Table 1
Criteria for diagnosis of large cell neuroendocrine carcinoma (1999, WHO [2]).

1. A tumor with a neuroendocrine morphology (organoid nesting, palisading, rosettes, trabeculae)
2. High mitotic rate: 11 or greater per 2 mm^2 (ten HPFa), a median of 70 per 2 mm^2 (ten HPFa)
3. Necrosis (often large zones)
4. Cytologic features of a NSCLC: large cell size, low nuclear to cytoplasmic ratio, vesicular or fine chromatin, and/or frequent nucleoli. Some tumors have fine nuclear chromatin and lack nucleoli, but qualify as NSCLC because of large cell size and abundant cytoplasm
5. Positive immunohistochemical staining for one or more NE markers (other than neuron specific enolase) and/or NE granules by electron microscopy

HPFa: high power field; NSCLC: non-small cell lung carcinoma.

Table 2
Proposed criteria for diagnosis of high-grade non-small cell neuroendocrine carcinoma (HNSCNEC) using biopsy specimens.

1. Solid tumor nesting without either acinar or squamous differentiation
2. Moderate or marked cellular atypia
3. Large cell size with low nuclear to cytoplasmic ratio or abundant cytoplasm
4. Vesicular and/or fine nuclear chromatin
5. Frequent nucleoli
6. Positive immunostaining for one or more neuroendocline markers (NCAM, chromogranin A, and synaptophysin)
7. Ki-67/MIB1 labeling index > 40% [10,11]
8. Frequent mitosis
9. Frequent massive necrosis
10. Intercellular space (cleft) with loose intercellular adhesion
11. Organoid nesting, basal palisading, rosettes, and/or trabecular architecture

LCNEC have not yet been completely defined. In the case of surgical specimens, diagnostic criteria for LCNEC have been established and are described in Table 3 of "Introduction of Histological Typing of Lung and Pleural Tumours" (Third Edition, Springer, 1999) [2] (reprinted in Table 1). For small biopsy specimens, however, a diagnosis of LCNEC that fully meets the criteria described in Table 1 is often difficult. Therefore, instead of diagnosing LCNEC, we have devised and proposed a set of criteria for diagnosing high-grade non-small cell neuroendocrine carcinoma (HNSCNEC) using small biopsy specimens (Table 2), based on the conventional criteria for LCNEC (Table 1). The first seven items are obligatory criteria, and the latter four items are facultative. Our HNSCNEC classification likely includes most LCNECs and large cell carcinomas with a neuroendocrine phenotype. The examination of a larger series of surgically resected LCNECs, along with preoperative biopsy specimens, would enable the validity of diagnoses of HNSCNEC based on biopsy specimens to be confirmed. Although we believe that HNSCNEC and LCNEC are, by definition, similar, evidence of such similarities is not yet available. As previous studies have reported that the response of LCNECs to chemotherapy is similar to the response of small cell carcinoma, rather than the response of NSCLCs [8,9], we compared the chemotherapeutic responses of HNSCNECs and ED-SCLCs in the present study.

2. Patients and methods

2.1. Criteria for diagnosing HNSCNEC (Figs. 1 and 2)

The criteria proposed for diagnosing high-grade non-small cell neuroendocrine carcinoma (HNSCNEC) using biopsy specimens were as follows (Table 2): (1) solid tumor nesting without either acinar or squamous differentiation, (2) moderate or marked cellular atypia, (3) large cell size with low nuclear to cytoplasmic ratio or abundant cytoplasm, (4) vesicular and/or fine nuclear chromatin, (5) frequent nucleoli, (6) positive immunostaining for one or more neuroendocrine markers (NCAM, chromogranin A, and/or synaptophysin), (7) Ki-67/MIB1 labeling index > 40% [10,11], (8) frequent mitosis, (9) frequent massive necrosis, (10) intercellular space (cleft) with loose intercellular adhesion, and (11) organoid nesting, basal palisading, rosettes, and/or trabecular architecture. When findings (1) to (7) were observed in a biopsy specimen, the patient was diagnosed as having a large cell carcinoma (with solid tumor nesting without either acinar or squamous differentiation, moderate or marked cellular atypia, large cell size with low nuclear to cytoplasmic ratio or abundant cytoplasm, vesicular and/or fine nuclear chromatin, and frequent nucleoli). Positive neuroendocrine markers confirmed a neuroendocrine nature. Moreover, a Ki-67/MIB1 labeling index > 40% indicated a high-grade tumor [10,11]. Tumors meeting these criteria were diagnosed as HNSCNEC and were most likely either LCNECs or a related tumor. The presence of one or more of findings (8), (9), and/or (11), which are included in the 1999 WHO LCNEC criteria (Table 1), were regarded to reinforce the possibility of LCNEC, although these findings are often absent in small transbronchial biopsy specimens. Transthoracic core aspiration biopsy specimens and specimens from metastatic lesions are usually large enough to enable a diagnosis based on the WHO LCNEC criteria. Finding (10) (intercellular space (cleft) with loose intercellular adhesion) is very common and enables LCNEC to be distinguished from classical large cell carcinoma, as described in our previous paper [3] discussing surgical cases of LCNEC. Thus, the first seven findings in Table 2 must always be present for the diagnosis of HNSCNEC, which likely includes LCNECs and large cell carcinoma with a neuroendocrine phenotype, although combined LCNECs, including combined small cell carcinoma and LCNEC and combined LCNEC and adenocarcinoma/squamous cell carcinoma/classical large cell carcinoma [2], may not be diagnosable using small biopsy specimens since one component of the combined histology can be easily missed.

Although there are no previous reports which compared the HNSCNECs in preoperative or pretreatment biopsy specimens with the diagnosis in surgical specimens or in autopsy, we have, for the present, six surgically resected cases, in which HNSCNEC had been diagnosed by biopsy before treatment.

2.2. Immunohistochemistry

Formalin-fixed paraffin sections were stained using a panel of neuroendocrine markers including an anti-neural cell adhesion molecule (NCAM) antibody (Zymed Technology Invitrogen, South San Francisco, CA), a polyclonal anti-chromogranin A antibody (DAKO, Glostrup, Denmark), and a monoclonal anti-synaptophysin antibody (SIGNET, Denver, CO). Neuroendocrine differentiation was identified by positive immunohistochemical staining for one or more of NCAM, chromogranin A, and synaptophysin. Immunostaining for each neuroendocrine marker was judged as positive when over 30% of the tumor cells were stained. The anti-human Ki-67 antigen was identified by use of a monoclonal mouse anti-human Ki-67 (clone MIB1) antigen (code No. M7240, DAKO Cytomation Denmark A/S). Only nuclear immunostaining was regarded as positive. The labeling index of the Ki-67/MIB1 in each tumor was estimated as percentage of positive cells by counting of 100–1000 tumor cells. All immunostaining results were determined by the consensus of at least two observers of R.W., II and T.K.

2.3. Patient selection

A total of 14 patients with a histologic diagnosis of pulmonary HNSCNEC made between September 2002 and October 2007 were enrolled in this retrospective study. As well, a total of 77 patients with histologically and clinically confirmed ED-SCLC who had received a platinum-based chemotherapy regimen such as cisplatin/irinotecan, cisplatin/etoposide, or carboplatin/etoposide were enrolled. None of the patients had received prior radiotherapy

