Papillary thyroid microcarcinoma: time to shift from surgery to active surveillance?

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The incidence of differentiated thyroid cancer is increasing greatly in high-income countries. Roughly 50% of this increase is attributable to the identification of intrathyroidal papillary thyroid microcarcinomas. Since mortality associated with these tumours remains low and stable, the increasing diagnosis has led to concerns about overdiagnosis and overtreatment. Management of papillary thyroid microcarcinomas should take into account the reported absence of mortality when diagnosed in the absence of lymph node metastases and distant metastases, as shown even in recent studies promoting active surveillance; a low recurrence rate of 1–5%; and the risk of permanent complications from surgery that cannot be decreased to less than 1–3%, even in high-volume tertiary care centres with experienced surgeons. On the basis of these data, active surveillance with curative intent, in which active treatment is delayed until the cancer shows signs of significant progression to avoid side-effects of treatment, should be considered in properly selected patients.

Introduction

Papillary thyroid microcarcinomas are small thyroid cancers measuring 1 cm or less. Most of these tumours are not palpable and are identified either through pathology examination of thyroid glands removed for benign conditions or from imaging procedures such as neck ultrasonography or CT scan for another cause. Much less commonly, papillary thyroid microcarcinoma presents with palpable neck node metastases or distant metastases, leading to the diagnosis of a yet unknown papillary thyroid cancer.

Epidemiology

Occult papillary thyroid microcarcinomas at autopsy

Findings from autopsy studies have shown that occult papillary thyroid microcarcinomas are present in 5–36% of the population (table 1).[1–11] In a meta-analysis of 989 autopsies from 15 studies, the prevalence was 11·5%.[12] Occult papillary thyroid microcarcinomas are characterised by a very small size, with the tumour smaller than 1 mm in 33–79% of cases, and a high frequency of multifocality, which is present in 27–50% of cases (table 1). The prevalence of occult papillary thyroid microcarcinomas is higher in people older than 40 years than in younger people, but is not associated with either iodine intake or sex. The main factor affecting the prevalence of these tumours is the method used for the autopsy analysis.[9] Occult papillary thyroid micro-carcinomas represent a major reservoir of unknown thyroid malignancies, which we estimate to affect roughly 20 million adults in the USA and 48 million in Europe. Indeed, the prevalence of occult papillary thyroid microcarcinomas identified at autopsy is 100–1000 times higher than that of clinical cancer.

Clinical papillary thyroid microcarcinomas

There has been a substantial rise in the incidence of thyroid cancer in developed countries during the past 30 years.[13–16] Roughly 50% of this increase is attributable to the identification of intrathyroidal papillary thyroid

microcarcinomas, which are present in at least 10% of thyroid glands removed for benign thyroid diseases.[15,17] The most common presentation of thyroid cancer is a papillary thyroid microcarcinoma, measuring less than 2 mm in 60% of patients, in a patient older than 45 years.[18,19] At the same time, mortality from papillary thyroid carcinoma remains low and stable.[17]

Several changes in medical practice in high-income countries have resulted in the increased identification of papillary thyroid microcarcinomas that were previously part of a large subclinical thyroid cancer reservoir. One of these developments is the increased detection of asymptomatic incidental thyroid nodules through highly sensitive imaging procedures, such as the widespread availability of neck ultrasonography that is often used for various neck conditions such as pain, discomfort, or any kind of thyroid disease, and the availability of other imaging procedures that are done for unrelated reasons, such as carotid artery doppler studies, neck MRI for cervical discopathy, and CT scan or ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET scans for non-thyroidal malignancies. Other developments that have led to increased identification of papillary thyroid microcarcinomas are the increased spatial resolution of the latest neck ultrasound machines, which can now detect nodules as small as 2 mm; the increased ability to take biopsy samples from very small thyroid nodules by use of ultrasound-guided fine needle aspiration; and a more thorough histological scrutiny of thyroid specimens obtained at surgery for benign thyroid diseases by sectioning and examining the entire thyroid gland.[20] During the past three decades, a large proportion of thyroid cancer diagnoses—up to 60% according to results from a recent study[21]—can be accounted for by these diagnostic changes. The introduction of a formal screening programme with ultrasonography in South Korea resulted in an increase in diagnosis of thyroid cancer by 15 times within 10 years, with clear concern regarding its usefulness.[22,23] A screening programme initiated in Fukushima following the Daiichi nuclear

