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**Review**

# Static and dynamic prognostic factors of papillary thyroid carcinoma

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**Abstract.** The two types of prognostic factors of papillary thyroid carcinoma (PTC) are static and dynamic. The following static prognostic factors have been conventionally adopted: age, tumor size, extrathyroid extension, lymph node metastasis, and distant metastasis based on pre-, intra- and post-operative findings. These factors are useful to decide therapeutic strategies for PTC patients, including the extent of surgery and radioactive iodine (RAI) ablation. However, even the combination of these factors evaluated pathologically postoperatively is not good enough at predicting recurrence in clinical settings. The dynamic prognostic factors of changes in serum thyroglobulin (Tg) and thyroglobulin antibody (TgAb) values in patients who have undergone a total thyroidectomy are important to evaluate the progression of carcinoma recurrence and to predict patients' cause-specific survival, regardless of their backgrounds and the clinicopathological features of their PTC. Dynamic prognostic factors are superior to static prognostic factors in terms of expressing the condition of recurrence on a real-time basis.

*Key words*: Prognostic factors, Papillary thyroid carcinoma, Thyroglobulin, Thyroglobulin antibody, Lymph node metastasis

**PAPILLARY THYROID CARCINOMA** (PTC) is the most common malignancy originating from the thyroid. Although it is generally indolent, several aggressive features of PTC predict a dire prognosis. The prognostic factors can be classified into two categories, *i.e.*, static and dynamic prognostic factors. Static prognostic factors are based on the patient's background, findings of preoperative imaging studies, intraoperative gross findings, and postoperative pathological findings. They are useful for decisions regarding the choice of therapeutic strategies such as the extent of surgery, radioactive iodine (RAI) ablation and thyroid-stimulating hormone (TSH) suppression. In contrast, dynamic prognostic factors are based on changes over time in serum thyrogloblulin (Tg) and thyroglobulin antibody (TgAb) levels after total thyroidectomy. They are very important to estimate whether and how recurred lesions progress in real time and to predict the cause-specific survival (CSS) of PTC patients. In this review, the static and dynamic prognostic factors for PTC are reviewed separately.

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## 1. Static prognostic factors

Static prognostic factors can be subdivided into three classifications based on the time of evaluation: pre-, intra-, and post-operation. The former two can be used to decide the extent of thyroidectomy and lymph node dissection.

### *1) Prognostic factors evaluated pre- or intra-operatively*

**A) Patient age**

The patient's age is adopted by prominent classification systems such as Age, Metastases, Extent and Size (AMES) [1], Metastasis, Age, Invasion, Completeness, and Size (MACIS) [2], and the Union for International Cancer Control (UICC) tumor, nodes, metastasis (TNM) classification [3]. How to include age as a prognostic factor in PTC is still a matter of debate, and previous studies have adopted various cutoffs as shown in Table 1 [3–9]. These studies' findings indicate that elderly patients are more likely to show recurrence and die of carcinoma compared to young patients.

However, previous studies reported that the disease-free survival (DFS) of young PTC patients was poorer than that of middle-aged patients. Mazzaferri *et al*. demonstrated that the recurrence rate of PTC and follicular carcinoma showed a triphasic pattern according to patient age [10]. Miyauchi *et al*. reported that persistent disease (*i.e.*, Tg not decreased after total thyroidectomy) was seen more frequently in young (<40 yrs) and old patients (≥60 yrs) compared to middle-aged patients (40–59 yrs), although the Tg-doubling time (Tg-DT [11], see chapter 2-1)) was not short in their young patients [12]. Ito *et al*. performed a multivariate analysis and found that not only old age (≥60 yrs) but also young age (<30 yrs) were independent predictors of locoregional and distant recurrence of PTC [13]. Ito and Miyauchi *et al*. also demonstrated that papillary microcarcinoma (PMC: PTC ≤1 cm) in young patients (≤40 yrs) is more likely to progress during observation [14, 15]. These findings suggest that the developing activity of PTC in young patients is high, although their CSS is excellent. In 2012, Cho *et al*. proposed that PTC is better classified into three groups: a ≤35 years group (likely to recur but unlikely to die), a 36–62.4 yrs group (unlikely to recur and die), and a ≥62.5 yrs group (likely to recur and die) [16]. The optimal age cutoffs remain to be decided on, but if an endpoint is set for both DFS and CSS, two cutoffs might be better than one cutoff (Table 1).

