Cytological and Ultrasound Features of Thyroid Nodules Correlate with Histotypes and Variants of Thyroid Carcinoma

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Statement of ethics

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Data publication was approved by the local institutional review committee (Comitato Etico di Area Vasta Nord Ovest – CEAVNO, n. 22768). Patients were informed and gave their consent to participate in the study.

ABSTRACT

Context. Prognosis is excellent for the papillary thyroid carcinoma (PTC), noninvasive follicular thyroid neoplasia with papillary-like nuclear features (NIFT-P) and the follicular thyroid carcinoma (FTC) while is poor for the poorly differentiated thyroid carcinoma (PDTC) and the anaplastic thyroid carcinoma (ATC). Among PTC, the prognosis is more favorable for the follicular (FV-PTC) and the classic (CV-PTC) than for the tall cell (TCV-PTC) and the solid (SV-PTC) variants.

Objectives. To associate histotypes and variants of thyroid carcinoma with ultrasound and cytological features.

Design. Histology of 1018 benign tumors and 514 PTC (249 CV, 167 FV, 49 TC, 34 SV and 15 other variants), 52 NIFT-P, 50 FTC, 11 PDTC and 3 ATC was correlated to fine-needle aspiration biopsy categories (Italian classification: TIR1, TIR2, TIR3A, TIR3B, TIR4 and TIR5) and ultrasound features.

Setting: Endocrinology Unit, University Hospital of Pisa.

Patients: 1117 patients with thyroid nodule(s) who underwent thyroidectomy.

Intervention: None.

Main Outcome Measure(s): None.

Results: Of PTC, 36.3% had an indeterminate cytology (TIR3A or TIR3B), 56.6% suspicious for malignancy or malignant (TIR4 or TIR5); 84.0% FTC and 69.3% NIFT-P were TIR3A or TIR3B. 72.5% FV-PTC and 73.6% SV-PTC were TIR3A or TIR3B, 79.9% CV-PTC and 95.9% TCV-PTC were TIR4 or TIR5. The association of a hypoechoic pattern, irregular margins and no microcalcifications was more frequent in TCV-PTC than in CV-PTC (p=0.02, PPV=38.9%; NPV=85.5%).

Conclusions: At cytology, most FTC, NIFT-P, FV-PTC and SV-PTC were indeterminate, most CV-PTC and TCV-PTC were suspicious for malignancy or malignant. Ultrasound can be helpful in ruling out TCV-PTC.

Freeform/Key Words: thyroid nodule, thyroid carcinoma, fine-needle aspiration biopsy, thyroid ultrasound.

INTRODUCTION

The prognosis of thyroid carcinoma, which is favorable in the majority of cases, is significantly influenced by the histotypes and the variants of the tumor (1,2). Papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), which account for 80-90% and 6-10% of all thyroid tumors, respectively (3,4), are characterized by an excellent prognosis, with a 30 years overall survival of 95% (5,6). On the other hand, the poorly differentiated thyroid carcinoma (PDTC) and the anaplastic thyroid carcinoma (ATC), which account for 1.8% and 3.6% of thyroid carcinomas, show a very aggressive behavior and a poor prognosis, with a 5 years overall survival rate of 60-70% for the PDTC and 5 to 6 months for the ATC (7–9). In the last few years several variants of PTC have been characterized: the classic (CV-PTC) and the follicular (FV-PTC), the most common subtypes (74.8% and 17.9% of the total PTC, respectively) show an excellent prognosis (3,10,11), whereas the tall cell (TCV-PTC), the solid (SV-PTC), the columnar and the hobnail variants show a more aggressive behavior (4). The incidence of TCV-PTC ranges from 1.2 to 13.0% of all PTC and its 5-year disease-survival rate is lower compared to that of the CV-PTC (81.9% vs 97.8%) (12–17). In addition, some Authors have reported a higher rate of lymph node involvement and a poorer prognosis of the SV-PTC compared to the CV-PTC, although these findings have not been confirmed by others (18–20). A new histopathological entity, noninvasive follicular thyroid neoplasia with papillary-like nuclear features (NIFT-P) was recently included in the group of tumors with low potential to develop metastasis (1).