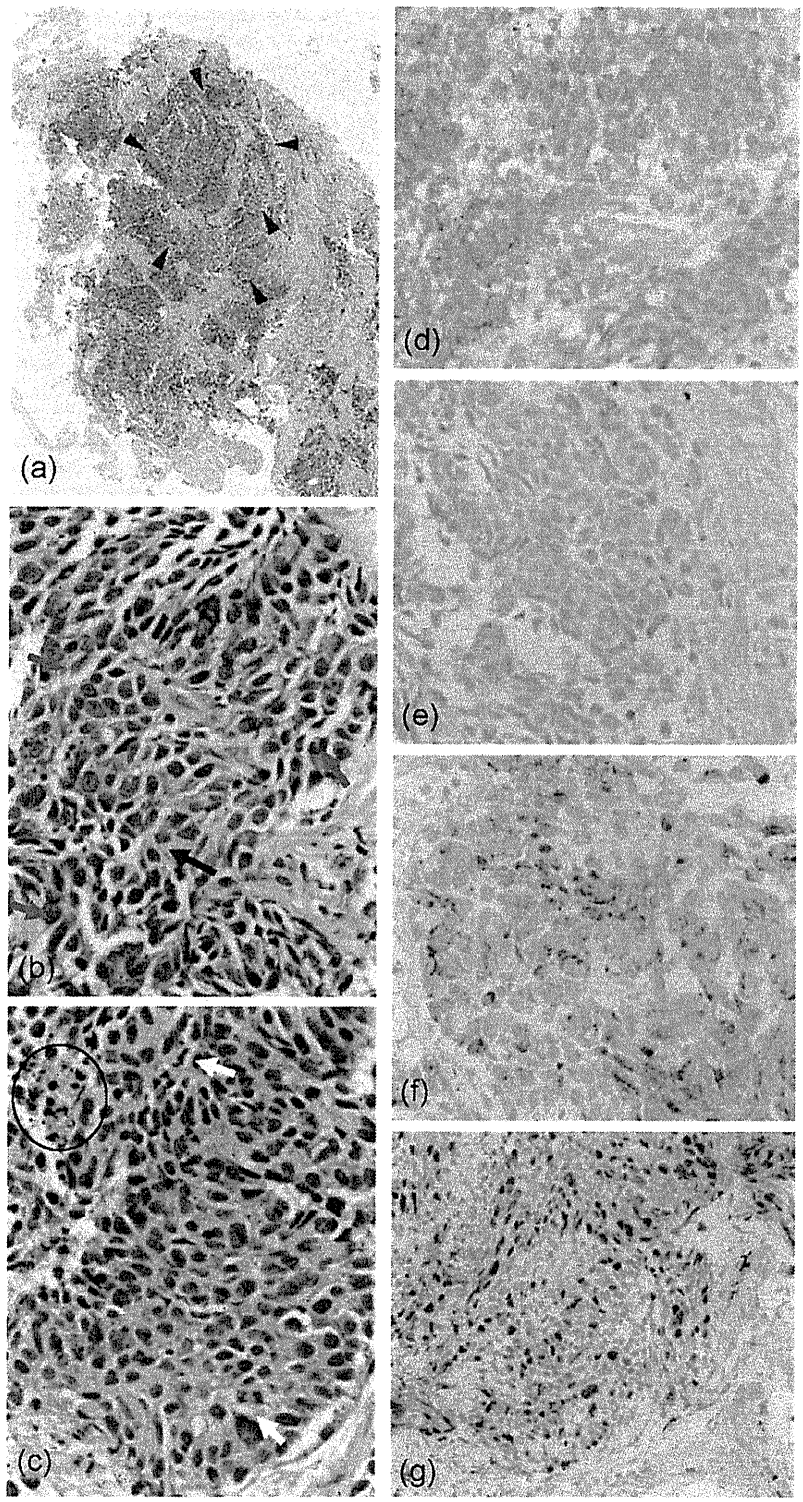

Fig. 1. A biopsy specimen diagnosed as HNSCNEC indicates histology of evident carcinoma which is composed of fused large organoid nests (red arrowheads) in which atypical polygonal cells proliferate, with no differentiation to acinar or squamoid features (a: ×4; b and c: ×40). Atypical cancer cells are dyscohesive to each other (green arrows), tend to form encircled and moulded cell arrangement, namely showing a rosette-like structure (red arrow), and have scattered mitoses (white arrow). Nucleoli are not obvious. In some areas, small aggregates of necrotic cells are observed (inside the circle). Immunohistochemically many cancer cells show positivity for NCAM (membranous, d, ×40), synaptophysin (granular, e, ×40), chromogranin A (granular, f, ×40). Ki-67/MIB1 labeling index is over 50% (g, ×20). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

or chemotherapy, and all the patients had been diagnosed as having unresectable HNSCNEC or ED-SCLC based on the results of chest radiography and computed tomography examinations of the chest and abdomen as well as other procedures such as magnetic resonance imaging (MRI) of the head and positron emission tomography (PET) or combined PET/computed tomography (PET-CT).

2.4. Evaluations

Tumor response was classified according to the Response Evaluation Criteria for Solid Tumors [12]. Patients were evaluated to determine the stage of their disease before treatment and to confirm whether their disease had progressed or relapsed using a complete medical history and physical examination including a chest radiograph, CT of the chest and abdomen, and other staging procedures such as MRI and PET.

2.5. Statistical analysis

Survival curves were calculated using the Kaplan–Meier method and were compared using a log-rank test between the HNSNEC and ED-SCLC groups. Overall survival was measured from the first day of treatment to the day of the last follow-up (cut-off) or death. The objective response rates were compared using a Fisher exact probability test. All the analyses were performed using SPSS ver. 2 (SPSS Inc., Chicago).

3. Results

Overall, 14 patients treated between September 2002 and October 2007 were recognized as having tumors with histopathological characteristics consistent with HNSCNEC, based on biopsy examinations. Among the biopsy specimens obtained in the 14 cases, we obtained ten specimens via transbronchial lung biopsy (Figs. 1 and 2) and four specimens via biopsy from a metastatic lesion (in the colon, liver, brain and adrenal gland, respectively).

We have, for the present, six surgically resected cases, in which HNSCNEC had been diagnosed by biopsy before treatment. Among these cases, five tumors were confirmed to be pure LCNEC (Figs. 3 and 4, and the other one to be combined LCNEC and small cell carcinoma by examination of surgical specimens.

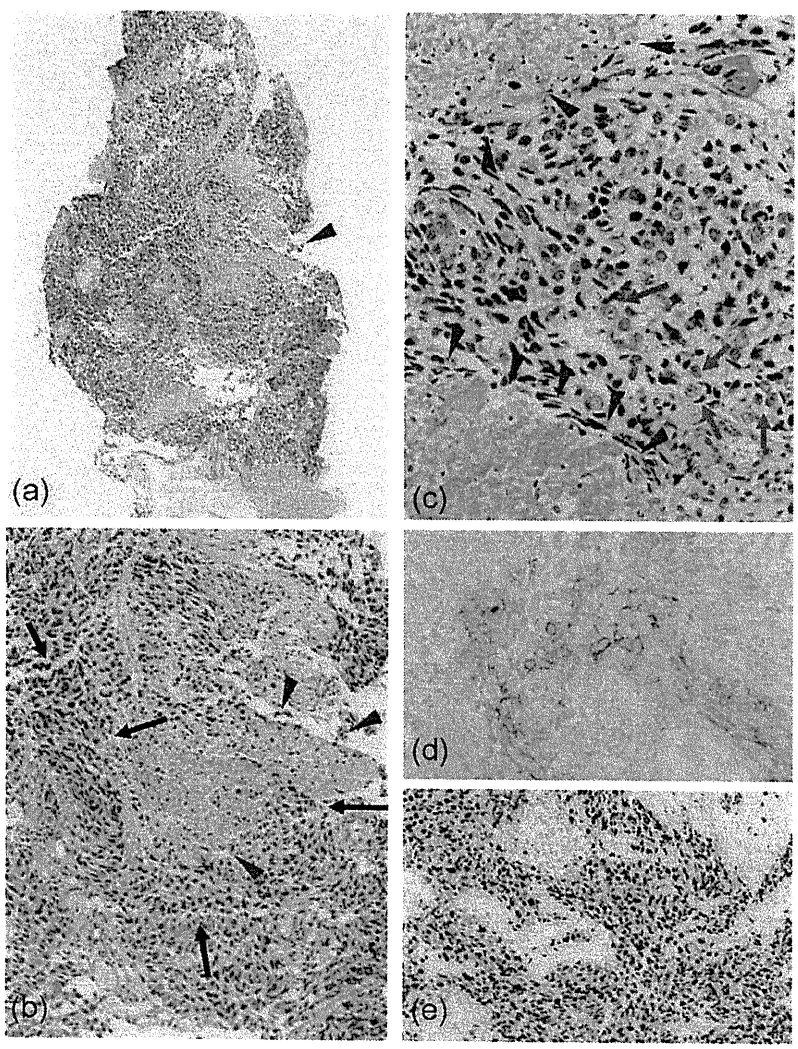

Fig. 2. A biopsy specimen diagnosed as HNSCNEC from another case shows confluent proliferation of cancer cells with remarkable necrotic foci (red arrowheads). Although organoid nesting is not obvious, polygonal cancer cells are dyscohesive (black arrows), and have prominent nucleoli (green arrows) (c, ×40). Immunohistochemically there is membranous positivity for NCAM (d, ×40), negativity for synaptophysin and chromogranin A (data not shown), and high labeling index of Ki-67/MIB1 over 90% (e, ×20). Magnification number in each parentheses indicates magnification of objective lens. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

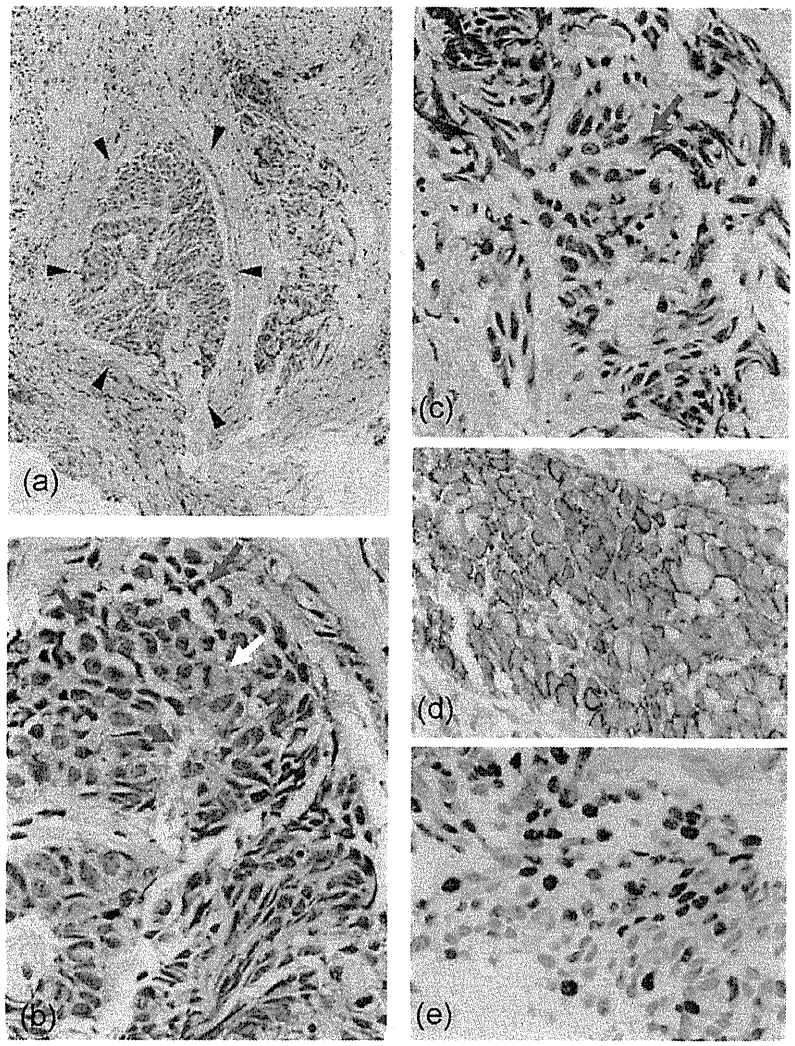

Fig. 3. A biopsy specimen before surgery was diagnosed as HNSCNEC (same figure) and the surgical specimen of the same patient revealed LCNEC (shown in Fig. 4). There was an organoid-like tumor-cell nest (a, ×10, red arrowheads) comprising large cells with abundant cytoplasm. Mitotic figures are rare (b, ×40, white arrow). Another tumor cell island was less organoid and lacking palisading arrangement in periphery. Note less cohesion of tumor cells and intercellular clefts in both nests (green arrows). The tumor cells are positive for NCAM (d, ×40), negative for chromogranin A and synaptophysin (not shown). The Ki-67/MIB1 labeling index is 62% (e, ×40). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

The characteristics of the patients are listed in Table 3. Among the 14 patients, the mean age was 70 years (range, 57–81 years), 13 patients (92%) were men, and 13 patients (92%) were current or former smokers. Two patients had stage IIIB disease, eleven patients had stage IV disease, and one patient had a postoperative recurrent case. The performance status (PS) of the patients was either PS 0 or 1 ($n=13$) or PS 2 ($n=1$). The following chemotherapy regimens were used: (i) cisplatin/irinotecan ($n=7$), (ii) carboplatin/etoposide ($n=2$), (iii) carboplatin/paclitaxel ($n=1$), (iv) cisplatin/paclitaxel ($n=1$), (v) irinotecan alone ($n=1$), (vi) vinorelbine ($n=1$), and (vii) docetaxel alone ($n=1$).

