristics of lung cancer patients developing radiation-induced lung injury treated with or without corticosteroid therapy.**

***Methods and materials*: Radiographic changes, symptoms, history of corticosteroid prescription, and clinical course after 50–70 Gy of thoracic radiotherapy were retrospectively evaluated in 385 lung cancer patients.**

***Results*: Radiation-induced lung injury was stable without corticosteroid in 307 patients (Group 1), stable with corticosteroid in 64 patients (Group 2), and progressive to death despite corticosteroid in 14 patients (Group 3). Fever and dyspnea were noted in 11%, 50% and 86% ($p < 0.001$), and in 13%, 44% and 57% ($p < 0.001$) patients in Groups 1–3, respectively. Median weeks between the end of radiotherapy and the first radiographic change were 9.9, 6.7 and 2.4 for Groups 1–3, respectively ($p < 0.001$). The initial prednisolone equivalent dose was 30–40 mg daily in 52 (67%) patients. A total of 16 (4.2%) patients died of radiation pneumonitis or steroid complication with a median survival of 45 (range, 8–107) days.**

***Conclusion*: Development of fever and dyspnea, and short interval between the end of radiotherapy and the first radiographic change were associated with fatal radiation-induced lung injury. Prednisolone 30–40 mg daily was selected for the treatment in many patients.**

Keywords: Radiation pneumonitis; Radiotherapy; Lung cancer; Corticosteroid

Thoracic radiotherapy is widely used for the curative and palliative treatment of lung cancer. Radiation-induced lung injury was first described as early as 1922 [1,2], and two types of lung injury, radiation pneumonitis and radiation fibrosis, were recognized in 1925 [3]. Radiation pneumonitis occurs in 5–15% of patients who have received radiation therapy for lung cancer. Its clinical symptoms are characterized by cough, dyspnea and fever developing between 1 and 3 months after the end of radiotherapy. Distinctive radiographic changes of radiation pneumonitis are a ground-glass opacification or diffuse haziness in early phase, and then alveolar infiltrates or dense consolidation in late phase in the region corresponding to the irradiated area [4–7]. Radiation pneumonitis may persist for a month or more and subside gradually. In severe cases, however, pneumonitis progresses to death due to respiratory failure within few weeks [4].

Use of adrenocorticotropic hormone (ACTH) and cortisone for radiation pneumonitis in a case was first reported in 1951 [8], and 9 cases of radiation pneumonitis treated with cortisone therapy in the literature were reviewed in 1968 [9]. Although no case series or clinical trials of corticosteroid therapy have been reported since that time, prednisolone has been given in patients with severe pneumonitis in clinical practice. The initial dose of prednisolone, approximately 30–100 mg daily, and very slow tapering schedule are in agreement among experts [4–6,10], because early withdrawal results in aggravation of pneumonitis [11–13]. There is no consensus, however, about criteria to define when steroids are required for radiation-induced lung injury. The objective of this study is to disclose general characteristics of lung cancer patients developing radiation-induced lung injury treated with or without corticosteroid therapy, to obtain data on the initiation criteria, dose, and taper schedule of corticosteroid therapy for further prospective trials.

Patients and methods

Consecutive lung cancer patients treated with thoracic radiotherapy at a total dose of 50–70 Gy in National Cancer

0167-8140/$ - see front matter doi:10.1016/j.radonc.2006.06.007

Center Hospital between January 1998 and December 2003 were subjects of this study. We retrospectively reviewed all chest X-ray films taken during 6 month period from the end of thoracic radiation to identify the first radiographic change and its progress. History of corticosteroid prescription, symptoms at the time of and one-month period after the first radiographic change in a chest X-ray film, and clinical course of radiation-induced lung injury were obtained from medical charts. The diagnosis of radiation-induced lung injury was defined as radiographic changes including opacification, diffuse haziness, infiltrates or consolidation conforming to the outline of the sharply demarcated irradiated area in a chest X-ray film. During clinical course, scarring (fibrosis) was developed within the irradiated area leading to a reduction in lung volume. In contrast, pulmonary infection spreads through anatomical structure of the lung, and the boundary of infiltrates corresponds to anatomical boundary of the lung. For patients with fever, the radiographical response to antibiotics was also evaluated. Observed differences in the proportions of patients in various patient subgroups were evaluated using Chi-square test. Differences between continuous variables were compared using Mann–Whitney tests. The Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan) was used for all statistical analyses.

Results

Of 544 lung cancer patients receiving thoracic radiotherapy at a total dose of 50–70 Gy, 111 patients were excluded from this study because they were not evaluable: loss of follow-up in 88 patients, early lung cancer progression in 18 patients, chemotherapy-induced neutropenic fever and pneumonia in three patients, death of bleeding from the esophageal stent in one patient, and no chest X-ray films available in one patient. In addition, 48 patients (11% of 433 evaluable patients) were also excluded because no radiation-induced lung injury was noted. Thus, the subject of this study was 385 patients.

Of the 385 patients, 78 (20%) received corticosteroid therapy for radiation-induced lung injury, and 307 did not. Radiation-induced lung injury was stable without corticosteroid in the 307 (80%) patients (Group 1), stable or in remission with corticosteroid in 64 (17%) patients (Group 2), and progressive to death despite corticosteroid in 14 (4%) patients (Group 3). No difference in sex, total dose, intent of radiotherapy, and combination chemotherapy was noted among three Groups, but median age of patients was higher in Group 3 (Table 1). Fever was developed in 50% of patients in Group 3 at the initial radiographic change, and in 86% of them during subsequent clinical course, while it was developed in only 11–12% of patients in Group 1 through their clinical course (Table 2). Dyspnea was developed in 57% of patients in Group 3 and in 44% of patients in Group 2 during clinical course, while it was developed in only 14% of patients in Group 1 (Table 2). A total of 88 patients developed fever at the initial change in chest X-ray and/or during subsequent clinical course. Of these, 43 patients received antibiotics, but no radiographical response was obtained in these patients. Five (2%) and seven (2%) patients in Group 1 developed bloody sputum and chest pain, respectively, but none in Group 2 or 3 developed these symptoms. The average interval of chest X-rays taken between the start of radiotherapy and the first appearance of radiographic change was 1.7 weeks for group 1, 1.3 weeks for group 2, and 0.9 weeks for group 3 ($P < 0.001$, Table 3). Interval between the end of radiotherapy and the first change in a chest X-ray was shorter in Group 3 than in Group 2 or Group 1 (Table 3). Of 57 patients in whom the first radiographic change was noted within three weeks, 9 (16%) died of pneumonitis, while radiation-induced lung injury that occurred 10 weeks or later after the end of radiation was easily managed with or without steroid therapy (Table 3). Oxygen content in the blood at the start of steroid therapy was examined in 70 patients of Groups 2 and 3. Oxygen content

