Table 3. Relationship between metastatic status of 14v and that of other regional lymph nodes with univariate analysis

a Perigastric lymph nodes

	1 (2,430)		2 (1,000)		3 (2,464)		4sa (909)		4sb (2,000)		4d (2,472)		5 (2,362)		6 (2,481)	
	–	+	–	+	–	+	–	+	–	+	–	+	–	+	–	+
14v–	1,851	303	736	141	1,147	1,039	718	68	1,595	165	1,443	749	1,910	170	1,369	823
14v+	177	99	75	48	41	237	102	21	192	48	81	199	213	69	26	263
p value[1]	<0.001		<0.001		<0.001		<0.01		<0.001		<0.001		<0.001		<0.001	
Odds ratio	3.41		3.34		6.38		2.17		2.41		4.73		3.63		16.83	

b Extra-perigastric lymph nodes

	7 (2,462)		8a (2,471)		9 (2,458)		11p (1,795)		12a (1,669)		16 (928)	
	–	+	–	+	–	+	–	+	–	+	–	+
14v–	1,788	399	1,756	431	1,835	342	1,388	222	1,417	52	642	144
14v+	137	138	93	191	117	164	91	94	161	39	47	95
p value[1]	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
Odds ratio	4.51		8.37		7.52		6.46		6.6		9.01	

Values in parentheses indicate available number. [1] Correlations were analyzed with a logistic regression analysis.

Table 4. Relationship between metastatic status of 14v and that of regional LNs and clinicopathological factors with multivariate analysis

Factors		Relative risk	95% CI	p
Tumor location	low/non-low	–	–	NS
Depth of invasion	MP or deeper/ M, SM	–	–	NS
P	+/–	–	–	NS
CY	+/–	–	–	NS
H	+/–	–	–	NS
1	+/–	–	–	NS
2	+/–	3.27	1.32–8.15	<0.05
3	+/–	–	–	NS
4sa	+/–	–	–	NS
4sb	+/–	–	–	NS
4d	+/–	–	–	NS
5	+/–	3.02	1.26–7.25	<0.05
6	+/–	6.42	2.02–20.41	<0.01
7	+/–	–	–	NS
8a	+/–	–	–	NS
9	+/–	–	–	NS
11p	+/–	–	–	NS
12a	+/–	–	–	NS
16	+/–	–	–	NS

Correlation was analyzed with a logistic regression analysis. CI = Confidence interval; NS = not significant; low = region including the lower third of the stomach.

Lymphatic drainage from any specific point has a preferred pathway [17–19]. There are mainly 3 lymphatic flows in the region of lower stomach, the lines of flow from 3 or 5 to 8a, from 6 to 8a and from 6 to 14v, and all the lymphatic flows reach 16, which then joins the thoracic duct (fig. 3) [20]. Lymphatic metastasis is believed to spread according to the lymphatic flow of the site of the primary tumor [21]. LN 6 is anatomically upstream of 14v in the lymphatic flow. In fact, the metastatic status of 14v was found to be most strongly influenced by that of 6 among clinicopathological factors in the present study (table 3, 4). Furthermore, the 6 status showed an extremely low false-negative rate (1.9%) for 14v metastasis. These findings are consistent with the above theory of stepwise lymphatic metastasis, and demonstrate that the 6 status can predict the absence of 14v metastases. Namely, 6 is the sentinel LN for 14v. It should be emphasized that 6 is a clinically effective and useful indicator for a 14v dissection, so that when the 6 status is found to be negative by intraoperative pathological examinations, a 14v dissection, which is associated with a risk of bleeding, can be safely avoided.

As expected, the patients with 14v metastasis had a high risk of recurrence and poor prognosis (table 2; fig. 2a, d). It should be noted that the 5-year survival rate of the patients with 14v metastasis was low in comparison

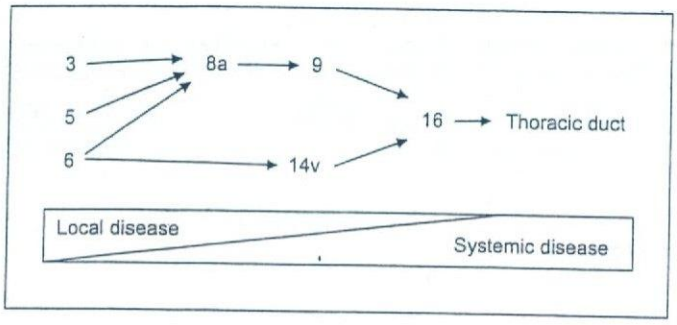

Fig. 3. The model of stepwise progress of LN metastasis according to lymphatic flow from the lower stomach.

to that with 6 metastasis, but it was similar to that with 16 metastasis which is classified as stage IV in the Japanese Classification [13], indicating systemic metastases (fig. 2a, b, c). Moreover, 14v metastases were correlated with metastases to 16 next to 6 and non-curative factors such as P, CY, and H (table 3). These results indicate that most patients with 14v metastasis are already in the state of systemic disease. However, we found as well that, in the patients with 14v metastasis, the 16-positive group had a significantly lower rate of overall survival than the negative group, although the difference was small (fig. 2e). This finding suggests that at least some of the patients with 14v metastasis might not be in the state of systemic disease but in the state of so-called local disease, and therefore could obtain some prognostic benefit from surgery with a 14v dissection. In addition, Sasako et al. [22] also reported that the majority of extra-perigastric LNs including a 14v show evidence of benefit from their dissection using a new method to evaluate the therapeutic value of LN dissection. These findings imply that the state of 14v metastasis indicates either systemic disease or local disease (fig. 3). Clinically, it is important to select patients which can get a prognostic benefit from 14v dissection among those with 14v metastasis. The detection of occult micrometastasis in the blood or bone marrow by molecular-based technique might help in selecting the patients with systemic disease from those with 14v metastasis [23]. Furthermore, a genome-wide analysis of the gene-expression of gastric cancer using a DNA microarray would also shed light on the mechanism of gastric cancer progression [24, 25].