Table 3
Patient characteristics in HNSCNEC ($n=14$) and ED-SCLC ($n=77$) groups.

	HNSCNEC	ED-SCLC
Age, median (range)	70 (57–81)	69 (51–86)
Male/female	13/1	62/15
Smoking	13/1	67/10
Staging IIB/IV postop.	2/11/1	–
Performance status		
0–1/≧2	13/1	51/26
Regimens		
IP/CE/CP/DTX	7/2/1/1	
PP/CPT-11/VNR	1/1/1	
PE/IP/CE		16/27/34

IP, cisplatin/irinotecan; PE, cisplatin/etoposide; CE, carboplatin/etoposide; CP, carboplatin/paclitaxel; PP, cisplatin/paclitaxel VNR, vinorelbine; CPT-11, irinotecan.

Seventy-seven cases of ED-SCLC were treated between September 2002 and October 2007. Fifteen patients were women, and 62 were men (80%); their median age was 69 years (range, 51–86 years), and 67 patients (86%) were current or former smokers. The patients had a PS of either PS 0 or 1 ($n=51$) or PS 2 ($n=26$). The following chemotherapy regimens were used: cisplatin/irinotecan ($n=27$), cisplatin/etoposide ($n=16$), or carboplatin/etoposide ($n=34$). The characteristics of the ED-SCLC cases are listed in Table 3.

Among the 14 patients with HNSCNEC, seven patients achieved a partial response (PR), with an overall response rate of 50% (Table 4). Four PRs were observed among the patients treated with cisplatin/irinotecan, and one PR was observed in each group of patients treated with cisplatin/paclitaxel, carboplatin/etoposide, or carbo-

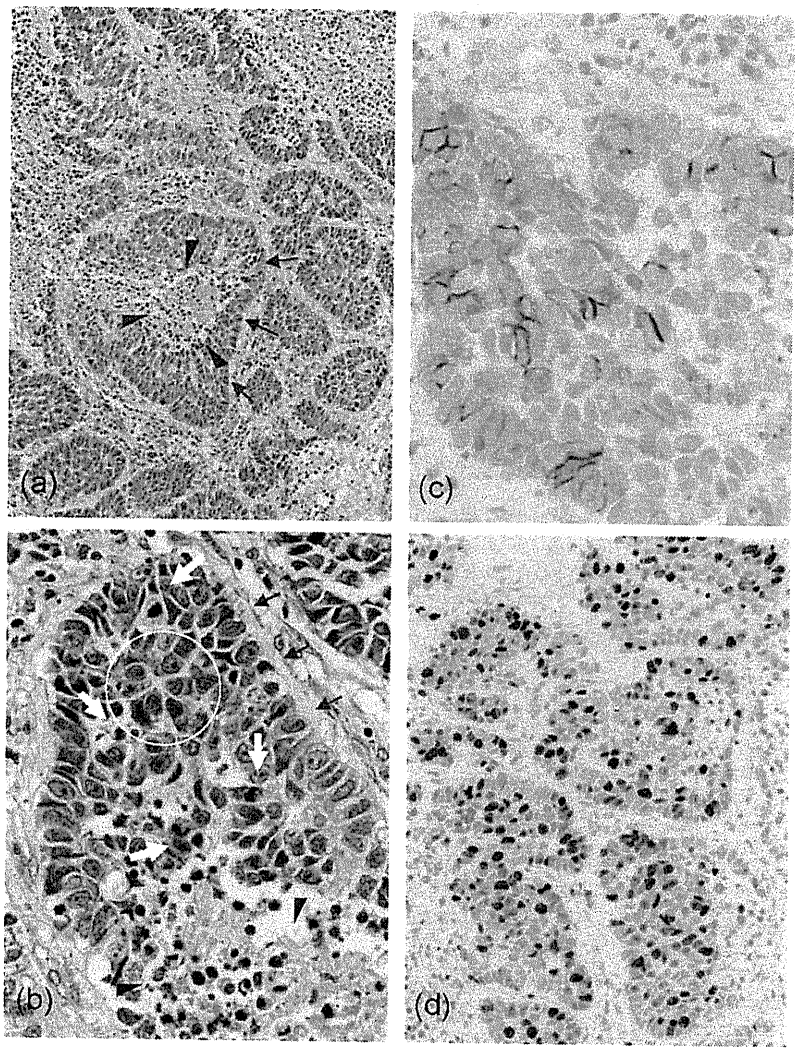

Fig. 4. A surgically resected specimen diagnosed as LCNEC. This patient was diagnosed as HNSCNEC by prior biopsy (shown in Fig. 3). We can find the histology typically characteristic of LCNEC in these two H&E pictures (a and b); central necrosis (a, ×10; and b, ×40, red arrowheads), peripheral palisading arrangement (a and b, blue arrows), rosette formation (b, white circle), and frequent mitoses (b, white arrows). Note that tumor cells are less cohesive, not like the pattern of adenocarcinoma. The results of immunostaining were the same as the biopsy specimen (c, ×40, positive for NCAM). The other neuroendocrine markers such as chromogranin A and synaptophysin were negative (not shown). The Ki-67/MIB1 labeling index was 56% (d, ×20). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

platin/paclitaxel. We evaluated overall survival using the data of 13 cases with HNSCNEC except one case with postoperative recurrence. The median survival time and one-year survival rate (as of treatment enrollment) were 10 months and 34%, respectively (Fig. 5).

Among the 77 patients with ED-SCLC, four CRs and 37 PRs were observed, with an overall response rate of 53% (Table 4). The median

Table 4
Clinical responses in HNSCNEC ($n = 14$) and ED-SCLC ($n = 77$) groups.

	HNSCNEC	ED-SCLC
CR		4
PR	7	37
SD	5	20
PD	1	13
NE	1	3
RR (%)	50%	53%

Evaluated according to RECIST Guideline.
RR, response rate; CR, complete response; PR; partial response; SD, stable disease; PD; progressive disease; NE, not evaluable.

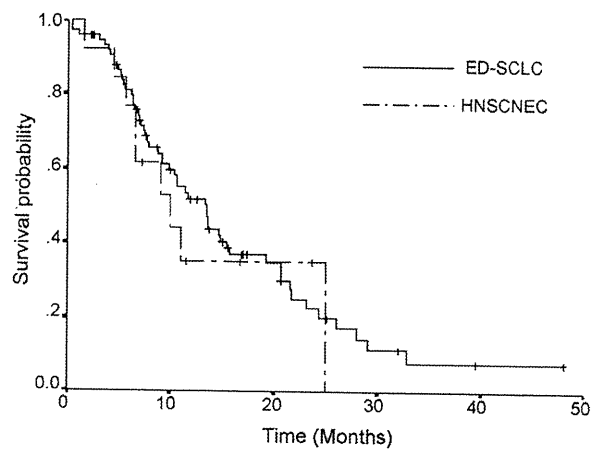

Fig. 5. Kaplan–Meier plot of overall survival of patients with HNSCNEC and patients with ED-SCLC.

survival time and one-year survival rate (after treatment) were 12.3 months and 48%, respectively (Fig. 5). No statistically significant differences were found in the objective response rates between the HNSCNEC and ED-SCLC groups ($p = 0.82$); similarly, no significant differences were found in overall survival between the HNSCNEC and ED-SCLC groups ($p = 0.68$). Thus, these results indicate that the response rate of HNSCNEC to various regimens of chemotherapy seems to be comparable to that of ED-SCLC.

4. Discussion

Two important results were obtained in this study. First, biopsy specimens were used to diagnose 14 cases of unresectable lung cancer as HNSCNEC, a category that likely includes most LCNECs and other related tumors. Until now, the diagnosis of LCNEC has mostly been made using surgically resected specimens and rarely or never by biopsy or cytology specimens alone. The architectural arrangement of tumor cells is often extremely difficult or almost impossible to appreciate using small tumor specimens, and diagnoses of biopsy or cytology specimens are usually limited to either non-small cell carcinoma, large cell carcinoma, poorly differentiated carcinoma, or, at best, suspected neuroendocrine carcinoma. Therefore, few details are known regarding the clinical efficacy of chemotherapy for patients with unresectable LCNEC and related tumors, and the establishment of diagnostic criteria for these tumors based on the examination of biopsy or cytology specimens alone is an urgent task. The difficulty in diagnosing LCNEC based on hematoxylin and eosin (H&E)-stained biopsy sections resides in the poorly differentiated states of such tumors. Organoid architectures (organoid nesting, trabecular, palisading or rosette-like growth patterns) enabling the recognition of neuroendocrine features may be scarce or absent [3], and pathologists may have difficulty making a diagnosis using small, imperfect specimens, such as dry specimens or specimens with crushing artifacts. Thus, we devised a series of pathological diagnostic criteria for high-grade non-small cell neuroendocrine carcinoma (HNSCNEC) that could be used with both routine H&E and immunostained sections of biopsy specimens. H&E sections can be used to identify massive necrosis, nuclear and cellular atypia, an abundance of cytoplasm, mitotic figures, intercellular incohesiveness, and, if discernible, some features of neuroendocrine morphology such as organoid nesting, basal palisading, rosettes and/or trabeculae. Immunostaining for Ki-67/MIB1 was used to evaluate whether a high-grade tumor was present, and immunostaining for NCAM, synaptophysin and chromogranin A were used to evaluate the neuroendocrine differentiation.

