

# Therapeutic Strategies for Papillary Microcarcinoma of the Thyroid

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**Abstract:** Papillary carcinoma of the thyroid is a common malignancy originating from the endocrine organs. The recent prevalence of ultrasonography (US) and US-guided fine needle aspiration biopsy (FNAB) can make us easily diagnose papillary carcinoma of 1.0 cm or less in maximal diameter, which is called papillary microcarcinoma. How to treat papillary microcarcinoma has been controversial. In autopsy studies, papillary carcinoma of 3-9.9 mm is frequently found as an occult carcinoma. Furthermore, papillary carcinoma of more than 3 mm was detected in 3.5% of otherwise healthy women aged 30 years or older by mass screening using US and FNAB, and 84% of them were less than 1.5 cm in diameter. These findings indicate that papillary microcarcinoma frequently remains occult. Thus, recently, a trial of observation without surgical treatment has been performed, which demonstrates that most papillary microcarcinoma do not grow or only slowly grow and observation can be a therapeutic strategy. On the other hand, previous reports demonstrated that papillary microcarcinoma frequently metastasizes to cervical lymph nodes and shows multiple tumor formation in the thyroid. Furthermore, cases with palpable nodal metastasis often show rapid progression and dire prognosis. In this review, we discuss the appropriate application of observation and surgical treatment of papillary microcarcinoma.

**Keywords:** Thyroid cancer, microcarcinoma, surgery, observation.

Papillary carcinoma of the thyroid is a common malignancy originating from the endocrine organs. Usually it grows very slowly with a good prognosis, although it frequently metastasizes to regional lymph nodes and shows multiple tumor formation in the thyroid. Recently, screening for thyroid or carotid artery lesion by ultrasonography (US) has been readily performed and various small thyroid lesions have frequently been detected [1]. Furthermore, the prevalence of US-guided fine needle aspiration biopsy (FNAB) has facilitated the frequent diagnosis of papillary carcinoma measuring 1.0 cm or less in maximal diameter, which is defined as papillary microcarcinoma (PMC) in the World Health Organization monograph on histological typing of thyroid tumors [2]. This review focuses on the clinical behavior of PMC and describes the standard of therapeutic strategy for this disease.

## 1. EPIDEMIOLOGY OF PMC

The thyroid is an organ in which latent asymptomatic carcinoma of small size is frequently detected. To date, there have been many reports from various countries describing latent thyroid carcinoma detected at autopsy, and the prevalence rates have ranged from 6.0 to 35.6 % as shown in Table 1 [3-9]. According to Harach *et al.* in Finland, who reported the highest prevalence of latent carcinoma, in a series of 101 autopsies, papillary carcinoma with a diameter ranging from 0.15mm to 14.0mm, was detected in 52 foci of 36 thyroids [3]. They demonstrated that 67 % of these tumors were less than 1.0 mm. As US can detect thyroid lesions measuring 3 mm or larger [1], the size clinically

detectable PMC requiring therapy ranges from 3.0-10.0 mm. Previous studies showed that latent papillary carcinomas in this size range were detected in 2.3-5.2% of autopsy cases.

However, there is one clinical study from Japan about the prevalence of US detectable thyroid carcinoma. Takebe *et al.* detected papillary carcinomas measuring more than 3mm in 3.5% of otherwise healthy women aged 30 years or older by mass screening using US and FNAB, and about 84% of these lesions were 15 mm or smaller [10]. All lesions were resected and histologically confirmed as papillary carcinoma. Based on the finding of Takebe *et al.* the prevalence of US-detectable papillary carcinoma is 3500 per 100, 000 females, which is not discrepant with those of previous autopsy studies. However, the prevalence of clinically apparent papillary carcinoma was only 1.9-11.7 per 100, 000 females and 1.0-4.8 per 100, 000 males [3, 7], which is about 1000 times lower than that of US-detectable papillary carcinoma. The great difference between these prevalences is notable and important in discussions of how to treat PMC.

