EXPERT REVIEWS

Low-risk papillary thyroid cancer: times are changing

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The prevalence of papillary thyroid cancer (PTC), particularly of low-risk PTC (MACIS <6), is rising due to the increasingly use of neck imaging techniques, fine-needle aspiration and whole body PET scans. Observational cohort studies carried out in the last two decades suggest that low-risk PTC are being overtreated due to the current management paradigm being built on studies done in the 70s and 80s that still echo in some influential guidelines. With the progressive adoption of total thyroidectomy and central neck dissection as the mainstay of treatment for PTC, and suppressed basal thyroglobulin and neck ultrasound once a year as the essential tools for follow-up, the use of radioiodine ablation, body scans and stimulated thyroglobulin concentrations has become obsolete for the vast majority of patients with low-risk PTC. Future guidelines on the management of differentiated thyroid cancer should discuss separately three different diseases: low-risk PTC, high-risk PTC and follicular cancer.

KEYWORDS: de-escalating • management • new paradigm • papillary • thyroid cancer

Papillary thyroid cancer (PTC) currently represents over 80% of all thyroid malignancies [1]. It has an excellent long-term prognosis, with 1–3% disease-specific mortality and 10–20% recurrence rate at 30 years. Besides its particular biological behavior, the favorable prognosis of PTC is mostly due to the fact that around 80–85% of cases currently diagnosed belong to the low-risk category: they are small, often diagnosed in young individuals, intrathyroidal, completely resected and better staged and risk-assessed [2].

These facts cast doubts on the adequacy of current management protocols and guidelines – which are conceptually based on studies done in the 70s and 80s – that still advocate the routine use of radioiodine ablation, expensive thyroglobulin stimulation tests and repeated body scans. This Perspective article will present data that challenge the need for such high-intensity management and follow-up protocols. It also makes a plea for a definitive 'scientific divorce' between papillary and follicular cancers that, for reasons difficult to understand, continue to be dealt with together in articles, lectures and guidelines written on so-called differentiated thyroid cancer. A change of paradigm is needed to avoid overtreatment and unnecessary costs. It seems desirable that in the forthcoming years low-risk PTC patients be submitted to comprehensive specialized surgery, will no be ablated and will be followed once a year with basal thyroglobulin measurements (under less intensive suppressive therapy) and neck ultrasound.

This article describes a significant piece of the history of our current understanding of low-risk PTC from the critical and multinational point of view of an independent observer, with no conflicts of interest in this field and not associated with any of the leading institutions that have shaped our views on this fascinating variety of thyroid carcinoma.

The Mazzaferri's paradigm: the good, the bad & the ugly

The basis for a systematic approach to PTC was laid in the late 70s when the late Ernest Mazzaferri produced two seminal articles [3,4] that shaped our understanding of this disease for many years. These initial studies on PTC focused on retrospective observations made on a registry of patients treated 'by a number of different physicians in many hospitals' during the previous two decades. Despite inherent limitations of these initial cohort studies due to the heterogeneity of diagnostic and therapeutic approaches (**Box 1**), it could be established that PTC has a very low disease-specific mortality and identified three major variables influencing

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Box 1. Limitations of Mazzaferri's 1977–1981 studies on papillary cancer.

- Multi-institutional and registry based
- Heterogeneity of the surgical procedures
  - Different extension of thyroidectomy
  - Diversified approach to metastatic nodes
- High (13.5%) permanent hypoparathyroidism rate after total thyroidectomy
- Poor assessment and management of nodal metastasis
- Histology not reviewed
- Completeness of resection could not be ascertained
- No risk stratification applied
- Risk factors not investigated by multivariant analysis
- 70% of I^{131} treatments for 'definite' cervical metastasis

clinical outcome: the size of the tumor, the age of the patient and the presence of extrathyroidal invasion. They also revealed that patients undergoing less than total thyroidectomy had a higher risk of recurrence. Suppressive thyroxine therapy and I^{131} ablation had some positive influence in clinical outcomes. These findings led the path for the design of staging systems, protocols and guidelines that were implemented in the following two decades and helped to reduce the degree of treatment variability across institutions all over the world. According to the best evidence available in the early 80s, the ideal approach to all PTCs >1–1.5 cm, would consist of some variant of bilateral thyroid resection, radioiodine ablation, follow-up body scans and lifelong TSH suppression with thyroxine [5,6].

