Pathologe 2019 · 40 (Suppl 1):S18–S24
https://doi.org/10.1007/s00292-018-0418-x
Published online: 19 February 2018
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Redaktion
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Proposal for an extended pTNM classification of thyroid carcinoma

Commentary on deficits of the 8th edition of the TNM classification

Tumor classifications are expected to adapt to dynamic processes, such as novel clinical and molecular biological/pathological findings, in order to meet their main purpose, namely the generation of international standardized clinicopathological data as the basis for worldwide comparability of the clinical management of malignant tumors.

High standards have to be particularly demanded for determination of the anatomical extent of malignant tumors by the cTNM/pTNM classifications, since these provide the most reliable basis for therapeutic decisions and estimation of prognosis. They support the generation of structured clinical and pathological reports, serve as an elementary basis for guidelines on therapeutic decision making for the individual patient, and provide data with an important influence on health policy with far-reaching effects on cancer patients. Therefore, all changes to the cTNM/pTNM classification must be (i) evidence based and (ii) compatible with previous version(s) in order to maintain the value of previously collected data when matching these with forthcoming data of a revised classification. The second aspect is of particular importance for thyroid carcinoma with its comparatively low biological aggressiveness and the resultant long follow-up periods necessary for collection of valid survival data.

The German version of this article can be found under https://doi.org/10.1007/s00292-017-0410-x.

Changes in the TNM classifications of thyroid carcinomas

The 2002 published changes in the categorization of thyroid carcinoma concerning the primary tumor (T/pT category) introduced in the 6th edition of the TNM classification [26] caused criticism in all disciplines involved in the diagnosis and therapy of thyroid carcinoma [21]. Particularly the lack of compatibility of the new classification with its predecessor classification (5th edition [25]) was criticized, since both carcinomas with a size <1 cm (inevitable for the management of patients with papillary microcarcinoma) and carcinomas with "minimal extrathyroidal extension" were no longer unequivocally identifiable by means of the TNM categorization system.

The commentaries and suggestions for the ramification of the categories T1/pT1 and T3/pT3 [30] presented in the subsequently published supplement to the 6th edition of the TNM classification [30], namely the subcategorization into T1a/pT1a and T1b/pT1b as well as T3a/pT3a andT3b/pT3b, fundamentally contributed to the required specification. Unfortunately, many pathologists and clinicians only use the original TNM classification and do not consider the commentaries and suggestions of the subsequently published TNM supplement; this TNM supplement is sometimes not even known to them. Thus, no international introduction and acceptance of the proposed ramifications could be achieved. Whereas the subcategorization of T1/pT1 into T1a/T1b or pT1a/pT1b was introduced into the 2009 published 7th edition of the TNM classification [24], thus contributing elementarily to the international categorization of microcarcinomas <1 cm, the equally necessary subdivision of the category T3/pT3 to clearly differentiate carcinomas restricted to the thyroid from those with "minimal extrathyroidal extension" was waivered.

It should be emphasized that the TNM/pTNM categorization [25] of thyroid carcinomas in use until 2002 was anything but ideal, but it was at least consistent and clearly applicable. Nevertheless, the fact that carcinomas with minimal extrathyroidal extension (i. e., microscopic evidence of tumor infiltration into the perithyroidal adipose tissue, regardless of tumor size) and carcinomas with (massive and life-threatening)

Table 1 Proposal for an extended TNM classification of thyroid carcinomas (8th edition [3]), modified according to [28]

