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Lateral Lymph Node Dissection Guided by Preoperative and Intraoperative Findings in Differentiated Thyroid Carcinoma

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Abstract
Background The lateral compartment frequently demonstrates metastasis from thyroid carcinoma. In contrast to that for central lymph node dissection, the indication for lateral node dissection remains controversial.
Methods In this review we evaluate the indication of lateral lymph node dissection in papillary and follicular carcinomas based on the findings of previous reports, including those from our institute.
Results Lymph node metastasis and recurrence at the lymph node are common events in papillary carcinoma. In particular, the lymph node recurrence rate in patients with clinically apparent lateral node metastasis (N1b) is high, not only in compartments that have not been dissected but also in those previously dissected, even if therapeutic lateral node dissection is performed. For N0 or N1a papillary carcinomas, male gender, being 55 or more years of age, a tumor larger than 3 cm, and massive extrathyroid extension are independent risk factors of lymph node recurrence, and patients with tumors having two or more of these clinicopathologic features showed high lymph node recurrence rates even if they underwent prophylactic lateral node dissection. In follicular carcinoma, node metastasis and recurrence at the node are rare events but they occasionally can be observed, especially in tumors with massive extrathyroid extension and poor differentiation.
Conclusion N1b is an absolute indication for lateral lymph node dissection. Prophylactic lateral node dissection is also recommended in N0 or N1a papillary carcinoma, if the lesion shows two or more of the aggressive characteristics indicated above. For follicular carcinoma, prophylactic node dissection is not mandatory but can be an option for tumors demonstrating aggressive characteristics or histologic types.

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There are two histologic types of differentiated thyroid carcinoma: papillary and follicular. Although both types have the same origin—thyroid follicular cells—their biological behaviors are different. Papillary carcinoma frequently metastasizes to the regional lymph nodes, ranging from 30% to 80% of patients [1]. However, follicular carcinoma rarely metastasizes to the lymph node but often metastasizes to distant organs such as the lung and bone. Therefore, different surgical methods should be used to treat these carcinomas and lymph node dissection has been considered more important for papillary carcinoma than follicular carcinoma.

There are three regional lymph node compartments to which thyroid carcinoma is likely to metastasize: lateral, central, and mediastinal. The central compartment is the most common because it is located adjacent to the lower pole of the thyroid [2, 3]. This compartment is dissected via the same incision used for thyroidectomy and wound extension is not required. In our data, the incidence of central node metastasis is very high for papillary carcinoma and 63% of patients were central node positive [4]. However, diagnostic accuracy of preoperative imaging for central node metastasis is terribly low [5]. Furthermore, previous studies indicated that reoperation on this compartment after thyroidectomy as an initial surgery is difficult and often induces significant complications such as recurrent nerve injury and permanent hypoparathyroidism [6–8]. Therefore, although the recommendation for routine central

node dissection still varies from country to country, in our opinion, the central compartment should be dissected at the time of thyroidectomy regardless of whether the dissection is considered therapeutic or prophylactic.

The mediastinal compartment is least commonly dissected for thyroid carcinoma. In general, metastasis to this compartment is thought to be from central or lateral cervical nodes, but skip metastasis directly from the tumor has also been reported [9]. Sugenoya et al. [10] assumed that contralateral lateral node metastases are indications for prophylactic mediastinal node dissection, and Mizuno et al. [11] reported that metastasis to this compartment was observed in 39.4% of cases undergoing anterosuperior mediastinal extirpation. However, at most institutes, mediastinal node dissection is performed only when metastasis in this compartment is confirmed or highly suspected by imaging studies. Indeed, clinically apparent recurrence in this compartment is not a common event and, in our opinion, prophylactic mediastinal node dissection is not recommended because the great surgical stress on patients undergoing median sternotomy may induce severe and even life-threatening complications such as atelectasis and mediastinitis.

The lateral compartment is the second most common region to which thyroid carcinoma metastasizes. It includes the fat tissue and lymph nodes around the internal jugular vein reaching from the carotid artery to the trapezoid muscle and from the subclavian vein to the hypoglossic nerve. This compartment is important because the presence of metastasis here reflects the biological aggressiveness of the carcinoma. In the UICC TNM classification and staging system, tumors that show only central node metastasis are classified as N1a, but if lateral node metastasis is also present they are classified as N1b. If patients are 45 or more years of age and their tumors do not meet the criteria for T4 (massive extrathyroid extension) or M1 (distant metastasis), the former would be staged as III and the latter would be upstaged to IVA [12]. However, the indication for lateral node dissection remains controversial because that procedure requires wound extension and increases the complaints of patients as well as the risks of various complications. In this review we focus on the indication for lateral node dissection based on the clinical significance of lateral node metastasis in differentiated thyroid carcinoma.

