The Journal of Laryngology & Otology (2013), ***127***, *942–946*.

doi:10.1017/S0022215113001606

CLINICAL RECORD

Small cell carcinoma of the head and neck: report of three cases

H MATSUYAMA, K YAMAZAKI, M TOMITA, S TAKAHASHI

Department of Otolaryngology, Faculty of Medicine, Niigata University, Japan

Abstract

Objective: Small cell carcinoma of the head and neck is rare and has unique histopathological characteristics that make it difficult to diagnose and treat. In this report, the Japanese Lung Cancer Treatment Guidelines were adapted to treat three patients with small cell carcinoma of the head and neck, and outcomes evaluated.

Methods: There was one case each of stage I small cell carcinoma of the nasal cavity, stage IV-B small cell carcinoma of the ethmoid sinus, and stage IV-A small cell carcinoma of the submandibular gland. All patients underwent chemoradiotherapy and achieved a partial response.

Results: Only case one underwent surgery after chemoradiotherapy; 31 months after treatment, this patient had suffered no recurrence. Case two died three months after treatment due to bone marrow metastasis. Case three had experienced no progression after 12 months of follow up.

Conclusion: In this small patient series, short-term results were equivalent to or better than usual treatment outcomes for small cell carcinoma of the lung.

Key words: Head And Neck Neoplasms; Carcinoma, Small Cell; Otolaryngology; Chemoradiotherapy; Guidelines

Introduction

Extrapulmonary small cell carcinoma is rare and has unique histopathological characteristics that make it difficult to diagnose and treat. In this study, we adapted the Japanese Lung Cancer Treatment Guidelines to treat three patients with small cell carcinoma of the head and neck, and we evaluated outcomes.[1–10]

When a head and neck tumour was diagnosed as small cell carcinoma, we determined whether the patient had limited or extensive disease and then developed an appropriate treatment plan (i.e. chemoradiotherapy plus surgery, chemoradiotherapy alone or chemotherapy alone). The chemotherapy regimen comprised four courses of platinum 80 mg/m^2 for 1 day each plus etoposide 100 mg/m^2 for 3 days. For chemoradiotherapy, a standard fractionation radiotherapy dosage (50 to 60 Gy) was given concurrently with chemotherapy.

Upon completion of treatment, we evaluated its effect according to the Response Evaluation Criteria in Solid Tumors[11] and developed a management plan (i.e. 'wait and scan', chemotherapy, surgery, or best supportive care).

Case reports

Case one

Our first patient was a 56-year-old man whose chief complaint was right nasal bleeding. The patient presented at another hospital with right nasal bleeding, and a tumour was discovered in his nasal cavity. After a biopsy revealed small cell carcinoma, he was referred to our hospital. The tumour completely filled his right nasal passage.

Magnetic resonance imaging (MRI) of the nasal cavity revealed a tumour limited to the inside of the right nasal cavity (Figure 1a). No abnormalities were detected upon computed tomography (CT) scanning of other regions, bronchoscopy, biopsy of the pulmonary hilum, or cranial MRI. Bone scintigraphy showed accumulation only in the right nasal cavity.

The tumour was diagnosed as stage I small cell carcinoma (tumour-node-metastasis (TNM) classification T_1 N_0 M_0), limited disease, with a primary lesion in the right nasal cavity.

Chemotherapy was undertaken, following a regimen of platinum 110 mg for 1 day and etoposide 140 mg for 3 days, for a total of four courses. A total radiotherapy dose of 50 Gy was given in 25 fractions, commencing with the second course of chemotherapy.

Upon completion of treatment, imaging revealed a 71.4 per cent reduction in tumour size, which was classified as a partial response according to the Response Evaluation Criteria in Solid Tumors system (Figure 1b). Adverse effects of treatment included grade IV bone marrow toxicity and grade II mucositis.

One month after the final chemotherapy treatment, removal of the middle turbinate was performed under general anaesthesia.

Thirty-one months after treatment, there was no sign of recurrence (Figure 1c).

