Table 2 Barriers to the provision of home care

Category/ Subcategory	General practitioners' (GPs') comments
① Concerns about skills	
Pain control	
	No clinical experience of opioids, although I am certified to administer them.
	No clinical experience of continuous subcutaneous injection of opioids, although I have administered oral and suppository opioids.
	Can't distinguish between different dosage forms such as patches, oral capsules and suppositories, since I don't use opioids in daily practice at all.
	Skills and knowledge related to palliative care and pain control are scarce in this area.
	Recent experience has made me realize that I need to gain more knowledge and skills related to pain control.
Other skills	
	I have no confidence in such treatments as gastronomic feeding and at-home IVH, since I have had no clinical experience of them. The increasing number of incident reports also discourages me from attempting them.
② Concerns about support and collaborative relationships with core hospitals	
Hospital backup in emergencies	
	There is no hospital support once a patient is discharged.
	Backup hospital beds for use in emergencies are would encourage home care service.
	The biggest concern patients' families have about home care is the lack of emergency beds in core hospitals available if there is a sudden change in the patient's condition.
	Access to a hospital pain control unit should be retained even when a patient is receiving care at home from a GP.
Availability of palliative care specialists for consultation	
	Consultation services should be provided by a core hospital; at present, they aren't.
	GPs in the area need ready access to hospital palliative care specialists.
Lack of hospital-clinic cooperation	
	Patients are seldom referred back to GPs after treatment at a core hospital.
	Few patients are referred to GPs after treatment at a core hospital.
	Hospitals refer patients to GPs too late: detailed information about patients should be shared, starting right after a surgery.
	A good patient-physician relationship should be established before the terminal care starts.
	Patients tend to be discharged too late: 2-3 months is a desirable home care period.
	One hospital referred a patient to me just before the patient died.
③ Readiness of patients, their families, and society as a whole to accept home care	
Lack of understanding about home care	
	It is questionable whether families actually prefer homecare.
	Families feel insecure when a relative is discharged from the hospital.
	The concept of home care at the terminal stage of an illness is not well accepted by society.
	It is difficult to build up a good trusting relationship with patients' families, as they tend to rely more on hospital specialists.
	Families are sometimes criticized by their neighbors for keeping very sick relatives at home.
	Communicating with a patient's family, especially when they are not living together, is difficult.
Loss of confidence in the home care system when the patient's condition changes	
	There is a tendency for families to request hospital admission for a relative right before death.
	Family members tend to give up at toward the very end.
	Families get worn out if of the patient's discharge from the hospital is not timed carefully.
	Even when families want to care for their relatives at home, they lose confidence as the illness becomes advanced.

Table 3 Possible measures to promote the involvement of general practitioners (GPs) in palliative care

1) Training and seminars
- Seminars or conferences at which GPs and hospital specialists can discuss the appropriate timing of discharge are necessary.
- I want to learn the necessary skills to carry out procedures like continuous subcutaneous injection of opioids and nephrostomy.
- I think I would be able to deal with such procedures as continuous subcutaneous injection and nephrostomy if I were trained; I just happen not to have received training.
- Doctors with different specialties focus on different issues, so seminars that can bring all the specialties together need to be organized.
- I would like to attend seminars on useful procedures such as IVH and continuous subcutaneous injection.
- Training is needed for all professionals, including home care nurses and care givers.

2) Good relationships between hospital doctors and GPs
- I want to enter into detailed discussion with hospital specialists as soon as the patient is diagnosed.
- Time is needed to build up a relationship with a patient, so hospitals should provide more information in advance of the patient's discharge.
- Networks are needed to establish close relationships between GPs and hospital specialists.
- Hospitals providing cancer treatment and GPs should collaborate to provide good care.
- Besides a reply to my referral letter, I want to know details about the progress of my patients after operations or treatment in the hospital.

3) Support from hospital palliative care team
- The core hospital should be ready to treat any patient who needs emergency pain control at any time.
- The core hospital and the 3 other hospitals in this area should cooperate to support patients according to the stage of their disease and symptoms.
- The first step is to establish a system which enables hospitals to discharge their patients so that they can receive care at home, and the second step is to establish a back-up system for emergencies.

4) Group practice
- It is impossible for one doctor to be available 24 hours a day. Three doctors working as a group can take care of more patients, but there are very few doctors who are prepared to cover nights.
- Group practice widens the range of care and treatment that can be provided.
- I think group practice and medical networks are effective, but my clinic is a long way from the city.
- Group practice requires trusting relationships among member doctors. We need to establish a system of group practice as the norm.

5) Education of patients, families and citizens
- Whether the family is ready to deal with it is the key to whether a patient can die at home.
- Some families prefer to communicate only with hospital doctors. Patients and their families need to be better educated about medical services.
- Education about health and disease prevention is also important in this area.
- Citizens need to be engaged in frank discussions about life and death.
- It may take a long ted to change citizens' perceptions of and attitudes toward home care.

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Original Article

Present situation of pTNM classification in Japan: Questionnaire survey of the pathologists of *Gan-shinryo-renkei-kyoten Byoin* (local core cancer hospitals) on pTNM classification

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pTNM classification is the most important element of surgical pathology. Internationally, the International Union against Cancer (UICC)-TNM is the standard TNM classification. In the present study questionnaires about the pTNM were sent to the pathology divisions of 288 institutions designated as *Gan-shinryo-renkei-kyoten Byoin* (local core cancer hospitals) on the basis of the *Cancer Control Act*. The questionnaire consisted mainly of questions about the TNM. There were 78 respondents, including 70 qualified pathology specialists, with a mean of 18.4 years of experience. The recognition rate of the important basic rules of the UICC-TNM were as follows: 'When in doubt, select the lower': 63.6% (49/77); 'Direct invasion to a lymph node is an N component': 61.0% (47/77); 'Only the extension of an invasive cancer is a T component': 45.5% (35/77). Few respondents knew the UICC criteria for judging whether multiple pulmonary lesions represent metastatic or multiple primary lesions. Only 26 (36.4%) of 77 pathologists were informed about cTNM routinely, suggesting that neither pathologists nor clinicians possess adequate knowledge about pTNM classification in many institutions. It is recommended that pathologists be informed about the rules and importance of pTNM through education, the revised Japanese classification of cancers, and self-assessment of their own institutes.

Key words: lung cancer, pTNM, stage, International Union against Cancer, uterine cervical cancer

The International Union against Cancer (UICC)-TNM classification (UICC-TNM) was developed by the UICC in cooperation with the American Joint Committee on Cancer (AJCC).[1–3] UICC-TNM is used internationally as the standard TNM classification. TNM and stage, a grouping of combined T, N and M according to vital risk, are essential for both research and intervention.[1,2] In Japan, cancer staging is reported on the basis of *Gan-toriatsukai-kiyaku*s (Japanese classification of cancers: JC) for each tumor site in most institutes, which are also based on TNM system.

