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Prognosis and prognostic factors of patients with papillary carcinoma showing distant metastasis at surgery (M1 patients) in Japan

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Abstract. Distant metastasis (DM) at surgery is a prominent prognostic factor in patients with papillary carcinoma of the thyroid. However, the clinical outcomes of these patients (M1 patients) remain unclear. In this study, we investigated the prognosis and prognostic factors of M1 patients. Seventy-one of 5969 patients who underwent initial surgery in Kuma Hospital between 1987 and 2004 were classified as M1 and enrolled in this study. Five-year and 10-year cause specific survival (CSS) rates were 78.8 ± 5.2% and 76.3 ± 5.7%, respectively. Patients aged 55 years or older, having tumor larger than 4 cm, massive extrathyroid extension to adjacent organs other than the recurrent laryngeal nerve and cricothyroid or inferior constrictor muscle, and DM to organs other than the lung showed a significantly worse CSS on univariate analysis. On multivariate analysis, the first three parameters were recognized as independent prognostic factors for M1 patients. Patients who underwent locally curative surgery, having DM showing radioactive iodine (RAI) uptake, and who underwent thyroid stimulation hormone (TSH) suppression therapy showed a better CSS rates than those who underwent only palliative surgery, having DM without RAI uptake, and who did not undergo TSH suppression therapy, although there was no significant difference in CSS between these groups. These findings suggest that evaluation of preoperative and intra-operative findings is important to predict the prognosis of M1 patients, the same as that in patients without DM. Locally curative surgery, RAI therapy, and TSH suppression therapy are actively recommended for M1 patients when conditions permit.

Key words: Papillary carcinoma, Thyroid, Prognostic factor, Distant metastasis

PAPILLARY CARCINOMA is the most common malignancy originating from the thyroid, and generally shows an indolent nature. However, cases showing certain characteristics are progressive and have a dire prognosis. It is well-known that papillary carcinoma frequently metastasizes to regional lymph nodes, but it can also show metastasis to distant organs with less frequency. Indeed, distant metastasis (DM) is regarded as one of the aggressive characteristics of papillary carcinoma [1, 2], although radioactive iodine (RAI) therapy is considered effective. To date, several groups have investigated the prognosis of papillary carcinoma patients demonstrating DM [3-8], but little is known about the prognosis of patients showing DM at surgery, corresponding to M1 patients according to UICC TNM classification [9]. In this study, we investigated prognostic factors predicting cause-specific survival (CSS) of M1 patients in a series of 71 patients who underwent initial surgery at Kuma Hospital. Furthermore, we also investigated the clinical significance of locally curative surgery, RAI therapy and TSH suppression therapy for M1 patients.

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Patients and Methods

Patients

Between January 1987 and December 2004, 5969 patients underwent initial surgical treatment for papillary carcinoma at Kuma Hospital. Of these patients, 71 (1%) were classified as M1. DM was detected on preoperative imaging studies such as roentgenography, CT scan, thallium scintigraphy and MRI in 50 patients. In the remaining 21 patients, DM was detect-

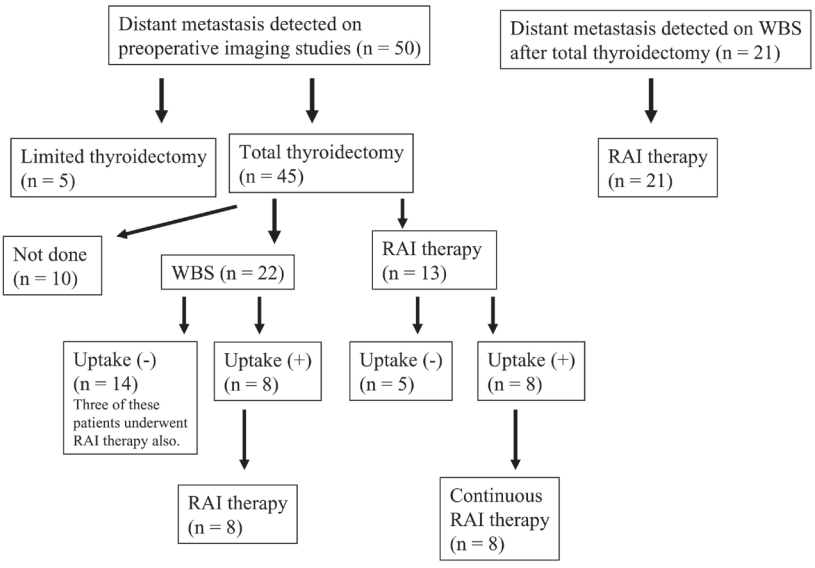

Fig. 1 Flow chart of postoperative treatment of 71 patients.

ed on postoperative whole body scan (WBS) using a small amount of RAI (3-13 mCi) 1-2 months after surgery. Patients consisted of 51 females and 20 males and ages ranged from 11 to 85 years (average 49 years). We excluded patients with a component showing anaplastic transformation or having other thyroid malignancies such as follicular carcinoma, medullary carcinoma and malignant lymphoma.