The route of carcinoma metastasis from the thyroid to lateral lymph node

The lateral compartment is more distant from the thyroid than the central compartment. Therefore, it is often regarded as the second line of metastasis, that is, carcinoma metastasizes to the lateral compartment via the central compartment. However, this is not true, because "skip metastasis" has been documented by Machens et al. [9]. Also in our study, both in microcarcinoma and in larger papillary carcinoma, the prevalence of lateral node-positive and central node-negative patients is similar to that of lateral node-negative and central node-positive patients [4, 5] (Tables 1, 2). Furthermore, Stoeckli et al. [13] showed that the sentinel lymph node, identified by lymphoscintigraphy and gamma probe, was located in the lateral compartment in three of six patients. Therefore, there is definitely a route of node metastasis from the thyroid directly to the lateral lymph node and both lateral and central compartments are in the first line of node metastasis from thyroid carcinoma. As shown in Table 3, microcarcinoma located in the upper pole or showing multicentricity is more likely to metastasize to the lateral

Table 1 Relationship between central and lateral node metastases in 319 microcarcinomas that underwent dissection of central and lateral compartments

		Central node metastasis		Total
		Absent	Present	
Lateral node metastasis	Absent	128	50	178
	Present	41	100	141
	Total	169	150	319

Table 2 Relationship between central and lateral node metastases in 694 papillary carcinomas that underwent dissection of central and lateral compartments

		Lateral metastasis		Total
		Absent	Present	
Central metastasis	Absent	159	78	237
	Present	105	352	457
	Total	264	430	694

Table 3 The relationship between the localization of microcarcinoma and lateral node metastasis

	Lateral node metastasis		Total
	Absent	Present	
Carcinoma spread			
Two or more regions	24	37	61
Only one region	154	104	258
		$p = 0.0064$	
Carcinoma occupying upper region			
Yes	38	68	106
No	140	73	213
		$p < 0.0001$	

nodes [14], indicating that these characteristics can induce initial metastasis to the lateral compartment of carcinoma.

Methodology and complication of lateral node dissection

As indicated in our previous review, modified radical neck dissection (MND) is the most common method of lateral node dissection [15]. Lymph nodes and surrounding fat tissue must be dissected en bloc with the preservation of the sternocleidomastoid muscle, jugular vein, phrenic nerve, and accessory nerve [16]. Dissection from the venous angle formed by the subclavian and internal jugular veins to the aponeurosis of the digastric muscle is required. Regarding the lateral edge of dissection, the supraclavicular nerve can be a good landmark.

Some complications such as chyle leakage, accessory and phrenic nerve paralysis, and Horner syndrome have been observed, although their incidences are not high [17, 18]. In our experience, chyle leakage requiring a fat-restricted diet was observed in 2.2% and the incidence of reoperation to repair the thoracic duct was 0.6% [19]. The incidence of phrenic nerve injury, facial nerve paralysis, accessory nerve paralysis, and Horner syndrome was in the range between 0.2% and 0.3% [19]. However, after surgery patients frequently complained of edema and insensitivity in the lateral region. Therefore, we can conclude that MND is a safe technique if performed by skilled surgeons, but we should study its application and select cases for which MND should be performed rather than recommend it as routine procedure.

Significance of lateral node dissection in papillary carcinoma

As indicated above, papillary carcinoma frequently metastasizes to the lymph node. Furthermore, the organ in which papillary carcinoma recurs is also the lymph node [19] and cases of repeated lymph node recurrence may become even more life-threatening due to dedifferentiation. Therefore, lymph node dissection in the appropriate range is important for decreasing the risk of lymph node recurrence. In this section, we focus on the diagnosis and therapeutic strategy for node metastasis in papillary carcinoma.

Diagnosis and diagnostic accuracy of lateral node metastasis

Since the mid-1980s, ultrasonography has been widely used to detect not only a primary tumor but also lymph node metastasis. Other imaging techniques such as scintigraphy, computerized tomography (CT), and magnetic resonance imaging (MRI) can also be used for the diagnosis of node metastasis. However, scintigraphy has low sensitivity and qualitative evaluation of nodes is often difficult with a CT scan and MRI. Therefore, ultraonography is the most useful for detecting regional lymph node metastasis except for metastasis to lymph nodes undetectable by ultrasonography such as the mediastinal and Rouvier lymph nodes. Antonelli et al. [20] listed the criteria for a diagnosis or suspicion of node metastasis on ultrasonography: (1) diameter 1 cm or more, (2) clear hypoechoic or nonhomogeneous pattern with alternating hypoechoic and hyperechoic areas, (3) irregular cystic appearance, (4) presence of internal calcification, and (5) rounded or bulging shape with increased anteroposterior diameter. Figure 1 shows typical ultrasonographic profiles of lymph node metastasis.

Preoperative evaluation of lateral node metastasis plays an important role in deciding the range of lymph node dissection, that is, whether only the central node is dissected or MND is added. When ultrasonography detects a node that one suspects of having metastasis, it may be better to perform fine needle aspiration biopsy (FNAB) of the node [21]. Furthermore, thyroglobulin measurement using wash-out from FNAB needles is also a useful method [21], which has an even higher sensitivity than FNAB of the node. Cases diagnosed as lateral node-positive by these techniques are classified as N1b and are strong candidates for therapeutic MND.