This study showed that advanced gastric cancer with invasion to the lower stomach was likely to metastasize to 14v, and 6-negative status can reliably predict the absence of 14v metastases. Moreover, some patients with 14v metastasis certainly have a chance to be cured by a curative dissection, although most patients with 14v metastasis have a poor prognosis, similar to the patients with systemic metastasis. In other words, in advanced gastric cancer with 6 metastasis, a gastrectomy with D2 including a 14v dissection would be recommended for the grading of tumor stage and a possible cure if the risk of a 14v dissection, such as bleeding, can be sufficiently controlled. Ideally, a randomized controlled study should be performed in order to clarify the significance of a 14v dissection.

Acknowledgements

We are grateful to Drs. T. Nakajima and T. Yamaguchi (Japanese Foundation for Cancer Research, Tokyo, Japan) for permitting the analysis using the Ganken Igan Database 1946–2004, and to Dr. H. Masuda for his critical reading of the manuscript.

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Jpn J Clin Oncol 2008;38(4)296–304
doi:10.1093/jjco/hyn010

Opioid Rotation from Oral Morphine to Oral Oxycodone in Cancer Patients with Intolerable Adverse Effects: An Open-Label Trial

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Received September 14, 2007; accepted February 2, 2008; published online March 7, 2008

Objective: We prospectively investigated the efficacy of opioid rotation from oral morphine to oral oxycodone in cancer patients who had difficulty in continuing oral morphine treatment because of inadequate analgesia and/or intolerable side effects.

Methods: Twenty-seven patients were enrolled and 25 were evaluated. The rate of patients who achieved adequate pain control, which provided an indication of treatment success, was evaluated as primary endpoint. The acceptability and pharmacokinetics of oxycodone were evaluated in addition to the assessment of analgesic efficacy and safety during the study period.

Results: In spite of intense pain, the morphine daily dose could not be increased in most patients before the study because of intolerable side effects. However, switching to oral oxycodone allowed ~1.7-fold increase as morphine equivalent dose. Consequently, 84.0% (21/25) of patients achieved adequate pain control. By the end of the study, all patients except one had tolerated the morphine-induced intolerable side effects (i.e. nausea, vomiting, constipation, drowsiness). Common side effects (>10%) that occurred during the study were typically known for strong opioid analgesics, and most were mild to moderate in severity. A significant negative correlation between creatinine clearance (CCr) value and the trough concentrations of the morphine metabolites was observed. On the other hand, no significant correlation was found between CCr value and the pharmacokinetic parameters of oxycodone or its metabolites.

Conclusions: For patients who had difficulty in continuing oral morphine treatment, regardless of renal function, opioid rotation to oral oxycodone may be an effective approach to alleviate intolerable side effects and pain.

Key words: opioid rotation – morphine – oxycodone – cancer pain – pharmacokinetics

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INTRODUCTION

Oral strong opioid analgesics such as morphine and oxycodone are essential for the treatment of moderate to severe pain, irrespective of which is attributed to cancer or not

Strong opioid analgesics have various pharmacological effects through opioid receptors, including not only analgesia but also nausea, vomiting, drowsiness and constipation, which are regarded as side effects during use for pain relief (1,2). Because of the difficulty in achieving pain relief without side effects at therapeutic dosages, appropriate treatment for side effects is necessary for a favorable balance between pain relief and side effects (1,2). In addition, when strong opioid analgesics are administered, both analgesia and side effects vary from patient to patient (1,2,5). Therefore, dose titration is required to determine the optimum dose for each patient.

The three-step analgesic ladder recommended by the World Health Organization (WHO) has been widely used in cancer pain management (1,6,7), and guidelines based on these steps have also been recommended for the treatment of non-cancer pain (8,9). However, some patients could not attain a favorable balance between pain relief and side effects because of the variability among patients in drug response (10–13). For instance, ~10–30% of the patients who were treated with oral morphine could not attain adequate pain control (10,14). Only a few of these patients are so-called 'morphine-intolerable patients' (1), who could not utterly accept morphine, having little or no effect despite of appropriate treatment for side effects or careful dose adjustment. Even in these patients, however, 'opioid rotation' can be expected to be effective.

Opioid rotation is a method of pain management in which one strong opioid analgesic is switched to another in the treatment of chronic pain when side effects are uncontrollable and/or pain relief is inadequate despite dose titration, or for other reasons (15–18). In clinical settings, when opioid rotation is considered to be better than the appropriate treatment for side effects or careful dose adjustment, it is often adopted according to the patient's disease symptoms, response to the opioids and side effects.

With increased clinical experience in opioid rotation in recent years, opioid rotation has been increasingly recognized as an effective approach in strong opioid medication. Although the efficacy of opioid rotation has been described in various reports and reviews, many of these are based on retrospective studies, and data from prospective clinical studies have still been limited (15,19–22).