Organs showing metastasis at surgery were the lung in 60 patients, bone in 5 patients, lung and bone in 5 patients, and lung and brain in 1 patient. Total thyroidectomy was performed for 66 patients and the remaining 5 underwent hemithyroidectomy. Sixty patients underwent both central node dissection and modified radical neck dissection (MND), and one of these also underwent mediastinal lymph node dissection. Seven patients underwent central node dissection only and lymph node dissection was not performed in the remaining 4. Fifty-seven patients underwent locally curative surgery but only palliative surgery was performed for the remaining 14.

Postoperative treatment and prognosis

Postoperative treatment of 71 patients is summarized in Fig. 1. All 21 patients whose DM was detected on postoperative WBS underwent RAI therapy using 100-150mCi from 1 to 14 times. Of 50 patients having DM detected on preoperative imaging studies, 45 underwent total thyroidectomy. Due to legal restrictions, the application of RAI therapy is limited in Japan. Therefore, we recommend RAI therapy for younger patients with DM that was preoperatively detected on a priority basis. In our series, 10 of 13 patients who underwent RAI therapy without WBS after initial surgery were younger than 55 years. Eight patients showed RAI uptake in DM. Twenty-two patients underwent WBS to investigate whether DM would show RAI uptake and 17 of these patients were aged 55 years or older. RAI uptake to metastatic lesions was observed in 8 of these patients and these 8 patients underwent RAI therapy. In 16 patients with DM that was detected on preoperative imaging studies and showed RAI uptake, RAI therapy was performed from 1 to 7 times. Of 14 patients without RAI uptake on WBS, 3 underwent RAI therapy thereafter. However, none of these 3 patients showed RAI uptake to DM. The remaining 10 did not undergo WBS or RAI therapy for various reasons such as advanced age, poor general conditions and patient refusal.

The follow-up periods after surgery ranged from 2 to 252 months (average 94 months). We generally recommend thyroid stimulating hormone (TSH) suppression therapy, which was performed for 56 patients in this series. The remaining 15 did not undergo TSH suppression therapy because of patient refusal, presence of cardiac disease, or advanced age. Nine patients underwent external beam radiation therapy and 5 underwent oral administration of anticancer drugs. Six patients showed recurrence to local organs. To date, fifteen patients (21%) have died of thyroid carcinoma.

Table 1 Comparison of backgrounds and clinicopathological features of M0 and M1 patients

	M1 patients (n=71)	M0 patients (n=5898)	*p* values
Gender (M/F)	20(28%)/51(79%)	638(11%)/5260(89%)	< 0.0001
Age (yrs)	49.5 ± 20.8	50.1 ± 14.1	Not significant
Tumor size (cm)	3.6 ± 1.5	2.2 ± 1.5	< 0.0001
Extrathyroid extension Massive/no or minimal	38(54%)/33(46%)	754(13%)/5144(87%)	< 0.0001
N factor N1b/N0, N1a	51(72%)/20(28%)	1078(18%)/4820(82%)	< 0.0001

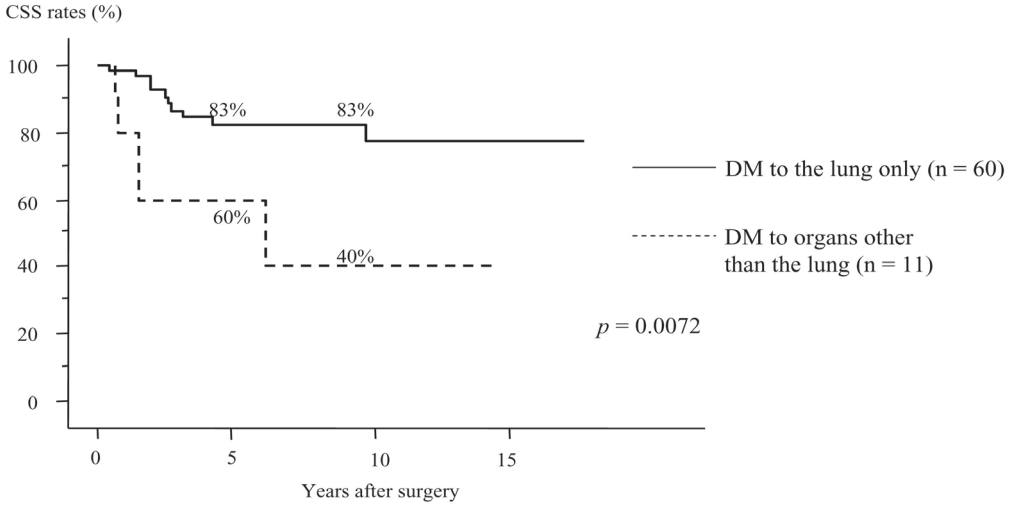

Fig. 2-a Comparison of CSS between patients with DM to the lung only and those to organs other than the lung.