It is interesting to note that the subsequent introduction of thyroglobulin assays, the increasing performance and proficiency of neck ultrasound for the diagnosis of disease extension and recurrences, and the improved risk prediction in the mid-90s did scarcely impact on the management protocols built on the observational studies of Mazzaferri. Instead of leading to some de-escalating strategies for low-risk PTCs, the 2006 and 2009 ATA guidelines [7,8] have just added these new tools to the time-honored therapeutic armamentarium of routine radioiodine ablation, body scans and repeated thyroglobulin levels all under stimulation with recombinant TSH. The result of this cumulative strategy is the disappointingly outdated, complex, aggressive and expensive management algorithm put forward in the last version of the ATA guidelines that, in addition, continue to mix PTC with follicular carcinoma. It is unfortunate that these guidelines were eagerly disseminated worldwide by industry-sponsored national experts and endocrinological societies, promoting overtreatment of thousands of patients.

This high-intensity management paradigm uniformly applied to all thyroid differentiated carcinomas began to crumble down starting in the mid-90s for several reasons:

- Specialized surgeons started to implement improved and more comprehensive procedures to deal with PTC;
- Many patients undergoing had very low/undetectable basal thyroglobulin concentrations after adequate surgery, giving no reason for routine radioiodine ablation;
- Ultrasound have improved preoperative staging and have progressively replaced body scans for the diagnosis of recurrences;
- Risk stratification did mature thanks to more refined statistical methods and a large group of PTCs with excellent prognosis was identified independently of radioiodine treatment and aggressive follow-up strategies;
- Disclosure statements, published for the first time in the ATA 2009 guidelines, revealed a heavy financial involvement of almost all authors with rTSH producing pharmaceutical companies.

The surgical crisis: two decades on controversies

Many patients included in the early Mazzaferri's observations were obviously undertreated from a surgical point of view. Thus, it was no surprise that the best results in terms of recurrence and mortality were obtained with 'bilateral' thyroidectomy. This finding and the experience at leading institutions, led to the formal proposal of total thyroidectomy as the standard surgical procedure for differentiated thyroid cancer by expert endocrine surgeons at the end of the 70s [9–11].

The widely quoted Orlo Clark's article [10] in favor of total thyroidectomy for differentiated thyroid cancer, largely grounded his proposals on Mazzaferri's studies and on the author's own experience with just 82 total thyroidectomies performed for a variety of disorders including 45 patients with PTC. Actually, this paper dealt with the feasibility of total thyroidectomy with a low complication rate rather than on the long-term prognosis of PTC treated with this procedure. In this same article, multifocal disease, persistence of cancer at reoperation and recurrence after less extensive procedures, were put forward as additional arguments in favor of total thyroid resection. The discussion at the end of Clark's paper [10] reveals, however, that total thyroidectomy for PTC was not well received, the general opinion being that PTC was a quite benign malignancy that was not worth risking the inherent permanent complications of such an extensive procedure. The main exception was Norman Thompson, a strong advocate of total thyroidectomy for a variety of disorders [11], whose group had already gathered a quite impressive series of over 500 thyroid cancers treated with total thyroidectomy.

The controversy on the most suitable surgical procedure for PTC raged for over two decades particularly fuelled by the Memorial Sloan Kettering group conservative approach [12–14] and the ambiguous position of the Mayo Clinic team [15]. From then on, several facts have favored the wide adoption of total/near-total thyroidectomy for non-occult (T >1 cm) PTC:

- Specialized endocrine surgeons can now perform total thyroidectomy with low rates of permanent complications;
- A thyroid remnant will produce false-positive high thyroglobulin plasma levels that cannot be differentiated from cancer recurrence.
- If required, treatment with radioiodine is not possible if a whole thyroid lobe is left *in situ*;

- *In silico* studies of large PTC databases have reported better long-term results for total/near total thyroidectomy [16];
- Some 5–15% of all patients treated for PTC with lobectomy will eventually require a contralateral resection for recurrence;
- Papillary cancer recurrences mostly occur in the thyroid surgical bed and the regional lymph nodes [17].