## 2. CLINICAL BEHAVIOR OF PMC

Two prominent clinical characteristics of papillary carcinoma are cervical lymph node metastasis and multicentricity. These characteristics were also observed in latent carcinoma in autopsy studies. Lang *et al.* showed that, of 63 latent carcinomas between 0.5 and 10.5 mm in diameter identified in autopsies, multicentricity was found in 46% and lymph node metastasis in 14% [8]. In a report from Japan describing 64 latent carcinomas obtained from 408 autopsy cases, 38% of these specimens showed multiple tumor formation [9]. Furthermore, a study using autopsy specimens from Hiroshima and Nagasaki demonstrated that, even among 141 latent papillary carcinomas less than 1.0 mm, 4 cases (2.8%) involved regional node metastasis [11].

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**Table 1. Prevalence Rates (%) of Occult Papillary Carcinoma in Autopsy Studies and the Distribution of Sizes**

	Number of autopsies	Prevalence rates	Tumor size (mm)			
			<1.0	1.0-2.9	3.0-9.9	>10.0
<sup>3)</sup> Finland	101	35.6	23.8	5.9	4.0	2.0
<sup>4)</sup> Hawaii	248	28.1	6.4	11.3	5.2	1.2
<sup>4)</sup> Japan (Sendai)	102	28.4	6.9	15.6	3.9	2.0
<sup>4)6)</sup> Japan (Hiroshima, Nagasaki)	391	28.4	16.0	11.0	0.5	1.0
<sup>4)</sup> Canada	100	6.0		3.0	3.0	
<sup>4)</sup> Poland	110	9.0	0.9	4.5	3.6	
<sup>4)</sup> Colombia	607	5.6	0.3	3.0	2.3	
<sup>5)</sup> USA	100	13.0				
<sup>7)</sup> Iceland	201	7.0	0.4	2.5	4.0	
<sup>8)</sup> Germany	1020	6.2				
<sup>9)</sup> Japan (Tokushima)	407	11.3				

Also in studies using surgical specimens, frequent node metastasis and multicentricity have been demonstrated as summarized in Table 2 [12-21]. The incidence of node metastasis ranged from 13.5% to 64.1%. Multicentricity of PMC could be observed in the range of 15.2% to 43.8% [12-21].

In conclusion, PMC, similar to larger papillary carcinoma, shows high incidences of regional lymph node metastasis and multiple tumor formation.

### 3. THERAPEUTIC STRATEGIES FOR PMC

As indicated above, discrepant characteristics of PMC have been demonstrated by previous clinical and autopsy studies: 1) PMC frequently remains latent, and 2) PMC frequently metastasizes to regional lymph nodes and shows multi centricity. These discrepant findings have caused

confusion regarding the optimal treatment of PMC. Most previous studies for the clinical behavior of PMC have been performed on the assumption that it is a disease requiring surgical treatment. Especially before the prevalence of US, PMC could be diagnosed mainly when it involves palpable lymph nodes. Even if the main tumors are small in size, such cases should be regarded as being in the advanced stage. Furthermore, recent studies demonstrated that PMCs frequently involve occult but pathologically diagnosed node metastasis, suggesting that thyroidectomy with lymph node dissection should be carefully performed for this disease. This trend still continues and most PMC patients undergo surgery at diagnosis.

However, some pathologists have expressed doubt regarding whether PMC should always undergo surgical treatment. Especially, Harach, a pathologist in Finland, clearly expressed doubt in the concept of routine surgery for these lesions. He and colleagues asserted that PMC can be

**Table 2. The Incidence of Lymph Node Metastasis and Multicentricity in PMC**

	No of cases	Nodal metastasis (%)	Multicentricity (%)
<sup>12)</sup> Iida <i>et al.</i>	33	48.5	
<sup>13)</sup> Hay <i>et al.</i>	535	32.0	20.0
<sup>14)</sup> Rodriguez <i>et al.</i>	36	16.7	
<sup>15)</sup> Lin <i>et al.</i>	97	18.6	
<sup>16)</sup> Rassael <i>et al.</i>	90	15.6	23.3
<sup>17)</sup> Sugitani <i>et al.</i>	178	36.0	34.2
<sup>18)</sup> Falvo <i>et al.</i>	89	13.5	15.0
<sup>19)</sup> Wada <i>et al.</i>	259	64.1	
<sup>20)</sup> Chow <i>et al.</i>	203	24.6	31.0
<sup>21)</sup> Ito <i>et al.</i>	600	48.0	43.8

