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Papillary Microcarcinoma: Is There Any Difference between Clinically Overt and Occult Tumors?

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Abstract

Introduction: Papillary microcarcinoma (PMC) is a subtype of papillary thyroid carcinoma (PTC) associated with excellent prognosis. However, clinical and biologic behaviors of PMC may vary considerably between tumors that are clinically overt and those that are occult.
Materials and Methods: From 1964 to 2003, 185 of 628 patients with PTC were identified as having PMC, based on tumor size ≤1 cm. There were 110 overt and 75 occult PMCs detected based on clinical presentation. The clinicopathologic features, treatment, and long-term outcome of PMCs were evaluated and compared between the two groups.
Results: There were 37 men and 148 women with a median age of 45 years (range: 11–84 years). The median tumor size was 6.2 mm. Thirty-eight (21%) patients presented with cervical nodal metastases. Three (1.6%) had distant metastases and 5 (2.7%) underwent incomplete resection. Bilateral procedures were performed for 129 patients (70%) and 53 (29%) received postoperative I^{131} treatment. During a mean follow-up of 8.2 years, 4 patients died of the disease and 13 developed recurrence. Clinically overt PMCs were significantly larger, were more likely to be multifocal, and more likely to lead to bilateral thyroidectomy. Extrathyroidal or lymphovascular invasion, nodal metastases, I^{131} ablation, high-risk tumors, and postoperative recurrence occurred in overt PMC only. Patients with nodal metastases had a decreased survival and an increase in locoregional recurrence.
Conclusions: Despite a relatively good prognosis in PMC, a distinction should be made between clinically overt and occult PMCs in which clinically overt PMC should be managed according to tumor risk profile and clinical presentation.

Papillary thyroid microcarcinoma (PMC) is a specific subgroup of papillary thyroid carcinoma (PTC)

based on the size of the primary tumors of 1.0 cm or less in diameter.[1] Most PMCs are clinically occult and detected incidentally during pathologic examination of thyroidectomy specimens for benign thyroid diseases or during autopsy of patients who die of non-thyroid-related diseases. In addition, with the advancement of ultrasonographic imaging and fine needle aspiration cytology

diagnosis for incidentally detected nonpalpable thyroid nodules,[2,3] occult PMC can be diagnosed with greater frequency.[3] Although the management of PMCs remains controversial, it is commonly accepted that this distinct variant of PTC based on size itself can be associated with excellent prognosis, and this should indirectly determine management principles.[4,5]

However, the fact that "not all occult papillary carcinomas are minimal" has been recognized,[6] and, in addition, not all PMCs remain clinically occult. A subset of patients with PMC can have a presentation that is clinically similar to conventional PTC, with cervical lymph node metastasis with or without detectable thyroid nodules as the most common clinical presentation.[5–12] It has been recognized that biologic behaviors of PMC may vary considerably between the really occult and the clinically overt tumors.[5–7,10]

In the present study, the clinicopathologic features, treatment, and outcome of PMC detected in our institution over the past 40 years was studied during a relatively long follow-up. Distinction is made between clinically overt and occult PMCs in order to compare them with regard to their clinical presentation, pathologic features, treatment delivered, and long-term outcome. Factors potentially affecting the outcome of patients with clinically overt PMC are evaluated and analyzed.