Table 1
Patient demographics and radiotherapy performance

Characteristics	Total *N* (%)	Group 1	Group 2	Group 3	*p*-value
		N (%)	*N* (%)	*N* (%)	
Total	385 (100)	307 (80)	64 (17)	14 (4)	
Sex					
Male	300 (78)	240 (78)	47 (73)	13 (93)	0.28
Female	85 (22)	67 (22)	17 (27)	1 (7)	
Age median (range)	65 (28–87)	63 (28–87)	65 (37–83)	71 (65–84)	0.008
Total dose (Gy)					
Median (range)	60 (50–70)	60 (50–70)	60 (50–61)	60 (50–60)	0.50
Intent of radiotherapy					
Curative	298 (77)	232 (76)	52 (81)	14 (100)	0.074
Palliative	87 (23)	75 (24)	12 (19)	0 (0)	
Chemotherapy					
None	121 (31)	101 (33)	15 (23)	5 (36)	0.48
Sequential	121 (31)	93 (30)	25 (39)	3 (21)	
Concurrent	143 (37)	113 (37)	24 (38)	6 (43)	

Table 2
Symptoms through clinical courses

Symptom	At the initial change in chest X-ray				During subsequent clinical course			
	Group 1	Group 2	Group 3	p	Group 1[a]	Group 2[b]	Group3[b]	p
Cough	96 (31)	35 (56)	5 (36)	0.001	85 (28)	38 (59)	5 (36)	<0.001
Sputum	32 (10)	11 (18)	4 (29)	0.049	30 (10)	11 (17)	3 (21)	0.12
Hemosputum	5 (2)	0 (0)	0 (0)	0.53	4 (1)	0 (0)	0 (0)	0.60
Chest pain	7 (2)	0 (0)	0 (0)	0.40	2 (0.6)	0 (0)	0 (0)	0.78
Fever								
None	269 (88)	35 (56)	7 (50)	<0.001	272 (89)	32 (50)	2 (14)	<0.001
37.0–37.9 °C	18 (6)	11 (18)	2 (14)	24 (8)	16 (25)	5 (35)		
38 °C≤	13 (4)	14 (22)	5 (36)	8 (3)	13 (20)	7 (50)		
Not specified	7 (2)	3 (4)	0 (0)	3 (1)	3 (4)	0 (0)		
Dyspnea	43 (14)	14 (22)	6 (43)	0.007	40 (13)	28 (44)	8 (57)	<0.001
Fever or dyspnea	75 (24)	37 (58)	10 (71)	<0.001	65 (21)	49 (77)	14 (100)	<0.001
Any	150 (49)	51 (81)	13 (93)	<0.001	118 (38)	60 (94)	14 (100)	<0.001

[a] During one month period following the initial change in the chest X-ray.
[b] At the start of steroid therapy.

Table 3
The chest X-ray intervals and first radiographic change

Weeks	Group 1	Group 2	Group 3	p-value
The average interval of chest X-rays (weeks)[a]				
Median (range)	1.7 (0.7 to 6.0)	1.3 (0.5 to 4.4)	0.9 (0.5 to 3.8)	<0.001
Duration between the end of radiotherapy and the first radiographic change (weeks)				
Median (range)	9.9 (−2.9 to 45.1)	6.7 (0 to 24.9)	2.4 (0.4 to 10.1)	<0.001
<6	82 (27)	26 (41)	11 (79)	<0.001
6–11.9	116 (38)	29 (45)	3 (21)	
12–17.9	71 (23)	7 (11)	0 (0)	
18≤	38 (12)	2 (3)	0 (0)	

[a] Calculated as follows: the average interval of chest X-rays = (the first radiographic change − the start of radiotherapy)/the number of chest X-rays taken during this period/7).

was slightly decreased (PaO2 = 70–74.9 Torr) in 12 (19%) patients of Group 2 and one (7%) patient of Group 3, and moderately to severely decreased (PaO2 ≤ 69.9 Torr or SpO2 ≤ 92%) in 21 (33%) patients of Group 2 and 7 (50%) patients of Group 3 ($p = 0.38$).

Prednisolone was administered as the initial therapy in 69 (88%) patients of Groups 2 and 3. The initial prednisolone equivalent dose of steroid was 30–40 mg daily in 52 (67%), and 60 mg of higher only in 8 (10%) patients (Table 4). The median duration of the initial dose was 10 (range, 2–64) days, and the dose was reduced within 14 days in 57 (77%) patients. The median duration of steroid therapy was 10 (range, 2–28) weeks (Table 4). Steroid pulse therapy (methylprednisolone 1000 mg daily for three days) was administered as the initial therapy in one patient, and as salvage therapy in six patients at the time of pneumonitis aggravation. Among the seven patients, six died of respiratory failure due to progressive radiation pneumonitis.

Outcome of steroid therapy was evaluated in 76 patients (Fig. 1). Symptomatic relief was obtained and the steroid dose was reduced in 71 (93%) of the 76 patients, while no effect was noted in the remaining five patients, who all died of radiation pneumonitis despite escalated steroid administration. Of the 71 patients, 15 (21%) developed recurrent symptoms at the median daily prednisolone dose of 20 mg (range, 10–40 mg) within median 33 days (range, 21–42 days) from the start of the steroid therapy, and required steroids to be escalated. Of the 15 patients, nine died of radiation pneumonitis and one died of complication of steroid therapy. A total of 54 (71%) patients were in remission from pneumonitis and steroid therapy was terminated. The remainder 22 patients died during steroid therapy, 14 of radiation pneumonitis, two of infectious complication (bacterial pneumonia in one, and lung aspergillosis in another patient), five of lung cancer progression, and one of hemoptysis. Thus, 16 patients, who accounted for 4.2% of 385 patients receiving 50–70 Gy of thoracic radiotherapy, and who accounted for 21% of 78 patients treated with steroid therapy, died of radiation pneumonitis or complication associated with steroid therapy. Median survival from the start of steroid therapy in these patients was 45 (range, 8–107) days.