In conclusion, age is one of the most important prognostic factors of PTC patients, and the biological behaviors of PTC show a bimodal or trimodal pattern according to patient age.

**B) Gender**

Recent PTC studies revealed controversial results regarding the prognostic significance of male gender. We found that male gender independently affected the DFS but not the CSS of patients [7, 17]. Male gender, together with old age, were predictors of the CSS of differentiated thyroid carcinoma (DTC), including PTC, after the detection of RAI-refractory metastasis [18]. We thus concluded that male gender has a moderate prognostic value in PTC patients, although a negative finding about the prognostic impact of gender has been published [19].

**C) Tumor size (TS)**

AMES classifies tumor size (TS) >5 cm as being high-risk [1], and UICC set the two cutoffs at 2 and 4 cm [3]. The prognostic significance of large TS has long been recognized, and in our series, TS >4 cm affected not only the DFS but also the CSS of patients [7, 8]. Matsuzu *et al*. also demonstrated that TS >4 cm is one of the risk factors of carcinoma death [4]. Most studies set the cutoff at 3–4 cm according to the prognosis of patients (Table 2) [1, 3, 4, 5, 7, 8, 20]. However, TS is also important to decide therapeutic strategies for PTC patients. Individuals with PTC ≤ 1 cm can be observed without immediate surgery unless they have any unfavorable features and if it is not too late to perform surgery after they show signs of progression such as TS enlargement and the novel appearance of lymph node metastasis [15]. Total thyroidectomy and RAI ablation are not necessary to treat solitary PTCs ≤2 cm without clinical node metastasis, distant metastasis, and massive extrathyroid extension (T1N0M0) [21]. The prognostic value of extrathyroid extension and clinical node metastasis, which are two prominent prognostic factors of PTC, are reversed between TS ≤3 cm and TS >3 cm [22]; that is, the prognostic value of extrathyroid extension is more significant than that of clinical node metastasis in PTC >3 cm, but vice versa in PTC ≤3 cm. TS is thus also important when deciding the treatment strategy.

**D) Extrathyroid extension (Ex)**

The prognostic value of extrathyroid extension (Ex) was described in detail in our last review article [23].

**Table 1** Cutoff age according to the prognosis of PTC patients

| Studies and classification systems | Age cutoffs |
|---|---|
| AMES classification [1] | 40 for males and 50 for females |
| UICC TNM classification [3] | 45 |
| Matsuzu *et al*. [4] | 45 |
| Siironen *et al*. [5] | 45 |
| Sugitani *et al*. [6] | 50 |
| Ito *et al*. [7, 8] | 55 |
| Mazurat *et al*. [9] | 55 |
| Miyauchi *et al*. [12] | 40 and 60 |
| Ito *et al*. [13] | 30 and 60 |
| Cho *et al*. [16] | 35 and 62.5 |

**Table 2** Cutoff tumor sizes according to the prognosis of PTC patients

| Studies and classification systems | Size cutoffs |
|---|---|
| AMES [1] | 5 cm |
| UICC TNM classification [3] | 2 cm, 4 cm |
| Herrera *et al*. [20] | 3 cm |
| Siironen *et al*. [5] | 4 cm |
| Ito *et al*. [7, 8] | 2 cm, 4 cm |
| Matsuzu *et al*. [4] | 4 cm |

Briefly, Ex is a very important prognostic factor for PTC patients, but grossly significant Ex (corresponding to T4 in the UICC TNM classification [3]) based on intraoperative findings is the most reliable prognostic factor. However, PTC with grossly significant Ex still includes patients with a wide range of aggressiveness, and a further subdivision of Ex might be helpful (see our previous review [23]).

**E) Clinical lymph node metastasis (N)**

Clinical lymph node metastasis (N) is another important prognostic factor. Its prognostic value was also described in our last review article [23]. Not only the presence of N but also the number and size of the metastases and extranodal tumor extension are important.