To be designated as *Gan-shinryo-renkei-kyoten Byoin* in Japan (local core cancer hospitals: LCCH), the *Cancer Control Act* requires LCCHs to perform hospital cancer registration. The registration is conducted using the UICC-TNM classification system.

In Japan little attention has been paid to the pTNM, although it is the most important component of surgical pathology. The handling of surgical specimens and the reporting of pathology findings are conducted in compliance with the JC at most institutes in Japan. JC is very useful for standardizing pathology reports, particularly for cancers of the stomach and large intestine.[4] Each JC is independent, however, and therefore the stage classification is conducted according to separate individual criteria. The absence of common rules may allow a pathologist to apply the criteria for the organ that they diagnose daily to other organs; for example, applying the criteria for a gastric cancer to a uterine cervical cancer. JC rarely have written criteria about points that are difficult to judge. JC have no help desk to respond to users' questions. In addition, JC cannot be used for international research or reporting because it consists of domestic rules. The UICC-TNM represents the international system. It has general rules and additional rules. The same rules are fundamentally used for all organs.[5] The UICC-TNM has a supplement book and a frequently asked questions (FAQ) section, and detailed rules are established according to various situations.[3] When stagers have further questions, the help desk can be contacted on the Web.[6] The same

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definitions used for the UICC-TNM have now been adopted for the TNM classification in various JC, for example thyroid cancer, the cancer of the head and neck, renal cancer, lung cancer, ovarian cancer and so on.

In the present study we administered a questionnaire survey (including quizzes) on pTNM classification to the pathologists of LCCH. The questions pertained to knowledge of the TNM classification itself and to the TNM staging of lung cancer. Although the survey was conducted only in Japan, it may be interesting for pathologists and other medical professionals abroad, because there have been no prior reports of questionnaire surveys of pathologists from cancer hospitals on the pTNM classification.

MATERIALS AND METHODS

Questionnaires on pTNM were sent to 288 LCCH in Japan that had been approved by 2007. The version that was translated into English and the summaries of the answers are shown in Tables 1–7. In the original Japanese version the inquiries did not have any number, but sequential numbers were then assigned for the purpose of the report. The major questions were about lung cancer because (i) the texts on TNM of the Japanese *Classification of Lung Cancer* by the Japan Lung Cancer Society (JCLC) are almost the same as those of the UICC-TNM;[7] (ii) the pTNM classification is complex;[1,2] (iii) lung cancer is an important cancer, because it is the leading and second leading cause of mortality in male and female subjects, respectively, in Japan;[10] and (iv) we assessed the pitfalls of the lung cancer pTNM classification in our previous study (N. Teramoto, R. Nishimura, H. Takahata, S. Sawada, T. Shinkai, unpubl. data, 2007).

RESULTS

We obtained 78 responses from 70 institutes by fax or mail. Each response was independent. The data from the authors' hospital (Shikoku Cancer Center) were not included. One response was not included in the total because it was a completely blank paper. In one response there were no answers to the questions pertaining to lung cancer because the response was from a pathologist of an institution that did not treat lung cancer patients. For 78 responses, the standard error at a risk rate of 0.05 is ±6.7% with a response rate of 10%/90%, ±8.9% with 20%/80%, and ±11.0% with 50%. For example, if 20% of 78 respondents selected answer A, it is estimated that 11.1–28.9% of the pathologists in Japan would select answer A at a risk rate of 0.05. Tables 1,2 list the questions and answers about the respondents themselves and institutions. Table 3 lists the questions and answers about the present situation of surgical pathology diagnoses at their institutions. Tables 4–7 outline the quizzes about and answers to the TNM classification. The correct answers to these quizzes are shown in bold underlined letters. The mean number of correct answers by correspondents to 19 of 20 questions was 9.4 ± 3.6 (1–17), excluding V-1, which was a subjective question.

Table 1 Section I: Inquiry about the respondents themselves

	Total
1. How many years have passed since you became a pathologist?	
Average: 18.4 years (0–40 years)	78
2. Are you a certified pathologist?	
Yes: 70 No: 8	78
3. What is your position at your institute?	
Full-time pathologist : 73, Part-time pathologist: 5	78
4. How do you rate your level of knowledge about lung cancer?	
Specialist: 2; Familiar: 4; average: 53; Little experience: 19	78
5. Do you think that you received enough education about TNM during your residency as a pathologist?	
Yes: 1 No: 70 No opinion: 7	78
6. Do you think you have attended a sufficient number of courses at academic conferences or workshops to learn about TNM?	
Yes: 1 No: 75 No opinion: 2	78

Table 2 Section II: About the respondents' institutions

	Total
1. How many beds are at your institute?	
average: 612 beds, (300–1200)	77
2. How many pathologists are working at your institute?	
average: 2.89 (1–16)	77
1 pathologist/institute: 16	
2 pathologists/institute: 21	
3. How many operated lung cancer specimens do you examine per year?	
Average: 63.4 (0–200)	75
4. How many operated uterine cervical cancer specimens do you examine per year?	
Average: 29.8 (0–130)	74

Respondents and institutions

There were 78 respondents with a mean length of experience of 18.4 years (Tables 1,2). Most of the 73 respondents were full-time specialists in pathology. Only one pathologist indicated that he had received satisfactory education about pTNM during his training to become a pathologist. Another indicated that he had received it at academic meetings.

Present status of surgical pathology diagnosis

Although pTNM is defined as a modification of cTNM on the basis of pathological findings, only 26 respondents (33.8%)

Table 3 Section III: Present status of pathological diagnosis of surgical specimens

		Total (*n*)
1. Do clinicians inform about cTNM on most cases?		
Yes: 26; No: 34; IDK: 17		77
2. Who classifies the T of pTNM of lung cancer?		
Pathologist: 55; Clinician: 20, Tumor registrar: 0; IDK: 2		77
3. Who classifies the M of pTNM of lung cancer?		
Pathologist: 9; Pathologist if possible: 29; Clinician in most cases: 29; Tumor registrar: 2; IDK: 7		77
4. Do you separately indicate the UICC-pTNM and JCLC-pTNM?		
UICC-TNM and JCLC separately	9	77
Only JCLC-TNM	38	
Only UICC-TNM	2	
Neither	17	
5. Who sections the surgical specimens?		
Pathologist: 67; Pathologist with surgeon: 4; Surgeon: 4; Laboratory technician: 2		76
6. Can you refer to the results of intraoperative lavage cytology while making a pathological diagnosis?		
Yes: 69 No: 7		76
7. Is the size of the lung cancer measured?		
Yes: 72 No: 5		77
7a. In the case of 'Yes', who determines the size?		
Pathologist: 62; Surgeon: 5; Pathologist with surgeon: 4; Laboratory technician: 1		72
7b. If the answer is 'No,' what is done instead?		
Transcription of the clinical size: 1; Size is not recorded in the report: 4		5
8. When is the tumor size measured?		
Size is measured on the gross examination of surgical specimens	43	77
Size is determined by mapping in the cut-out figure.	12	
Determination in HE specimens	9	
Not measured	5	
Others	7	
9. Do you routinely prepare tissue sections for screening of metastases to the peribronchial lymph nodes in the hilar region, in addition to preparing sections of the lymph node specimens collected separately?		
Yes: 49 No: 28		77
10. When pleural invasion is suspected, is the site of maximal invasion always excised?		
Yes: 76 No: 1		77
11. How is intrapulmonary metastasis from primary cancer of the lung differentiated from multiple primary lesions?		
Differentiated according to the UICC-AJCC criteria	8	76
Differentiated on an individual basis, but I know the UICC-AJCC criteria.	4	
Differentiated on an individual basis. I do not know the UICC-AJCC criteria.	42	
Not differentiated	15	
Others	7	