Case two

Our second patient was a 55-year-old woman whose chief complaint was protrusion of her left eyeball. She presented initially at a neighbourhood clinic, with a protruding left

Accepted for publication 13 November 2012 First published online 8 August 2013

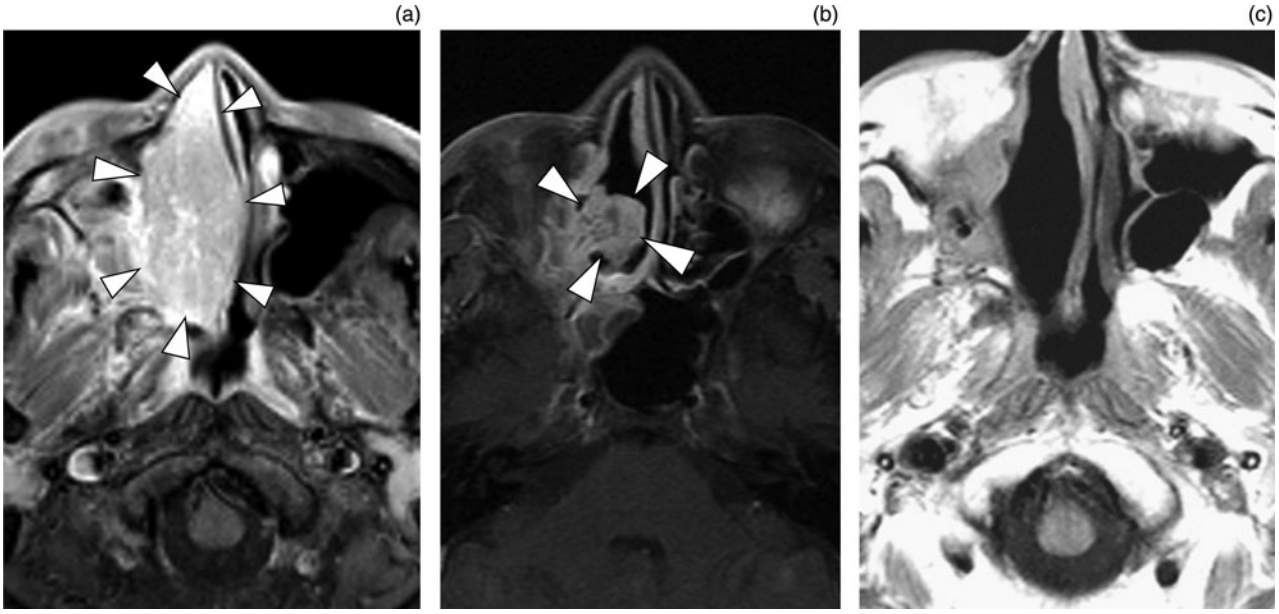

FIG. 1

Imaging studies for case one. (a) Axial, gadolinium-enhanced, T1-weighted magnetic resonance imaging (MRI) scan before treatment. (b) Axial, gadolinium-enhanced, T1-weighted MRI scan after initial treatment. (c) Axial, T2-weighted MRI scan taken 31 months after treatment. Arrowheads indicate the tumour.

eyeball. An MRI revealed a tumour in the left ethmoid sinus, which led to her referral to our institution.

Upon examination, the patient's left eyeball was noticeably protuberant. An enlarged lymph node was detected upon palpation of the submandibular region of the neck. A biopsy of the tumour via the left middle nasal passage revealed small cell carcinoma.

Magnetic resonance imaging revealed a tumour centred within the left ethmoid sinus. The mass extended to the nasal cavity, orbit and cranium, but with no evidence of brain metastasis (Figure 2a). A CT revealed metastasis to submandibular lymph nodes but no abnormalities in other regions. Bone scintigraphy showed accumulation only in the left nasal cavity.

The tumour was diagnosed as stage IV-B small cell carcinoma (T_{4b} N_{2b} M_0), limited disease, with a primary lesion in the left ethmoid sinus.

Chemotherapy was commenced, following a regimen of platinum 120 mg for 1 day and etoposide 150 mg for 3 days, for a total of four courses. A total radiotherapy dose of 60 Gy was given in 30 fractions, commencing with the second course of chemotherapy.