pTNM	Proposal for an extended TNM classification of thyroid carcinomas	Comments
pT—Primary Tumor	Including papillary, follicular, poorly differentiated, Hürthle cell, and anaplastic thyroid carcinomas	Tumor entities for application extended by medullary thyroid carcinoma
pTX	Primary tumor cannot be assessed	–
pT0	No evidence of primary tumor	–
pT1a1	Tumor 1 cm or less in greatest dimension, limited to the thyroid	–
pT1a2	Tumor 1 cm or less in greatest dimension, with "minimal extrathyroidal extension"	Definition of "minimal extrathyroidal extension" see text
pT1b1	Tumor more than 1 cm but not more than 2 cm in greatest dimension, limited to the thyroid	–
pT1b2	Tumor more than 1 cm but not more than 2 cm in greatest dimension, with "minimal extrathyroidal extension"	Definition of "minimal extrathyroidal extension" see text
pT2a	Tumor more than 2 cm but not more than 4 cm in greatest dimension, limited to the thyroid	–
pT2b	Tumor more than 2 cm but not more than 4 cm in greatest dimension, with "minimal extrathyroidal extension"	Definition of "minimal extrathyroidal extension" see text
pT3a1	Tumor more than 4 cm in greatest dimension, limited to the thyroid	–
pT3a2	Tumor more than 4 cm in greatest dimension, with "minimal extrathyroidal extension"	Definition of "minimal extrathyroidal extension" see text
pT3b	Tumor of any size with gross extrathyroidal extension invading strap muscles (sternohyoid, sternothyroid, or omohyoid muscles)	A microscopic confirmation of the macroscopic finding is highly desirable
pT4a	Tumor extends beyond the thyroid capsule and invades any of the following: subcutaneous soft tissues, larynx, trachea, esophagus, recurrent laryngeal nerve	–
pT4b	Tumor invades prevertebral fascia, mediastinal vessels, or encases carotid artery	–
N0/pN—Regional lymph nodes		
NX/pNX	Regional lymph nodes cannot be assessed	–
N0/pN0	No regional lymph node metastasis	Histological examination of a selective neck dissection specimen will ordinarily include six or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0
N1a1/pN1a1	Metastasis in Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes), or upper/superior mediastinum, restricted to the lymph node(s) involved without extracapsular extension	–
N1a2/pN1a2	Metastasis in Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes), or upper/superior mediastinum, with extracapsular extension	Extranodal extension of lymph node metastasis is associated with a significantly poorer prognosis [4, 12, 19]
N1b1/pN1b1	Metastasis in other unilateral, bilateral or contralateral cervical (levels I, II, III, IV, or V) or retropharyngeal lymph nodes, restricted to the lymph node(s) involved without extracapsular extension	–
N1b2/pN1b2	Metastasis in other unilateral, bilateral or contralateral cervical (levels I, II, III, IV, or V) or retropharyngeal lymph nodes, with extracapsular extension	Extranodal extension of lymph node metastasis is associated with a significantly less favorable prognosis [4, 12, 19]
pM—Distant Metastasis		
pM1	Distant metastasis microscopically confirmed	pM0 and pMX are not applicable categories

TNM tumor-node-metastasis, *pTNM* „pathological tumor-node-metastasis"

tumor infiltration of structures such as esophagus, trachea, or large vessels were commonly categorized as pT4 category, made little biological sense.

The changes made in 2002 (6th edition [26]), i.e. that carcinomas with minimal extrathyroidal extension (definition below) were no longer assigned to the same T/pT category as carcinomas infiltrating designated anatomical structures of the neck was therefore to be welcomed. This step forward was substantially diminished by the decision to put carcinomas with minimal extrathyroidal extension without distinct subdivision into the same T3/pT3 category as carcinomas with more than 4 cm in greatest dimension but limited to the thyroid. The tumor size of the carcinomas with "minimal extrathyroidal extension" again remained unconsidered. The common categorization was not evidence based; nevertheless, this obvious deficiency could have been easily eliminated by the subcategorization T3a/pT3a and T3b/pT3b proposed in the TNM supplement published in 2003 [30].

