Prognostic Significance of Simultaneous Presence of Histological and Immunohistochemical Metastasis to Lymph Nodes in Patients with Esophageal Cancer

Tatsuya Kinjo, MD,1 Hideaki Shimoji, MD,1 Masayoshi Nagahama, MD,1 Hiroyuki Karimata, MD,1 Naoki Yoshimi, MD,2 and Tadashi Nishimaki, MD1

Purpose: Presence of simultaneous pathological and immunohistochemical nodal metastasis (pNM and iNM, respectively) and/or other clinical factors may be reliable prognostic predictors of survival in esophageal cancer patients who have undergone multidisciplinary treatment.

Methods: Univariate and multivariate analysis of the data collected from 77 patients who had undergone R0 esophagectomy was performed to determine the significance of presence of INM or pNM, presence of simultaneous pNM, and other clinical factors as prognostic indicators in patients who had (n = 40) and had not (n = 37) undergone preoperative treatment.

Results: Presence of pNM was found to be a significant prognostic predictor in patients who had undergone preoperative treatment, presence of iNM in patients who had not undergone preoperative treatment, and presence of simultaneous pNM and iNM in both patient groups. Multivariate analysis indicated that the sole prognostic predictor for patients who had undergone preoperative treatment was presence of simultaneous pNM and iNM while that of patients who had not undergone preoperative treatment was clinical T category.

Conclusion: Assessment of simultaneous presence of pNM and iNM may facilitate highly accurate prediction of survival in esophageal cancer patients undergoing R0 esophagectomy, regardless of whether they have undergone preoperative treatment.

Keywords: esophagectomy, lymph node metastasis, micro-metastasis, multidisciplinary treatment, prognostic predictor

Introduction

Precise knowledge of prognostic predictors is important not only in the diagnosis and treatment of patients in clinical practice but also in the performance and evaluation of clinical trials of patients with esophageal cancer. Presence of pathological nodal metastasis (pNM), number of positive nodes, and ratio of positive nodes to all dissected nodes have been reported as reliable prognostic predictors after resection for esophageal cancer.1,2 Furthermore, presence of immunohistochemical nodal metastasis (iNM), which is detected by immunohistochemical analysis of
kinjo t, et al.

individual or clusters of tumor cells in the resected lymph nodes, has been reported to be a strong and independent indicator of poor survival of patients undergoing radical esophagectomy for esophageal cancer.1,2) Although several studies have reported that the predictive value of iNM differs among patients according to the number of pathological lymph node metastases,3) the significance of simultaneous pNM and iNM has not been reported to date.

Since the early 1980s, extended radical esophagectomy with 3-field lymphadenectomy has been performed to improve the prognosis of patients with esophageal cancer, mainly in Japan. This procedure has been reported to be effective in improving survival, with the reported 5-year survival rate after this procedure ranging from 40% to 60%.5) Nevertheless, analysis of post-surgical data has identified subgroups of patients whose survival rates remain poor despite complete tumor resection. Among patients who have undergone radical esophagectomy for esophageal cancer, the variables of presence of 5 or more positive lymph nodes; simultaneous metastasis to the cervical, mediastinal, and abdominal lymph nodes; diagnosis with advanced disease corresponding to stage III and IV; and presence of intramural metastasis have been reported to be unfavorable prognostic factors.6,7)

To improve overall survival rates, chemotherapy or chemoradiotherapy has been increasingly performed in combination with radical esophagectomy, either before or after surgery. To investigate the efficacy of multidisciplinary treatment, we had previously conducted a prospective cohort study examining the effect of chemotherapy or chemoradiotherapy followed by complete tumor resection, referred to as R0 esophagectomy, in esophageal cancer patients with unfavorable prognostic factors. However, the extent to which presence of pNM and/or iNM is predictive of patient survival after undergoing multidisciplinary treatment remained unclear after analysis of the study data. We aimed to clarify this relationship in the present study by determining whether the presence of pNM, iNM, and/or simultaneous pNM and iNM, as well as several other prognostic factors, are significant predictors of the survival of esophageal cancer patients who had undergone multidisciplinary treatment in our prospective cohort study using univariate and multivariate analysis.