Statistical analyses

Fisher's exact test and Mann-Whitney U test were used to compare variables. Kaplan-Meier method and log rank test were used to analyze time-dependent variables. These analyses were performed using StatView-J 5.0. A *p* value less than 0.05 was regarded as significant. Cox-hazard regression model was adopted for multivariate analysis.

Results

Table 1 indicates the backgrounds and clinicopathological features of M0 and M1 patients. The incidences of male gender, massive extrathyroid extension and N1b (clinical lateral node metastasis [9]) were significantly higher in M1 patients than those in M0 patients. Furthermore, tumor size was larger in M1 patients than that in M0 patients.

We investigated the CSS of 71 patients with DM at surgery. As indicated above, 15 of these patients have died of carcinoma during follow-up to date. Five-year and 10-year CSS rates were 79% (78.8 ± 5.2%) and 76% (76.3 ± 5.7%), respectively. Sixty patients showed metastasis at surgery in the lung only and 5 showed metastasis in the bone only. Metastasis to the lung and bone was observed in 5 patients and the remaining 1 showed metastasis in the brain. Patients displaying DM to organs other than the lung ($p = 0.0072$) showed a significantly worse CSS than those displaying DM only to the lung (Fig. 2-a). We then investigated how conventional prognostic factors of papillary carcinoma are linked to the prognosis of M1 patients. Patients aged 55 or older ($p = 0.0003$) and having tumor larger than 4 cm ($p = 0.0010$) were more likely to die of carcinoma (Figs. 2-b, c). Thirty-eight patients (54%) showed extrathyroid extension corresponding to T4a in the UICC classification [9]. Of these 38 patients, 12 showed extension only to the recurrent laryngeal nerve, cricothyroid muscle, or inferior constrictor muscle. In this study, we re-classified these 12 as negative for massive extrathyroid extension and the remaining 26 showing extension to the trachea, esophagus, jugular vein, innominate vein, or larynx as positive for massive extension. These 26 patients showed

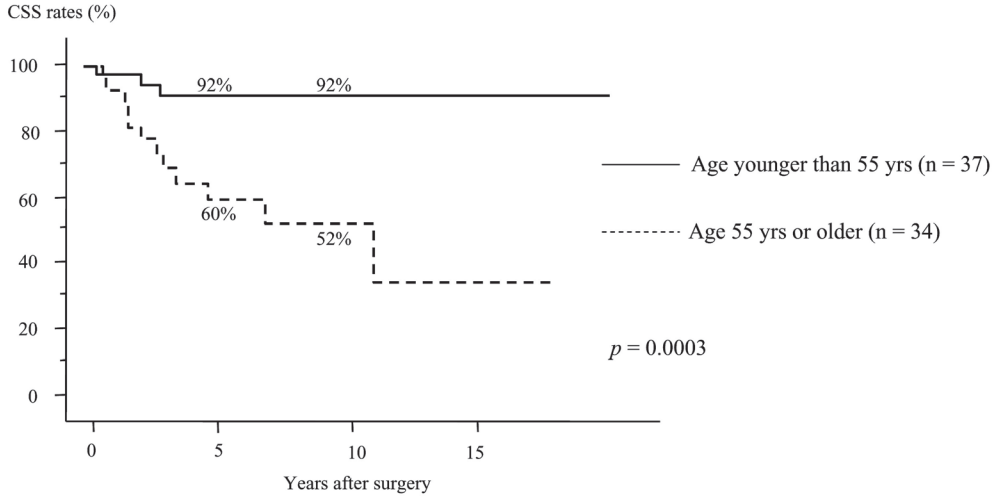

Fig. 2-b Comparison of CSS between patients 55 yrs or older and those younger than 55 yrs.

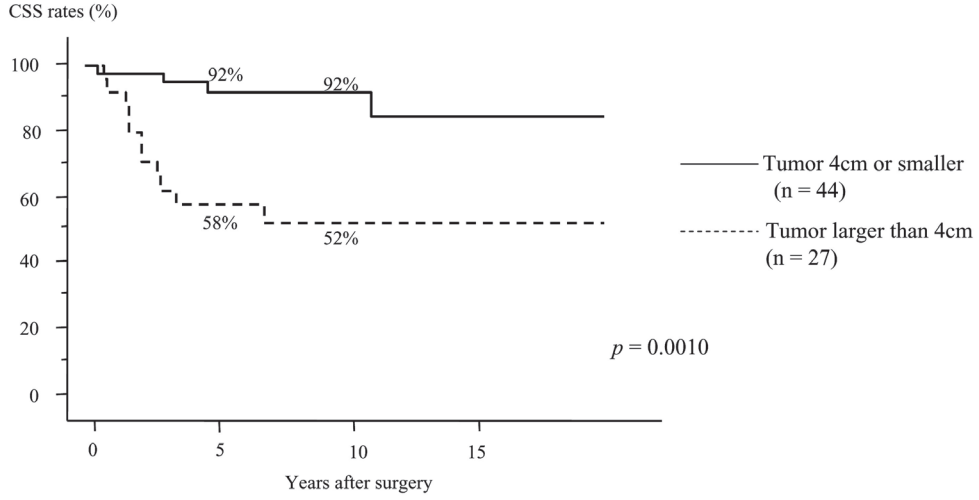

Fig. 2-c Comparison of CSS between patients having tumor larger than 4 cm and those having tumor 4cm or smaller.