8th edition of the TNM classification of thyroid carcinomas

In the 8th edition of the TNM/pTNM classification of thyroid carcinomas [3], which was introduced at the beginning of 2017 [3] and has been incorporated in the recently released new World Health Organization (WHO) classification of thyroid tumors [29], a problem concerning its practical use can be identified. The new TNM/pTNM categories only distinguish carcinomas limited to the thyroid (T1/pT1, T2/pT2, T3/pT3a) and carcinomas with grossly (!) identifiable tumor extension into explicitly designated anatomical structures. These defined structures include the sternohyoid, sternothyroid, and/or omohyoid muscles (T3b/pT3b), or subcutaneous soft tissue, larynx, trachea, esophagus, recurrent laryngeal nerve (T4a/pT4a), the prevertebral fascia, and/or mediastinal vessels, or encasing of the carotid artery (T4b/pT4b). Microscopically evident extrathyroidal tumor infiltration in perithyroidal soft tissue ("minimal extrathyroidal extension") is explicitly not mentioned, although this is not a rare finding. Interestingly, the TNM classification of the American Joint Committee on Cancer (AJCC) simply states that minimal extrathyroidal extension should not be considered in either the T-category or the stadium definition [2].

The proposed changes to the TNM classification (**Table 1**) would, for the first time, provide the opportunity to standardize "minimal extrathyroidal extension" in relation to tumor size (pT category) and make it available for prospective scientific analysis. For this purpose it is necessary to define the term "minimal extrathyroidal extension" in the context of particular anatomical features of the thyroid gland and its capsular borders histologically more precisely.

Abstract · Zusammenfassung

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Proposal for an extended pTNM classification of thyroid carcinoma. Commentary on deficits of the 8th edition of the TNM classification

Abstract

In the 8th edition of the TNM classification of thyroid carcinomas, which was introduced in 2017, carcinomas with minimal extrathyroidal extension are no longer mentioned, which might cause problems. These tumors were explicitly categorized in previous TNM classifications (5–7th editions). Studies on the prognostic relevance of minimal extrathyroidal extension have shown conflicting results. Moreover, the vast majority of these studies retrospectively analyzed only subgroups of thyroid carcinomas (e.g. differentiated thyroid carcinoma, papillary thyroid carcinoma). The proposed subcategorization of the current TNM classification (8th edition) ensures the continuity of the parameter minimal extrathyroidal extension within the TNM categorization of thyroid carcinomas and also offers the possibility to prospectively analyze in a standardized manner the potential biological relevance of minimal extrathyroidal extension in relation to tumor categories (T/pT category).

Keywords

Carcinoma · Papillary thyroid cancer · Prognosis · Thyroid neoplasms · Tumor staging

Vorschlag zu einer erweiterten pTNM-Klassifikation der Schilddrüsenkarzinome. Kommentar zu Defiziten der 8. Auflage der TNM-Klassifikation

Zusammenfassung

In der seit diesem Jahr anzuwendenden 8. Auflage der TNM-Klassifikation der Schilddrüsenkarzinome tritt das Problem auf, dass die in den vorangegangen Versionen (5.–7. Auflage) explizit zu kategorisierenden Karzinome mit „minimaler extrathyroidaler Ausbreitung" keine Erwähnung mehr finden. Wissenschaftliche Studien zur prognostischen Relevanz einer „minimalen extrathyroidalen Ausbreitung" gelangten zu sehr unterschiedlichen Ergebnissen. Hinzukommt, dass sich praktisch alle Studien lediglich mit der retrospektiven Datenauswertung von Subgruppen von Schilddrüsenkarzinomen (z. B. differenzierte Schilddrüsenkarzinome, papilläre Schilddrüsenkarzinome) beschäftigen. Die von uns hier vorgeschlagene Subkategorisierung der aktuellen TNM-Klassifikation (8. Auflage) gewährleistet einerseits die Kontinuität des Parameters „minimale extrathyroidale Ausbreitung" innerhalb der TNM-Kategorisierung von Schilddrüsenkarzinomen und eröffnet andererseits die Möglichkeit die „minimale extrathyroidale Ausbreitung" bezogen auf die Tumorgröße (T/pT-Kategorie) standardisiert prospektiv auf deren biologische Relevanz zu untersuchen.