AJCC, American Joint Committee on Cancer; IDK, I do not know (includes no answer); JCLC, Japanese Classification of Lung Cancer; UICC, International Union against Cancer.

Table 4 Section IV: Quizzes concerning general knowledge of UICC-TNM

	% of correct answers	*n*	Ref
1. When in doubt between T1 and T2, T2 is chosen from the point view of benefit of the patient.			
Yes: 11, **No: 49**, IDK: 17	63.6	77	5
2. Direct invasion of cancer to the lymph nodes is regarded as an N component.			
Yes: 47, No: 17, IDK: 13	61.0	77	1,5
3. When cancer cell spillage into the body cavity occurs during the surgical procedure, the case is regarded as M1.			
Yes: 0, **No: 54**, IDK: 23	70.1	77	1,5
4. In patients in whom preoperative chemotherapy was efficient, pT is judged from the spread of the cicatricial tissue.			
Yes: 10, **No: 42**, IDK: 25	54.5	77	1,5
5. All primary malignant tumors (excluding hematopoietic neoplasms) of the tumor sites that have UICC-TNM classification can be classified according to TNM classification.			
Yes: 33, **No: 20**, IDK: 24	26.0	77	1,2,5

Bold underlined, correct answers. Ref: reference providing evidence for the correct answer.
IDK, I do not know; 'no response' was totalized as IDK; UICC, International Union against Cancer.

Table 5 Section Va: Quizzes concerning UICC-TNM of lung cancer

		% of correct answers	*n*	Ref
1. It is stated in the JCLC that TNM is the same as UICC-TNM for lung cancer.				
Yes: 14 No: 17 IDK: 46		—	77	1,2,7
2. It is stated in the AJCC staging manual that AJCC-TNM is the same as UICC-TNM for lung cancer.				
Yes: 13, No: 3, IDK:61		16.9	77	1
3. TNM in the Japanese Classification of Lung Cancer is the same as UICC-TNM.				
Yes: 27, **No: 17**, IDK: 33		22.1	77	1,3,7
4. Bronchioloalveolar carcinoma (BAC) is now defined as a non-invasive tumor according to the WHO tumor classification. Thus, how is pT of BAC classified?				
pTis	18	53.9	76	6,8
pT1	8			
The maximum diameter of the BAC is measured, and pT is decided from the size (diameter).	41			
Others	9			
5. The UICC-TNM supplement says that 'When size is the criterion for the cT/pT category, the size is the measurement of invasive component.' Then, how is pT decided in the case of infiltrating cancer with BAC (e.g. in the case of mixed BAC and papillary adenocarcinoma)?				
pT1	2	59.2	76	6,8
Only the size of the infiltrating cancer excluding BAC is measured to determine the T.	22			
The size including the BAC is measured to determine the pT.	45			
Others	7			
6. Pleural invasion is a T component. What are the criteria for T2 among the following?				
Extension to a site near the visceral pleura	1	43.7	77	9
Invasion of the elastic lamina of the visceral pleura.	31			
Exposure of tumor cells to the visceral pleural surface	37			
Invasion of the parietal pleura	2			
Others	6			
7. Microscopic examination of the lung cancer specimens revealed small cancer nodules at a site distant from the main tumor, which were not detected macroscopically. Both cancer nodules were pure papillary adenocarcinomas, composed of invasive cancer alone.				
Regarded as intrapulmonary metastasis	35	11.7	77	1
Not regarded as intrapulmonary metastasis	9			
Cannot say for certain without actual observation of the specimens under a microscope	29			
Others	4			

Bold underlined, correct answers. Ref: reference providing evidence for the correct answer.
IDK, I do not know. 'No response' was in totalized as IDK in 1–3 and omitted in 4–7.
AJCC, American Joint Committee on Cancer; IDK, I do not know (includes no answer); JCLC, Japanese Classification of Lung Cancer; UICC, International Union against Cancer; WHO, World Health Organization.

answered that they were informed about the cTNM by clinicians in most cases (Table 3). There were 20 respondents who indicated that they did not judge the pT by themselves (III-2). There were 71 respondents (93.4%) who indicated that they performed sectioning of surgical specimens by themselves (III-5). Fifteen respondents, however, indicated that the lung tumor size for determining T was not determined by pathologists, including five respondents who indicated that the size was not measured on pathological specimens (III-7). Twenty-eight respondents (36.4%) indicated that they do not prepare specimens of peribronchial lymph nodes from the hilar region, which are the first targets of lymph node metastasis of lung cancer (III-9).

Answer validation of the quizzes

Section IV: Quizzes concerning general knowledge of UICC-TNM

Section IV includes questions on general knowledge of the UICC-TNM (Table 4). When there is a doubt, the tumor must be classified into the lower category according to the UICC-TNM general rule No.4 (IV-1).[5] It is also an important rule of the UICC-TNM that direct invasion to lymph nodes is regarded as the N component (IV-2).[5] Neither of the two rules is specified in any of the JC. The correct answer rates were 63.6% and 61.0%, respectively, but considering that these questions had two choices, the number of pathologists who had sufficient knowledge for the rules will be much smaller. ypT is judged from the actual existing tumor, not from the cancer scar (IV-3).[1,5] Tumor spillage during surgery has no influence on the TNM of tumors except for ovarian tumors (IV-4).[1,5] Carcinoid, sarcoma and melanoma, as well as hematopoietic tumors, are excluded from the TNM classification in most tumor sites (IV-5) because they do not have a similar prognosis as the carcinomas of the same TNM.[1,2]

Section Va: Quizzes concerning UICC-TNM of lung cancer

Section Va includes questions about the TNM classification of lung cancer (Table 5). In the JCLC it is implied but not written clearly that the JCLC-TNM and UICC-TNM are the same.[7] We do not know the correct answer to V-1, but JCLC-

Table 6 Section Vb: Quizzes concerning intrapulmonary metastasis and size of lung cancer