	Country	N	Prevalence	Prevalence, male	Prevalence, female	Size (mm)	Tumour size <1 mm	Multifocal tumours
Sampson et al (1974)[1]	USA	157	9 (5·7%)	7/99 (7·1%)	2/58 (3·5%)	NA	NA	NA
Sobrinho-Simoes et al (1979)[2]	Portugal	600	39 (6·5%)	9/338 (2·7%)	30/262 (11·5%)	NA	NA	12/39 (30·8%)
Bondeson et al (1981)[3]	Sweden	500	39* (7·8%)	17/279 (6·0%)	22/221 (10·0%)	NA	NA*	NA
Harach et al (1985)[4]	Finland	101	36 (35·6%)	23/53 (43·4%)	13/48 (27·1%)	NA	40/52 (76·9%)	10/36 (27·8%)
Lang et al (1988)[5]	Germany	1020	63 (6·2%)	39/599 (6·5%)	24/421 (5·7%)	NA	NA	29/63 (46·0%)
Ottino et al (1989)[6]	Argentina	100	11 (11·0%)	8/59 (13·6%)	3/41 (7·3%)	Median 2·1	6/18 (33·3%)	3/11 (27·3%)
Yamamoto et al (1990)[7]	Japan	408	46 (11·3%)	26/247 (10·5%)	20/161 (12·4%)	Mean 1·98	23/64 (35·9%)	14/46 (30·4%)
Furmanchuk et al (1993)[8]	Belarus	215	19* (8·8%)	10/138 (7·2%)	9/77 (11·7%)	Mean 1·7; median 1·1	13/28 (46·4%)	6/19 (31·6%)
Martinez-Tello et al (1993)[9]	Spain	100	22 (22·0%)	16/66 (24·2%)	6/34 (17·6%)	NA	42/53 (79·2%)	11/22 (50·0%)
Kovacs et al (2005)[10]	Hungary	433	21 (4·7%)	NA	NA	Mean 2·45	9/21 (42·8%)	2/21 (9·5%)
Neuhold et al (2001)[11]	Austria	118	10 (8·6%)	6/57 (10·5%)	4/61 (6·6%)	Mean 4·9	0	3/10 (30·0%)

Data are n (%), unless otherwise indicated. NA=not available. *Tumour size was less than 3 mm in 15 (38%) cases.

Table 1: Prevalence and characteristics of occult papillary thyroid microcarcinomas at autopsy

power plant accident diagnosed thyroid cancer with an incidence 30 times higher than the national incidence in children and adolescents in both contaminated and non-contaminated regions.[24] Futhermore, in high-income countries, the increase in diagnosis of papillary thyroid microcarcinomas is related to the economic status of the patients, because economic status is associated with access to medical facilities through medical health insurance.[19,25] Although financial incentives to track coding of malignancy might have contributed to the increase in diagnoses of thyroid cancer in the USA, this is not the case in France or Italy where similar increases in papillary thyroid microcarcinomas have been reported despite the absence of financial remuneration for thyroid cancer coding.[13,26,27]

Clinical and occult papillary thyroid microcarcinomas from autopsy series are distinct entities, as reflected by differences in their sex ratio and size. Although clinical differentiated thyroid cancer is three times more frequent in women than men, the prevalence of latent papillary thyroid microcarcinomas does not differ between men and women in autopsy studies (table 1).[12] The size of papillary thyroid microcarcinomas has been shown to be larger in clinical studies than in autopsy studies.[12] Cohort studies of papillary thyroid microcarcinoma include patients with both clinical and occult (found at surgery) carcinomas because there are no formal criteria to distinguish one from the other. However, the prognosis of both clinical and occult papillary thyroid microcarcinomas is excellent.