Schlüsselwörter

Karzinom · Papilläres Schilddrüsenkarzinom · Prognose · Schilddrüsentumoren · Tumorstaging

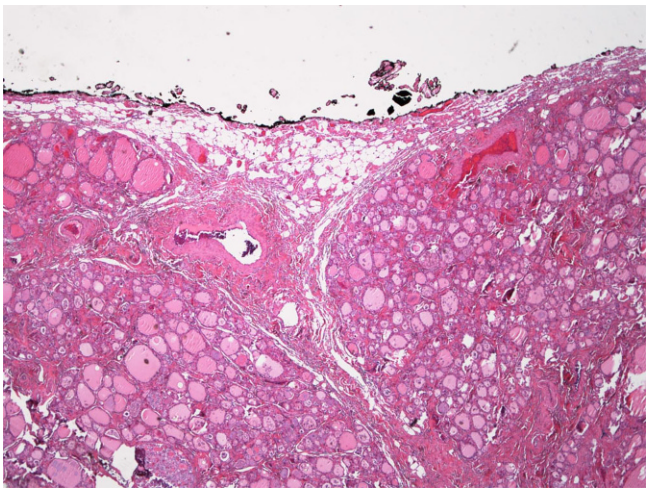

Fig. 1 ▲ Normal thyroid tissue from the isthmus with lobulated structure without distinct thyroid capsule; the thyroid tissue is in close contact with striated muscle tissue. HE, × 25. (From [28])

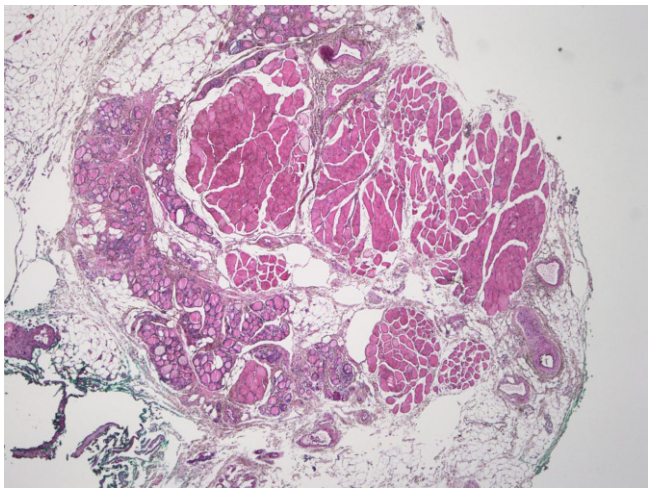

Fig. 2 ▲ Normal thyroid tissue. Superficially located between the thyroid lobules is a triangular shaped cluster of adipose tissue, which is delimited by an incomplete thin fibrous capsule from adjacent thyroid tissue. HE, × 25. (From [28])

Anatomy of the thyroid gland

The human thyroid gland is a bilobate organ in the midportion of the neck, embedded in soft tissue (fat, striated strap muscle). The two lobes, which are divided into lobules, are connected by the isthmus; approximately 40% of individuals have a pyramidal lobe which is a vestige of the thyroglossal duct. The ventral and lateral portions of the thyroid are covered by a thin fibrous capsule. The dorsal thyroid surface may show a less distinguished and even thinner fibrous coverage. Due to the lobulated structure of the thyroid, triangular clusters of fat tissue may reach between the lobules (◘ **Fig. 1**); however, there are pronounced individual differences. Both the isthmus and the pyramidal lobe partially lack a defined fibrous capsule. Within the thyroid tissue of the isthmus and the pyramidal lobe, regularly striated muscle tissue can be demonstrated (◘ **Fig. 2**).

Definition of "minimal extrathyroidal extension" of thyroid carcinomas

In histopathology, invasive/infiltrative growth is defined as invasion of tumor cells into adjacent structures. In almost all cases, the tumor extension will be in non-neoplastic tissue surrounding the invasively growing tumor. Occasionally the invasive tumor may infiltrate another neoplasm (e. g., thyroid carcinoma infiltrating a parathyroid tumor). Both in the 6th and 7th editions of the TNM classifications [24, 26], for thyroid carcinoma, a clear distinction between a variety of designated anatomical structures (T4a/pT4a, T4b/pT4b) and "minimal extrathyroidal extension" (T3/pT3) was made. However, microscopic judgement of "minimal extrathyroidal extension" is obviously subject to broad individual interpretation.