a significantly worse CSS of patients (Fig. 2-d). Male patients tended to show worse CSS than female patients, but the difference was not significant (p = 0.0566). Other clinicopathological features such as clinical and pathological lymph node metastases, multifocality, and involvement of poorly differentiated lesion [10] were not related to CSS of patients (data not shown). Table 2 indicates the results of multivariate analysis. Tumor size larger than 4 cm, age 55 or older, and massive extrathyroid extension were regarded as independent prognostic factors.

Table 3 indicates the relationship of locally curative surgery, RAI uptake, timing of DM detection (preoperative imaging studies or postoperative WBS), and TSH suppression therapy to patient age. All these variables were positively correlated with patient age and especially, all patients except for one whose DM was detected on postoperative WBS were younger than 55 years. Ten-year CSS rate of patients who underwent locally curative surgery was 78%, which was 15% better than that of those who received locally palliative surgery, although there was no significant difference in CSS between these groups (Fig. 3-a). As shown in Figs. 3-b and c, uptake of RAI and timing of DM detectioin did not significantly affect CSS of patients, but there were significant differences in the 10-year CSS rates between groups, 6% and 23%, respectively. Of 37 patients showing RAI uptake, 10-year CSS rates of 21 whose DM was detected on postoperative WBS were 19% better than that of 17 whose DM was ob-

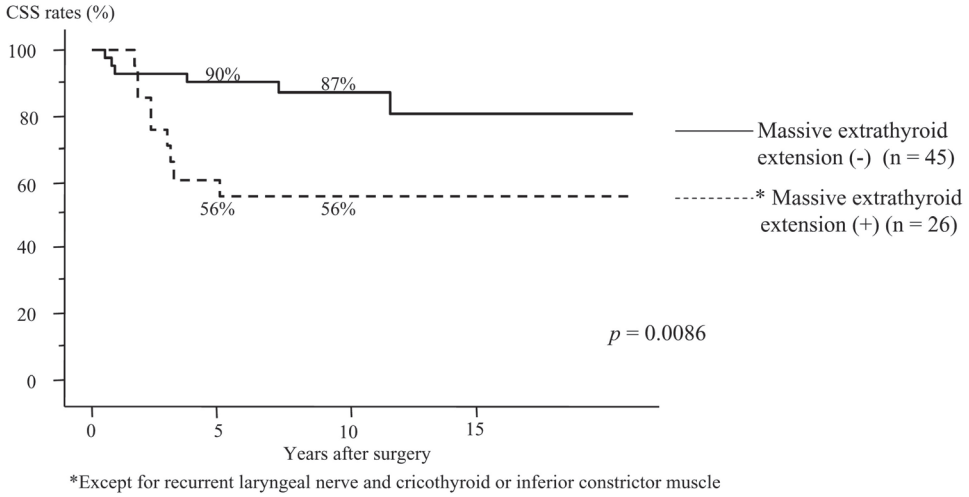

Fig. 2-d Comparison of CSS between patients having and not having massive extrathyroid extension to organs other than the recurrent laryngeal nerve and cricothyroid or inferior constrictor muscle.

Table 2 Multivariate analysis regarding CSS of M1 patients

Variables	*p* values	Hazard ratio (95% confidence interval)
Tumor size larger than 4cm	0.0075	5.78 (1.59-20.8)
Age 55 yrs or older	0.0056	7.66 (1.81-32.34)
*Massive extrathyroid extension	0.0289	3.58 (1.14-11.23)
DM to organs other than the lung	0.1805	2.30 (0.68-7.81)

Table 3 Relationship of locally curative surgery, RAI uptake, timing of DM detection, and TSH suppression therapy to patient age

Age	younger than 55 yrs	55 yrs or older	*p* values
Locally curative surgery Yes/No	35(95%)/2(5%)	22(65%)/12(35%)	0.0022
RAI uptake (+/-)	32(91%)/3(9%)	5(24%)/16(76%)	< 0.0001
Timing of DM detection Preoperative/postoperative	17(46%)/20(54%)	33(97%)/1(3%)	< 0.0001
TSH suppression therapy Yes/No	33(89%)/4(11%)	23(68%)/11(32%)	0.0406

served on preoperative imaging studies, although the difference in CSS between these two groups did not reach significance (Fig. 3-d). Similarly, TSH suppression therapy did not significantly affect patient prognosis in our series (Fig. 3-e), but CSS rates of patients receiving TSH suppression therapy were better than those without TSH suppression therapy (15% for between-group difference for 10-year CSS rates).

