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Clinical Outcomes of Patients with Papillary Thyroid Carcinoma after the Detection of Distant Recurrence

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Abstract
Purpose Papillary thyroid carcinoma generally has an excellent prognosis but can have recurrence to the distant organs that is often life-threatening. To date, prognosis and prognostic factors of papillary carcinoma have been intensively investigated, but our knowledge regarding prognosis after the detection of distant recurrence remains inadequate.
Methods We investigated the prognosis and prognostic factors of papillary carcinoma after distant recurrence was detected during follow-up in a series of 105 patients who underwent locally curative surgery between 1987 and 2004.
Results To date, 30 patients (29%) have died of carcinoma, and the 5-year and 10-year cause-specific survival (CSS) rates after the detection of distant recurrence were 71 and 50%, respectively. Patients aged 55 years or older at recurrence or with massive extrathyroid extension of primary lesions demonstrated a significantly worse CSS. On multivariate analysis, these two parameters were recognized as independent prognostic factors. Gender, tumor size, and lymph node metastasis did not affect patient prognosis. Uptake of radioactive iodine (RAI) to distant metastasis was not significantly linked to CSS, but none of the patients younger than aged 55 years showing RAI uptake died of carcinoma. Appearance of distant recurrence to organs other than lung also predicted a dire prognosis.
Conclusions Age at recurrence and extrathyroid extension of primary lesions were significantly related to patient prognosis after the detection of distant recurrence. RAI therapy is effective, especially for younger patients, if metastatic lesions show RAI uptake.

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Introduction

Papillary carcinoma is the most common malignancy originating from the thyroid. Although papillary carcinoma generally has mild biological characteristics and an excellent prognosis if competently resected, it can show recurrence during postoperative follow-up. The organ to which papillary carcinoma most likely recurs is the regional lymph nodes [1, 2]. However, with less frequency, it also can show recurrence to distant organs, such as the lung, bone, and brain. Distant recurrence is more life-threatening than local recurrence, although radioactive iodine (RAI) therapy is considered effective. To date, prognosis and prognostic factors of papillary carcinoma have been intensively investigated, but those of patients after the detection of distant recurrence have not been completely elucidated. In this study, we investigated clinical outcomes and prognostic factors using a series of 105 patients with papillary carcinoma after the detection of distant recurrence during follow-up.

Patients and methods

A total of 105 patients with papillary thyroid carcinoma who underwent initial and locally curative surgery between January 1987 and December 2004 but showed recurrence to distant organs during follow-up were enrolled in this study. Of these, three were diagnosed with poorly differentiated

carcinoma according to the WHO classification [3] and nine were diagnosed with tall cell variant. Six patients were classified as having familial nonmedullary thyroid carcinoma (FNMTC), because one of their first-degree relatives suffered papillary carcinoma [4]. No patient in our series has a history of radiation exposure. Distant metastasis was not detected on imaging studies for these patients at the time of initial surgery or on whole body scan (WBS) using 3–10 mCi RAI 1 or 2 months after the initial surgery. Patients consisted of 16 men and 89 women, and their age at initial surgery ranged from 8 to 84 (average, 53) years. We excluded patients with a component showing anaplastic transformation or having other thyroid malignancies, such as follicular carcinoma, medullary carcinoma, and malignant lymphoma. We also excluded patients with inadequate follow-up.

Eighty-one patients underwent total thyroidectomy at initial surgery. Of the remaining 24 who underwent more limited thyroidectomy, 13 underwent completion total thyroidectomy. Four of these 13 patients underwent completion total thyroidectomy for RAI therapy using 50–150 mCi RAI after the detection of distant recurrence on other imaging studies. The remaining nine underwent second surgery, including completion total thyroidectomy, for local recurrence to regional lymph nodes and/or remnant thyroid. Distant recurrence in these nine patients was detected on imaging studies performed as preoperative examinations for the second surgery or on WBS after the second surgery. Ninety-nine patients underwent central node dissection and modified radical neck dissection (MND), and 35 of these patients underwent bilateral MND. Three of 64 patients who underwent unilateral MND also underwent mediastinal node dissection. Three patients underwent central node dissection only, and the remaining three did not undergo node dissection. The average period from initial surgery to the detection of distant recurrence was 76 (range, 5–246) months.