The herein used definition of "minimal extrathyroidal extension" includes all primary thyroid carcinomas (the vast majority of cases are non-encapsulated tumors) that microscopically infiltrate into perithyroidal soft (adipose) tissue without extension into designated anatomical structures (categories T3b/pT3b, T4a/pT4a, and T4b/pT4b). In these parts of the thyroid clearly confined by a fibrous thyroid capsule, "minimal extrathyroidal extension" requires tumor infiltration throughout the complete capsule. However, in carcinomas with stromal desmoplasia, precise evaluation of the pre-existing thyroid capsule may be difficult or even impossible. In analogy to other organs (e. g., prostate), an imaginary line representing the original thyroid capsule may aid assessment of extrathyroidal extension (◘ **Fig. 3**, **4**, **5**, **6** **and** **7**).

A special situation exists in the area of the interlobular triangular adipose tissue described above; each tumor infiltration of this adipose tissue is consequently considered as "minimal extrathyroidal extension." However, this does not include tumor infiltrates in islands of mature adipose tissue, which can be found regularly both within non-neoplastic thyroid tissue and thyroid neoplasms (adenomas and carcinomas).

In thyroid areas with no defined capsular boundary (isthmus, pyramidal lobe), every tumor infiltration of adipose tissue by a carcinoma is regarded as "minimal extrathyroidal extension;" occasionally there is also a microscopic extension of carcinoma into intrathyroidally located striated muscle tissue. Since published studies in the field have arrived at quite contradictory results [1, 10, 11, 14, 18], we do not agree with Mete et al. [13] that "minimally invasive" tumor infiltration of the perithyroid soft tissue per se has no biological relevance, thus not justifying a separate pT category. A prospective categorization of thyroid carcinomas extending from their tissue of origin into perithyroidal soft tissue should be based on the proposed modifications (◘ **Table 1**) of the 8th edition of the TNM classification [3]. This offers the possibility to scientifically analyze the putative biological relevance of "minimal extrathyroidal extension" in thyroid car-

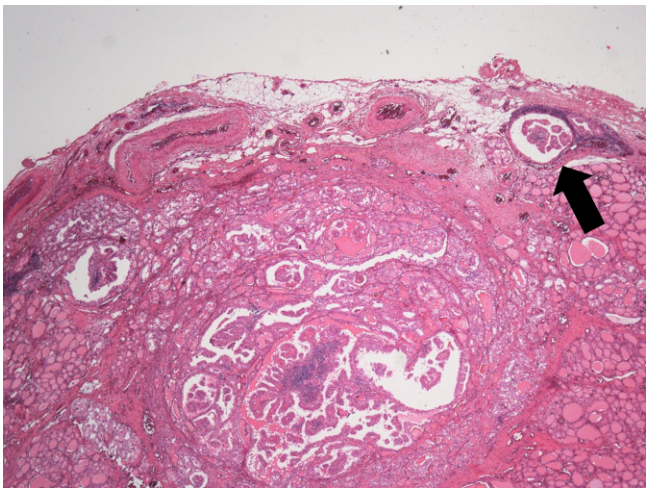

Fig. 3 ▲ Papillary microcarcinoma (4 mm diameter) situated peripherally, with "minimal extrathyroidal extension" (pT1a2, see **Table 1**); only a few tumor cell clusters infiltrate into perithyroidal adipose tissue (*arrow*). The carcinoma does not extend to the surgical resection margin (R0). HE, × 25. (From [28])