MATERIALS AND METHODS

From 1964 to 2003, 185 of 628 patients with PTC were identified as having PMC based on tumor size ≤1 cm in our thyroid cancer database. Patients with PMC had a significantly better cause-specific survival (CCS) than those with conventional PTC. The 10-year CSS was 95% and 90% for PMC (n = 185) and conventional PTC (n = 443), respectively (P = 0.016) (Fig. 1). There were 75 occult PMCs detected incidentally during histologic examination of thyroidectomy specimens for benign goiters; another 110 patients with clinically detectable primary tumors or nodal metastases were included as clinically overt PMC. Tumors detected incidentally during autopsy examination of the thyroid gland of patients who died of non-thyroid-related disease and multifocal tumors in patients with conventional clinically overt PTC > 1 cm in size were excluded. Because of the occult nature of the PMC in thyroidectomy specimens for benign thyroid diseases, the size of the tumors was documented by the pathologist, usually during histologic examination. For patients with clinically overt tumors, the size of the primary tumors was frequently documented by the surgeons or pathologists before histologic examination.
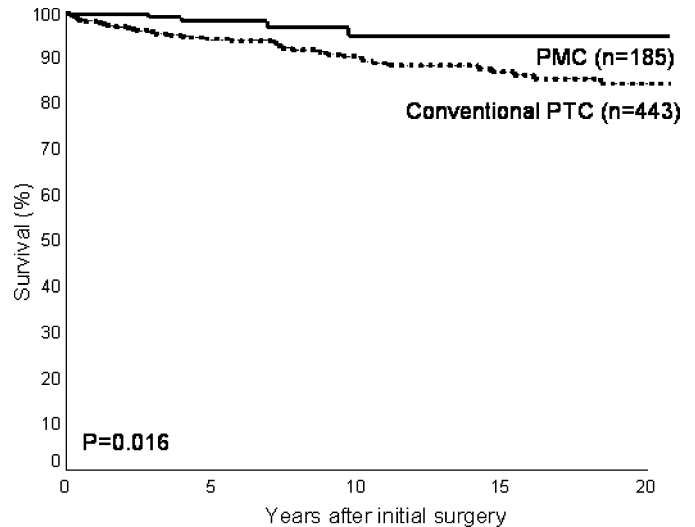

Figure 1. Actuarial survival curve comparing cause-specific survival between patients with papillary microcarcinoma (solid line) and other conventional papillary thyroid carcinomas (dotted line).

Completion total thyroidectomy was not usually adopted in the presence of incidentally detected occult PMCs after unilateral lobectomy for benign goiter. Bilateral thyroidectomy with therapeutic neck dissection was the procedure of choice for PMC with cervical node metastases diagnosed preoperatively. For PMC diagnosed preoperatively without nodal metastasis, prophylactic neck dissection was not routinely performed, but suspicious lymph nodes in the central compartment were sampled accordingly. Radioiodine (I^{131} therapy) was administered to high-risk patients who were observed to have extrathyroidal invasion, incomplete tumor excision, or cervical nodal and/or distant metastases after bilateral thyroidectomy. Patients were followed up and attended by both surgeons and oncologists at a combined thyroid cancer clinic. Thyroxine suppressive therapy was administered to patients after I^{131} therapy, and thyroglobulin monitoring was available beginning in 1991. Follow-up data, including overall mortality, tumor-related mortality, death from other causes, locoregional recurrence, and distant metastasis were obtained. Information on details of deaths was retrieved from the Hong Kong Hospital Authority territory-wide computerized medical system, death certificates, and autopsy reports if available. Patient follow-up averaged 8.2 years (range: 0.1–38 years).

The clinical presentations, pathology, treatment, and long-term outcome of patients with PMCs were analyzed. Tumor risk profile was assigned according to commonly adopted AMES (Age, Metastasis to distant sites, Extrathyroidal invasion, and Size) risk group stratification,[13]

Degroot classification,[14] UICC (International Union Against Cancer) pTNM staging,[15] and MACIS (Metastasis, Age, Completeness of excision, Invasiveness, and Size) scoring systems.[16] Comparison of clinicopathological features, treatment, tumor risk profile, and outcome was made based on the clinical presentation of PMCs. Statistical analysis was performed by the chi-squared test or Fisher's exact test to compare categorical variables, and by Student's t-test to compare continuous variables between groups. Potential factors affecting the CSS including age (< 40 years and ≥ 40 years), sex, tumor size (< 5 mm and ≥ 5 mm), any evidence of extrathyroidal or lymphovascular invasion, the presence of nodal or distant metastases, the types of thyroidectomy (bilateral thyroidectomy or unilateral thyroid lobectomy), the completeness of excision (as determined by the operating surgeons), and the administration of postoperative I[131] ablation were evaluated in patients with clinically overt tumors. The CSS and disease-free survival (DFS) rates were calculated at 10 years after the initial surgical treatment with standard life-table methods analyzed by the Kaplan-Meier method[17] and compared with the log-rank test. Statistical analyses were performed using the SPSS for Windows 10.0 computer software (SPSS Inc., Chicago, IL). A value of $P < 0.05$ was regarded as statistically significant.