Upon completion of treatment, imaging revealed a 64.4 per cent reduction in tumour size, which was classified as a partial response (Figure 2b). Adverse effects of treatment included grade IV bone marrow toxicity and grade II mucositis. Following treatment, we opted for 'wait and scan' management.

Two months after treatment, the patient developed disseminated intravascular coagulation. Histological examination revealed tumour cells in the peripheral blood. These findings indicated that the cancer had metastasised to bone marrow. Additional treatment was contraindicated due to the patient's poor general condition. She died two weeks after diagnosis of metastasis.

Case three

Our final patient was a 58-year-old man who presented at another hospital complaining mainly of swelling in the left submandibular area. After an open biopsy revealed small cell carcinoma, the patient was referred to our hospital.

Palpation revealed a hard mass approximately 60 mm in size at the location of the left submandibular gland, with strong adhesion to the mandibular bone. There was reduced sensitivity in the area of the lesion.

An MRI revealed a tumour centred within the left submandibular area (Figure 3a). A CT scan revealed metastases in submandibular and submental lymph nodes. There were no visible abnormalities in other regions. Bone scintigraphy showed accumulation only under the left mandible.

The tumor was diagnosed as stage IV-A small cell carcinoma (T_{4a} N_{2b} M_0), limited disease, with a primary lesion in the left submandibular gland.

The patient underwent a chemotherapy regimen of platinum 140 mg for 1 day and etoposide 170 mg for 3 days, for a total of three courses. A total radiotherapy dose of 60 Gy was given in 30 fractions, commencing with the second course of chemotherapy. Because of adverse effects, including febrile neutropenia and drug-induced renal dysfunction, the final course of chemotherapy was changed from platinum to carboplatin (area under the curve, 5.0 mg·min/ml), and the etoposide dosage was reduced to 80 mg/m^2. The fourth course was therefore carboplatin 450 mg for 1 day (carboplatin dosage as per Calvert: (creatinine clearance 65 ml/min + 25) × area under the curve 5 mg·min/ml) plus etoposide 135 mg for 3 days.[12]

Upon completion of treatment, imaging revealed a 31.1 per cent reduction in tumour size, which was classified as a partial response (Figure 3b). The tumour was no longer detectable by palpation, and the overlying reduced sensitivity had disappeared. Adverse effects of treatment included grade IV bone marrow toxicity and grade IV mucositis.

Following treatment, we opted for 'wait and scan' management.

Thirteen months after completion of treatment, there had been no tumour progression.

https://doi.org/10.1017/S0022215113001606 Published online by Cambridge University Press

