

# Immunohistochemical analysis of E-cadherin, $\alpha$ -catenin, $\beta$ -catenin, $\gamma$ -catenin, and neural cell adhesion molecule (NCAM) in chordoma

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## Abstract

**Aims**—the epithelioid features seen in chordoma are unique among mesenchymal tumours. However, no detailed analysis regarding cell–cell communication has been conducted in this epithelioid tumour. The aims of this study were to investigate cell–cell communication in chordoma.

**Methods**—By means of immunohistochemical techniques that incorporated a panel of monoclonal antibodies against cell adhesion molecules (CAMs), including E-cadherin,  $\alpha$ -catenin,  $\beta$ -catenin,  $\gamma$ -catenin, and neural cell adhesion molecule (NCAM), the expression of CAMs was studied in 15 specimens of chordoma and eight specimens of chondrosarcoma.

**Results**—Most chordoma specimens showed some positive immunoreactivity for all the CAMs examined. For the various CAMs investigated, between two and five cases showed diffuse immunoreactions, indicating well preserved expression. Well preserved expression of all the CAMs examined was limited to only one case, thus indicating that the expression of CAMs was decreased in most of the chordoma specimens; however, no significant correlation was found between the decreased expression of CAMs and the histological grade of malignancy, cellular growth pattern, or clinical parameters in chordoma. In chondrosarcoma, only a few specimens showed positive immunoreactivity for CAMs and the expression of E-cadherin,  $\beta$ -catenin,  $\gamma$ -catenin, and NCAM was seen more frequently in the chordoma specimens than in the chondrosarcoma specimens.

**Conclusions**—These results suggest that the expression of CAMs is associated with the formation and maintenance of chordoma tissue architecture, just as it is in other epithelial tumours or normal tissue. Immunohistochemistry for CAMs was found to be of diagnostic value for discriminating chordoma from chondrosarcoma, and these markers could be used along with the cytokeratins, which are already used for this purpose.

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Keywords: chordoma; E-cadherin; catenin; neural cell adhesion molecule

Chordoma is a relatively rare malignant bone tumour that occurs in close relation to the axial skeleton. It is also well known that this tumour

shows epithelioid histological features in the form of a syncytial arrangement, which closely resembles the embryonal notochord. This is a characteristic feature that is very different from that of other mesenchymal tumours, and it thus seems important to investigate the epithelioid features seen in chordoma to understand its tumour biology. To confirm the epithelioid characteristics of chordoma, numerous immunohistochemical analyses of cytokeratin expression have been undertaken and these have proved useful in the differential diagnosis of chordoma from chondrosarcoma. However, no detailed analysis regarding cell–cell communication has been conducted in this non-epithelial, yet epithelioid, tumour.

Cadherins are a family of cell adhesion molecules essential for the tight connections between cells.<sup>1,2</sup> E-cadherin is the major Ca<sup>2+</sup> dependent cell adhesion molecule expressed by epithelial cells. Cadherins form a complex with cytoplasmic proteins, collectively known as catenins. The interaction between cadherins and catenins is thought to be crucial for anchoring them to the cytoskeleton.<sup>3–6</sup> Loss or reduced expression of E-cadherin in cancer has been reported to be associated closely with invasive capacity or highly metastatic potential.<sup>7,8</sup> In addition, decreased expression of E-cadherin and/or  $\alpha$ -catenin is reported to be related to high tumour grade and prognosis in some cancers.<sup>9–17</sup> In contrast, neural cell adhesion molecule (NCAM) is a Ca<sup>2+</sup> independent cell adhesion molecule, which was originally isolated on the basis of its role in neural cell adhesion.<sup>18</sup> NCAM was found to be expressed in a variety of developing mesenchymal tissues, and was reported to be associated with poor prognosis or malignant potential in some cancers.<sup>19–21</sup> In the cases of sarcoma, little is known about the relevance of the expression of these molecules.

In our study, we investigated the expression of E-cadherin,  $\alpha$ -catenin,  $\beta$ -catenin,  $\gamma$ -catenin, and NCAM in both chordoma and chondrosarcoma, using immunohistochemical techniques, to evaluate cell–cell adhesion in these two types of malignant bone tumours, which possess morphological similarities. Because of the epithelioid morphological composition, including the syncytial arrangement or diffuse proliferating pattern in chordoma, it is of interest not only to investigate the diagnostic value of the expression of CAMs, but also to know how CAMs are involved in growth or differentiation in chordoma.