regarded as a “normal” finding, and in order to avoid unnecessary surgery, they proposed that PMC less than 5 mm in diameter be called “occult papillary TUMOR” instead of carcinoma, on the ground that all PMC with distant metastasis were 6 mm or larger. This prospective was considered quite epoch-making in the 1980’s [3, 22]. Later, in 1991, after the prevalence of FNAB, Harach *et al.* claimed that unnecessary surgeries had been performed on patients with virtually harmless occult papillary carcinoma and warned that this is a pitfall of FNAB [23]. From a surgical prospective, Takebe, a Japanese surgeon, concurred that PMC should not always undergo surgery at diagnosis [10]. As indicated above, he and coworkers demonstrated considerable difference between the prevalence of thyroid carcinoma detected by mass screening and that of clinically apparent thyroid carcinoma. Furthermore, their data indicated that the rate of detection of thyroid carcinoma by mass screening peaked around age 40 and then decreased with age [24]. If all thyroid carcinomas grew constantly, the rate of detection would increase with age. Based on these findings, Takebe *et al.* hypothesized that the number of thyroid carcinomas is actually enormous but most lesions remain latent or even vanish. In conclusion, they contended that, in order to avoid unnecessary surgical treatment of thyroid carcinoma detected incidentally on US screening, guidelines regarding the application of surgical therapy to small thyroid carcinoma must be urgently established.

Based on the high frequency of incidental PMC detected in autopsy specimens as well as our clinical impression, we consider that most PMCs do not require immediate surgical treatment. If this hypothesis is correct, we may have previously recommended unnecessary surgical treatment for patients. To confirm our hypothesis, there is only one strategy available, that is, to conservatively observe PMC patients without surgical treatment. Therefore, since 1993, we have performed a trial for observation of PMC patients and reported the preliminary results in 2003 [25]. In the following chapter, the outline of our method and outcomes will be described.

#### 4. OBSERVATION OF ASYMPTOMATIC PMC WITHOUT IMMEDIATE SURGERY

Since 1993, our department has performed observation as a therapeutic strategy for PMC. We routinely perform US screening in all patients referred from other clinics as having or suspected of having thyroid disease, regardless of the presence or absence of nodular lesions in the thyroid or lymph node swelling. When nodules were found in the thyroid, we performed FNAB to determine whether these nodules were benign or malignant. For patients diagnosed as having asymptomatic PMC, we have presented two therapy options, immediate surgical treatment or observation without surgery. However, we have recommended surgical treatment for patients with PMC showing the following features, which may be signs of aggressive characteristics expected to reduce the quality of life for patients in the future; 1) tumors located adjacent to the trachea, 2) tumors possibly invading the recurrent laryngeal nerve, 3) FNAB findings suggesting high grade malignancy, 4) lymph node findings on US highly suggestive of metastasis (or confirmed as metastasis by FNAB). We diagnosed lymph

nodes as metastatic on US when they met the following criteria: 1) diameter 1cm or more; 2) clear hypoechoic pattern or dyshomogeneous pattern, with alternating hypoechoic and hyperechoic areas; 3) irregular cystic appearance; 4) presence of internal calcification; and 5) rounded or bulging shape with increased antero-posterior diameter.

Between January 1993 and March 2002, 751 patients were diagnosed as PMC by US and FNAB. We recommended surgical treatment for 67 patients because they had unfavorable features. Two hundred and eleven patients preferred observation without immediate surgical treatment. Table 3 indicated change in size of these patients compared to the beginning of follow-up. The tumor size in more than 70% of the patients decreased or did not change at each follow-up, compared to the baseline data. However, tumor size during follow-up exceeded 10mm in 19 patients (9.0%), and lymph node metastasis developed in the lateral compartment in 2 patients (0.9%). Seven of 19 patients showing tumor enlargement and 2 with the appearance of metastasis underwent surgical treatment. Our experience suggests that, instead of surgical treatment immediately after diagnosis, observation can be the initial therapeutic strategy for asymptomatic PMC.