Discussion

Patients with radiation-induced lung injury have been managed in compliance with the expert opinions, because there has been no case series or clinical trial report on clinical course and corticosteroid use for this lung injury. This

Table 4
Corticosteroid, dose and duration of steroid therapy

	N (%)
Corticosteroid	
Prednisolone	69 (88)
Dexamethasone	4 (5)
Betamethasone	4 (5)
Methylprednisolone	1 (1)
Initial dose, mg/body daily (prednisolone equivalent)	
Pulse therapy	1 (1)
60	7 (9)
50	1 (1)
40	10 (13)
30	42 (54)
10–25	17 (22)
Duration of the initial dose, days	
Median (range)	10 (2–64)
≤14	57 (77)
15–28	9 (12)
29≤	8 (11)
Not evaluable	4
Total duration of steroid therapy, weeks	
Median (range)	10 (2–28)
≤6	16 (30)
6.1–12	19 (35)
12.1–18	14 (26)
18.1≤	5 (9)
Not evaluable	24

study is the first systemic review of these patients both who received corticosteroid therapy and who did not. Comparison between the expert opinions and the results of this study is given below. First, radiation-induced lung injury is severer when a radiographic change appears earlier [5]. In this study, the initial change in a chest X-ray film was observed in 9.9 (range, −3 to 45) weeks in Group 1, in 6.7 (range, 0–25) weeks in Group 2, and 2.4 (range, 0–10) weeks in Group 3 after the end of thoracic radiotherapy. If patients present with symptoms, presumably they receive a chest X-ray. Thus, the patients with symptoms may have radiographic findings seen sooner, since they receive an X-ray when they complain of symptoms. The average interval of chest X-rays taken between the start of radiotherapy and the first appearance of radiographic change was longer in Group 1 than that in groups 2 and 3. The difference, however, was negligibly small when compared with the difference in duration between the end of radiotherapy and the first radiographic change. Second, steroid administration is determined generally based on the severity of symptoms [5]. In this study steroid was used when patients developed dyspnea or fever. Dyspnea has been thought to be the cardinal symptom of radiation pneumonitis but fever to be unusual [5,10]. In this study, however, fever was highly associated with fatal radiation pneumonitis; fever was noted in 12% patients of Group 1, in 58% patients of Group 2, and 86% patients of Group 3. This study failed to show utility of blood gas analysis. An oxygen content in the blood was decreased moderately to severely in only 28 (36%) patients in Groups 2 and 3, and did not differ between the two groups. The oxygen content in Group 1 was measured in only small number of patients, and therefore it was not evaluable in this study. Third, 30–100 mg/day of prednisolone has been recommended as the initial dose [4–6,10]. In our practice, a dose of 30–40 mg was the most frequently used. We selected this relatively low dose of steroid mostly because steroid therapy was started in out patient clinic. Forth, duration of the initial dose was within two weeks in 73% of patients, which is consistent to most expert opinions [6,10]. In contrast, tapering schedules varied between a pa-

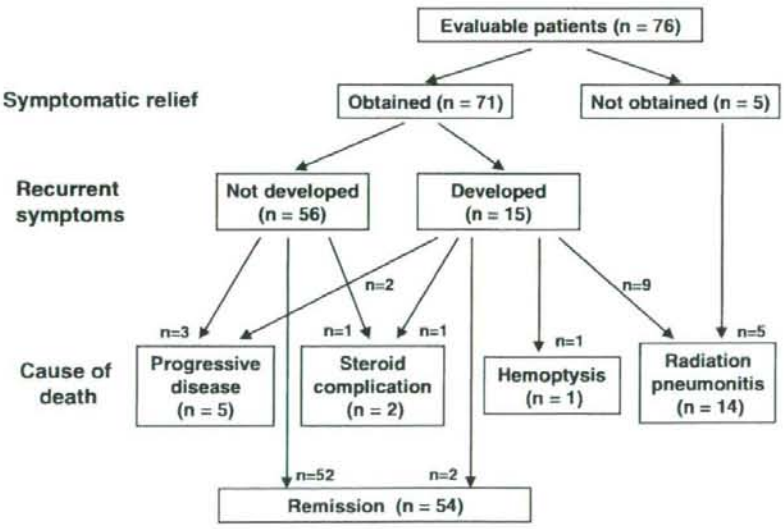

Fig. 1. Outcome of patients who received steroid therapy. Two patients were excluded because of loss of follow-up. Of 76 evaluable patients, 71 (93%) experienced symptomatic relief by steroid therapy.

tient and another in this study. This may be partly due to the diversity in clinical course of radiation pneumonitis, but mostly due to lacking in available recommendation for tapering schedules. In this study, median total duration of steroid therapy was 10 weeks, which may be a tentative guide. A guideline of taper schedule appeared in the latest textbook: the dose should be tapered by 10 mg every two weeks, and be terminated in 12 weeks [10].

Although our clinical practice mostly followed the expert opinions on the management of radiation-induced lung injury as mentioned above, there is little evidence that our steroid use, dose and duration for radiation-induced lung injury were correct. In this study, 21% of patients received steroid therapy and 4% of patients died of radiation pneumonitis among lung cancer patients treated with thoracic radiotherapy at a total dose of 50 Gy or higher. These figures are comparable to the incidence of grade 3 pneumonitis, 3–20%, and that of fatal pneumonitis, 1–4%, in other reports [10].

In conclusion, development of fever and dyspnea, and short interval between the end of radiotherapy and the first radiographic change were associated with fatal radiation-induced lung injury. Prednisolone 30–40 mg daily for two weeks followed by slow taper was selected for the treatment in many patients.

Acknowledgements

This work was supported in part by Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan. We thank Yuko Yabe and Mika Nagai for preparation of the manuscript.