The more detailed histological characterization led to a change in the management of thyroid carcinoma. While in the past the majority of patients were advised total thyroid ablation (thyroidectomy plus remnant ablation by ^{131}I) (21), the latest guidelines suggest that treatment should be tailored according to risk stratification that includes histological features, among others (18).

Indication for surgery of thyroid nodules is mainly based on the results of fine-needle aspiration biopsy (FNAB) (18). Classifications of thyroid cytology include 5-6 categories (22–25). The 2014 Italian consensus for the classification of thyroid cytology identifies TIR1/1C as non-diagnostic/cystic, TIR2 as benign, TIR3A as low-risk indeterminate lesion, TIR3B as high-risk indeterminate lesion, TIR4 as suspicious for malignancy and TIR5 as malignant (22). The corresponding Bethesda classes are Thy I for TIR1/1C, Thy II for TIR2, Thy III for TIR3A, Thy IV for TIR3B, Thy V for TIR4 and

Thy VI for TIR5 (22,26). TIR3 category is the main limitation of FNAB because it identifies the follicular pattern that includes both benign (adenomatous hyperplasia and follicular adenoma) and malignant lesions (FTC, Hürthle tumors and FV-PTC); the differential diagnosis is based on the capsular involvement and vascular invasion at histology (27). At thyroid ultrasound, hypoechogenicity, irregular margins and spot microcalcifications are associated with a higher risk of malignancy (18). Molecular testing on FNAB specimens can add information to reduce false positive and false negative results in TIR3A and TIR3B nodules (28).

Surgery is usually recommended for TIR3B, TIR4 and TIR5 nodules, which turn out malignant at histology in 15-30%, 60-80% and > 95% of cases respectively, while for TIR3A nodules active surveillance is advised, because their rate of malignancy is < 10% (18,22). For TIR3B, TIR4 and TIR5 nodules, when metastatic disease and local invasion have been excluded, the latest American Thyroid Association (ATA) guidelines suggest active surveillance or lobectomy when diameter is < 1 cm and lobectomy when diameter is > 1cm and < 4 cm. Total or near total thyroidectomy is recommended for nodules > 4 cm (18). When the aggressive variants (i.e., TCV-PTC, hobnail, columnar) are diagnosed at histology, completion surgery and ^{131}I therapy can be taken into account (18).

In this study, we correlated the histotypes and the variants of thyroid carcinoma with the cytological and ultrasound features observed before surgery, to provide a more complete characterization of thyroid nodules and help choose the proper therapeutical approach.

PATIENTS AND METHODS

Design and study population

We retrospectively evaluated the consecutive histopathological records of 1117 patients who underwent thyroidectomy at the University Hospital of Pisa, Italy, from January to December 2017 and had previously undergone FNAB at the same institution. Since some patients harbored more nodules, we evaluated a total of 1668 nodules, 1018 benign and 650 malignant. Histological and cytological results were correlated to ultrasound data, available in 1110 patients. It is worth mentioning that in the year 2017 patients harboring TIR3B, TIR4 and TIR5 nodules were all advised surgery. Among patients with TIR1/1C, TIR2 and TIR3A nodules, surgery was suggested in few, namely those with clinical suspicion, large nodules, symptomatic goiter, or cosmetic damage.

Histology

Pathologists of the University Hospital of Pisa who are expert in thyroid diseases performed the histological evaluation. Tissue samples obtained at surgery were fixed in formalin and embedded in paraffin. Each section was stained with hematoxylin and eosin. The histological diagnosis was made according to the World Health Organization guidelines (4). Malignant neoplasms were classified as PTC, NIFT-P, FTC, medullary thyroid carcinoma (MTC), PDTC, ATC and others (solitary fibrous tumor, B-cell lymphomas). PTC was sub-grouped into its variants: CV-PTC, FV-PTC, TCV-PTC, SV-PTC, columnar and hobnail (29).