RESULTS

Demographic Data, Clinicopathologic Features, and Outcome of Patients with PMC

There were 37 men and 148 women with a median age of 45 years (range: 11–84 years). There was no difference in gender ratio (male/female: 25/85 versus 12/63; $P = 0.35$) or age (mean ± s.d.: 45 ± 16 versus 48 ± 13 years; $P = 0.1$) between clinically overt and occult tumors. Eighteen patients had a history of thyrotoxicosis treated by either antithyroid medication (n = 13) and/or I[131] (n = 5) before presentation.

Occult PMCs were diagnosed in patients undergoing thyroidectomy for pathologies including nodular goiter (n = 57), Graves' disease (n = 8), follicular adenoma (n = 7), and thyroiditis (n = 3). Patients with clinically overt disease presented primarily with palpable/visible thyroid nodules (n = 94), cervical lymph node metastasis (n = 13), hoarseness of voice (n = 2), or imaging (n = 1). Thirty-eight of 110 patients with overt tumors (35%) had clinically apparent cervical lymph node metastases and two (1.1%) presented with preoperative unilateral vocal cord paralysis.
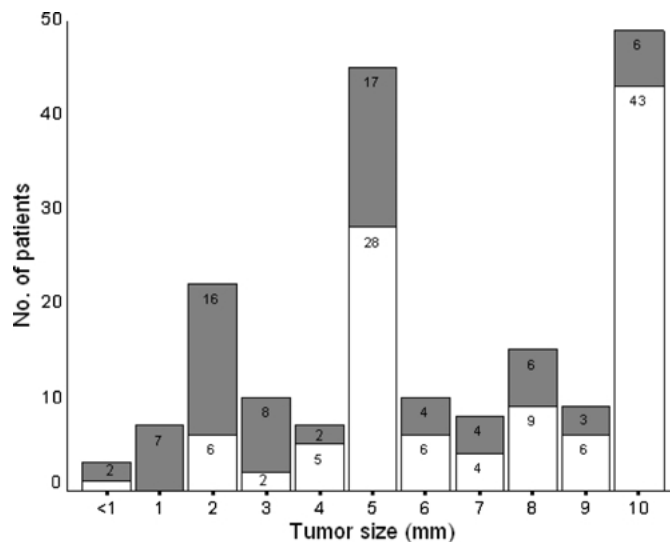

Figure 2. Bar chart showing the size of the primary tumor categorized into clinically overt (white bar) and occult (dark bar) tumors.

Operative procedures included total (n = 98) or near total (n = 14) thyroidectomy, unilateral lobectomy (n = 56), subtotal thyroidectomy (n = 10), and completion total thyroidectomy (n = 7). Total thyroidectomy was achieved by completion total thyroidectomy after initial unilateral lobectomy in 11 patients, including 1 patient with an occult 5-mm PMC after unilateral lobectomy for a 4-cm benign thyroid nodule. Bilateral thyroidectomies were performed for 129 patients (70%) with concomitant neck dissections done for 38 of 110 patients (35%) with clinically overt PMC; including 14 functional, 12 selective, and 2 radical neck dissections, as well as 10 lymph node excisions. Three patients underwent bilateral neck dissection for extensive nodal metastases. The mean tumor size was 5 mm (median: 6.2 mm) (Fig. 2). Extrathyroidal extension was detected in 21 patients (11%). Forty-three patients had histologically documented nodal metastases (23%), and 3 had distant metastases detected at presentation (1.6%), all in the clinically overt group. Five patients (2.7%) underwent incomplete shave resection with residual tumors, and 4 received postoperative external irradiation. I[131] therapy was administered to 53 (48%) of 110 patients with clinically overt tumors. During follow-up, 12 patients died of unrelated causes and 4 died of recurrent cancer. Thirteen patients (7%) developed recurrent disease over a median duration of 56 months: 6 with lymph node recurrence, 5 with tumor bed recurrence, and 2 with distant metastases.