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Received 11 October 2005; received in revised form 19 April 2006; accepted 23 May 2006; Available online 3 July 2006

References

[1] Groover TA, Christie AC, Merritt EA. Observations on the use of the copper filter in the roentgen treatment of deep-seated malignancies. South Med J 1922;15:440–4.
[2] Hines LE. Fibrosis of the lung following roentgen-ray treatments for tumor. JAMA 1922;79:720–2.
[3] Evans WA, Leucutia T. Intrathoracic changes induced by heavy radiation. Am J Roentgenol 1925;13:203–20.
[4] Gross NJ. Pulmonary effects of radiation therapy. Ann Intern Med 1977;86:81–92.
[5] Stover D, Kaner R. Pulmonary toxicity. In: DeVita Jr V, Hellman S, Rosenberg S, editors. Cancer: principles and practice of oncology. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 2894–904.
[6] McDonald S, Rubin P, Phillips TL, Marks LB. Injury to the lung from cancer therapy: clinical syndromes, measurable endpoints, and potential scoring systems. Int J Radiat Oncol Biol Phys 1995;31:1187–203.
[7] Inoue A, Kunitoh H, Sekine I, et al. Radiation pneumonitis in lung cancer patients: a retrospective study of risk factors and the long-term prognosis. Int J Radiat Oncol Biol Phys 2001;49:649–55.
[8] Cosgriff SW, Kligerman MM. Use of ACTH and cortisone in the treatment of post-irradiation pulmonary reaction. Radiology 1951;57:536–40.
[9] Rubin P, Casarett GW. Clinical Radiation Pathology. Philadelphia: WB Saunders Co; 1968.
[10] Machtay M. Pulmonary complications of anticancer treatment. In: Abeloff M, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG, editors. Clin. Oncol.. Philadelphia: Elsevier Churchill Livingstone; 2004. p. 1237–50.
[11] Pezner RD, Bertrand M, Cecchi GR, et al. Steroid-withdrawal radiation pneumonitis in cancer patients. Chest 1984;85:816–7.
[12] Parris TM, Knight JG, Hess CE, Constable WC. Severe radiation pneumonitis precipitated by withdrawal of corticosteroids: a diagnostic and therapeutic dilemma. Am J Roentgenol 1979;132:284–6.
[13] Castellino RA, Glatstein E, Turbow MM, et al. Latent radiation injury of lungs or heart activated by steroid withdrawal. Ann Intern Med 1974;80:593–9.

Docetaxel Consolidation Therapy Following Cisplatin, Vinorelbine, and Concurrent Thoracic Radiotherapy in Patients with Unresectable Stage III Non-small Cell Lung Cancer

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Background: To evaluate the feasibility and efficacy of docetaxel consolidation therapy after concurrent chemoradiotherapy for unresectable stage III non–small cell lung cancer (NSCLC).

Patients and Methods: The eligibility criteria included unresectable stage III NSCLC, no previous treatment, age between 20 and 74 years, and performance status 0 or 1. Treatment consisted of cisplatin (80 mg/m^2 on days 1, 29, and 57), vinorelbine (20 mg/m^2 on days 1, 8, 29, 36, 57, and 64), and thoracic radiotherapy (TRT) (60 Gy/30 fractions over 6 weeks starting on day 2), followed by consolidation docetaxel (60 mg/m^2 every 3 to 4 weeks for three cycles).

Results: Of 97 patients who were enrolled in this study between 2001 and 2003, 93 (76 males and 17 females with a median age of 60) could be evaluated. Chemoradiotherapy was well tolerated; three cycles of chemotherapy and 60 Gy of TRT were administered in 80 (86%) and 87 (94%) patients, respectively. Grade 3 or 4 neutropenia, esophagitis, and pneumonitis developed in 62, 11, and 3 patients, respectively. Docetaxel consolidation was administered in 59 (63%) patients, but three cycles were completed in only 34 (37%) patients. The most common reason for discontinuation was pneumonitis, which developed in 14 (24%) of the 59 patients. During consolidation therapy, grade 3 or 4 neutropenia, esophagitis, and pneumonitis developed in 51, 2, and 4 patients, respectively. A total of four patients died of pneumonitis. We calculated a V_{20} (the percent volume of the normal lung receiving 20 Gy or more) on a dose–volume histogram in 25 patients. Of these, five patients developed grade 3 or more severe radiation pneumonitis. A median V_{20} for these five patients was 35% (range, 26–40%), whereas the median V_{20} for the remaining 20 patients was 30% (range, 17–35%) (p = 0.035 by a Mann–Whitney test). The response rate was 81.7% (95% confidence interval [CI], 72.7–88.0%), with 5 complete and 71 partial responses. The median progression-free survival was 12.8 (CI, 10.2–15.4) months, and median survival was 30.4 (CI, 24.5–36.3) months. The 1-, 2-, and 3-year survival rates were 80.7, 60.2, and 42.6%, respectively.

Conclusion: This regimen produced promising overall survival in patients with stage III NSCLC, but the vast majority of patients could not continue with the docetaxel consolidation because of toxicity.

Key Words: Non-small cell lung cancer, Chemoradiotherapy, Consolidation, Docetaxel.

(*J Thorac Oncol.* 2006;1: 810–815)

Locally advanced unresectable non–small cell lung cancer (NSCLC), stage IIIA with bulky N2 and stage IIIB disease without pleural effusion, is characterized by large primary lesions and/or involvement of the mediastinal or supraclavicular lymph nodes and occult systemic micrometastases. A combination of thoracic radiotherapy and chemotherapy is the standard medical treatment for this disease, but the optimal combination has not been established.[1] Although the available data are insufficient to accurately define the size of a potential benefit,[2] concurrent chemoradiotherapy using a platinum doublet has been shown to be superior to the sequential approach in phase III trials of this disease.[3–5] However, third-generation cytotoxic agents, which have provided better patient survival with extrathoracic spread than the old-generation agents, must be reduced when administered concurrently with thoracic radiotherapy.[6] Thus, it has been hypothesized that the addition of systemic dose chemotherapy with a new cytotoxic agent to concurrent chemoradiotherapy, either as induction or as consolidation chemotherapy, might further improve patient survival.[1]

The consolidation chemotherapy with docetaxel was based on the observation that this drug was highly active in the primary treatment of metastatic NSCLC, producing a response rate (RR) as high as 20% after platinum-based chemotherapy failed.[7–9] Highly encouraging results of a me-