FNAB cytology

FNAB was performed under ultrasound guidance using a 23-gauge needle attached to a 10-mL syringe. Samples were air-dried, stained with Papanicolaou and Giemsa and interpreted by experienced cytologists. The adequacy of aspirates was defined according to the guidelines of the Papanicolaou Society. Results of cytology were reported according to the 2014 Italian consensus for the classification of thyroid cytology (22).

Thyroid ultrasonography

Thyroid ultrasound was performed using a real-time instrument (Esaote SPA, My Lab 70 machine with a linear transducer of 8–13 MHz). Authors involved in the study as sonographers (T.R., R.E., F.S. and F.L.) had more than 20 years of experience. We considered the main features associated with malignancy, i.e., hypoechogenicity, irregular margins, microcalcifications and the association of 2 or 3 of them. According to echogenicity, nodules were classified as “hypoechoic” or “non hypoechoic” (cystic, isoechoic and hyperechoic). Margins were classified as “irregular”, when they were microlobulated, poorly defined or have spiculated margins or “regular”, when they were polycyclic or showed a continuous halo. Hyperechoic spots < 1 mm without posterior acoustic shadowing were classified as “microcalcifications”, absent microcalcifications and macrocalcifications as “no microcalcifications” (30).

Laboratory evaluation

Basal or calcium gluconate stimulated serum calcitonin was measured by a chemoluminescent immunometric assay (Immulite Siemens Healthcare Diagnostic Products Ltd., Lianberis, Gwynedd LL55 4EL, UK, reference values < 11.5 pg/mL; DiaSorin Cat# 310630, RRID: AB_2811286)

Statistical analysis

Statistical analysis was performed using SPSS 21 (IBM Corp., Armonk, NY). Major demographic, clinical and histological features are reported as median value with interquartile range (IQR) or as number and percentage, as indicated. The Chi-squared or Fisher exact tests were used to compare the distribution of ultrasound features between different PTC variants. Statistical significance was assumed for $p < 0.05$.

RESULTS

Histological, cytological and ultrasound features

General features of the study population, histotypes and PTC variants are reported in table 1. The cohort of 1117 patients harbored 1668 nodules, 1018 benign and 650 malignant. Cytological and ultrasound features of benign and malignant nodules are reported in table 2.

Cytological classes of benign nodules and carcinomas according to the histotypes

Out of 650 thyroid carcinomas, 514 (79.1%) were PTC (figure 1). Among them, 84 (16.3%) were TIR3A, 103 (20.0%) TIR3B, 129 (25.1%) TIR4 and 162 (31.5%) TIR5, while of 50 FTC, 21 (42.0%) were TIR3A, 21 (42.0%) TIR3B, 3 (6.0%) TIR4 and none TIR5. A minority of PTC and FTC had been diagnosed as TIR1 or TIR2. The cytological distribution of PTC and FTC was significantly different ($p < 0.001$).

Of 52 NIFT-P, 14 (26.9%) had turned out TIR2, 22 (42.4%) TIR3A, 14 (26.9%) TIR3B, none TIR4 and 1 (1.9%) TIR5 (figure 1). Six out of 11 PDTC had been diagnosed as TIR3B whereas 14/16 MTC had resulted TIR4 or TIR5. All MTC patients had positive serum calcitonin before surgery.

Of 249 CV-PTC, 2 (0.8%) had resulted TIR3A, 35 (14.1%) TIR3B, 88 (35.3%) TIR4 and 111 (44.6%) TIR5 (figure 2). Among 49 TCV-PTC, none had resulted TIR3A, 1 (2.0%) had been diagnosed as TIR3B, 11 (22.4%) TIR4 and 36 (73.5%) TIR5. Of 167 FV-PTC, 70 (42.0%) had resulted TIR3A, 51 (30.5%) TIR3B, 22 (13.2%) TIR4 and 4 (2.4%) TIR5. Among 34 SV-PTC, 11 (32.4%) had been diagnosed as TIR3A, 14 (41.2%) TIR3B, 5 (14.7%) TIR4 and 2 (5.9%) TIR5 (figure 2).