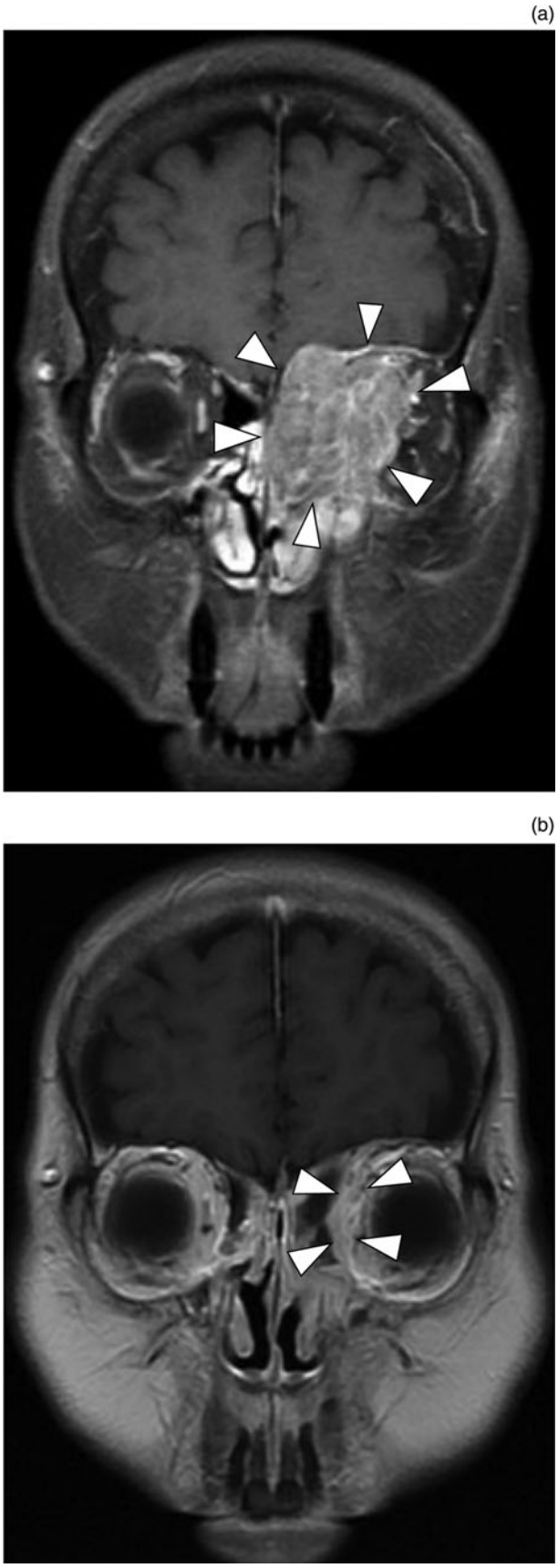

FIG. 2

Imaging studies for case two, showing coronal, gadolinium-enhanced, T1-weighted magnetic resonance imaging scans (a) before treatment and (b) after initial treatment. Arrowheads indicate the tumour.