Materials and Methods

Tumor categorization and treatment assignment

Before beginning the prospective cohort study, each esophageal tumor had been classified into 1 of 3 categories in accordance with the sixth edition of the TNM Classification of Malignant Tumors (TNM), a cancer staging system developed by the International Union Against Cancer (UICC),7) based on the relationship between initial tumor status and applicability of upfront R0 resection for esophageal cancer. In accordance with this system, esophageal tumors that had been immediately resectable but associated with any of the unfavorable prognostic factors (five or more positive nodes; simultaneous metastasis to the cervical, mediastinal, and abdominal lymph nodes; advanced disease corresponding to stage III or IV; and/or intramural metastasis) were defined as Category 3 tumors; tumors that had been initially unresectable or marginally unresectable due to T4 stage were defined as Category 2 tumors; and tumors that had not been associated with any unfavorable prognostic factors were defined as Category 1 tumors. Each tumor was classified based on the analysis of data collected using a variety of imaging techniques, including esophagography; esophagoscopy; computed tomography (CT); and, if indicated, positron emission tomography (PET)-CT or bronchoscopy. Tumors were staged and assigned to T and N categories as previously reported.8) Chemotherapy consisting of administration of 5-fluorouracil, doxorubicin, and nedaplatin (FAN) followed by radical esophagectomy was assigned to patients with Category 3 tumor; induction chemotherapy or chemoradiotherapy followed, if feasible, by esophagectomy to patients with Category 2 tumor; and immediate radical esophagectomy to patients with Category 1 tumor. FAN chemotherapy was provided as a form of induction chemotherapy to patients who had been referred to our hospital for treatment of Category 2 tumors between April 2002 and June 2006.

Chemotherapy consisting of administration of 5-fluorouracil and nedaplatin or docetaxel alone with concurrent radiotherapy has been used as a form of induction chemoradiotherapy since July 2006. Since November 2008, when the results of the JC099907 trial showing the significantly positive prognostic impact of neoadjuvant chemotherapy on patients with Stage II disease were published,9) patients with Category 1 tumor corresponding to Stage II disease have undergone the same form of chemotherapy (FAN) that is provided as a form of neoadjuvant chemotherapy.

Patients

The patients examined in the present study were 77 of the 138 patients who had been selected for participation in a prospective cohort study that had been initiated in
April 2002. Between April 2002 and December 2011, 238 patients with esophageal cancer presented at the University Hospital of the Ryukyus. Of these, 100 had been excluded from study participation due to presence of early cancer, greatly advanced disease, or active malignancies synchronously developing in extra-esophageal organs; poor performance status; and/or patient preference for other treatment modalities. The remaining 138 patients with Stage I or more advanced disease had undergone the previously described forms of treatment according to tumor categorization.

Of the 138 patients enrolled in the prospective cohort study, 77 patients had undergone R0 resection of esophageal tumor, and composed the subjects of the present study. In terms of disease category, 40, 21, and 16 had been classified as Category 1, 2, and 3 disease patients, respectively. In terms of demographics, 68 were male and 9 female, and the average age of all patients was 64 years, ranging from 40 to 81 years. In accordance with the guidelines for treatment according to category, 37 patients had undergone immediate esophagectomy, 27 chemotherapy followed by radical esophagectomy, and 13 chemoradiotherapy followed by radical esophagectomy. Table 1 summarizes the characteristics and tumor categorization of the patients, who were divided into two groups according to whether they had or had not undergone preoperative treatment (40 and 37 patients, respectively). Before beginning the study, informed consent had been obtained in written form from all patients and approval for its performance had been obtained by the Ethical Committee of the University of the Ryukyus.

Chemotherapy
When indicated for treatment, FAN chemotherapy had been performed in the same manner as previously reported. Chemotherapy consisted of continuous intravenous infusion of 600 mg/m² of 5-fluorouracil on days 1 to 7 and days 29 to 35, 30 mg/m² of doxorubicin on days 1 and 29, and 50 mg/m² of nedaplatin for 2 h on days 1 and 29. For cases in which toxicity higher than grade 3 had been observed after the first cycle, the dose of all drugs had been decreased by 30% in the second cycle. In cases of intolerable toxicity or tumor progression, chemotherapy had been discontinued and the patient referred for surgery.