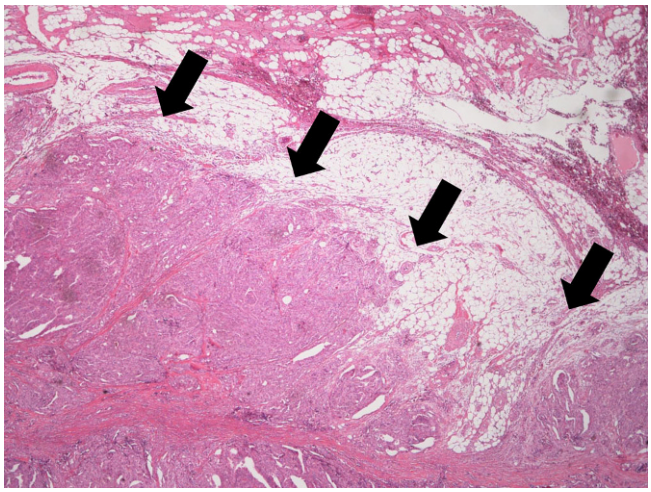

Fig. 4 ▲ Papillary thyroid carcinoma (3.2 cm in diameter; pT2b, see **Table 1**) with "minimal extrathyroidal extension," which, however, presents as broad infiltration of the adipose tissue (*arrows*); the carcinoma was nevertheless resected in sano (R0). HE, × 25. (From [28])

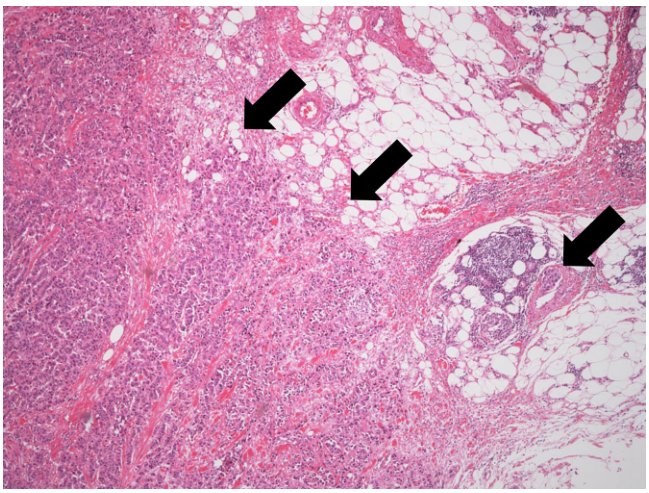

Fig. 5 ▲ Poorly differentiated medullary thyroid carcinoma with "minimal extrathyroidal extension" (*arrows*) of the perithyroidal fat tissue (pT2b, see **Table 1**) and tumor-free surgical resection margins (R0). HE, × 50. (From [28])

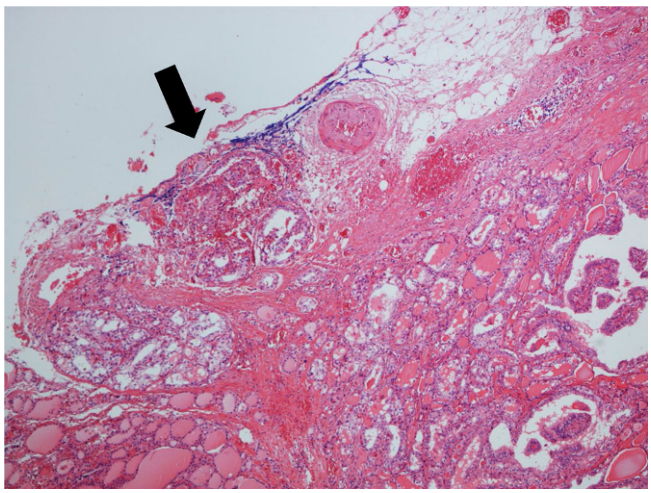

Fig. 6 ▲ Papillary microcarcinoma (6 mm in diameter) with "minimal extrathyroidal extension" into perithyroidal adipose tissue; carcinoma cells are infiltrating the color-marked surgical resection margin (pT1a2, R1, see **Table 1**). HE, × 100. (From [28])

cinoma (combined with the respective pT category, indicating the respective tumor size).