We thus conducted these prospective studies to investigate the efficacy and safety of switching from oral morphine to oral oxycodone. These opioids were selected because the WHO guideline recommends use of oral preparations for cancer pain treatment as far as possible (1), and morphine and oxycodone are the only oral strong opioid preparations currently available in Japan.

In addition to the variability in response to opioids among individuals, it is known that increase in oral morphine-induced side effects in patients with renal impairment is caused by accumulation of metabolites, particularly morphine-6-glucuronide (M6G), in the central nervous system (16,23). On the other hand, oral oxycodone-induced side effects are commonly speculated to be less influenced by renal impairment as compared with oral morphine, because the plasma concentration of the active metabolite, oxymorphone, is quite low (24,25). But no study has been conducted to investigate the pharmacokinetics of oxycodone and its metabolites following multiple doses of controlled-release oxycodone hydrochloride tablets (CR oxycodone) in patients with renal impairment, which has become a problem in actual clinical settings. We thus simultaneously conducted another study in patients with renal impairment (Study #1234) in addition to the study in patients without renal impairment (Study #1233).

Both studies were conducted in similar study patients. The study in patients with renal impairment (Study #1234) was designed to investigate the pharmacokinetics after multiple doses of CR oxycodone, but the other aspects of the two studies were similar, adopting the same study designs and major endpoints. Thus, the outcomes of efficacy and safety evaluation from the two studies were basically combined, as presented below.

PATIENTS AND METHODS

Patients

The two studies (Studies #1233 and #1234) were conducted at 14 medical institutions in Japan. Patients were enrolled from February 2004 to December 2005.

The main inclusion criteria were that patients currently used oral morphine for the cancer pain treatment and had been confirmed to have difficulty in continuing oral morphine treatment. A patient was regarded to have difficulty in continuing oral morphine treatment when the patient met any of the following:

(i) At the study enrollment, the pain intensity score self-assessed on a four-point categorical (CAT) scale (0 = no pain, 1 = slight pain, 2 = moderate pain, 3 = severe pain) was two or three (moderate or severe) (26), but dose increase could not be conducted because of intolerable side effect.
(ii) The pain intensity on the CAT scale at the study enrollment was two or three (moderate or severe), but occurrence of intolerable side effects had been confirmed at previous (during seven days prior to the study enrollment) dose increase.
(iii) The pain intensity on the CAT scale at the study enrollment was one (slight pain), but at previous (during 7 days prior to the study enrollment) dose reduction to alleviate intolerable side effects, it was confirmed that pain intensity had increased to two or three (moderate or severe).

'Intolerable side effect' was defined as a persistent side effect which was intolerable for the patient despite appropriate treatments for side effects.

Other inclusion criteria were (i) inpatients aged 20 years or older who were expected to be able to take oral

medication for at least 2 weeks from the study entry and able to keep a patient diary; (ii) patients without moderate or more severe hepatic impairment (ALT and AST $\leq$2.5 times the upper limit of normal); and (iii) in Study #1233, patients without moderate or more severe renal impairment (serum creatinine (Scr) $\leq$1.5 times the upper limit of normal), or in Study #1234 patients with estimated creatinine clearance (CCr), as calculated by the Cockcroft–Gault formula from Scr levels (27), $<$60 ml/min.

Exclusion criteria were (i) patients with a history of hypersensitivity to opioids analgesics; (ii) patients in whom the use of oxycodone or morphine was contraindicated; and (iii) patients who had undergone surgery or a medical procedure for pain over the previous 2 weeks before the study entry or had been scheduled to undergo such treatments during the study period.

On the basis of the success rate (87%) of previous study in patients who had changed their pain treatment from morphine to oxycodone (22), it was estimated that 20 patients including withdrawal would be required to reject null hypotheses (adequate pain control rate: 50%) and accept alternate hypotheses (adequate pain control rate: 85%) by using binomial test with 80% or more power and one-side 2.5% level of significance.

Study Design

Both studies were multicenter, open-label, dose titration studies. CR oxycodone was administered twice daily in the morning and evening as regular doses. Rescue analgesic for breakthrough pain or incident pain was immediate-release oral oxycodone powder (IR oxycodone). CR oxycodone 5 and 20 mg tablets (OxyContin®) and IR oxycodone 2.5 and 5 mg powder were supplied by Shionogi & Co., LTD. (Osaka, Japan).

The initial daily dose of CR oxycodone was individually determined based on the patient's pre-study daily morphine dose using a 3:2 conversion ratio (2,18,28). The dose could be titrated against the intensity of pain. If the patient reported their pain intensity as 'moderate' or 'severe' on the CAT scale or more than three times use of IR oxycodone as rescue dose within a 24-h period, the dose could be titrated with the use of 5 and 20 mg CR oxycodone every 24 h. Conversely, the doses could be reduced if the patients experienced intolerable side effects. Dose titration was continued until an adequate pain control with minimal side effect was obtained. The maximum daily dose of CR oxycodone permitted in both studies was 240 mg. The rescue dose was $\sim$1/6 of the patient's total daily CR oxycodone dose.

In both studies, titration was rated as successful, if adequate pain control was achieved within a maximum 10 days. Study #1233 was completed with achievement of adequate pain control. On the other hand, Study #1234 was completed when blood sampling for PK evaluation of oxycodone was finished on the day after achievement of adequate pain control.