Discussion

To date, several studies about the prognosis of patients with thyroid carcinoma showing DM have been published [3-9]. However, most studies analyzed patients with DM at surgery and those showing DM during follow-up after surgery as a single group. Some studies investigated the prognosis of patients with DM at presentation, but analyzed both papillary and follicular carcinomas as "differentiated carcinoma" in a single group [6, 7]. This study investigated the prognosis of papillary carcinoma showing DM at surgery, including cases of DM detected on WBS in the immediate postoperative period.

DM at surgery (M1) is the strongest prognostic factor of papillary carcinoma as shown previously [11], and M1 patients more frequently had clinicopathologi-

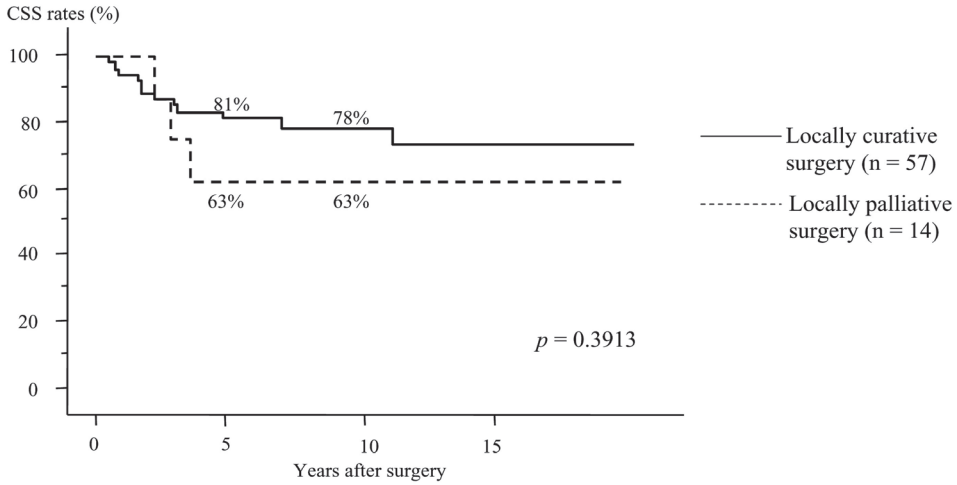

Fig. 3-a Comparison of CSS between patients who underwent and did not undergo locally curative surgery.

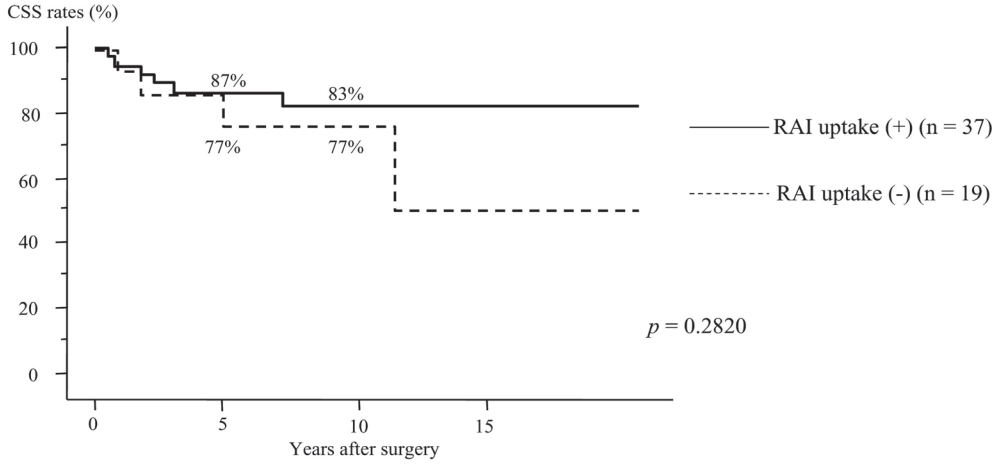

Fig. 3-b Comparison of CSS between patients with and without RAI uptake.