Table 1 The clinicopathological and immunohistochemical data of the 15 chordoma specimens

| Case | Age | Sex | Anatomical location | Subtype    | Histological grade | E-cadherin | $\alpha$ -Catenin | $\beta$ -Catenin | $\gamma$ -catenin | NCAM |
|------|-----|-----|---------------------|------------|--------------------|------------|-------------------|------------------|-------------------|------|
| 1    | 22  | M   | Base of skull       | Solid      | 1                  | 1          | –                 | 2                | 1                 | 3    |
| 2    | 22  | F   | Thigh (metastasis)  | Solid      | 2                  | 3          | –                 | 3                | –                 | 3    |
| 3    | 34  | M   | Sacrum              | Solid      | 2                  | 1          | 3                 | –                | 1                 | 3    |
| 4    | 35  | M   | Sacrum              | Trabecular | 1                  | 3          | 3                 | 2                | 3                 | 2    |
| 5    | 42  | M   | Sacrum              | Trabecular | 2                  | –          | –                 | –                | –                 | 2    |
| 6    | 48  | F   | Cervical            | Solid      | 2                  | 1          | –                 | 2                | –                 | 1    |
| 7    | 57  | F   | Cervical            | Trabecular | 1                  | –          | 2                 | 3                | 2                 | 1    |
| 8    | 63  | M   | Sacrum              | Solid      | 2                  | 2          | –                 | 2                | 1                 | 2    |
| 9    | 63  | F   | Sacrum              | Trabecular | 1                  | –          | –                 | 1                | –                 | 1    |
| 10   | 64  | M   | Sacrum              | Trabecular | 1                  | 1          | –                 | 2                | –                 | 1    |
| 11   | 64  | M   | Sacrum              | Trabecular | 2                  | 1          | 2                 | 1                | 2                 | 3    |
| 12   | 64  | F   | Sacrum              | Solid      | 2                  | 2          | 1                 | 2                | 2                 | 2    |
| 13   | 67  | M   | Base of skull       | Solid      | 1                  | 3          | 3                 | 3                | 3                 | 3    |
| 14   | 72  | F   | Sacrum              | Solid      | 2                  | –          | –                 | 2                | 1                 | 1    |
| 15   | 73  | M   | Sacrum              | Trabecular | 1                  | 3          | 2                 | 3                | 2                 | –    |

## Materials and methods

### SPECIMENS

Fifteen chordomas obtained from either biopsy or surgical specimens were collected from the files of the department of anatomic pathology, Kyushu University, dating between 1970 and 1996 (table 1). The patients, comprising nine men and six women, ranged from 22 to 73 years of age (median, 63). Eight surgical specimens of chondrosarcoma were also collected from files dating between 1990 and 1995 (table 2). The patients, comprising two men and six women, ranged from 17 to 64 years of age (median, 55.5). All the histological sections obtained from samples were stained with haematoxylin and eosin for the diagnosis of chordoma and chondrosarcoma, and the histological section exhibiting the most characteristic features for each specimen was selected for immunohistochemical studies. All light microscopic and immunohistochemical studies were performed on formalin (10%) fixed materials embedded in paraffin wax. Among the eight chondrosarcomas, six were conventional subtype, whereas two were clear cell subtype. The histological grading of chondrosarcoma was made according to Evans *et al*,<sup>22</sup> on a scale of 1 to 3. According to our previously proposed subclassification,<sup>23</sup> we divided the 15 classic chordoma specimens into two groups—trabecular type (seven cases), mainly consisting of foci demonstrating a cord-like or trabecular pattern; and solid type (eight cases), mainly consisting of a diffuse proliferation of tumour cells; however, each solid type specimen always possessed some foci, whether many or few, while showing either a trabecular or a syncytial arrangement of the tumour cells, which corresponded to the so called classic chordoma area. No chondroid or dedifferentiated types were observed. In addition, the histological grading<sup>23</sup> was made according to the nuclear atypia on a

scale of 1 to 3. Seven specimens were determined to be grade 1 nuclear atypia whereas eight specimens were determined to be grade 2 nuclear atypia. The histological diagnosis of chordoma was also supported by the immunohistochemistry results—all 15 specimens showed positive immunoreactivity for S-100 protein, vimentin, and cytokeratins 8 and 19.