No other opioid analgesics were allowed during the study. New addition of non-opioid analgesics or adjuvant analgesics for pain relief was not allowed during the study. Change in dose regimen or increase in dose of non-opioid analgesics or adjuvant analgesics was not allowed from the day before the study. Anti-side effect agents for morphine-induced intolerable side effects were allowed during the study provided they had been given on a regular basis before the study. Appropriate use of anti-side effect agents for other side effects was allowed. Patients who could attain adequate pain control within 10 days were discontinued.

In both studies, all patients provided written informed consent before the study enrollment, and the study protocols were approved by the institutional review boards at each center before the initiation of the study. Both studies were carried out in compliance with the Good Clinical Practice (GCP) guidelines and the ethical principles stated in the Declaration of Helsinki.

PK Evaluation

In both studies, plasma trough concentrations of morphine and its metabolites were measured in patients while under oral morphine medication before the study treatment. In patients with renal impairment (Study #1234), the pharmacokinetics after multiple dosing of CR oxycodone were also investigated.

Plasma trough concentrations of morphine and its main metabolites, M3G and M6G, were measured in blood samples taken just before a regularly scheduled dosing time. Steady-state plasma concentration of oxycodone and its metabolites, noroxycodone and oxymorphone were measured in blood samples taken just before and at 1, 3, 5, 8 and 12 h after CR oxycodone dosing after achievement of adequate pain control. The PK parameters (C_{max}, maximum plasma concentration; $t_{1/2}$, elimination half-life; AUC, area under the concentration–time curve) were calculated by non-compartmental analysis using WinNonlin™ (Pharsight).

Blood concentrations of morphine, oxycodone and their metabolites were measured by validated liquid chromatography coupled to tandem mass spectrometry (LC/MS/MS).

Endpoints and Measurements

The primary endpoint was adequate pain control rate, i.e. the rate of patients who achieved stable and adequate pain control. Pain control was considered adequate when, over 48 h period, the dose of CR oxycodone was unchanged, the patient rated pain intensity as 'no' or 'slight' on the CAT scale, $\leq$two rescue medication per 24 h, side effects were tolerable for the patient, the dosing regimen of analgesics or adjuvant analgesics were unchanged.

The secondary endpoints included pain intensity and acceptability of therapy. Every morning, patients evaluated the mean pain intensity during the last 24 h on the CAT scale and VAS (Visual Analog Scale: 0–100 mm). At the

same time, they also rated the acceptability of the cancer pain treatment on a five-point CAT scale (1, very poor; 2, poor; 3, fair; 4, good; 5, excellent) and recorded it in their pain diaries.

Safety was evaluated daily on the basis of the frequency, severity, seriousness, causality and tolerability of adverse events. The safety data were obtained from daily clinical symptoms and clinical laboratory tests performed at the start and end of the study. The severity of adverse events was assessed in terms of three grades according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) (29), i.e. Grade 1 = mild, Grade 2 = moderate, and Grade 3 or higher = severe.

Statistical Analyses

Adequate pain control rate was analysed using the Clopper–Pearson method with two-sided 95% confidence intervals. The changes in dose, CAT, VAS, acceptability and intolerable side effects were analysed using the Wilcoxon signed-rank test. The plasma trough concentrations of morphine were analysed using *t*-tests to assess the level of significant difference between Studies #1233 and #1234.

RESULT

Patient Population

Of 27 cancer patients enrolled in these studies (18 patients in Study #1233, 9 in Study #1234), 25 were included in the efficacy population and two were excluded: one was discontinued from the study without intake of the study medication because of worsening of a morphine-induced side effect (delirium), and the other did not meet the inclusion criteria (insufficient treatment for side effects during morphine use). Of the 25 patients in the efficacy population, four patients withdrew from the study because of inadequate pain relief in one patient, adverse event in two patients and consent withdrawn (due to non-preference for taking the rescue medication as powder formulation) in one patient. The safety population included 26 patients except for one patient who was discontinued from the study without intake of the study medication.

The detailed information on patient characteristics in the efficacy population are given in Table 1. As to renal function, which was the major difference between the two studies, Scr (mean ± SD) was lower in Study #1233 (0.7 ± 0.2 mg/dl) than in Study #1234 (1.3 ± 0.7 mg/dl). In Study #1234, to confirm the presence of renal impairment among the patients evaluated for the pharmacokinetics of oxycodone, CCr was also measured using 24 h pooled urine samples after achievement of adequate pain control. As the results, the maximum, the minimum and the mean ± SD of CCr values were 54, 16.9 and 37.2 ± 14.2 ml/min, respect-

Table 1. Patient characteristics of efficacy population

Characteristic	Total ($n = 25$)	Study #1233 ($n = 16$)	Study #1234 ($n = 9$)
Age (years)[a]	62.8 ± 11.6	58.8 ± 10.6	70.0 ± 10.0
Gender			
Male	19	11	8
Female	6	5	1
Weight (kg)[a]	52.8 ± 7.0	52.5 ± 7.9	53.5 ± 5.5
Main inclusion criteria[b]			
a)	22	14	8
b)	0	0	0
c)	3	2	1
Primary site (>10%)			
Lung	6	5	1
Breast	3	3	0
Pancreas	3	2	1
Pain location (>10%)			
Shoulder, upper extremities	4	3	1
Chest	6	4	2
Abdomen	5	3	2
Lumbar	3	2	1
Laboratory test value for renal function[a]			
Scr (mg/dl)	0.9 ± 0.5	0.7 ± 0.2	1.3 ± 0.7
CCr (ml/min)	—	—	37.2 ± 14.2

(a) Pain intensity (CAT) was 'moderate' or 'severe', but dose increase could not be conducted because of intolerable side effect. (b) CAT was 'moderate' or 'severe', but occurrence of intolerable side effects had been confirmed at the previous dose increase. (c) CAT was 'slight pain', but an increase to 'moderate' or 'severe' had been confirmed at the previous dose reduction to alleviate intolerable side effects.
[a]Mean ± SD.
[b]Main inclusion criteria are as follows: at the study enrollment.
Scr, serum creatinine; CCr, creatinine clearance.