Of 112 aggressive thyroid tumors (PDTC, ATC and aggressive PTC variants i.e., SV-PTC, TC-PTC, columnar and hobnail), 3 (2.7%) had been diagnosed as TIR1 or TIR1C, 2 (1.8%) TIR2, 14 (12.5%) TIR3A, 23 (20.5%) TIR3B, 21 (18.8%) TIR4 and 49 (43.7%) TIR5 (figures 1 and 2).

Ultrasound features of benign and malignant nodules

At ultrasound, hypoechogenicity, irregular margins and microcalcifications were more common in malignant than in benign nodules (table 2).

Considering the ultrasound features of nodules classified as TIR3B, 75 benign and 77 malignant, the pattern characterized by irregular margins regardless of hypoechoic pattern and microcalcifications was associated with malignancy (p =0.03) (PPV =88.9%, NPV =51.7%) (table 3).

Among 21 FV-PTC and 12 SV-PTC, microcalcifications were detected in 5 (23.8%) FV-PTC and 4 (33.3%) SV-PTC (p =0.69), irregular margins in 4 (19.0 %) FV-PTC and 4 (33.3%) SV-PTC (p =0.42) and a hypoechoic pattern in 18 (85.7%) FV-PTC and 9 (75.0%) SV-PTC (p =0.64). FV-PTC didn't differ from SV-PTC when the association of the three ultrasound characteristics was evaluated.

Ultrasound features were available in 135 CV-PTC and 28 TCV-PTC. The echographic pattern characterized by the coexistence of hypoechogenicity and irregular margins in the absence of microcalcifications was more frequent in TCV-PTC (7/28) (25.0%) compared to CV-PTC (11/135) (8.1%) (p =0.02) (PPV =38.9%, NPV =85.5%) (Table **4**).

DISCUSSION

The prognosis of thyroid carcinoma varies according to histotypes, being more favorable in PTC, NIFT-P and FTC than in PDTC and ATC. In addition, the most recent histopathological classifications of thyroid cancer have characterized the variants of PTC (1,31). The CV-PTC and the FV-PTC, the most frequent variants, are characterized by an indolent course and an excellent prognosis (5,6,18,32). Conversely, the TCV-PTC, the hobnail and the columnar subtypes are characterized by a more aggressive behavior (18,33). Data about the prognosis of SV-PTC are controversial (20,34,35). Neither ultrasound nor FNAB can identify the more aggressive PTC variants among TIR3B, TIR4 and TIR5 cytology (30).

In the present study we first linked 1668 consecutive histopathological records with the cytological and ultrasound features of the nodules of 1117 patients-who had undergone thyroidectomy

in 2017. We then aimed to characterize the ultrasound pattern that could differentiate benign from malignant nodules and help identify the most aggressive variants of PTC.

As expected, of benign nodules, many had been diagnosed as TIR2. The relatively high percentage of TIR2 and TIR3A observed among carcinomas was likely due to the inclusion in our cohort of patients who were advised surgery because of clinical or ultrasound suspicious features.

Most tumors were PTC, NIFT-P or FTC, whereas the more aggressive PDTC and ATC were rare. Therefore, conservative surgery as the first-line treatment for thyroid carcinomas, proposed by the latest guidelines, is justified by the prevalence of indolent tumors. Furthermore, the diagnosis of PDTC and ATC is not challenging because they usually present with the clinical features of aggressive tumors.

Among the PTC, the most common sub-type was the CV-PTC, which is characterized by pseudoinclusions, large size nuclei, membrane thickening, empty appearance of the nucleoplasm, grooves or the prominent organization in papillary structures (4). The TCV-PTC, the most frequent aggressive subtype of PTC, was also mainly diagnosed as TIR4-5. This result is in agreement with previous studies showing an association between cytological categories and adverse histopathologic features (36,37).

