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ORIGINAL ARTICLE

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Prognosis of patients with differentiated thyroid carcinomas having a preoperative cytological report of indeterminate at low or high risk. A multicenter study

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Abstract

Background Italian cytology system for thyroid fine-needle aspiration (FNA) includes indeterminate lesions at low- (Tir 3A) and high-risk (Tir 3B). The present retrospective multicenter study was undertaken to compare the histological type of cancers and disease-free survival in these two groups.

Methods Eight institutions participated. Thyroid cancer patients diagnosed and followed-up after Tir 3A or Tir 3B were reviewed. Histological diagnosis was adopted as the gold standard. Patients were defined with cancer recurrence or no evidence of disease. Disease-free survival (DFS) was calculated. A non-parametric statistical analysis was used. DFS was estimated by Kaplan–Meier method and Hazard Ratio (HR) defined the slope of curves.

Results Two hundred and nine patients (median DFS 24 months) were enrolled and a 6.3% of these recurred. Tir 3B group had higher age ($p = 0.014$), larger cancer size ($p = 0.0002$), shorter DFS ($p = 0.003$), higher number of aggressive cancers ($p = 0.006$), and relapse frequency double than Tir 3A. At survival curves analysis, Tir 3B group had HR of 2.37 with respect to Tir 3A. At Cox's proportional hazard regression analysis histology was the only significant predictor of relapse.

Conclusions While patients with thyroid FNA of Tir 3B should be addressed to surgery due to high likelihood of more aggressive cancer, a diagnostic surgery could be avoided in patients with Tir 3A if concurrent unsuspicious clinical features are found.

Keywords Fine-needle aspiration (FNA) · Indeterminate nodules · Thyroid · Carcinoma · Follow-up

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Introduction

Fine-needle aspiration (FNA) cytology is recognized as the main tool for evaluating thyroid nodules, being it essential to diagnose malignant lesions [1, 2]. Unfortunately, the indeterminate reports, usually represented by follicular lesions, limit thyroid FNA accuracy. These FNA reports occur in up to 20–25% of various institutional series and only one in four of these nodules is expected to be a cancer at histology. Then, preoperative identification of indeterminate nodules with lower risk represents a major challenge in clinical practice [3]. To better discriminate indeterminate nodules at high risk of malignancy and requiring surgery from those at low risk to be followed-up clinically, international societies published their guidelines for reporting thyroid cytology and estimating the risk of malignancy of a nodule [4]. Initially, the British Thyroid Association (BTA) proposed the subclassification of indeterminate category into Thy 3a (where "a" means atypia) and Thy 3f (where "f" means follicular) [5]. Later, the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) introduced the subcategories of AUS/FLUS (atypia of undetermined significance/follicular lesion of undetermined significance) and FN/SFN (follicular neoplasm/suspicious for a follicular neoplasm) [6]. Also, the Italian consensus for the classification and reporting of thyroid cytology (ICCRTC) included Tir 3A (low risk) and Tir 3B (high risk) [7]. The latter system was published after BTA [5] and TBSRTC [6] and was based on that previous experience. In ICCRTC Tir 3A is defined as "*increased cellularity with numerous microfollicular structures in a background of scant colloid*" and includes nodules with cytological or architectural changes (i.e. not atypia suspicious for papillary carcinoma) and compromised specimens (by smearing artifacts or blood contamination), while Tir 3B is defined as "*high cellularity in a monotonous microfollicular/trabecular arrangement with scant or absent colloid*" and includes cases with "mild/focal nuclear atypia" (cytological atypia). This choice of putting not only follicular patterned lesions (such as FN/SFN of TBSRTC), but also cytological alterations in the high-risk category aimed to better stratify the malignancy risk in a crescent scale among categories [7]. As a proof of concept, a meta-analysis found a highly significant difference between Tir 3A and Tir 3B in terms of prevalence of malignancy [8]. Also, another meta-analysis on a larger number of indeterminate nodules showed that Tir 3B is associated with a significantly higher risk of malignancy than Tir 3A [9]. These findings are encouraging for all users of ICCRTC, being Tir 3B nodules more likely to undergo surgery and Tir 3A lesions to be selected for clinical follow-up.