With respect to diagnostic accuracy, ultrasonography is known to have high positive predictive value (PPV) and sensitivity, but low negative predictive value (NPV) and specificity (Tables 4, 5) [22, 23]. Furthermore, in our study of 1740 papillary carcinoma patients, only 230 (13.2%) were classified as N1b but as many as 1005 (57.8%) were considered pN1b, because lateral node metastasis was confirmed by postoperative pathologic examination for these patients [19]. These findings suggest that although lateral node metastasis was diagnosed as negative by preoperative ultrasonography, more than half of these cases had microscopic lateral node metastasis detectable by pathologic examination. Actually, NPV and specificity were even lower for detection of central node metastasis (Table 6) [15], but this is not problematic since central node dissection should be routinely performed.

Backgrounds about the indication of MND

As indicated above, lateral node metastasis is very common in papillary carcinoma and nearly 60% of papillary carcinomas were classified as pN1b [19]. If these lymph nodes would have to be dissected, MND should routinely be

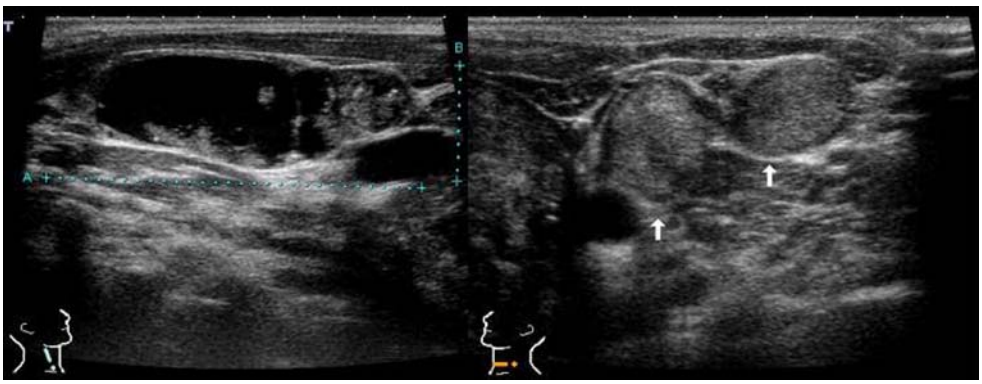

Fig. 1 Typical ultrasonographic profiles of metastatic lymph nodes in the lateral compartment

Table 4 The accuracy of US diagnosis of lateral node metastasis compared to pathologic diagnosis in microcarcinoma

		Pathologic diagnosis		Total
		Absent	Present	
US diagnosis	Absent	165	87	252
	Present	13	54	67
	Total	178	141	319

Positive predictive value = 80.6%; negative predictive value = 65.5%; sensitivity = 38.3%; specificity = 92.7%

Table 5 The accuracy of US diagnosis of lateral node metastasis compared to pathologic diagnosis in papillary carcinoma

		Pathologic diagnosis		Total
		Absent	Present	
US diagnosis	Absent	194	261	455
	Present	77	98	105
	Total	201	359	560

Positive predictive value = 93.3%; negative predictive value = 42.6%; sensitivity = 27.2%; specificity = 96.5%

Table 6 Relationship between US-diagnosed and pathologically diagnosed central node metastases in microcarcinomas

		Pathologically diagnosed metastases		Total
		Absent	Present	
US-diagnosed metastases	Absent	339	231	570
	Present	3	27	30
	Total	342	258	600

Positive predictive value = 90.0%; negative predictive value = 59.5%; sensitivity = 10.5%; specificity = 99.1%

required for all patients with papillary carcinoma regardless of their clinicopathologic features, including tumor size. Indeed, many Japanese endocrine surgeons perform MND routinely, regardless of whether lateral node metastasis was grossly detected. Therefore, in the past, subtotal thyroidectomy (or lobectomy with isthmectomy) together with central node dissection and MND was standard surgical procedure for papillary carcinoma located in one lobe. In Japan, the use of radioiodine is strictly limited by law, which prevents us from performing ablation therapy. Therefore, the aim of this surgical design is to eliminate as much carcinoma as possible under such circumstances. Noguchi et al. [24] showed that even if carcinoma is located in only one lobe, the incidence of metastasis to the contralateral lateral nodes was high when carcinoma metastasizes to the paratracheal node contralateral to the tumor. They therefore recommended bilateral MND for such patients. However, not all Japanese endocrine surgeons have recommended routine MND and Sato et al. [25] demonstrated that the presence of node metastasis did not have prognostic significance for patients and concluded that the routine application of MND should be reevaluated. In Western countries, lymph node metastasis was thought to have little prognostic impact and a "wait and see" policy for lateral node dissection has been widely adopted except for cases of gross node metastasis [26–28]. However, there are studies that propose prophylactic MND even for patients without gross metastasis when their tumors have apparent central node metastasis, are large, or show high AMES scores [29–31].

