Prognostic Significance of Dysadherin and E-cadherin Expression in Patients with Head and Neck Cancer Treated by Radiation Therapy

HIROYUKI MURAMATSU[1,2], TETSUO AKIMOTO[1], KATSUYA MAEBAYASHI[1], MIDORI KITA[3] and NORIO MITSUHASHI[1]

[1]*Department of Radiology, Tokyo Women's Medical University School of Medicine, Shinjuku-ku, Tokyo 162-8666;*
[2]*Radiology, Kiryu Kosei General Hospital, Kiryu 376-0024;*
[3]*Radiology, Huchu Hospital, Huchu 183-8524, Japan*

Abstract. *Background: The aim of this study was to evaluate the impact of dysadherin and E-cadherin expression on the clinical outcomes, including the treatment outcomes and recurrence pattern, in patients with head and neck cancer. Patients and Methods: Tumor specimens were obtained from 48 head and neck cancer patients who were treated by radiation therapy and the specimens were immunohistochemically stained for dysadherin and E-cadherin. The expressions were graded according to the percentage area occupied by cancer cells showing positive staining for E-cadherin and dysadherin as follows: grade 0, less than 10% ; grade 1, 10-50% ; grade 2, more than 50% . The correlations between the expression of E-cadherin and dysadherin and the clinical outcomes, including the treatment outcomes and recurrence pattern, were analyzed. Results: The complete response (CR) rate in the patients with a dysadherin expression grade of 0 or 1 was 70% and that in the patients with dysadherin expression grade of 2 was 38% ; the difference was significant ($p<0.05$). Regarding the pattern of recurrence, the expression grade of dysadherin or E-cadherin alone was not correlated with the recurrence pattern; however, patients with a difference in the expression grade between dysadherin and E-cadherin (Dys-Ecad value) of 1 or 2 showed a significantly higher rate of lymph node and/or distant metastasis (55%) as compared with those with a Dys-Ecad value of <1 (22%) ($p<0.05$). Conclusion: Dysadherin and E-cadherin expression might serve as useful prognostic factors in patients with head and neck cancer treated by definitive radiation therapy.*

Correspondence to: Tetsuo Akimoto, MD, Ph.D., Department of Radiology, Tokyo Women's Medical University School of Medicine, 8-1 Kawada-cho, Shinjuku, Tokyo 162-8666, Japan. Tel: +81 3 5269 7355, Fax: +81 352697355, e-mail: t-akimoto@rad.twmu.ac.jp

Key Words: Head and neck cancer, radiation therapy, E-cadherin, dysadherin.

Radiation therapy has been one of the most important approaches for the treatment of head and neck cancer, because the preservation of organ function in this region influences the quality of life (QOL) of the patients (1-3). However, radiation therapy alone does not yield a satisfactory local control rate in cases of locally advanced head and neck cancer because of the high rate of local recurrence and distant metastasis to the regional lymph nodes and organs such as the lung and bone. In recent years, several approaches have been investigated to improve the radiotherapeutic outcomes in head and neck carcinomas. Prospective clinical trials and meta-analyses have since revealed that chemoradiotherapy, especially concurrent chemoradiotherapy and/or hyperfractionated radiation therapy, yield improved local control and survival rates in these cases as compared with radiation therapy alone (4-7). However, even with this approach, a substantial number of patients developed recurrence or metastasis outside the radiation field, which affected the clinical outcome, including the survival rate.

Predictive factors for radiotherapeutic outcomes in head and neck cancer have been reported. Ang *et al*. analyzed the expression of epidermal growth factor receptor (EGFR) in head and neck cancer patients treated with definitive radiation therapy, and demonstrated that an elevated expression of EGFR was associated with reduced disease-free and overall survival rates even in the absence of any differences in the distribution of the TNM stage or distant metastasis rate between the two groups (8). This may have been partly attributable to the relative radioresistance of head and neck carcinomas showing high expression levels of EGFR. The rates of distant metastasis or metastasis to the lymph nodes have a greater impact on the treatment

outcomes in locoregional treatment approaches including surgery and/or radiation therapy, hence, prediction of the characteristics of the tumors would be useful for the selection of treatment modalities such as the addition of neoadjuvant or adjuvant chemotherapy.