The FV-PTC as well as the FTC and NIFT-P had been mainly classified as TIR3A or TIR3B. Indeed, the cytological diagnosis of the FV-PTC is challenging because it lacks the typical nuclear features of the CV-PTC (4,29). At variance with two small previous studies reporting TIR4 and TIR5 as the predominant categories, in our series most SV-PTC had been diagnosed as TIR3A or TIR3B (38,39).

PDTC had been mainly diagnosed as TIR3A or TIR3B, in agreement with a previous small series, showing that PDTC shares cytomorphological features with follicular neoplasm (40).

We tried to identify ultrasound features that could differentiate benign from malignant nodules and the more aggressive histotypes and variants. Regarding TIR3B nodules, the only feature differentiating benign from malignant nodules was the irregular margins found in the latter. The ultrasound did not help differentiate SV-PTC from FV-PTC.

We observed that the coexistence of irregular margins and a hypoechoic pattern with absent microcalcifications was more common in TCV-PTC than in CV-PTC. This finding could be due to the

lower percentage of papillary structures and psammoma bodies observed in the TCV-PTC compared to the CV-PTC (41,42). Psammoma bodies correlate with microcalcifications at ultrasound and are typical of the CV-PTC (43). Although some studies reported that the ultrasound features identified in the CV-PTC are also present in the more aggressive variants of PTC, in another study investigating a small cohort of patients, microcalcifications were more common in CV-PTC compared to TCV-PTC, which in turn showed more frequently irregular margins (44–47).

In conclusion, according to the data extensively reported, in our cohort the PTC was by far the most common thyroid carcinoma, followed by the NIFT-P and the FTC, whereas the most aggressive histotypes (PDTC and ATC) were rare. Most FTC and NIFT-P had been classified as TIR3. At variance, the cytological classification of PTC differed according to its variants, the CV-PTC being diagnosed as TIR4 or TIR5 and the FV-PTC mainly as TIR3. Of the aggressive histotypes, the ATC, TCV-PTC, columnar and hobnail had been mainly diagnosed as TIR4 or TIR5, whereas the PDTC and the SV-PTC had a TIR3 cytology. Microcalcifications, a hypoechoic pattern and irregular margins, the ultrasound features usually correlated with malignancy, are typical of the CV-PTC. Among TIR3B nodules, irregular margins regardless of hypoechoic pattern and microcalcifications were associated with malignancy. We were not able to identify ultrasound features typical of the SV-PTC. The ultrasound pattern characterized by the hypoechogenicity, irregular margins and no microcalcifications is more frequent in TCV-PTC than in CV-PTC.

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Data Availability: data generated and analyzed during this study are included in this published article or in the data repositories listed in References.

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LEGEND OF TABLES

Table 1. Main clinical and histological features of 1117 patients who underwent thyroidectomy, for a total of 1668 nodules.

Abbreviations: PTC, Papillary thyroid carcinoma; FTC, Follicular thyroid carcinoma; NIFT-P: noninvasive follicular thyroid neoplasia with papillary-like nuclear features; PDTC, Poorly differentiated thyroid carcinoma; ATC anaplastic thyroid carcinoma; MTC medullary thyroid carcinoma. Others: 1 solitary fibrous tumor and 3 B-cell lymphomas.

Table 2. Cytological and ultrasound features of benign and malignant nodules

Ultrasound was available in 720 benign and 390 malignant nodules. + Results of cytology are reported according to the 2014 Italian consensus for the classification of Thyroid cytology. ++"No microcalcifications" include macrocalcifications.

Table 3. Ultrasound patterns of benign and malignant nodules classified as TIR3B

Patterns were defined according to the presence (+), absence (-) or independently (±) of the ultrasound features. Ultrasound was available for 75 benign (B) and 77 malignant (M) nodules that had been classified as TIR3B. The number of benign and malignant nodules with the p value for each ultrasound feature and pattern are reported.