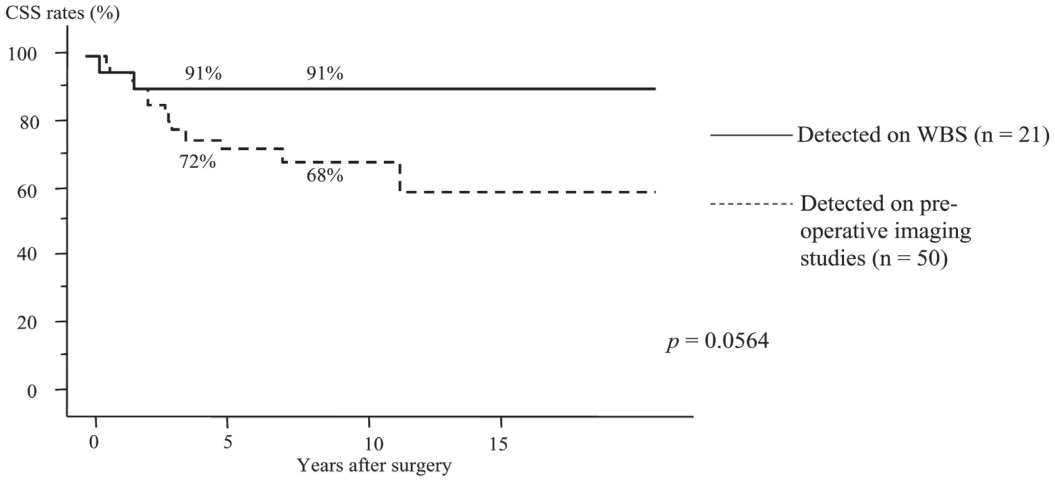

Fig. 3-c Comparison of CSS between patients whose DM was detected on postoperative WBS and on preoperative imaging studies.

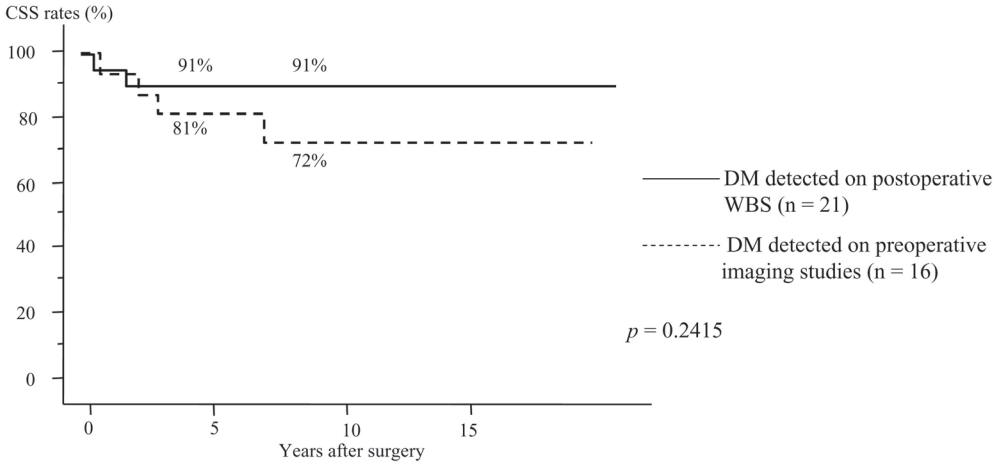

Fig. 3-d Comparison of CSS between 17 patients with RAI uptake whose DM was detected on preoperative imaging studies and 21 patients whose DM was detected on postoperative WBS.

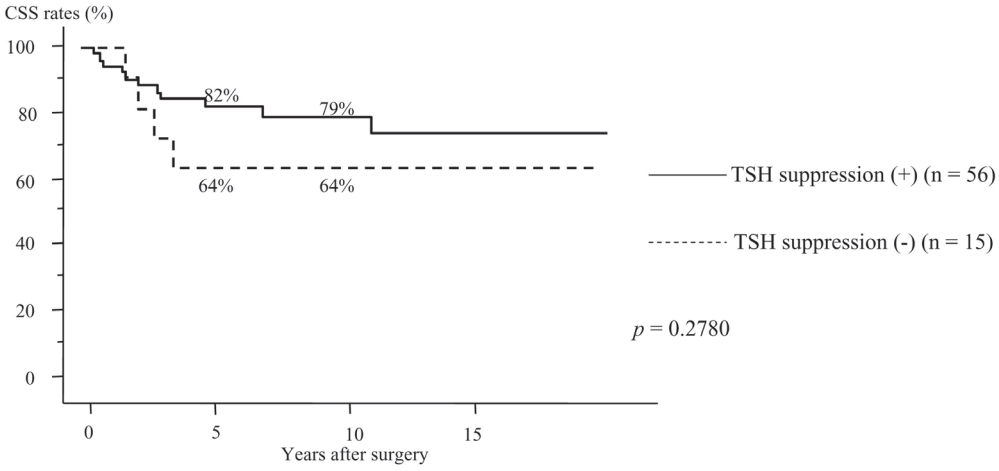

Fig. 3-e Comparison of CSS between patients who underwent and did not undergo TSH suppression.

