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Surgical Strategy for Papillary Thyroid Microcarcinoma

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It is generally agreed that papillary thyroid microcarcinoma (PTMC) demonstrates indolent biological behavior. But PTMCs include at least two biologically distinct subpopulations: indolent tumors with minimal or no potential for progression, and tumors with the propensity for aggressive behavior and dissemination. The ability to stratify those relatively few patients with aggressive PTMC from the vast majority who are low-risk is crucial to offer most appropriate clinical management. Risk factors such as tumor size, age, sex, tumor multifocality, vascular or capsular invasion, extrathyroidal extension, lymph node metastases, histological variants of papillary thyroid cancer (PTC), the presence of mutational markers, and incidentalness need to be considered for a risk-adapted algorithmic approach that would hope to achieve minimal morbidity while still anticipating optimal outcomes at less cost to the patient and to society. But risk factors for recurrence have not been confirmed because of such low recurrence rates, rare mortality rate, and several selection (or therapeutic) biases present in any retrospective series. Larger scale cohort studies showed that recurrence rates did not differ statistically between patients treated with unilateral lobectomy and those treated with bilateral resection, so long as complete tumor resection was achieved. Similarly, more aggressive nodal dissection failed to yield the anticipated reduction in recurrence rates. In conclusion, selection of the minority of PTMC who deserves more aggressive surgery is important, reserving less aggressive treatments for the other, the large majority cases. The ability to stratify those relatively few patients with aggressive PTMC from the vast majority who are low-risk is crucial to offer most appropriate surgical strategy.

Key Words: Papillary thyroid microcarcinoma (PTMC), Risk factors, Surgical strategy

Introduction

It is generally agreed that papillary thyroid microcarcinoma (PTMC) demonstrates indolent biological behavior. Although they generally have an excellent prognosis, PTMC are not always completely innocuous. Indeed, many authors have reported excellent surgical outcomes for PTMC.[1-3] But some authors reported that patients with PTMC with bulky lymph node metastasis or with a distant metastasis sometimes experience an unfavorable course.[4] PTMCs include at least two biologically distinct subpopulations such as indolent tumors with minimal or no potential for progression, and tumors with the propensity for aggressive behavior and dissemination. But there is still no consensus on the biological aggressiveness of PTMC and on the appropriate therapy. Treatment modalities range from observation alone to an aggressive treatment with total thyroidectomy with lymph node dissection, and radioiodine ablation. The ability to stratify those relatively few patients with aggressive PTMC from the vast majority who are low-risk is crucial to offer most appropriate clinical management. But

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at present it would not seem to be possible to identify confidently the PTMCs that will run an aggressive course. Therefore it is not surprising that there are arguments in the literature to support a conservative or aggressive strategy in the treatment of PTMC.

Prevalence Rate of PTMC

PTMCs are very common. Its prevalence continues to rise. In fact, PTMC represents the fastest growing type of thyroid cancer. Based on the Surveillance, Epidemiology, and End Results (SEER) data, papillary carcinomas 1 cm or less constituted about 30% of all papillary carcinoma in 1988 and about 40% in 2003.[5] Similar trends have been observed in France, and many other countries around the world.[6]

In autopsy series, they are found in 3–9% of thyroid glands in many regions of North America, Europe, and South America,[7–12] but the highest prevalence (36%) was reported by Harach et al.[13] in Finland.

In surgical series, PTMC is reported in 5–24% of patients who have a thyroidectomy for benign lesions.[14–17]

Clinical–pathologic Characteristics and Outcome of Patients with PTMC

PTMC is generally considered clinically innocuous, although some have an aggressive clinical behavior. The clinical and pathologic characteristics of PTMC at the time of diagnosis are variable in different studies. Bilateral and multiple foci have been observed in 2.9[18] to 48%[19] and 7.1[20] to 56.8%[21] respectively. The prevalence of extracapsular invasion and lymph node metastasis at diagnosis ranged between 2[22] and 62.1%[23] and 0[24] and 64%[25] respectively. In one study, it was reported that lymph node metastases were present in 40.5% of patients with microcarcinoma, even though the patients were diagnosed as node negative before surgery.[26]

The largest series of PTMC patients reviewed came from SEER Cancer Database of 18,445 patients. The series reported that 92 of these patients (0.5%) died of the disease, and the survival rate was 99.5 and 99.3% at 10 and 15 years, respectively.[27] A meta–analysis study of 17 articles including 9259 patients with PTMC reported that local/lymph node recurrent disease has been observed with variable prevalence, with values ranging between 0.3 and 37%. Combining the results of different studies, local/lymph node recurrence has been observed in 2.4% out of 9379 patients. In these studies, distant metastases were clearly reported in 0.27% of 9379 cases. Cancer–related death has been reported in 0.34% of 9379 patients with PTMC.[28]