Total thyroidectomy & more

A further step forward in the surgical management of PTC was taken by Scandinavian surgeons implementing paratracheal lymphadenectomy as part of the operation for PTC. Hoie *et al.* [18] reported a very reasonable 15% recurrence rate in 730 PTCs treated between 1956 and 1978 at a single Norwegian institution and followed for over 15 years without I^{131} ablation. Tisell *et al.* from Göteborg, Sweden, in their outstanding 1996 publication [19], emphasized the need for meticulous lymph node dissection, including the central neck compartment, and were able to keep recurrences and mortality to a minimum with only 12 (6%) of their 195 patients being treated with radioiodine: four for distant metastasis and eight for remnant ablation. They concluded that surgical technique and strategy do influence positively the survival of patients with PTC and were among the first to suggest that radioiodine therapy did not offer advantages to properly operated patients.

The proposal of routinely adding a paratracheal node dissection to total thyroidectomy for PTC was backed by endocrine oncologists [6] on the basis of its common involvement, hidden site for recurrence and difficult to detect with current imaging techniques. In addition, careful pathology studies on lymph node involvement in PTC have revealed that the central neck compartment is the most common site of nodal involvement at the time of initial surgery, even for microcarcinomas [20–22], and the preferred site for recurrence in patients treated with isolated total thyroidectomy plus radioiodine ablation [17]. Finally, recent data coming from either meta-analysis of current evidence or from cohort studies at leading institutions, suggest that prophylactic central neck dissection may reduce local recurrence rates [23–26].

Central neck dissection has had a major impact on surgical practice. Surgeons should now be fully conscious that some 30–40% of patients with PTC have macroscopic nodal involvement of the central neck nodes and that these must be removed at the time of initial surgery. No surgeon should trust on radioiodine to cure structurally evident disease in compartment VI. Thus, therapeutic central neck dissection has found its place as an accompanying surgical strategy to total thyroidectomy and is here to stay [8].

Currently, the controversy persists on the need to perform a prophylactic central compartment dissection in patients in whom no macroscopic lymph node involvement is detected at the time preoperative assessment by neck ultrasound nor at the time of surgery. Several observational studies have demonstrated that about half of these normally looking central compartment lymph nodes harbor metastatic papillary cancer [25–29] largely confirming the seminal work done by Noguchi *et al.* [30] that established that metastasis of PTC occurs first in the paratracheal nodes regardless of the location of the primary tumor. The literature on prophylactic neck dissection is massive and has mainly focused on the rate of early and permanent postoperative complications in relation to its potential long-term benefits in terms of preventing local recurrences [23,31]. Briefly, the pros and cons of adding a prophylactic neck dissection to total thyroidectomy are shown in Table 1.

The most common adverse effect of prophylactic central lymphadenectomy is temporary hypocalcemia that occurs two- to three-times more often than with isolated total thyroidectomy. Factors involved are accidental parathyroidectomy, the addition of thymectomy and the extension of surgery [26,32]. Thus, thymectomy should be avoided and central dissection should be limited to ipsilateral and pretracheal (subithsmic) lymph nodes [26,33,34]. Data provided by recent reviews suggest that there may be a small increase in the rate of permanent hypoparathyroidism [23,31]. Single unit cohort studies have reported discordant results [25,35–37].

Parathyroid risk increases according to the extension of surgery, even in the hands of dedicated teams [32,38–41]. Postoperative kinetics of PTH serum concentrations after thyroidectomy [36] have shown unequivocally that adding a nodal dissection to total thyroidectomy results in a more pronounced and long-lasting reduction of PTH concentrations. Our own experience suggests, however, that the majority of cases of permanent hypoparathyrodism are observed in patients with advanced PTC requiring therapeutic bilateral central neck dissection and thymectomy, often associated with a lateral modified radical neck dissection. Permanent hypoparathyroidism after prophylactic ipsilateral thymus preserving central neck dissection should be very uncommon, particularly if performed by experienced surgeons able to properly identify the parathyroid glands and preserve the thyro-thymic ligaments. The issue, however, remains open.

Similarly, the rate of permanent nerve injury does not seem to be increased after central neck dissection. The most recent meta-analysis [23] involving over 1700 patients did not find a higher rate of permanent recurrent nerve injury in patients undergoing prophylactic central nerve dissection when compared with patients undergoing total thyroidectomy alone.

