Abstract. Anaplastic carcinoma arises from differentiated carcinoma and generally shows a dire prognosis. Anaplastic transformation may occur not only in primary tumors but also in metastatic lymph nodes. We encountered 5 cases of papillary carcinoma showing anaplastic transformation in lymph nodes that were curatively resected. Patient ages ranged from 67 to 85 years. Two of these patients showed anaplastic transformation at the initial surgery and the remaining 3 showed anaplastic transformation after repeated recurrence to the lymph nodes. After resection of anaplastic lesions of the nodes, 2 patients underwent radiation therapy, whereas the remaining 3 did not receive any adjuvant therapy. One patient died of rapid growth of lung metastasis 5 months after the resection. One patient died of carcinoma 63 months after surgery. Two patients have survived to date, 6 and 85 months after resection, respectively. The remaining one patient died of heart failure 11 months after surgery. It is therefore suggested that long-term survival can be expected for patients with differentiated carcinoma showing anaplastic transformation in the lymph node if the lesions can be curatively resected.

Key words: Anaplastic carcinoma, Thyroid, Lymph node metastasis

DIFFERENTIATED thyroid carcinoma, which consists of papillary and follicular carcinomas, arises from thyroid follicular cells and usually shows a mild biological characteristic. However, occasionally, differentiated carcinoma dedifferentiates and becomes anaplastic (undifferentiated) carcinoma which is one of the most rapidly growing forms of human solid carcinomas. Although previous studies have identified some prognostic factors, long-term survival could not be expected for most patients even if they underwent multimodal therapy, combining surgery, chemotherapy, and radiotherapy [1–9].

Anaplastic transformation can occur not only in primary lesions, but also in metastatic lesions to regional lymph nodes and distant organs. Furthermore, although it was initially a differentiated carcinoma, dedifferentiation can occur during repeated recurrence to the lymph nodes. Undifferentiation of metastatic lymph nodes can also be life-threatening, indicating a dire prognosis for the patient. However, in our experience, patients with papillary carcinoma in primary lesions who demonstrated anaplastic carcinoma lesions in metastatic nodes at the initial surgery or surgery for recurrent nodes can achieve long-term survival if locally curative surgery would be performed. In this manuscript, we present our experience with the clinical courses and outcomes of five patients demonstrating papillary carcinoma in primary lesions but showing anaplastic transformation in the metastatic nodes that were curatively resected.
Patients and Methods

In 5 patients who underwent locally curative surgery as either the initial surgery or subsequent surgery to dissect lymph nodes showing carcinoma recurrence between 1990 and 2007, anaplastic carcinoma lesion was pathologically detected in metastatic nodes. Primary lesions of all these patients were pathologically confirmed as papillary carcinoma without anaplastic transformation. Anaplastic lesions in the metastatic nodes were detected in the initial surgery in 2 patients and in the second to 10th surgery in the remaining 3 patients. Patients consisted of 3 females and 2 males and patient ages ranged from 67 to 85 years. Lymph nodes with anaplastic transformation were located in the lateral compartment in 5 patients, submandibular node in 1 patient, and axillary node in 1 patient. Hematoxylin and eosin sections of all these specimens were reexamined by one of our coauthors (M.H.) and were confirmed as anaplastic carcinoma. Three patients also had metastasis to distant organs at surgery.

Results

We encountered 5 patients with papillary carcinoma demonstrating anaplastic transformation in the lymph nodes, but not in primary tumors, that were curatively resected. Tables 1 and 2 summarize the clinicopathological features at the initial surgery and clinical courses, respectively. The pathology of the primary tumors in these five patients was conventional papillary carcinoma. There were no patients who underwent radioiodine ablation therapy.

### Table 1. Backgrounds and clinicopathological features of 5 patients at initial surgery

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Age at initial surgery (years)</td>
<td>64</td>
<td>80</td>
<td>51</td>
<td>79</td>
<td>77</td>
</tr>
<tr>
<td>Size of primary tumor (cm)</td>
<td>3.5</td>
<td>2.5</td>
<td>2.5</td>
<td>1.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Pathology of primary tumor</td>
<td>Conventional</td>
<td>Conventional</td>
<td>Conventional</td>
<td>Conventional</td>
<td>Conventional</td>
</tr>
<tr>
<td>Preoperatively detected lymph node metastasis</td>
<td>Lateral</td>
<td>Lateral</td>
<td>None</td>
<td>Lateral</td>
<td>Lateral</td>
</tr>
<tr>
<td>The number of pathologically confirmed lymph node metastases</td>
<td>18</td>
<td>23</td>
<td>Unknown</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Organs to which primary tumor or lymph node extended</td>
<td>RN*, JV**</td>
<td>JV, muscle</td>
<td>None</td>
<td>RN</td>
<td>Skin, JV</td>
</tr>
</tbody>
</table>

*RN; recurrent laryngeal nerve. **JV; internal jugular vein.