**F) Distant metastasis at diagnosis (M)**

The prognostic factor of distant metastasis at diagnosis (M) is the strongest predictor of carcinoma-related death of PTC patients. For lung metastasis, RAI therapy is the first-line treatment, and it is reported to be effective especially for young patients [24]. RAI therapy is less effective for bone metastasis, but Bernier *et al*. demonstrated that RAI therapy was related to the improvement of patients' survival and that the cumulative dose of RAI therapy was an independent prognostic factor [25]. For a solitary bone metastasis, complete resection of the lesion might be the best therapy [25]. External radiotherapy is also effective for the relief of pain and neurological symptoms. RAI therapy was reported to be ineffective for brain metastasis [26], and other modalities such as gamma knife treatment and (if there are multiple metastases) whole-brain radiation should be considered.

There is one report from Japan about the prognosis of M1 PTC patients. Its authors demonstrated that age $\geq$55 yrs, TS $>$4 cm, and massive extrathyroid extension were independent prognostic factors for CSS [27].

### *2) Prognostic factors evaluated in a postoperative pathological or molecular examination*

**A) Ki-67 labeling index (LI)**

The protein Ki-67 is immunohistochemically expressed in cells in the G1-S phase, and a high Ki-67 labeling index (LI) indicates a high level of proliferating activity in a carcinoma. Although the Ki-67 LI is generally low in PTC, PTC patients with a high Ki-67 LI are likely to show recurrence and die of carcinoma, and high Ki-67 LI is an independent prognostic factor for the DFS and CSS [28]. Miyauchi *et al*. also demonstrated that Ki-67 is significantly associated with persistent disease after total thyroidectomy and has an inverse correlation with Tg-DT (see chapter 2-1) [29].

**B) Poorly differentiated carcinoma and aggressive variants**

In Japan, less than 1% of PTC patients are diagnosed as having poorly differentiated carcinoma according to the World Health Organization (WHO) classification [30, 31]. These patients are known to show a dire prognosis. There are other aggressive variants such as tall-cell variant and columnar-cell variant displaying poor prognoses [30, 32, 33]. Although the details will not be covered here, pathological findings can be useful to detect specific variants affecting patients' prognoses.

**C) $BRAF^{V600E}$ mutation**

BRAF is one of the three Raf kinases activating the MAPK pathway, and its most significant hot-spot mutation is a thymine-to-adenine transversion at nucleotide 1799 in exon 15, resulting in a valine to glutamate substitution at residue 600 (V600E). To date, many studies showed that PTC with $BRAF^{V600E}$ mutation is aggressive and has a dire prognosis [34–46]. Some studies showed that even low-risk PTC or PMC are aggressive if the patient is positive for $BRAF^{V600E}$ mutation [40, 45, 46]. However, in Japan, there has been no evidence that $BRAF^{V600E}$ mutation significantly affects patients' prognosis, except in high-risk cases [47, 48]. A routine examination for $BRAF^{V600E}$ mutation is thus not recommended in light of the results of our analysis of a large number of patients.

## 2. Dynamic prognostic factors

In contrast to the static prognostic factors for PTC, dynamic prognostic factors predict patients' prognoses by following the postoperative changes in serum Tg and/or TgAb. The available findings regarding these dynamic prognostic factors are summarized in Table 3.

### *1) Tg-doubling time (Tg-DT)*

The Tg-doubling time (Tg-DT) as a dynamic prognostic factor was proposed by Akira Miyauchi in 2011 [11]. Miyauchi *et al*. calculated the Tg-DT of 426 PTC patients negative for TgAb with four or more Tg measurements, who underwent total thyroidectomy with thyroid-stimulating hormone (TSH) suppression. A short Tg-DT ($<$1 yr) had a stronger prognostic value than conventional static prognostic factors and in a multivariate analysis, it was recognized as an independent prognostic factor for both DFS and CSS [11]. Use of the Tg-DT is very convenient because patients' prog-

**Table 3** Prognostic value of changes in Tg and TgAb in PTC patients who underwent total thyroidectomy

| Study | Patients | Findings |
|---|---|---|
| Miyauchi *et al*. [11] | TgAb-negative PTC | Short Tg-DT (<1 yr) is an independent prognostic factor for DFS and CSS. |
| Miyauchi *et al*. [12] | TgAb-negative PTC | Short Tg-DT (<2 yrs) is significantly related to high Ki-67 labeling index. |
| Miyauchi *et al*. [29] | TgAb-negative PTC | Short Tg-DT (<2 yrs) is significantly related to patients' age (≥60 yrs). |
| Kim *et al*. [51] | TgAb-positive PTC | The recurrence rate was high in patients with TgAb values 6–12 months after ablation decreased by <50% compared to the TgAb value at the time of remnant ablation. |
| Tsushima *et al*. [52] | TgAb-positive PTC | Postoperative (1–2 yrs) TgAb level that did not decrease by >50% compared to the preoperative TgAb level was a strong indicator of poor prognosis. |
| Yamada *et al*. [53] | TgAb-positive PTC | TgAb level that increased >20% compared to the TgAb level 1 yr after surgery and positive Tg 1 yr after surgery can predict carcinoma recurrence in the early phase. |

noses can be predicted in real-time during the postoperative follow-up.