From the oncological and follow-up strategies points of view, prophylactic central lymphadenectomy provides valuable information. First, it will upstage about a third of patients >45 years old, making them potential candidates for radioiodine ablation and/or more intensive follow-up [27]. Second, the number of involved central neck lymph nodes predicts the risk of future lateral recurrences [26,37]. In the study by Pereira *et al.* [26], no lateral recurrences were observed when less than six compartment VI nodes were positive, whereas 5/11 (45%) patients with more than five metastatic nodes developed a lateral neck recurrence despite they were all treated with radioiodine. Third, it may render more patients thyroglobulin and ultrasound negative after the initial surgical procedure [41,42].

Table 1. Pros and cons of prophylactic central neck dissection for papillary cancer.

For pCND	Against pCND
Subclinical central lymph node metastasis is common	Only a small proportion of subclinical central lymph node metastasis will develop clinically significant recurrences
Lymph node metastasis leads to higher recurrences and poorer survival	There is no level-one evidence to suggest that pCND could improve survival
Pre- and intraoperative evaluation of central compartment nodal metastasis is not reliable	Continuous improvement of imaging techniques
Can be safely performed in experienced hands	Majority of thyroidectomy are performed by low-volume surgeons
Improved tumor staging and stratification of tumors	Tumor upstaging leads to more radioiodine ablation which might not be necessary
Reduces the need for reoperation in central recurrence which is associated with greater morbidity	Operation in recurrent case could be safely performed by experienced surgeons
May reduce recurrence and lower postoperative thyroglobulin levels	Increased surgical morbidities (hypoparathyroidism and recurrent laryngeal nerve injury)

pCND: Prophylactic central neck dissection.

Briefly, central neck dissection associated with total thyroidectomy is gaining momentum as a comprehensive and optimized surgical approach to PTC. Patients with low-risk PTC treated in this way are in an excellent position for a low-intensity postoperative management and follow-up protocols.

Risk stratification

A major confounder in controversies around the best treatment for low-risk PTC is the concept of risk stratification. Although predictive models are important for all types of cancer, they seem particularly relevant for PTC because the vast majority of patients can be cured by surgery alone.

From the early days in the history of differentiated thyroid cancer, experts recognized the very favorable course of many patients with PTC [43,44]. Cady *et al.* [44] at the Lahey Clinic were indeed the pioneers of the concept of tailoring the aggressiveness of management to the risk of the tumor.

This concept, however, did not gain much popularity. Mazaferri was against the idea of risk stratification guiding treatment or follow-up of differentiated thyroid cancer on the following grounds [45]:

- They cannot predict recurrence;
- Male sex is not accounted for in risk classification;
- Tumor size is less reliable than histology;
- The variability of initial treatment;
- Only useful for epidemiological studies;
- They often mix papillary and follicular cancer.

Time has shown that some these arguments lack consistency while others have been overcome by improved predictive models. It is out of the scope of this article to review the different risk scores designed to predict clinical outcomes of differentiated thyroid cancer (most of them were meant to apply to both, PTC and follicular carcinomas). The MACIS score [46], however, deserves to be considered separately. It was developed from a cohort of 1779 patients with PTC treated at the same institution, many of them followed-up for over 20 years. It was the first score addressing the risk of death from PTC and has shown to be the one with the best predictive power. It has several methodological advantages over its predecessors:

- It includes the positive influence of completeness of resection, a new concept in risk assessment that would eventually replace that of extrathyroidal extension. Both the Mayo Clinic and the MSK group have confirmed that extrathyroidal extension will not jeopardize survival in patients <45 year provided the tumor is completely resected [47];
- It treats age and tumor size – the two most relevant prognostic factors – as continuous variables;
- It incorporates the presence of distant metastasis at diagnosis.
- It aims at predicting cause-specific death at 20 years;
- It identifies a group of patients with 99% 20-year survival (MACIS <6);
- It derives from PTC exclusively and does not include follicular cancer patients.

Lang *et al.* [48] carried out a comprehensive literature review of risk scores for differentiated thyroid cancer and applied 14 of them to 589 PTCs treated at their institution. The best performing scores were the EORTC, the TNM and MACIS. The authors conclude that the MACIS score "is the most predictive staging system and so should be the staging system of choice for PTC in the future." This is no surprise since the EORTC was designed for all types of thyroid cancer [49] and the TNM classifies the vast majority of PTC patients in stage I.