A number of molecules that are associated with metastasis have been reported (9, 10). Among these, E-cadherin has been shown to be closely associated with the metastatic potential of cancer. The cadherins mediate calcium-dependent cell-cell adhesion and are essential for the maintenance of tissue structure. The role of E-cadherin expression in locoregional progression or development of metastasis of cancer has been well investigated (11, 12). Published studies have demonstrated a negative correlation between the expression of E-cadherin and the metastatic potential in several types of cancer (13-15). In contrast to E-cadherin, dysadherin has been isolated as a molecule that promotes the metastatic activity of cancer. Dysadherin is a cancer-associated cell membrane-type of glycoprotein that was originally isolated and named by Ino *et al*. (16). They demonstrated that transfection of the cDNA of dysadherin resulted in post-transcriptional inactivation of E-cadherin function and that, therefore, dysadherin plays an important role in tumor progression and metastasis. Dysadherin is overexpressed in many types of cancer cells, in contrast to its limited expression in normal cells. In regard to head and neck cancer, Kyzas PA *et al*. reported that dysadherin expression was correlated with an advanced clinical stage, a high rate of lymph node metastasis and a high intratumoral lymphatic density (17). However, to the best of our knowledge, there have been no reports on the dysadherin expression level as a prognostic factor for the clinical outcomes after radiation therapy.

In this context, the expression of E-cadherin and dysadherin in patients with head and neck cancer who were treated with definitive radiation therapy was investigated, and the correlation between the expression of E-cadherin and dysadherin and the clinical outcomes, including the local response rates to radiation therapy, and the recurrence and survival rates was analyzed.

Patients and Methods

Patients. Among patients with head and neck cancer who were treated by definitive radiation therapy, a total of 48 patients who provided informed consent for this analysis and for whom specimens were available for immunohistochemistry were included in this study. The patients ranged in age from 24 to 92 years, with an average age of 61 years. The male to female ratio was 3.4/1.0. The distributions of the primary sites was as follows: nasal cavity, 2 patients; paranasal sinus, 11 patients; oral cavity, 26 patients; nasopharynx, 2 patients; oropharynx, 4 patients, and hypopharynx, 3 patients. The patients were staged according to the International Union against Cancer (UICC) criteria (18) as follows: stage II, 11 patients; stage III, 8 patients and stage IV, 29 patients. The median follow-up duration after radiation therapy was 38 months, and the follow-up duration of the patients who were alive at the time of this analysis was more than 5 years.

All the patients received definitive radiation therapy for head and neck cancer with curative doses with a range of 60-72 Gy. Out of the 48 patients, 34 (71%) received neoadjuvant and/or concurrent systemic chemotherapy. The local response was estimated one month after the completion of radiation therapy by computed tomography (CT) or magnetic resonance image (MRI) of the head and neck. Local failure or recurrence was considered to have occurred when there was either clinical persistence of the cancer at the end of the radiation therapy or local recurrence developed after initial complete response (CR).

Immunohistochemistry. Freshly cut 4-μm-thick paraffin-embedded tumor slides were used. The tumor samples were deparaffinized in xylene and rehydrated through graded concentrations of alcohol. The endogenous enzyme activity was blocked in 0.3% H_2O_2 in methanol (0.01M) for 10 minutes. Next, the slides were heated an autoclave for 30 minutes for antigen retrieval, blocking with citrate (pH 6.0). After washing with phosphate-buffered saline (PBS) for 5 minutes, the samples were incubated overnight with a monoclonal antibody (dilution 1: 1000) directed against either E-cadherin (ECD-1; TaKaRa Bio, Hyogo, Japan) or dysadherin (antibody was kindly provided by Dr Hirohashi, National Cancer Center Research Institute, Tokyo, Japan). The slides were incubated with a goat antimouse secondary antibody conjugated with peroxidase-labeled polymere and then with diaminobenzidine chromogen solution (Histofine Kit; NichireiVaioscience, Tokyo, Japan). The slides were then mounted after counterstaining with hematoxylin. For the negative control, the first antibody was substituted with a mouse immunoglobulin of the same class.