Distant recurrence was detected on various imaging studies, such as roentgenography, CT scan, MRI, PET-CT, WBS, and RAI therapy. The distant organs to which carcinoma recurred were lung in 94 patients, bone in 24 patients, brain in 12 patients, liver in 1 patient, adrenal gland in 1 patient, and breast in 1 patient. Twenty-four patients showed distant recurrence in two or more organs. Seventy-seven patients underwent WBS and/or RAI therapy for distant recurrence. RAI uptake was observed in 23 of these patients, and 20 continuously underwent RAI therapy one or more times. RAI therapy also was performed at least once for the other 29 patients, but they did not show RAI uptake.

Average follow-up periods after the detection of distant recurrences was 55 (range, 6–238) months. Cause-specific survival (CSS) of patients was investigated using our records and/or information obtained from a questionnaire to patients or their families. To date, 30 patients (29%) have died of carcinoma during follow-up.

Statistical analyses

Fisher's exact test was adopted for comparing variables. The Kaplan–Meier method and log-rank test were adopted to analyze time-dependent variables. These analyses were performed using StatView-J 5.0. A p value <0.05 was regarded as significant. Cox-hazard regression model was adopted for multivariate analysis.

Results

We investigated the clinical outcomes of 105 patients with papillary carcinoma who showed distant recurrence after the initial surgery. To date, 30 patients (29%) have died of carcinoma. Five of these patients were younger than aged 55 years and the remaining 25 were aged 55 years or older. Five-year and 10-year CSS rates were 71 and 50%, respectively.

For the next step of this study, we investigated the relationships between CSS of patients and various clinicopathological features. Five-year and 10-year CSS rates of patients aged 55 years or older at recurrence were 59 and 19%, respectively, which were significantly lower than those of patients younger than aged 55 years, which were 95% and 88%, respectively ($p < 0.0001$; Fig. 1a). Similarly, patients with massive extrathyorid extension in the primary lesions showed significantly worse 5-year and 10-year CSS rates, 55% and 48%, respectively than those without massive extension, which were 84% and 55%, respectively ($p = 0.0097$; Fig. 1b). Gender, tumor size, status of lymph node metastasis, and multicentricity of carcinoma were not linked to patient prognosis (data not shown). We performed multivariate analysis for age and massive extrathyroid extension and found that both were regarded as independent prognostic factors of patients after showing distant recurrence (Table 1).

Distant recurrence was initially detected only in lung in 83 patients, in lung and other organs simultaneously in six patients, and in organs other than lung in 16 patients. CSS of patients showing initial distant recurrence only to the lung did not differ from that of other patients ($p = 0.1894$). However, patients showing distant recurrence to organs other than the lung initially or during further follow-up showed a significantly worse prognosis (5-year and 10-year CSS rates were 49 and 37%, respectively) than that of those showing recurrence to the lung only (78 and 60%, respectively; $p = 0.0147$; Fig. 1c). The periods between initial