Table 4. Ultrasound patterns of classic and tall cell variants of PTC

Patterns were defined according to the presence (+), absence (-) or independently (±) of the ultrasound features. Ultrasound was available for 135 classic (CV) and 28 tall cell (TCV) variant PTC. The number of CV and TCV of PTC with the p value for each ultrasound feature and pattern are reported.

LEGEND OF FIGURES

Figure 1. Distribution of cytological classes in 650 thyroid carcinomas according to histotypes.

PTC: papillary thyroid carcinoma; FTC: follicular thyroid carcinoma; NIFT-P: noninvasive follicular thyroid neoplasia with papillary-like nuclear features; PDTC: poorly differentiated thyroid carcinoma; MTC: medullary thyroid carcinoma; others: solitary fibrous tumor, B-cell lymphomas

Figure 2. Distribution of cytological classes in 514 papillary thyroid carcinomas according to variants. CV-PTC: classic variant; TCV-PTC: tall cell variant; FV-PTC: follicular variant; SV-PTC: solid variant; other aggressive variants: columnar and hobnail variants.

Patients (n. 1117)	
Mean age (years)	49.75± 5.3
Sex • Female (%) • Male (%)	 813 (72.8) 304 (27.2)
Thyroidectomy • Hemi- • Total	 145 (13.0) 972 (87.0)
Histological features (n. 1668)	
• Benign (%) • Malignant (%)	1018 (61.0) 650 (39.0)
Histotype (n. 650) (%) • PTC • FTC • NIFT-P • PDTC • ATC • MTC • Others [+]	 514 (79.1) 50 (7.7) 11 (1.7) 52 (8.0) 3 (0.4) 16 (2.5) 4 (0.6)
PTC variants (n. 514) (%) • Classic • Tall cell • Follicular • Solid • Columnar • Hobnail	 249 (48.4) 49 (9.5) 167 (32.5) 34 (6.6) 9 (1.8) 6 (1.2)

Table 1.

Cytological features [+] (n. 1668)		Benign	Malignant	p value
• TIR 1 or TIR 1C	151 (9.0)	123	28	< 0.001
• TIR 2	606 (36.3)	573	33	< 0.001
• TIR 3A	328 (19.7)	198	130	0.78
• TIR 3B	260 (15.6)	115	145	< 0.001
• TIR 4	148 (8.9)	9	139	< 0.001
• TIR 5	175 (10.5)	0	175	< 0.001
Ultrasound features (n. 1110)		Benign	Malignant	p value
Echogenicity (%) • Hypoechoic • Cystic, iso- or hyperechoic	 475 (42.8) 635 (57.2)	 230 490	 245 145	 < 0.001
Irregular margins (%)				

• Yes	158 (14.2)	71	87	
• No	952 (85.8)	649	303	< 0.001
Microcalcifications (%)				
• Yes	224 (20.2)	107	117	
• No[++]	886 (79.8)	613	273	< 0.001

Table 2

Hypoechogenicity	Microcalcifications	Irregular Margins	B vs M (n.)	p value
+	±	±	40 vs 45	0.62
±	+	±	12 vs 15	0.67
±	±	+	1 vs 8	0.03
+	-	-	30 vs 31	1.00
-	+	-	3 vs 3	1.00
-	-	+	0 vs 3	0.25
+	+	-	9 vs 10	1.00
+	-	+	1 vs 3	0.62
-	+	+	0 vs 1	1.00
+	+	+	0 vs 1	1.00
-	-	-	32 vs 25	0.24

Table 3.

Hypoechogenicity	Microcalcifications	Irregular Margins	CV vs TCV (n.)	p value
+	±	±	97 vs 23	0.37
±	+	±	67 vs 11	0.43
±	±	+	46 vs 14	0.17
+	-	-	36 vs 6	0.73

-	+	-	10 vs 1	0.69
-	-	+	4 vs 0	1.00
+	+	-	26 vs 3	0.41
+	-	+	11 vs 7	0.02
-	+	+	7 vs 0	0.60
+	+	+	24 vs 7	0.39
-	-	-	13 vs 4	0.49

Table 4.