Evaluation of dysadherin and E-cadherin expression. Two observers without prior knowledge of the clinical parameters and outcomes of the patients independently reviewed the immunohistochemically stained sections to evaluate the strength of expression of dysadherin and E-cadherin. All discrepancies were resolved by a joint review of the relevant slides.

The expression of E-cadherin was considered to be positive if the tumor cells were as strongly stained as the normal keratinocytes adjacent to the tumor. The expression of dysadherin was considered to be positive if the tumor cells were as strongly stained as the basal cells in the adjacent epidermis and the endothelial cells. The expression intensity was then semi-quantitatively graded into the following three groups based on the percentage area occupied by the cancer cells showing positive staining for E-cadherin and dysadherin: grade 0, 0-10%; grade 1, 11-50% and grade 2, over 50%. Representative sections showing positive staining for E-cadherin and dysadherin are shown in Figure 1.

Statistical analysis. Statistical analyses were conducted using SPSS software, version 11.0 (SPSS Inc, Chicago, IL, USA). For comparisons of the correlations between the expression of E-cadherin and dysadherin and the clinicopathological variables, the chi-square test was used; *p*-values of less than 0.05 were considered as denoting statistical significance. The Kaplan-Meier method was used to draw the time-to-event curves (19). The length of follow-up for estimation of the cause-specific survival rates was calculated