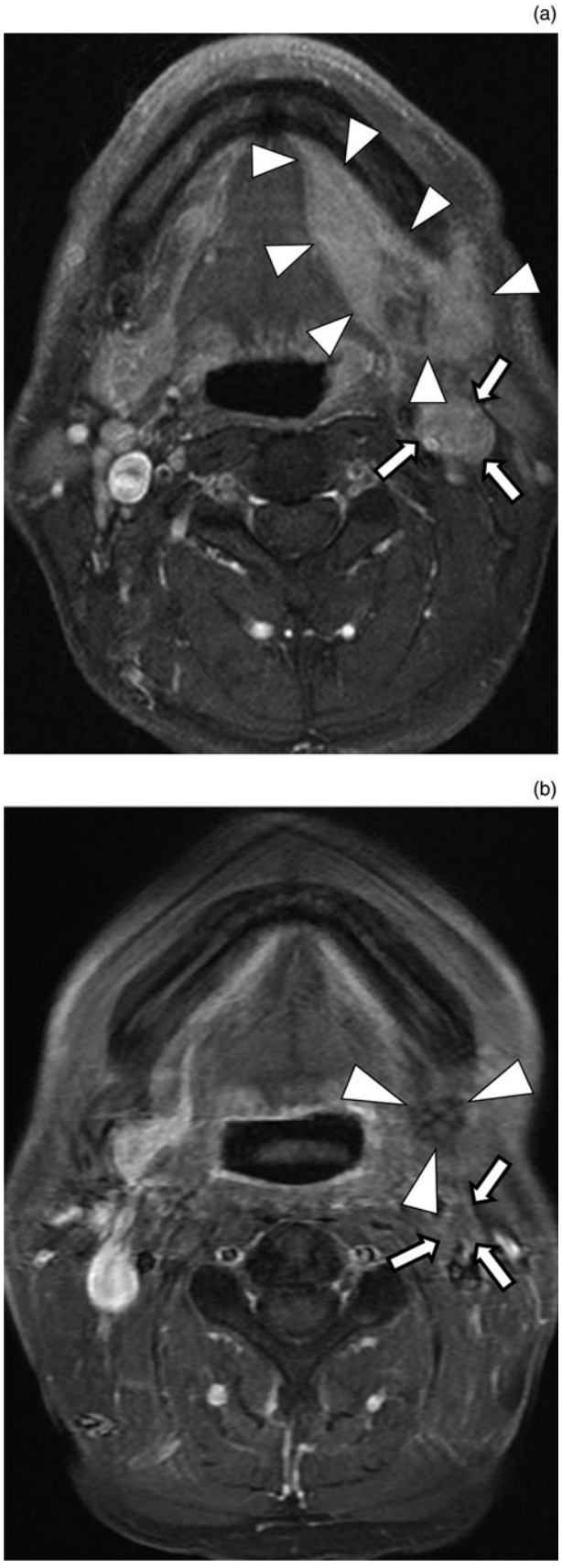

FIG. 3

Imaging studies for case three, showing axial, gadolinium-enhanced, T1-weighted magnetic resonance imaging scans (a) before treatment and (b) after initial treatment. Arrowheads indicate the tumour; arrows indicate an enlarged lymph node.

https://doi.org/10.1017/S0022215113001606 Published online by Cambridge University Press

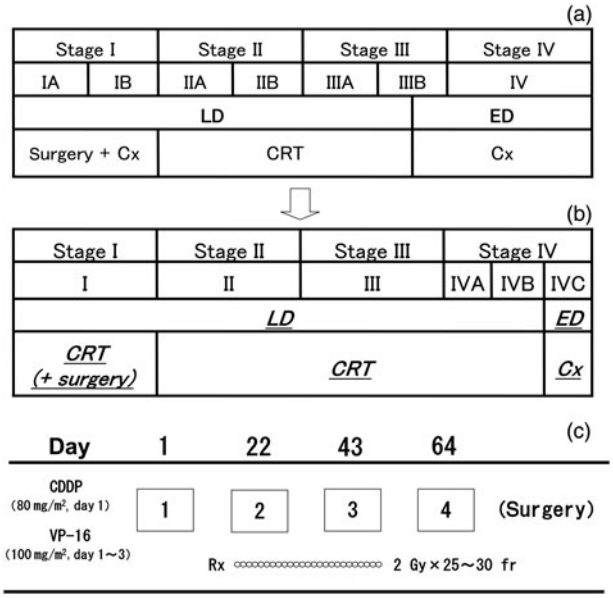

FIG. 4

(a) Treatment outline for small cell lung carcinoma, as specified in the Japanese Lung Cancer Treatment Guidelines. (b) Proposed treatment outline for small cell carcinoma of the head and neck. (c) Chemoradiotherapy regimen for small cell carcinoma of the head and neck. LD = limited disease; ED = extensive disease; Cx = chemotherapy; CRT = chemoradiotherapy; CDDP = platinum; VP-16 = etoposide; Rx = radiotherapy; fr = fractions

Discussion

The Japanese Lung Cancer Treatment Guidelines are now commonly used for treating small cell lung carcinoma; however, there are no guidelines for the treatment of extrapulmonary small cell carcinoma.[13–15] Some reports have suggested that extrapulmonary small cell carcinoma is pathologically dissimilar from small cell lung carcinoma and should therefore be treated as an entirely different condition.[16] Nevertheless, extrapulmonary small cell carcinoma is typically treated using the guidelines for small cell lung carcinoma, which are strongly supported by evidence.[17,18] Thus, it is reasonable to adapt the Japanese Lung Cancer Treatment Guidelines for treatment of small cell carcinoma of the head and neck.

In the above patient series, we selected full-body CT scan and bone scintigraphy to diagnose small cell carcinoma of the head and neck. Furthermore, due to the histological characteristics of this cancer, we would advise MRI scanning of both the affected area and the cranium.[18,19]

Figure 4(a) shows the strategy for treating small cell lung carcinoma, while Figure 4(b) shows our proposed strategy for treating small cell carcinoma of the head and neck. First, it is necessary to classify the extent of the carcinoma: either limited disease or extensive disease.[1,2] Limited disease is defined as disease 'limited to an area for which radiotherapy is potentially curative'.[20] If this criterion was used to classify small cell carcinoma of the head and neck, all but stage IV-C cases would be classified as limited disease. Because simple chemotherapy is unusual for cancers of the head and neck, we maintain that chemoradiotherapy is indicated even for stage I disease.[13,14,19] Many reports emphasise that small cell carcinoma should be treated as systemic rather than localised disease; thus, we believe that chemoradiotherapy is the appropriate first-line treatment for stage I disease, and that the decision to undertake surgical treatment should be based on the results of chemoradiotherapy.[18,21,22]