Because of the high frequency of papillary thyroid microcarcinomas in autopsy studies and the increasing incidence of clinical papillary thyroid microcarcinomas, there is concern about overdiagnosis and overtreatment of lesions that would not cause any harm if left untreated. To minimise this problem, a working group suggested a change in terminology, with use of the term indolent lesion of epithelial origin rather than cancer.[28] Some radiologists suggested "turn[ing] off the ultrasound machines",[29] whereas others suggested that thyroid micro-incidentalomas should be ignored rather than explored.[30]

Natural history and prognosis
Mortality
Mortality related to papillary thyroid microcarcinoma is very low, reaching up to 0·3% in clinical series that included patients with palpable lymph nodes and distant metastases at initial presentation (table 2).[31–42] Furthermore, in the absence of treatment, no deaths have been attributed to thyroid cancer in patients undergoing active surveillance.[43] There is no excess mortality caused by papillary thyroid microcarcinoma diagnosed without clinical lymph nodes or distant metastases.

Risk of recurrence and predictive factors for recurrence
In series with more than 250 patients, clinical recurrences occurred in 1–5% of patients with papillary thyroid microcarcinoma, irrespective of the presence of palpable lymph nodes at initial diagnosis (table 2).[31–41] When patients with palpable lymph nodes were excluded, the rate of recurrence decreased to less than 1%.[33] In a meta-analysis, investigators reported a recurrence rate of 0·5% (four of 854) in patients with incidental papillary thyroid micro-carcinoma (diagnosed on histological examination of thyroid specimens following thyroid surgery for non-cancer diagnoses), compared with 7·9% (173 of 2669) in patients with non-incidental papillary thyroid microcarcinoma (diagnosed preoperatively); however, non-incidental papillary thyroid microcarcinoma included tumours diagnosed on imaging undertaken for non-thyroid reasons and those diagnosed because of clinical nodal metastasis, a distinct clinical entity.[42]

In a single-institution series of 1066 patients with papillary thyroid microcarcinoma, an increased risk of locoregional lymph node metastases at diagnosis was significantly associated with male sex, younger age (≤45 years), multifocal lesions, extrathyroidal extension,

and larger tumour size (>6 mm).[41] Furthermore, the likelihood of lateral neck lymph node involvement was associated with extrathyroidal extension, multifocal lesions, central neck lymph node involvement, and location of the tumour in the upper third of the thyroid lobe.

Microscopic extrathyroidal extension, subcapsular location of the primary tumour, and multifocal disease have been associated with a higher risk of recurrence and locoregional metastases at diagnosis in some,[36,40,44–46] but not all studies.[47–51] Results from other studies have suggested that the risk factors associated with recurrence might differ between younger (<45 years at diagnosis) and older patients.[52] In a recent meta-analysis, clinical recurrences were associated with multifocal tumours, locoregional metastases at diagnosis, and younger age, but not with sex, size of the primary tumour, or extrathyroidal extension.[53] Buffet and colleagues[40] proposed a scoring system to predict recurrences in papillary thyroid microcarcinoma that relies on histological features, including tumour multifocality, extrathyroidal extension, and lymph node involvement. The negative effect of N1 (ie, neck lymph node metastases) should not be overestimated. Among patients with N1 disease, the size and number of metastatic lymph nodes as well as the presence or absence of extracapsular extension should be taken into account to assess the effect of N1 on the risk of relapse.[54–56] In the 2015 American Thyroid Association (ATA) guidelines, patients with N1 disease were classified as low, intermediate, or high risk on the basis of the number and size of N1, whereas in the 2009 ATA classification, all patients with neck lymph node metastases were classified as intermediate risk.[55,57]

Potential histological and biological prognostic factors (including mutation status) have been analysed. Desmoplastic stromal reaction is associated with lymph node metastases and histological invasive features such as peritumoral infiltration and vascular invasion.[58] Furthermore, an infiltrative growth pattern of the primary tumour and tumour-associated fibrosis is significantly associated with locoregional lymph node involvement at diagnosis.[59] In a clinicopathological study of 60 patients with papillary thyroid microcarcinoma, multivariate analysis showed peritumoural lymphatic vessel density as the only independent variable associated with a higher rate of locoregional neck metastases.[60]