Discussion

The recently introduced 8th edition of the TNM classification [3] only categorizes thyroid carcinomas which are either limited to the thyroid (T1/pT1, T2/pT2, T3a/pT3a) or show extension into designated anatomical structures. Accordingly, an already grossly (!) recognizable tumor infiltration of the sternohyoid, sternothyreoideus, or omohyoid muscles (T3b/pT3b), or macroscopic or microscopic extension into subcutaneous soft tissue, larynx, trachea, esophagus, recurrent nerve (T4a/pT4a), the prevertebral fascia, and/or mediastinal vessels, or enclosing the carotid artery (T4/pT4) are categorized, too. Microscopic demonstration of "minimal extrathyroidal extension" into perithyroidal soft tissue without concomitant infiltration of named anatomical structures is not included, although this is not a rare event and was explicitly categorized in previous editions of the TNM classification [24–26]. It has been consistently and widely used both by pathologists and clinicians [23]. A histologically proven "minimal extrathyroidal extension" of thyroid carcinomas has a clearly defined impact on the postoperative management of the respective patients, and this not only in Germany [7].

Table 1 summarizes a recent proposal to categorize thyroid carcinomas with "minimal extrathyroidal extension" [28]. The pT categories pT1a, pT1b, pT2, and pT3a are each subdivided into true

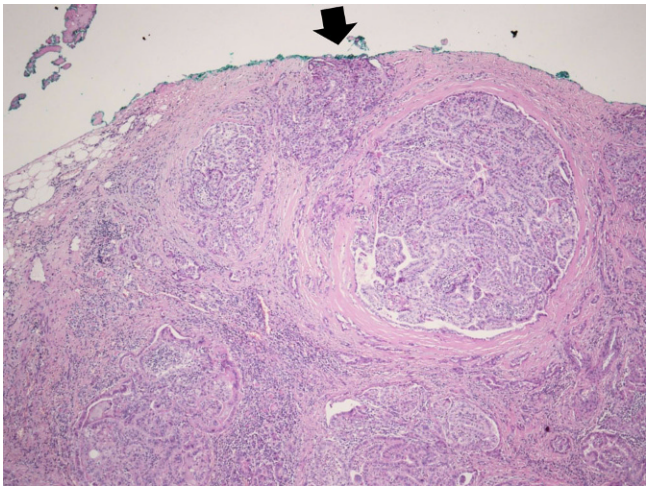

Fig. 7 ▲ Papillary thyroid carcinoma (1.8 cm in diameter, tall cell variant with a desmoplastic stroma), infiltrating the color-marked surgical resection margins (R1). On the left side perithyroidal adipose tissue, suggesting that the carcinoma shows "minimal extrathyroidal extension" into the perithyroidal adipose tissue (pT1b2, see **Table 1**). HE, ×25. (From [28])

thyroid-restricted carcinomas (pT1a1, pT1b1, pT2a, pT3a1) and carcinomas with "minimal extrathyroidal extension" (pT1a2, pT1b2, pT2b, pT3a2). This proposal [28] combines, in contrast to previous editions of the TNM classification, "minimal extrathyroidal extension" with tumor size (pT category) as a putative prognostic and treatment-guiding parameter. The possible biological relevance of this combined parameter is provided by the study by Radowsky et al. [18].

According to the 8th edition of the TNM classification [3], the extrathyroidal extension of the primary tumor (T/pT category) is considered an essential prognostic factor as well as the exclusion or detection of residual tumor (R0 vs. R1 vs. R2). Comparative studies have shown considerable inter- and intraobserver variation among pathologists in the evaluation of extrathyroidal growth of thyroid carcinomas [27], which inevitably questions the significance of this parameter as an independent prognostic factor. One of the main reasons for this may be differences in the definition of the "minimal extrathyroidal extension." In order to remedy this shortcoming, we recently recommended a strict definition of "minimal extrathyroidal extension" [28]. According to these recommendations, any microscopically detectable extension of a primary thyroid carcinoma into perithyroidal soft (adipose) tissue is consistently rated as "minimal extrathyroidal extension," regardless of whether or not the tumor extension is delimited by a (thin) connective tissue capsule. These recommendations constitute the morphological and scientific basis for demonstration or exclusion of the biological relevance of a microscopically proven "minimal extrathyroidal extension."

