Review Article

Thyroid follicular microcarcinoma

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Abstract: Differentiated thyroid cancers are the most common malignancies arising in thyroid gland. Papillary thyroid cancer presents a very favorable prognosis, while follicular type is slightly more aggressive, mainly for its attitude to hematogenous spreading with distant metastases. Papillary microcarcinoma (10 mm or less) has an excellent prognosis, largely demonstrated, and its management is changed in the last few years, reducing surgical procedure, role of radio iodine ablation (RAI) and TSH suppression. But no effective data are available for follicular thyroid microcarcinoma (mFTC); very few reports and studies are present in literature about mFTC, mainly for its low incidence. Aim of this paper is to review current literature to reach, in absence of evidence, some suggestion in managing mFTC.

Keywords: Follicular carcinoma; follicular microcarcinoma; thyroid cancer; follicular tumor; thyroid neoplasm

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Introduction

Differentiated thyroid cancers are the most common malignancies arising in thyroid gland, deriving from thyroid follicular cells. Papillary histology is the most frequent, followed by follicular thyroid cancers (1,2).

Thyroid microcarcinoma (TMC) is defined as a tumor having 10 mm or less as maximum diameter, but some authors have extended this limit to 15 mm (3).

Incidence of TMC is rising in the last two decade, both for a real increased onset and increased ultrasonographic detection (4-6).

Most microcarcinomas arise from thyroid follicular cells and, again, papillary carcinoma and its follicular variant (FV) are absolutely the majority (mPTC, micro papillary thyroid carcinoma) (5). Large series studying mPTC are available, demonstrating its prognosis as excellent (5-8). But very few reports are available regarding follicular thyroid microcarcinoma (mFTC).

Follicular carcinoma has been clearly defined and it must have been distinguished from follicular adenoma and FV of papillary carcinoma (9).

mFTC is a very rare thyroid lesion (10). The rarity of this tumor is probably due to its own lower incidence in comparison to mPTC and to the lack of suspicious signs at ultrasonographic evaluation (such as absence of calcifications, marked hypoechogenicity, interrupted borders etc.), leading to less frequent cytological assessment by fine needle aspiration (FNA).

Moreover, definitive diagnosis of any follicular carcinoma needs the assessment of capsular or vascular invasion, so histological confirmation by very fine specimen section is needed (9).

Tumour diameter is an important risk factor for both papillary and follicular neoplasms, it is linearly related to extra thyroidal growth, node and distant metastases and, thus, to patient prognosis and disease-specific survival (11-13).

Actually no preoperative investigation is really effective on predicting malignancy in follicular neoplasms or follicular lesions, especially <10 mm in maximum diameter.

So, first surgical procedure is, usually, diagnostic thyroid lobectomy for a cytological founding of Bethesda III or IV nodule (13,14): completion total thyroidectomy and radio iodine ablation (RAI) is recommended in case of malignancy confirmation. But only a low percentage of patients will develop distant metastases and should need this kind of complete therapy (13).

Most frequently mFTC is diagnosed incidentally after thyroid surgery for other malignancy or other unrelated causes (3), so the question is "how to manage this tumor?" when the diagnosis is made post-operatively?

Follicular thyroid carcinoma (FTC) seems to be more aggressive in comparison to papillary thyroid carcinoma (PTC) with a poorer prognosis in terms of local recurrence and distant metastases occurrence and overall disease-specific survival; age at diagnosis, tumor size, widely invasiveness rather than minimally invasiveness and presence of distant metastases at the moment of first diagnosis are the main predictive factors (12,13,15). But no data are available for follicular microcarcinoma.

Some authors define mFTC like an indolent tumor (3), some other highlight its increased risk for local recurrences, lymph nodes involvement or distant metastases occurrence (12,16).

Preoperative diagnosis

In most cases the diagnosis obtained pre-operatively by FNA is suspicious for follicular neoplasm (Bethesda III, AUS/FLUS and Bethesda IV, Follicular Neoplasm or Suspicious for Follicular Neoplasm) and needs a histological confirmation. Thus, any effort to guide preoperatively surgical indication and the extension of surgical procedure is needed. Repeated FNA, core needed biopsy, ultrasonographic features, elastography, molecular tests and patients preferences are actually used to guide surgical decision making.

Core needle biopsy

Trimboli *et al.* (17) compared core needle biopsy (CNB) *vs.* diagnostic surgery showing that CNB was able to identify benign lesions in 42.4% of cases, malignant in 20.8%, leaving 36.8% with indeterminate result to diagnostic surgery. This procedure may avoid surgery in more than 40% of patients, saving complications and about 215,000 Euros every 100 patients.

Same Authors suggest that immunohistochemical (ICH) panel with galectin-3 + HBME-1 increases sensitivity and specificity from 79% to 100% and from 73% to 96%, respectively, when applied to CNB (18).