Prognostic significance of clinically apparent and pathologically detected lateral node metastases (N1b and pN1b)

To elucidate the indication for MND, it is important to investigate the biological significance of N1b (clinically apparent lateral node metastasis detectable by preoperative imaging studies including ultrasonography) and pN1b (lateral node metastasis by postoperative pathologic examination) separately. Figure 2a shows the Kaplan-Meier curve of papillary microcarcinoma patients with N1b and N0 or N1a. Even in microcarcinoma, N1b patients had

a rather high incidence of carcinoma recurrence and their disease-free survival (DFS) was significantly worse [22, 32]. This was confirmed by another study of a series with larger papillary carcinomas [23]. Furthermore, as shown in Figure 2b and Table 7, N1b also affects the cause-specific survival (CSS) of patients with papillary carcinoma on both univariate and multivariate analyses. However, pN1b patients showed a worse CSS on univariate analysis (Fig. 2c), but pN1b was not recognized as an independent prognostic factor of CSS (Table 7). It is therefore suggested that N1b is one of the important prognostic indicators of papillary carcinoma, while pN1b is not [19]. Indeed, a previous immunohistochemical study showed that microcarcinoma with N1b had more biologically aggressive characteristics than pN0 microcarcinoma, but lateral node metastasis detectable only by pathologic examination did not cause aggressive behavior [33].

Table 7 Univariate and multivariate analyses of CSS for clinicopathologic parameters

	Univariate	Multivariate	Hazard ratio (95% CI)
Age (>55 years)	<0.0001	0.0001	7.19 (2.63–19.6)
N1b	<0.0001	<0.0001	5.74 (2.41–13.6)
pN1b	0.0070	0.5961	1.56 (0.33–7.35)
pT4a	<0.0001	0.0003	5.26 (2.15–12.8)

Analysis for 1475 patients who underwent CND and MND

Therapeutic lateral node dissection for N1b patients

There is no argument regarding the indication for therapeutic lateral node dissection in N1b patients. As shown above, N1b is a marker of the aggressive character of carcinoma and predicts a worse prognosis. Therefore, therapeutic lateral node dissection should be performed carefully to avoid recurrence, at least in the same compartment, because it becomes difficult to reoperate on a previously dissected compartment. However, in N1b microcarcinoma, recurrence to node in the lateral compartment ipsilateral to the dissection was observed more frequently than recurrence to node in the contralateral lateral compartment [33]. A similar tendency was seen in studies of larger papillary carcinomas [19, 34]. A previous article showed that patients with gross lateral node metastasis had recurrence to the contralateral lateral compartment more frequently than those without gross metastasis; the authors recommended not only unilateral therapeutic MND but also prophylactic MND of the contralateral side for such patients [34]. However, according to their data, the incidence of such a recurrence was low at 1.8% for patients without gross metastasis and only 3.1% for those with gross metastasis. Furthermore, it is not very difficult to dissect a compartment that was not previously dissected. Therefore, it is definitely most important for surgeons to carefully dissect the compartment in which gross metastasis is present to reduce the incidence of recurrence in a previously dissected compartment.

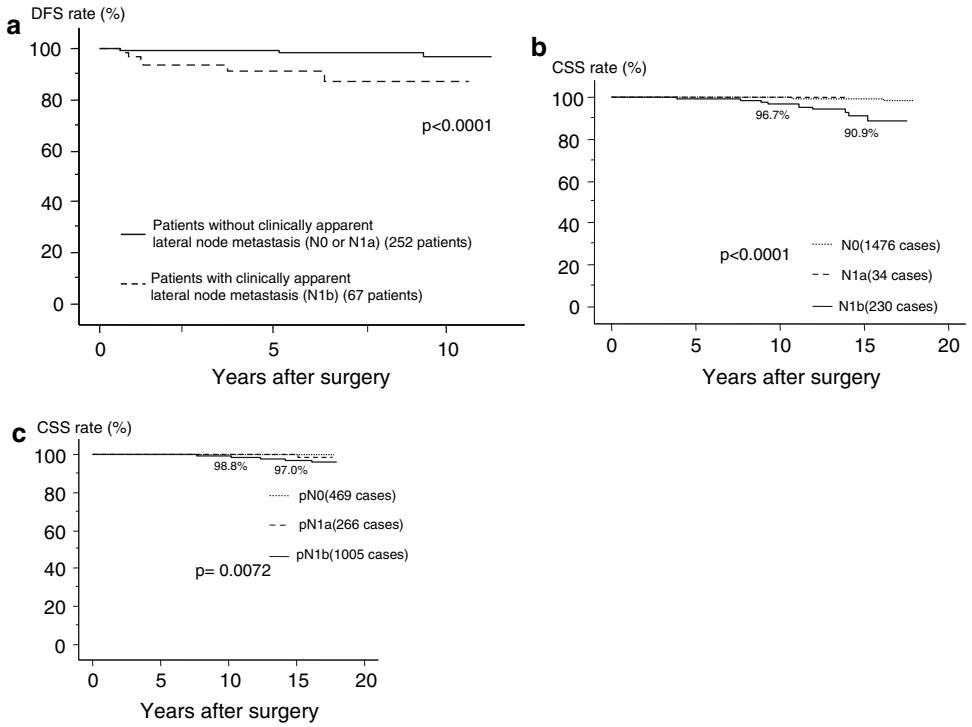

Fig. 2 **a** Kaplan-Meier curves of DFS of microcarcinoma patients with clinically apparent lateral node metastasis N1b (dashed line, 67 patients) and those without clinically apparent lateral node metastasis N0 or N1a (solid line, 252 patients). **b** Kaplan-Meier curves of CSS of patients with papillary carcinoma classified as N0 (····, 1476 cases), N1a (—, 34 cases), and N1b (—, 230 cases). **c** Kaplan-Meier curves of CSS of patients with papillary carcinoma classified as pN0 (—, 469 cases), pN1a (—, 226 cases), and pN1b (—, 1005 cases)