Comparison of Clinically Overt and Occult PMC

Table 1 summarizes and compares the clinicopathologic features and treatment of patients with clinically

Table 1.
Comparison of clinicopathologic features and treatments of clinically overt and occult papillary microcarcinomas (PMCs)

Parameters	Overt PMC	Occult PMC	P Value
Size (mm)			< 0.001
≤ 5	42	52	
> 5	68	23	
Multifocality			0.002
Yes	35	9	
No	75	66	
Extrathyroidal extension			< 0.001
Yes	21	0	
No	89	75	
Lymphovascular invasion			0.002
Yes	13	0	
No	97	75	
Histologic lymph node metastases			< 0.001
Yes	43	0	
No	67	75	
Bilateral thyroidectomy			< 0.001
Yes	89	40	
No	21	35	
Lymphadenectomy			< 0.001
Yes	38	0	
No	72	75	
I[131] ablation			< 0.001
Yes	53	0	
No	57	75	

Table 2.
Comparison of commonly adopted tumor risk group stratification and staging systems of clinically overt and occult PMC

Risk group stratification	Overt PMC (n = 110)	Occult PMC (n = 75)	P Value
AMES[13]			0.001
Low risk	96	75	
High risk	14	0	
Degroot[14]			< 0.001*
I	60	75	
II	31	0	
III	16	0	
IV	3	0	
pTNM stage[15]			< 0.001*
I	79	75	
II	3	0	
III	25	0	
IV	3	0	
MACIS[16]			0.017**
< 5	80	65	
5–5.99	19	7	
6–6.99	6	3	
7–7.99	1	0	
> 8	4	0	

*Comparing stage/class I with stage/class II–IV by Fisher's exact test.
**Comparing MACIS score < 5 with ≥ 5 by Fisher's exact test.

overt and occult PMCs. Clinically overt PMCs were significantly larger than occult tumors (7.3 ± 2.6 mm versus 4.5 ± 2.9 mm; $P < 0.001$). They were more frequently greater than 5 mm in size (62% versus 31%; $P < 0.001$) and had a higher incidence of multifocal tumors (32% versus 12%; $P = 0.002$) than occult PMCs. Extrathyoidal extension ($P < 0.001$), lymphovascular invasion ($P = 0.002$), and cervical lymph node metastases ($P < 0.001$) occurred in patients with overt tumors but not in those with occult tumors. A higher proportion of patients with clinically overt tumors than with occult PMC underwent bilateral thyroidectomy. Of 75 patients (53%) with occult tumors, 40 underwent bilateral thyroidectomy, whereas 89 of 110 (81%) patients with clinically overt PMC had the bilateral procedure ($P < 0.001$). In addition, postoperative I[131] was administered to 53 of 110 patients (48%) with clinically overt PMC only ($P < 0.001$). High-risk tumors, as defined by AMES risk group stratification, Degroot classification (> stage I), UICC pTNM staging (> stage I) were present in overt PMC only. Although there was no significant difference in MACIS score between overt and occult tumors (4.4 ± 1.4 versus 4.2 ± 0.9; $P = 0.2$), 30 of 110 (27%) patients with overt tumors had a MACIS score > 5 compared with 10 of 75 (13%) pa-

tients with occult PMC ($P = 0.017$) (Table 2). Postoperative recurrence developed in 13 of 110 patients with overt PMC only ($P = 0.003$).