### 5. SURGICAL TREATMENT FOR PMC

#### 1) Prognostic Factors for PMC

Although PMC can usually be followed without immediate and careful surgical treatment, it is also true that some lesions demonstrate an aggressive character. Patients with aggressive PMC should undergo immediate surgical treatment. Furthermore, even for asymptomatic PMC, we should perform surgery, when the patients choose that option. In this chapter, we describe the standard surgical design for PMC.

Generally, PMC shows an excellent prognosis if resected properly. There are two studies in large series of PMC patients with long-term follow-up. One is from Hay *et al.* at the Mayo Clinic in 1992 [13]. They reviewed 535 cases of PMC initially treated between 1940 and 1989, and demonstrated that the twenty-year tumor recurrence rate was 6% and only two patients (0.6%) died of thyroid carcinoma. Another is a report by Yamashita *et al.* at Noguchi Thyroid Clinic and Hospital Foundation [26]. Their series was huge, with 1743 patients, including some cases showing other histological types such as follicular and medullary microcarcinomas, who were treated between 1970 and 1994 (their follow-up period averaged 11.2 years). According to their data, recurrence was noted only in 31 patients (1.7%) and only 4 (0.2%) died of recurrent thyroid carcinoma. Furthermore, in our department, 600 PMC patients underwent surgical treatment between 1993 and 2001 (the follow-up period averaged 4.5 years), and to date, 13 patients (2.2%) have demonstrated recurrence but none of the patients developed distant metastasis or died of carcinoma recurrence.

However, it is also true that PMCs with certain characteristics show constant progression. Previous reports demonstrated risk factors of PMC with aggressive characteristics and the likeliness of recurrence or even life-

**Table 3. Change in Size of Microcarcinoma During Follow-up**

Time of follow-up	Total	Number of patients (%)		
		*Increased	Unchanged	Decreased
0 (beginning of follow-up)	211			
One year	177	25 (14.1%)	131 (74.0%)	21 (11.9%)
Two years	183	34 (18.6%)	131(70.4%)	18 (9.8%)
Three years	126	25 (19.8%)	89 (70.6%)	12 (9.5%)
Four years	84	25 (29.8%)	53 (63.1%)	6 (7.1%)
Five years	64	19 (22.6%)	42 (65.6%)	6 (9.4%)
*Six years or more	47	12 (25.5%)	29 (61.7%)	6 (12.8%)

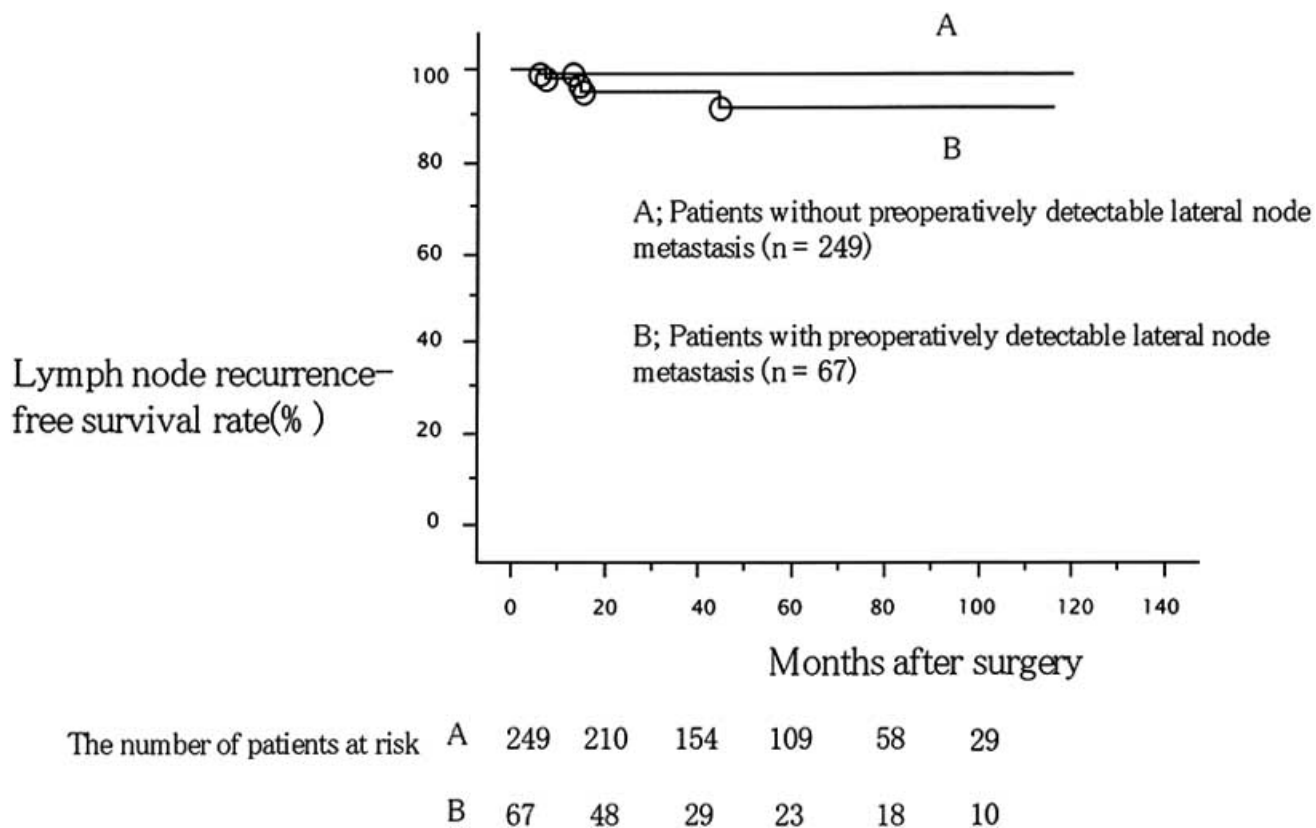
\*Size was compared with that at the beginning of follow-up in each case. Increased: 2mm or more increase in maximal diameter on ultrasonography, Decreased: 2mm or more decrease in maximal diameter on ultrasonography.