There are other variables that may affect the prognosis of PTC but they occur infrequently or do not add significantly to the predictive ability of the MACIS score. The presence of large (>3 cm) metastatic lymph nodes [50] or the extracapsular invasion of involved lymph nodes [51,52] – often associated with

large primary tumors – have been shown to increase the probability of tumors persistence and disease progression. Some uncommon histological variants of PTC [53] are also associated with a worse postoperative course. Angioinvasion has been identified as a poor prognosis variable but this probably results from the angioinvasive PTCs being larger than non-angioinvasive PTCs [54]. BRAF mutation is considered by some a risk factor for PTC progression, but this remains controversial since the effect of this molecular marker on mortality is not independent and remains linked to conventional demographic and tumor-related variables. The largest study published so far has been unable to confirm a significant association between BRAF V600E with most clinicopathologic features of more aggressive disease [55]. In the future, however, basic research may characterize other molecular mediators that may be relevant for the diagnosis of PTC and for target-oriented chemotherapy in advanced cases. It is unlikely, however, that these can be on any benefit for low-risk patients.

The Ian Hay/Mayo Clinic de-escalating program

Using the MACIS score as a conceptual guideline for risk assessment, the Mayo Clinic group has pioneered new strategies to de-escalate the management protocols applied to low-risk PTC. In the years that followed the proposal to use the MACIS score <6 to define low-risk PTCs, they critically reviewed the use of radioiodine ablation, defined the relevant role of thorough nodal assessment by preoperative ultrasound and put a special emphasis on a more comprehensive initial surgical treatment implementing total/near total thyroidectomy plus central neck dissection. From this author's point of view, they have succeeded in recent years in defining a rational, cost-effective approach to manage most patients with low-risk PTC [56] grounded in four main concepts:

- Abandoning routine postoperative radioiodine administration;
- Confirming the increasing role of neck ultrasound, and putting body scans in the second line of imaging techniques;
- Abandoning thyroglobulin stimulation;
- Emphasizing the surgical nature of low-risk PTC and the need for a comprehensive initial surgical procedure performed by an experienced surgeon.

Long-term prognosis & treatment with I^{131}

Initial evidence for the limited effect of radioiodine ablation came from Japanese large case series in which excellent recurrence and mortality rates were obtained without radioiodine ablation [57,58]. Japanese surgeons – as well as the Scandinavian groups previously cited – have traditionally relied on more extensive nodal dissection rather than on radioiodine administration to prevent recurrences; time has proved that they were correct. Already in the mid-90's experienced nuclear medicine specialists acknowledged that survival was not significantly different with or without I^{131} ablation where there were no distant metastases [59].

In 2006, Ian Hay critically reviewed the literature on radioiodine ablation and reported the experience at Mayo Clinic [60]. He concluded that radioactive iodine did not significantly improve the outcome of low-risk (MACIS <6 or Stage I) PTC patients treated initially with near-total or total thyroidectomy. In their large cohort of patients, no benefit of I^{131} treatment was observed even for node positive MACIS <6 PTCs.

An additional piece of information that indirectly speaks against the efficacy of radioiodine is that in both retrospective observational studies [61] and prospective trials [62], small versus high I^{131} dosages appeared equivalent in terms of clinical outcome. Because of the lack of a control group, this author feels that the interpretation of findings in both these studies is biased and that actually what happens is that high or low doses are equally ineffective. This does not rule out potential effectiveness in patients ablated after inappropriate surgical treatment or in patients with high-risk tumors. A recent systematic review of the literature available since 1966, does conclude that "a majority of very low-risk and low-risk patients, as well as select cases of patients with moderate risk do not demonstrate survival or disease-free survival benefit from postoperative RAI treatment, and therefore we recommend against postoperative RAI in these cases" [63]. Even the MSK Center group – that has fully supported the current ATA guidelines – has recently acknowledged that following appropriate surgical management, the majority of patients with low-risk disease, and even some patients with more advanced-stage (pT3) tumors or regional metastases, have low rates of recurrence and high rates of survival when managed without radioiodine ablation [64].

I^{131} ablation after surgical treatment of clinical recurrence is also questionable. Coburn *et al.* reported that the addition of I^{131} ablation to curative resection does not appear to improve survival [65]. These authors also emphasize that whenever structural recurrence is detected it would exceptionally be salvaged by radioiodine, an opinion that is currently shared by all experts in the field.

