

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

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### 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 with 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].

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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

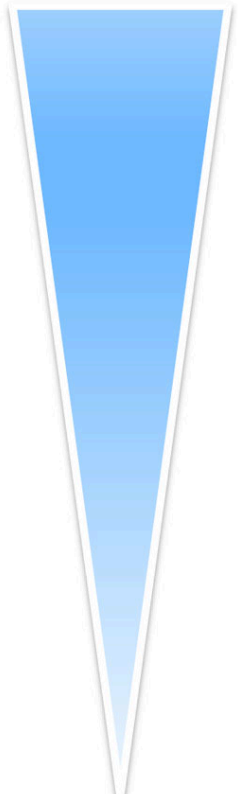
In view of the relatively low aggressiveness of differentiated PTC with excellent prognosis, surgical procedures may have to be weighed against the risk for surgical complications. The invasiveness of the thyroid surgery should thus match the presumed aggressiveness of the tumour.

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-

**Figure 1:** Description of the risk for structural disease recurrence as a continuum in differentiated thyroid cancer (adapted from [1]) in patients without structurally identifiable disease after first initial therapy.

Biological / clinical features	Estimated risk for structural disease recurrence
Follicular thyroid cancer with extensive vascular invasion	30-55%
pT4a gross extrathyroidal extension	30-40%
pN1 with extranodal extension, > 3 LN involved	40%
PTC >1cm, TERT mutated ± BRAF mutated	>40%
pN1, any LN >3cm	30%
PTC, extrathyroidal extension (ETE), BRAF mutated	10-40%
PTC, vsacular invasion	15-30%
Clinical N1	20%
pN1, >5 LN involved	20%
Intrathyroidal PTC, < 4cm, BRAF mutated	10%
pT3 minor ETE	3-8%
pN1, up to 5 LN < 0.2cm	5%
Intrathyroidal PTC, 2-4 cm	5%
Multifocal papillary thyroid microcarcinoma (PTMC)	4-6%
pN1 without extranodal extension, up to 3 LN involved	2%
Minimally invasive FTC	2-3%
PTC intrathyroidal, <4 cm, no BRAF wild type	1-2%
Intrathyroidal unifocal PTMC, BRAF mutated	1-2%
Intrathyroidal, encapsulated follicular variant PTC	1-2%
Unifocal PTMC	1-2%



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

Papillary thyroid cancer with all of the following:	All macroscopic tumour has been resected
	Absence of local or distant metastases
	Without tumour invasion of loco-regional tissues
	No aggressive feature on histology (e.g., tall cell, hobnail variant, columnar cell carcinoma)
	If <sup>131</sup> I is given, no evidence for radioiodine-avid foci outside the thyroid bed on first post-treatment whole-body radioiodine scan
	No vascular invasion
	No clinical evidence for lymph node metastases or LN1 with up to five micrometastases (<0.2 cm in largest dimension)
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	

ceeds 2 cm, as has been described in an observational study involving 366 patients with PTC [17]. This is the reason why it was decided at the thyroid cancer board meeting to limit the low-risk definition to a size of 2 cm or less, in contrast to the ATA guidelines where no formal size limit was set in the definition of low risk. The ATA guidelines also included in their risk assessment for PTC microscopic lymph node involvement and one could argue that without collection of lymph nodes use of such a criterion for proper risk estimation of PTC would be impossible.

In contrast to the ATA guidelines, we decided to limit the low-risk definition to the size of 20 mm. With a PTC of 20 mm or less, the risk for clinically relevant lymph node involvement is very low [17]. It is for this reason that we also do not recommend routine ipsilateral prophylactic clearance of lymph nodes. This recommendation does not, however, exclude exceptional cases such as familial forms of PTC or postradiation PTC, where a different approach, including total thyroidectomy and/or prophylactic clearance of lymph nodes, 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 uninodular PTC of 20 mm or less, a lobectomy could be sufficient and should be discussed with patient.

### Nuclear medicine perspective

For a long time, routine radioiodine ablation was an established standard of care in differentiated thyroid cancer (DTC) patients, an exception being the PTC microcarcinoma (less than 10 mm). In these cases, there is an overall agreement to refrain from radioiodine treatment if total thyroidectomy was performed, and from completion

surgery if lobectomy was the initial treatment and the diagnosis of the microcarcinoma an incidental finding.

According to the new ATA guidelines, radioiodine ablation on a routine basis in low-risk DTC patients is not recommended. This recommendation, however, was made in spite of the presence of conflicting observational data. In absence of <sup>131</sup>I administration, the adjuvant and *a fortiori* therapeutic goals of radioiodine will be lost in patients with unsuspected persistent metastatic disease foci after surgery. Only 2 out of 101 ATA 2015 recommendations were supported by a high level of evidence and the ATA guidelines were challenged by many other scientific societies owing to the observational character of the studies that were the basis for this recommendation and because such an approach had not been tested in prospective studies.

For example, a reduction of recurrences and better outcome are expected in patients with low-risk PTCs larger than 20 mm when radioiodine ablation is part of their treatment, and these differences are relevant for clinical decision making. Indeed, low-risk radioiodine ablated DTC patients with an excellent response can be safely considered cured. A minimal follow-up (clinical examination and thyroglobulin measurement) should be arranged every 1 to 2 years for such patients, thus increasing their comfort and saving resources.

On the other hand, the occurrence of non-thyroidal primary malignancies and the potential association with radioiodine treatment are important concerns in patients with DTC.

An increased incidence of second cancer has been reported after radioiodine treatment for thyroid cancer, but data were conflicting and a causal relationship may be difficult to establish [23–25]. An increased risk of second malignancies is definitely proved when cumulative exposures exceed 37 GBq (1000 mCi). It should be noted, however, that these levels are reached only in patients with advanced disease and a high risk of disease-related death. Additionally, the absolute risk for single patients remains low even in these cases, with standardised incidence ratios about 1.3 to 1.5 [26]. Notably, significantly lower activities (0.8–3.7 GBq [20–100 mCi]) are currently employed to ablate DTC in low-risk patients and recent studies concluded that the risk of a second primary malignancy is not increased in patients receiving these levels of radioiodine compared with those who did not receive radioiodine [27].

Notwithstanding, the risks and benefits of any treatment must be weighted and administration of radioiodine must be justified and optimised according to the ALARA (as low as reasonably achievable) concept. This a specific task of nuclear medicine physicians, as stated in national and international regulations.

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

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

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

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  $^{131}\text{I}$  as thus far the course of the disease with  $^{131}\text{I}$  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]. TERT 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 Mazzaferri 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.

**Disclosure statement**

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