### IMMUNOHISTOCHEMICAL STUDY

Histological sections were cut (4  $\mu$ m thick), mounted on glass slides coated with 3-aminopropyltriethoxysilane, and then air dried overnight at room temperature. The sections were dewaxed in xylene and rehydrated in ethanol, and endogenous peroxidase was blocked by methanol containing 0.3% H<sub>2</sub>O<sub>2</sub> for 30 minutes. The sections were rinsed with 50 mmol/litre (pH 7.2) Tris buffered saline, 150 mmol/litre of Ca<sup>2+</sup> (TBS<sup>+</sup>) for E-cadherin staining and PBS for  $\alpha$ -catenin,  $\beta$ -catenin,  $\gamma$ -catenin, and NCAM staining. For the antigen retrieval, the sections were immersed in citrate buffer with 0.1% Tween 20 and then heated three times in a microwave oven at 99–100°C for five minutes for E-cadherin and the catenins. The sections were treated at 4°C overnight with primary antibodies for the CAMs listed in table 3, followed by staining with an avidin–biotin–peroxidase kit (Nichirei, Tokyo, Japan). The sections were finally reacted with a 3,3'-diaminobenzidine peroxyltrichloride substrate solution and counterstained with haematoxylin before being mounted. The degree of expression of CAMs was determined as follows: (3+), more than 50% of the cells showed a positive immunoreaction in the cell membrane; (2+), 10–50% of the cells were positive; (1+), less than 10% of the cells were positive; (–), cells were completely negative throughout the specimen. No

Table 2 The clinicopathological and immunohistochemical data of the eight chondrosarcoma specimens

| Case | Age | Sex | Anatomical location | Subtype      | Histological grade | E-cadherin | $\alpha$ -Catenin | $\beta$ -Catenin | $\gamma$ -Catenin | NCAM |
|------|-----|-----|---------------------|--------------|--------------------|------------|-------------------|------------------|-------------------|------|
| 1    | 17  | F   | Pubis               | Conventional | 2                  | –          | –                 | –                | –                 | –    |
| 2    | 40  | M   | Femur               | Clear cell   | 2                  | –          | –                 | 1                | –                 | 1    |
| 3    | 42  | F   | Humerus             | Conventional | 1                  | –          | –                 | –                | –                 | –    |
| 4    | 53  | F   | Femur               | Conventional | 2                  | –          | –                 | –                | –                 | –    |
| 5    | 58  | F   | Humerus             | Conventional | 2                  | –          | 1                 | –                | –                 | –    |
| 6    | 59  | F   | Femur               | Conventional | 1                  | –          | –                 | –                | –                 | –    |
| 7    | 64  | M   | Tibia               | Clear cell   | 2                  | –          | –                 | –                | –                 | –    |
| 8    | 64  | F   | Scapula             | Conventional | 2                  | –          | –                 | –                | –                 | –    |

NCAM, neuronal cell adhesion molecule.

Table 3 Summary of monoclonal antibodies used

| Antibody to       | Source                    | Dilution | Pretreatment |
|-------------------|---------------------------|----------|--------------|
| E-cadherin        | Takara Biomedicals        | 1/1000   | Microwave    |
| $\alpha$ -Catenin | Transduction Laboratories | 1/200    | Microwave    |
| $\beta$ -Catenin  | Transduction Laboratories | 1/200    | Microwave    |
| $\gamma$ -Catenin | Transduction Laboratories | 1/200    | Microwave    |
| NCAM              | Novocastra Laboratories   | 1/100    | None         |

NCAM, neuronal cell adhesion molecule.

cases demonstrated perfectly preserved expression of all epithelial CAMs, unlike some epithelial tumours. Therefore, we categorised cases that showed a (3+) immunoreaction as “well preserved” and cases that showed a (2+) or (1+) immunoreaction as “poorly preserved”. A (-) immunoreaction or cytoplasmic staining with no membranous pattern was determined as negative. An adenocarcinoma specimen of the stomach was used as a positive control for the staining of E-cadherin and the catenins, and a specimen of colonic submucosal nerve plexus or a specimen of neurofibroma was used for the staining of NCAM. All these specimens used as positive controls showed diffusely positive immunoreactivity (3+). The difference in incidence of the expression of CAMs between chordoma and chondrosarcoma specimens was estimated by Fisher’s exact probability test.

## Results

The results are summarised in tables 1, 2, 4, and 5. In chordoma, positive immunoreactivity for E-cadherin (fig 1A),  $\alpha$ -catenin,  $\beta$ -catenin (fig 1B),  $\gamma$ -catenin (fig 2), and NCAM (fig 3) was seen in 11, seven, 13, 10, and 14 specimens, respectively (table 4). Among them, diffusely positive (3+) immunoreactivity suggesting the well-preserved expression of E-cadherin,  $\alpha$ -catenin,  $\beta$ -catenin,  $\gamma$ -catenin, and NCAM was seen in four, three, four, two, and five specimens, respectively (table 5). Negative immunoreactivity (-), which is considered to be the complete loss of expression of E-cadherin,  $\alpha$ -catenin,  $\beta$ -catenin,  $\gamma$ -catenin, and NCAM, was seen in the remaining four, eight, two, five, and one specimen(s), respectively (table 5). Only one specimen of solid type with grade 1 nuclear atypia scored (+3) immunoreactivity for all the CAMs examined (table 1; case 13). There was no specimen that

showed complete loss of expression of all the CAMs examined. No correlation was seen between the expression of CAMs and clinical