Patients not ablated with detectable-low Tg concentrations can be safely followed-up with neck ultrasound and careful observation for any rising trend of Tg serum concentrations until structural disease is detected and amenable for surgery.

Withering body scans, coming up neck ultrasound

Over 95% of recurrences of PTC take place in the neck [17,60]; less than 2% will ever develop distant metastasis. In fact, about half of patients with lung metastasis have already metastasized at the time of initial diagnosis [66]. Furthermore, so-called lymph node recurrences are, as a matter of fact, persistent disease undiagnosed at the time of the initial evaluation and surgical treatment. Thus, why are body scans still recommended for the follow-up of all PTCs [8,67]? One reason for this may be the obsolete proposal of including low-risk PTC, high-risk PTC and follicular carcinomas in a single follow-up strategy. Another one may be to encourage the repeated (but unnecessary) use of rTSH.

There is growing consensus that neck ultrasound, combined with basal serum thyroglobulin measurements, has become the more accurate follow-up strategy to detect local recurrences, has the advantage of delineating the anatomy of the recurrence and can obtain cytological proof through fine needle aspiration or biochemical proof through thyroglobulin determination in the aspirate. It is over a decade ago that experts claimed that ultrasound plus (stimulated) thyroglobulin is sufficiently sensitive to be used as the principal test in the follow-up management of low-risk PTC and that the routine used of diagnostic whole body scanning in follow-up should be discouraged [68]. Frasoldati *et al.* [17,69] have reported that ultrasound detects recurrences even in the absence of thyroglobulin elevation and negative body scans and that should be performed as the first-line test. This, however, does not appear to have been appropriately translated to the ATA long-term follow-up algorithm in which repeated body scanning still holds a relevant place.

Is thyroglobulin stimulation necessary?

According to the Mayo Clinic group, there is no convincing evidence that stimulated thyroglobulin has any advantage over non-stimulated thyroglobulin in the follow-up of low-risk PTC [56]. This opinion is currently shared by other authors [70–72] and has been reinforced by the use of the high-sensitive thyroglobulin assays. Rosário *et al.* [70] have reported compelling evidence that thyroglobulin stimulation can be avoided in low-risk PTC. They found that undetectable thyroglobulin on suppressive T4 treatment had a negative predictive value for metastasis of 92% that increased to 99% when combined with a neck ultrasound. Similarly, Melandrino *et al.* [72] reported a negative predictive value for recurrence of 98.6% for basal undetectable thyroglobulin serum concentrations. Thus, at present, a basal thyroglobulin under T4 and a neck ultrasound once a year should be considered the mainstay of follow-up for low-risk PTC.

Low-risk papillary cancer: a surgical disease

Medical management is losing momentum for patients with low-risk PTC. Almost all of them will be rendered disease-free if properly assessed at the time of diagnosis and subjected to a comprehensive initial surgical procedure. It is unlikely that this will be less than total/near total thyroidectomy and therapeutic or prophylactic central neck dissection [73]. The issue is well summarized at the end of Hay's 2006 review [60]: "patients with low-risk PTC have a very high chance of cure after adequate initial surgery and only levothyroxine therapy, and we would caution others that our 25-year cause-specific survival rate of 100% for 636 node negative MACIS <6 PTC patients treated by near-total or total thyroidectomy alone cannot be improved by remnant ablation."

Young patients with massive central and lateral neck nodal involvement will still challenge the surgeon although most of them still fall into MACIS <6, low-risk category. They are unlikely to benefit from radioiodine [60,64,74–77], and repeat surgery will be necessary in some 10–20% of them for recurrent lymph node metastasis [78]. A moderately conservative approach is warranted in these patients with mild and stable thyroglobulin elevations and dubious or <1 cm lymph node metastasis since small-volume local metastatic disease can be followed-up safely until definitive surgery can be properly planned [79]. Radiofrequency and percutaneous ethanol injection has been used with success in some of these patients [80].

TSH suppression

The current role of TSH suppression in low-risk PTC patients without residual disease is also under scrutiny. A large randomized trial has shown that disease-free survival in PTC (both high and low-risk) was similar whether patients were TSH suppressed or substituted [81]. A sensible approach would be to put low-risk patients in substitutive and not suppressive therapy immediately after surgery, and to put in a near-suppressive therapy (between 0.5 and 0.1 mcUI/ml) only the patients at high-risk for recurrence. In those with poorly differentiated tumors, suppressive or near-suppressive thyroxine therapy is useless. An additional reason for not suppressing TSH in patients without signs of residual disease is that it is probably more useful to measure sensitive thyroglobulin when TSH is not totally suppressed.