\*\*11 years in patients followed the longest follow-up.

threatening complications. Sugitani *et al.* demonstrated that “symptomatic” PMC, that is, PMC causing hoarseness of patients due to invasion of the recurrent laryngeal nerve, shows a significantly worse prognosis [17]. Multicentricity, age and serum thyroglobulin measured at one month after surgery [15, 20] are also listed as risk factors for recurrence of PMC. Furthermore, high Ki-67 labeling index and TGF 3 positivity on immunohistochemical study have been established as predictors of recurrence [27]. However, the most accepted risk factor for recurrence is lymph node metastasis. Several groups have demonstrated the

relationship between lymph node status and prognosis of PMC. Among these, Wada *et al.* demonstrated that PMCs with palpable lymph node metastasis are more likely to show recurrence, even if therapeutic lymph node dissection is performed [19]. Similar results have been presented by Chow *et al.* [20]. Furthermore, extracapsular invasion and size of metastatic lymph nodes have also been regarded as risk factors [26, 27]

Since the first half of the 1990’s, US has been widely used for diagnosing and evaluating thyroid tumors, and at present, it is undoubtedly the most useful tool for evaluating



**Fig. (1).** The Kaplan-Meier curves of patients who underwent lateral node dissection for node metastasis that was and was not preoperatively detected.

lymph node status of PMC. Therefore, we should re-evaluate the prognostic significance of lymph node metastasis based on the availability of US. Our department preoperatively investigates the presence of lymph node metastasis in all PMC patients by US. Furthermore, after surgery, we perform follow-up by US once or twice per year to monitor recurrence in the lymph node or remnant thyroid. Figure 1 indicates the prognostic significance of US-diagnosed metastasis in PMC investigated in our department. Tumors with preoperatively US-diagnosed (clinically apparent) metastasis in the lateral compartment are more likely to show recurrence, even if therapeutic lateral node dissection is performed [28]. Furthermore, as shown in (Fig. 2), whether or not prophylactic node dissection is performed was not related to the recurrence of tumors with no clinically apparent metastasis [28]. However, interestingly, the accuracy of US-diagnosis of lymph node metastasis is not high, as shown in Table 4 [21]. Although the positive predictive value (PPV) is about 80%, sensitivity was only around 40%, indicating that there were many false-negatives in our series. Thus, we can easily speculate that cases without clinically apparent metastasis often involve pathologically confirmed (latent) metastasis and if prophylactic lateral node dissection is not performed for such lesions, residual metastasis definitely remains. Despite this fact, the recurrence rate did not differ between patients with and without prophylactic dissection. It is therefore suggested that such metastatic nodes are not likely to become clinically apparent. We previously compared the cell proliferating activity and apoptotic index among tumors with clinically apparent metastasis, with only latent metastasis, and with no metastasis [29]. As a result, tumors with clinically apparent metastasis showed higher cell proliferating activity and apoptotic index than those with latent or no metastasis, but there was no difference found between those with latent and no metastasis. A similar difference was noted between carcinoma cells in clinically apparent and latent node metastasis. These findings indicate that tumors with clinically apparent metastasis are biologically aggressive, but latent metastasis does not make tumors aggressive. In conclusion, we must carefully perform lymph node dissection for PMCs with clinically apparent node metastasis, although dissection of the lateral compartment is not necessary for those without such metastasis.