Table 1. Summary of clinicopathologic characteristics of PTMC

Characteristics	Frequency
Multifocality	7.1–56.8%
Bilaterality	2.9–48%
Cervical nodes metastasis	0–64%
Extracapsular extension	2–62.1%
Distant Metastasis at Dx	0–3%
Recurrence	1–8.3%
Mortality	0–2.2%

Dx: diagnosis, PTMC: papillary thyroid microcarcinoma

And another meta–analysis encompassing over 4000 cases of PTMC reported that 28% of tumors had lymph node metastasis, 0.6% distant metastasis, 3.3% of patients experienced disease recurrence, and tumor–related mortality was 0.3%.[29] In the series of Buffet et al.[30], recurrences were observed in 4.0% of 1669 patients with PTMC managed from 1960 to 2007 during a 47–year period. And the long term large scale cohort study performed at Mayo Clinic for nine hundred PTMC patients showed that 98% of the PTMC were intrathyroidal, 30% had neck nodal involvement, 0.3% had distant metastases at diagnosis, and 3 patients (0.3%) died of PTMC. Twenty–year and 40–year tumor recurrence rates were 6% and 8%, respectively (Table 1).[2]

Risk Factors

Clinical characteristics or parameters such as tumor size, age, sex, tumor multifocality, vascular/capsular invasion, extrathyroidal extension (ETE), lymph node metastases, histological variants of papillary thyroid

Table 2. Outcome and its prognostic factors of patients with PTMC

Authors	Follow-up	Year	Series	Recurrence	Mortality	Prognostic factors
Yu et al.[27]	15	2011	18,445	ND	0.5%	Age>45, male, L/N metastasis, ETE
Lin et al.[61]		2009	7,818	ND	0.12%	Only increasing age
Noguchi et al.[41]	15	2008	2,070	3.5%	0.6%	Autoimmunity, size>6 mm, Age>56, L/N +
Lee et al.[42]	12	2013	2,014	6.3%	0%	ND
Yamashita et al.[66]	11	1997	1,743	1.5%	0.2%	Lymph node metastasis
Buffet et al.[30]	6.5	2012	1,669	4%	0%	L/N metastases, multifocality, male sex
Hay et al.[2]	17.2	2008	900	6% (20 year)	0.3%	Multicentricity, positive lymph node
Ross et al.[34]	4	2009	661	6.2%	0.15%	Multifocality, L/N metastasis
Ito et al.[43]	10	2006	626	5.0%	0%	ND
Pelizzo et al.[56]	8.5	2006	403	6%	0.2%	Size >0.5 cm, limited surgery
Baudin et al.[1]	7.3	1998	281	3.9%	ND	Multifocality, limited operation
Chow et al.[31]	10	2003	203	7.3%	1%	Multifocality, limited surgery

ETE: extrathyroidal extension, L/N: lymph node, ND: no data, PTMC: papillary thyroid microcarcinoma

cancer (PTC), the presence of mutational markers (BRAF etc.), and incidentalness that might require more aggressive management need to be considered to make a risk-adapted algorithm for a rational approach for PTMC. But risk factors have not been confirmed because of such low recurrence rates (2-4%), and rare mortality rate (less than 1%) at 10 and 15 years. And any significant difference of recurrence rate may be due to one of several selection (or therapeutic) biases present in any retrospective series. However, as the clinician is faced with conflicting data pertaining to the potential management of PTMC, it would seem logical that some form of risk stratification is required to determine which course of action to take (Table 2).

Multifocality

Multiple tumor foci are found in 20% to 80% of patients, depending on how meticulously the thyroid gland is examined. One of the more consistently reported features associated with the risk of tumor recurrence or metastasis is tumor multifocality or bilaterality.[1,31,32] Multiple intrathyroidal tumors are associated with an increased risk of loco-regional, distant metastases and persistent disease. Lymph node involvement was much higher in multifocal than in non-multifocal microcarcinomas. Moreover, multifocality occurred more frequently in both larger (>6 mm) and extrathyroidal PTMC with respect to smaller (<6 mm) and intrathyroidal PTMCs.[33]