If a biopsy specimen fulfills our proposed criteria (Table 2), a diagnosis of either LCNEC, which has both a neuroendocrine morphology and differentiation, or large cell carcinoma with neuroendocrine differentiation, which lacks neuroendocrine morphology but exhibits neuroendocrine markers upon immunostaining [2,13], would be plausible, although the incidence of the latter classification is likely to be much lower than that of the former among related tumors [13]. Classic large cell carcinoma, which lacks both neuroendocrine morphology and differentiation, could be ruled out. The possible misdiagnosis of combined subtypes (combined small cell carcinoma and large cell neuroendocrine carcinoma, combined large cell neuroendocrine carcinoma and squamous cell carcinoma or adenocarcinoma, and lastly combined large cell neuroendocrine carcinoma and classic large cell carcinoma) is unavoidable, although the true incidence of combined subtypes remains to be established.

As mentioned in Section 3, all six surgically resected cases, in which HNSCNEC had been diagnosed by biopsy before treatment, were confirmed to be pure LCNEC or combined LCNEC and small cell carcinoma. At present, we are making an on-going multi-institutional study on comparison of diagnosis of more than 30 cases of both by biopsy and surgical specimens of the same patients, and there is increasing evidence that most LCNECs and their related tumors are included in the HNSCNEC category.

The clinical importance of this paper is that the chemotherapeutic responsiveness and survival of the patients with unresectable HNSCNEC was similar to those of ED-SCLC patients treated during the same period. Although seven of 11 cases except for cases with the monotherapy were responsive to chemotherapy and the rate (63.6%) was higher than that of ED-SCLC, there was no significant difference between them.A previous study reported an objective response rate to platinum-based chemotherapy of 64% in chemonaive patients with unresectable LCNEC, which is somewhat higher than the chemotherapy response rates of other histological subtypes of NSCLC and appears to be comparable to that of SCLC [8]. In the above-mentioned study, five patients of post-operative recurrence and 15 patients who were found to have histological characteristics consistent with the diagnosis of LCNEC by autopsy had received cisplatin-based chemotherapy.

Platinum-doublet regimens, especially platinum-etoposide, have been reported to be significantly correlated with favorable survival in both an adjuvant setting and in metastatic cases with LCNEC [9]. The results of these previous studies seem to agree with the results of our study. Equally important, the fact that a male predominance (92%) and a high rate of smokers (92%) were seen in the HNSCNEC group, similar to the rates reported for LCNEC (85–90% and 50–99%, respectively) [4,5,6,14], suggests that most LCNECs are included among HNSCNECs.

In conclusion, the results of this study suggest that the clinical efficacy of chemotherapy for unresectable HNSCNECs, which likely includes most LCNECs, is comparable to that of ED-SCLC. However, because of the retrospective design and the small sample size of this study, we could not arrive at satisfactory and definitive conclusion. At present, we are making a multi-institutional study to examine a large series of specimens and to confirm whether most LCNECs are included in the HNSCNEC category.

Conflict of interest

None declared.

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Desire for Information and Involvement in Treatment Decisions

Lung Cancer Patients' Preferences and Their Physicians' Perceptions: Results from Okayama Lung Cancer Study Group Trial 0705

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Introduction: This study explores patient preferences for involvement in lung cancer treatment decisions and the extent of concordance between the views of patients and physicians on decisional roles. The impact of demographic and psychosocial characteristics on the decisional role of patients is also examined.

Methods: Patients with relapsed non-small cell lung cancer who were candidates for a phase II trial of erlotinib monotherapy were recruited. Patients were interviewed after they had learned of their relapse and the treatment decision had been made but before pharmacologic intervention.

Results: Most of the 28 participants were married, had a smoking history, and were well educated. They reported moderate levels of depression and anxiety. Initially, 14% of the patients reported a preference for active decision making; later, 29% believed that the primary responsibility for the treatment decision had been theirs. Only 54% of the patients agreed with the physician's assessment of how the treatment decision was made ($\kappa = 0.31$; test of symmetry, $p = 0.23$). The depression score was significantly associated with a patient's preferred level of control ($p < 0.01$).

Conclusions: The limited concordance between patient preference and perception and between patient and physician perceptions regarding how the treatment decision was made suggests that physicians should more accurately identify patient preferences by directly asking patients at the beginning of each clinical encounter.

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Key Words: Decisional role, Non-small cell lung cancer, Perception, Preference.

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The past 2 decades have witnessed increased research in patient preferences for information and decisional roles in the treatment process, and a shift to a more patient-centered approach to healthcare delivery. This movement, often termed shared decision making, emphasizes a more active, participatory role for patients and a more tailored approach to patient education by healthcare providers.[1–3]

A growing body of literature demonstrates that decision making shared between patients and providers can result in a variety of benefits, including improved patient satisfaction and clinical outcomes.[4–11] Considerable attention has focused on identifying patient preferences and the extent to which these preferences are met in patient-provider interactions. These issues have been extensively examined with breast cancer patients[12,13] but not fully with lung cancer patients.

We investigated the degree of desired involvement in treatment decisions of a sample of lung cancer patients who were enrolled in a phase II trial of erlotinib therapy, and we explored the extent to which these patient preferences were met. We also examined whether anxiety and depression play a role in decision-making preferences.

METHODS

Patients

Between January and December 2008, Japanese patients with non-small cell lung cancer in six institutes affiliated with Okayama Lung Cancer Study Group who relapsed to the first-line or second-line chemotherapy participated in a prospective phase II trial of erlotinib monotherapy.[14] The phase II trial included the current study as a preplanned subset analysis. Of the 30 patients, 28 consented to this subset

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TABLE 1. Control Preferences Scale: Three Parallel Versions

Patient Preference Scale	Patient Perception Scale	Physician Perception Scale
I prefer to make the final selection about which treatment I will receive.	I made the final decision about which treatment I would receive.	The patient made the final decision about which treatment she or he would receive.
I prefer to make the final selection of my treatment after seriously considering my doctor's opinion.	I made the final selection of my treatment after seriously considering my doctor's opinion.	The patient made the final decision about which treatment she or he would receive after seriously considering my opinion.
I prefer that my doctor and I share responsibility for deciding which treatment is best for me.	My doctor and I shared responsibility for deciding which treatment was best for me.	I shared responsibility with the patient for making the final decision about treatment she or he would receive.
I prefer that my doctor make the final decision about which treatment will be used but seriously consider my opinion.	My doctor made the final decision about which treatment would be used but seriously considered my opinion.	I made the final decision about which treatment the patient would receive, after seriously considering the patient's opinion.
I prefer to leave all decisions regarding my treatment to my doctor.	My doctor made all the decisions regarding my treatment.	I made the final decision about which treatment the patient would receive.

In this study, the scale was collapsed to three levels: mostly patient for the first and second options; shared decision making for the third; and mostly physician for the fourth and fifth options of the patient preference, patient perception, and physician perception scales (see *Methods*).

TABLE 2. Clinical, Psychosocial, and Sociodemographic Characteristics

No. of patients	28
Sociodemographic characteristics	
Median age (range), yr	67 (35–88)
Gender (male/female)	22 (79%)/6 (21%)
Smoking history (yes/no)	20 (71%)/8 (29%)
Marital status (married/unmarried)	24 (86%)/4 (14%)
Education (posthigh-school graduate/high-school graduate or less)	17 (61%)/5 (18%)[a]
Clinical characteristics	
Tumor histology (adenocarcinoma/other)	19 (68%)/9 (32%)
Performance status (0/1–2)	6 (21%)/22 (79%)
Prior chemotherapy regimens (<2/≥2)	12 (43%)/16 (57%)
Prior platin use (yes/no)	20 (71%)/8 (29%)
Respiratory comorbidity (yes/no)	5 (18%)/23 (82%)
Psychosocial characteristics, median (range)	
HADS anxiety score	6 (0–12)
HADS depression score	6 (0–16)

[a] Data were not available for six patients.
HADS, Hospital Anxiety and Depression Scale.

analysis; the other 2 declined to participate. This study was approved by the institutional review boards of all participating institutes.

Study Flow

The main outcome measures of this study were three parallel versions of a control preferences scale (Table 1).[15] All the study patients were interviewed on recruitment to the study,[14] which was after they had learned of their lung cancer recurrence and the treatment decision had been made, just before therapy began. Patients were interviewed using questionnaires that assessed sociodemographic characteristics, psychosocial constructs, and decisional-role outcome measures (patient perceptions; Table 1). Sociodemographic variables included date of birth, marital status, and education. Patients also completed the Hospital Anxiety and Depression Scale (HADS),[16] which screens psychiatric problems in medically ill patients by using a 4-point, 14-item self-assessment scale to measure 2 factors of psychologic distress: anxiety and depression. Physicians attending the patients were also interviewed to assess their perceptions.

Data Analysis

Differences among the groups were evaluated using Fisher's exact test and the Kruskal-Wallis equality-of-populations rank test. To determine where deviations occurred between patient perceptions before and after the treatment decision and between patients' and physicians' perceptions, κ statistics and a test for symmetry were applied to assess agreement and discordance. For these analyses, the patient preference scale was collapsed to three levels, similar to those of previous studies (mostly patient, shared decision making, and mostly physician; Table 1)[17–19] because of the sparse number of responses at the tails. Statistical analyses were conducted using STATA version 10 software (College Station, TX). Values of $p < 0.05$ (two sided) were considered statistically significant.

RESULTS

Patient Characteristics

Table 2 summarizes the patient characteristics. Most were married males with a smoking history and high education level. With regard to the clinical information, most had adenocarcinoma and a history of platin use.

Patients posted relatively low baseline HADS scores for both anxiety and depression. The median score was 6 for each, with a range of 0 to 12 for anxiety and 0 to 16 for depression. In general, women reported relatively high levels of anxiety in communicating with their physician (median scores: 8 for females versus 5 for males; $p = 0.03$), whereas the depression score was comparable between female and male patients (median: 7.5 for females versus 6 for males; $p = 0.35$). The 28 patients were attended by a total of 17 physicians (15 male and 2 female), whose ages were in the twenties to forties (median, thirties).