Another important finding is extranodal tumor extension [35–37]. Yamashita et al. [38] showed that 50 patients with papillary carcinoma with distant metastasis were more likely to have pathologic extracapsular invasion of nodal metastasis than the 50 control cases. However, they did not perform an adequate multivariate analysis, and such a pathologic finding provides only limited benefit to surgeons because it can hardly be preoperatively or intraoperatively ascertained. Apart from that, we occasionally encounter metastatic nodes that are severely adherent to (nodal ex1) or invading (nodal ex2) adjacent organs such as the juglar vein, recurrent laryngeal nerve, and phrenic nerve. In our experience, this event was observed in 135 of 1312 patients (10.2%) and affected the CSS of patients (Fig. 3) (Table 8) [37]. Surgeons should recognize this phenomenon as an indication of aggressive behavior and be more careful with dissection and perform closer postoperative follow-up of patients with nodal ex. Interestingly, CSS of nodal ex1 patients and that of nodal ex2 patients did not differ, although dissection of adjacent organs should be performed only for nodal ex2 patients [37].

Furthermore, the size and number of metastatic nodes are thought to affect patient prognosis [4, 39]. Surgeons should consider that cases of large or multiple gross metastases are likely to show recurrence and should undergo radical node dissection regardless of primary tumor size.

Prophylactic lateral node dissection for N0 or N1a patients

The indication for prophylactic lateral node dissection in papillary carcinoma patients without clinically apparent lateral node metastasis remains debatable and

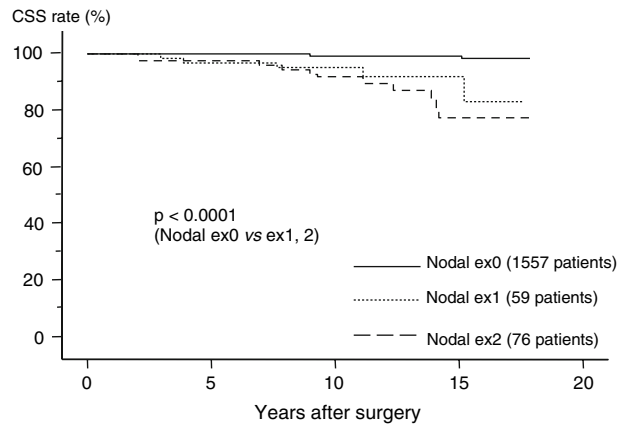

Fig. 3 Kaplan-Meier curves of CSS of patients with papillary carcinoma classified as nodal ex0 (—, 1557 patients), 1 (—-, 59 patients), and 2 (—, 76 patients)

Table 8 Univariate and multivariate analyses of CSS based on clinicopathological parameters of 1312 papillary carcinoma patients with node metastasis

	Univariate	Multivariate	Hazard ratio (95% CI)
Extranodal tumor extension	<0.0001	0.0136	4.15 (1.34–12.8)
PT4a	<0.0001	0.1739	2.02 (0.73–5.56)
Size > 4.0 cm	0.0263	0.5658	1.36 (0.48–3.90)
N1b	<0.0001	0.9682	1.02 (0.38–2.73)
PN1b	0.0202	0.7635	1.37 (0.17–11.2)
Male gender	0.0016	0.1712	2.00 (0.74–5.41)
55 years or older	<0.0001	<0.0001	7.87 (2.82–22.2)
Metastatic nodes ≥ 10	0.0301	0.5384	1.37 (0.50–3.72)
Distant metastasis	<0.0001	0.0507	3.57 (0.94–13.5)
High postoperative thyroglobulin level	<0.0001	<0.0001	9.18 (3.21–26.27)

controversial. As indicated above, lateral node metastasis is a common event in papillary carcinoma but the incidence of preoperative detection on imaging is not high. This suggests that lateral node metastasis can remain undissected if we dissect only N0 or N1a carcinomas in the central compartment. In microcarcinoma, as shown in Figure 4, the prognosis of N0 or N1a patients who underwent prophylactic MND did not differ from that of those who did not undergo MND [22]. This finding is somewhat surprising because almost 40% of N0 or N1a microcarcinomas actually have lateral node metastasis that remains undissected if prophylactic MND is not performed (Table 4). It is therefore suggested that in microcarcinoma, latent node metastasis that is only microscopically detectable only occasionally grows to become clinically apparent and prophylactic MND does not improve the prognosis of patients. However, we still have limited knowledge about whether and how prophylactic MND affects the prognosis of patients with larger N0 or N1a papillary carcinoma. Noguchi et al. [40] showed that MND improved the prognosis of patients with extrathyroid extension tumors as well as that of females and patients over 60 years old. However, their study examined patients who underwent surgery between 1946 and 1975, which is before the development and widespread use of various imaging modalities such as ultrasonography. Therefore, the preoperative evaluation of N factor for those patients was definitely less accurate than that of today. Unfortunately, there are no studies of this issue that used a large series of surgical cases after imaging studies became prevalent in the mid-1980s.