Hay et al.[2] compared the recurrence rate between multicentric and unicentric PTMC in 900 patients observed in a 60-year period, and found that multicentric tumor had more tendency of recurrence. Also a recent meta-analysis revealed that recurrence of PTMC was associated with tumor multifocality.[28] The National Thyroid Cancer Treatment Cooperative Study Group Registry was analyzed for recurrences in patients with unifocal versus multifocal micropapillary cancer, depending upon the extent of surgery. Recurrences did not differ between patients with unifocal and multifocal disease overall, however, among patients who received less than a near-total thyroidectomy (NTT), those with multifocal disease had more recurrences than those with unifocal disease. Patients with multifocal disease who had a total (TT) or NTT trended toward fewer recurrences than those undergoing less than an NTT.[34]

However, there are arguments that multifocality cannot be used by itself as an accurate marker of tumor virulence because tumor multifocality is common and is found in as many as 30-40% of all PTMC.[29,35-37] One explanation for this observation is that multifocality most often is the result of the development of multiple independent tumors and not a manifestation of intra-glandular dissemination, as demonstrated by recent molecular investigations of multifocal PTCs. Each of the different microtumors in multifocal PTMC seem to have the same limited growth potential as their singular counterparts, indicating that the vast majority of

incidentally detected multifocal PTMCs are innocuous lesions.[38-40]

Age

The largest series reviewed from SEER Cancer Database showed that risk factors of recurrence included age greater than 45 years.[27] And another study also reported that patients older than 55 years had more recurrence (40% at 30 years) than younger patients who had a recurrence rate of less than 10%.[41] In sharp contrast to above study, a meta-analysis by Roti et al.[28] revealed that recurrence of PTMC was associated with younger age (<45 years).

However there are arguments that age was not a significant factor in predicting disease recurrence or survival.

Size

Cancer size does not seem a convincing explanation for the different recurrence/persistence rate of disease in the different studies. The study of 2070 patients with PTMC showed that among PTMCs, larger tumors (6-10 mm) recurred in 14% at 35 years compared with 3.3% in patients with smaller tumors.[41]

But other observations have found that tumor size does not correlate with aggressive disease.[25,31]

A meta-analysis study also showed that recurrence of PTMC was not associated with tumor size.[28] The series of Buffet et al.[30] also reported that size was not a significant variable in 1669 patients with PTMC. Moreover, a study contended that tumor size 0.5 cm was not a significant determinant of the extent of surgery in patients with PTMC.[42]

Extrathyroidal extension

The largest series showed that risk factors of recurrence included ETE.[27] And extracapsular invasion by the primary tumor also had a higher recurrence rate in a study performed in Japan.[41]

But there are arguments about the ETE as a risk factor. A meta-analysis study revealed that recurrence of PTMC was not associated with ETE.[28] ETE did not appear as an independent variable as it was significantly associated with recurrence in the multivariate analysis. It is notable that ETE and lymph node metastases were interrelated ($p<0.0001$).[30]

Lymph node metastasis

It is not clear whether the presence of lymph node metastases at the time of diagnosis is a risk factor for the recurrence or persistence of disease. The SEER Cancer Database showed that risk factors of recurrence included lymph node metastases.[27] And the series of 1669 patients with PTMC also revealed initial lymph node metastases were significantly associated with recurrence.[30] In study of 900 patients with PTMC, Hay et al.[2] also contended that node positive (30%) was risk factor shown to increase the risk for recurrence. And a meta-analysis reported also that recurrence of PTMC was associated with lymph node metastasis at presentation.[28]

But a certain study argued that clinically confirmed central node metastasis did not affect the disease free survival (DFS) rate of PTMC patients.[43]

Incidentalness

Neuhold et al.[44] defined the incidental tumor as microcarcinoma detected incidentally via ultrasonography or during the histological workup of thyroid specimens resected for other nonmalignant conditions. But many other authors only include the microcarcinoma detected incidentally in the thyroid gland resected for benign disease.

The biological behavior is different between the non-incidental and incidental PTMC. Univariate analysis showed that bilaterality, autoimmune thyroid disease, size of tumor >5 mm, multifocality, lymph node metastasis, and capsule invasion were significantly associated with non-incidental PTMC.[45] A national, unselected, prospective cohort study of 406 PTMC patients diagnosed in Denmark showed that 10 year cause-specific survival rate was 100% for the incidental group while 10 year cause-specific was 98.5% in the non-incidental group.[46]

It suggests that the biological behavior may be different in the 2 categories. And certain authors contend that non-incidental PTMC presented with aggressive characteristics similar to those of conventional PTC

Table 3. Clinical-pathological features of PTMC incidental or non-incidental in different series