Na *et al.* studied 643 nodules diagnosed as AUS/FLUS at FNA, studying 158 of them both with repeated FNA and CNB; they found a significant higher rate of surgery decision in patients with follicular lesions (20.8% *vs.* 5.6%, P=0.007) and they concluded that CNB is significantly more useful than repeated FNA to make decision about surgery in this category of lesions (19).

US and elastography

A meta-analysis published in 2014 included 8 studies in the review, the majority of which was prospective; the sensitivity of real time elastography (RTE) ranged from 11% to 89% (pooled 69%), specificity from 6% to 100% (pooled 75%), accuracy from 35% to 94% (pooled 73%), with PPV and NPV of 63% and 82% respectively (20). The authors concluded that RTE should not be used for select which patients are candidate to surgery.

Garino *et al.* proposed an increased accuracy of RTE with a high NPV (94%) combining US suspicious features with elastography obtaining an OR for cancer up to 23.8 (P<0.0001), if two or more US signs were combined with significant RTE (21).

Ulisse *et al.* (22) published about improvement of surgical decision combining TI-RADS score with cytology classification (using SIAPEC - Italian Cytology Classification): TIR3A (AUS/FLUS) has a risk of malignancy of about 13%, while Tir3B (FN/SFN) has a risk of about 44%. A similar risk could seem high, but other casistic report similar findings, as Ho *et al.* (23) from MSKCC of NYC. Ulisse *et al.* found that TIR3A cytology combined with low TI-RADS score had a decreased risk of 8.3% to be a cancer; TIR3B nodules combined with high TI-RADS score had a significant increased risk of 80% to be malignant (P 0.001); they described an intermediate risk class composed both by Tir3A nodules + high TI-RADS score and TIR3B nodules + low TI-RADS score, with a 21.4% risk of malignancy. Similar conclusion are reported by Rosario who analyzed 150 patients (135 operated): he combined cytology with US suspicious or not suspicious features finding a 87% risk of malignancy when suspicious US findings were present in AUS lesions (46.6% in FLUS lesions) and decreasing the risk to 11.4% in AUS lesions when US was not suspicious (3.9% for FLUS lesions) (24).

For other Authors, as Chaigneau *et al.* TI-RADS score

has positive correlation only with Bethesda V nodules, so its usefulness in managing AUS/FLUS and FN/SFN nodules is poor (25).

Anyway it's important to underline that TI-RADS score features may be absent in follicular neoplasms (26).

Patient preferences and specific-factors

Correct patient information is crucial in managing Bethesda III and IV nodules. Actually, after being widely informed, patients can accept clinical observation for Bethesda III nodules and diagnostic lobectomy for Bethesda IV nodules, while some of them prefer to undergo only once to surgery, choosing total thyroidectomy rather than diagnostic lobectomy.

Lee *et al.* demonstrated that the preference of the patient is influenced by prognosis and risk of malignancy, and majority of patients choose surgery versus observation when malignancy risk is referred as over 38.6% (27).

Moreover, patient-specific factors can influence surgeon decision: the presence of contralateral nodes, hypothyroidism, history of neck irradiation, patient comorbidity, family history of thyroid cancer, nodal growth can be the strongest predictor of a total thyroidectomy, as shown by Angell *et al.* (OR 45.63; P<0.0001) (28).

Molecular testing

In a recent review and meta-analysis (29), based on 32 selected articles out of 522 initially retrieved, Jinih *et al.* described a high specificity of $BRAF^{V600E}$ (100% specificity) but a overall low sensibility of 40%, and falled to 21% in Thy3a subgroup. Three thousand and one hundred fifty indeterminate nodules underwent to surgery and 21.3% of them was positive for $BRAF^{V600E}$ mutation; 1,487 cancer were found and 44.5% was positive for $BRAF^{V600E}$ mutation. Histology was PTC in about 99.9% of all, with only one HCC and no FTC were found.

Kleiman *et al.* (30) studied 960 patients, of which 274 (28.5%) had a Bethesda III–IV nodule. Incidence in $BRAF^{V600E}$ mutation was present in only 3% of Bethesda III–IV nodules, rising to 42% in Bethesda V (P<0.001), with a sensitivity of 3% and specificity of 100%, PPV 100% and NPV 78%. Even in presence of cytological atypia sensitivity remains very low (sn 4%, NPV 86%). These results lead authors to conclude that $BRAF^{V600E}$ mutation preoperative screening cannot guide preoperative decision making in surgical strategy of indeterminate nodules. Similar results have been reported by Trimboli and colleagues (31) in a review and meta-analysis including 8 papers and 1,361 patients with indeterminate nodules, concluding that BRAF-analysis is not cost-effective.