Chemoradiotherapy
Along with concurrent chemotherapy, all patients had undergone radiotherapy at the tumor site in the form of external beam radiotherapy of a total dosage ranging from 40 to 66.6 Gy, with a single fraction ranging from 1.8 to 2 Gy, 5 days per week. Fit patients had undergone 1 to 2 courses of chemotherapy, with a 4-week interval between courses for those subjected to 2 courses, that each consisted of intravenous administration of 90 mg/m² of nedaplatin on day 1 and 800 mg/m² of 5-fluorouracil on days 2 to 6. Unfit patients had undergone intravenous administration of 10 mg/m² of docetaxel per week during radiotherapy.

Surgery
Transthoracic esophagectomy with 3-field lymphadenectomy had been performed in patients with upper or mid esophageal cancer (n = 27); transthoracic esophagectomy with 2-field lymphadenectomy, in patients with lower esophageal cancer (n = 40); and transhiatal esophagectomy or lower esophagectomy as well as proximal gastrectomy with en bloc resection of lower mediastinal lymph nodes, in patients with esophagogastric junctional cancer (n = 10). Reconstruction surgery had been performed using either a gastric tube (n = 71) or the colon (n = 3) through either the substernal route (n = 30) or the posterior mediastinal route (n = 44). Jejunal interposition between the thoracic esophagus and the distal gastric remnant had been performed as a form of reconstructive surgery in 2 patients and Roux-en-Y anastomosis using the jejunum after total gastrectomy in 1 patient. The average number of lymph nodes dissected per patient was 42.5 in those who had undergone 3-field lymphadenectomy, 26.5 in those who had undergone 2-field lymphadenectomy, and 12.5 in those who had undergone transhiatal esophagectomy or lower esophagectomy plus proximal gastrectomy. Esophageal resection had been performed 3 to 4 weeks after completion of chemotherapy or chemoradiotherapy.

Immunohistochemistry
Immunohistochemistry was performed using the anti-cytokeratin antibody cocktail AE1/AE3 (Dako, Kyoto, Japan) at a dilution ratio of 1:800 and the streptavidin–biotin immunoperoxidase method. Immunohistochemical staining was automatically performed on 4-μm thick sections obtained from embedding all lymph nodes resected in paraffin blocks using the VENTANA HX system (Ventana, Yokohama, Japan).

Definition of immunohistochemical nodal metastasis
In accordance with a previous report, iNM was defined as the presence of either a single cell or a cluster
of 5 or fewer cells in a lymph node that tests immunohistochemically positive for cytokeratin. Although reticular cells and plasma cells can show staining for cytokeratin, these non-neoplastic cells can be discriminated from iNM by their different staining patterns.

**Follow-up data**

Follow-up data after the treatment were available for all patients. Of the 77 patients, 15 remained alive and had experienced no recurrence for more than 5 years after surgery (i.e., had been “cured”), 33 remained alive but had experienced recurrence within 5 years of surgery, and 29 had died within 5 years of surgery. The cause of death for the 29 patients who had died was recurrent disease for 19 and unrelated causes for 10. The follow-up duration for the surviving patients ranged from 2 to 110 months (median, 45 months).

**Statistical analysis**

Differences in frequencies were detected by the $\chi^2$ test or Fisher’s exact probability test for smaller numbers. Differences between means were assessed by Student’s $t$-test. Cumulative survival rates after surgery were examined using the Kaplan–Meier method. The equality of survival curves was assessed using the log rank test. Independent prognostic factors were identified by multivariate analysis using the Cox proportional hazards model. All analyses were performed using the SPSS 19 software package (SPSS Japan, Tokyo, Japan). Differences that reached a $p < 0.05$ level of significance were considered significant.

**Results**

**Prevalence of iNM**

Of the 2334 lymph nodes surgically excised from the 77 patients, immunohistochemical examination revealed the presence of iNM in 104 (4.5%). Of all patients, iNM was found to be present in 34 (44.2%). In terms of tumor category, iNM was present in 12 (30%), 11 (52.4%), and 11 (68.8%) of the 40, 21, and 16 Category 1, 2, and 3 patients, respectively. A significant difference in iNM frequency was found among these 3 patient groups ($p = 0.019$). iNM was detected in 13 (35.1%) of the 37 patients who had undergone immediate esophagectomy and 21 (52.5%) of the 40 patients who had undergone preoperative treatment. No significant difference in iNM frequency was found between these 2 patient groups.