	% of correct answers	*n*	Ref
Questions 8–12. Choose the case in general terms. A clue: Questions 8, 9 and 12 refer to the presence of cancer nodules in the same lobe, and questions 10 and 11 refer to the presence of cancer nodules in different lobes.			
8. Two tumor lesions not adjacent to each other were visualized at the time of preoperative CT. Examination of tissue specimens from both tumors revealed the same histological type of adenocarcinoma. The smaller node does not have BAC around it. If the smaller lesion is regarded as intrapulmonary metastasis, the case would be evaluated as pT4pN0cM0 and stage IIIB. If it is not regarded as intrapulmonary metastasis, the case would be evaluated as pT1pN0cM0 and stage IA. Which of the evaluations is valid?			
Regarded as intrapulmonary metastasis: 61			
Not regarded as intrapulmonary metastasis: 10	13.2	76	1,6
Others: 5			
9. Under the same conditions as those in Question 8, metastasis was detected in the #12 lymph node alone. If the smaller lesion is regarded as intrapulmonary metastasis, pT4pN1cM0 and stage IIIB. If it is not regarded as intrapulmonary metastasis, pT1pN1cM0 and stage IIA.			
Regarded as intrapulmonary metastasis: 59			
Not regarded as intrapulmonary metastasis: 8	78.7	75	1,6
Others: 8			
10. Under the same conditions as those in Question 8, metastases were detected in the #12 lymph node alone. If the smaller lesion is regarded as an intrapulmonary metastasis, pT1pN1pM1 (PUL) and stage IV. If it is not regarded as an intrapulmonary metastasis, pT1pN1cM0 and stage IIA.			
Regarded as intrapulmonary metastasis: 49			
Not regarded as intrapulmonary metastasis: 16	21.1	76	1,6
Others: 11			
11. Under the same conditions as those in Question 8, metastases were detected in #7 lymph node alone. If the smaller lesion is regarded as an intrapulmonary metastasis, pT1pN2pM1 (PUL) and stage IV. If it is not regarded as an intrapulmonary metastasis, pT1pN2cM0 and stage IIIA.			
Regarded as intrapulmonary metastasis: 54			
Not regarded as intrapulmonary metastasis: 11	71.1	76	1,6
Others: 11			
12. Under the same conditions as those in Question 8, metastasis was detected in the liver. If the smaller lesion is regarded as an intrapulmonary metastasis, pT4pN0cM1 (HEP) and stage IV. If it is not regarded as an intrapulmonary metastasis, pT1pN0cM1 and stage IV.			
Regarded as intrapulmonary metastasis: 61			
Not regarded as intrapulmonary metastasis: 8	80.3	76	1,6
Others: 7			
13. The size measured by CT was 3.2 cm, while the size after fixation at the time of resection was 2.8 cm. The lesion is evaluated as cT2, but pT is evaluated as pT1.			
Yes: 56, No: 11 IDK: 10	72.7	77	5
14. The size measured after fixation was 3.2 cm, while the size in the HE specimen was 2.8 cm.			
Yes: 12 **No:54** IDK: 11	70.1	77	5

Bold underlined, correct answers. Ref: reference providing evidence for the correct answer.
BAC, Bronchioloalveolar carcinoma; IDK, I do not know; 'no response' was totalized as IDK.

Table 7 Section VI: Quiz concerning extension of intra-epithelial component

	Answer
1 The extension of cervical cancer to the portio supravaginalis is a factor for classification as T2a in cases of cervical squamous cell carcinoma;	
a In the presence of histological evidence of carcinoma *in situ*, the lesion is evaluated as pT2a, if vaginal extension is suspected macroscopically.	5
b In the presence of histological evidence of carcinoma *in situ*, the lesion is evaluated as pT2a, even if vaginal extension is not suspected macroscopically.	32
c **When evidence of invasive squamous cell carcinoma of the vagina is present histologically, it is evaluated as pT2a, even if vaginal involvement is not suspected macroscopically.**	35
d When vaginal involvement is suspected macroscopically, the lesion is evaluated as pT2a, even if evidence of carcinoma in situ is absent histologically.	0
e When vaginal involvement is suspected macroscopically, the lesion is evaluated as pT2a, even if evidence of infiltration is absent histologically.	0
No answer	5

The correct answer is c. The percentage of correct answers was 45.5%. Four respondents marked letters a–c together. They were dealt with as 'b' because b includes all the conditions.

TNM is distinctly different from UICC-TNM on minor rules (V-3).[1–3] For example, see the answer for V-6 in the next paragraph. AJCC-TNM and UICC-TNM of lung cancer are identical (V-2). UICC and AJCC worked together to make the same TNM system for all organs in the sixth edition,[1] although there are small numbers of minor differences.

It is plausible to evaluate bronchioloalveolar carcinoma (BAC) as pTis, because it is now defined as a non-invasive carcinoma.[11,12] It is also plausible to measure the size from the invasive component alone according to the principles of UICC-TNM.[5] At the moment, however, BAC is exceptionally regarded as an invasive cancer in UICC-TNM (V-4, -5).[6,8] The T2 criterion of JCLC-TNM requires complete exposure of the tumor cells to the visceral pleural surface,[7] while that of UICC-TNM includes the invasion of the elastic lamina (V-6).[9] The frequency with which JCLC-T1 is UICC-T2 depends on the patients who undergo surgery at each institution. At Shikoku Cancer Center, for example, JCLC-T1 is UICC-T2 according to the criterion in approximately 5% of patients (N. Teramoto, R. Nishimura, H. Takahata, S. Sawada, T. Shinkai, unpubl. data, 2007). Microscopic nodules that cannot be confirmed macroscopically or radiologically, are not evaluated as intrapulmonary metastases (V-7).[1,5] The correct response rate was only 11.7%. The criteria of intrapulmonary metastasis are summarized in Table 8.

Section Vb: Quizzes concerning intrapulmonary metastasis and size of lung cancer

Questions V-8–12 include questions about the differentiation of intrapulmonary metastasis from multiple primaries (Table 6). These questions were offered with the sentences 'You may think that you cannot choose a correct answer without checking the actual specimens. But please select an answer that fits best to the rules in general terms'. The UICC-TNM FAQ section says 'A 2-cm primary adenocarcinoma with multiple deposits of adenocarcinoma in another lobe, negative lymph nodes and no other metastasis is M1' (Table 8).[9] But this is a cancer showing multiple deposits. According to the AJCC staging manual, a subject with 2 nodules can be regarded as having intrapulmonary metastasis if at least one of the following three criteria is met: (i) lymph node metastasis of the common lymphatic drainage; (ii) mediastinal metastasis; or (iii) extrathoracic metastasis (Table 8).[1] Therefore, case V-8 with N0M0 is not regarded as intrapulmonary metastasis (pT1N0M0).