Our recent study of 1231 patients with N0 or N1a who underwent prophylactic MND between 1987 and 1995 may clarify, at least to some extent, the indication for

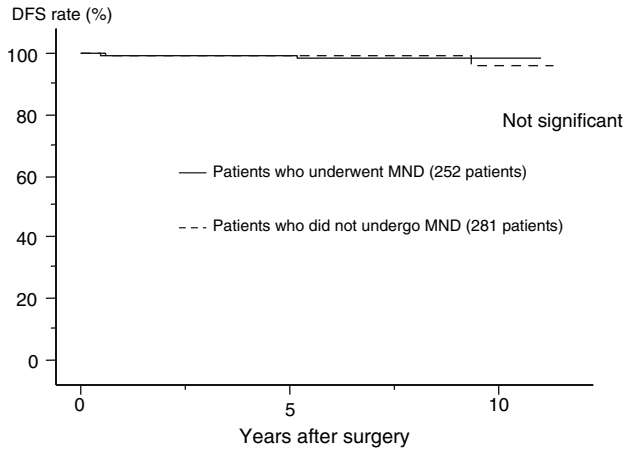

Fig. 4 Kaplan-Meier curves of DFS of patients with N0 or N1a microcarcinoma who did (solid line, 252 patients) and did not (dashed line, 281 patients) undergo prophylactic MND

prophylactic MND [18]. It is true that the incidence of latent lateral node metastasis and the number of metastastic nodes increased with the size of primary tumor with N0 or N1a (Table 9), indicating that the incidence of recurrence to the lymph node would increase with tumor size. Indeed, as shown in Figure 5a, the 10-year lymph node disease-free survival (LN-DFS) rate of patients with tumors larger than 3 cm was only 87.1%, even if they underwent at least unilateral prophylactic MND, which was significantly lower than 97.5% for those with tumors 3 cm or smaller. Furthermore, pT4 patients were much more likely to show lymph node recurrence than pT1-3 patients (Fig. 5b). Table 10 gives univariate and multivariate analyses for clinicopathologic parameters that can be evaluated preoperatively or intraoperatively. In addition to these two features, 55 or more years of age and male gender are also recognized as risk factors for lymph node recurrence. Patients were then scored from 0 to 4 based on the number of these four characteristics present and Figure 5c shows the Kaplan-Meier curves for lymph node recurrence in patients classified by these scores. The 10-year LN-DFS rates of patients scored 0, 1, 2, and 3 or 4 were 98.4%, 95.6%, 88.5%, and 68.7%, respectively. Because all these patients underwent prophylactic MND, the LN-DFS rates would further decrease if only central node dissection was performed for these patients. Therefore, according to these findings, prophylactic MND, at least ipsilateral to the primary tumor, is recommended for patients with papillary carcinoma that had two or more of the following characteristics as preoperative or intraoperative findings: male gender, age 55 or older, maximal tumor diameter greater than 3 cm, and massive extrathyroid extension (T4). The number of metastatic nodes and aggressive histologic types such as tall-cell-variant, poorly differentiated carcinoma proposed by Sakamoto et al. [41] also affected lymph node recurrence, but these factors could not be preoperatively or intraoperatively evaluated. Actually, these clinicopathologic features are also recognized as general prognostic factors, and extensive node dissection is recommended for tumors with aggressive behavior, which should be quite reasonable.

Table 9 Relationship between lateral node metastasis and tumor size

Tumor size (cm)	Number of metastases (%)			
	0	1–4	5 or more	Total
1.0 or less	78 (59.5)	43 (32.8)	10 (7.6)	131
1.1–2.0	191 (47.9)	143 (35.8)	65 (16.3)	399
2.1–3.0	111 (30.2)	151 (41.0)	106 (28.8)	368
3.1–4.0	41 (22.2)	79 (42.7)	65 (35.1)	185
4.1 or more	20 (13.5)	69 (46.6)	59 (39.9)	148

Lymph node metastasis of follicular carcinoma

Regardless of the histologic type of primary thyroid carcinoma, therapeutic MND is mandatory if there is clinically apparent lateral node metastasis. What remains debatable is whether prophylactic node dissection is necessary for follicular carcinoma. Follicular carcinoma is less likely to cause lymph node metastasis, which ranged up to 18%, and most previous studies did not recommend prophylactic lymph node dissection [42–47]. Only one study proposed prophylactic MND for T3 and T4 tumors because, in the authors' experience, lymph node metastasis affected patient prognosis [48].