**Clinicopathological factors correlating with iNM**

The clinicopathological factors found to be significantly correlated with iNM in the 77 patients are shown in **Table 2**. Clinical T category (c T), clinical N category (c N), clinical stage (c Stage), pathologic N category (pNM), and pathologic stage (p Stage) were found to be significantly correlated with iNM. In terms of preoperative treatment, c T, c Stage, pNM, and p Stage were found to be significantly correlated with iNM in the 37 patients who had not undergone preoperative treatment, whereas c N was the only factor found to be significantly correlated with iNM in the 40 patients who had undergone preoperative treatment (data not shown).
Significance of Simultaneous Histological and Micro-Nodal Metastasis

Table 2  Clinicopathologic factors correlating with immunohistochemically detected micro-nodal metastasis in all patients

<table>
<thead>
<tr>
<th>Factors</th>
<th>Positive iNM (n = 34)</th>
<th>Negative iNM (n = 43)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>19</td>
<td>20</td>
<td>0.41</td>
</tr>
<tr>
<td>≥65 years</td>
<td>15</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Man</td>
<td>30</td>
<td>38</td>
<td>1</td>
</tr>
<tr>
<td>Woman</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>c T</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1, T2</td>
<td>7</td>
<td>26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T3, T4</td>
<td>27</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>c N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>7</td>
<td>22</td>
<td>0.005</td>
</tr>
<tr>
<td>N1</td>
<td>27</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>c Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I, II</td>
<td>8</td>
<td>25</td>
<td>0.002</td>
</tr>
<tr>
<td>III, IV</td>
<td>26</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>p T</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1, T2</td>
<td>19</td>
<td>28</td>
<td>0.41</td>
</tr>
<tr>
<td>T3, T4</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>p N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>7</td>
<td>27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N1</td>
<td>27</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>p Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I, II</td>
<td>10</td>
<td>30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>III, IV</td>
<td>24</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Hx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SqCC</td>
<td>30</td>
<td>41</td>
<td>0.25</td>
</tr>
<tr>
<td>Adenoca</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

iNM: immunohistochemical nodal metastasis; c: clinical; p: pathological; Hx: tumor histology; Adenoca: adenocarcinoma; SqCC: squamous cell carcinoma

Long-term survival

The overall survival rate of the 77 patients was 52.8% at 5 years after esophageal resection. In terms of tumor category, the 5-year survival rates of Category 1, 2, and 3 patients were 57.1, 45.3, and 44.3%, respectively. In terms of pNM status, the 5-year survival rate of the 43 patients with pNM was 37.9% whereas that of 34 patients without pNM was 71.7%, percentages that indicate a significant difference in survival according to pNM status (p = 0.009) (Fig. 1A). In terms of iNM status, the 5-year survival rate of the 34 patients with iNM was 42.5%, whereas that of the 43 patients without iNM was 61.8% (Fig. 1B). While these percentages alone do not indicate a significant difference (p = 0.06) in survival according to iNM status, iNM status becomes a significant factor when considered together with pNM status. Specifically, the 5-year survival rate of the 27 patients with simultaneous pNM and iNM was 30.6% while that of the 50 patients without simultaneous pNM and iNM was 65.1%, percentages that indicate a significant difference in survival between these groups (p = 0.001; Fig. 1C).

Univariate analysis of prognostic factors

Univariate analysis revealed that c T (p = 0.003) and p Stage (p = 0.0002) were significant prognostic predictors besides pNM (p = 0.009) and simultaneous pNM and iNM (p = 0.001) in the 77 patients. In the 37 patients who had not undergone preoperative treatment, c T (p = 0.0002), p Stage (p = 0.004), iNM (p = 0.04), and simultaneous pNM and iNM (p = 0.03) were significant prognostic predictors, whereas pNM (p = 0.02), p Stage (p = 0.03), and simultaneous pNM and iNM (p = 0.008) were significant prognostic predictors in the 40 patients who had undergone preoperative treatment. Presence of iNM was a significant prognostic predictor only in patients who had not undergone preoperative treatment, whereas presence of pNM was significant only for patients who had undergone preoperative treatment (Figs. 2A, 2B, 3A, and 3B). In contrast, presence of simultaneous pNM and iNM was a significant prognostic indicator in both patient groups (Figs. 2C and 3C).