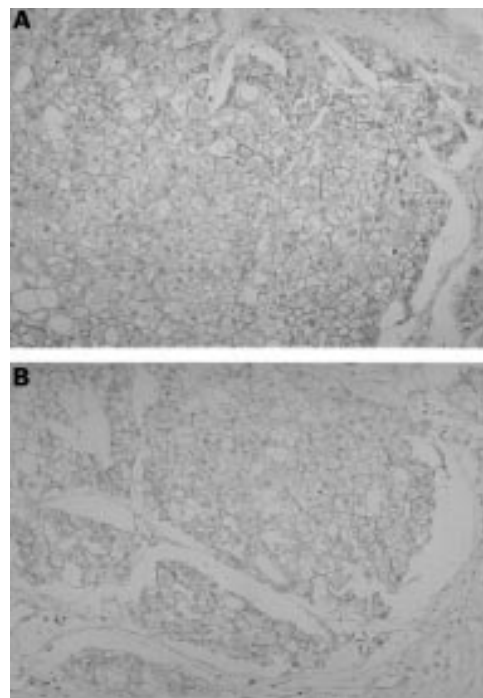


Figure 1 A solid type, grade 2 metastatic lesion in the thigh of a 22 year old woman (case 2). (A) Tumour cells proliferating in sheets show E-cadherin reactivity in the cell membrane. (B) Rather weak but definite expression of  $\beta$ -catenin can be seen in the cell membrane.

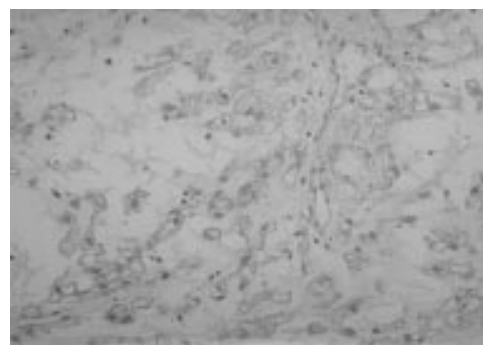


Figure 2 A trabecular type, grade 1 lesion in the sacrum of a 35 year old man (case 4). Tumour cells proliferating in nests show  $\gamma$ -catenin reactivity in the cell membrane.

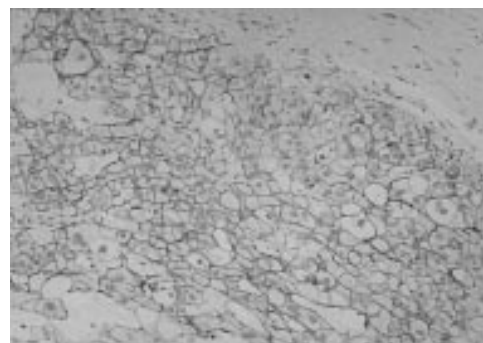


Figure 3 A trabecular type, grade 2 lesion in the sacrum of a 64 year old man (case 11). Tumour cells arranged in sheets seen in this area show strong nerve cell adhesion molecule reactivity in the cell membrane.

Table 4 Expression of cell adhesion molecules in 16 chordomas and eight chondrosarcomas

|                | E-cadherin | $\alpha$ -Catenin | $\beta$ -Catenin | $\gamma$ -Catenin | NCAM   |
|----------------|------------|-------------------|------------------|-------------------|--------|
| Chordoma       | 11         | 7                 | 13               | 10                | 14     |
| Chondrosarcoma | 0          | 1                 | 1                | 0                 | 2      |
| p Value        | 0.0014     | 0.18              | 0.001            | 0.0027            | 0.0017 |

NCAM, neuronal cell adhesion molecule.

Table 5 Expression of cell adhesion molecules in 15 specimens of chordoma

|                  | E-cadherin | $\alpha$ -Catenin | $\beta$ -Catenin | $\gamma$ -Catenin | NCAM |
|------------------|------------|-------------------|------------------|-------------------|------|
| Well preserved   | 4          | 3                 | 4                | 2                 | 5    |
| Poorly preserved | 7          | 4                 | 9                | 8                 | 9    |
| Completely lost  | 4          | 8                 | 2                | 5                 | 1    |

NCAM, neural cell adhesion molecule.

findings including age, sex, anatomical distribution, and prognosis or pathological findings, including histological subtype and nuclear grade.