In the Japanese Lung Cancer Treatment Guidelines, the first-line chemotherapy regimen used within chemoradiotherapy is four courses of platinum plus etoposide.[3] These Guidelines recommend concurrent radiotherapy and chemotherapy.[4,5] However, because our centre required approximately 10 days to plan and prepare a course of radiotherapy, we commenced patients on chemotherapy immediately, and began standard fractionated radiotherapy concurrently with the second course of chemotherapy. As regards radiotherapy dose fractionation, the Guidelines recommend 45 Gy of accelerated hyperfractionation.[6] However, several studies have reported that accelerated hyperfractionation can lead to spinal cord toxicity, and there is insufficient evidence to support the use of the same radiotherapeutic dose employed for carcinoma of the head and neck (i.e. 50–60 Gy).[7] Thus, we selected standard fractionation of 50 to 60 Gy in 25 to 30 fractions over five to six weeks (Figure 4c).

With regard to treatment planning, the Japanese Lung Cancer Treatment Guidelines recommend that if initial treatment produces a partial response or better, then the usual approach should be to simply 'wait and scan'. In cases with tumour reduction of less than 30 per cent, or in the event of a relapse, the approach should comprise chemotherapy, extensive surgical removal or best supportive care.[8–10]

- **Three patients with small cell carcinoma of the head and neck are presented**
- **Treatment was adapted from the Japanese Lung Cancer Treatment Guidelines for small cell lung carcinoma**
- **All patients underwent chemoradiotherapy; one case also had subsequent surgery**
- **Short-term results were equivalent to or better than usual outcomes for small cell lung carcinoma**

The short-term results of the present study were equivalent to or better than the usual treatment outcomes for small cell lung carcinoma. Some questions remain to be answered, however, including: (1) whether better results might be obtained with accelerated hyperfractionation; (2) whether surgical intervention is indicated even for patients with stage II or III disease; and (3) whether starting both radiotherapy and chemotherapy on day 1 would ultimately yield better results. Finally, clinical trials are needed to identify optimal treatment strategies for small cell carcinoma of the head and neck.[23]

Acknowledgements

The authors thank the Bioscience Medical Research Center, Second Department of Medicine, Department of Radiology, Department of Molecular Genetics, Division of Cellular and Molecular Pathology, and Division of Molecular and Diagnostic Pathology, at Niigata University.

References

1 Pignon JP, Arriagada R, Ihde DC, Johnson DH, Perry MC, Souhami RL *et al.* A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med* 1992;**327**:1618–24

https://doi.org/10.1017/S0022215113001606 Published online by Cambridge University Press