Multivariate analysis of prognostic factors

The results of multivariate analysis indicated that for all 77 patients, the independent prognostic predictors significantly associated with survival were simultaneous pNM and iNM (P = 0.03, hazard ratio [HR] 9.484, 95% confidence interval [CI] 1.245 to 72.274) and c T (p = 0.012, HR: 2.965, 95%, CI: 1.273 to 6.902). When categorized according to preoperative treatment status, the results indicated that the sole predictor for the 37 patients who had not undergone preoperative treatment...
Kinjo T, et al.

was c T (p = 0.0003, HR: 8.234, 95%, CI: 2.646 to 25.628), whereas the sole predictor of the 40 patients who had undergone preoperative treatment was simultaneous pNM and iNM (p = 0.013, HR 3.808, 95%, CI 1.324 to 10.951).

Discussion

In many cases of solid tumor, the use of immunohistochemical techniques has allowed for the detection of individual or clusters of tumor cells in the lymph nodes or bone marrow that are undetectable by conventional histological examination. Although their clinical significance has been controversial, such micro-tumor cells have been observed in the lymph nodes of patients with esophageal cancer, even those with only superficial esophageal cancer. Based on the results of a meta-analysis, a recent study reported that in node-negative esophageal cancer, the immunohistochemically detectable iNM prevalence rate ranges between 11% and 56%, and that the presence of iNM is significantly predictive of poor survival after esophagectomy. As this meta-analysis and most previous studies limited their investigation to node-negative esophageal cancer treated by esophagectomy alone, the clinical implications of iNM remain unclear in cases of node-positive esophageal cancer or cases treated with neoadjuvant treatment.

A meta-analysis of the results of clinical trials conducted to date indicates that treatment with neoadjuvant chemotherapy and chemoradiotherapy provides a survival benefit over surgery alone in patients with esophageal cancer. Based on observation of a significant reduction in iNM prevalence or decreased tumor cell load, as measured by ratio of number of lymph nodes affected by
Significance of Simultaneous Histological and Micro-Nodal Metastasis

micrometastasis in patients with a major response to neoadjuvant therapy compared to those without a major response, several investigators have suggested that neoadjuvant treatment might improve patient survival through eradication of micro-tumor cells. However, the present study failed to find a significant difference in iNM frequency between patients who had and had not undergone preoperative treatment, although the clinical response rate to preoperative chemotherapy or chemoradiotherapy had been approximately 50% in our prospective cohort study (data not shown). This discrepancy between previous reports and the present study may be explained by a treatment criterion used in this prospective cohort study; namely, that only those patients who initially presented with unfavorable prognostic factors were assigned to undergo preoperative chemotherapy or chemoradiotherapy. The fact that one unfavorable factor—heavy tumor burden—was used to assign preoperative treatment in the present study might have confounded analysis of the effects of preoperative treatment on iNM frequency. The most direct way to determine whether neoadjuvant treatment prolonged survival of esophageal cancer patients through iNM eradication was thus comparison of iNM prevalence between patients who had undergone neoadjuvant treatment and patients who had undergone surgery alone as part of a previous randomized clinical trial.

Whether iNM is a significant prognostic indicator in patients who undergo preoperative treatment is not fully understood due to the limited number of studies investigating the relationships among the factors that may affect survival. In the present study, iNM status was not found to be a significant predictor of overall survival in patients who had undergone R0 esophagectomy.
Kinjo T, et al.

For esophageal cancer, although a trend emerged indicating better overall survival in patients without iNM compared with those with iNM who had undergone preoperative treatment ($p = 0.06$). However, when the patients were divided by preoperative treatment status, iNM was found to be a significant predictor of poor survival of patients who had not undergone preoperative treatment. In this study, patients who had not undergone preoperative treatment were classified as having Category 1 disease, i.e. not having unfavorable prognostic factors. These facts suggest that iNM is a significant prognostic indicator after esophagectomy only in patients with esophageal cancer but without any other unfavorable prognostic factors.