In 2013, Miyauchi *et al*. demonstrated that the Ki-67 LI in primary tumors was inversely linked to the Tg-DT, and they concluded that evaluation of the Ki-67 LI may allow the prediction of the postoperative Tg status, Tg-DT, and patients' prognoses [29]. As indicated above, the postoperative Tg status and the Tg-DT are also linked to the patients' age [12]. Persistent disease was found more frequently in young (< 40 yrs) and old (≥ 60 yrs) patients than in middle-aged patients (40–59), whereas a short Tg-DT (< 2 years) was more likely to be found in the old patients. These findings are not discrepant with those of Mazzaferri *et al*. in that the DFS showed a triphasic pattern but the CSS increased with patient age.

The Tg-DT is a very useful marker to predict patients' prognoses in real-time, and its use may be helpful when making decisions regarding the administration of molecular-target agents such as sorafenib and lenvatinib.

***2) Pre- and postoperative TgAb values***

The Tg-DT is useful for TgAb-negative patients but not for TgAb-positive patients, since serum Tg values are not reliable in the presence of TgAb. The impact of TgAb values as a static prognostic factor has been investigated. Durante *et al*. showed that PTC patients with a positive TgAb titer during the first year after primary treatment were more likely to have persistent/recurrent disease [49]. McLeod *et al*. demonstrated that perioperative TgAb was not an independent predictor of DFS [50].

In contrast to these static studies, Kim *et al*. compared TgAb at two points — the time of remnant ablation (TgAb1) and 6–12 months thereafter (TgAb2) — and they found that the patients in whom the TgAb2 concentration decreased by less than 50% or even increased compared to TgAb1 were likely to show carcinoma recurrence, whereas none of the patients whose TgAb2 decreased by more than 50% recurred during the follow-up [51]. Kim *et al*. thus proposed that a change in TgAb concentration during the early post-ablation period is a prognostic indicator of recurrence.

Tsushima *et al*. investigated the changes in serum TgAb levels of pre- and post-total thyroidectomy patients (1–2 years after surgery), and the multivariate analysis revealed that patients whose TgAb levels decreased by less than 50% or increased were likely to show recurrence [52]. Yamada *et al*. demonstrated that, of 426 TgAb-positive patients, 12 showed recurrence (median follow-up period, 35 months) and 11 of these patients showed either or both a > 20% increase in TgAb levels compared with those 1 year after surgery and Tg positivity 1 year after surgery [53]. Together the above-described findings suggest that postoperative serum TgAb levels may be usable as a surrogate dynamic tumor marker for TgAb-positive PTC after total thyroidectomy.

## 3. Conclusions

Conventionally, static prognostic factors have been adopted to predict patients' prognoses. They are useful to decide the therapeutic strategies such as the extent of thyroidectomy and lymph node dissection and whether RAI ablation should be performed postoperatively. They can also predict patients' prognoses to some extent. In contrast, dynamic prognostic factors can capture whether and how carcinoma recurs during the follow-up in real-time and whether recurred lesions progress from moment to moment and become life-threatening, regardless of the patient's static prognostic factors. It is clinically important to investigate

dynamic prognostic factors when we follow patients who have undergone a total thyroidectomy, regardless of their static prognostic factors. Dynamic prognostic factors may also be usable to decide the timing of the administration of molecular-target agents, if recurred lesions are RAI-refractory. We demonstrated that CSS of DTC patients after the detection of RAI-refractory recurrence is rather good: 5-year and 10-year CSS rates were 95 and 70%, respectively [18]. Therefore, only limited number of patients with RAI-refractory recurrence has an indication of molecular-target agent therapy. Dynamic prognostic factors, together with progression of metastasis on imaging studies, should be useful to decide when we use and quit using molecular-target agents for their therapy.

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