### Table 2. Clinical courses of 5 patients enrolled in this study

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval between initial surgery and anaplastic transformation of lymph node (months)</td>
<td>46</td>
<td>0</td>
<td>266</td>
<td>74</td>
<td>0</td>
</tr>
<tr>
<td>Number of the surgery at which anaplastic Carcinoma was detected</td>
<td>2</td>
<td>1</td>
<td>10</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Age at detection of anaplastic carcinoma (years)</td>
<td>67</td>
<td>80</td>
<td>73</td>
<td>85</td>
<td>77</td>
</tr>
<tr>
<td>Lymph node compartment with anaplastic transformation</td>
<td>Lateral</td>
<td>Lateral</td>
<td>Submandibular Lateral, Axillary</td>
<td>Lateral</td>
<td>Lateral</td>
</tr>
<tr>
<td>Findings on needle aspiration biopsy</td>
<td>TAC 1</td>
<td>PDC 2</td>
<td>PDC 2</td>
<td>Papillary</td>
<td>Papillary or PDC</td>
</tr>
<tr>
<td>Organs showing distant metastasis at surgery for anaplastic carcinoma</td>
<td>Lung</td>
<td>Lung</td>
<td>None</td>
<td>Lung</td>
<td>None</td>
</tr>
<tr>
<td>Prognosis of patients after surgery for anaplastic carcinoma</td>
<td>5 mos DOC*</td>
<td>85 mos Alive</td>
<td>63 mos DOC</td>
<td>11 mos DOD**</td>
<td>6 mos Alive</td>
</tr>
</tbody>
</table>

1 Anaplastic carcinoma. 2 Poorly differentiated carcinoma.

*Died of carcinoma. **Died of other diseases.
Patient 1 underwent total thyroidectomy and bilateral modified radical neck dissection (MND). The right recurrent nerve and internal jugular vein were also dissected due to the invasion of primary tumor and lymph node. Lung metastasis was detected before the initial surgery. Forty-six months after the initial surgery, the patient underwent surgical resection of bilateral lymph nodes measuring 1.3–1.6 cm in which carcinoma had recurred, and they were diagnosed as anaplastic carcinoma. Thereafter, he was transferred to another hospital to undergo radiotherapy. However, he died of lung metastasis that grew rapidly 5 months after surgery. There was no local recurrence detected antemortem.

Patient 2 was referred to our hospital for the treatment of papillary carcinoma with lymph node and lung metastases. FNAB for metastatic node and primary tumor indicated poorly differentiated carcinoma. Therefore, left lobectomy with isthmectomy and bilateral MND was performed. Total thyroidectomy was not performed because of her advanced age and poor risk. The left internal jugular vein and part of the sternocleidomastoid muscle were dissected because of extranodal tumor extension. Pathological findings showed conventional papillary carcinoma in the primary lesion (Fig. 1-a). However, lymph nodes in the left lateral compartment showed anaplastic transformation (Fig. 1-b). The patient currently remains alive 85 months after surgery, with no progression of lung metastasis or signs of local recurrence.

Patient 3 underwent only right lobectomy during the initial surgery. Thereafter, she underwent systematic lymph node dissection or extirpative surgery 8 times in total for recurrences to the lymph node. Completion total thyroidectomy was also performed during the fourth surgery and she underwent radiation therapy between the 6th and 7th surgeries. At the 10th surgical treatment when she was 73 years old, metastatic nodes in the right lateral compartment and submandibular nodes ranging from 1.4 cm to 3.0 cm were dissected. Although FNAB findings of these nodes were poorly differentiated carcinoma, they were pathologically diagnosed as anaplastic carcinoma. Thereafter, she underwent dissection of axillary nodes that were also diagnosed as anaplastic carcinoma. Lymph node recurrence of anaplastic carcinoma in the right lateral compartment was again detected 47 months after the 10th surgery, but dissection was impossible because of the encased carotid artery. Although chemotherapy was performed with weekly paclitaxel, she died of carcinoma 63 months after the 10th surgery.

Patient 4 underwent left lobectomy with isthmectomy and MND for solitary papillary carcinoma. Although lung metastasis was detected at surgery, total thyroidectomy was not adopted because of his advanced age. The primary tumor extended to the recurrent laryngeal nerve and was shaved from the surface of the nerve, but persistent vocal cord paralysis occurred. Thirty-three months later, he underwent extirpative surgery in the ipsilateral metastatic nodes of which histology was papillary carcinoma, tall cell variant. Thereafter, novel node metastasis measuring 1.5 cm appeared in the same compartment, and FNAB indicated papillary carcinoma. However, surgery was repeatedly postponed because he developed pneumonia and ischemic heart disease. The node enlarged to 3.6 cm over the next 6 months. The third surgery was...
then performed to remove the node 74 months after the initial surgery. Although the node was adhesive to the clavicle, it was sharply dissected and grossly curative surgery could be performed. The pathological finding was anaplastic carcinoma. He died of heart failure 11 months after the third surgery. There were no signs of local recurrence and the lung metastasis had not progressed overall.