cal features reflecting biologically aggressive behaviors such as male gender, large tumor size, extrathyroid extension and clinical lymph node metastasis (Table 1). In our series, the incidence of M1 patients was 1% and the 5-year and 10-year CSS rates of M1 patients were 79% and 76%, respectively. Previous studies from western countries adopting various study designs showed a higher incidence and worse prognosis of patients with DM [3-7]. Furthermore, Sugitani *et al*. used a series of 86 Japanese patients, including 44 showing recurrent DM after surgery, and demonstrated that the incidence of patients having DM at presentation or recurrent DM was 8% and the 5-year and 10-year survival rates were 63% and 45%, respectively [8], which were worse than those in our series. All of these studies included patients who were treated before the prevalence of ultrasound for mass screening of the thyroid and carotid artery, which have contributed markedly to the detection of thyroid carcinoma in the early stage. Our series consisted only of patients accumulated in the era of routine ultrasound since the latter 1980s, which may be a reason for this discrepancy.

In this study, we investigated how conventional prognostic factors of papillary carcinoma affect patient prognosis and demonstrated that age 55 years or older, tumor size larger than 4 cm, and massive extrathyroid extension independently affected the CSS of M1 patients. In a series of 6015 papillary carcinoma patients, we previously showed that tumor size larger than 4 cm, massive extrathyroid extension, age 55 or older, male gender, and clinical lymph node metastasis in the lateral compartment are independent prognostic factors for CSS together with M1 [11]. Interestingly, the first three of these factors were also regarded as in-

dependent prognostic factors for the subset of M1 patients. Male patients tended to show a worse prognosis, although the p value did not reach significance ($p = 0.0566$). Thus, the prognosis of M1 patients can be predicted by preoperative and intra-operative evaluation of clinicopathological features of patients in the same manner as those without DM. However, in our series, lymph node metastasis did not affect the prognosis of M1 patients, which is consistent with the findings of previous studies [3-7]. Sugitani *et al*. showed that node metastasis 3 cm or larger was a prognostic factor of patients with DM [8]. We also analyzed the prognostic value for this factor but obtained a negative result ($p = 0.1742$). The reason for this discrepancy remains unknown, but the 10-year CSS rate of patients with node metastasis 3 cm or larger was 16% lower (66% *vs* 82%) than that of those without node metastasis 3 cm or larger, indicating the possibility of type II error due to the lack of statistical power.

Previous studies showed discrepant data for the prognostic value of metastatic sites [3-8]. In our series, DM to organs other than the lung worsens patient prognosis on univariate but not on multivariate analysis. This may be because only 11 patients (15%) showed DM to the sites other than the lung, but at least at present, it is tentatively concluded that metastatic site is not a stronger prognostic factor than the three listed above for M1 patients.

Local curativity, RAI therapy and TSH suppression therapy are important issues for therapeutic strategy of M1 patients. As shown in Table 3, local curativity was inversely linked to patient age, indicating that M1 papillary carcinoma in patients with advanced age is more invasive than that in those in younger patients. There are controversial findings in previous studies about the prognostic significance of local curativity [12-14]. In our series, although local curativity was not significantly related to patient prognosis, CSS rates of patients receiving locally curative surgery were better than those of patients without locally curative surgery. In order to decrease the incidence of death from local carcinoma growth and to improve the quality of life for patients, locally curative surgery should be recommended for M1 patients whenever possible.

RAI therapy is known as a standard adjuvant therapy for thyroid carcinoma predominantly in western countries and is effective especially for younger patients [15-17]. However, Sugitani *et al*. showed that RAI therapy was not significantly linked to patient prognosis [8]. In our series, the prognosis of patients showing RAI uptake to DM did not significantly differ from that of those without RAI uptake. However, there was a marked difference of CSS rates between these groups, indicating that the lack of significance is due to a type II error. We can therefore conclude that all M1 patients fundamentally have an indication for RAI therapy and if their DM shows RAI uptake, continuous therapy should be performed. In our series, 22 patients underwent WBS instead of RAI therapy to investigate whether their DM would show RAI uptake. WBS screening is time-consuming but it was performed because of legal restrictions on the administration of large amounts of RAI. In our series, RAI uptake was inversely linked to patient age, indicating that RAI therapy without WBS should be recommended for younger patients on a priority basis, if the capacity is limited. Patients whose DM was detected on postoperative WBS showed a better CSS rates than those whose DM was preoperatively detected on imaging studies and showed RAI uptake. This may be because the volume of metastatic sites reflects the prognosis of patients and patients having DM with undetectable volume on imaging studies might show more favorable outcomes.

TSH suppression therapy has been widely adopted in western countries and previous studies from western countries showed that TSH suppression therapy decreased the risk of recurrence and death from differentiated carcinoma [18, 19]. In our series, although there was no significant difference, CSS of patients with TSH suppression was markedly better than that of those without it, indicating that TSH suppression therapy is actively recommended for M1 patients unless they have complications that contraindicate TSH suppression such as cardiac disease and osteoporosis.