**Table 4. The Accuracy of US Diagnosis of Lymph Node Metastasis in the Lateral Compartment Comparing to Pathological Diagnosis**

Lymph node metastasis in the lateral compartment			
Pathological diagnosis			
	Absent	Present	Total
US diagnosis only			
Absent	165	87	252
Present	13	54	67
178	141	319	

Positive predictive value; 80.6% (54 of the 67 patients)  
 Sensitivity; 38.3% (54 of the 141 patients)  
 Specificity; 92.7% (165 of the 178 patients)

## 2) Surgical Design of PMC

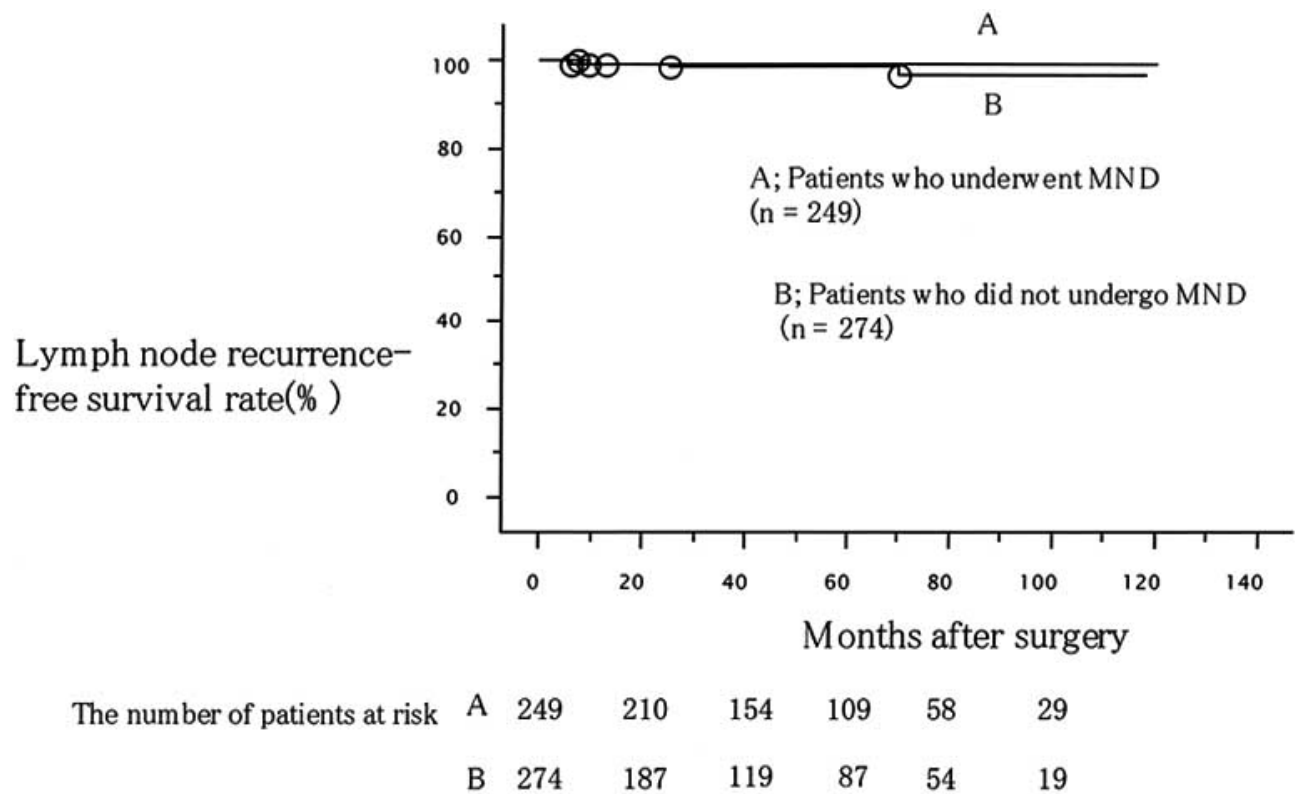
Based on the above findings, the appropriate surgical design of PMC is proposed in this chapter. Surgical treatment of thyroid carcinoma consists of two compartments, thyroidectomy and lymph node dissection. When tumors are detected in only one lobe by US examination, we perform limited thyroidectomy such as lobectomy with or without isthmectomy. Of the 326 cases undergoing limited thyroidectomy to date, only 5 (1.5%) showed recurrence in the remnant thyroid. We consider this incidence acceptable, and do not usually perform total or near total thyroidectomy unless tumors are located in both lobes.