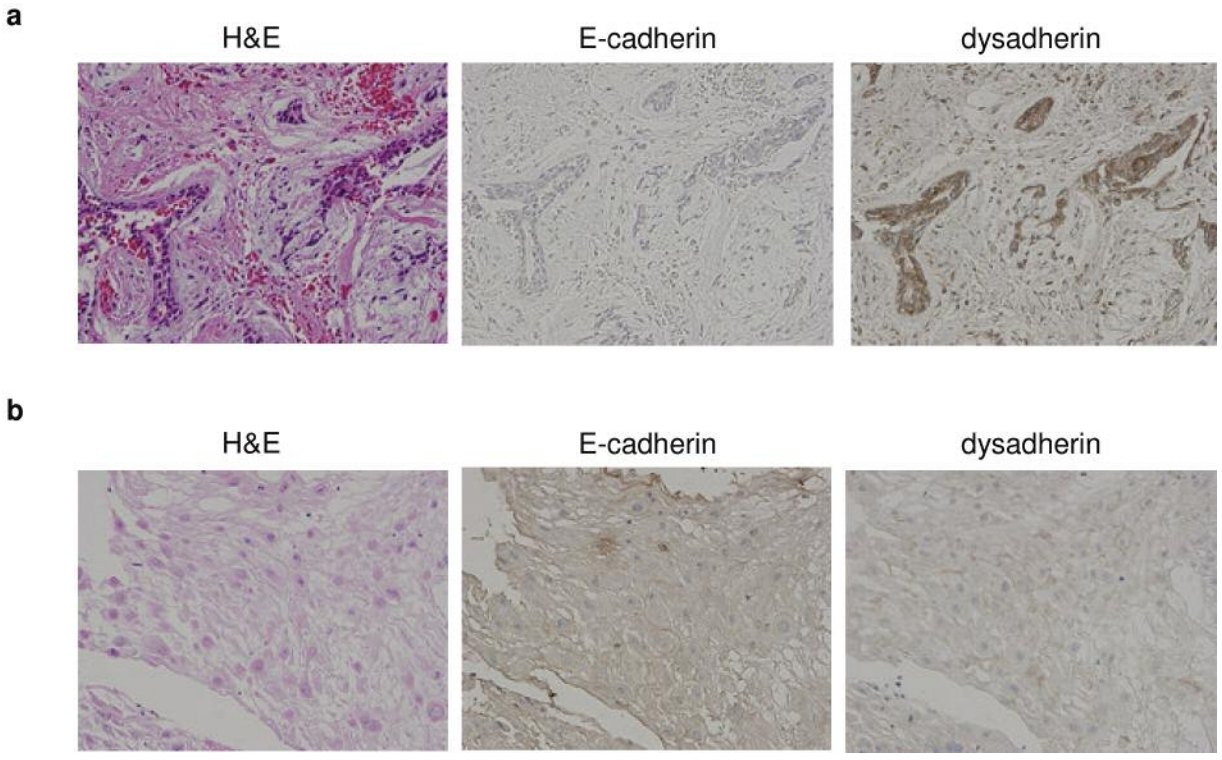

Figure 1. *Immunohistochemistry for E-cadherin and dysadherin. The section for E-cadherin or dysadherin was the same as the section for hematoxylin and eosin (H&E) staining. a) Grade of E-cadherin expression was 0 and that of dysadherin was 2. b) Grade of E-cadherin expression was 2 and that of dysadherin was 0.*

from the start of the treatment and the Generalized Wilcoxon test was used to evaluate the statistical significance of a comparison of survival in different subgroups.

Results

Clinical outcomes. The response to radiation therapy was classified as CR in 26 patients, partial response (PR) in 18 patients and stable disease (SD) in 4 patients. Salvage surgery was performed in 4 patients, and the overall cause-specific survival rate at 5 years was 52% . In regard to the recurrence pattern, 4 patients developed local recurrence and 25 patients developed lymph node (outside of radiation field or marginal recurrence) and/or distant metastasis (lymph node metastasis in 16 patients, distant metastasis in 6 patients, both lymph node and distant metastases in 3 patients).

Correlation between the clinical outcomes and the expression of E-cadherin and dysadherin. Expression of E-cadherin was observed in the cell-cell border between epithelial cells and cancer cells, and that of dysadherin was observed in the membranes of the cancer cells, but not in non-cancerous cells. The distributions of the expression of E-cadherin and dysadherin were as follows. E-cadherin: grade 0, 24 patients; grade 1or 2, 24 patients; dysadherin: grade 0, 2 patients; grade 1, 22 patients; grade 2, 24 patients. Among the 24 patients with grade 0 E-cadherin expression, 10 patients (42%) showed grade 0 dysadherin expression and the remaining 14 patients (58%) showed grade 1 or 2 dysadherin expression. Among the 24 patients with grade 1 or 2 E-cadherin expression, 14 patients (58%) showed grade 0 dysadherin expression and the remaining 10 patients (42%) showed grade 1 or 2 dysadherin expression. There was a trend towards inverse correlation between E-cadherin and dysadherin expression, however, the correlation was not statistically significant.

In regard to the impact of the E-cadherin or dysadherin expression grade on the cause-specific survival, the 5-year cause-specific survival rates in the patients with grade 0 and grade 1 or 2 dysadherin expression were 53% and 50%, respectively; the difference was not significant. The 5-year cause specific survival rates in the patients with grade 0 and grade 1 or 2 E-cadherin expression were 54% and 50%, respectively; this difference was also not significant.

In the analysis of the correlation between the response to radiation therapy and the expression grade of E-cadherin or dysadherin, the CR rates in the patients with an E-cadherin expression of grade 0 or 1 and grade 2 were 50 and 58%,

Table I. *Correlation between the response to radiation therapy and the expression grade of E-cadherin and dysadherin.*

E-cadherin	CR	Non-CR
0	12	12
1 or 2	14	10
Dysadherin		
0 or 1	17	7
2	9	15
Dys-Ecad		
<1	11	7
1 or 2	16	14

Dys-Ecad: Expression grade of dysadherin minus expression grade of E-cadherin The difference in the CR rate between patients with grade 0 or 1 dysadherin expression and those with grade 2 dysadherin expression was statistically significant ($p<0.05$).