2 Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. *J Clin Oncol* 1992;**10**:890–5
3 Noda K, Nishiwaki Y, Kawahara M, Negoro S, Sugiura T, Yokoyama A *et al*. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002;**346**:85–91
4 Jeremic B, Shibamoto Y, Acimovic L, Milisavljevic S. Initial versus delayed accelerated hyperfractionated radiation therapy and concurrent chemotherapy in limited small-cell lung cancer: a randomized study. *J Clin Oncol* 1997;**15**:893–900
5 Takada M, Fukuoka M, Kawahara M, Sugiura T, Yokoyama A, Yokota S *et al*. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. *J Clin Oncol* 2002;**20**:3054–60
6 Choi NC, Herndon JE 2nd, Rosenman J, Carey EW, Chung CT, Bernard S *et al*. Phase I study to determine the maximum-tolerated dose of radiation in standard daily and hyperfractionated-accelerated twice-daily radiation schedules with concurrent chemotherapy for limited-stage small-cell lung cancer. *J Clin Oncol* 1998;**16**:3528–36
7 Macbeth FR, Wheldon TE, Girling DJ, Stephens RJ, Machin D, Bleehen NM *et al*. Radiation myelopathy: estimates of risk in 1048 patients in three randomized trials of palliative radiotherapy for non-small cell lung-cancer. The Medical Research Council Lung Cancer Working Party. *Clin Oncol (R Coll Radiol)* 1996;**8**:176–81
8 Ettinger DS, Finkelstein DM, Abeloff MD, Ruckdeschel JC, Aisner SC, Eggleston JC. A randomized comparison of standard chemotherapy versus alternating chemotherapy and maintenance versus no maintenance therapy for extensive-stage small-cell lung cancer: a phase III study of the Eastern Cooperative Oncology Group. *J Clin Oncol* 1990;**8**:230–40
9 Sculier JP, Paesmans M, Bureau G, Giner V, Lecomte J, Michel J *et al*. Randomized trial comparing induction chemotherapy versus induction chemotherapy followed by maintenance chemotherapy in small-cell lung cancer. European Lung Cancer Working Party. *J Clin Oncol* 1996;**14**:2337–44
10 Ebi N, Kubota K, Nishiwaki Y, Hojo F, Matsumoto T, Kakinuma R *et al*. Second-line chemotherapy for relapsed small cell lung cancer. *Jpn J Clin Oncol* 1997;**27**:166–9
11 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;**45**:228–47
12 Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE *et al*. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989;**11**:1748–56
13 Galanis E, Frytak S, Lloyd RV. Extrapulmonary small cell carcinoma. *Cancer* 1997;**79**:1729–36
14 Kim KO, Lee HY, Chun SH, Shin SJ, Kim MK, Lee KH *et al*. Clinical overview of extrapulmonary small cell carcinoma. *J Korean Med Sci* 2006;**21**:833–7
15 Gregory R. Small cell carcinoma of the head and neck: a review. *Semin Oncol* 2007;**34**:3–14
16 Ferlito A, Barnes L, Rinaldo A, Gneep DR, Milroy CM. A review of neuroendocrine neoplasms of the larynx: update on diagnosis and treatment. *J Laryngol Otol* 1998;**112**:827–34
17 Rosenthal DI, Barker JL, EL-Naggar AK. Sinonasal malignancies with neuroendocrine differentiation: patterns of failure according to histologic phenotype. *Cancer* 2004;**101**:2567–73
18 Barnes L, Eveson JW, Reichert P, Sidransky D. *Pathology and Genetics of Head and Neck Tumors (World Health Organization Classification of Tumors)*. Lyon: IARC Press, 2005;135–9
19 Mills SE. Neuroectodermal neoplasms of the head and neck with emphasis on neuroendocrine carcinomas. *Mod Pathol* 2002;**15**:264–78
20 Micke P, Faldum A, Metz T, Beeh KM, Bittinger F, Hengstler JG *et al*. Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer—what limits limited disease? *Lung Cancer* 2002;**37**:271–6
21 Lee CH, Lin HC. Descriptive study of prognostic factors influencing survival of patients with primary tracheal tumors. *Chang Gung Med J* 1995;**18**:224–30
22 Muller AC, Gani C, Weinmann M, Mayer F, Sipos B, Bamberg M *et al*. Limited disease of extra-pulmonary small cell carcinoma. Impact of local treatment and nodal status, role of cranial irradiation. *Strahlenther Onkol* 2012;**188**:269–73
23 Lee SS, Lee JL, Ryu MH, Chang HM, Kim TW, Kim WK *et al*. Extrapulmonary small cell carcinoma: single center experience with 61 patients. *Acta Oncol* 2007;**46**:846–51

Address for correspondence:
Dr Hiroshi Matsuyama,
Department of Otolaryngology,
Niigata University,
Faculty of Medicine,
1-757 Asahimachi-dori, Chuo-ku,
Niigata-shi 951-8510, Japan

Fax: +81 25 227 0786
E-mail: matsuhiroshi@med.niigata-u.ac.jp

Dr H Matsuyama takes responsibility for the integrity of the content of the paper
Competing interests: None declared