What we do not know until now is which cancer types should be expected in a nodule cytologically classified as Tir 3A or Tir 3B; also, we have no information about the post-treatment follow-up of carcinomas with preoperative FNA report of Tir 3A or Tir 3B. Based on TBSRTC [6] data, follicular neoplasm diagnosis identifies a larger proportion of follicular thyroid cancer than do other cytological reports [10]. To know whether cancer's outcome found in the two indeterminate subcategories of ICCRTC is different or not can have a significant impact on the clinical practice; in fact, clinicians could manage these patients by addressing them to surgery or clinical follow-up. Thus, the present multicenter study was undertaken to answer the above relevant question. Accordingly, primary end-point was to analyze the histological type of cancers found in the group of nodules with preoperative Tir 3A and Tir 3B; secondary end-point was to compare the disease-free survival in the two groups.

Material and methods

Study design and patients' selection

Eight institutions participated in the present retrospective multicenter survey, seven from Italy and one from the Italian speaking region of Switzerland. The study design included that the medical records of all thyroid cancer patients diagnosed after an indeterminate FNA as Tir 3A or Tir 3B, treated and followed-up at participating centers were reviewed to extract a standardized dataset. As the main inclusion criterion, the institutions searched in their database all nodules cytologically classified during the clinical practice as indeterminate according to 2014 version of ICCRTC and having a final histological diagnosis after surgery. Only patients undergone total thyroidectomy and radioiodine could be included in the study. Nodules with pre-surgical indeterminate FNA and a final benign histology with incidental cancer in another nodule were excluded from the study. Nodules classified as indeterminate before the introduction of 2014 ICCRTC were not enrolled in this study. All patients finally included were screened to analyze their follow-up after therapy, and their data (i.e. no evidence of disease, or evidence of structural disease and when) were recorded.

Reference standards of the study

Histological diagnosis was adopted as the reference standard to identify the cancers. Histology of neoplastic lesions was reported in agreement with the current Edition of WHO for endocrine tumors [11]. Cases diagnosed before 2017 were revised to match the 4th Edition. Patients with cancer after histology were classified as alive with no evidence of disease (NED) if there was no clinical, imaging, or

cytological/histological evidence of disease. Patients who did not fulfill these criteria were classified as alive with disease; furthermore, patients with proven structural evidence of disease were considered as alive with structural recurrence (REC). The overall survival was calculated from the date of radioiodine ablation to the date of disease-related death. The disease-free survival (DFS) was calculated from the date of radioiodine ablation to the date of the last follow-up for NED patients or the date of relapse detection for REC patients.

Statistical analysis

A non-parametric approach was used for statistical analysis and continuous variables were reported in the text as median and 25th–75th percentiles. Mann–Whitney U was used to analyze differences between unpaired numerical variables in two groups of patients. Age at cancer diagnosis was analyzed as a continuous variable and as a risk factor when higher than 55 years according to the last version of the AJCC/UICC Staging System [12]. Comparison of frequencies was performed by chi-square or Fisher test, when indicated. DFS was estimated by using the Kaplan–Meier method and differences between curves were analyzed by log-rank or Mantel–Haenszel test. Hazard Ratio (HR) was used to define the slope of the survival curves. The Cox's proportional hazard model was performed in univariate and multivariate analyses to evaluate the effect over time of each potential predictor of cancer relapse (expressed as HR). The confidence intervals (CIs) were set at 95%. Statistical significance was set at $p < 0.05$. Statistical analyses were performed by GraphPad Prism version 7 (GraphPad Software, Inc., La Jolla, CA 92037 USA) or StatsDirect statistical software (StatsDirect Ltd; Altrincham, UK), when indicated.

