Multidisciplinary approach for risk-oriented treatment of low-risk papillary thyroid cancer in Switzerland

Zulewski Henryk a, Giovanella Luca b, Bilz Stefan c, Christ Emanuel d, Haldemann Andreas e, Steinert Hans f, Weidner Sabine g, Oertli Daniel h, Triponez Frédéric i, Clerici Thomas j, Minder Anna k, Dettmmer Matthias l, Komminoth Paul m

a Division of Endocrinology and Diabetes, Stadtpital Triemli, Zurich, Switzerland
b Nuclear Medicine, Oncology Institute of Southern Switzerland and Competence Centre for Thyroid Diseases, Ente Ospedaliero Cantonale, Bellinzona, Switzerland
c Division of Endocrinology and Diabetes, Kantonsspital St Gallen, Switzerland
d Division of Endocrinology and Diabetes, University Hospital Basel, Switzerland
e Nuclear Medicine, Stadtpital Triemli, Zurich, Switzerland
f Interdisciplinary Thyroid Centre, Division of Nuclear Medicine, University Hospital Zurich, Switzerland
g Division of Nuclear Medicine and Division of Endocrinology and Diabetes, University Hospital Bern, Switzerland
h Clinic for Surgery, University Hospital Basel, Switzerland
i Clinic for Surgery, University Hospital Geneva, Switzerland
j Clinic for Surgery, Kantonsspital St Gallen, Switzerland
k Division of Endocrinology and Diabetes, Kantonsspital Liestal, Switzerland
l Pathology, University Hospital Bern, Switzerland
m Pathology, Stadtpital Triemli, Switzerland

Introduction

After the update of the American Thyroid Association (ATA) guidelines on diagnosis and treatment of patients with thyroid cancer in 2015 [1], it became evident that, for patients with low-risk thyroid cancer, these recommendations presented views on the requirement for adjuvant radioiodine therapy different from the recommendations of the European Thyroid Association (ETA) [2] and daily practice in Switzerland. In order to avoid offering differing treatment options to patients and thus potential uncertainties, it is important that physicians who take care of such patients have similar views on the matter. With the intention to find a common view on the management of patients with low-risk papillary thyroid cancer (PTC), a multidisciplinary working group was initiated by the Swiss Society for Endocrinology and Diabetes and endorsed by the Swiss Society for Nuclear Medicine and the working group of Swiss Endocrine Surgeons. The working group thus included the endocrinologists, nuclear medicine physicians, pathologists and endocrine surgeons who are authors of this report. The discussions started after a meeting at the Triemlihospital in Zurich on 11 May 2016 and were followed by various written exchanges of opinion during the preparation of a manuscript. The report presented herein is a summary of the meeting and the post-meeting discussions.

The care of patients with thyroid cancer is a wide area that covers presurgical management of thyroid nodules, the choice of the appropriate surgery and postsurgical care including radioiodine treatment. Our discussions focused primarily on the identification of patients with low-risk PTC and their initial treatment options.

Obtaining high-level evidence on patients with low-risk PTC is difficult because the disease progresses very slowly and controlled long-term studies lasting many years in thousands of patients are needed in order to acquire the necessary data. These trials are very difficult to perform. It is, therefore, not surprising that a substantial part of the evidence is based on retrospective and/or observational data. The need for long-term intervention and the actual quality of the data result in different opinions/strategies of the various involved stakeholders, which are also summarised in this article.

Endocrine perspective

The incidence of differentiated thyroid cancer (DTC) has increased in the past 20 years, which is primarily the result of the more frequent use of ultrasound imaging in the management of thyroid disorders. The higher prevalence is almost entirely due to the discovery of small PTCs of less than 2 cm. This observation had already been reported 10 years ago in the USA [3]. The most convincing association between increased use of thyroid ultrasound and increased incidence of small PTCs was reported recently from South Korea [4]. Here, the addition of routine thyroid ultrasound in patients who were screened primarily for other malignancies such as breast cancer led to a more than ten-fold increase in thyroid cancer incidence that was almost entirely due to the accidental discovery of small PTCs [4].
In Switzerland also, the incidence of thyroid cancer increased, although to lesser extent than in the USA, Italy or South Korea [5, 6].

For many years, patients with low-risk DTC were treated with total thyroidectomy, radioiodine treatment and thyroid stimulating hormone-suppressive thyroxine therapy. Various observational studies examined the impact of adjuvant radioiodine therapy in low-risk patients and found no convincing benefit [7–11]. Indeed, the disease-specific survival was excellent and similar with and without radioiodine treatment in these studies, with 99% disease-specific survival after 20 years [6]. Similarly, the tumour recurrence rate was comparable and was estimated to be 1 to 4% after 7 to 20 years of follow-up [11–13]. Although these were retrospective observational studies and different risk scores were used to define low-risk, their results were quite consistent. Concerns were raised regarding the long-term safety of radioiodine treatment in patients with low-risk DTC, and everybody can agree that unnecessary exposure to radiation should be avoided.