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TABLE 3. Patient Preferences Stratified by Clinical and Sociodemographic Characteristics

Factor	Patient Preferences			p
	Active	Shared	Passive	
Age (yr)				
≥67[a]	2 (13)	9 (60)	4 (27)	>0.99
<67[a]	2 (15)	8 (62)	3 (23)	
Gender				
Male	3 (14)	13 (59)	6 (27)	>0.99
Female	1 (17)	4 (67)	1 (17)	
Smoking history				
Yes	2 (10)	12 (60)	6 (30)	0.52
No	2 (25)	5 (63)	1 (13)	
Marital status				
Married	4 (17)	13 (54)	7 (29)	0.31
Unmarried	0	4 (100)	0	
Tumor histology				
Adenocarcinoma	3 (16)	13 (68)	3 (16)	0.26
Others	1 (11)	4 (44)	4 (44)	
Performance status				
0	0	5 (83)	1 (17)	0.54
1–2	4 (18)	12 (55)	6 (27)	
No. of prior chemotherapy regimens				
≥2	1 (7)	9 (64)	4 (29)	0.75
<2	3 (21)	8 (57)	3 (21)	
Prior platin use				
Yes	3 (15)	12 (60)	5 (25)	>0.99
No	1 (13)	5 (63)	2 (25)	
Respiratory comorbidity				
Yes	0	5 (100)	0	0.28
No	4 (17)	12 (52)	7 (30)	
Patient knowledge of epidermal growth factor receptor-tyrosine kinase inhibitors				
Yes	3 (23)	7 (54)	3 (23)	0.49
No	1 (7)	10 (67)	4 (27)	

Data are presented as *N* (%).
[a] Median age.
EGFR, epidermal growth factor receptor.

Decision Control Preferences

Seven (25%) of the patients favored a passive role in treatment decision making, whereas 14% favored an active role, and 61% preferred a collaborative role. Preference for a passive role did not correlate with any of the clinical or sociodemographic factors evaluated (Table 3). In contrast, patient preferences were affected by their depression status, with median depression scores of 7, 7, and 3 for the active, shared, and passive roles, respectively ($p < 0.01$; Figure 1*A*). The groups also differed in anxiety status, with median anxiety scores of 3, 7, and 3, respectively ($p < 0.01$; Figure 1*B*).

Patient Perceptions Versus Patient Preferences and Physician Perceptions

Table 4 shows that 67.9% of the patients perceived that they made the decision they had initially preferred, resulting in between patient preferences and perceptions ($\kappa = 0.48$; test of symmetry, $P = 0.10$). Table 5 contrasts the views of patients and physicians with regard to the treatment decision. Only 53.6% of patients agreed completely with those of their physicians concerning who made the treatment decision ($\kappa = 0.31$; test of symmetry, $P = 0.23$), that is, compared with the patients' perceptions of their involvement in treatment decisions, physicians tended to perceive that patients were more actively involved. There was less discordance between the patient preferences and physician perceptions with κ of 0.23 (% agreement: 46.4%; Table 6).

DISCUSSION

Our results show that the perceptions of patients and physicians with respect to their roles in treatment decisions agreed in only half of the 28 cases. In addition, two thirds of the 28 patients perceived that they made the decision in the manner they had initially preferred. These results indicate that concerns and management strategies were insufficiently discussed between the patients and physicians.

One possible explanation for the discrepancy between the views of patients and physicians regarding the patient decisional role is that the physicians based their perceptions on behavioral cues, which have been shown to be inconsistent with patient perceptions.[20,21] Physicians who want to meet patient expectations may need to ask directly about role preferences, instead of trying to discern them from opinions offered or questions asked by the patient.[12]

We also used HADS to investigate depression and anxiety status and the relationship between these states and patient preferences. First, we observed relatively low overall HADS depression and HADS anxiety scores, which were almost identical to those of primary breast cancer patients.[13] Generally, in contrast to breast cancer patients, patients with relapsed non-small cell lung cancer have a poor prognosis, with a median survival time of approximately 7 months.[22] Thus, we initially thought that the 28 patients would report higher HADS scores. Given that the general condition of these patients was good enough for accrual into the clinical trial, the HADS scores of these patients might have been lower than what we had initially expected.

Second, we showed that HADS scores may affect patient preferences. Although our data do not allow for causal interpretation, patients with passive decision-making preferences had lower depression scores, compared with patients with collaborative or active preferences. In contrast, in a neoadjuvant setting for newly diagnosed breast cancer, patients with passive role preferences had higher HADS depression scores, perhaps because patients who are depressed because of their symptoms prefer to leave their treatment responsibility to the physician.[13] Our findings are also in contrast to two other studies that found no differences in HADS scores among role preferences.[12,23] These conflicting results may be explained by differences in assessments, samples, data analysis, or ethnicity.[12,23] Further studies are needed to determine the impact of depression and anxiety on decision-making preferences.

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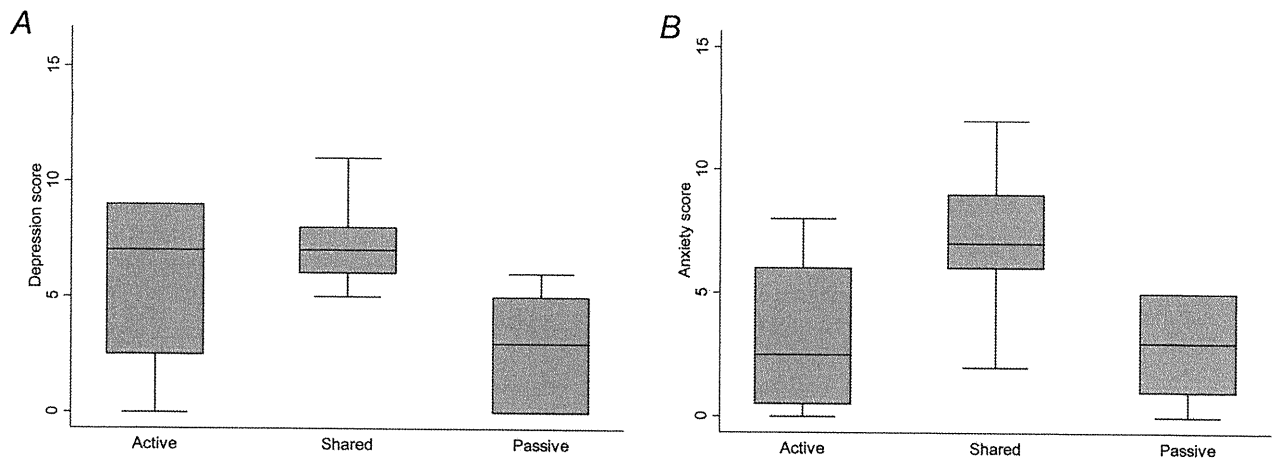

FIGURE 1. Box and whisker plots. The bottom and top of the box represent the 25th and 75th percentile (lower and upper quartile), respectively. The band near the middle of the box is the 50th percentile (median). *A*, Association between patient preferences and depression status. The higher the depression score (*y* axis), the more likely the patient is in a depressive state. *B*, Association between patient preferences and anxiety status. The higher the anxiety score (*y* axis), the more likely the patient is in an anxiety condition.

TABLE 4. Patient Preferences and Perceptions

Patient Preferences	Patient-Perceived Level of Control (*N*)			
	Active	Shared	Passive	Total, *N* (%)
Active	3[a]	0	1	4 (14.3)
Shared	5	11[a]	1	17 (60.7)
Passive	0	2	5[a]	7 (25.0)
Total, *N* (%)	8 (28.6)	13 (46.4)	7 (25.0)	28 (100)

% agreement = (3 + 11 + 5)/28 = 67.9%.
[a] Complete agreement.

TABLE 5. Patient Perceptions and Physician Perceptions

Patient Perceptions	Physician Perceptions (*N*)			
	Active	Shared	Passive	Total, *N* (%)
Active	6[a]	2	0	8 (28.6)
Shared	5	5[a]	3	13 (46.4)
Passive	2	1	4[a]	7 (25.0)
Total, *N* (%)	13 (46.4)	8 (28.6)	7 (25.0)	28 (100)

% agreement = (6 + 5 + 4)/28 = 53.6%.
[a] Complete agreement.

We have several limitations. Because there were 17 physicians attended 28 patients meaning less than 2 patients by physician, we could not sure that they provide the patients with the same information. This may influence the principal results. In addition, the sample size did not allow us to do subgroup analyses. Furthermore, the control preferences scale and the way physicians understood how patients took decisions have not yet fully been validated extensively. Thus, our results should be interpreted cautiously.

In conclusion, despite our small sample size, the HADS score, and not the sociodemographic or clinical factors assessed in this study, was associated with a preferred decisional role. The overall lack of concordance between physician and patient perceptions of the decisional context indicates a gap that must be narrowed. One reasonable and unobtrusive approach would be for physicians to directly ask about a patient's preferences at the beginning of each clinical encounter and to then check on the patient's level of satisfaction with the decision-making process.

TABLE 6. Patient Preferences and Physician Perceptions

Patient Preferences	Physician Perceptions (*N*)			
	Active	Shared	Passive	Total, *N* (%)
Active	3[a]	1	0	4 (14.3)
Shared	8	6[a]	3	17 (60.7)
Passive	2	1	4[a]	7 (25.0)
Total, *N* (%)	13 (46.4)	8 (28.6)	7 (25.0)	28 (100)

% agreement = (3 + 6 + 4)/28 = 46.4%.
[a] Complete agreement.