In chondrosarcoma, no positive immunoreaction for CAMs was seen in six of the eight specimens (table 2). One of the two remaining specimens showed (1+) immunoreaction for  $\alpha$ -catenin (case 5). The other remaining specimen of clear cell type showed (1+) immunoreaction for  $\beta$ -catenin and NCAM, but this was limited in the osteoblastoma-like areas (case 2). A positive immunoreaction (1+, 2+, 3+) for E-cadherin,  $\beta$ -catenin,  $\gamma$ -catenin, and NCAM was seen more frequently in the chordoma specimens than in the chondrosarcoma specimens (table 4).

### Discussion

Chordoma is a unique bone tumour that shows epithelial histological features, such as a trabecular or syncytial arrangement in the tumour cells. Several immunohistochemical analyses of cytokeratin have been conducted to support the epithelial characteristics of chordoma,<sup>24-28</sup> and the detection of cytokeratin was found to be very useful for the differential diagnosis of chordoma from other mesenchymal tumours, especially chondrosarcoma. However, little is known regarding cell-cell binding in mesenchymal tumours, and it is still not clear whether CAMs are expressed in chordoma cells or whether these molecules contribute to the formation of the epithelioid structure of chordoma.

The expression of CAMs has been studied extensively in carcinomas. Loss or reduced expression of E-cadherin often correlates with invasiveness, dedifferentiation, or metastatic potential in a wide range of human cancers. The loss of E-cadherin expression has been reported to be associated with tumour aggressiveness in head and neck squamous cell carcinoma<sup>29</sup> and cutaneous papillomas and squamous cell carcinomas<sup>30</sup>; with differentiation in meningiomas,<sup>31</sup> a variety of gynaecological malignancies,<sup>32</sup> and urinary bladder transitional cell carcinoma<sup>33</sup>; and also with the high grade of tumour and dedifferentiation in hepatocellular carcinomas.<sup>34</sup> In the case of sarcomas, some investigators have noted the association of E-cadherin expression with epithelioid appearance. Matsuzaki and colleagues<sup>35</sup> and Mege and colleagues<sup>36</sup> reported that the transfection of N-cadherin and E-cadherin into spindle mouse S180 sarcoma cells resulted in the development of an epithelioid phenotype. Smith *et al* showed that E-cadherin was not expressed by either normal Schwann cells or the common type of Schwann cell tumours, but was expressed in the epithelioid phenotype of Schwann cell tumours.<sup>37</sup> In contrast, epithelioid sarcoma, a type of sarcoma whose morphology shows an epithelioid pattern, was not reported to express E-cadherin.<sup>38</sup> Thus, E-cadherin expression may not be essential in all cases of sarcoma of the epithelioid phenotype, although this needs further clarification. Several studies have shown that the cadherin-catenin complex is crucial for functional

cadherin mediated adhesion.<sup>12-39</sup> Normal adhesive function of cadherins requires the interaction of three proteins, termed  $\alpha$ -catenin,  $\beta$ -catenin, and  $\gamma$ -catenin,<sup>3-5</sup> and E-cadherin, and the catenins show an identical pattern of expression in normal cells. It has been shown that mutants of these proteins prevent the correct functioning of cadherins. In adenocarcinomas of the prostate, breast, oesophagus, lung, stomach, and colon, and in squamous cell carcinomas of the oesophagus and the head and neck, decreased E-cadherin and/or  $\alpha$ -catenin expression correlated with high tumour grade and poor prognosis.<sup>9-17</sup> In addition, high frequencies of decreased  $\beta$ -catenin expression were seen in several gastrointestinal cancers.<sup>40</sup> In contrast, little is known about the expression of catenins in either normal soft tissue or soft tissue tumours. Alman *et al* found higher concentrations of  $\beta$ -catenin protein in desmoid tumours,<sup>41</sup> and Iwao *et al* also detected increased expression of  $\beta$ -catenin in osteosarcoma, synovial sarcoma, rhabdomyosarcoma, and malignant fibrous histiocytoma.<sup>42</sup> NCAM is expressed in a variety of developing mesenchymal tissues.<sup>43-45</sup> In chondrogenesis, Widelitz *et al* revealed that NCAM is transiently expressed during the formation of precartilaginous condensations but disappears in mature chondrocytes, and they suggested that NCAM is involved in the chondrogenesis pathway by mediating the formation of precartilaginous condensations.<sup>45</sup> In muscle, NCAM transfected myoblasts have enhanced myogenesis.<sup>46</sup> In osteogenesis, NCAM is strongly expressed in most osteoblasts along bone trabeculae that coexist in the presence of collagen I and alkaline phosphatase activity.<sup>47</sup> These results suggest that NCAM is indeed a mesenchymal adhesion molecule.<sup>45</sup> In contrast, some investigators have found that NCAM positive carcinomas have a more malignant behaviour than NCAM negative carcinomas.<sup>19-21 48-50</sup>