In fact, in Japan, the prognosis of follicular carcinoma is much better than that in most Western countries; 10-year DFS and CSS rates were 75.3% and 90.4%, respectively [49]. This may be because of the high quantity of iodine in the Japanese diet. However, there are some clinicopathologic parameters that worsen the prognosis of patients. As shown in Figure 6, patients with poorly differentiated carcinoma (WHO classification [50]) had significantly worse CSS, and, as shown in Table 11, poor differentiation was recognized as an independent prognostic factor. Furthermore, massive extrathyroid extension also predicts a worse prognosis, although it did not independently affect CSS possibly because of the small number of cases (only 7). Regarding lymph node dissection in our institute, we usually do not dissect the lymph node, and in a series of 334 patients, lymph node dissection was performed in only 46 patients (13.8%); 22 underwent only central node dissection and the remaining 24 underwent MND together with central node dissection. Only one patient, who was diagnosed as N1b, underwent therapeutic MND, while the

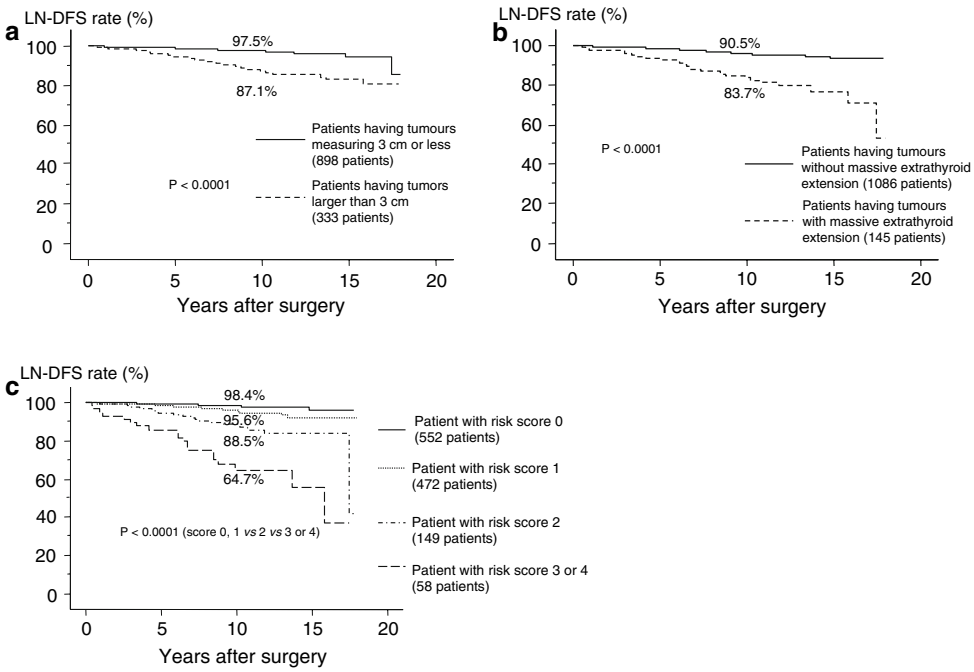

Fig. 5 **a** Kaplan-Meier curves of lymph node DFS (LN-DFS) of patients with papillary carcinoma larger than 3 cm (solid line, 898 patients) and 3 cm or less (dashed line, 333 patients). **b** Kaplan-Meier curves of lymph node DFS (LN-DFS) of patients with papillary carcinoma with (solid line, 1086 patients) and without (dashed line, 145 patients) massive extrathyroid extension. **c** Kaplan-Meier curves of lymph node DFS (LN-DFS) of patients with papillary carcinoma showing a risk score of 0 (—, 552 patients), 1 (....., 472 patients), 2 (-· -·, 149 patients), or 3 or 4 (— — —, 58 patients)

Table 10 Univariate and multivariate analyses of LN-DFS for clinicopathologic features

	Univariate	Multivariate	Hazard ratio (95% CI)
Age (≥55 years)	<0.0001	0.0004	2.38 (1.47–3.85)
Male gender	<0.0001	0.0149	2.20 (1.17–4.15)
Massive extrathyroid extension	<0.0001	<0.0001	2.77 (1.67–4.59)
Tumor size > 3.0 cm	<0.0001	<0.0001	3.26 (1.98–5.38)

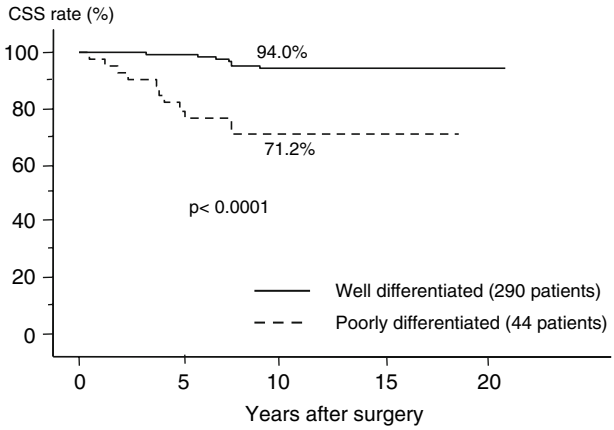

Fig. 6 Kaplan-Meier curves of CSS of patients with poorly (dashed line, 44 patients) and well-differentiated (solid line, 290 patients) follicular carcinomas

remaining patients underwent prophylactic dissection because surgeons intraoperatively suspected papillary carcinoma or because they evaluated the tumors as having aggressive characteristics. Of these patients, 11 (3.3%) were confirmed as node-positive on pathologic examination. As shown in Figure 7, patients with lymph node metastasis tended to have a dire prognosis, although the difference did not reach significance. Furthermore, Table 12 shows that lymph node metastasis is significantly related to prominent prognostic factors such as poor differentiation and extrathyroid extension. Lymph node recurrence was observed in ten patients and eight of these ten were poorly differentiated or widely invasive carcinomas. Therefore, it is suggested that lymph node metastasis and recurrence to the lymph node reflect aggressive behavior of follicular carcinoma. However, because these are rare events, prophylactic node dissection, including MND, is not routinely necessary but may be adopted as a therapeutic option if the tumor shows evidence of aggressive characteristics such as a preoperative cytologic finding of high-grade malignancy and preoperative or intraoperative detection of massive extrathyroid extension to adjacent organs.