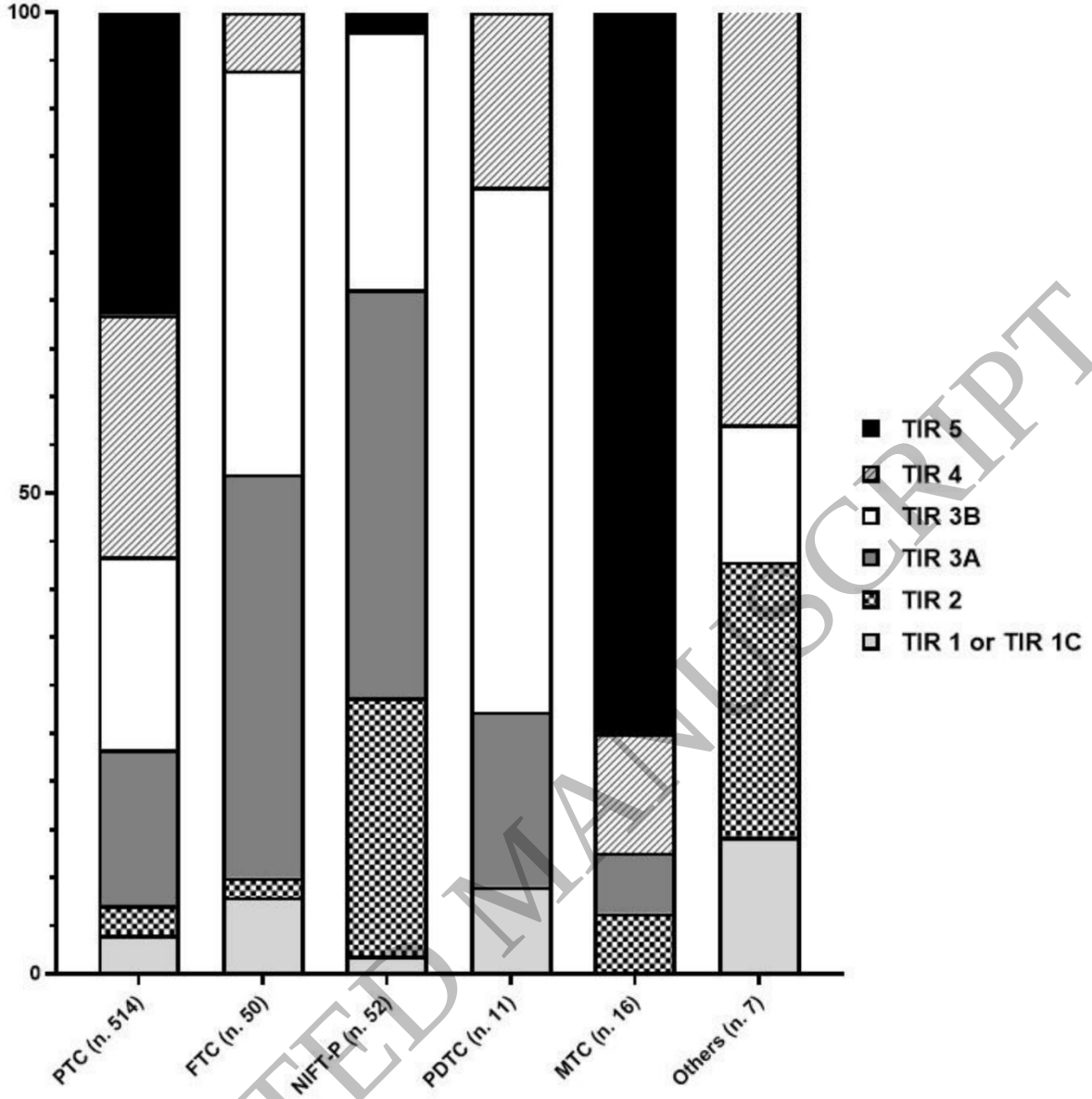

Fig.1

Figure 1
165x175 mm (x DPI)