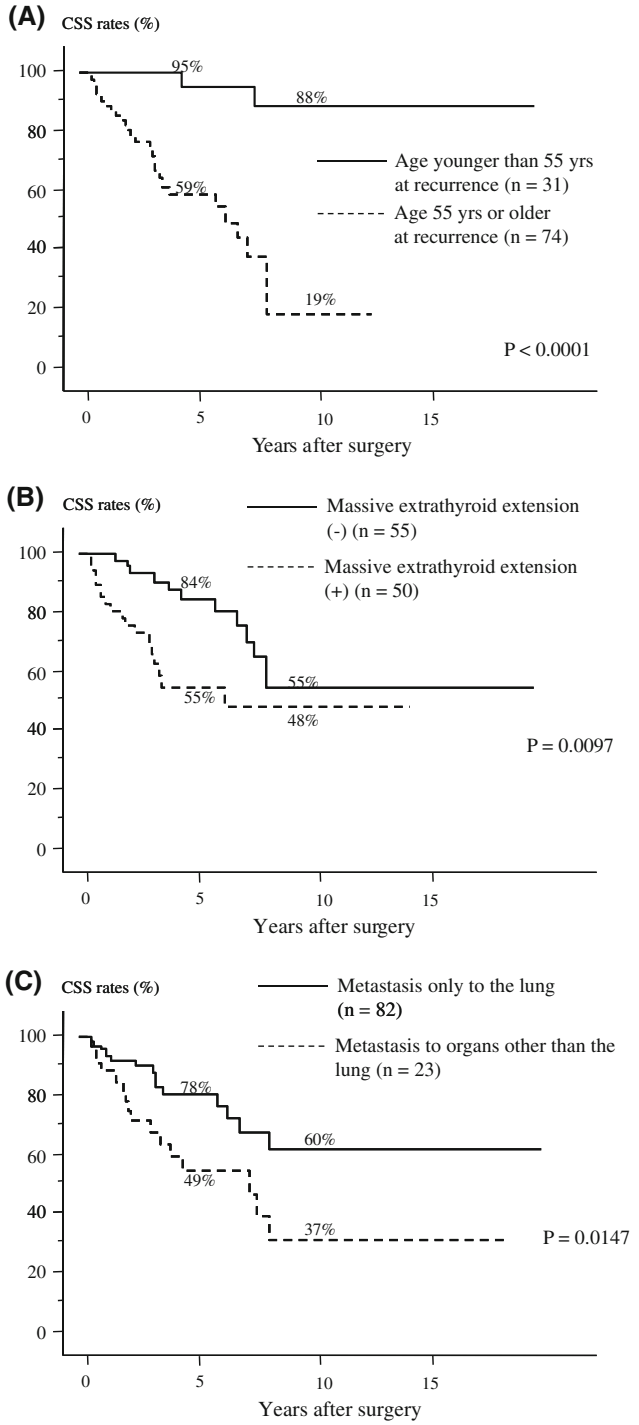

Fig. 1 **a** Comparison of CSS between patients aged 55 years or older and those younger than aged 55 years. **b** Comparison of CSS between patients having and not having massive extrathyroid extension. **c** Comparison of CSS between patients showing distant recurrence only to the lung and those showing distant recurrence to an organ other than the lung

surgery and the detection of distant recurrence and the presence of local recurrence before distant recurrence did not affect the prognosis of patients (data not shown).

Our series included three patients with poorly differentiated carcinoma and nine with tall cell variant: two patients (67%) with poorly differentiated carcinoma and five (56%) with tall cell variant died of carcinoma. Of the six patients classified with FNMTC, only one (17%) died of carcinoma.

WBS and/or RAI therapy were performed for 77 patients. Fourteen of 30 patients younger than aged 55 years (47%) and 9 of 47 patients aged 55 years or older (19%) showed RAI uptake, and RAI uptake was inversely linked to patient age ($p = 0.0203$). CSS of patients showing uptake to metastasis did not differ from that of those without such uptake ($p = 0.1432$). However, in the subset of patients younger than aged 55 years, none of those showing RAI uptake to the distant recurrence died of carcinoma, whereas five with RAI uptake aged 55 years or older died of carcinoma.

Discussion

Several studies have been published regarding the outcomes of patients with thyroid carcinoma showing distant metastasis, but most studies analyzed patients with distant metastasis at presentation and those showing distant recurrence during follow-up and/or patients with papillary carcinoma and those with follicular carcinoma as a single group [5–10]. In this study, we investigated the prognosis of only papillary carcinoma patients with distant recurrence during follow-up and showed that massive extrathyroid extension at the initial surgery and age 55 years or older at recurrence were independently associated with worse CSS. These factors were recognized as prominent prognostic factors in primary lesions at the time of initial surgery [1, 2, 11–13].