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ISSN: 1556-0864/06/0108-0810

dian survival time (MST) of more than 2 years and a 3-year survival rate of nearly 40% were obtained in a phase II trial of docetaxel consolidation after chemoradiotherapy with cisplatin and etoposide in patients with stage IIIB NSCLC (SWOG study S9504).[10]

We have developed a combination chemotherapy schedule with cisplatin and vinorelbine concurrently administered with thoracic radiotherapy at a total dose of 60 Gy in 30 fractions in patients with unresectable stage III NSCLC. The results of a phase I study in 18 patients were very promising, with a RR of 83%, a MST of 30 months, and a 3-year survival rate of 50%.[6] Thus, addition of docetaxel consolidation to this regimen is a particularly interesting therapeutic strategy. The objectives of the current study were to evaluate the feasibility of docetaxel consolidation therapy after concurrent chemoradiotherapy with cisplatin and vinorelbine and to evaluate the efficacy and safety of the whole treatment regimen including both the chemoradiotherapy and consolidation therapy in patients with unresectable stage IIIA and IIIB NSCLC.

PATIENTS AND METHODS

Patient Selection

The eligibility criteria were histologically or cytologically proven NSCLC; unresectable stage IIIA or IIIB disease; no previous treatment; measurable disease; tumor within an estimated irradiation field no larger than half the hemithorax; age between 20 and 74 years; Eastern Cooperative Oncology Group performance status (PS) of 0 or 1; adequate bone marrow function (12.0×10^9/liter ≥ white blood cell [WBC] count ≥4.0×10^9/liter, neutrophil count ≥2.0×10^9/liter, hemoglobin ≥10.0 g/dl, and platelet count ≥100×10^9/liter), liver function (total bilirubin ≤1.5 mg/dl and transaminase no more than twice the upper limit of the normal value), and renal function (serum creatinine ≤1.5 mg/dl and creatinine clearance ≥60 ml per minute); and a PaO_2 of 70 torr or more under room air conditions. Patients were excluded if they had malignant pleural or pericardial effusion, active double cancer, a concomitant serious illness such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonia or lung fibrosis identified by a chest x-ray, chronic obstructive lung disease, infection or other diseases contraindicating chemotherapy or radiotherapy, pregnancy, or if they were breast feeding. All patients gave their written informed consent.

Pretreatment Evaluation

The pretreatment assessment included a complete blood cell count and differential count, routine chemistry determinations, creatinine clearance, blood gas analysis, electrocardiogram, lung function testing, chest x-rays, chest computed tomographic (CT) scan, brain CT scan or magnetic resonance imaging, abdominal CT scan or ultrasonography, and radionuclide bone scan.

Treatment Schedule

Treatment consisted of a chemoradiotherapy phase with three cycles of cisplatin and vinorelbine followed by a consolidation phase with three cycles of docetaxel (Figure 1). Cisplatin 80 mg/m^2 was administered on days 1, 29, and 57 by intravenous infusion for 60 minutes with 2500 to 3000 ml of fluid for hydration. Vinorelbine diluted in 50 ml of normal saline was administered intravenously on days 1, 8, 29, 36, 57, and 64. All patients received prophylactic antiemetic therapy consisting of a $5HT_3$-antagonist and a steroid.

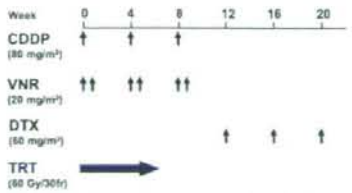

FIGURE 1. Treatment schema. CDDP, cisplatin; DTX, docetaxel; TRT, thoracic radiotherapy; VNR, vinorelbine.

Radiation therapy was delivered with megavoltage equipment (≥6 MV) using anterior/posterior opposed fields up to 40 Gy in 20 fractions including the primary tumor, the metastatic lymph nodes, and the regional nodes. A booster dose of 20 Gy in 10 fractions was given to the primary tumor and the metastatic lymph nodes for a total dose of 60 Gy using bilateral oblique fields. A CT scan–based treatment planning was used in all patients. The clinical target volume (CTV) for the primary tumor was defined as the gross tumor volume (GTV) plus 1 cm taking account of subclinical extension. CTV and GTV for the metastatic nodes (>1 cm in shortest dimension) were the same. Regional nodes, excluding the contralateral hilar and supraclavicular nodes, were included in the CTV, but the lower mediastinal nodes were included only if the primary tumor was located in the lower lobe of the lung. The planning target volumes for the primary tumor, the metastatic lymph nodes, and regional nodes were determined as CTVs plus 0.5- to 1.0-cm margins laterally and 1.0- to 2.0-cm margins craniocaudally, taking account of setup variations and internal organ motion. Lung heterogeneity corrections were not used.

The criteria for starting consolidation chemotherapy were completion of three cycles of cisplatin and vinorelbine and a full dose of thoracic radiotherapy, the absence of progressive disease, adequate general condition within 6 weeks of the start of the third cycle of cisplatin and vinorelbine (PS 0 or 1, WBC count ≥3.0×10^9/liter, neutrophil count ≥1.5×10^9/liter, hemoglobin ≥9.0 g/dl and platelet count ≥100×10^9/liter, total bilirubin ≤1.5 mg/dl and transaminase no more than twice the upper limit of the normal value, and a PaO_2 of 70 torr or more at room air). Docetaxel (60 mg/m^2) was administered intravenously for 1 hour every 3 to 4 weeks for three cycles.