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ORIGINAL ARTICLE

hOGG1 Ser326Cys polymorphism and risk of lung cancer by histological type

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Human 8-oxoguanine DNA glycosylase 1 (*hOGG1*) has a major role in the repair of 8-hydroxyguanine, a major promutagenic DNA lesion. The genetic polymorphism rs1052133, which leads to substitution of the amino acid at codon 326 from Ser to Cys, shows functional differences, namely a decrease in enzyme activity in *hOGG1*-Cys326. Although several studies have investigated the association between rs1052133 and lung cancer susceptibility, the effect of this locus on lung cancer according to histology remains unclear. We therefore conducted a case–control study with 515 incident lung cancer cases and 1030 age- and sex-matched controls without cancer, and further conducted a meta-analysis. In overall analysis, the homozygous Cys/Cys genotype showed a significant association with lung cancer compared to Ser allele carrier status (odds ratio (OR)=1.31, 95% confidence interval (CI)=1.02–1.69). By histology-based analysis, the Cys/Cys genotype showed a significantly positive association with small-cell carcinoma (OR=2.40, 95% CI=1.32–4.49) and marginally significant association with adenocarcinoma (OR=1.32, 95% CI=0.98–1.77). A meta-analysis of previous and our present study revealed that this polymorphism is positively associated with adenocarcinoma, although suggestive associations were also found for squamous- and small-cell lung cancers. These results indicate that rs1052133 contributes to the risk of adenocarcinoma of lung.
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Keywords: *hOGG1*; lung cancer; polymorphism

INTRODUCTION

Cancer is linked to environmental exposure to various carcinogens, of which tobacco smoke is a well-known example. Exposure leads to various types of DNA damage, such as oxidative damage. Genetic variations in DNA repair genes are associated with DNA repair capacity, suggesting a consequent association with cancer risk.[1]

8-Hydroxyguanine, produced by reactive oxygen species in tobacco smoke, is a major form of DNA damage.[2] This alteration to the DNA structure causes G:C to T:A transversions, and may thus be responsible for mutations that lead to carcinogenesis.[3] Human 8-oxoguanine DNA glycosylase 1 (*hOGG1*) has been extensively studied as the main enzyme involved in the repair of 8-oxoG DNA adducts. Although it has a major role in the repair of 8-hydroxyguanine, however, its role in carcinogenesis has not been well elucidated.[4] Genetic polymorphisms of *hOGG1* have been documented, and the polymorphism Ser326Cys (rs1052133) is associated with complementation activity for *Escherichia coli* mutants that are defective in the repair of 8-hydroxyguanine. Activity in the repair of 8-hydroxyguanine is greater with the *hOGG1*-Ser326 protein than the *hOGG1*-Cys326 protein,[5] and the possible contribution of this locus to the risk of a variety of human cancers has been reported.[6]

A number of studies[7–14] and systematic approaches[15–17] have examined the role of the Ser326Cys polymorphism in lung cancer susceptibility. One meta-analysis showed that the overall odds ratio (OR) of homozygotes for the *hOGG1*-326Cys allele against those for the *hOGG1*-326Ser allele was 1.24 (95% confidence interval (CI)=1.01–1.53), suggesting that the locus is involved in susceptibility to overall lung cancer.[17] In contrast, another meta-analysis reported no significant association.[15] A recent pooled analysis from the International Lung Cancer Consortium involving a substantial number of cases and controls showed a suggestive association for this polymorphism in Caucasians.[16] One question that remains unanswered is whether the impact of rs1052133 differs according to histological subtype of lung cancer.

Here, we evaluated the role of the *hOGG1* Ser326Cys polymorphism in lung cancer susceptibility among a Japanese population in

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consideration of histology. We also conducted a meta-analysis of the literature to evaluate the impact of this polymorphism by histology.

MATERIALS AND METHODS

Subjects

The case subjects were 515 patients who were newly and histologically diagnosed with lung cancer and who had no history of cancer. Controls were randomly selected from among the 2395 cancer-free individuals and matched by age (±3 years) and sex to cases in a 1:2 case/control ratio. All subjects were recruited within the framework of the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC), as described elsewhere,[18,19] and were exactly the same cohort we reported on in a previous paper.[20] In brief, information on lifestyle factors was collected using a self-administered questionnaire from all first-visit outpatients at Aichi Cancer Center Central Hospital aged 18–79 who were enrolled in the HERPACC between January 2001 and November 2005. Response was checked by a trained interviewer. Outpatients were also asked to provide blood samples. Each patient was asked about their lifestyle when healthy or before the current symptoms developed. Approximately 95% of eligible subjects completed the questionnaire and 60% provide blood samples. The data were loaded into the HERPACC database and routinely linked with the hospital-based cancer registry system to update the data on cancer incidence. All participants gave written informed consent and the study was approved by institutional ethical committee of Aichi Cancer Center.

Genotyping of *hOGG1*

DNA from each sample was extracted from the buffy coat fraction using a BioRobot EZ1 with an EZ1 DNA Blood 350 μl kit or QIAamp DNA Blood mini kit (Qiagen KK, Tokyo, Japan). Polymorphisms of *hOGG1* Ser326Cys were examined based on TaqMan assays by Applied Biosystems (Foster City, CA, USA). The principle of the TaqMan real-time polymerase chain reaction (PCR) assay system using fluorogenic probes and 5′ nuclease has been described by Livak.[21] All of the assays were carried out in 96-well PCR plates using a 7500 Fast Real-Time PCR System (Applied Biosystems) coupled with the 7500 Fast System SDS software. Amplification reactions (5 μl) were carried out in duplicate with 30 ng of template DNA, 2× TaqMan Universal Master Mix buffer (Applied Biosystems) and 20× primer and probe mix (Applied Biosystems). Thermal cycling was initiated with a first denaturation step of 20 s at 95 °C, and then by 40 cycles of 3 s at 95 °C and 30 s at 62 °C. Genotyping quality was statistically assessed using the Hardy–Weinberg test in our laboratory; when allelic distributions for controls departed from the Hardy–Weinberg frequency, genotyping was assessed using another method.

Consumption of tobacco, alcohol, fruits and vegetables

Cumulative smoking dose was evaluated as pack-years (PY), the product of the number of packs consumed per day and the number of years of smoking. Smoking habit was entered in the four categories of never, former, and current smokers of <40 and ≧40 PY. Former smokers were defined as those who quit smoking at least 1 year before the survey. Drinking habit was categorized in the three categories of never, former and current drinkers. Former drinkers were defined as those who quit drinking at least 1 year before the survey. Consumption of fruits and vegetables was determined using a semiquantitative food frequency questionnaire (SQFFQ), described in detail elsewhere.[22] Briefly, the SQFFQ consisted of 47 single food items with frequencies in eight frequency categories. We estimated average daily intake by multiplying the frequency of intake by the serving size of food (in grams). Energy-adjusted intake of fruits and vegetables was calculated by the residual method.[23] The SQFFQ was validated using a 3-day weighed dietary record as standard, which showed that reproducibility and validity were acceptable.[24]

Statistical analysis

To assess the strength of associations between *hOGG1* polymorphism and risk of lung cancer, we estimated ORs with 95% CIs, using conditional logistic models adjusted for potential confounders. For stratified analyses exploring interactions, we applied unconditional logistic regression models because matching was not retained after stratification by smoking and drinking habit and carotene intake in conditional models. Fruit and vegetable intake was categorized into three levels by applying thresholds of tertiles among controls. Potential confounders considered in the multivariate analyses were age, sex, smoking habit (never smokers, former smokers, current smokers of less than 40 or 40 or more PY), drinking habit (never, former and current drinkers), total energy intake (as a continuous variable), and dietary fruit and vegetable intake (g per day, tertiles). Missing values for each covariate were treated as dummy variables and were included in the model. Trend for genotype was assessed by application of a score test value for each genotype (0, homozygous for reference allele or combined reference genotypes; 1, heterozygote or one reference genotype and 2, homozygous nonreference allele or nonreference genotype). Differences in categorized demographic variables between cases and controls were tested by the χ^2-test. Mean values for age and total energy intake were compared for cases and controls by Wilcoxon's signed-rank test. Accordance with the Hardy–Weinberg equilibrium was checked for controls using the χ^2-test and the exact *P*-value was used to assess any discrepancies between

Table 1 Characteristics of case and control subjects

	Cases (n=515) n *(%)*	*Controls (n=1030)* n *(%)*	*P-value*
Age			
<50	53 (10.3)	108 (10.5)	
50–59	142 (27.6)	283 (27.5)	
60–69	193 (37.5)	389 (37.8)	
70–79	127 (24.7)	250 (24.3)	1.00
Mean age (range)	61.9 (23–79)	61.8 (26–79)	0.87
Sex			
Male	381 (74.0)	762 (74.0)	
Female	134 (26.0)	268 (26.0)	1.00
Smoking (Pack-years)			
<5	136 (26.4)	424 (41.2)	
5–19.9	31 (6.0)	118 (11.5)	
20–39.9	88 (17.1)	208 (20.2)	
>40	258 (50.1)	275 (26.7)	<0.001
Unknown	2 (0.4)	5 (0.5)	
Drinking status			
Never	196 (38.1)	378 (36.7)	
Former[a]	15 (2.9)	56 (5.4)	
Current	304 (59.0)	596 (57.9)	0.08
Fruit/vegetable consumption (g per day)			
Tertile 1 (<118.4)	199 (38.8)	342 (33.2)	
Tertile 2 (118.4–211.3)	140 (27.3)	341(33.1)	
Tertile 3 (>211.4)	166 (32.4)	341(33.1)	0.03
Unknown	8(1.6)	6 (0.6)	
Total energy intake (kcal, s.d.)[b]	1670 (371)	1676 (352)	1.00
Histology			
AD	316 (61.4)		
SQ	91 (17.7)		
SM	55 (10.7)		
LA	40 (7.8)		
Others	13 (2.5)		

Abbreviations: AD, adenocarcinoma; LA, large-cell carcinoma; SM, small-cell carcinoma; SQ, squamous-cell carcinoma.
[a]Former drinkers were defined as subjects who had quit drinking at least 1 year previously.
[b]Energy-adjusted.

genotypes and allele frequencies, with a *P*-value of less than 0.05 considered statistically significant. All analyses were performed using STATA version 10.1 (Stata, College Station, TX, USA).