In our series, age at the time of recurrence was distinctly and independently associated with CSS of patients, regardless of the biology of primary lesions. RAI therapy is known as a standard adjuvant therapy, which is effective especially for younger patients [14–16]. In our series, incidence of RAI uptake was higher in patients younger than aged 55 years. Furthermore, although we failed to establish the relationship between RAI uptake and patient outcomes, none of the patients younger than aged 55 years with RAI uptake died of carcinoma, whereas five patients aged 55 years or older with RAI uptake died of carcinoma. Possible reasons for our findings are, therefore, high avidity and effectiveness of RAI of metastatic lesions in younger patients. Sugitani et al. showed the negative results of the effectiveness of RAI therapy for patients with distant metastasis, but they analyzed patients with distant metastasis at presentation together with those with distant recurrence during follow-up [10]. We previously analyzed

Table 1 Multivariate analysis regarding CSS of patients after the detection of distant recurrence

Variable	*p* Value	Hazard ratio (95% confidence interval)
Age 55 year or older	0.0006	13.3 (3.0–58.8)
Massive extrathyroid extension	0.0355	2.3 (1.1–4.9)

70 patients who had distant metastasis at surgery and demonstrated that three patients younger than aged 55 years and showing RAI uptake died of carcinoma [17]. Further studies using a large number of patients with longer follow-up are required, but the time lag between the appearance and detection of distant metastasis may have caused this discrepancy.

Mihailovic et al. showed that, in differentiated carcinoma with distant metastasis, patient age is a stronger prognostic factor than RAI uptake [18], indicating that there are reasons for the better prognosis of younger patients with distant metastasis other than RAI avidity. Siironen et al. showed that Ki-67 labeling index and COX-2 expression increased with patient age in papillary carcinoma [19, 20]. It is therefore suggested that, apart from RAI avidity, biological aggressiveness of papillary carcinoma becomes higher with advanced age, which also may explain our findings for newly developed metastatic lesions.

In addition to patient age at recurrence, massive extrathyroid extension is one of the biological characteristics of primary lesions, which also significantly affected CSS of patients after showing distant metastasis. This factor was associated with a delay in mortality, although the influence of the reduction in mortality over time is less remarkable (Fig. 1b), indicating that newly appeared metastases in distant organs from aggressive primary lesions tend to grow more rapidly than those from indolent lesions. In our series, nine tall cell variants and three poorly differentiated carcinomas were included. Because of the small number of patients, we did not perform further analysis for them, but their mortality rates were high, which was similar to our previous findings for primary lesions [21]. This can be considered further evidence that the tumor biology of primary lesions also significantly affects CSS of patients after they show distant metastasis. Our series also included six patients with FNMTC. In contrast to previous studies [4, 22], we showed that the prognosis of FNMTC did not differ from that of papillary carcinoma in patients without a relevant family history [2]. In this series, only one patient died of carcinoma, which is not discrepant with our previous findings.

In the present series, although the specific organ that was the initial site of distant recurrence did not affect patient prognosis, appearance of distant recurrence to organs other than lung predicted a worse prognosis. Regarding this issue, several studies present discrepant data [5–10]. Findings similar to ours were reported by Sugitani et al. using a series of Japanese patients [10], indicating that cases with distant recurrence to organs other than lung have more aggressive biological features than those with recurrence only to lung, at least in Japanese patients.

In our series, lymph node metastasis did not affect patient prognosis, which was consistent with previous studies of similar designs [5–9], although clinical lymph node metastasis strongly affected DFS and CSS of patients at initial surgery [1, 2]. This finding indicates that node metastasis has a different clinical implication from the growth of distant metastasis. Sugitani et al. analyzed 86 patients who showed distant metastasis at presentation or distant recurrence during postoperative follow-up and showed that node metastasis measuring 3 cm or larger independently affected CSS of patients [10]. We also showed that large lymph node metastasis significantly affected DFS and CSS of patients with papillary carcinoma [23], but in this study using a subset of patients showing distant recurrence, this finding was not related to patient prognosis (data not shown). The reason for this discrepancy remains to be elucidated, although it may be because of a difference in the background of the two groups of patients.

In summary, we showed that age 55 years or older at recurrence and extrathryoid extension of the primary lesions are independent prognostic factors of papillary carcinoma patients after the detection of distant recurrence and that appearance of distant recurrence in organs other than lung also was associated with a worse prognosis. RAI therapy is especially effective for patients younger than aged 55 years if their metastatic lesions show RAI uptake.

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