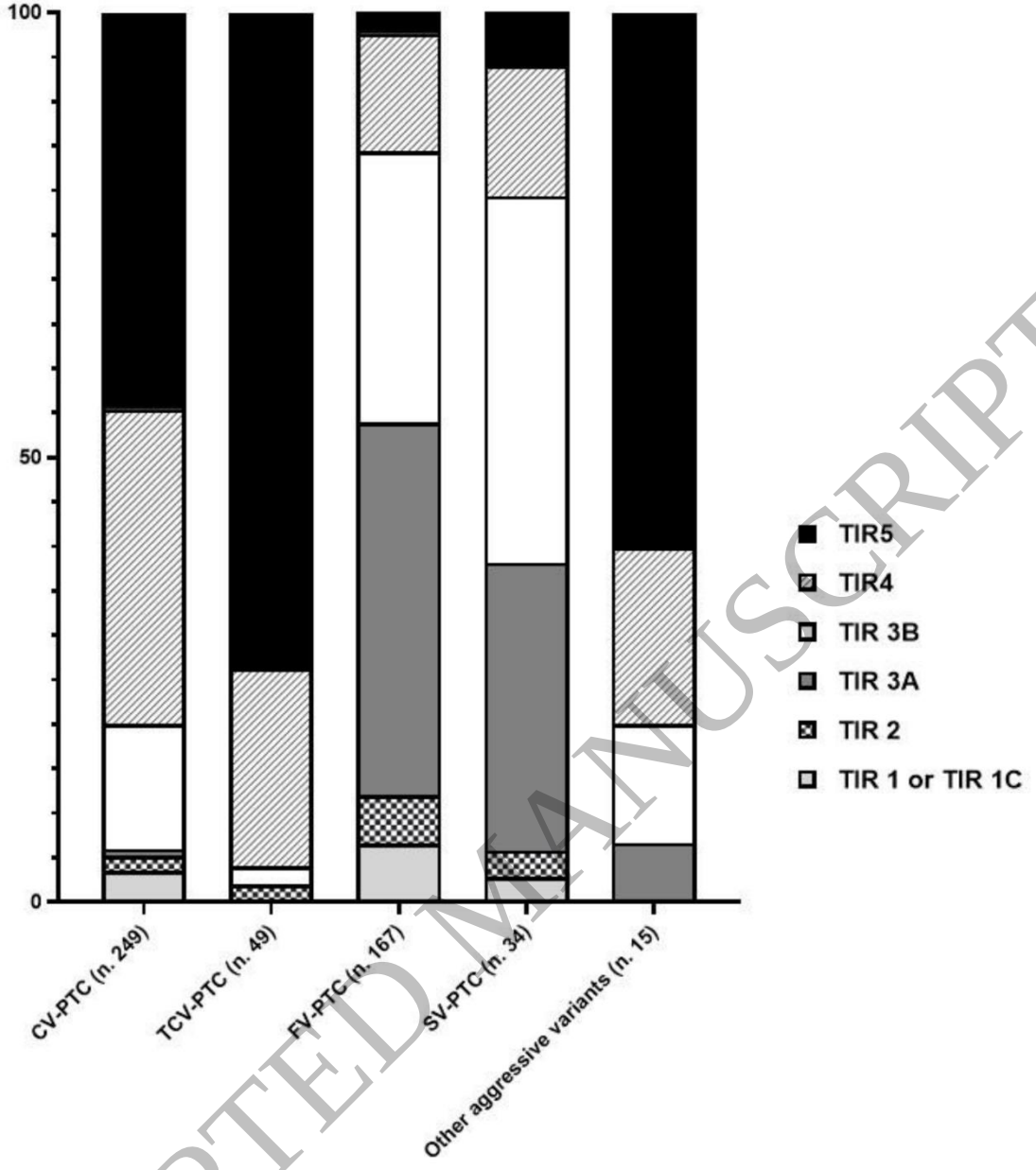

Fig.2

Figure 2
154x180 mm (x DPI)