Authors	Diagnosis	Patients	Multicentric	Bilateral	Invasive	L/N Mx.	Distant Mx.
Londero et al.[46]	Incidental	250	52 (21%)	ND	4 (2%)	6 (2%)	0 (0%)
	Non-incidental	156	59 (38%)[a]	ND	14 (9%)[a]	88 (56%)[a]	4 (3%)[a]
Baudin et al.[1]	Incidental	189	56 (30%)	25 (13%)	21 (11%)	41 (22%)	0 (0%)
	Non-incidental	92	56 (61%)[a]	21 (23%)[a]	21 (23%)[a]	89 (91%)[a]	8 (8.6%)[a]
Roti et al.[67]	Incidental	52	10 (19%)	6 (11%)	8 (15%)	2 (4%)	0 (0%)
	Non-incidental	191	68 (36%)	39 (20%)	34 (18%)	30 (16%)	4 (2%)
Pellegriti et al.[32]	Incidental	151	37 (24.5%)	22 (14.6%)	16 (10%)	24 (16%)	1 (0.7%)
	Non-incidental	148	58 (39.2%)[a]	33 (22.3%)	38 (25%)[a]	66 (45%)[a]	7 (4.7%)
Lo et al.[68]	Incidental	75	9 (12%)	ND	0 (0%)	0 (0%)	0 (0%)
	Non-incidental	110	35 (32%)[a]	ND	21 (19%)[a]	43 (39%)[a]	3 (2.7%)

[a]significantly different
L/N: lymph node, Mx.: metastasis, ND: no data, PTMC: papillary thyroid microcarcinoma

Table 4. Comparison of outcome between the patients underwent total thyroidectomy and patients underwent limited surgery for PTMC in different series

Authors	Follow up	Year	Series	Result
Bilimoria et al.[60]	5.8	2007	10,247	No difference in recurrence and mortality
Lin et al.[61]	ND	2009	7,818	No difference in mortality
Ito et al.[62]	10	2010	2,638	No difference in recurrence
Lee et al.[42]	12	2013	2,014	No difference in recurrence
Buffet et al.[30]	6.5	2012	1,669	No difference in 10 year recurrence
Hay et al.[2]	20	2008	900	No difference in 20 year recurrence
Pelizzo et al.[56]	8.5	2006	403	Difference in recurrence
Baudin et al.[1]	7.3	1998	281	Difference in recurrence
Chow et al.[31]	10	2003	203	Increased recurrence after limited surgery

ND: no data, PTMC: papillary thyroid microcarcinoma

and should be treated likewise (Table 3).[47]

BRAF mutation

More recently, genetic markers have been explored to assess tumor behavior in papillary thyroid carcinoma, including PTMC. Several recent studies have described correlation of BRAF V600E with ETE, advanced stage at presentation, lymph node metastasis, tumor size >5 mm, and multifocality in patients with PTMC.[48-51]

Although there are many reports of the BRAF V600E mutation as a marker for poor prognosis in patients with PTC, however, some suggest the opposite, especially in Korean patients with a high prevalence of the BRAF V600E mutation. In Korea, the prevalence of the mutation of PTMC is relatively high at 52-62.8%, and it is unlikely that such a large proportion of these tumors would have aggressive behavior. Therefore, the presence of a BRAF mutation in any given tumor would not be an absolute predictor of tumor aggressiveness.[52-54]

Surgery

Once risk factors have been identified, the next step is to tailor therapy, including thyroid surgery and lymph node dissection that would hope to achieve minimal morbidity while still anticipating optimal outcomes at less cost to the patient and to society.

Extension of thyroid surgery

Considerable debate has centered on the clinical significance of PTMC and whether these tumors should be managed as aggressively as conventional PTC (Table 4).

1) Proponent of total/near total thyroidectomy

Since TT is a more radical surgical procedure it can eliminate the multifocal/bilateral disease that is frequently observed. Proponents of TT contend that other advantages are lower local recurrence because of removal of all potential foci in both lobes, facilitating ablation of the tumor, greater sensitivity of thyroglobulin, and allowing the use of ^{131}I in the detection of metastasis and recurrence. So some authors advise bilateral thyroidectomy if patients who have PTC are diagnosed before surgery, irrespective of tumor size. And because a high rate of PTMC presented one or more risk factors including multifocality, bilaterality, capsule invasion, and lymph node metastasis, others suggest total thyroidectomy as the treatment of choice.[31,45,55] And Baudin et al.[1] also reported that the two parameters of histologic foci and the extent of initial thyroid surgery significantly influenced recurrence in the study for 281 patients. Furthermore, TT and radioactive iodine (RAI) therapy when necessary, and TSH-suppressive hormonal therapy has been suggested for all patients with PTMC independent of tumor size by some extreme groups.[45,56]

2) Proponent of lobectomy

Proponents of this therapeutic approach emphasize the minimal morbidity associated with this procedure, which seems appropriate if tumors with a relatively benign biological behavior are to be treated. In addition, hemithyroidectomy may reduce the need for lifelong thyroid hormonal replacement compared with TT. However, the proponent of TT argued that this procedure might include a higher risk of recurrence, the contraindication of RAI therapy, and the possible need for subsequent completion thyroidectomy.

