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Review

Prognostic values of clinical lymph node metastasis and macroscopic extrathyroid extension in papillary thyroid carcinoma

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Abstract. In papillary thyroid carcinoma (PTC), macroscopic extrathyroid extension (Ex) and clinical node metastasis (N) are prominent prognostic factors. Ex is divided into two grades in the UICC TNM classification: minimal and massive Ex. Massive Ex significantly affects patients' prognoses, whereas minimal Ex has little prognostic value. N is also divided into two grades in the TNM classification: N1a and N1b, depending on the location of metastasis, with N1b graded higher than N1a. However, massive Ex and/or N-positive PTC includes patients with a wide range of biological characteristics and prognoses, depending on their degrees of Ex and N. Other clinicopathological features such as age, gender, and tumor size also influence the prognosis. In evaluations of the biological characteristics of PTC patients with Ex and/or N, we should consider the degrees and relationships of Ex and N with other clinicopathological features.

Key words: Papillary thyroid carcinoma, Prognostic factor, Extrathyroid extension, Clinical node metastasis

1. Introduction

Papillary thyroid carcinoma (PTC) is the most common malignancy arising from follicular cells. It generally has an indolent character, but several clinicopathological features that worsen PTC patients' prognoses have been identified. Among them, macroscopic extrathyroid extension (Ex) based on pre- and intraoperative findings and clinical lymph node metastasis (N) based on preoperative imaging studies are prominent.

Ex is an important and conventional prognostic factor that was adopted in various classification systems such as the 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]. Note that N (lymph nodes) is not included in the AMES and MACIS classifications. This is probably because they were established before the era of routine ultrasonography, which is the most useful tool for N evaluation.

In this review, we focus on the prognostic significance of Ex and N of PTC, based mainly on recent publications, including our own.

2. Extrathyroid extension (Ex)

In the UICC TNM classification [3], Ex is divided into two grades and is included in the T factor together with tumor size. One grade is 'minimal Ex,' such as extension to the perithyroid soft tissue or sternothyroid muscle. Tumors with minimal Ex are classified as T3, regardless of their sizes. The other grade is 'massive Ex,' classified as T4, including extension to subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve (T4a), and extension to prevertebral fascia, mediastinal vessels, or carotid artery (T4b). It is difficult to perform a curative surgery for T4b tumors.

2-1. Minimal Ex

In 2006, we investigated the prognostic significance of minimal Ex in PTC patients [4, 5]. We found that it was not related to the disease-free survival (DFS) of PTC patients, and their prognoses were similar to those of patients with PTC without Ex. More recently, sev-

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eral studies were published showing the lack of prognostic value of minimal Ex for PTC or well-differentiated thyroid carcinoma (WDTC, most of which were PTC) [6–10] (Table 1). In the TNM classification, tumors >4 cm are classified as T3, and those with minimal Ex are also upgraded as T3 even though their sizes are ≤4 cm. However, based on these data, it is concluded that upgrading of T3 for PTC with minimal Ex and measuring ≤4 cm is inappropriate.

2-2. Massive Ex

2-2.1. The difference in prognostic significance between minimal and massive Ex

It is difficult to evaluate massive Ex preoperatively, unless vocal cord paralysis due to PTC extension and/or tumor protrusion to the lumen of trachea or esophagus is detected. Massive Ex is thus diagnosed based mainly on macroscopic findings during surgery. To date, several studies demonstrated that, in contrast to minimal Ex, massive Ex has a strong prognostic value (Table 2). In 2006, we showed that the DFS of PTC patients with massive Ex was significantly poorer than that of the patients with minimal or no Ex [5]. Hu *et al*. revealed that, in a subset of PTC patients with Ex, PTC with massive Ex showed a poorer DFS than PTC with minimal Ex, although external beam radiation therapy might improve the prognosis of PTC with massive Ex [11]. Thereafter, Rivera *et al*. demonstrated that PTC patients with massive Ex had a higher recurrence rate than PTC patients with minimal Ex if they were N-negative [12]. Riemann *et al*. obtained similar findings [13]. Therefore, in clinical studies, PTC cases with minimal and massive Ex should not be analyzed as a single group; rather, the cases should be analyzed separately.