Mete et al. [13] considered "minimal extension" of thyroid carcinoma into perithyroidal soft tissue (adipose tissue) not to be a relevant prognostic factor, while (gross) tumor extension into designated structures (strap muscles, subcutaneous soft tissue, larynx, trachea, esophagus, recurrent laryngeal nerve, prevertebral fascia, mediastinal vessels) was associated with an unfavorable prognosis. This viewpoint is supported by some studies [1, 10, 11], while other studies have demonstrated a significant prognostic relevance of "minimal extrathyroidal extension" [14, 18]. However, virtually all studies investigated only subgroups of thyroid carcinoma (e. g., differentiated carcinomas, papillary thyroid carcinomas, pT2/pT3 carcinomas), although the biological relevance of "minimal extrathyroidal extension" may be important for further management of all thyroid carcinomas (all histological subtypes, all degrees of differentiation, all tumor sizes).

A further proposal (also included in **Table 1**) concerns extracapsular extension of lymph node metastases of thyroid carcinoma, a parameter shown to be of significant prognostic relevance [4, 12, 19]. Here, too, the categories pN1a and pN1b are subdivided into the subcategories pN1a1/pN1b1 (metastases limited to lymph nodes) and pN1a2/pN1b2 (metastases with extranodal extension).

The incidence of thyroid carcinoma has increased almost threefold in the last three decades, which is now seen as an "epidemic of diagnosis" of an, in the vast majority of cases, biologically indolent tumor, rather than an actual increase in thyroid carcinoma [6, 17]. The proposal to rename unifocal papillary microcarcinoma limited to the thyroid gland as papillary microtumors [20], however, unfortunately found no international acceptance [29]. Encapsulated follicular carcinomas without angioinvasion, diagnosis of which is based exclusively on a capsular breakthrough (minimally invasive follicular thyroid carcinoma [FTC] according to the new WHO classification [29]), are considered very low-risk carcinomas [5, 7–9, 15, 22, 29]. The introduction of "non-invasive follicular neoplasia with papillary-like nuclear features (NIFTP)" [16], an encapsulated thyroid neoplasm with by definition "extremely low malignant potential" [29], also points in the same direction and has necessitated a change in the definition of papillary thyroid carcinoma [29]. Until unequivocal scientific proof of its biological indolence, in thyroid carcinoma, we oppose downplaying of the local tumor extension beyond the organ capsule (a prognostic parameter considered relevant in a broad variety of other malignancies), even if it is restricted to perithyroidal soft tissue "only" [13].

Conclusion

- **The 2017 introduced TNM classification categorizes thyroid carcinoma either as carcinomas restricted to the thyroid or carcinomas that grossly infiltrate into designated anatomical structures, whereas a "minimal extrathyroidal extension"**

into perithyroidal adipose tissue no longer appears in this classification.
- In the present paper, a proposal is made for the subcategorization of pT categories pT1a, pT1b, pT2, and pT3a. As a basis, strict histopathological criteria for the diagnosis of "minimal extrathyroidal extension" of thyroid carcinoma are defined.
- The aim of this proposal is to create a standardized pT classification scheme for the proof or exclusion of the prognostic and therapeutic relevance of "minimal extrathyroidal extension" of thyroid carcinoma in conjunction with tumor size, although the suggestion made causes additional work and may therefore be perceived by pathologists as complicated in everyday use.

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Compliance with ethical guidelines

Conflict of interest. K.W. Schmid, S. Synoracki, H. Dralle, and C. Wittekind declare that they have no competing interests.

This article does not contain any studies with human participants or animals performed by any of the authors.

The supplement containing this article is not sponsored by industry.

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