Change in Oxycodone Daily Dose

In spite of intense pain, the morphine daily dose could not be increased in most patients before the study enrollment because of their intolerable side effects. However, switching to CR oxycodone allowed an ~1.7-fold significant ($P = 0.0007$) increase in the morphine equivalent dose as compared with the dose just before switching by reducing the severity of side effect (Table 2).

Stable Adequate Pain Control

The adequate pain control rate, which provided an indication of treatment success, was 84.0% (21/25 patients) in total, and the length of time to adequate pain control was 2.3 days.

Table 2. Changes in CR-oxycodone daily doses

	Mean ± SD (mg)		
	Morphine daily dose	Morphine equivalent daily dose[a] (CR oxycodone daily dose)	
	Before switching	First day	Last day
Total ($n = 24$)[b]	44.4 ± 33.8	45.0 ± 33.7 (30.0 ± 22.5)	63.8 ± 40.4 (42.5 ± 26.9)

[a]Converted daily dose of CR oxycodone into morphine.
[b]One patient was excluded from calculation due to receipt of only one dose.

analgesia was inadequate; two patients due to adverse event; and one patient (not detailed below) who withdrew consent.

In the patient that withdrew due to inadequate analgesia, after switching from CR morphine 40 mg/day to CR oxycodone 20 mg/day, a morphine-induced intolerable drowsiness improved but nausea and dizziness newly developed, and no adequate pain relief could be attained in spite of dose titration, leading to discontinuation 4 days after study initiation. This patient subsequently attained pain relief after switching to transdermal fentanyl preparation and addition of NSAID and antidepressant.

Of the two patients that withdrew due to adverse events, one patient had had intolerable constipation, which persisted without improvement even after switching from a controlled-release morphine sulfate tablet (CR morphine) 60 mg/day to CR oxycodone 40 mg/day, and intolerable nausea and vomiting additionally developed. Despite careful dose adjustment, pain control was difficult and CR oxycodone was thus discontinued 3 days after study initiation. This patient subsequently attained adequate pain control after switching to continuous subcutaneous infusion of morphine.

In another patient, after switching from CR morphine 20 mg/day to CR oxycodone 10 mg/day, morphine-induced intolerable nausea and vomiting improved, but severe drowsiness newly developed, leading to discontinuation 2 days after study initiation. After switching to NSAID treatment, the drowsiness resolved and adequate pain control was attained.

Pain Intensity and Acceptability of Treatment

The results of the pain intensity self-assessments on the CAT scale showed that the mean score at the study entry was 1.9 (corresponding to 'moderate pain'), which was found to have significantly decreased to one ('slight pain') at the end of the study ($P = 0.0001$). The pain intensity on the VAS showed a similar tendency to that on the CAT scale, with a significant decrease from 53.5 mm at the study entry to 27.6 mm at the end of the study ($P < 0.0001$).

The acceptability of the treatment was assessed as 'very poor' and 'poor' at the study entry in 12 and 64% of patients, respectively, totaling ~80%. At the end of the

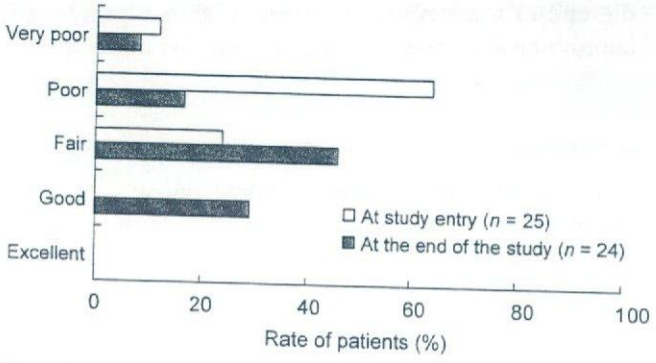

Figure 1. Patients' ratings of the acceptability of therapy at study entry and at the end of the study.

Table 3. Number of patients with intolerable side effects

	Worst value for 7 days before the study enrollment	At the end of study	P value[a]
Nausea ($n = 13$)	13	0	0.0003
Vomiting ($n = 5$)	5	0	0.0253
Constipation ($n = 5$)	5	1	0.1797
Drowsiness ($n = 7$)	7	0	0.0082

[a]Paired t-test.

respectively, while the proportions of 'fair' (45.8%) and 'good' (29.2%) increased (Fig. 1). The mean acceptability score was 2.1 (corresponding to 'poor') at the study entry, and had significantly increased to 3.0 (corresponding to 'fair') at the end of the study ($P = 0.0004$).

Change in Intolerable Side Effects Before and After the Study Treatment

In both of these studies, morphine-induced intolerable side effects, which were the main inclusion criteria, were actually only four types, i.e. nausea, vomiting, constipation and drowsiness. During the observation period prior to the study enrollment, all patients assessed at least one of the four side effects as intolerable. At the end of the study, however, those intolerable side effects became tolerable in all patients except for one patient who had constipation (Table 3).