Results

General results

During the study period, the mean surgical rate of all Tir 3A and Tir 3B nodules recorded at the eight institutions was 18.1 and 65.7%, respectively. A number of 239 thyroid cancers (median size 19 mm) from 239 patients (median age 48 years, median DFS 24 months) were finally enrolled in the present study (Table 1). These 239 patients underwent surgery because of FNA report of Tir 3A ($n = 77$) or Tir 3B ($n = 162$). Seventy-two (30.1%) patients were older than 55 years at the moment of diagnosis. At histology, 192 (80.3%) papillary carcinomas (PTC), 9 (3.8%) Hürthle carcinomas, and 38 (15.9%) follicular carcinomas (FTC) were found. During the follow-up after treatment 15 (6.3%) cancer relapses were observed. No patient died.

Table 1 Characteristics of the overall series of indeterminate cases and in two subgroups at low and high risk

	All cases ($n = 239$)	Tir 3A ($n = 77$)	Tir 3B ($n = 162$)
F/M	180/59	54/23	126/36
Age[a]	48 (36–58)	45 (32–53)	49 (38–61)
Age > 55 years	72 (30.1)	18 (23.4)	55 (33.9)
Size[a]	19 (14–28)	15 (14–19)	23 (15–30)
DFS[a]	24 (14–38)	28 (16–42)	22 (13–36)
REC	15 (6.3)	3 (3.9)	12 (7.4)

Gender was expressed as number

Age at diagnosis, size of lesion, and DFS were expressed as median and 25th to 75th percentile ranges

Age > 55 years and REC is reported as number (%)

Results of statistical analysis were reported in the text

F females, *M* males, *DFS* disease-free survival, *REC* patient with cancer relapse during follow-up Gender was expressed as number

[a]indicates variable in which there was a significant difference between Tir 3A and Tir 3B groups

Clinical features and histological characteristics

Main characteristics of the series were illustrated in Table 1. These features were compared between Tir 3A and Tir 3B subgroups. No significant difference was observed in gender ($p = 0.26$). Age was significantly higher in Tir 3B ($p = 0.014$). Cancers of the Tir 3B group showed significantly larger size ($p = 0.0002$). DFS was significantly shorter in patients of Tir 3B group ($p = 0.003$). Cancer persistence was almost double in Tir 3B group with respect to Tir 3A, even if this difference was not significant ($p = 0.44$). No significant difference was observed in frequency of patients older than 55 years ($p = 0.15$).

Histological characteristics were evaluated and the difference between Tir 3A and Tir 3B analyzed. Table 2 detailed the histological types recorded in the overall series of patients and in the two subgroups of Tir 3A and Tir 3B. Interestingly, a significant difference was observed in the distribution of histologies in Tir 3A and Tir 3B ($p = 0.008$). This was due to the follicular variant of papillary thyroid carcinoma which was significantly more prevalent in Tir 3A group ($p = 0.0004$); furthermore, more aggressive PTC subtypes (i.e. sclerosing variant PTC, tall cell variant PTC), insular carcinoma, Hürthle cell carcinoma, and FTC were significantly more frequent in Tir 3B group ($p = 0.006$).

Outcome over time (Kaplan–Meyer curves and Cox proportional hazard regression)

The Kaplan–Meier method was used to estimate the DFS of patients. As above mentioned, no patients of our multicenter series died during the follow-up after treatment. As shown in Fig. 1, Tir 3B group had a lower rate of DFS over time than Tir 3A group, while HR was positive but not

Table 2 Histological diagnoses recorded in the overall series of indeterminate cases and in the two subgroups at low and high risk