Regardless of the US findings, we routinely dissect the central lymph nodes, because such dissection can be performed without extension of the wound and re-operation would be very difficult because of the risk of injuring the recurrent nerve, when recurrence of this compartment is found. The decision to perform lateral node dissection depends on US findings. As shown in Table 4, the PPV of US for lateral metastasis is about 80 %, indicating that 20% of cases diagnosed as having metastasis by US were actually false positives. To reduce the incidence of false positives, we have recently performed FNAB for lateral lymph nodes suspected of metastasis. In addition, we have measured thyroglobulin in wash-out needles. Then, the PPV for diagnosing metastatic nodes can reach nearly 100%. For cases diagnosed as metastasis in the lateral nodes, careful node dissection in this compartment is necessary to avoid recurrence of ipsilateral nodes of performing dissection. However, if we cannot find metastasis in the lateral compartment by US, lateral node dissection is not necessary and latent metastasis in this compartment can be ignored.

## 6. CONCLUSION

Recent prevalence of US and FNAB, PMC can easily and very frequently be found by mass screening. However, it is doubtful to perform surgical treatment for all of them, because previous pathological and clinical studies definitively demonstrated that most PMCs are harmless to the hosts. We recommend observation without immediate surgery for PMC patients as a first line of therapeutic strategy, if the lesion site is not close to trachea or recurrent laryngeal nerve and lymph node metastasis is not detected on US. We do not consider it too late to perform surgical treatment after a tendency toward enlargement or appearance of nodal metastasis can be detected during observation, and, according to our experience, the incidence should not be high. In our department, we follow up the change in size and appearance of node metastasis by US twice per year as a standard.

However, some PMCs show aggressive characteristics. Indeed, we must not forget that all advanced papillary carcinomas, including those showing anaplastic transformation, were once PMCs. The most important and well established factor reflecting progressive activity of PMCs is the presence of clinically apparent (US detectable) lymph node metastasis. The recurrence rate of such cases is rather high and we must not consider them as usual slow



**Fig. (2).** The Kaplan-Meier curves of patients without preoperatively detected lateral node metastasis, who did and did not undergo lateral node dissection.

growing cases. For these cases, we should carefully perform thyroidectomy and lymph node dissection and carefully follow-up after surgery, without unguarded attitude that the disease is only PMC.

Actually, our ultimate goal for the treatment of PMC is to be able to predict whether or not each tumor will become progressive in future at the time of diagnosis by analyzing the aspirates of FNAB. If we know that the case will progress in the future, we can easily remove the lesion before it reaches an advanced stage. Otherwise, we can regard it as a 'normal finding' and avoid unnecessary surgery. The discovery of markers useful for discriminating between progressive and non-progressive PMCs is intensively expected. For the moment, we consider it the best strategy to perform observation for PMC without unfavorable features and evaluate the nature of each case, that is, whether it constantly does or does not progress. Our final conclusion regarding the treatment of PMC is that we must do our best to avoid unnecessary surgical treatment, but must perform careful surgery, including lymph node dissection, when needed.

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