Intrapulmonary metastasis within a lobe is T4, while that in different lobes is M1(PUL). Because case V-9 is T4N1M0 or T1N1M0, it is certain that two nodules were in the same lobe. Therefore, the metastasis to lymph node 12 (lobar nodes bronchi) is in a common lymphatic drainage. Case V-9 can be regarded as intralobular pulmonary metastasis (pT4N1M0) according to criterion A. In contrast, case V-10, pT1N1M1(PUL) or pT1N1M0 is a multiple primary case because the case involved two nodules in different lobes and lymph node 12 is not in common lymphatic drainage. None of the A-C criteria are met in case V-10 (pT1N1M0). Case V-11 with N2 (mediastinal metastasis) can be regarded as intrapulmonary metastasis even if the node is present in different lobes (criteria A and B; pT1N2M1). Case V-12 with distant metastasis is M1(PUL) due to criterion C (pTN0M1). The correct answer rates for V-8 and V-10 (right answer: 'Not regarded as intrapulmonary metastasis') were very low (Table 6). The right answer rates for V-9, -11, and -12 (correct answer: Regarded as intrapulmonary metastasis) were high, probably because 44 (57.9%) of the 76 respondents answered all the cases as intrapulmonary metastasis.

When pT is determined by tumor size, the size of unfixed material is used first, the size of a fixed tumor as next best if measurement of unfixed material is impossible, and the size on preparatory slides is used as a last resort (V-13, -14).[5,6] The size measured on CT is not used as the pathology size if the actual size of a pathology specimen can be measured.

Section VI: Quiz concerning extension of intra-epithelial component

This question was submitted as a quiz concerning uterine cervical cancer to conceal the fact that this question was actually about the extension of an intra-epithelial component. In general, the extension of an intra-epithelial component does not change the T (VI-1).[5,6] The correct answer to this question was given by 35 (45.5%) of the 77 respondents (Table 7).

Table 8 Criteria of intrapulmonary metastasis

Description	Ref
Microscopic nodules that are not found radiologically or macroscopically are not regarded as intrapulmonary metastasis.†	1,5
A primary adenocarcinoma with *multiple deposits* of adenocarcinoma in another lobe, with/without lymph nodal and/or distal metastasis is M1.‡	9
Two separate nodules are not likely to be metastatic without any of the following‡	1,6
A Lymph node metastasis of the common lymphatic drainage	
B Mediastinal metastasis	
C Extrathoracic metastasis.	

†This rule is written in the AJCC staging handbook, Part IV. It is based on UICC-general rule No. 5.

‡Note that the rule for multiple deposits and that for two (or a few) nodules are different. The former will also be true for carcinomas other than adenocarcinoma. The latter is described only in the AJCC staging handbook but is also valid on UICC-TNM.[6]

AJCC, American Joint Committee on Cancer; IDK, I do not know (includes no answer); JCLC, Japanese Classification of Lung Cancer; UICC, International Union against Cancer.

DISCUSSION

Questionnaires were sent to the pathologists working in LCCH. When considering the mean number of beds (approx. 600) and the mean number of pathologists (approx. three; Table 2), and that these pathologists belonged to LCCH, the responders handle many cancer cases routinely. Because there were only 78 respondents, there was a standard error of approximately 10%, but the purpose of the questionnaire survey was not to precisely estimate the correct answer rate from the population. We consider the results of this questionnaire survey sufficient to represent Japanese pathologists' knowledge about pTNM. As shown by this questionnaire survey, there is insufficient knowledge about the UICC-TNM among pathologists in Japan, but we expected these results.

It is noteworthy that the percentage of correct answers to questions concerning the following important criteria was only approximately 60%, despite the fact that the question presented two choices: for example, 'When it is difficult to judge TNM, the lesion is classified into the lower category' (IV-1), 'direct invasion of the lymph node is an N component' (IV-2) and so on (Table 4). It was even less recognized that the extension of a non-invasive component of a carcinoma does not raise T (Table 7).

Because pTNM classification is assigned by modification of cTNM based on the pathological findings,[3] pTNM classification without information on the cTNM makes little sense. In >60% of the institutions, however, the pathology division was not informed on the cTNM by the clinical divisions, suggesting that not only pathologists, but also the majority of clinicians give little importance to evaluating the pTNM of the pathological specimens (Table 3). Judging whether multiple pulmonary lesions are multiple primary tumors or multiple metastases changes the stage of a lung cancer considerably. According to III-11, the differential diagnosis between intrapulmonary metastatic tumors versus multiple primary tumors is not based on the UICC-AJCC criteria or on any other common criteria, but rather on individual judgment in most institutes (Table 3). The results of judgment based on the UICC-AJCC criteria are not always the most appropriate in actual clinical cases. It is not justified, however, for each pathologist to decide pTNM on their own individual criteria, without knowing the common criteria. Because staging is based on the surveys of TNM and prognosis at many institutions, it is not possible to stage a case without using common criteria shared among institutions.[1,2] Accumulating information on cancers precisely staged on common criteria is essential to improving the reliability of the TNM system in the future.

When a pathologist explains the pathological findings of a cancer to a patient directly in the pathologist's office, pTNM assumes great importance, because it is the most important prognostic predictor. The prognosis is the major concern of patients. Appropriate sectioning of a surgical specimen is impossible without comprehension of the pTNM classification. Wrong pTNM will lead to deviations of cTNM. It goes without saying that pTNM classification must be determined by the pathologists who make the pathological diagnosis, not by clinicians or tumor registrars who do not actually examine the specimens.

The results of the questionnaire survey indicated the faults of the surgical pathology system in Japan. For the establishment of evidence-based medicine, pTNM must be standardized. TNM classification itself is not difficult (according to our experience from unpublished data). The certification test for a pathology specialist in Japan should include questions to test knowledge of TNM. Because most responders answered that they had not been educated about TNM at all, education through training sessions at conferences might also be useful. Most JC cite the texts of UICC-TNM of the organs, but the basic rules of UICC-TNM, which TNM stagers should know before use, are not described. The JC needs to include information explaining the importance of staging, a detailed explanation of the UICC-TNM, and a list of reference books.

In addition to questionnaire surveys, investigating the accuracy of actual recorded pTNM is necessary to determine whether the pTNM is being correctly used. The present survey was performed in Japan. It is not certain how much pathologists in other countries know about the rules of pTNM. It is recommended that the accuracy of pTNM be investigated to assure the quality assurance of pathological diagnoses.

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Baclofen as an Adjuvant Analgesic for Cancer Pain

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Purpose: Baclofen is a γ-aminobutyric acid receptor agonist commonly used for managing many types of neuropathic pain. The effect of baclofen on cancer pain has not previously been studied. This retrospective study evaluated the efficacy of baclofen in patients with cancer pain.

Methods: We reviewed the medical records of all patients given baclofen orally as an analgesic for cancer at 5 institutions.