Conclusions

There is no argument about the indication for therapeutic MND in patients with N1b differentiated carcinoma. In particular, N1b is recognized as an independent prognostic factor that affects DFS and CSS in patients with papillary carcinoma. Furthermore, the lymph node is the organ in which papillary carcinoma is most likely to recur and the incidence of recurrence in the previously dissected

Table 11 Univariate and multivariate analyses of CSS for clinicopathologic features of follicular carcinoma

	Univariate	Multivariate	Hazard ratio
Carcinoma differentiation	<0.0001	0.0043	5.25
Curativity	<0.0001	<0.0001	18.2
pT4a	<0.0001	0.2900	2.24
Age (≥45 years)	0.0093	0.2750	3.26
Tumor size (>4 cm)	0.0181	0.5761	1.40

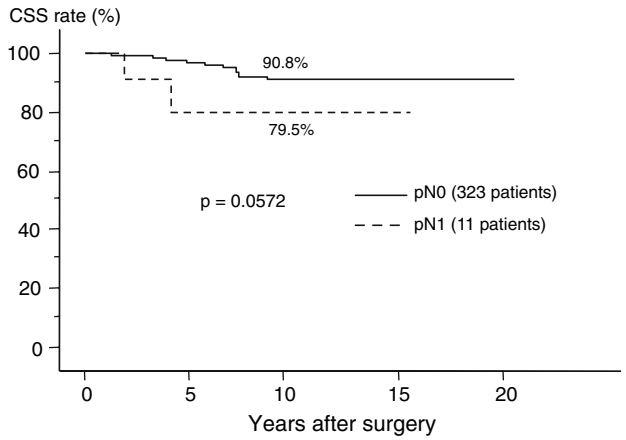

Fig. 7 Kaplan-Meier curves of CSS of patients with follicular carcinoma with and without lymph node metastasis (solid line: pN0, 323 patients; dashed line: pN1, 11 patients)

compartment is similar to or even more frequent than that of recurrence in the compartment that has not been previously dissected. Because reoperation of previously dissected compartments is exceedingly difficult and we have occasionally had cases of repeated lymph node recurrence in the previously dissected compartment being dedifferentiated and causing death, we have to do our best to prevent node recurrence, at least in previously dissected compartments. Surgeons are apt to underestimate the aggressive behavior of N1b microcarcinoma and limit the range of node dissection, but the 5-year lymph node recurrence rate of N1b microcarcinoma was rather high at 8.5%. Therefore, careful node dissection covering the full range of the compartment is mandatory for N1b carcinomas regardless of tumor size.

The indication for prophylactic MND for N0 or N1a papillary carcinoma patients remains controversial because there are no randomized studies comparing the prognosis of patients who did and did not undergo prophylactic MND. However, our experience has shown that there are four clinicopathologic features that can be evaluated preoperatively or intraoperatively to predict high lymph node recurrence for N0 or N1b papillary carcinomas even if the patient has undergone prophylactic MND: male gender,

Table 12 Relationship between lymph node metastases and clinicopathologic features of follicular carcinoma

	Node metastasis		Total	*p* values
	Absent	Present[a]		
Age (years)				
> 45	191	8	199	
≤ 45	132	3	135	N.S.
Gender				
Male	57	3	60	
Female	266	8	274	N.S.
Differentiation				
Poor	37	7	44	
Good	286	4	290	<0.0001
Massive extrathyroid extension				
Present	2	5	7	
Absent	321	6	327	<0.0001
Size (cm)				
>4	187	7	194	
<4	136	4	140	N.S.

N.S. = not significant

[a] Metastasis in the central node for 4 patients and lateral node for 7 patients. Only 1 patient showed clinically apparent node metastasis (N1b)

55 or more years of age, massive extrathyroid extension, and tumor size larger than 3 cm. In particular, there was a high lymph node recurrence rate in patients with tumors showing two or more of these features. The recurrence rate would be even higher if we omit MND, and, thus, prophylactic MND is recommended for such papillary carcinomas.

The incidence of lymph node metastasis is very low in follicular carcinoma and, in most cases, prophylactic node dissection is not necessary. However, cases showing massive extrathyroid extension or aggressive histologic types such as poorly differentiated carcinoma according to WHO classification and widely invasive carcinoma are more likely to have lymph node metastasis and show recurrence in the lymph node. Therefore, prophylactic node dissection including MND for such cases can be an option.

Lymph node metastasis and recurrence are very common events in differentiated carcinoma, especially in papillary carcinoma. From the current findings, we conclude that lymph node dissection, including MND, should be systematically and carefully performed regardless of whether dissection is therapeutic or prophylactic and regardless of whether the carcinoma demonstrates any aggressive characteristics in order to minimize the risk of lymph node recurrence in previously dissected compartments.

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