The increased incidence of mainly low-risk DTC, the lack of evidence for the therapeutic benefit of total thyroidectomy and of radioiodine therapy in these patients [7–11], as well as the safety concerns mentioned above thus prompted a reassessment of the management of patients with low-risk PTC.

This led to the new comprehensive recommendations released by the ATA in 2015 [1]. The definition of low-risk thyroid cancer according to the new ATA guidelines is given in table 1. As compared with previous guidelines (of the ATA and ETA), the new guidelines additionally describe the risk of structural disease recurrence in patients without structurally identifiable disease after initial therapy as a continuum based on various features including the number of microscopic lymph node metastases, vascular invasion and biological features of the tumour, but without defining a size limit for the primary PTC (fig.1).

**Surgeons’ perspective**

In view of the relatively low aggressiveness of differentiated PTC with excellent prognosis, surgical procedures may have to be weighed against the risk for surgical complications. The invasiveness of the thyroid surgery should thus match the presumed aggressiveness of the tumour.

Numerous studies have shown that in patients with isolated PTC, less invasive surgical procedures such as lobectomy had similar outcomes as total thyroidectomy regarding survival, but with significantly reduced complication rates, namely, reduced frequency of recurrent nerve palsy and reduced rate of permanent hypoparathyroidism [14–16].

The risk for local and distant metastases increases with increasing size of the PTC, especially if the tumour size ex-
thyroidectomy was performed, and from completion (less than 10 mm. In these cases, there is an overall evidence of lymph node metastases and the presence of a macroscopic lymph node metastases. In the absence of evidence of lymph node metastases.

The planning of the initial thyroid procedure should there- fore be risk oriented, based on the available preoperative data, especially ultrasound studies to detect potential macroscopic lymph node metastases. In the absence of macroscopic lymph node metastases and the presence of a unimodular PTC of 20 mm or less, a lobectomy could be justified. Given the higher risk of complications, such procedures should be limited to very experienced surgeons [18–22]. However, as there are no proven benefits concerning long-term outcome [21, 23–25] and most thyroid procedures in Switzerland are not performed by subspecialised surgeons, prophylactic lymph node dissection cannot be recommended as a standard procedure in patients with small a PTC without macroscopic evidence of lymph node metastases.

The planning of the initial thyroid procedure should therefore be risk oriented, based on the available preoperative data, especially ultrasound studies to detect potential macroscopic lymph node metastases. In the absence of macroscopic lymph node metastases and the presence of a unimodular PTC of 20 mm or less, a lobectomy could be sufficient and should be discussed with patient.

Table 1: Characteristics of a low-risk thyroid cancer according to the new ATA 2015 guidelines (adapted from [1]).

<table>
<thead>
<tr>
<th>Papillary thyroid cancer with all of the following:</th>
<th>All macroscopic tumour has been resected</th>
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<tbody>
<tr>
<td></td>
<td>Absence of local of distant metastases</td>
</tr>
<tr>
<td></td>
<td>Without tumour invasion of loco-regional tissues</td>
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<tr>
<td></td>
<td>No aggressive feature on histology (e.g., tall cell, hobnail variant, columnar cell carcinoma</td>
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<tr>
<td></td>
<td>If $^{131}$I is given, no evidence for radiodine-avid foci outside the thyroid bed on first post-treatment whole-body radiiodine scan</td>
</tr>
<tr>
<td></td>
<td>No vascular invasion</td>
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<tr>
<td></td>
<td>No clinical evidence for lymph node metastases or LVI with up to five micrometastases ($&lt;0.2$ cm in largest dimension)</td>
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</table>

Intrathyroidal, encapsulated follicular variant of PTC

Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal ($<4$ foci) vascular invasion

Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including BRAF mutation

Table 1: Characteristics of a low-risk thyroid cancer according to the new ATA 2015 guidelines (adapted from [1]).

In conclusion, since the literature cannot provide a basis for advice for or against current guidelines, further long-term follow-up studies are needed before recommendations to change effective clinical practice are accepted as standard of care.

Prospective randomised trials in Europe (ESTIMABL2, IoN) and South Korea (Clinical trial.gov identifier NCT01837745, NCT01398085, and NCT02418247) to assess the potential benefit of radioiodine ablation in low-risk patients are underway and first results will be available.
in ~5 years from now. As long as the results of such studies are still pending, it would be prudent to refrain from a strong position against \([131]\) as thus far the course of the disease with \([131]\) therapy has been so good.