Toxicity Assessment and Treatment Modification

Complete blood cell counts and differential counts, routine chemistry determinations, and a chest x-ray were performed once a week during the course of treatment. Acute toxicity was graded according to the NCI Common Toxicity Criteria, and late toxicity associated with thoracic radiother-

apy was graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme. Vinorelbine administration on day 8 was omitted if any of the following were noted: WBC count $<3.0 \times 10^9$/liter, neutrophil count $<1.5 \times 10^9$/liter, platelet count $<100 \times 10^9$/liter, elevated hepatic transaminase level or total serum bilirubin of at least grade 2, fever $\geq 38°C$, or PS ≥ 2. Subsequent cycles of cisplatin and vinorelbine chemotherapy were delayed if any of the following toxicities were noted on day 1: WBC count $<3.0 \times 10^9$/liter, neutrophil count $<1.5 \times 10^9$/liter, platelet count $<100 \times 10^9$/liter, serum creatinine level ≥ 1.6 mg/dl, elevated hepatic transaminase level or total serum bilirubin of at least grade 2, fever $\geq 38°C$, or PS ≥ 2. The dose of cisplatin was reduced by 25% in all subsequent cycles if the serum creatinine level rose to 2.0 mg/dl or higher. The dose of vinorelbine or docetaxel was reduced by 25% in all subsequent cycles if any of the following toxicities were noted: WBC count $<1.0 \times 10^9$/liter, platelet count $<10 \times 10^9$/liter, or grade 3 or 4 infection or liver dysfunction. Thoracic radiotherapy was suspended if any of the following were noted: fever $\geq 38°C$, grade 3 esophagitis, PS of 3, or PaO_2 <70 torr. Thoracic radiotherapy was terminated if any of the following were noted: grade 4 esophagitis, grade 3 or 4 pneumonitis, PS of 4, or duration of radiotherapy of over 60 days. The use of granulocyte colony-stimulating factor during radiotherapy was not permitted unless radiotherapy was on hold. The criteria for termination of docetaxel consolidation were not defined in the protocol.

Response Evaluation

Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumor.[11] Local recurrence was defined as tumor progression in the primary site and in the hilar, mediastinal, and supraclavicular lymph nodes after a partial or complete response; regional recurrence as the development of malignant pleural and pericardial effusions; and distant recurrence as the appearance of a distant metastasis.

Study Design, Data Management, and Statistical Considerations

This study was conducted at three institutions: the National Cancer Center Hospital, National Cancer Center Hospital East, and Tochigi Cancer Center. The protocol and consent form were approved by the institutional review board of each institution. Registration was conducted at the registration center. Data management, periodic monitoring, and the final analysis were performed by the study coordinator.

The primary objective of the current study was to evaluate the feasibility of docetaxel consolidation therapy. The secondary endpoints were toxicity observed during chemoradiotherapy and consolidation therapy, the best response, and overall survival in all patients eligible to participate in this study. Because no standard method to evaluate consolidation chemotherapy after chemoradiotherapy has been established, we arbitrarily defined the primary endpoint of this study as a ratio (R) of the number of patients receiving docetaxel without grade 4 nonhematological toxicity or treatment-related death to the total number of patients receiving docetaxel. The sample size was initially estimated to be 34 patients with a power of 0.80 at a significance level of 0.05, under the assumption that a R of 0.95 would indicate potential usefulness, whereas a R of 0.8 would be the lower limit of interest, and that 85% of patients would move into the consolidation phase. An analysis of the first 13 patients, however, showed that only 8 (61%) patients advanced into the consolidation phase. The reasons for not receiving docetaxel were disease progression in one, delay in completion of chemoradiotherapy in two, grade 3 esophagitis in one, and death due to hemoptysis in one patient. Considering that the SWOG trial S9504 included 83 patients, we decided to revise the number of patients in the current study. According to Simon's two-stage minimax design, the required number of patients was calculated to be 59 with a power of 0.80 at a significance level of 0.05, under the assumption that a R of 0.85 would indicate potential usefulness, whereas a R of 0.7 would be the lower limit of interest.[12] Assuming that 61% of registered patients would move into the consolidation phase, the sample size was determined to be 97 patients.

Overall survival time and progression-free survival time were estimated by the Kaplan–Meier method, and confidence intervals (CI) were based on Greenwood's formula.[13] Overall survival time was measured from the date of registration to the date of death (from any cause) or to the last follow-up. Progression-free survival time was measured from the date of registration to the date of disease progression, death (from any cause), or the last follow-up. Patients who were lost to follow-up without event were censored at the date of their last known follow-up. A CI for RR was calculated using methods for exact binomial CIs. The Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan) was used for statistical analyses.

RESULTS

Registration and Characteristics of the Patients

A total of 97 patients were enrolled in this study between April 2001 and June 2003. Four patients were excluded from this study before the treatment was started because the radiation treatment planning disclosed that their tumors were too advanced for curative thoracic radiotherapy. Thus, 93 patients who received the protocol-defined treatment were the subjects of this analysis (Figure 2). There were 76 males and 17 females, with a median age of 60 (range 31–74). Body weight loss was less than 5% in 77 patients; adenocarcinoma histology was noted in 57 patients, and stage IIIA disease was noted in 41 patients (Table 1).

Treatment Delivery

Treatment delivery was generally well maintained in the chemoradiotherapy phase (Table 2). Full cycles of cisplatin and vinorelbine and the full dose of thoracic radiotherapy were administered in 80 (86%) and 87 (94%) patients, respectively. Delay in radiotherapy was less than 5 days in 61 (66%) patients. In contrast, the delivery of docetaxel was poor (Table 2). A total of 59 (63%) patients could enter the consolidation phase, and only 34 (37%) patients completed three cycles of docetaxel chemotherapy. The reasons for not

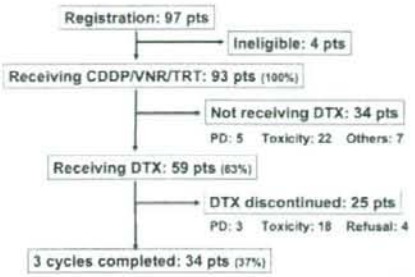

FIGURE 2. Patient registration. CDDP, cisplatin; DTX, docetaxel; TRT, thoracic radiotherapy; VNR, vinorelbine.

receiving consolidation were toxicity in 22 (65%) patients including pneumonitis in seven patients, myelosuppression in five patients, esophagitis in four patients, liver dysfunction in two patients, infection in two patients, other toxicity in two patients, progressive disease in five (15%) patients, patient refusal in three (9%) patients, early death due to hemoptysis in one (3%) patient, and other reasons in three (9%) patients. Of the 59 patients, 18 (31%) discontinued docetaxel consolidation because of toxicity, including pneumonitis (n = 14) and esophagitis, infection, gastric ulcer, and allergic reaction (n = 1 each), four (7%) because of patient refusal, and three (5%) because of progressive disease.