Table II. *Correlation between the recurrence rate in cervical lymph node and/or distant sites and the expression grade of E-cadherin and dysadherin.*

E-cadherin	+	–
0	12	12
1 or 2	8	16
Dysadherin		
0 or 1	9	15
2	11	13
Dys-Ecad		
<1	4	14
1 or 2	16	14

Dys-Ecad value: Expression grade of dysadherin minus expression grade of E-cadherin, +: development of recurrence, –: no recurrence. Patients with a Dys-Ecad value of 1 or 2 showed a significantly higher rate of lymph node and/or distant metastasis (55%) as compared with those with a Dys-Ecad value of less than 1 (22%) ($p<0.05$).

respectively (Table I); the difference was not significant. In contrast, the CR rates in the patients with a dysadherin expression grade of 0 or 1 and grade 2 were 70% and 38%, respectively; this difference was significant ($p<0.05$), indicating that patients with high expression levels of dysadherin tended to show a poor response to radiation therapy (Table I). According to the difference in the expression grade between dysadherin and E-cadherin (Dys-Ecad value), the CR rates in the patients with a Dys-Ecad value of less than 1 and that of 1 or 2 were 69% and 53%, respectively (Table I). The difference was not significant.

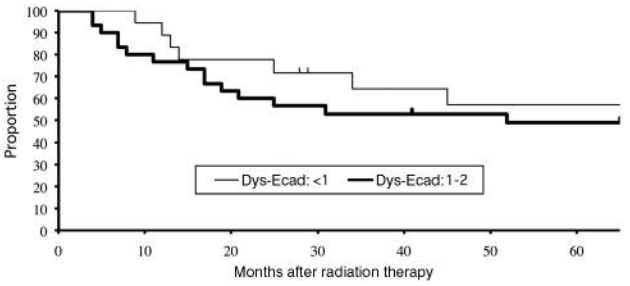

Figure 2. *The cause specific survival rates. The 5-year cause-specific survival rates in the patients with a Dys-Ecad value of 1 or 2 and those with a Dys-Ecad value of less than 1 were 49% and 57%, respectively, but the difference was not significant.*

In regard to the pattern of recurrence, neither the grade of dysadherin nor E-cadherin expression was correlated with the recurrence pattern (Table II). Twelve patients (50%) with an E-cadherin expression grade of 0 developed lymph node and/or distant metastasis and 33% of those with an E-cadherin expression of grade 1 or 2 developed lymph node and/or distant metastasis. Nine patients (38%) with a dysadherin expression grade of 0 or 1 developed lymph node and/or distant metastasis, and 46% of patients with a dysadherin expression grade of 2 developed lymph node and/or distant metastasis. The difference in the rate of lymph node and/or distant metastasis according to the expression grade of E-cadherin or dysadherin was not significant. However, patients with a Dys-Ecad value of 1 or 2 showed a significantly higher rate of lymph node and/or distant metastasis (55%) as compared with those with a Dys-Ecad value of less than 1 (22%) ($p<0.05$) (Table II). The 5-year cause-specific survival rates in the patients with a Dys-Ecad value of 1 or 2 and those with a Dys-Ecad value of less than 1 were 49% and 57%, respectively (Figure 2). While there was a trend for the prognosis of patients with a Dys-Ecad value of 1 or 2 being poorer as compared with that of those with a Dys-Ecad value of less than 1, the difference in prognosis between the two groups was not significant. The incidence of lymph node and/or distant metastasis did not differ significantly between the patients who received chemotherapy and those who did not receive chemotherapy, although 71% of the patients analyzed in this study received neoadjuvant and/or concurrent systemic chemotherapy.