To confirm the change of tolerability described above, the change in severity score (0, Grade 0; 1, Grade 1; 2, Grade 2; 3, Grade 3 or higher) of each intolerable side effect before the study was compared with that at the end of the study. The mean severity scores for nausea and drowsiness were 2.3 and 2.1, respectively, during the 7-day observation period prior to the study enrollment. At the end of the study, however, the mean scores were found to have decreased to 0.4 and 0.9, respectively, with significant improvement (nausea: $P = 0.0005$, drowsiness: $P = 0.0313$). Vomiting

the end of the study). Constipation showed only a slight improvement, from 2.2 before, to 1.6 at end of the study.

Adverse Events

A total of 139 adverse events occurred among all 26 patients of the safety population. Of these, 76 adverse events in 26 patients were assessed as at least possibly related to the study medication (side effect). Common side effects (>10%) were as follows: constipation in 24 patients (92.3%), drowsiness in 17 (65.4%), nausea in 13 (50.0%), vomiting in 8 (30.8%) and pruritus in 4 (15.4%). Most of the side effects were Grade 1 or 2 in severity. Severe side effects (Grade 3 or 4) occurred in six patients (6/26 patients, 23.1%), specifically: constipation in five patients, drowsiness in 3 and nausea in 1. As detailed above, two patients withdrew form the study due to side effects, one patient due to continued constipation and newly developed nausea/vomiting and one patient due to drowsiness. No death occurred during either of the studies. There was one serious adverse event of thrombocytopenia, which the investigator considered to be caused by disease progression and not related to the study medication.

Newly occurred common side effects (>10%) after switching to CR oxycodone were: vomiting in five patients, drowsiness in four, nausea in four and constipation in four.

Pharmacokinetics

Trough concentrations of morphine and its main metabolites (M3G, M6G) were compared between the two studies (Table 4). Morphine concentrations did not significantly differ between the studies, but the concentrations of M3G and M6G were significantly higher in Study #1234, conducted in patients with renal impairment, than those in Study #1233.

In patients with renal impairment (Study #1234), significant negative correlation was observed between M6G and CCr ($P = 0.0292$). The relationship between trough concentration of M6G and CCr is shown in Fig. 2. M3G also had a significant negative correlation with CCr ($P = 0.0038$), though no correlation was observed between morphine and CCr ($P = 0.5742$).

Pharmacokinetic profile and parameters for oxycodone, its main metabolite (noroxycodone), and active metabolite (oxymorphone) in patients with renal impairment (Study #1234) is shown in Fig. 3 and Table 5, respectively. The AUC_{0-12h} and C_{max} of oxycodone and noroxycodone were comparable. With regard to oxymorphone, however, the C_{max} and AUC_{0-12h} were very low as compared with those of oxycodone, at ~1.4 and 1.7%, respectively. In patients with renal impairment (Study #1234), no significant correlation was observed between C_{max} and AUC_{0-12h} of oxycodone or its metabolites and CCr. The relationship of C_{max} of oxycodone and its metabolites with CCr is shown in Fig. 4.

Table 4. Comparison of trough concentration of morphine and its metabolites between patient with normal renal function (Study#1233) and patient with impaired renal function (Study#1234)

	Mean ± SD (ng/ml)		*P* value[a]
	Study #1233 ($n = 17$)	Study #1234 ($n = 9$)	
Morphine	10.0 ± 10.1	11.3 ± 6.4	0.7345
M3G	384 ± 332	791 ± 373	0.0088
M6G	60.0 ± 51.2	109 ± 44	0.0240

Values were adjusted to 20 mg dose. M3G, morphine-3-glucuronide; M6G,

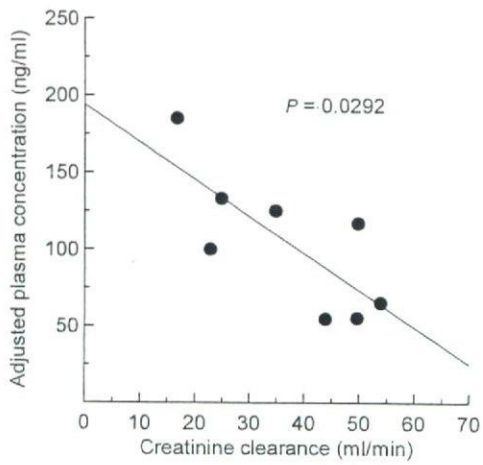

Figure 2. Results of linear regression for dependence of creatinine clearance on trough concentration of morphine-6-glucuronide (adjusted to 20 mg dose, $n = 8$).

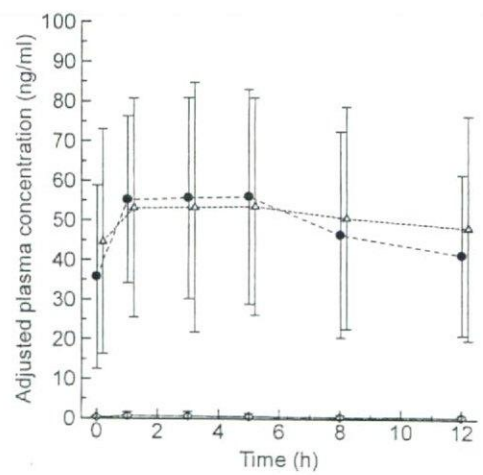

Figure 3. Mean plasma concentration profiles of oxycodone and its metabolites in patients with renal impairment (adjusted to 20 mg dose). Mean ± SD (0–8 h, $n = 7$; 12 h, $n = 5$). Filled circle, Oxycodone, open triangle,

DISCUSSION

We conducted two prospective studies in Japanese cancer patients who had difficulty in continuing oral morphine treatment because of inadequate analgesia and/or occurrence of intolerable side effects in order to investigate the efficacy of the pain management regimen of switching to oral oxycodone. In particular, Study #1234 is the first study conducted to investigate pharmacokinetics of oxycodone and its metabolites at steady-state in patients with renal impairment. In these studies, 'patients who have difficulty in continuing oral morphine treatment' did not always mean 'morphine-intolerable patients' but the patients who could not have favorable pain control by morphine in actual clinical settings.