Meta-analysis

We conducted a meta-analysis of relevant articles reporting associations between the *hOGG1* polymorphism and lung cancer in consideration of the histological subtypes adenocarcinoma, squamous-cell carcinoma and small-cell carcinoma. Medline was searched for papers published between January 1995 and March 2009 and indexed with the terms (lung neoplasms AND (hOGG1 OR OGG1)). Inclusion criteria were (1) reporting of ORs or risk ratios calculated by comparing the Ser/Ser to the Cys/Cys or Cys allele carrier according to histological subtype; (2) a cohort, nested case–control, population-based case–control or hospital-based case–control study design and (3) use of cancer-free controls. All potentially relevant papers were independently reviewed by at least two investigators (TO and KM) and any disagreements were resolved by consensus. The reference lists of studies identified through the search process were also checked. Among the 65 papers identified through this process, 7 were considered eligible.[5,7–11,17] Two investigators (TO and KM) abstracted the data independently. We used OR from a random-effect model as a summary statistic for association.[25] Heterogeneity among the studies was examined based on the *Q* and I^2 statistics. The latter indicates the proportion of variation in summary estimates attributable to heterogeneity.[26] We determined which model to use to calculate summary OR and its 95% CI, a random- or fixed-effect model, based on significance in the *Q* statistics. The meta-analysis was conducted using the 'metan' command[27] in STATA version 10.1.

RESULTS

Characteristics of the 515 cases and 1030 controls are shown in Table 1. Age and sex were appropriately matched. Smoking habits differed remarkably between cases and controls, with the proportion of current smokers of 40 PY or more significantly higher in cases. Former drinkers tended to be more common among cases, albeit without statistical significance. Consumption of fruits and vegetables was significantly lower among cases. The distribution of histological type among cases was as follows: adenocarcinoma, 61.4% (n=316); squamous-cell carcinoma, 17.7% (n=91); small-cell carcinoma, 10.7% (n=55); large cell carcinoma, 7.8% (n=40) and others, 2.5% (n=13).

Table 2 presents the frequency distribution of *hOGG1* genotypes and ORs with 95% CI for lung cancer cases compared with controls. No significant dissociation from the Hardy–Weinberg equilibrium was observed among controls. In overall analysis, Cys/Cys showed a significantly positive association with lung cancer. The confounder-adjusted OR for Cys/Cys relative to Ser/Ser+Ser/Cys was 1.31 (1.02–1.69, P=0.036). In histology-based analysis, those with the Cys/Cys genotype were at significantly increased risk of small-cell carcinoma and marginally significantly increased risk of adenocarcinoma, compared to those with the Ser/Cys and Ser/Ser genotypes combined. No significant associations were observed for squamous-cell carcinoma.

Table 3 shows associations between *hOGG1* Ser326Cys polymorphism combined with smoking and lung cancer risk. In overall analysis, the effect of cumulative smoking dose was stronger in those with Cys/Cys. In analyses by histology, a similar trend was observed for adenocarcinoma and small-cell carcinoma but not for squamous-cell carcinoma. This trend was more prominent for small-cell carcinoma. Adjusted ORs for heavy smoking (PY≧40) were 26.3 (5.34–129.6) for the Ser allele carrier and 72.3 (14.6–358.2) for those with the Cys/Cys.

To further examine the impact of *hOGG1* Ser326Cys polymorphism according to histology, we conducted a meta-analysis. Table 4 shows a summary of studies that have investigated the association between *hOGG1* Ser326Cys polymorphism and lung cancer risk, including the present study. As shown in Figure 1, *hOGG1* Ser326Cys polymorphism summary ORs showed a significant association with adenocarcinoma (OR=1.44, 95% CI=1.18–1.77) with no significant heterogeneity. Although squamous-cell carcinoma showed a similarly increased risk (OR=1.81, 95% CI=1.06–3.07), the significant heterogeneity across studies (I^2=58.5) was a limitation. Although without significance and from a limited number of studies, the pooled estimate was 2.05 (0.91–4.63), suggesting an increased risk for small-cell carcinoma.

Table 2 *hOGG1* genotype distribution and ORs for lung cancer

Genotype	*Cases* n=*515*	*Controls* n=*1030*	*OR1 (95% CI)*[a]	*P-value*	*OR2 (95% CI)*[b]	*P-value*
Overall						
Ser/Ser	117	250	1.00 (reference)		1.00 (reference)	
Ser/Cys	257	544	1.01 (0.77–1.32)		0.96 (0.72–1.26)	
Cys/Cys	141	236	1.28 (0.94–1.73)	0.054	1.27 (0.93–1.75)	0.047
Ser/Ser+Ser/Cys	374	794	1.00 (reference)		1.00 (reference)	
Cys/Cys	141	236	1.27 (1.00–1.62)	0.05	1.31 (1.02–1.69)	0.036
Adenocarcinoma						
Ser/Ser+Ser/Cys	227	794	1.00 (reference)		1.00 (reference)	
Cys/Cys	89	236	1.29 (0.97–1.72)	0.085	1.32 (0.98–1.77)	0.066
Squamous-cell carcinoma						
Ser/Ser+Ser/Cys	72	794	1.00 (reference)		1.00 (reference)	
Cys/Cys	19	236	0.99 (0.58–1.70)	0.98	1.10 (0.63–1.94)	0.73
Small-cell carcinoma						
Ser/Ser+Ser/Cys	34	794	1.00 (reference)		1.00 (reference)	
Cys/Cys	21	236	2.22 (1.26–3.92)	0.006	2.40 (1.22–4.12)	0.009

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Adjusted for age and sex.
[b]Adjusted for age, sex, smoking habit, drinking habit, total energy intake and energy-adjusted fruit/vegetable intake.

Table 3 Associations between *hOGG1* Ser326Cys polymorphisms and smoking by PY on lung cancer risk

	Ser (+)		*Cys/Cys*	
Histology	*Case/Control*	*OR (95% CI)*[b]	*Case/Control*	*OR (95% CI)*[b]
Overall[a]				
Smoking (pack-years)		Ser (+)		Cys/Cys
<5	95/317	1.0 (reference)	41/107	1.35 (0.88–2.09)
5–19.9	22/89	1.26 (0.72–2.21)	9/29	1.29 (0.55–3.03)
20–39.9	66/160	2.38 (1.53–3.68)	22/48	2.54 (1.39–4.63)
>40	191/223	5.26 (3.54–7.78)	67/52	7.44 (4.53–12.2)
Adenocarcinoma				
Smoking		Ser (+)		Cys/Cys
<5	89/317	1.0 (reference)	39/107	1.36 (0.87–2.13)
5–19.9	15/89	0.95 (0.50–1.79)	5/29	0.70 (0.23–2.13)
20–39.9	39/160	1.62 (0.98–2.66)	13/48	1.75 (0.86–3.54)
>40	84/223	2.75 (1.77–4.28)	30/52	3.99 (2.25–7.08)
Squamous-cell carcinoma				
Smoking		Ser (+)		Cys/Cys
5–19.9	3/406	1.0 (reference)	3/136	3.22 (0.64–16.3)
20–39.9	13/160	6.99 (1.93–25.4)	5/48	8.99 (2.04–39.5)
>40	56/223	19.5 (5.87–64.3)	11/52	16.6 (4.37–63.0)
Small-cell carcinoma				
Smoking		Ser (+)		Cys/Cys
5–19.9	2/406	1.0 (reference)	1/136	1.50 (0.13–16.7)
20–39.9	8/160	12.6 (2.39–66.2)	4/48	18.8 (3.09–114.3)
>40	24/223	26.3 (5.34–129.6)	16/52	72.3 (14.6–358.2)

Abbreviations: CI, confidence intervals; OR, odds ratios.
[a]Five controls and two cases are excluded from analysis because of smoking information unknown.
[b]ORs were adjusted for age, sex, smoking habit, drinking habit, total energy intake and energy-adjusted fruit/vegetable intake.

Table 4 Summary of published studies examining association between *OGG1* polymorphism and lung cancer risk according to histology

		Subjects in each study								
		Case						*Odds ratio (95% CI) for Cys/Cys relative to Ser/Ser*		
Author	*Year*	*Total*	*Adeno*	*Squamous*	*Small*	*Control*	*Ethnicities*	*Adeno*	*Squamous*	*Small*
Sugimura *et al.*[7]	1999	241	1974	78	118	197	Japanese	1.34 (0.53–3.39)	2.27 (0.92–5.60)	0.51 (0.09–2.87)
Wikman *et al.*[8]	2000	105	50	50	NA	105	Caucasian	1.84 (0.41–14.41)	1.76 (0.24–13.1)	NE
Ito *et al.*[9]	2002	138	138	0	0	241	Japanese	0.81 (0.44–1.52)	NE	NE
Le Marchand *et al.*[10]	2002	298	141	66	43	405	Caucasian, Japanese and Hawaiian	2.1[a] (1.1–3.9)	3.7[a] (1.7–8.3)	3.4[a] (1.1–10.4)
Park *et al.*[11]	2004	179	63	56	32	358	Caucasian	4.20 (1.10–15.8)	4.8 (1.1–21.0)	NE
Hung *et al.*[17]	2005	2188	499	902	0	2198	Caucasian	1.66 (1.04–2.66)	1.02 (0.63–1.64)	NE
Kohno *et al.*[12]	2006	1097	1097	0	0	394	Japanese	1.47 (1.02–2.13)	NE	NE
Our study	2009	515	316	91	55	1030	Japanese	1.32 (0.98–1.77)	1.10 (0.63–1.94)	2.40 (1.22–4.12)

Abbreviations: CI, confidence intervals; NE, not estimated; OR, odd ratios.
[a]ORs are calculated as that of the homozygous Cys/Cys genotype compared to those with the Ser/Ser and Ser/Cys genotype combined.