Expert commentary

There is very little chance that in the field of PTC, scientific progress will ever come from prospective randomized trials. PTC requires long-term control, has an excellent prognosis and, depending on the primary variable under study, the number of patients to be enrolled is far too high. As happened in the past, future changes in the clinical approach to PTC will most probably be based on careful observational studies of homogeneously treated cohorts in reputed institutions. The initial retrospective studies published in the late 70s were seminal to structure and delineate the most appropriate therapeutic approach for PTC at that time. They were also instrumental for the design of the first guidelines dealing with differentiated thyroid cancer. In the next 40 years, however, new evidence has been gathered suggesting overtreatment of the low-risk category of PTC; this calls for an update of the management guidelines: they should deal with papillary and follicular separately and consider the specific characteristics of low-risk PTC. De-escalating management strategies are already leading to less aggressive therapeutic and follow-up protocols reducing or abandoning whole body scans and TSH stimulation and restricting the use of radioiodine ablation. Emphasis has been given to a comprehensive initial surgical approach – performed by well-trained surgeons able to perform total thyroidectomy and lymph node dissection with low morbidity – since surgery is all that is needed for the vast majority of patients with low-risk PTC.

Five-year view

The prevalence of low-risk PTC will continue to rise due to early diagnosis and increased use of neck imaging techniques.

In some institutions, mean T size of all PTCs is currently below 2 cm [73]. Thus, new guidelines will be developed to specifically address the management of these patients. A simplified algorithm such as that recently proposed by Durante *et al.* [82] is a good example to follow. High-quality preoperative ultrasound will provide the surgeon the best 'road map' to undertake a radical surgical procedure [83] with appropriate handling of the parathyroid glands. pN1 patients will probably be subclassified not only according to the compartments involved but also according to the number and/or size of lymph nodes involved. Radioiodine will not be administered to the typical patient with MACIS <6 PTC – neither for 'postoperative remnant ablation' nor 'postoperative risk assessment' [84] – and will be restricted to patients with incomplete tumor resection, unfavorable histology or distant metastasis. Future guidelines should be free of intellectual and financial conflicts of interest in order to appropriately reflect scientific progress, avoid overtreatment and reduce follow-up costs [85]. An international effort should be made in order to unify concepts and avoid the 'continental' and even the 'national' guidelines contest, recently enriched with the German surgery perspective [86].

Future research in low-risk PTC will address some important issues that have been obscured by early postoperative ablation and TSH suppression such as: the rate of athyroglubulinemia that can be achieved by comprehensive surgery alone, the relationship between non-stimulated thyroglobulin values (or trend) and ultrasonographic finding and the influence of thyroxine therapy on thyroglobulin concentrations. Clinical research and guidelines on 'differentiated thyroid cancer' will clearly distinguish between follicular, low-risk and high-risk PTC, since they appear to be three quite different diseases. It seems unlikely that molecular markers of risk will be of any value for the management of low-risk PTC. Up to now they have fallen too short our expectations.

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Key issues

- Low-risk papillary thyroid cancer (PTC) (MACIS <6) now represents over 80% of all PTCs and is on the rise due to the increasing use of imaging techniques.
- Current management paradigm and guidelines for differentiated thyroid cancer treatment are based on Mazzaferri's initial studies that mixed papillary (low- and high-risk) with follicular cancer and included patients with inappropriate surgical treatment.
- Most of the current algorithms for PTC management propose an unnecessarily aggressive follow-up with routine radioiodine ablation, repeated body scans and TSH stimulation.
- Comprehensive surgery (total thyroidectomy plus central neck dissection) performed by dedicated teams, has shown to be more than enough for most patients with low-risk PTC.
- Medical treatment has limited role in the postoperative management of low-risk PTC.
- A radical change of paradigm for managing low-risk papillary cancer is urgently needed to avoid morbidity, overtreatment and increased follow-up costs.
- In future guidelines, PTC and follicular cancer should de discussed separately and they should not be sponsored by the pharmaceutical industry.

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