Result: Twenty-five patients received 10 to 40 mg of baclofen for cancer pain relief. Twenty patients have undergone neuropathic pain such as paroxysmal or lancing, sharp, or like an electric shock. Baclofen was effective in 21 of 25 patients and significantly reduced Numeric Rating Scale (pain score, 0-10; $P < .0001$). Nine patients reported mild adverse events: none of these 9 patients had to discontinue baclofen due to adverse events.

Conclusion: Our findings suggest that baclofen may be a useful adjuvant analgesic in the treatment of cancer pain.

Keywords: baclofen; $GABA_B$; cancer pain; adjuvant analgesic; neuropathic pain; paroxysmal pain; Lioresal

Introduction

Baclofen is a γ-aminobutyric acid (GABA) derivative with an antispasmodic action and is used as a central acting muscle relaxant. GABA is a suppressive neurotransmitter widely distributed in the peripheral and central nervous systems.[1] GABA receptors have been classified into 3 subtypes to date, that is, $GABA_A$, $GABA_B$, and $GABA_C$ receptors,[2] and baclofen is considered to show its antispasmodic activity by activating $GABA_B$ receptors.[3]

In addition, baclofen has been reported since 1975 to produce an analgesic effect by systemic administration in various experimental pain models,[4-7] and it has also been reported to be clinically effective for the management of neuropathic pain such as trigeminal neuralgia[7-11] and headache.[12,13]

Concerning the analgesic mechanism of baclofen, inhibition of Ca^{2+} channels via $GABA_B$ receptors,[14] inhibition of the release of pain-causing agents such as substance P from the posterior horn of the spine,[7] direct inhibition of posterior horn neurons,[15] and inhibition of pain transmission in the thalamus[16] have been reported. Also, as the analgesic effect of baclofen is antagonized by $GABA_B$ antagonists but not by naloxone or $GABA_A$ antagonists, it is considered to be mediated selectively by $GABA_B$ receptors.[6] Moreover, baclofen, a $GABA_B$ receptor agonist, has been reported to show suppressive effects on allodynia and hyperalgesia in various neuropathic pain models.[17,18] In addition, because $GABA_B$ receptors are widely distributed in the central nervous system and Aδ and C fiber nerve terminals

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Table 1. Ramsay Sedation Score[21]

Ramsay Sedation Score
1. Awake: anxious and agitated or restless or both
2. Awake: co-operative, orientated, and tranquil
3. Awake: responds to commands only
4. Asleep: brisk response to a light glabellar tap or loud auditory stimulus
5. Asleep: sluggish response to a light glabellar tap or loud auditory stimulus
6. Asleep: no response to a light glabellar tap or loud auditory stimulus

Table 2. Support Team Assessment Schedule[22]—Evaluation of Nausea[a]

0 None.
1 Occasional or grumbling single or few symptom(s). Patient can pursue usual activity and is not bothered by symptoms.
2 Moderate distress, occasional bad days, symptoms limit some activity due to extent of disease.
3 Severe symptom(s) often present. Activities and concentration markedly affected by symptom(s).
4 Severe and continuous overwhelming symptom(s). Unable to think of other matters.

[a] Japanese version of the STAS (STAS-J) was used in this study to evaluate nausea.

involved in pain sensation, baclofen is expected to be effective as an analgesic.[19]

Furthermore, baclofen is mentioned as an adjuvant analgesic in the Guidelines for the Treatment of Cancer Pain by the Japanese Society for Palliative Medicine.[20]

However, there have been few reports evaluating the usefulness of baclofen in the management of cancer pain. In this study, we investigated patients that were administered baclofen for cancer pain at multiple facilities and evaluated its usefulness.

Methods

Participants

From February 2003 to May 2006, all patients administered baclofen (Lioresal or gabalon) for cancer pain on palliative care wards or by the palliative care teams of 5 facilities (8 patients at 2 facilities and 5, 3, and 1 patient at 1 facility each) were reviewed. The exclusion criteria were as follows.

- The dose of a nonsteroidal anti-inflammatory drug (NSAID), acetaminophen, or opioid was increased within 24 hours prior to the administration.
- The dose of an adjuvant analgesic was increased within 72 hours prior to the administration.
- The patient is receiving radiotherapy for palliation of pain.
- Chemotherapy was performed within 2 weeks prior to the administration.

Baclofen was used with oral consent by the patients at each facility because the management of cancer pain using baclofen is not covered by insurance.

Evaluation

The charts of the patients were reviewed retrospectively. At each facility, the physicians participating in this study investigated the age and gender of the patients, cause of pain, pain occurrence pattern, nature of the pain, and drugs being administered for the palliation of pain. Pain intensity was evaluated using a numeric rating scale (NRS, 0-10), sleepiness using the Ramsay Sedation Score (RSS; Table 1),[21] and nausea using a Japanese version of the Support Team Assessment Schedule (STAS-J;Table 2).[22] Other adverse events were also evaluated. These evaluations were performed on the basis of the records on the day before the beginning of baclofen administration and on the day after its administration at a maintenance dose.

In this study, a 50% or greater reduction in pain on the NRS was regarded as "effective". A 30% reduction in pain was also reported.

These evaluation methods were agreed on by the physicians participating in this study.

Statistical procedures

Pain evaluated using the NRS before and after baclofen administration was compared using Wilcoxon's signed rank test. SPSS ver.12.0 was used for statistical analyses.

Results

Background

The subjects were 25 patients, consisting of 11 men and 14 women aged 46 to 77 years (mean, 63 years). Tables 3 and 4 show all participants. The cause of pain was spinal metastasis and pelvic plexus invasion

Table 3. Characteristics of Patients and Pain

Patient	Age	Sex	Origin of Cancer	Cause of Pain	Characteristics of Pain	
1	52	F	Uterine cervix	Lumbosacral plexopathy	PAP	lancinating
2	74	M	Sacrum(chordoma)	Lumbosacral plexopathy	PAP	lancinating
3	58	F	Lung	Chest wall invasion	PAP	lancinating
4	59	M	Prostata	ESCC	PAP	sharp
5	77	M	Parotid gland	Cervical plexopathy	PAP	sharp
6	62	F	Lip (ACC)	Chest wall invasion	PAP	ESL
7	56	M	Lung	Bone metastasis	PAP	ESL
8	54	F	Hypopharynx	Glossopharyngeal neuralgia	PAP	lancinating, sharp, ESL
9	59	M	Colon	ESCC	PAP	dull
10	63	F	Lung	Chest wall invasion	PAP	dull
11	68	M	Renal pelvis	Retroperitoneal tumors invasion	PAP	dull
12	46	F	Colon	ESCC	PAP, PEP	lancinating
13	70	M	Lung	Bone metastasis	PAP, PEP	lancinating
14	61	M	Thalamus	Thalamic pain	PAP, PEP	lancinating, sharp, ESL, tingling
15	72	F	Uterine	Lumbosacral plexopathy, Bone metastasis	PAP, POP	sharp, tight
16	64	F	Uterine cervix	Lumbosacral plexopathy	PAP, PEP, POP	sharp
17	54	F	Pseudomyxoma peritonei	Lumbosacral plexopathy	PAP, PEP, POP	ESL, tingling
18	61	F	Breast	Brachial plexopathy	PEP	ESL, tingling, tight
19	73	M	Lung	ESCC	PEP	tingling
20	71	F	Malignant lymphoma	ESCC	PEP	tingling
21	64	F	Multiple myeloma	ESCC	PEP	tight
22	54	F	Lung	Chest wall invasion	PEP	tight
23	67	F	Hypopharynx	Cervical plexopathy	PEP	tight, dull
24	79	M	Lung	Chest wall invasion	PEP, POP	lancinating, tight
25	57	M	Rectum	Lumbosacral plexopathy	POP	lancinating, sharp