The primary endpoint in these studies was adequate pain control rate, and the rationale was that cancer pain management with strong opioids is regarded as successful only in the achievement of a favorable balance between pain relief and side effects (10,14).

For study patients who have difficulty in continuing oral morphine treatment, most of the patients could not increase morphine dose despite of intense pain because of intolerable side effects. However, switching to CR oxycodone from oral morphine allowed the dose to increase, while alleviating the side effects. As the result, an adequate pain control rate was 84.0% in total, or above 80% in each study. These results were comparable to those of a previous report in which success rate of opioid rotation from oral morphine to oxycodone was 87% (22), and also similar to success rates of opioid rotation between other strong opioid preparations, e.g. morphine, methadone, hydromorphone, fentanyl (64–87%) (19,20,22). High adequate pain control rate was demonstrated in Study #1234, conducted in patients with renal impairment, as it was in patients without renal impairment in Study #1233. Therefore, it is speculated that switching to oxycodone has decent efficacy in patients who had difficulty in continuing oral morphine treatment, regardless of their renal function.

The acceptability of treatment as a secondary endpoint is also an index of overall assessment of analgesia and side effects by the patients themselves. The acceptability was significantly ($P = 0.0004$) improved from the study entry to the end of the study, which is supportive of the high adequate pain control rate in these present studies. Though two patients rated the acceptability of treatment as 'very poor' (Fig. 1), these assessments were made at the time when both patients withdrew from the study because of failure to attain a favorable balance between pain relief and side effects.

The duration of the efficacy evaluation, until adequate pain control was achieved, was relatively short: ~5 days. In order to investigate whether the efficacy of switching is sustained, an extension study was conducted in patients who attained adequate pain control and consented to continuation of oxycodone treatment. All the 22 patients who attained adequate pain control attended to the extension study (maximum durations of treatment were 260 days) followed by two studies. The extension study was conducted under another protocol and there was no safety issue in relation to longer administration in this study. The pain intensity was maintained around 'slight pain' on the CAT scale. This indicated that the achieved adequate pain control by CR oxycodone was maintained as favorable for long period even in patients who had difficulty in continuing oral morphine treatment (data not shown).

Table 5. Pharmacokinetic parameters of oxycodone and its metabolites following multiple administration of CR-oxycodone

	C_{max}^{a} (ng/ml)	T_{max} (h)	$AUC_{0-12h}^{a,b}$ (ng h/ml)	$t_{1/2}^{b}$ (h)
Oxycodone	61.0 ± 25.1	4.00 ± 2.52	679.0 ± 279.5	9.2 ± 2.6
Noroxycodone	57.1 ± 28.0	3.71 ± 2.21	660.0 ± 372.9	21.2 ± 10.5
Oxymorphone	0.742 ± 1.095	3.86 ± 2.97	8.19 ± 10.57	31.7 ± 20.0

Mean ± SD ($n = 7$).
[a]Adjusted to 20 mg dose.
[b]$n = 5$: Two patients could not be estimated for $AUC_{0-12\,h}$ because of missing concentration data at 12 h after CR oxycodone dosing.
C_{max}, maximum plasma concentration; AUC, area under the concentration–time curve; $t_{1/2}$, elimination half-life.

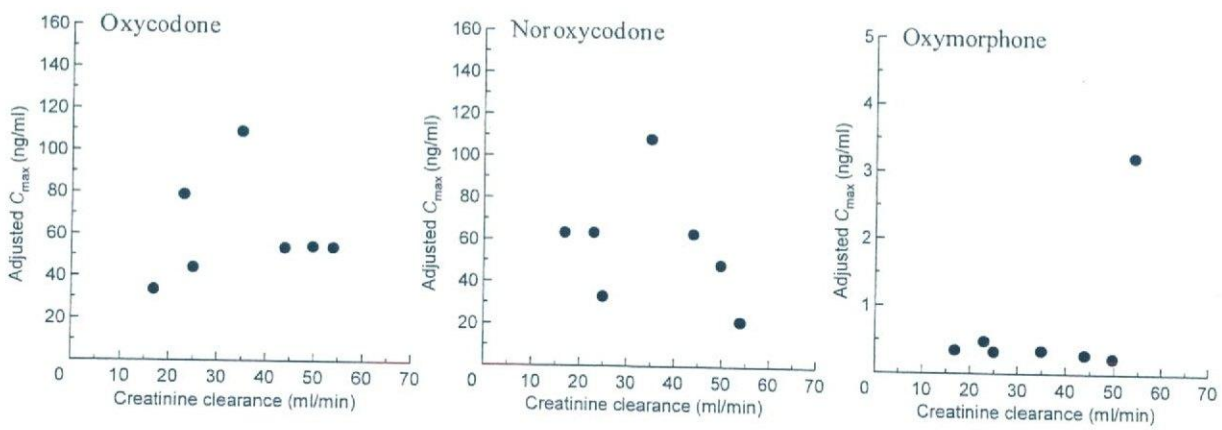

Figure 4. Results of linear regression for dependence of CCr on C_{max} of oxycodone and its metabolites (adjusted to 20 mg dose, $n = 7$).