	All cases ($n = 239$)	Tir 3A ($n = 77$)	Tir 3B ($n = 162$)
PTC	84 (35.2)	23 (29.9)	61 (37.7)
PTC (FV)	97 (40.1)	44 (57.1)	52 (32.1)
PTC (SV)	8 (3.4)	2 (2.6)	7 (4.3)
PTC (TCV)	2 (0.8)	–	2 (1.2)
ITC	1 (0.4)	–	1 (0.6)
HTC	9 (3.8)	–	9 (5.6)
FTC	38 (15.9)	8 (10.4)	30 (18.5)

Histological types were reported as number (%)

Results of statistical analysis were reported in the text

PTC papillary thyroid carcinoma, *PTC (FV)* follicular variant PTC, *PTC (SV)* sclerosing variant PTC, *PTC (TCV)* tall cell variant PTC, *ITC* insular thyroid carcinoma, *HTC* Hürthle carcinoma, *FTC* follicular thyroid carcinoma

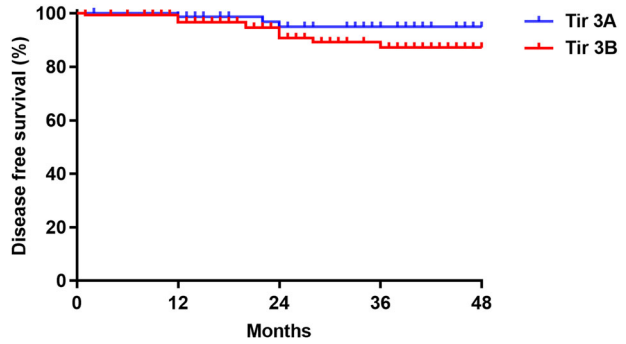

Fig. 1 Kaplan–Meyer curves of disease-free survival according to the preoperative cytological diagnosis

significant (2.37, 95%CI from 0.83 to 6.77). The Cox's proportional hazard regression analysis was done to determine the prognostic value of clinico-pathological factors (Table 3); in this univariate analysis, histology was the only significant predictor of relapse.

Discussion

Recently, the rate of malignancy among low-risk (Tir 3A) and high-risk (Tir 3B) indeterminate lesions according to ICCRTC was found significantly different in a meta-analysis including a large number of nodules and articles. Particularly, Tir 3A and Tir 3B had 17 and 47% cancer rate, respectively [9]. In addition, the analysis of OR of Tir 3B vs. Tir 3A found that the risk was significantly higher in Tir 3B. These data could justify different management strategies for the cytologically indeterminate cases. Actually, a surgical indication was significantly more frequent in Tir 3B lesions (65.9% of cases) than in Tir 3A (19.9%). This major

Table 3 Cox regression analysis of potential predictors of outcome of cancer over time

	HR	95%CI	*p*
Histology	3.08	1.03–9.21	0.04
Age	1.02	0.98–1.06	0.27
FNA report	1.43	0.38–5.42	0.60
Size	1.01	0.98–1.05	0.51

Histology and FNA report were analyzed as categorical variables (ie, aggressive histology vs. the other ones and Tir 3B vs. Tir 3A, respectively)