In contrast with iNM status, the prognostic significance of pNM status was confirmed in the present study. Specifically, pNM was found to be a significant predictor of poor survival after esophagectomy when all 77 patients were analyzed. However, when the patients were divided by preoperative treatment status, pNM was found to be a significant predictor of poor survival of patients who had undergone preoperative treatment, but to have no impact on the survival of those who had not undergone preoperative treatment. Furthermore, the results of multivariate analysis indicated that pNM was not an independent prognostic factor. In this study, patients who had undergone preoperative treatment were classified as having Category 2 or 3 disease, i.e. having unfavorable prognostic factors. In other studies, esophageal cancer patients with stage III or IV disease or intramural metastasis have been reported to have a higher prevalence and a greater number of positive nodes compared to patients with Category 1 disease.$^{16,18}$ Based on these findings, extensive nodal metastasis is considered a common

Fig. 3 Survival curves according to (A) the presence or absence of pathological nodal metastasis (pNM), (B) immunohistochemical nodal metastasis (iNM), and (C) simultaneous pathological nodal metastasis and immunohistochemical nodal metastasis (pNM + iNM) in patients who had undergone preoperative treatment based on the results of Kaplan–Meier analysis.
Significance of Simultaneous Histological and Micro-Nodal Metastasis

characteristic of patients with unfavorable prognostic factors, i.e. Category 2 and 3 patients, while less extensive pNM is considered a characteristic of Category 1 patients. As all of the patients in the non-preoperative treatment group were Category 1 patients, the characteristics of Category 1 patients may explain why pNM was not found to be a significant prognostic predictor in this group. Specifically, presence of pNM may cease to be an indicator of poor survival in patients with lighter tumor load, such as Category 1 patients, after they have undergone radical esophagectomy with appropriate extent of lymphadenectomy.

While it is generally accepted that iNM is a significant prognostic predictor in node-negative esophageal cancer patients after esophagectomy, little is known regarding the role of iNM in node-positive esophageal cancer patients. Of the limited research conducted to date, Komukai, et al. found that the predictive power of iNM in node-positive esophageal cancer patients varies according to the number of positive nodes, being a significant indicator of poor survival in patients with four or fewer positive nodes but not in patients with five or more.3) Thus, the identification of a new predictor of overall survival for all patients with esophageal cancer undergoing R0 resection, regardless of whether they undergo preoperative treatment—the simultaneous presence of pNM and iNM—in the present study is significant. Specifically, simultaneous presence of pNM and iNM was found to be the only independent prognostic factor in patients who had undergone preoperative treatment, and not a factor in patients who had not undergone preoperative treatment. Nevertheless, the results of the present study and those of Komukai, et al.3) indicate the importance of considering the simultaneous presence of pNM and iNM for more accurately predicting the overall survival of patients with potentially curable esophageal cancer.

Conclusion

Assessment of presence of pNM or iNM alone does not allow for the highly accurate prediction of patient survival after curative esophagectomy for esophageal cancer. However, assessment of simultaneous presence of pNM and iNM, a novel and potentially powerful prognostic predictor identified and examined in the present study, may allow for the highly accurate prediction of the survival of esophageal cancer patients who have undergone R0 esophagectomy, regardless of whether they have also undergone preoperative treatment. As such, presence or absence of simultaneous pNM and iNM may become an important component of a new staging system for esophageal cancer that allows for more accurate prediction of patient prognosis. Furthermore, the results of the present study may enable physicians to individualize postoperative management and follow-up of patients after esophagectomy, and might contribute to identification of adequate candidates for future treatment strategies including immunotherapy and molecular targeting agent therapies after surgery.

Acknowledgements

The authors appreciate Kohei Akazawa, PhD, Department of Medical Informatics, Niigata University Graduate School of Medicine and Dental Sciences, for giving us technical advice in statistical analyses of the data.

Disclosure Statement

The authors have no conflict of interest to disclose with respect to this article.

References