Discussion

The results of this study demonstrated that the difference in the expression grade between dysadherin and E-cadherin had a significant impact on the incidence of development of lymph

node and/or distant metastasis after radiation therapy for head and neck cancer. In addition, the expression grade of dysadherin was closely associated with the initial response to radiation therapy. After radiation therapy, a significantly higher lymph node and/or distant metastasis rate was observed in the patients with a Dys-Ecad value of 1 or 2 than in those with a Dys-Ecad value of less than 1. This indicated that the patients who showed a higher expression of dysadherin than E-cadherin might be at a potentially higher risk of the development of metastasis as compared with those with a higher expression of E-cadherin than of dysadherin. Since the development of lymph node and/or distant metastasis directly affects the survival of the patients, the results of this study demonstrated that the 5-year cause-specific survival rate in the patients with a dysadherin expression grade of 1 or 2 was lower (49%) than that in those with a dysadherin expression grade of less than 1 (57%). Nakanishi *et al*. also reported that dysadherin expression was significantly correlated with a high tumor-node metastasis and a poor prognosis in cases of tongue cancer (20).

The inverse correlation between dysadherin and E-cadherin expression did not reach statistical significance in the present study, perhaps partly because of the small number of patients analyzed, but the possible influence of inactivation or dysfunction of E-cadherin function by dysadherin on the metastatic potential cannot be excluded. Concerning the inverse correlation between dysadherin and E-cadherin expression, the published results differ according to the analyzed cancer types. For example, while no inverse correlation between dysadherin and E-cadherin expression was observed in cases of non-small cell lung cancer, colon cancer, breast cancer and gastric cancer, a significant inverse correlation between the two was reported in cases of tongue and thyroid carcinoma, and head and neck squamous carcinoma, suggesting that down-regulation of E-cadherin may be an important contributory mechanism in the progression and development of metastases in head and neck carcinomas (17, 20-24). In other words, the E-cadherin-independent action of dysadherin on the regulation of cancer invasion activity or metastasis may dominate in some tumor types, or as Nam *et al*. have suggested, dysadherin might affect E-cadherin function rather than its expression (25). In fact, Batistatou A *et al*. recently reported the existence of a correlation between the invasiveness of breast cancer and the expression grade of dysadherin and E-cadherin, and suggested that dysadherin may play an important role in breast cancer progression by promoting invasion in an E-cadherin independent manner (26). Hence, further study is necessary to clarify the roles of dysadherin and E-cadherin expression in head and neck carcinomas in tumor progression and metastasis.

Besides the impact of dysadherin expression on the metastatic potential, the results of this study also demonstrated that the expression of dysadherin was closely associated with the initial response rate to radiation therapy. The patients with a high expression grade of dysadherin tended to show a poor response to radiation therapy. Since only on the expression of E-cadherin and dysadherin was focused on in this study, whether or not other factors might also have had an influence could not be determined. There have been a few reports focusing on the relationship between the radiosensitivity or radioresponse of cancer cells and the expression or activation of cell adhesion molecules. Sandfort *et al*. demonstrated that the integrins and their associated downstream signaling pathways, as well as cooperative interactions of the integrins with receptor tyrosine kinases, mediate defensive mechanisms that promote the therapeutic eradication of tumor cells by radiation therapy (27). We formerly reported that radiation exposure modified the E-cadherin and alpha-catenin expression in tumor cells, which led to a decrease in the invasive capacity of a human lung cancer cell line *in vitro* (28, 29). Hence, it may be possible that cell adhesion molecules play an important role in the cellular response to radiation. Recently, Nam *et al*. reported that dysadherin expression was associated with enhanced activity of the NF-κB pathway in a breast cancer model system, although the link between dysadherin and NF-κB activation is still unknown (25). NF-κB, a nuclear transcription factor, is activated in certain carcinomas and in response to chemotherapy and radiation. The transcriptional activation of genes associated with cell proliferation, angiogenesis, metastasis and suppression of apoptosis appears to lie at the heart of the ability of NF-κB to promote cancer cell resistance to therapy (30). This is also consistent with the finding that dysadherin expression was largely localized to infiltrating tumor cells or cells dissociating from the tumor mass (22). Considering these findings, it can easily be speculated that carcinomas showing high expression levels of dysadherin also show a radioresistance profile in addition to exhibiting prometastatic characteristics as compared with those showing low expression levels of dysadherin; this might serve as an explanation for the results of this study, with the results indicating that the expression of dysadherin was closely associated with the initial response to radiation therapy.