RAS mutation is described in follicular neoplasms (32). Patel *et al.* (33) studied 2,590 patients with indeterminate cytology, finding RAS-positive nodules only in 3.6% of cases. Among patients who received surgical treatment, malignancy was assessed in 76% and most common cancer type was FVPTC (83%), PTC was 12%, poorly differentiated 3.5% and follicular carcinoma only in 1.5%.

Clinkscales *et al.* (34) found same results in a review and meta-analysis, extracting 1,025 patients from 7 studies; the pooled sensitivity was low (34.3%), pooled specificity 93.5%, PPV 78% and NPV 64%. They concluded that detection of RAS mutation alone ddoes not change surgical strategy.

Dedhia *et al.* (35) studied the influence of Afirma gene expression profiling (GEP), concluding that its use could influences surgical decision in less than 20% of cases and it could avoid surgery in only 7.2% of cases (6.2 if only follicular lesions and neoplasms are considered). Same conclusion has been reached by Noureldine *et al.* (36), collecting retrospective data of 273 patients with Bethesda III and IV nodules who received Afirma GEC testing. In this series histology was follicular or Hurtlhle cells carcinoma in 24.4% of patients; use of Afirma GEC examination would have change surgical planes in only 13.5% of patients.

Similar conclusions results were described by Harrell *et al.* (37), suggesting that its NPV is not so strong to be used in improving surgical decision making in Bethesda III and IV thyroid nodules.

Valderrabano *et al.* (38). analyzed the usefulness of oncogene panels (miRInform and ThyroSeq 2) applied in 193 patients *vs.* 456 patients studied without oncogene panel. Oncogene panel evaluation increased the odds to be treated with total thyroidectomy by 160% (P<0.001); but only 16% of the patient with positive panel had an intermediate- or high-risk cancer, so in 84% of cases a lobectomy could have been sufficient. If all indeterminate nodules had a diagnostic lobectomy, less than 10% would have required a completion thyroidectomy.

Differently, Nikiforov *et al.* (39) suggested that Thyroseq 2 should improve the management of indeterminate nodules, having a PPV significantly higher than Afirma; the study, however, had different limitations because the two panels were applied in two different cohort of patients; moreover, ThyroSeq study was performed in an unique

institution, while Afirma data came from 49 different clinical sites.

So there is no evidence, nowadays, that oncogene panel evaluation may be useful in changing surgical planes in patients with Bethesda III and IV thyroid nodules.

Literature

Megwalu *et al.* (40) retrospectively studied 203 patients operated between 1988 and 2009 with a final histologic diagnosis of mFTC, extracting data from 18 different database in USA. Total thyroidectomy was performed in 145 patients and lobectomy in 58 patients. Kaplan-Meier 5-year survival was 99% and 98% respectively, without significant difference, even after adjusting allocation bias. Authors conclude that total thyroidectomy does not give any advantage in comparison to lobectomy in terms of 5-year survival. But detection of distant metastases has to be carefully evaluated. It is well known that follicular carcinoma presents a higher risk, in comparison to PTC, for distant metastases (most frequently to lung and bones); this risk is actually unclear for mFTC.

Lobectomy may impair chance to detect distant metastases for impossibility to use serum thyroglobulin levels and investigation with whole-body scan.

So, if completion thyroidectomy is not chosen, alternative imaging modalities have to be used to monitor distant metastases occurrence.

Kuo *et al.* (41) described 371 patients with mFTC, treated between 1988 and 2009; the studied population included other 193 patients with Hurtle cells microcarcinoma (mHCC). These 564 mFHCC patients have been compared with 22,174 patients with mPTC.

The most relevant data is that mFHCC (studied as a unique group) had >8 times (11 times for mFTC alone) increased rate of distant metastases in comparison to mPTC (4.1% *vs.* 0.5%, respectively; P<0.001). Nodal metastases were significantly higher in mPTC in comparison to mFHCC (33.5% *vs.* 9.6%; P<0.001).

On multivariate analysis tumor size >7 mm was the only independent predictor of extra thyroidal local extension in mFHCC; age >65 (OR 9.40) and Asian race (OR 9.18) were independent predictors of distant metastases.

Regarding survival, follicular or Hurtle cell histology was an independent risk factor of reduced survival (hazard ratio 5.30; P<0.001); disease specific-survival was decreased in mFHCC group in comparison to mPTC at 5 years (89.7% *vs.* 99.6%), 10 years (95.4% *vs.* 99.3%) and 15 years (94.4% *vs.* 99%; P<0.001), even in small tumors.

Also in this report total thyroidectomy did not supply any advantage in comparison to lobectomy in terms of 10 years disease specific-survival (93.7% *vs.* 97.3%; P=0.523); same findings for RAI compared with no RAI (95.6% *vs.* 98.7%; P=0.097).