In summary, we demonstrated that tumor size larger than 4 cm, age 55 years or older, and massive extrathyroid extension to adjacent organs other than the recurrent laryngeal nerve and cricothyroid or inferior constrictor muscle are independent predictors of CSS for patients with papillary carcinoma showing DM at surgery. Evaluation of preoperative and intra-operative findings is important to predict prognosis of these patients, the same as it is in those without DM. For M1 patients, total thyroidectomy, RAI therapy and TSH suppression therapy are recommended in order to decrease carcinoma death rates as and when conditions permit.

References

1. Cady B, Rosai R. (1988) An expanded view of risk group definition in differentiated thyroid carcinoma. *Surgery* 104: 947-953.
2. Sugitani I, Kasai N, Fujimoto Y, Yanagisawa A. (2004) A novel classification system for patients with PTC: addition of the new variable of large (3 cm or greater) nodal metastases and reclassification during the follow-up period. *Surgery* 135: 139-148.
3. Dinneen SF, Valimaki MJ, Bergstralh EJ, Boellner JR, Gorman CA, Hay ID. (1995) Distant metastasis in papillary thyroid carcinoma: 100 cases observed at one institution during 5 decades. *J Clin Endocrinol Metab* 80: 2041-2045.
4. Schlumberger M, Tubiana M, de Vathaire F, Hill C, Gardet P, Travagli JP, Fragu P, Lumbroso J, Caillou B, Parmentier C. (1986) Long-term results of treatment of 283 patients with lung and bone metastasis from differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 63: 960-967.
5. Pacini F, Cetani F, Micolli P, Mancusi F, Ceccarelli C, Lippi F, Marino E, Pinchera A. (1994) Outcome of 309 patients with metastatic differentiated thyroid carcinoma treated with radioiodine. *World J Surg* 18: 600-604.
6. Shoup M, Stojadinovic A, Nissan A, Ghossein RA, Freedman S, Brennan MF, Shah JP, Shaha AR. (2003) Prognostic indicators of outcomes in patients with distant metastases from differentiated thyroid carcinoma. *J Am College Surg* 197: 191-197.
7. Haq M, Harmer C. (2005) Differentiated thyroid carcinoma with distant metastases at presentation: prognostic factors and outcome. *Clin Endocrinol* 63: 87-93.
8. Sugitani I, Fujimoto Y, Yamamoto N. (2008) Papillary thyroid carcinoma with distant metastases: survival predictors and the importance of local control. *Surgery* 143: 35-42.
9. Sobin LH, Wittekind Ch., eds. (2002) UICC: TNM classification of malignant tumors, 6th ed. New York: Wiley-Liss.
10. Sakamoto A, Kasai N, Sugano H. (1983) Poorly differentiated carcinoma of the thyroid. A clinicopathologic entity for a high-risk group of papillary and follicular carcinomas. *Cancer* 52: 1849-1855.
11. Ito Y, Miyauchi A. (2009) Prognostic factors and therapetutic strategies for differentiated carcinoma of the thyroid. *Endocr J* 56: 177-192.
12. Sugino K, Kure Y, Ozaki O, Ito K. (1993) Surgical treatment of locally advanced thyroid cancer. *Surg Today* 23: 791-794.
13. Kowlaski LP, Filho JG. Results of the treatment of locally invasive thyroid carcinoma. (2002) *Head Neck* 24: 340-344.
14. Tanaka K, Sonoo H, Yamamoto Y, Udagawa K, Arime I, Kunisue H, Yamamoto S, Kurebayashi J, Shimozuma K. (1999) Analyses of the outcome of locally invasive papillary thyroid carcinoma. *Thyroid* 9: 1017-1022.
15. Durante C, Haddy N, Baudin E, Leboulleux S, Harti D, Travagli JP, Caillou B, Ricard M, Lumbroso JD, De Vathaire F, Schulumberger M. (2006) Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *J Clin Endocrinol Metab* 91: 2892-2899.
16. Dottorini ME, Vignati A, Mazzucchelli L, Lomuscio G, Colombo L. (1997) Differentiated thyroid carcinoma in children and adolescents: a 37-year experience in 85 patients. *J Nucl med* 38: 669-675.
17. Schlumberger M, Challeton C, De Vathaire F, Travagli JP, Gardet P, Lumbroso JD, Francese C, Fontaine F, Ricard M, Parmentier C. (1996) Radioactive iodine treatment and external radiotherapy for lung and bone metastases from thyroid carcinoma. *J Nucl Med* 37: 598-605.
18. Biondi B, Filetti S, Schlumberger M. (2005) Thyroid-hormone therapy and thyroid cancer: a reassessment. *Nat Clin Pract Endocrinol Metab* 1: 32-40.
19. McGriff NJ, Csako G, Gourgiotis L, Lori CG, Pucino F, Sasrlis NJ. (2002) Effects of thyroid hormone suppression therapy on adverse clinical outcomes in thyroid cancer. *Ann Med* 34: 554-564.