In conclusion, the expression grade of dysadherin is closely correlated with the response to radiation therapy and the rate of distant metastasis after radiation therapy. A firm conclusion cannot be drawn from the results of this study because of the small number of patients analyzed and the retrospective nature of this study; nonetheless, it is proposed that dysadherin and E-cadherin expression levels might serve as useful prognostic factors in patients with head and neck cancer treated with definitive radiation therapy.

Acknowledgements

This study was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan, and by Health Science Research Grants from the Ministry of Health and Welfare.

References

1 Akimoto T, Mitsuhashi N, Hayakawa K *et al*: Split-course accelerated hyperfractionation radiotherapy for advanced head and neck cancer: influence of split time and overall treatment time on local control. Jpn J Clin Oncol *27(4)*: 240-243, 1997.

2 Rosenthal DI and Ang KK: Altered radiation therapy fractionation, chemoradiation, and patient selection for the treatment of head and neck squamous carcinoma. Semin Radiat Oncol *14(2)*: 153-166, 2004.

3 Akimoto T, Nonaka T, Kitamoto Y *et al*: Radiation therapy for T2N0 laryngeal cancer: A retrospective analysis for the impact of concurrent chemotherapy on local control. Int J Radiat Oncol Biol Phys *64(4)*: 995-1001, 2006.

4 Adelstein DJ, Lavertu P, Saxton JP *et al*: Mature results of a phase III randomized trial comparing concurrent chemoradiotherapy with radiation therapy alone in patients with stage III and IV squamous cell carcinoma of the head and neck. Cancer *88(4)*: 876-883, 2000.

5 Adelstein DJ, Li Y, Adams GL, Wagner H Jr *et al*: An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol *21(1)*: 92-98, 2003.

6 Bourhis J, Overgaard J, Audry H *et al*: Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) Collaborative Group. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet *368(9538)*: 843-854, 2006.

7 Langer CJ, Harris J, Horwitz EM *et al*: Phase II study of low-dose paclitaxel and cisplatin in combination with split-course concomitant twice-daily reirradiation in recurrent squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Protocol 9911. J Clin Oncol *25(30)*: 4800-4805, 2007.

8 Ang KK, Berkey BA, Tu X *et al*: Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. Cancer Res *62(24)*: 7350-7356, 2002.

9 Trzpis M, McLaughlin PM, de Leij LM and Harmsen MC: Epithelial cell adhesion molecule: more than a carcinoma marker and adhesion molecule. Am J Pathol *171(2)*: 386-395, 2007.

10 Dittmar T, Heyder C, Gloria-Maercker E, Hatzmann W and Zänker KS: Adhesion molecules and chemokines: the navigation system for circulating tumor (stem) cells to metastasize in an organ-specific manner. Clin Exp Metastasis *25(1)*: 11-32, 2008.

11 Akimoto T, Kawabe S, Grothey A and Milas L: Low E-cadherin and beta-catenin expression correlates with increased spontaneous and artificial lung metastases of murine carcinomas. Clin Exp Metastasis *17(2)*: 171-176, 1999.

12 Hirohashi S and Kanai Y: Cell adhesion system and human cancer morphogenesis. Cancer Sci *94(7)*: 575-581, 2003.

13 Wijnhoven BP, Dinjens WN and Pignatelli M: E-cadherin-catenin cell-cell adhesion complex and human cancer. Br J Surg *87(8)*: 992-1005, 2000.