Patient 5 was referred to our hospital with a diagnosis of papillary carcinoma on pathological examination of a lymph node biopsy specimen obtained from the right lateral compartment. She had become aware of lymph node adenopathy one year earlier, but did not seek medical attention despite rapid growth. On ultrasonography, there was only one small calcification measuring 4 mm in the right lobe of the thyroid, which was suspected of being the primary lesion. Lymph node metastasis measured 4 cm and FNAB performed in our hospital indicated poorly differentiated carcinoma. While waiting for surgery, the node suddenly enlarged and-invaded the skin forming an ulcerated lesion. Then emergent surgery consisting of lobectomy with isthmectomy and right MND was performed, because anaplastic transformation was highly suspected. Although the metastatic node extended to the skin and jugular vein, grossly curative surgery could be performed. Pathological findings showed one papillary microcarcinoma in the thyroid that corresponded to the calcification on ultrasonographic finding, but the metastatic lymph node was diagnosed as anaplastic carcinoma. Although systematic dissection of the central and lateral compartments was performed, there was no other node metastasis detected pathologically. Radiotherapy was performed after surgery, and she has survived for 6 months since surgery with no signs of recurrence to date.

**Discussion**

Anaplastic transformation is an important event affecting the prognosis of differentiated carcinoma. Although it generally shows a dire prognosis, a previous study demonstrated that patients with primary anaplastic carcinoma can expect long-term survival if the primary lesion is curatively resected [9]. In our experience, there are 5 patients with anaplastic carcinoma who underwent locally curative surgery without distant metastasis and survived longer than 5 years, while all patients receiving only palliative surgery or having distant metastasis at diagnosis died of carcinoma within 18 months after diagnosis (our unpublished data). In this study, we demonstrated the clinical outcomes of 5 patients showing anaplastic transformation of the lymph node even though the primary tumors were papillary carcinoma. All five patients underwent locally curative surgery and 3 patients (patients 2–4) achieved prolonged survival. It is therefore suggested that even if anaplastic transformation is detected in resected specimens of the lymph nodes at the initial surgery or re-operation to dissect recurrent lymph nodes, long-term survival can be expected if locally curative surgery would be performed. This finding is consistent with that for primary anaplastic carcinoma.

This study demonstrated that there are two clinical courses leading to anaplastic transformation of the lymph node even though the primary lesion is differentiated carcinoma. One is anaplastic transformation in the nodes at the initial surgery as seen in patients 2 and 5. This did not seem related to the histology of the primary lesion or degree of metastasis, because the primary lesion of patient 5 was a solitary microcarcinoma measuring 4 mm and there were no other metastatic nodes detected pathologically in this patient. Another is anaplastic transformation after repeated recurrence to the lymph node as seen in patients 1, 3, and 4. This finding is not discrepant with that of the previous study demonstrating that there were higher incidences of histologic features of poor differentiation in metastatic nodes that recurred repeatedly [10]. Of these patients, it is unknown whether patient 3 showed any clinicopathological features reflecting aggressive features because this patient underwent initial surgery before the era of routine imaging studies such as ultrasonography. The remaining 2 patients, patients 1 and 4, had clinically apparent lymph node metastasis, massive extrathyroid extension and distant metastasis at the initial surgery, which are independent prognostic factors reflecting a poor prognosis [11, 12]. Furthermore, all patients were elderly, aged 51 years or older at initial surgery, which also predicts worse prognosis [11, 12]. It is therefore suggested that papillary carcinoma showing anaplastic transformation of metastatic lymph nodes after repeated recurrence had aggressive characteristics at the initial surgery.

How to treat such high-risk patients in order to prevent repeated recurrence to the lymph node remains an open question. Needless to say, careful therapeutic
lymph node dissection is mandatory for patients with clinically apparent node metastasis. Furthermore, in Europe and the United States, radioiodine ablation therapy 6–12 months after total thyroidectomy has been widely adopted. Previous studies demonstrated that radioiodine ablation therapy was associated with a lower rate of local relapse as well as recurrence to distant organs [13–16]. One problem is that patients in our series were over 50 years old and radioiodine ablation therapy is less likely to be effective in this age group [17]. However, it is possible that radioiodine ablation therapy after the initial surgery can reduce the rate of repeated recurrence to regional lymph nodes and should be considered for patients with papillary carcinoma having clinicopathological features that indicate biologically aggressive behaviors and poor prognoses.

In this study, we presented our experience with patients demonstrating differentiated carcinoma and having lymph node metastasis with anaplastic transformation that was curatively resected. Since long-term survival can be expected for patients showing anaplastic transformation in the lymph nodes if the nodes are curatively resected, surgeons should make an effort to dissect the lymph nodes systematically and carefully both at the initial surgery and at re-operation in order to minimize the risk of further recurrence.

**References**