Toxicity

Acute severe toxicity in the chemoradiotherapy phase was mainly leukopenia and neutropenia, whereas grade 3 or 4 thrombocytopenia was not noted (Table 3). Severe nonhematological toxicity was sporadic, and grade 3 esophagitis and pneumonitis were observed in only 11 (12%) and 3 (3%) patients, respectively. Acute severe toxicity in the consolidation phase also consisted of neutropenia and associated infection (Table 4). In addition, grade 3 or 4 pneumonitis developed in 4 (7%) patients. The R observed in this study was 0.05 (3 out of 57 patients), which was much lower than the hypothetical value. Grade 3 or 4 late toxicities were included lung toxicity in four patients, esophageal toxicity in two patients, renal toxicity in one patient, and a second esophageal cancer that developed 35.4 months after the start of the chemoradiotherapy in one patient. Treatment-related

TABLE 1. Patient Characteristics

Characteristics	n	%
Gender		
Male	76	82
Female	17	18
Age median (range)	60	31–74
Weight loss		
<5%	76	81
5–9%	12	13
≥10%	3	3
Unknown	2	2
Histology		
Adenocarcinoma	57	61
Squamous cell carcinoma	23	25
Large cell carcinoma	12	13
Others	1	1
Stage		
IIIA	41	44
IIIB	52	56

TABLE 2. Treatment Delivery

Variables	n	%
Cisplatin and vinorelbine chemotherapy		
Total number of cycles		
3	80	86
2	10	11
1	3	3
Number of vinorelbine skips		
0	63	68
1	25	27
2–3	5	5
Thoracic radiotherapy		
Total dose (Gy)		
60	87	94
50–59	4	4
<50	2	2
Delay (days)		
<5	61	66
5–9	20	22
10–16	6	6
Not evaluable (<60 Gy)	6	6
Docetaxel consolidation		
Number of cycles		
3	34	37
2	12	13
1	13	14
0	34	34

TABLE 3. Acute Toxicity in Chemoradiotherapy (n = 93)

	Grade			
Toxicity	3	4	3 + 4	%
Leukopenia	54	18	72	77
Neutropenia	33	29	62	67
Anemia	21	0	21	23
Infection	15	1	16	17
Esophagitis	11	0	11	12
Hyponatremia	11	0	11	12
Anorexia	9	1	10	11
Nausea	5	—	5	5
Pneumonitis	3	0	3	3
Syncope	2	0	2	2
Hyperkalemia	2	0	2	2
Ileus	0	1	1	1
Cardiac ischemia	1	0	1	1

TABLE 4. Acute Toxicity in Consolidation Therapy ($n = 57$)

Toxicity	Grade 3	Grade 4	Grade 3 + 4	%
Leukopenia	33	11	44	77
Neutropenia	24	26	50	88
Anemia	5	0	5	9
Infection	5	1	6	11
Esophagitis	2	0	2	3
Anorexia	1	0	1	2
Pneumonitis	2	2	4	7

death was observed in four (4%) patients. Of these, three received docetaxel, and one did not. The reason for death was pneumonitis in all patients. We calculated a V_{20} (the percent volume of the normal lung receiving 20 Gy or more) on a dose–volume histogram in 25 patients. Of these, five patients developed grade 3 or severer radiation pneumonitis. A median V_{20} for these five patients was 35% (range, 26–40%), whereas that for the remaining 20 patients was 30% (range, 17–35%) ($p = 0.035$ by a Mann–Whitney test).

Objective Responses, Relapse Pattern, and Survival

All 93 patients were included in the analyses of tumor response and survival. Complete and partial responses were obtained in 5 (5%) and 71 patients (76%), respectively, for an overall RR of 81.7% (95% CI, 72.7–88.0%). Stable and progressive diseases occurred in 12 (13%) and 5 (5%) patients, respectively. With a median follow-up period of 29.7 months, 38 patients developed locoregional recurrence, 32 developed distant recurrence, 4 developed both locoregional and distant recurrences, and 19 did not. The median progression-free survival time was 12.8 (95% CI, 10.2–15.4) months (Figure 3). Two patients underwent salvage surgery for a recurrent primary tumors. Conventional chemotherapy and gefitinib monotherapy were administered after recurrence in 20 and 25 patients, respectively. The median overall survival time was 30.4 (95% CI, 24.5–36.3) months. The 1-, 2-, and 3-year survival rates were 80.7, 60.2, and 42.6%, respectively. (Figure 4).

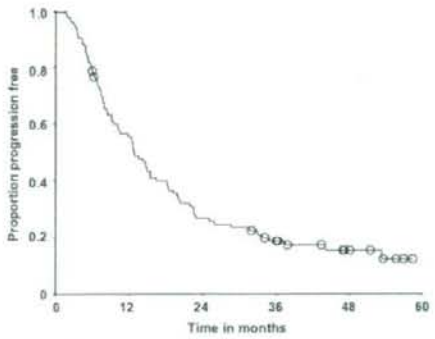

FIGURE 3. Progression-free survival ($n = 93$). The median progression-free survival time was 12.8 (95% CI, 10.2–15.4) months.

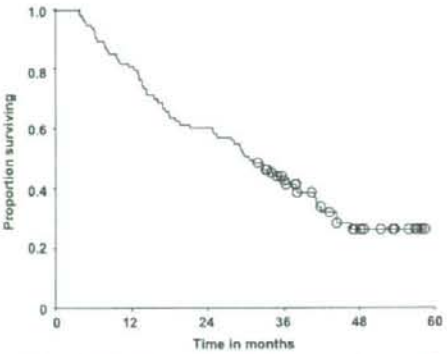

FIGURE 4. Overall survival ($n = 93$). The median overall survival time was 30.4 (95% CI, 25.4–35.4) months. The 1-, 2-, and 3-year survival rates were 80, 60, and 40%, respectively.