14 Kase S, Sugio K, Yamazaki K *et al*: Expression of E-cadherin and beta-catenin in human non-small cell lung cancer and the clinical significance. Clin Cancer Res *6(12)*: 4789-4796, 2000.

15 Bremnes RM, Veve R, Hirsch FR and Franklin WA: The E-cadherin cell-cell adhesion complex and lung cancer invasion, metastasis, and prognosis. Lung Cancer *36(2)*: 115-124, 2002.

16 Ino Y, Goto M, Sakamoto M *et al*: Dysadherin, a cancer-associated cell membrane glycoprotein, down-regulates E-cadherin and promotes metastasis. Proc Natl Acad Sci USA *99(1)*: 365-370, 2002.

17 Kyzas PA, Stefanou D, Batistatou A *et al*: Dysadherin expression in head and neck squamous cell carcinoma: association with lymphangiogenesis and prognostic significance. Am J Surg Pathol *30(2)*: 185-193, 2006.

18 Sobin LH and Wittekind C: TNM Classification of Malignant Tumours. 5th Ed. New York Tront: Wiley-Liss, 1997.

19 Kaplan EL and Meier PL: Nonparametric estimation from incomplete observation. J Am Stat Assoc *53*: 457-481, 1958.

20 Nakanishi Y, Akimoto S, Sato Y *et al*: Prognostic significance of dysadherin expression in tongue cancer: immunohistochemical analysis of 91 cases. Appl Immunohistochem Mol Morpho *12(4)*: 323-328, 2004.

21 Batistatou A, Charalabopoulos AK, Scopa CD *et al*: Expression patterns of dysadherin and E-cadherin in lymph node metastases of colorectal carcinoma. Virchows Arch *448(6)*: 763-767, 2006.

22 Tamura M, Ohta Y, Tsunezuka Y *et al*: Prognostic significance of dysadherin expression in patients with non-small cell lung cancer. J Thorac Cardiovasc Surg *130(3)*: 740-745, 2005.

23 Simada Y, Yamasaki S, Hashimoto Y *et al*: Clinical significance of dysadherin expression in gastric cancer patients. Clin Cancer Res *10(8)*: 2818-2823, 2004.

24 Sato H, Ino Y, Miura A, Abe Y *et al*: Dysadherin: expression and clinical significance in thyroid carcinoma. J Clin Endocrinol Metad *88(9)*: 4407-4412, 2003.

25 Nam JS, Hirohashi S and Wakefield LM: Dysadherin: A new player in cancer progression. Cancer Lett *255(2)*: 161-169, 2007.

26 Batistatou A, Peschos D, Tsanou H *et al*: In breast carcinoma dysadherin expression is correlated with invasiveness but not with E-cadherin. Br J Cancer *96(9)*: 1404-1408, 2007.

27 Sandfort V, Koch U and Cordes N: Cell adhesion-mediated radioresistance revisited. Int J Radiat Biol *83(11-12)*: 727-732, 2007.

28 Akimoto T, Mitsuhashi N, Saito Y *et al*: Effect of radiation on the expression of E-cadherin and alpha-catenin and invasive capacity in human lung cancer cell line *in vitro*. Int J Radiat Oncol Biol Phys *41(5)*: 1171-1176, 1998.

29 Ebara T, Mitsuhashi N, Akimoto T *et al*: Change in E-cadherin expression after X-ray irradiation of human cancer cell line *in vitro* and *in vivo*. Int J Radiat Oncol Biol Phys *41(3)*: 669-674, 1998.

30 Orlowski RZ and Baldwin AS Jr: NF-kappaB as a therapeutic target in cancer. Trends Mol Med *8(8)*: 385-389, 2002.

Received May 17, 2008
Revised July 15, 2008
Accepted August 18, 2008