In our series, all but one chordoma specimen demonstrated an incomplete E-cadherin-catenin complex, in terms of either decreased E-cadherin staining or/and decreased catenin staining. Only one case of a solid type tumour with grade 1 nuclear atypia had a 3+ staining score, thus demonstrating well preserved expression of both E-cadherin and catenins. Conversely, only one case of trabecular type tumour with grade 2 atypia showed complete loss of expression of both E-cadherin and catenins. In contrast, NCAM expression was preserved in more than 90% of the chordoma specimens. The above findings suggest that CAMs might be, at least in part, supplied by the connection of chordoma cells and might be necessary for the maintenance of the chordoma tissue architecture, although decreased expression of CAMs is observed in most of the specimens. Morphologically, lesions showing collapse of well differentiated architecture are considered to be of metastatic potential in carcinomas, and such lesions with a collapsed trabecular arrangement or compactly packed cell proliferation, whether many or few, are generally seen in chordoma specimens. Although no associations between the expression

of CAMs and either the pathological or clinical findings were found, and the importance of decreased expression of CAMs in our series of chordoma remains unclear, the decreased expression of CAMs seen in chordoma may also reflect the potent metastatic behaviour that is seen in the late clinical course of patients with chordoma.

Occasionally, chordoma can resemble chondrosarcoma, a malignant cartilaginous tumour, when the chordoma possesses few physaliphorous cells and lacks any typical trabecular or syncytial arrangement. The differential diagnosis between chordoma and chondrosarcoma is possible based on the immunohistochemistry of CAMs, except for those cases where the chordoma specimens demonstrate complete loss of expression of CAMs.

In summary, CAMs are thought to play a role in the maintenance of chordoma tissue architecture; however, further investigations are still necessary to understand the correlation between CAMs and the development, differentiation, invasive capacity, or metastatic potential of chordoma.

The surgical specimens of chordoma and chondrosarcoma were obtained from the following institutions: Kyushu University, National Kyushu Medical Centre Hospital, National Kyushu Cancer Centre, Spinal Injuries Centre, Saga Medical School, Karatsu Red Cross Hospital, Shin-Kokura Hospital, Kitakyushu City Medical Centre, and Toyama Prefectural Central Hospital. We sincerely thank these institutes for contributing their cases. We also thank K Miller (Royal English Language Centre, Fukuoka, Japan) for proofreading the English used in this article. This work was supported in part by Grants in Aid for Scientific Research (06280105, 06280115) from the Ministry of Education, Science and Culture, Japan.