The 10-year CSS and DFS was 94% and 87%, respectively, for overt PMC. None of 75 patients with occult PMC compared with 4 of 110 patients with overt PMC died of thyroid carcinoma ($P = 0.15$). There was no significant difference in CSS ($P = 0.19$) between clinically overt and occult PMC, but overt tumors had a significantly lower DFS than occult PMC ($P = 0.05$; Fig. 3). The details of four patients with PMC who died of thyroid carcinoma are summarized in Table 3. Potential risk factors for decreased survival were analyzed in patients with clinically overt tumors only. Old age (> 40 years at presentation) ($P = 0.04$), tumor size (≥ 5 mm) ($P = 0.018$), the presence of extrathyroidal invasion ($P = 0.004$), cervical lymph node ($P = 0.046$) or distant metastases ($P < 0.0001$), incomplete resection ($P < 0.0001$) and postoperative recurrence ($P < 0.0001$) are risk factors for decreased survival. Among those patients with lymph node metastases, 36 (95%) underwent bilateral thyroidectomy and 28 (74%) received I[131] ablation. The CSS and DFS of patients with cervical lymph node metastases were less favorable than for those without lymph node metastases (Fig. 4). Patients with nodal metastases also had a higher
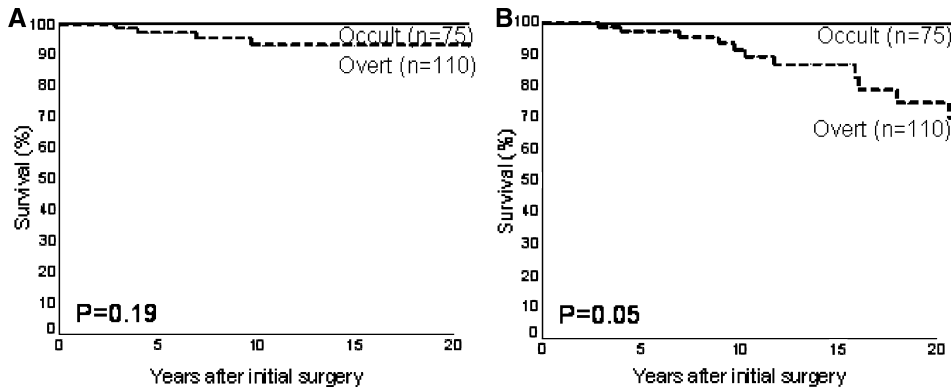
Figure 3. Actuarial survival curves comparing the cause-specific survival (**A**) and disease-free survival (**B**) between clinically overt (dotted line) and occult (solid line) papillary microcarcinomas.

incidence of locoregional recurrence. Four of 72 patients without nodal metastases developed locoregional recurrence compared with 7 of 38 patients with nodal metastases ($P = 0.045$).

DISCUSSION

Clinically undetectable or occult thyroid cancer is very common, and the description of this entity has been evolving over time.[4,5] According to the latest World Health Organization histologic classification, the term "papillary microcarcinoma" defines a tumor focus of 1.0 cm or less in diameter; it replaces the term "occult" and describes this subgroup of tumors.[1] Although these tumors represent distinct entity with stringent but simple diagnostic criteria, the clinical relevance of PMCs remains uncertain, and there is much controversy with respect to their clinical manifestation, molecular origin, biological behavior, prognosis, and optimal management.[4,5,18] In addition, the term "small" (≤ 1.5 cm) tumors is still commonly used.[19]

Papillary microcarcinoma is a common finding during autopsy and histologic examination of thyroidectomy specimens for benign diseases. In autopsy series, the incidence of occult or small PTC varied from 1% to 35.6% in patients who died of non-thyroid-related diseases,[4] and the incidence of incidental or multifocal PMC during thyroidectomy for benign goiter was 0.8%–10.8%.[4] Although the prevalence of thyroid carcinoma has been steadily documented to be increasing, there is, an obvious discrepancy between the prevalence of clinically recognized thyroid carcinoma and PMC. The rise in prevalence is attributed to the increasingly diagnosed PMC.[5] With advanced diagnostic imaging such as ultrasonography and improved preoperative diagnostic technique such as fine needle aspiration, PMCs can also be diagnosed definitively for surgical treatment and hence are not clinically occult.[2–5,9]