2-2.2. Massive Ex as a prognostic factor

In 2004, Sugitani *et al*. proposed their own classification system and showed that massive Ex is one of the high-risk factors for DFS and CSS in patients aged 50 years or older [14]. In 2012, we demonstrated that massive Ex independently predicted recurrence to the regional lymph nodes, lung and bone, and carcinoma-related death [15]. More recently, Verburg *et al*. showed that patients ≥45 years with massive Ex had a reduced life expectancy [16]. Taken together, these

Table 1 Recent studies regarding the prognostic value of minimal Ex

Authors	Patients	No. of patients	Prognostic impact of minimal Ex
Ito *et al*. [4]	PTC (≥ 45 years)	502	None
Ito *et al*. [5]	PTC	1,067	None
Moon *et al*. [6]	PTC ≤ 1cm	288	None
Nixon *et al*. [7]	WDTC	869	None
Hotomi *et al*. [8]	PTC	930	None
Shin *et al*. [9]	PTC (with and without minimal Ex)	332	None
Chereau *et al*. [10]	PTC ≤ 1cm	2,482	None

WDTC, well-differentiated thyroid carcinoma.

Table 2 Recent studies regarding the prognostic value of massive Ex

Authors	Patients	No. of patients	Prognostic impact of massive Ex
Ito *et al*. [5]	PTC	1,067	Independent predictor of DFS
Sugitani *et al*. [14]	PTC	604	One of the high-risk factors for patients ≥ 50 years
Hu *et al*. [11]	WDTC	55	Poorer DFS than minimal Ex if EBRT was not performed
Rivera *et al*. [12]	PTC	829	Poorer DFS than minimal Ex
Riemann *et al*. [13]	DTC	347	Stronger prognostic impact than minimal Ex
Fukushima *et al*. [21]	PTC	5,918	Strong predictor of DFS and CSS for tumors > 3 cm
Ito *et al*. [15]	PTC	5,768	Independent predictor of recurrence to the lymph node, lung, bone and of carcinoma-related death
Ito *et al*. [23]	PTC and node metastasis	5,508	Independent predictor of DFS and CSS. Much stronger than minimal Ex.
Hotomi *et al*. [8]	PTC	930	Predictor of DFS and CSS
Verburg *et al*. [16]	DTC	2,011	Reduced life expectancy for patients ≥ 45 years

CSS, cause-specific survival; DFS, disease-free survival; DTC, differentiated thyroid carcinoma; EBRT, external beam radiation therapy.

findings indicate that massive Ex significantly affects CSS, especially that of older patients. Recent studies regarding the prognostic impact of massive Ex are summarized in Table 2.

2-2.3. Factors affecting the prognostic impact of massive Ex

As described above, massive Ex is an important prognostic factor in PTC, but its prognostic impact was shown to be affected by the following clinicopathological features.

1) Age

The patient's age influences the prognostic impact of massive Ex, as noted above. The AMES [1], UICC TMM [3], and CIH classifications [14] do not include massive Ex in young patients as a high-risk feature. The incidence of massive Ex significantly increases with patient age. In one of our studies, only 3.8% of patients ≤20 years had massive Ex, whereas the incidence was 33.7% for patients >70 years [17]. In 2011, we set the cutoff age at 55 and found that massive Ex was an independent predictor of local recurrence in young and old (≥ 55 year-old) women and old men, of distant recurrence in women and men regardless of their age, and of carcinoma-related death in old women and men [18]. We also showed that, in the subset of patients ≤20 years, massive Ex was an independent predictor of distant recurrence [19]. Therefore, the prognostic impact of massive Ex is stronger in old patients than young patients if CSS is set as an endpoint, but in young patients it still has a prognostic impact for carcinoma recurrence.