Comparing to mHCC, mFTC had a higher rate of distant metastases (5.4% *vs.* 1.6%, P=0.03), but no differences in disease-specific survival (P=0.783).

At multivariate analysis the presence of distant metastases is the most relevant factor predicting disease-specific mortality (hazard ratio: 12.86; P<0.001).

Other risks are related to different factors, such as nodal metastases (hazard ratio: 3.36; P<0.001) and extra thyroidal extension (hazard ratio: 4.63; P<0.001).

Clerici and colleagues (42) collected data from a survey in Germany but, when all cases were revalued, a diagnosis of mFTC was possible only in 4 cases out of 90 patients found, concluding that the real incidence of this specific histotype is very rare in Germany, Austria and Switzerland. On the other hand, diagnosis was wrong in most cases and about two third of these patients underwent to unnecessary completion thyroidectomy and L-thyroxine therapy; about 85% of patients received unnecessary RAI.

Siassakos *et al.* (3) reported about 29 incidental micro carcinomas (defining the limit at 15 mm in maximum diameter): surprisingly, mFTC were 62.1% of cases whereas mPTC were 34.5%. No mortality, recurrences or metastases are reported.

Probably most of malignancies described as follicular microcarcinoma were FV of mPTC.

Passler *et al.* (13) analyzed 403 patients with pT1 and pT2 PTC and FTC, dividing patients in three groups according to tumor diameter. Two patients with mFTC had distant metastases at diagnosis and one patient died for mFTC.

Statistically significant difference in cancer specific survival and in disease free survival according to 10 mm threshold has been demonstrated only for papillary histology (P=0.03 and P=0.02, respectively). This difference was not assessed for follicular histology, suggesting that also small tumors may have a bad prognosis.

Conclusions

Currently, malignancy in follicular neoplasm can be assessed only by histology; but only 20–35% of lesions or neoplasms diagnosed as follicular at FNA result malignant at definitive

histology. So two third of patients usually undergo to surgery for benign lesions. Risk factors (such as family history, neck irradiation, atypic at FNA and others), must be considered in surgical strategy. The impact of molecular testing in surgical decision making is still debated, especially for follicular lesions; after initials observations, many Authors reported a low sensibility (despite a high specificity) concluding that pre-operative detection rate of malignancy is low and not cost-effective. So most authors stated that nowadays molecular tests are insufficient in changing operative planning in indeterminate thyroid nodules.

Lower incidence of mFTC in comparison to mPTC may have more than one explanation. In last two decade increasing incidence of PTC and mPTC has been demonstrated, while the same increasing did not happen for FTC. Second: PTC has been largely studied in its ultrasonographic features and specific US risk features have been described, while follicular lesions often do not have these US characteristic of suspicious. Thus, third: PTC often is studied by FNA when is very small, lower than 10 mm. These factors lead to an early diagnosis of mPTC and, probably, to their over treatment. This is not possible for FTC: follicular lesions often appear at US investigation as isoechoic, very similar to normal gland parenchyma, so their visualization occurs (as compact nodules, without calcifications, with regular borders) when diameter is greater than 10 mm, maximum diameter to define carcinoma as micro. So, mFTC is mainly discovered as incidental malignancy after thyroid surgery done for different reasons.

It is crucial to underline that nodule size seems to be strictly related to local invasiveness and distant metastases, which are the strongest predicting factor for a poorer prognosis.

Regarding the extension of surgical treatment, ATA guidelines are clear for mPTC but not for mFTC. Authors are still discordant about the following strategy, because some assess that mFTC is quite indolent (like mPTC), some others assess that even small follicular tumor may present at diagnosis with distant metastases, correlating with a higher risk of cancer related mortality and poorer prognosis.

So correct surgical management of incidental microfollicular carcinoma has no consensus; prospective studies are difficult to be planned and performed, due to post-surgical diagnosis of this tumor and its rarity and only multicentric study could collect enough data.

Increased mortality in patient with mFTC in comparison to patient with mPTC (3.5% *vs.* 0.4%) was reported with a significantly decreased disease-specific survival at 5, 10 and 15 years (41); total thyroidectomy and RAI did not give any significant advantage in comparison to lobectomy in terms of survival (40,41), but retrospective nature of the study makes difficult the interpretation of these results. Moreover, follow-up is more challenging after lobectomy because thyroglobulin and WBS cannot be used, so alternative imaging technique should be used.

Anyway at the present moment, in presence of histological confirmation of follicular microcarcinoma, total thyroidectomy may be completed with RAI; if lobectomy has been the first procedure, at the moment common practice and experience may suggest prudential treatment by completion thyroidectomy and RAI, to treat unknown distant metastases and to allow a correct follow-up by thyroglobulin level and WBS.

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Footnote

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