Disease-specific death in PTC is uncommon and is particularly rare in low-risk patients, including those with PMC.[8,11,12,20,21] In a study of 535 patients with PMC for whom follow-up data are available for 17.5 years, two patients died of thyroid carcinoma, and all-causes survival did not differ from expected.[8] Similarly, reports on large series of patients with a relatively long follow-up showed that disease-specific death was a rare event, even though a significant proportion of patients developed recurrence.[8–11,19,20] Sampson et al. concluded that even if occult thyroid carcinomas had metastasized locally, they rarely affected the patient's life or health.[21] As in other reports,[8,14] the present study confirmed that PMC could be identified as a specific subgroup of papillary thyroid cancer with an overall improved prognosis.[4] Papillary microcarcinoma patients have an overall low risk for disease mortality, according to commonly used risk group stratification or staging systems, and their overall survival should be significantly better than other PTC patients.

Although the overwhelming majority of PMCs are clinically occult, a significant proportion of patients can present clinically with symptoms similar to conventional PTC. Patients with PMCs can present with a visible or palpable thyroid nodule, symptoms related to local invasion, cervical nodal metastases and, rarely, distant metastases. Cervical nodal metastasis with or without a linically detectable thyroid nodule is the most commonly reported presentation.[7–11] Papillary microcarcinomas detected incidentally during autopsy or histological examination may represent a different form of tumors compared with clinically overt tumors. For studies identifying occult tumors as a subgroup, the proportion of occult or incidental PMCs ranged from 13% to 83%,[8–12,19] depending on differences in the selection criteria, data collection, histological reporting, and management protocols. In the present study, occult PMCs accounted for 41% of all PMCs and behaved indolently, like a benign tumor, without any risk of invasiveness, metastases, recurrence, or mortality. Commonly used tumor risk group stratification

Table 3.
Details of patients who died of papillary microcarcinomas

Sex/Age (yr)	Presentation	Primary tumors	DM	Treatment	Survival (months)
M/75	Cervical LN	5 mm Multifocal	Lung	CT + I[131]	116 (LR)
M/70	Cervical LN + cord palsy	5 mm Extrathyroidal	Mediastinal LN + lung	TT[a] + mediastinal resection + EBR	34 (DM)
F/76	Thyroid nodule	5 mm Multifocal Exthrathyroidal	–	Lobectomy[a]	83 (DM)
F/70	Nodular goiter + cervical LN	Not found[b]	–	TT + I[131]	47 (LR)

LN: lymph node metastasis; CT: completion total thyroidectomy; TT: total thyroidectomy; I[131]: radioiodine ablation; EBR: external beam irradiation; LR: local recurrence; DM: distant metastases.
[a]Incomplete shave resection.
[b]Patient had two radioiodine treatments for thyrotoxicosis due to toxic nodular goiter before presentation; tumors not identified in thyroidectomy specimen despite serial sectioning.

and staging systems identified them as extremely low-risk and distinguished them from clinically overt tumors. Although early surgical treatment before clinical manifestation might account for the excellent clinical outcome, aggressive treatment such as completion total thyroidectomy, prophylactic neck dissection, and postoperative adjuvant radioiodine is not indicated for this subgroup of PMCs when diagnosis has been confirmed. Patients with incidentally detected PMC diagnosed after surgery should be treated as if they had a benign disease. The issue of whether to inform the patient of a "cancer" diagnosis,[22] because of its potential social and economic implications, should be left to the individual surgeon to decide.[4] As increasing numbers of occult PMCs are diagnosed preoperatively with the wide application of ultrasonography screening and fine needle aspiration cytology,[2,3] the question arises whether patients with occult PMCs without clinical manifestation could be managed by nonoperative means. This needs further evaluation as well as longer term follow-up,[23,24] although most patients would prefer therapy to observation.[25]