2) Tumor size

Kim showed that massive Ex of PTC ≤1 cm (PMC) is significantly related to lateral lymph node metastasis [20]. However, that report did not reveal that massive Ex directly affected the prognosis of PMC patients. Fukushima *et al*. compared the prognostic impact between massive Ex and N1b and showed that massive Ex had stronger prognostic value than N1b in tumors >3 cm [21]. Moreover, we demonstrated that the DFS and CSS rates of PTC patients with massive Ex became poorer with the increase of tumor size [22]. These findings suggested that massive Ex is a stronger prognostic factor in large PTC. This may be because, in small PTC, the range of extension is small and limited.

3) Organs to which the PTC extends

It has been shown that the prognostic impact of massive Ex varies according to the organs to which the PTC extends. We found that PTC patients showing posterior extension had poorer DFS than those showing anterior extension [5]. We also demonstrated that the DFS of PTC extending to the recurrent laryngeal nerve only was better than that of PTC extending to other organs [5]. More recently, we further divided massive Ex into two grades: Grade 2, extension to the sternothyroid muscle, recurrent laryngeal nerve, subcutaneous soft tissues, inferior constrictor muscle, muscular layer of the esophagus, or tracheal cartilage, and Grade 3, extension to the esophageal mucosa, tracheal mucosa, internal jugular vein, vagal nerve, phrenic nerve or sternocleidomastoid muscle. Our study analyzed extension from primary lesions and metastatic nodes as a single group, but the DFS and CSS of the Grade 3 patients were significantly poorer than those of the Grade 2 patients [23].

Hotomi *et al*. showed that the prognosis of patients with extension to the tracheal mucosa, esophageal mucosa, or recurrent laryngeal nerve with vocal cord paralysis was poorer than that of the patients with extension to other organs (including recurrent laryngeal nerve without vocal cord paralysis)[5]. Regarding extension to the recurrent laryngeal nerve, in our data, preoperative vocal cord paralysis did not worsen the patients' prognosis [24], which is discrepant with the finding reported by Hotomi *et al*. However, it is true that PTC with massive Ex includes cases with a wide range of biological aggressiveness. In order to more accurately predict patients' prognoses, a further subdivision of massive Ex based on the range and depth of extensions might be helpful.

3. Clinical lymph node metastasis (N)

N is divided into two grades in the UICC TNM classification [3]: N1a, metastasis to the central compartment only, and N1b, metastasis to the lateral and/or upper mediastinal compartment. N1b is regarded as being a higher grade than N1a.

3-1. Factors affecting the prognostic impact of N1b

1) Location of metastasis

As noted above, N1b is the highest N grade in the TNM classification. The prognostic impact of N1b on DFS and CSS has been investigated, revealing that N1b significantly predicted the DFS and CSS of PTC patients [16, 21, 25–29] (Table 3). However, in our recent study comparing N1b and N1a patients without massive Ex, the DFS and CSS of the two groups did not differ [30]. Thus, the issue of whether it is appro-

Table 3 Recent studies regarding the prognostic value of N1b

Authors	Patients	No. of patients	Prognostic impact of N1b
Ito *et al*. [25]	PTC ≤ 1 cm	600	Affected the DFS of patients
Ito *et al.* [26]	PTC > 1 cm	560	Affected theDFS of patients
Ito *et al*. [27]	PTC	1,740	An independent predictor of DFS and CSS
Kim *et al*. [28]	PTC ≤ 1 cm	293	An independent predictor of DFS
Ito *et al*. [29]	PTC ≤ 1 cm	1,055	An independent predictor of DFS
Fukushima *et al*. [21]	PTC	5,918	Strong predictor of DFS and CSS for tumors ≤ 3 cm
Verburg *et al*. [16]	DTC	2,011	Reduced life expectancy
Ito *et al*. [30]	PTC	5,043	DFS and CSS similar to those of N1a patients

Abbreviations: explained in Table 2.