DISCUSSION

This study showed that concurrent chemoradiotherapy with cisplatin, vinorelbine, and standard thoracic radiotherapy was well tolerated, with a high completion rate exceeding 80%. The incidence of acute toxicity, including 67% (62/93) of grade 3 or 4 neutropenia, 12% (11/93) of grade 3 esophagitis, and 3% (3/93) of grade 3 pneumonitis, were comparable with other reports of concurrent chemoradiotherapy.[3,4,10] In contrast, consolidation docetaxel could be administered in only 59 of 93 (63%) patients eligible to participate in this study. Of the remaining 34 patients, 22 (65%) patients did not receive consolidation chemotherapy because of toxicities affecting various organs. Other studies also showed that not all patients proceeded to the consolidation phase after completion of concurrent chemoradiotherapy: 61 to 78% of patients after two cycles of cisplatin and etoposide with radiotherapy,[3,10] and 54 to 75% of patients after weekly carboplatin and paclitaxel with radiotherapy.[14,15] Thus, for 20 to 40% of the patients, concurrent chemoradiotherapy was as much as they could undergo, and the additional chemotherapy was not practical.

Furthermore, the number of patients who fulfilled the three cycles of consolidation docetaxel was only 34 (58%) of the 59 patients, which corresponded to only 37% of those eligible in this study. The reason for the termination of docetaxel in the 25 patients was toxicity in 18 (72%) patients, especially pneumonitis in 14 (56%) patients. The grade of pneumonitis during the consolidation phase was within grade 2 in most cases, and this was probably because docetaxel was discontinued early. Considering that pneumonitis associated with cancer treatment is more common in Japan, docetaxel consolidation is not thought to be feasible in the Japanese population. The MST and the 3-year survival rate in all eligible patients were 33 months and 44% in this study, but docetaxel consolidation was unlikely to contribute to these promising results because only 37% of patients received full cycles of docetaxel. This contrasts clearly with the result of

the SWOG study S9504, a phase II trial of two cycles of cisplatin and etoposide with thoracic radiation followed by three cycles of docetaxel. In this trial, 75% of patients starting consolidation and 59% of those entering the trial received full cycles. In addition, docetaxel consolidation seemed to prolong survival, although this was drawn from a retrospective comparison of the results between the two SWOG studies S9504 and S9019.[10]

There is no widely used definition of consolidation therapy following chemoradiotherapy. Given that consolidation therapy is arbitrarily defined as chemotherapy with three cycles or more after the completion of concurrent chemoradiotherapy, only one randomized trial is available in the literature. The randomized phase III trial of standard chemoradiotherapy with carboplatin and paclitaxel followed by either weekly paclitaxel or observation in patients with stage III NSCLC showed that only 54% of patients proceeded to randomization, and overall survival was worse in the consolidation arm (MST, 16 versus 27 months).[15] Thus, there have been no data supporting the use of consolidation therapy, especially when a third-generation cytotoxic agent such as paclitaxel and vinorelbine is incorporated into concurrent chemoradiation therapy.

The low complete-response rate of 5% in this study may be explained partly by an inability to distinguish between inactive scarring or necrotic tumor and active tumor after radiotherapy. Positron emission tomography (PET) using 18F-fluorodeoxyglucose showed a much higher rate of complete response than conventional CT scanning and provided a better correlation of the response assessment using PET with patterns of failure and patient survival.[16] In addition, the high locoregional relapse rate in this study clearly showed that the conventional total dose of 60 Gy was insufficient. Three-dimensional treatment planning, omission of elective nodal irradiation, and precise evaluation of the gross tumor volume by PET may facilitate the escalation of the total radiation dose without enhanced toxicity.

In conclusion, cisplatin and vinorelbine chemotherapy concurrently combined with standard thoracic radiotherapy and followed by docetaxel consolidation produced promising overall survival in patients with stage III NSCLC, but the vast majority of patients could not continue with the docetaxel consolidation because of toxicity.

ACKNOWLEDGMENTS

We thank residents and staff doctors in the National Cancer Center Hospital, National Cancer Center Hospital East, and Tochigi Cancer Center for their care of patients and valuable suggestions and comments on this study. We would also like to thank Fumiko Koh, Yuko Yabe, and Mika Nagai for preparation of the manuscript.

This study was supported in part by Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan.

REFERENCES

1. Vokes EE, Crawford J, Bogart J, et al. Concurrent chemoradiotherapy for unresectable stage III non-small cell lung cancer. *Clin Cancer Res* 2006;11:5045s–5050s.
2. Auperin A, Le Pechoux C, Pignon JP, et al. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. *Ann Oncol* 2006;17:473–483.
3. Fournel P, Robinet G, Thomas P, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupeqqfrancaisqqqq de Pneumo-Cancerologie NPC 95-01 Study. *J Clin Oncol* 2006;23:5910–5917.
4. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17:2692–2699.
5. Curran W, Scott CJ, Langer C, et al. Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemo-radiation for patients with unresected stage III NSCLC: RTOG 9410. *Proc Am Soc Clin Oncol* 2003;22:621 (abstr 2499).
6. Sekine I, Noda K, Oshita F, et al. Phase I study of cisplatin, vinorelbine, and concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer. *Cancer Sci* 2004;95:691–695.
7. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol* 2000;18:2354–2362.
8. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000;18:2095–2103.
9. Fossella FV, Lee JS, Shin DM, et al. Phase II study of docetaxel for advanced or metastatic platinum-refractory non-small-cell lung cancer. *J Clin Oncol* 1995;13:645–651.
10. Gandara DR, Chansky K, Albain KS, et al. Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. *J Clin Oncol* 2003; 21:2004–2010.
11. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92: 205–216.
12. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989;10:1–10.
13. Armitage P, Berry G, Matthews J. Survival analysis. In Armitage P, Berry G, Matthews J (eds.), *Statistical Methods in Medical Research* (4th ed.). Oxford: Blackwell Science Ltd, 2002, pp. 568–590.
14. Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol* 2006;23:5883–5891.
15. Carter D, Keller A, Tolley R, et al. A randomized phase III trial of combined paclitaxel, carboplatin, and radiation therapy followed by either weekly paclitaxel or observation in patients with stage III non-small cell lung cancer. *Proc Am Soc Clin Oncol* 2006;22:635s (abstr 7076).
16. Mac Manus MP, Hicks RJ, Matthews JP, et al. Metabolic (FDG-PET) response after radical radiotherapy/chemoradiotherapy for non-small cell lung cancer correlates with patterns of failure. *Lung Cancer* 2006; 49:95–108.