For patients with clinically overt PMCs, distinction should be made for those presenting with cervical lymph node metastases. Cervical nodal metastases in patients with PMC at presentation are frequently associated with recurrence[8,9] and occasional disease-related death.[9] The incidence of PMC presenting with cervical nodal metastases ranged from 9.3% to 32%.[8–11] In addition, histologically documented nodal metastasis could occur in the central and lateral compartments of 60.9% and 39.5% of PMC patients without clinically detectable nodal metastases after prophylactic neck dissection.[9] Nodal recurrence was more common in patients presenting with palpable nodal metastases (16.7%), despite therapeutic neck dissection; however, prophylactic neck dissection was not recommended for patients without clinically palpable nodal metastases because nodal recurrence did not differ between the prophylactic and the no-dissection group.[9] In the present study, prophylactic neck dissection was not routinely performed for PMC patients without nodal metastases, and radioiodine was administered to the majority of them after bilateral thyroidectomy. The presence of cervical lymph node metastases was associated with decreased survival and an increase in locoregional recurrence. Although the impact of surgical treatment or radioiodine in reducing recurrence could not be demonstrated in the present study, others have shown the role of either bilateral thyroidectomy[8] or I[131] ablation[19] in decreasing locoregional and lymph node recurrence of PMCs. Dissection of nonpalpable lymph nodes is probably not essential as long as postoperative I[131] is planned.[25]
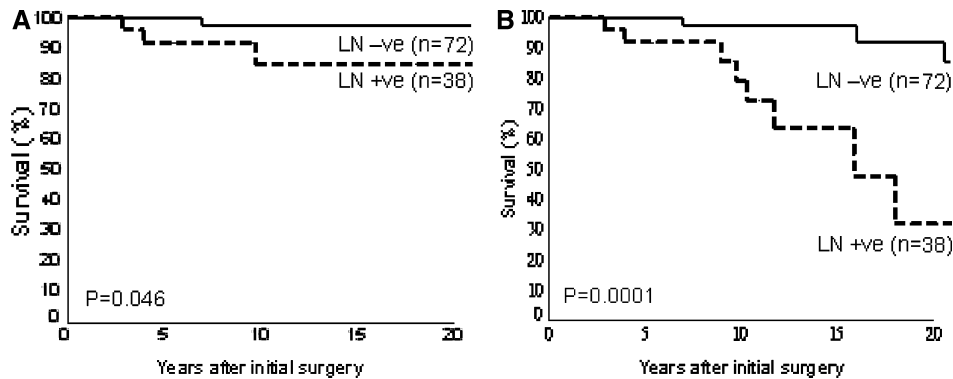
Figure 4. Actuarial survival curves comparing cause-specific survival (**A**) and disease-free survival (**B**) between patients with clinically overt papillary microcarcinomas presenting with (dotted line) and without cervical nodal metastases (solid line).

It is difficult to group all PMCs together and to recommend a management strategy based solely on size because of the heterogeneous presentation of this disease.[4] The nature of surgical therapy should depend on the clinical presentation and must be achieved with minimal morbidity.[4] In addition to the presence of cervical nodal metastases, other commonly used risk factors such as old age, incomplete excision, presence of distant metastases, and postoperative recurrence have been identified as prognostic factors for poor survival in patients with clinically overt PMCs. As with other types of PTC, risk profile consideration should be applied for the management of individual PMC patients. Near-total thyroidectomy with radioiodine should be considered to decrease locoregional recurrence for low risk[14] or early stage disease[26] and be recommended for the management of high-risk patients.[27]

In conclusion, patients with PMC have an overall excellent prognosis, although the distinction needs to be made with reference to the clinical presentation. Clinically occult tumors are invariably incidental and indolent in behavior, whereas those that are clinically overt demonstrate more aggressive behavior. In evaluating patients presenting with clinically overt disease, selected high-risk patients could be identified by the commonly adopted risk group stratification or staging systems. In addition, patients presenting with cervical nodal metastases are at risk of recurrence and disease-related death. In such cases, more aggressive treatment achieved with an acceptable level of morbidity can be considered. In addition to using clinical presentation as the basis for management, treatment should be individualized, preferably by risk group stratification and not by considering patients with PMC as a specific subgroup.

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