Table 4 Recent studies regarding the prognostic value of N factors other than the location of metastasis

Authors	Patients	No. of patients	Prognostic impact of N1b
Sugitani *et al*. [14]	PTC	604	N ≥ 3 cm; high-risk for patients ≥ 50 years
Wada *et al*. [31]	PTC ≤ 1 cm	259	Palpable nodes: risk factor for DFS
Wada *et al*. [32]	PTC > 1 cm	231	Palpable nodes: risk factor for DFS of patients ≥ 45 years
Sugitani *et al.* [33]	Symptomatic PTC ≤ 1 cm	56	N ≥ 2 cm: predictor of adverse outcomes
Asanuma *et al*. [36]	PTC	46	Extranodal extension: risk factor for recurrence
Ito *et al*. [37]	PTC	1,692	Extranodal extension: An independent prognostic factor for CSS
Ito *et al*. [30]	PTC	5,043 (Subset analysis for 621 N1b patients)	1) N ≥ 3 cm: Independent prognostic factor for DFS of patients ≥ 55 years. 2) Five or more N: Independent prognostic factor for DFS of patients < 55 years. 2) Extranodal extension: A predictor of DFS and CSS
Ito *et al*. [15]	PTC	5,768	1) Prognostic impact of N ≥ 3 cm for DFS was much higher than N < 3 cm 2) N ≥ 3 cm and extranodal extension: Independent predictors of carcinoma death

Abbreviations: explained in Table 2.

priate that N1b is graded higher than N1a remains controversial.

2) Size of metastasis

In 2004, Sugitani *et al*. proposed a novel classification for PTC patients, and they regarded patients ≥50 years with node metastasis ≥3 cm as being high-risk [14]. Wada *et al*. showed that palpable lymphadenopathy was a prognostic factor of DFS for both PTC ≤ 1 cm [31] and PTC > 1 cm and patient age ≥45 years [32]. In the subset of PMC, Sugitani *et al*. demonstrated that N ≥2 cm was related to adverse outcomes [33]. We also showed that N could be an independent predictor for locoregional and distant recurrence, and N ≥3 cm, but not N <3 cm, independently affected the CSS of our patients [15] (Table 4). The above findings thus suggest that the size of the metastatic node(s) is an important factor to predict patients' prognoses.

3) Macroscopic extranodal extension

Yamashita *et al*. (in 1999) and Leboulleux *et al*. (in 2005) demonstrated the prognostic impact of extranodal extension, mainly by pathological examination [34, 35]. In 2001, Asanuma *et al*. showed that PTC with macroscopic extranodal extension is more likely to show recurrence [36], and in 2007, we analyzed a larger series of patients and found that it was an independent predictor of carcinoma-related death [37]. We obtained similar results in a subset analysis of N1b patients [30] (Table 4). For another larger series of patients, extranodal extension was also an independent predictor for CSS of patients [15]. It remains an open question whether extranodal extension should be evenly classified with extension from primary tumor, but in our findings, at least the CSS of patients with massive Ex from primary lesions and metastatic nodes did not differ significantly.

4) Age

Although the patient cutoff age varies among the studies, some groups found that N was related to the prognosis of older patients more significantly than in young patients [14, 30]. Large node metastasis is especially important for old patients. In young patients, it was demonstrated that the number of N (rather than

their size) is a predictor of adverse outcomes [14, 30].

4. Summary

Massive Ex and N are definitely representative prognostic factors of PTC. However, such cases include tumors with a wide range of biological characteristics, and the prognoses of massive Ex and/or N-positive patients are influenced by other clinicopathological characteristics. The prognoses of patients with massive Ex differ according to patient age, the range and depth of the Ex, and tumor size, and the prognoses of patients with N is affected by patient age, tumor size, size of N, and extranodal extension. We must note that the prognosis of Ex- and/or N-positive patients is generally poor but varies according to other clinicopathological features and the patients' backgrounds.

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