Age and size were analyzed as continuous variables

HR hazard ratio

propensity to surgical treatment for diagnosis was confirmed in the present multicenter series. It is worth to underline that a meta-analysis on the reliability of TBSRTC did not find differences between the category III and IV which were associated with a rate of malignancy of 27 and 31%, respectively [13]. Also, it was found a positive predictive value of 15.9% for AUS/FLUS and 26.1% for FN/SFN [14]. These differences in the malignancy risk between the two indeterminate subcategories in TBSRTC and Italian system should be due to the different interpretation of nuclear atypia which are included into AUS/FLUS (low-risk) and Tir 3B (high-risk) category. Two recent meta-analyses on studies using the TBSRTC evaluated the odds of malignancy of nuclear/cytologic atypia over the rate of malignancy of other types of atypia in aspirates with indeterminate cytology [15, 16]. Both studies found that the odds of malignancy were around 2.5-fold higher for aspirates with nuclear/cytologic atypia and suggested the need for standardizing the definition of nuclear atypia and identifying it in the cytology reports. These data support the decision of the ICCRTC of incorporating nuclear/cytologic atypia into the high-risk category (Tir 3B). An interesting discussion for clinical practice may be addressed. It was demonstrated that the prevalence of cancer among nodules with FNA report of Tir 3B is significantly higher than that of Tir 3A [8, 9]. Overall, thyroid cancers are not frequent in the indeterminate class, and the prognosis of malignant lesions with this preoperative assessment is generally good [17–20]. Also, a stability of indeterminate nodules managed with surveillance only was reported [21]. With the present study we raised two questions. First, do the subcategories Tir 3A and Tir 3B harbor histologically different cancers? Second, are post-treatment outcomes different in cancer patients with preoperative FNA of Tir 3A or Tir 3B?

As the first result of the present study, several clinical and histological differences were found between Tir 3A and Tir 3B. Patients of Tir 3A group were significantly younger and their cancers significantly smaller with respect to Tir 3B

ones. Furthermore, Tir 3B cancers included aggressive PTC subtypes (i.e. sclerosing and tall cell variant of PTC), and a higher prevalence of insular carcinoma, Hürthle cell carcinomas and FTC. Aggressive subtypes of PTC were not found in Tir 3A cases, supporting the ability of this category to identify more indolent lesion.

Second, we found a low rate of cancer persistence during follow-up and no death in this large multicenter series of patients. This result corroborates previous data [17–20]. As showed in the Cox regression analysis, final histology significantly predicted cancer relapse. As a relevant consequence of above findings, probably due to the higher rate of aggressive histology, DFS was found to be shorter in Tir 3B group. Finally, a different trend of NED rate over time was observed (Kaplan–Meyer curves) between Tir 3A and Tir 3B, and the cancer persistence/relapse rate was double in Tir 3B. The latter two differences were not statistically significant probably due to herein enrolled sample size. All in all, the indeterminate category of thyroid cytology includes a few cancers with recurrence after treatment; interestingly, ICCRTC is able to detect specific clinicopathological features in these cases. Present data, combined with previous ones [8, 9, 13, 17–20], encourage the more conservative approach (i.e. wait and see) in patients with low risk indeterminate FNA (Tir 3A) due to their high likelihood to carry benign lesions or indolent cancers. Our data also provide information of correct use of indeterminate cytological categories among different centers. The ability in differentiating cases to be categorized as Tir 3A and Tir 3B seems to be an acquired skill for cytopathologists in agreement with inclusion morphological criteria reported for such categories. This observation further supports the use of conservative management for Tir 3A nodules.

Limitations of the present study should be disclosed. First, a number of patients with preoperative indeterminate FNA but not subsequently operated were excluded from the present study. Second, to have a homogeneous series of differentiated thyroid carcinomas we selected those treated by radioiodine in addition to surgery while cases in whom radioiodine was not indicated (ie, microcarcinomas) were not included. Third, this is a multicenter study from eight institutions; then, even if these institutions managed patients according to ICCRTC, some differences might be present between different centers in terms of FNA indication, cytological assessment, management of indeterminate cases (in some institutions patients with Tir 3A report receive a second FNA), surgical approach (partial or total thyroidectomy), and indication for radioiodine. These issues might introduce some selection biases. Finally, the follow-up period was of up to 4 years because we included only patients operated upon after a nodule read as Tir 3A or Tir 3B during the clinical practice; this issue might influence the statistical analysis of Kaplan–Meyer curves.

Conclusions

Present data corroborate the different management proposed by ICCRTC. Patients with thyroid FNA report of Tir 3B should be addressed to surgery due to high likelihood of more aggressive cancer. In patients with Tir 3A a diagnostic surgery could be avoided especially when concurrent unsuspicious clinical features are found.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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