- 1 Takeichi M. Functional correlation between cell adhesive properties and some cell surface proteins. *J Cell Biol* 1977;75:464-74.
- 2 Takeichi M. Cadherin cell adhesion receptors as a morphogenetic regulator. *Science* 1991;251:1451-5.
- 3 Nagafuchi A, Takeichi M. Cell binding function of E-cadherin is regulated by the cytoplasmic domain. *EMBO J* 1988;7:3679-84.
- 4 Nagafuchi A, Takeichi M. Transmembrane control of cadherin-mediated cell adhesion: a 94 kD protein functionally associated with a specific region of the cytoplasmic domain of E-cadherin. *Cell Regul* 1989;1:37-44.
- 5 Ozawa M, Ringwald M, Kemler R. Uvomorulin-catenin complex formation is regulated by a specific domain in the cytoplasmic region of the cell adhesion molecule. *Proc Natl Acad Sci U S A* 1990;87:4246-50.
- 6 Fujimori T, Takeichi M. Disruption of epithelial cell-cell adhesion by exogenous expression of a mutated nonfunctional N-cadherin. *Mol Biol Cell* 1993;4:37-47.
- 7 Oka H, Shiozaki H, Kobayashi K, et al. Immunohistochemical evaluation of E-cadherin adhesion molecule expression in human gastric cancer. *Virchows Arch A Pathol Anat Histopathol* 1992;421:149-56.
- 8 Oka H, Shiozaki H, Kobayashi K, et al. Expression of E-cadherin cell adhesion molecules in human breast cancer tissues and its relationship to metastasis. *Cancer Res* 1993;53:1696-701.
- 9 Schipper JH, Frixen UH, Behrens J, et al. E-cadherin expression in squamous cell carcinomas of head and neck: inverse correlation with tumor dedifferentiation and lymph node metastasis. *Cancer Res* 1991;51:6328-337.
- 10 Shiozaki H, Tahara H, Oka H, et al. Expression of immunoreactive E-cadherin adhesion molecules in human cancers. *Am J Pathol* 1991;139:17-23.
- 11 Umbas R, Schalken JA, Aalders TW, et al. Expression of the cellular adhesion molecule E-cadherin is reduced or absent in high-grade prostate cancer. *Cancer Res* 1992;52:5104-9.
- 12 Morton RA, Ewing CM, Nagafuchi A, et al. Reduction of E-cadherin levels and deletion of the alpha-catenin gene in human prostate cancer cells. *Cancer Res* 1993;53:3585-90.
- 13 Kadowaki T, Shiozaki H, Inoue M, et al. E-cadherin and alpha-catenin expression in human esophageal cancer. *Cancer Res* 1994;54:291-6.
- 14 Matsui S, Shiozaki H, Inoue M, et al. Immunohistochemical evaluation of alpha-catenin expression in human gastric cancer. *Virchows Arch* 1994;424:375-81.
- 15 Shiozaki H, Iihara K, Oka H, et al. Immunohistochemical detection of alpha-catenin expression in human cancers. *Am J Pathol* 1994;144:667-74.
- 16 Bongiorno PF, Al-Kasspoles M, Lee SW, et al. E-cadherin expression in primary and metastatic thoracic neoplasms and in Barrett's oesophagus. *Br J Cancer* 1995;71:166-72.