DISCUSSION

In this case–control study, we found that the *hOGG1* 326Cys/Cys genotype, which results in weaker activity, was associated with a significantly increased risk of lung cancer overall. By subtype we found a significant association of the Cys/Cys genotype with small-cell carcinoma and a marginally significant association with adenocarcinoma. Moréover, in our subsequent meta-analysis of epidemiological studies based on histology, we observed that this genotype was associated with an increased risk of adenocarcinoma. Although results for squamous- and small-cell carcinoma were not conclusive,

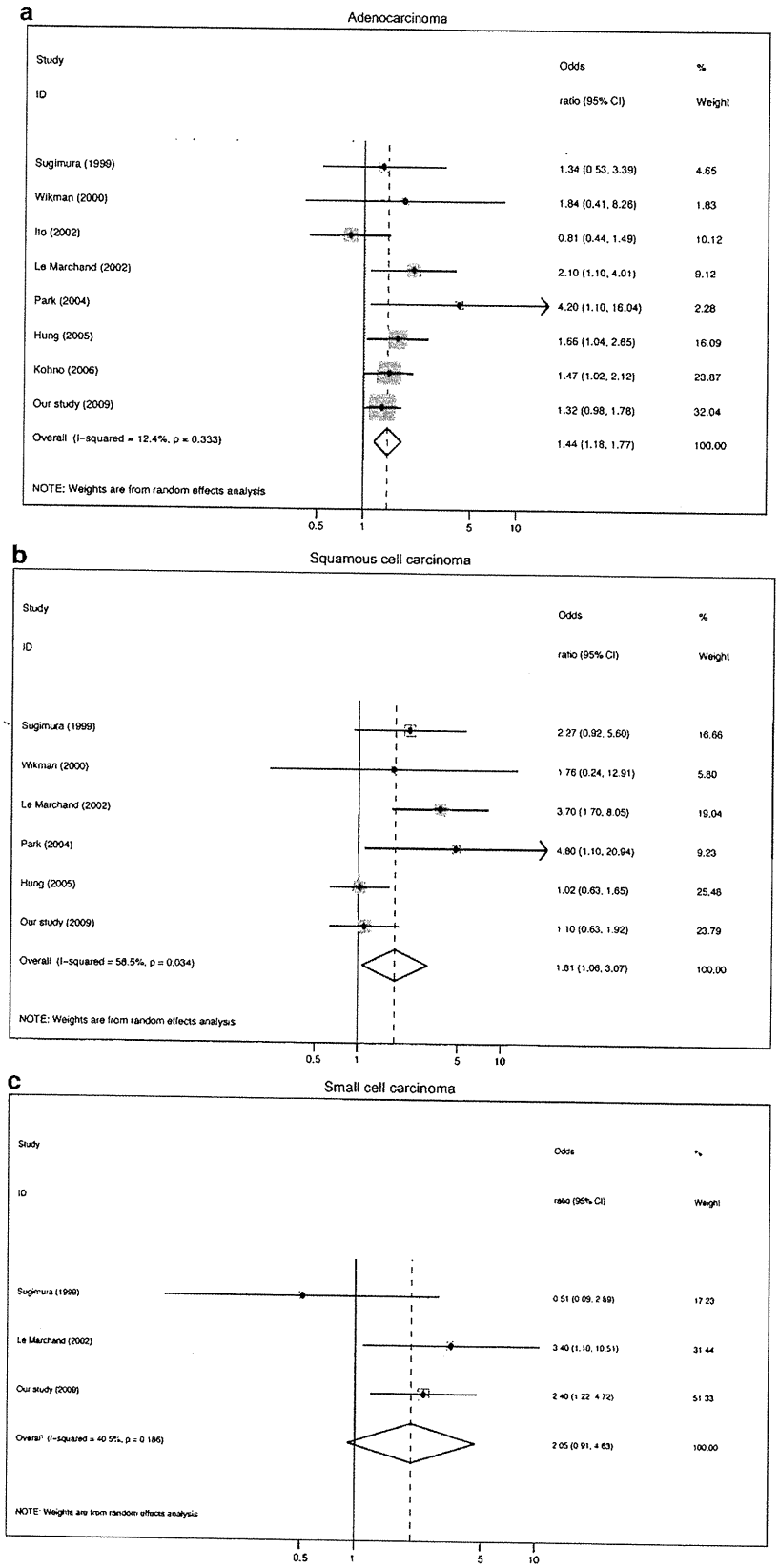

Figure 1 Meta-analysis for human 8-oxoguanine DNA glycosylase 1 (hOGG1) polymorphism according to histological subtype. A meta-analysis was conducted of the studies listed in Table 4. We extracted the ORs and 95% CIs for the Cys/Cys homozygotes of *hOGG1* relative to the Ser/Ser according to histological subtype from each study. We applied a random-effect model. An OR >1.0 indicates a higher risk with the Cys/Cys genotype than with Ser/Ser homozygotes. I^2 indicates the proportion of variation in summary estimates attributable to heterogeneity. All analyses were performed using the 'metan' command in STATA (version 10.1).

we also identified a potentially increased risk for these types of lung cancer.

Results of a number of studies examining the role of the *hOGG1* Ser326Cys polymorphism in lung cancer susceptibility conducted to date have been inconsistent.[7–12,17] Our case–control study showed a significant association between *hOGG1* Ser326Cys polymorphism and lung cancer overall, supporting the potential effect of this polymorphism on lung cancer susceptibility. Because the question of whether the effect of this polymorphism differed by histology remained unanswered, we also conducted a meta-analysis with consideration to histology. To the best of our knowledge, this is the first report to summarize the association between *hOGG1* polymorphism and susceptibility by histological type. Results of our meta-analysis indicated that the effect is consistent for adenocarcinoma, but not for squamous- or small-cell carcinoma. This inconsistency might be due to the heterogeneity of populations and distribution of subtypes across studies. The subjects included in the analyses were mainly Japanese and Caucasian. The most common subtype was adenocarcinoma in Japanese but squamous-cell carcinoma in Caucasians. Given that the magnitude of effect of smoking on risk differs by histological subtype,[28] the magnitude of effect of the *hOGG1* polymorphism might also differ across subtypes and populations. Even within the same histological subtype, the effect of smoking differs with the presence of certain gene mutations in cancer.[29] A comprehensive understanding of the *hOGG1* polymorphism will thus require further study, with particular focus on squamous- and small-cell carcinomas.

Our case–control study had several potential limitations. One methodological issue was the selection of hospital-based patients without cancer as controls. However, because cases and controls were selected from the same hospital and almost all patients lived in the Tokai area of central Japan, the internal validity of this case–control study is likely acceptable. External validity (generalizability of the results) has been confirmed in our previous study.[30] In addition, to dilute any bias that might have resulted from the inclusion of a specific diagnostic group that is related to the exposure, we did not set eligibility criteria for control diseases. As for allele frequencies in the subjects, given that our frequencies were comparable to those previously reported in public databases such as HapMap JPT,[31] bias in the distribution of selected polymorphisms was negligible. Second, the self-reported values for lifestyle factors considered as potential confounders may be inaccurate. If present, however, any such misclassification would likely be nondifferential, and would likely underestimate the causal association. The meta-analysis was based on published data, and the potential for publication selection bias could not be ruled out even if heterogeneity across the studies was limited for adenocarcinoma.

In conclusion, we found a positive association between lung cancer and Cys/Cys individuals in a Japanese population. The association was clear for small-cell carcinoma and adenocarcinoma of the lung in this population. Further systematic evaluation revealed that associations with the locus were conclusive for adenocarcinoma. Further studies are needed to clarify the effect of genotype on squamous-cell carcinoma and small-cell carcinoma.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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original article

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A phase II study of palonosetron combined with dexamethasone to prevent nausea and vomiting induced by highly emetogenic chemotherapy

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Background: This is a randomized, double-blind, dose-ranging study in patients receiving highly emetogenic chemotherapy (HEC) to evaluate the safety, efficacy, and pharmacokinetics of palonosetron, in combination with dexamethasone.

Materials and methods: We randomized 233 patients to receive palonosetron as a single i.v. bolus dose of 0.075, 0.25, or 0.75 mg before administration of HEC. Dexamethasone (12–16 mg i.v. on day 1, 8 mg i.v. on day 2, and 4–8 mg i.v. on day 3) was administered for prophylactic antiemesis. Pharmacokinetics of palonosetron was analyzed in 24 patients.

Results: In this study, all patients were given ≥50 mg/m^2 cisplatin, which was considered to be HEC. No significant differences in complete response (CR: no emesis and no rescue medication) rates were found in the first 24 h between the 0.075-, 0.25-, and 0.75-mg groups (77.6%, 81.8%, and 79.5%, respectively). In the 120-h period of overall observation, CR rates increased in a dose-dependent manner. In the 0.75-mg group, we observed a significantly longer time to treatment failure than in the 0.075-mg group (median time >120 versus 82.0 h, $P = 0.038$). Palonosetron was tolerated well and did not show any dose-related increase in adverse effects.

Conclusions: Palonosetron at doses of 0.25 and 0.75 mg was shown to be effective in preventing chemotherapy-induced nausea and vomiting with high CR rates of patients treated with HEC in Japan. All tested doses of palonosetron were tolerated well.

Key words: CINV, emesis, 5-HT$_3$ receptor antagonist, palonosetron

introduction

Many anticancer therapies have debilitating side-effects such as chemotherapy-induced nausea and vomiting (CINV). Caregivers should provide the best available support therapies to reduce the burden of chemotherapy and improve quality of life (QoL). A recent assessment in cancer patients found that poor control of CINV substantially lowers perceived QoL [1, 2]. Good control of CINV may also improve compliance and increase completion of chemotherapy.

The 5-hydroxytryptamine 3 (5-HT$_3$) receptor antagonists were studied intensely after their interactions with CINV mechanisms were discovered in the 1980s. Several related agents, including ondansetron, granisetron, tropisetron, and dolasetron, were developed in the 1990s. The 5-HT$_3$ receptor antagonists were found to suppress acute CINV at higher rates than antihistamines or dopamine antagonists [3]. Although these four 5-HT$_3$ receptor antagonists differ in receptor-binding affinity, selectivity, and metabolism, there is no meaningful clinical difference [4]. Despite the acute relief obtained with these agents, CINV, and particularly delayed CINV (≥2 days after chemotherapy), remains a dreaded side-effect of chemotherapy.

Palonosetron is a new 5-HT$_3$ receptor antagonist approved by the Food and Drug Administration and it is also approved by the European Medicines Agency for the prevention of CINV caused by moderately emetogenic chemotherapy and highly emetogenic chemotherapy (HEC) [5].

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