**Pathologists’ perspective**

A critical element in the classification of PTC as low risk is its biology. For proper decision making, it is therefore important that the pathology results report all histological features of the cancer associated with its biology, as well as all information related to the Union Internationale Contre le Cancer (UICC) TNM cancer staging system. This should include the histological type of the primary tumour, whether it is encapsulated or not, the presence or absence of capsular and vascular invasion, and the number and size of lymph node metastases (if lymph nodes were removed). It is also important to note that the lesions formerly classified as the encapsulated follicular variant of PTC have been recently reclassified as so-called noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) in order to reduce overtreatment of indolent lesions \([28]\). The presence or absence of features associated with an adverse outcome such as tall cells, the columnar cell variant or the hobnail variant, and lymph or haemangio-invasion should be noted. These features are summarised and updated in synoptic reporting systems such as the one used by the College of American Pathologists (CAP). Such a system can be readily implemented in the Swiss situation and was recently introduced into the department of pathology of the University of Bern (see table 2).

Molecular testing of thyroid carcinomas for prediction of patient outcome is evolving rapidly; however, to date no single gold standard molecular marker has been identified. \(BRAF\) mutation testing is not routinely recommended because prognostic information is controversial in many different studies \([29–31]\). \(BRAF\) mutation testing may have a role in conjunction with molecular testing of TP53, \(AKT1\) or PIK3CA via a targeted NGS (next generation sequencing) approach, since these double mutant PTCs are more aggressive \([32]\). TERMT promoter mutations, on the other hand, can well be used as a prognostic marker – the drawback is that they are only found in a subset of about 7 to 8% of PTCs \([33]\).

**Discussion**

The current practice of total thyroidectomy followed by radioiodine therapy in patients with DTC started a long time before the advent of evidence-based medicine, in 1943 \([34]\, and was used thereafter with lifesaving effects for many patients with severe metastatic disease. The landmark publication by Mazzaferrri and Kloos on the treatment of patients with DTC, with 40 years of follow-up \([35]\, was an observational cohort study summarising data from more than 1500 patients and describing the beneficial effect of radioiodine therapy in patients diagnosed before availability of computed tomography or ultrasound. Similarly, the disputed studies that challenged the benefit of radioiodine therapy in patients with low-risk PTC have a very comparable level of evidence; they also were observational and retrospective.

All participants agreed on the general concept of risk-adapted treatment of patients with low-risk PTC. Many, however, felt very uneasy with the suggested definition of low-risk PTC in the new ATA guidelines, which did not include a size limit of the primary tumour (table 1), citing the association between tumour size and the risk for local and distant metastases, which showed that the risk for local extension of PTC increased significantly when the primary tumour exceeded 20 mm \([17]\).

Therefore, we agreed to limit the definition of low risk to those PTCs up to 20 mm in size, while acknowledging the general concept for the definition of low risk as outlined by the ATA. Thus, patients with a PTC up to 20 mm and without local extension of the tumour and without macroscopic evidence for lymph node metastases or other negative histological feature (such as hobnail or tall cell cancer, vascular invasion) can be considered as having low-risk PTC.

We may have to take into account that today patients, as well as their primary care physicians, are more informed than some years ago and that the ATA guidelines are widely published and discussed. Therefore we may have to discuss these guidelines and explain why our recommendations differ from those proposed by the ATA.

**Conclusion**

- In patients with low-risk PTC below 10 mm in size that was incidentally discovered after surgery, no further action is required (no completion thyroidectomy if lobectomy was the first surgical procedure and no radioiodine).

- For low-risk PTC as defined above and a size up to 20 mm a hemithyroidectomy should be the standard procedure without the need for routine ipsilateral prophylactic lymph node clearance and no completion thyroidectomy. Routine radioiodine treatment is not recommended. In these patients completion thyroidectomy should be recommended only if histological features representing higher aggressiveness should be seen in the definitive histological evaluation, requiring radioiodine ablation. As an exception, for patients who (after discussing the low but existing risk for recurrence) request maximal treatment another approach including completion thyroidectomy and radioiodine treatment can be appropriate as well.

- For patients with proven PTC on cytology and a primary tumour size of 21 to 40 mm we recommend a total thyroidectomy followed by radioiodine treatment.

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**Table 2: Proposed standardised reporting for differentiated thyroid cancer.**

<table>
<thead>
<tr>
<th>Diagnosis according to the TNM system (e.g., (pT2,pNx, L1, V0, R0))</th>
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<tbody>
<tr>
<td>Histological type: e.g., classical papillary thyroid cancer</td>
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<tr>
<td>Size of the tumour</td>
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<tr>
<td>Extrathyroidal extension</td>
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<tr>
<td>Complete resection?</td>
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<tr>
<td>Multifocal: yes or no</td>
</tr>
<tr>
<td>Tall cell variant: present, if yes how many cells (10% or more)?</td>
</tr>
<tr>
<td>Invasion in blood vessels and lymphatic vessels</td>
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<tr>
<td>Metastases in lymph nodes, if yes, how many are macro metastases and how may micro metastases (micro &lt;0.2 cm)?</td>
</tr>
</tbody>
</table>

- [125]
- [130]
- [28]
- [30]
- [31]
- [33]