- 17 Rimm DL, Sinard JH, Morrow JS. Reduced alpha-catenin and E-cadherin expression in breast cancer. *Lab Invest* 1995;72:506-12.
- 18 Hoffman S, Sorkin BC, White PC, et al. Chemical characterization of a neural cell adhesion molecule purified from embryonic brain membranes. *J Biol Chem* 1982;257:7720-9.
- 19 Moolenaar CECK, Muller EJ, Schol DJ, et al. Expression of neural cell adhesion molecule-related sialoglycoprotein in small cell lung cancer and neuroblastoma cell lines H69 and CHP-212. *Cancer Res* 1990;50:1102-6.
- 20 Kibbelaar RE, Moolenaar CECK, Michalides RJAM, et al. Neural cell adhesion molecule expression, neuroendocrine differentiation and prognosis in lung carcinomas. *Eur J Cancer* 1991;27:431-5.
- 21 Mooy CM, Luyten GPM, De Jong PTVM, et al. Neural cell adhesion molecule distribution in primary and metastatic uveal melanoma. *Hum Pathol* 1995;26:1185-90.
- 22 Evans HL, Ayala AG, Romsdahl MM. Prognostic factors in chondrosarcoma of bone: a clinicopathologic analysis with emphasis on histologic grading. *Cancer* 1977;40:818-31.
- 23 Naka T, Fukuda T, Chuman H, et al. Proliferative activities in conventional chordoma: a clinicopathologic, DNA flow cytometric, and immunohistochemical analysis of 17 specimens with special reference to anaplastic chordoma showing a diffuse proliferation and nuclear atypia. *Hum Pathol* 1996;27:381-8.
- 24 Salisbury JR, Isaacson PG. Demonstration of cytokeratins and an epithelial membrane antigen in chordomas and human fetal notochord. *Am J Surg Pathol* 1985;9:791-7.
- 25 Abenzo P, Sibley RK. Chordoma: an immunohistologic study. *Hum Pathol* 1986;17:744-7.
- 26 Coindre JM, Rivel J, Trojani M, et al. Immunohistological study in chordomas. *J Pathol* 1986;150:61-3.
- 27 Listrom MB, Dalton LW. Comparison of keratin monoclonal antibodies MAK-6, AE1:AE3, and CAM-5.2. *Am J Clin Pathol* 1987;88:297-301.
- 28 Naka T, Iwamoto Y, Shinohara N, et al. Cytokeratin subtyping in chordomas and the fetal notochord: an immunohistochemical analysis of aberrant expression. *Mod Pathol* 1997;10:545-51.
- 29 Field JK. Oncogenes and tumour-suppressor genes in squamous cell carcinoma of the head and neck. *Eur J Cancer B Oral Oncol* 1992;28B:67-76.
- 30 Ruggeri B, Caamano J, Slaga TJ, et al. Alterations in the expression of uvomorulin and Na<sup>+</sup>, K<sup>+</sup> adenosine triphosphatase during mouse skin tumor progression. *Am J Pathol* 1992;140:1179-85.
- 31 Tohma Y, Yamashita T, Yamashita J. Immunohistochemical localization of cell adhesion molecule epithelial cadherin in human arachnoid villi and meningiomas. *Cancer Res* 1992;52:1981-7.
- 32 Inoue M, Ogawa H, Miyata M, et al. Expression of E-cadherin in normal, benign, and malignant tissues of female genital organs. *Am J Clin Pathol* 1992;98:76-80.
- 33 Ross JS, Del Rosario AD, Figge HL, et al. E-cadherin expression in papillary transitional cell carcinoma of the urinary bladder. *Hum Pathol* 1995;26:940-4.
- 34 Shimoyama Y, Hirohashi S. Cadherin intercellular adhesion molecule in hepatocellular carcinomas: loss of E-cadherin expression in an undifferentiated carcinoma. *Cancer Lett* 1991;52:131-5.
- 35 Matsuzaki F, Mege RM, Jaffe SH, et al. cDNAs of cell adhesion molecules of different specificity induce changes in cell shape and border formation in cultured S180 cells. *J Cell Biol* 1990;110:1239-52.
- 36 Mege RM, Matsuzaki F, Gallin WJ, et al. Construction of epithelioid sheets by transfection of mouse sarcoma cells with cDNAs for chicken cell adhesion molecules. *Proc Natl Acad Sci U S A* 1988;85:7274-8.
- 37 Smith MEF, Cowley GP, Dogan A, et al. E-cadherin is a differentiation antigen of normal Schwann cells and is expressed in epithelioid Schwann cell tumours. *J Pathol* 1994;173:181A.
- 38 Smith ME, Brown JI, Fisher C. Epithelioid sarcoma: presence of vascular-endothelial cadherin and lack of epithelial cadherin. *Histopathology* 1998;33:425-31.
- 39 Shimoyama Y, Nagafuchi A, Fujita S, et al. Cadherin dysfunction in a human cancer cell line: possible involvement of loss of alpha-catenin expression in reduced cell-cell adhesiveness. *Cancer Res* 1992;52:5770-4.
- 40 Takayama T, Shiozaki H, Shibamoto S, et al.  $\beta$ -Catenin expression in human cancers. *Am J Pathol* 1996;148:39-46.
- 41 Alman BA, Li C, Pajerski ME, Diaz-Cano S, et al. Increased  $\beta$ -catenin protein and somatic APC mutations in sporadic aggressive fibromatoses (desmoid tumors). *Am J Pathol* 1997;151:329-34.
- 42 Iwao K, Miyoshi Y, Nawa G, et al. Frequent  $\beta$ -catenin abnormalities in bone and soft-tissue tumors. *Jpn J Cancer Res* 1999;90:205-9.
- 43 Chuong CM, Edelman GM. Expression of cell adhesion molecules in embryonic induction: I. Morphogenesis of nestling feathers. *J Cell Biol* 1985;101:1009-26.
- 44 Chuong CM. Adhesion molecules NCAM and tenascin in embryonic development and tissue regeneration. *J Craniofac Genet Dev Biol* 1990;10:147-61.
- 45 Widelitz RB, Jiang TX, Murray BA, et al. Adhesion molecules in skeletogenesis: II. neural cell adhesion molecules mediate precartilaginous mesenchymal condensations and enhance chondrogenesis. *J Cell Physiol* 1993;156:399-411.
- 46 Dickson G, Peck D, Moore SE, et al. Enhanced morphogenesis in NCAM-transfected mouse myoblasts. *Nature* 1990;344:348-51.

- 47 Lee YS, Chuong CM. Adhesion molecules in skeletogenesis: I. transient expression of neural cell adhesion molecules (NCAM) in osteoblasts during endochondral and intramembranous ossification. *J Bone Miner Res* 1992;7:1435-46.
- 48 Pujol JL, Simony J, Demoly P, et al. Neural cell adhesion molecule and prognosis of surgically resected lung cancer. *Am Rev Respir Dis* 1993;148:1071-5.
- 49 Kibbelaar RE, Moolenaar KE, Michalides RJ, et al. Neural cell adhesion molecule expression, neuroendocrine differentiation and prognosis in lung carcinoma. *Eur J Cancer* 1991;27:431-5.
- 50 Berendsen HH, deLeij L, Poppema S, et al. Clinical characterization of non-small-cell lung cancer tumors showing neuroendocrine differentiation features. *J Clin Oncol* 1989;7:1614-20.



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