Before study enrollment all patients had some intolerable side effect, but those side effects became tolerable at the end of the study in all patients except one patient who experienced intolerable constipation. The severity of those side effects also significantly improved, except for constipation which showed only a slight improvement. The reason was considered as follows: The severity of constipation is determined based on the types of laxatives following the NCI-CTC. Additionally, among side effects of strong opioid analgesics tolerance to constipation is known to be hard to develop (30). Therefore, there was a possibility that the unchanged severity of constipation resulted from continuing use of the same laxative agents throughout the study treatment.

Regarding constipation, there are reports that the incidence with oral oxycodone was almost equivalent to that with oral morphine (31). However, present studies suggest that switching to oral oxycodone resulted in improvement of constipation only in intolerable cases. As with other side effects, the improvement of constipation after switching to oral oxycodone may be caused by variability of response to strong opioids.

Side effects that carried over from morphine treatment and newly occurred side effects were observed in all patients after switching to oral oxycodone. However, all of these were typical of opioids and most were Grade 1 or 2 in severity. Although the number of subjects in these studies may not have been sufficient for safety evaluation, opioid rotation from oral morphine to oral oxycodone was considered unlikely to raise serious safety concerns in terms of side effects.

For pharmacokinetics of oxycodone, it has been reported that the C_{max} and AUC of oxycodone after single dose of CR oxycodone in subjects with renal impairment were ~1.4 and 1.6 times higher, respectively, than those in normal subjects (32). Previously, no study has been reported regarding the pharmacokinetics of oxycodone after multiple doses of CR oxycodone in patients with renal impairment. We therefore investigated the degree of accumulation of oxycodone and its metabolites in patients with renal impairment, and compared these with the degree of accumulation of morphine metabolites.

As for morphine, the severity of renal impairment (corresponding to CCr value) showed a significant correlation with plasma concentrations of M3G and M6G, which was consistent with previous reports (31,33), thereby confirming the tendency of their accumulation. As for oxycodone, on the other hand, the severity of renal impairment had no correlation with plasma concentrations of oxycodone or its active metabolites (oxymorphone), and therefore it is considered that the concentration of oxycodone and oxymorphone may not prominently increase according to the severity of renal impairment in comparison to M6G. In fact, the C_{max} and AUC of oxycodone from this study were approximately twice as high as that from a multiple dose study in healthy patients (34,35) and increasing rate of these parameters was comparable with that from single dose study.

In patients with renal impairment, the concentration of oxycodone following multiple dose administration should show higher value to a certain degree. However, the degree of the increases of oxycodone and oxymorphone is smaller, as compared that of M6G, which is ~5–6 times higher in patients with renal impairment. Moreover, the package inserts give precautions that in patients with renal impairment dose initiation should follow a conservative approach and dosage should be adjusted according to clinical situation. Therefore, we consider it is not a matter in clinical settings that patients with renal impairment receive oxycodone pain treatment with appropriate dose titration for each patient.

The present studies had some restrictions on study design due to difficult recruitment of the target patients. First, the present studies could not be conducted as randomized controlled studies. The results of the present prospective studies can be still considered quite meaningful even though these are open-label studies in a small number of patients, since many studies investigating the efficacy of opioid rotation have been retrospective.

Second, tolerability of side effects, a main inclusion criterion of the present studies, is based on subjective complaints of the patients. Since this assessment, as with pain intensity, is based on self-reported evaluation without any judgment by investigators, this assessment can be regarded as reliable only to a certain extent.

In conclusion, the results of the present studies suggested that switching to oral oxycodone from oral morphine was effective in the aspects of side effect and pain relief in Japanese patients who had difficulty in continuing oral morphine treatment because of inadequate analgesia and/or occurrence of intolerable side effects, regardless of renal function. Particularly in patients with renal impairment, it is also considered likely that the smaller increase in plasma concentration of oxycodone and its metabolites contributes to the high success rate of switching to oral oxycodone.

Acknowledgments

The authors would like to thank all the investigators who were involved in these studies in many medical settings. They would also like to thank Dr Tomoyuki Hamaguchi and Ms Tomoko Motomiya (Shionogi & Co., Ltd, Osaka, Japan) for help in preparing the manuscript. These studies were sponsored by Shionogi & Co., Ltd, Osaka, Japan.

Conflict of interest statement

None declared.

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Appendix: List of Advisory Committee for Oxycodone Study

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Pathology International 2009; 59: 167–174 doi:10.1111/j.1440-1827.2009.02345.x

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-kiyakus* (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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Received 23 April 2008. Accepted for publication 10 November 2008.

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) 1 pathologist/institute: 16 2 pathologists/institute: 21	77
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 hac 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	16
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	16
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	16
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	16
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	16
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.

ACKNOWLEDGMENTS

This work was partly supported by a grant-in-aid for cancer research from the Ministry of Education, Science, Sports, Culture and Technology of Japan. We would like to thank all the respondents of the survey. We especially appreciate Dr Yoji Urata of Kyoto City Hospital, who gave the most correct answers to our questions. We also appreciate Dr Leslie H. Sobin and the UICC-TNM online help desk staff. Finally, thanks also go to Ms Minobu Watanabe, *Hirokaze* and Narumi Teramotos for their help dispatching the questionnaire forms.

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