Abbreviations: ACC, adenoid cystic carcinoma; ESCC, epidural spinal cord compression; PAP, paroxysmal pain; PEP, persistent pain; POP, postural pain; ESL, electric shock-like.

in 6 each, thoracic wall invasion in 5, neck invasion in 3, bone metastasis in 2, and brachial plexus invasion, celiac plexus invasion, and thalamic pain in 1 each. The pain occurrence pattern was paroxysmal in 17, sustained in 12, and associated with body movements in 5 (some patients showed 2 or more pain occurrence patterns). The pain types were "lancing" in 8, "sharp" in 7, "electric shock-like" in 6, "numbing" in 5, "squeezing" in 5, and "dull" in 4 (some patients showed 2 or more pain types).

Opioid was used in 19 patients. Among other drugs with analgesic effects, NSAIDs were used in 21, acetaminophen in 7, and adjuvant analgesics in 12 (Table 4).

Doses of baclofen

The median initial dose (per day) was 10 mg (5-30 mg) in 1-3 divided doses (5 or 10 mg each), and the median maintenance dose (/day) was 20 mg (10-40 mg) in 2 to 4 divided doses (5 or 10 mg each; Table 5). In 9 cases the initial dose was the same as the maintenance dose. In the other 16 cases, the dose was increased every second day.

Analgesic effect

Of the 25 patients, 84% (21 patients) had 50% or greater pain reduction on NRS which include 30% in pain reduction (Table 5). The NRS rating improved significantly ($P < .0001$) after compared with before the administration (Figure 1).

Adverse events

Sleepiness appeared in 6 patients (24%). The RSS was 2 (no sleepiness) in all these patients before the administration, but became 3 after the administration. Baclofen administration was discontinued in 2 of the 6 patients who complained of sleepiness, because pain was not alleviated. Baclofen was not

Table 4. Co-medication

Patient	Opioid (mg)	NSAIDs	Acetaminophen	Adjuvant Analgesics (mg)
1	TDF (7.5)	+	+ (2400)	-
2	TDF (20), Mor (60)	+	+ (1800)	Lidocaine (240)
3	TDF (2.5)	+	-	VPA (100)
4	Oxy (50)	+	-	IFEN (180), CZP (1)
5	-	+	-	-
6	TDF (60)	+	+ (3000)	IFEN (120), CZP (1), VPA (1200), MEX (300)
7	Oxy (40)	+	+	-
8	TDF (22.5)	+	-	-
9	Oxy (30)	+	-	CZP (1)
10	Oxy (150)	+	-	CZP (1)
11	Oxy (15)	+	-	-
12	I.V.Oxy (110), TDF (17.5)	+	-	Ketamine (100)
13	Oxy (15)	+	-	Ketamine (150)
14	-	-	-	CBZ (400)
15	Oxy (20)	+	-	-
16	-	-	-	-
17	-	-	-	CBZ (200), MEX (300)
18	-	+	-	-
19	TDF (10)	+	+ (2400)	IFEN (120), CZP (1) VPA (400)
20	Mor (30)	-	-	-
21	TDF (65), Oxy (440)	+	+ (3000)	IFEN (180), CZP (1), VPA (1200), FLE (150)
22	Oxy (80)	+	+	-
23	-	+	-	-
24	Oxy (10)	+	-	-
25	Oxy (80)	+	-	-

Abbreviations: CBZ, carbazepine; CZP, clonazepam; FRE, flecainide acetate; IFEN, ifenprodil tartrate; I.V. Oxy, I.V. oxycodone infusion; MEX, mexiletine hydrochloride; Mor, oral morphine; Oxy, oral oxycodone; TDF, transdermal fentanyl; VPA, sodium valproate.

discontinued or reduced in the other patients, in whom the administration was effective.

Nausea deteriorated in 2 patients, in whom the STAS-J score increased from 1 to 3 at 10 mg. Nausea was alleviated by the administration of an antiemetic (diphenhydramine·diprophylline in 1, risperidone in 1), and baclofen was not discontinued or reduced. In the 2 patients who complained of nausea before the administration (Patients 15 and 18), the level of nausea remained unchanged after the administration.

Lower limb weakness was noted in 1 patient, but a reduction or discontinuation of baclofen was unnecessary.

Administration period

The administration was discontinued with death due to progression of cancer in 9 of the 21 patients in whom baclofen was effective. In the remaining 12 patients, the administration was still being continued as of June 30, 2006. The median administration period in the 21 patients was 114 days (25-1606 days; Table 5).

Discussion

This retrospective study suggested the usefulness of baclofen as an adjuvant analgesic for the control of cancer pain. There has been no report on the analgesic effect of baclofen against cancer pain according to our review of the literature.

Baclofen has been reported to be effective for the control of paroxysmal, lancing, sharp, and electric shock–like pain of trigeminal neuralgia.[8,9,23] There were also a few reports stating that baclofen has been effective for the management of neuropathic pain in conditions such as tabes dorsalis, postherpetic neuralgia,[10,24] and glossopharyngeal neuralgia.[25] On the other hand, there have also been a small number of reports in which it showed no marked effect on pain due to diabetic neuropathy or spinal postherpetic neuralgia.[24] Clinical reports on the systemic

Table 5. Results of Oral Baclofen Administration

Patient	Baclofen		NRS		RSS		Other side effect	Treatment Duration (Days)
	Initial Dose (mg/day)	Final Dose (mg/day)	Pre-baclofen Pain Score (0-10)	Post-baclofen Pain Score (0-10)	Pre-baclofen	Post-baclofen		
1	15	25	5	2	2	2	nausea (STAS-J: 1 II 3)	83
2	15	30	8	0	2	2		100
3	5	10	6	3	2	2		200
4	20	20	8	8[a]	2	3[b]		28
5	15	30	6	2	2	3[b]		50
6	5	15	6	0	2	2		730
7	10	40	6	0	2	2		26
8	10	20	8	2	2	2		171
9	10	10	4	0	2	2		25
10	10	10	5	5[a]	2	2	Nausea (STAS-J: 1 II 3)	4
11	10	10	5	0	2	2		151
12	10	10	6	3	2	2		108
13	10	10	3	0	2	2		110
14	30	30	7	0	2	3[b]		690
15	10	20	10	3	3	3		1606
16	10	20	10	0	2	2		127
17	20	20	7	2	2	3[b]		44
18	10	30	7	7[a]	2	3[b]		7
19	5	15	7	1	2	3[b]		61
20	5	15	10	0	2	2		114
21	15	30	6	2	2	2		410
22	10	20	4	4[a]	2	2		22
23	15	30	5	2	2	2	Leg weakness	602
24	15	15	3	1	2	2		102
25	10	20	6	2	2	2		191

Abbreviations: NRS, Numeric Rating Scale (Pain score, 0-10); RSS, Ramsay Sedation Score; STAS-J: Japanese version of the Support Team Assessment Schedule.