But several studies have found that no survival benefits were evident after more extensive thyroidectomy of PTMC patients.[27,44,57-59] Similar conclusions have been recently reported in a series of 900 patients with PTMC treated during a 60-year period, which failed to disclose a significant difference in the recurrence rates of PTMC for patients treated by unilateral lobectomy and those receiving TT.[2] And in the study of total patients 12,469 with the PTC $<$1 cm (TT 8775, lobectomy 3686) from the National Cancer Data Base (1985-1998), the extent of surgery did not impact recurrence or survival (p=0.24, p=0.83 respectively).[60]

Lin et al.[61] also compared disease-specific survival (DSS) and overall survivals according to extent of thyroidectomy for patients of 7818 from the SEER Database (1988-2005). There were no significant differences in DSS for patients who underwent TT, NTT, or lobectomy (p=0.239) on multivariate analysis.

And in the recent study, an author reported that 1% of 1601 patients who received limited thyroidectomy showed recurrence to the remnant thyroid, and patients with TT or NTT had a better DFS, but the difference disappeared if recurrence to the remnant thyroid was excluded.[62]

In latest study, Lee et al.[42] compared the outcomes between TT and lobectomy after propensity score matching. The long-term rates of death and loco-regional recurrence were similar in patients with PTMC who underwent thyroid lobectomy (LT) with central neck lymph node dissection (CLND) and those who underwent TT with CLND.

Prophylactic central neck node dissection

Some studies reported that the role of CLND in PTMC remains uncertain because no evidence has demonstrated that CLND improves locoregional control or survival in PTMC.[63,64] And the 2009 American Thyroid Association guidelines recommend (recommendation rating: C) that prophylactic central neck dissection may not be appropriate for small (T1 or T2), noninvasive, clinically node-negative PTCs and most follicular cancer.[65]

Wada et al.[25] compared the recurrence rate of 235 patients with PTMC who underwent prophylactic neck dissection with that of 155 patients with incidental PTMC who did not undergo neck dissection. After a 60-month follow-up, the recurrence rate was 0.43% for the dissection group and 0.65% for the non-dissection group. No statistical significance was observed. And another study also showed that more aggressive nodal dissection failed to yield the anticipated reduction in recurrence rates in nine hundred PTMC pa-

tients had initial treatment at Mayo Clinic during 1945–2004.[2] And Ito et al.[43] also found that neither US–diagnosed nor pathologically confirmed central node metastasis affected the DFS rate of PTMC patients. Furthermore, in cases where PTMC was located only in one lobe, central node dissection in the contralateral lobe did not improve the DFS rate.

Completion thyroidectomy

There are few studies reporting the consequence of completion thyroidectomy comparing with lobectomy for PTMC. A national, unselected, prospective cohort study in Denmark compared the recurrence between patients with lobectomy and completion thyroidectomy cases having incidental PTMC. And the study showed that the incidence of recurrence was not significantly different in the cases receiving completion thyroidectomy. When the carcinoma is not the index tumor for surgery, this study implies that completion thyroidectomy does not improve prognosis.[46] And another recent study comparing the long term outcomes of TT versus LT also contend that completion thyroidectomy may not be recommended unless recurrence after LT is definitely detected in low–risk PTMC patients, and close follow–up is adequate in these patients.[42]

Conclusion

No consensus has yet been reached on the biological aggressiveness of PTMC or on which therapy is the most appropriate. And the risk factors associated with aggressive behavior of PTMCs are not well defined.

Larger scale cohort studies showed that recurrence rates did not differ statistically between patients treated with unilateral lobectomy and those treated with bilateral resection, so long as complete tumor resection was achieved. Similarly, more aggressive nodal dissection failed to yield the anticipated reduction in recurrence rates. Selection of the minority of PTMC who deserves more aggressive surgery is important, reserving less aggressive treatments for the other, the large majority cases. The ability to stratify those relatively few patients with aggressive PTMC from the vast majority who are low–risk is crucial to offer most appropriate surgical strategy.

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