[a] Case not showing analgesic effect.

[b] Case showing sleepiness.

administration of baclofen have been limited, and sufficient evaluation of pain types in which it is effective is impossible, but many reports have been concerned with neuropathic pain. In this study, consecutive patients administered baclofen were sampled, but this sampling was biased by the physicians' selection of patients, precluding evaluation of the types or nature of pain that can be effectively controlled by the agent. However, baclofen was found to be effective when it was administered to patients with neuropathic pain, such as that caused by pelvic plexus invasion, so that it is also likely to be effective for neuropathic cancer pain. In animal experiments, baclofen administered with opioid was reported to enhance the analgesic effect of opioid,[2] and baclofen is expected to be more useful for the management of cancer pain, for which opioid administration is a basic treatment. Many patients administered baclofen in this study complained of paroxysmal pain and lancing, sharp, or electric shock–like pain, which were interestingly in agreement with the types of non-cancer pain against which baclofen has been reported to be used. To evaluate the types of pain against which baclofen is more effective, prospective studies free of bias concerning the cause or nature of pain are necessary.

There is no established method for the administration of baclofen against cancer pain, but reports of its use against neuropathic pain, which has primarily been trigeminal neuralgia, were useful as references. Baclofen administration is often started at 10 to 30 mg/day, and, while observing the patients

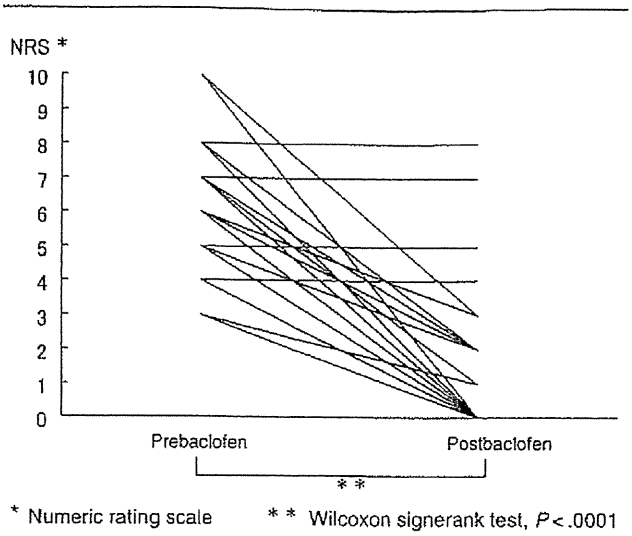

Figure 1. Changes in numeric rating scale (NRS) pain score. NRS was reduced in 21 of 25 patients.

for the analgesic effect and side effects, the dose is increased by 10 mg at a time to 80 mg. The maintenance dose is about 30 to 60 mg/day. The dose is increased every day, every 2 days, 2 times a week, or once a week.[8,9,13,23-25] It took about 2 hours for peak circulating concentration to take effect after oral baclofen was administered, and the half-life was 3 to 4 hours.[26,27] In addition, baclofen is mostly excreted in urine in an unmetabolized form, and about 80% is excreted within 24 hours. In this study, the effects of the drug were evaluated on the day after the administration, and both the analgesic effect and side effects could be evaluated the next day. Although its clearance rate is high, cancer patients, who may develop renal dysfunction during the course, must be carefully observed for side effects due to decreases in its excretion.

Of the 25 patients evaluated in this study, 50% or greater improvements in the condition on the NRS were observed in 21 by administering baclofen at an initial dose of 5 to 30 mg/day and increasing the dose to 40 mg depending on the symptoms. Therefore, the maintenance dose that was 10 mg or higher was considered to be appropriate as an initial dose.

Further, side effects such as sleepiness and gastrointestinal symptoms can be alleviated by starting baclofen administration at a low dose and increasing the dose slowly. The frequency of the occurrence of intolerable side effects despite these measures has been reported to be 10%.[7] Therefore, starting the administration at a lower dose is considered to be a method to reduce side effects, even if no sufficient analgesic effect is expected at that dose. A practical interval of dose increases would be 1 day if no side effect is observed and several days to 1 week if there are side effects.

The doses in the patients who showed no change in pain on the NRS were 10 mg in 1, 20 mg in 2, and 30 mg in 1. Because the analgesic effect of baclofen is dose-dependent,[5,9,18] a desirable analgesic effect might have been obtained by increasing the dose. However, no further increase was possible, because sleepiness appeared in 1 patient each at 20 mg and 30 mg.

Sleepiness, weakness, and nausea are generally reported as problematic side effects. In this study, sleepiness was observed in 6 of the 25 patients, but they all wished to continue the use of baclofen, and there was no discontinuation or decrease of baclofen administration due to sleepiness. Discomfort caused by sleepiness varies among individuals. On using baclofen, it is important to pay attention to sleepiness and discomfort of the patients and to increase the dose by monitoring the state of pain.

Animal experiments have indicated that baclofen prevents nausea due to opioids.[2] Clinically, however, gastrointestinal symptoms and nausea/vomiting have been reported as side effects of baclofen administration.[8,10,11] In this study, nausea deteriorated in 2 patients, and no antiemetic effect of the administration was noted in patients who had nausea from before the administration. Bcause both patients complained of nausea before baclofen administration, it was considered to have been unrelated to baclofen administration.

Because baclofen is a muscle relaxant, weakness is a side effect that requires particular attention. However, weakness was noted in only 1 patient in this study.

In this study, sleepiness, nausea, and weakness were noted as adverse events, but they did not lead to a decrease or discontinuation of the administration of baclofen, and the drug was used safely in general.

In the patients evaluated in this study, the maximum duration of administration was 1606 days. Because the treatment of spastic paralysis is often prolonged, baclofen is likely to be administered over a long period. For these reasons, baclofen is generally regarded as a highly tolerable drug for long-term use.

These observations suggest that baclofen can be an alternative adjuvant analgesic for the management of cancer pain.

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