A combination of tumour size and maximum standardised uptake value of the primary tumour on 18F-FDG PET scanning has been shown to predict the likelihood of central neck lymph node metastasis from papillary thyroid microcarcinoma with a sensitivity of 68% and a specificity of 71%.[61] In another study, researchers showed the absence of correlation between 18F-FDG uptake and BRAF mutation in papillary thyroid microcarcinoma.[62] However, even when multiple clinical factors are combined, the specificity and positive predictive value of these models are too poor to provide useful

	Number of patients	Follow-up (years)	Palpable lymph nodes, n (%)	Relapse, n (%)	Thyroid cancer-related death, n (%)
Baudin et al (1998)[31]	281	7·3	89 (31·6%)	11 (3·9%)	0
Yamashita et al (1999)[32]	1743	11·2	90 (5·2%)	31 (1·8%)	4 (0·2%)
Wada et al (2003)[33]	259	5·2	24 (9·3%)	6 (2·3%)*	0
Pelizzo et al (2006)[34]	403	8·5	NA	6 (1·5%)	1 (0·2%)
Ito et al (2007)[35]	317	8·9	0	7 (2·2%)	0
Hay et al (2008)[36]	900	17·2	131 (14·6%)	5·7%†	3 (0·3%)
Noguchi et al (2008)[37]	2070	15·1	NA	73 (3·5%)	2 (0·2%)
Besic et al (2009)[38]	254	4·7	51 (20·1%)	7 (2·7%)	0
Moon et al (2011)[39]	288	6·0	NA	12 (4·2%)	0
Buffet et al (2012)[40]	1668	6·5	NA	68 (4·1%)	0
Zhang et al (2012)[41]	1066	2·7	99 (9·3%)	10 (0·9%)	0

Studies shown included more than 250 patients with papillary thyroid microcarcinoma. *Rate of recurrence: four (16·7%) of 24 patients in the presence of palpable lymph nodes, two (0·4%) of 235 patients in the absence of palpable lymph nodes. †At 20 years. NA=not available.

Table 2: Frequency of relapse and thyroid cancer-related mortality in patients with papillary thyroid microcarcinoma

preoperative risk stratification.[63] Furthermore, many of the potentially important risk factors can only be determined postoperatively on the basis of thyroid pathology.

BRAF mutations are present in 30–67% of patients with papillary thyroid microcarcinomas[64–75] and are associated with locoregional metastases, extrathyroidal extension, and an increased American Joint Committee on Cancer (AJCC) stage at presentation.[67,68,72,74,76,77] In a meta-analysis of data from 2247 patients with papillary thyroid microcarcinoma, an increased risk of recurrence was reported in those with a BRAF mutation (odds ratio 2·09 [95% CI 1·31–3·33]; p=0·002).[78] The histopathological and molecular profiles (BRAF, RAS) of papillary thyroid microcarcinoma were studied in a cohort of 29 patients with locoregional metastases and compared with a cohort of 30 patients matched for age, sex, and tumour size, but with papillary thyroid microcarcinoma confined to the thyroid.[46] Tumours with locoregional metastases were more likely to have extrathyroidal extension, infiltrative borders, multiple foci, and to harbour a BRAF mutation. Additionally, a subcapsular location of the tumour was also associated with nodal metastases. A predictive score that incorporated three histological features (superficial tumour location, intraglandular spread or multifocality, and tumour fibrosis) with BRAF status was more predictive of locoregional spread than BRAF status or the histological characteristics alone. However, this score has limited applicability to the selection of patients for active surveillance, since two of the variables (multifocality and tumour fibrosis) can only be assessed postoperatively.

TERT promoter mutations are present in fewer than 10% of patients with papillary thyroid microcarcinoma,[79,80] with some studies showing a correlation between TERT promoter mutation and aggressive clinicohistological features. Recently, the association of BRAF and TERT

promoter mutations present in 22 (3%) of 653 patients with papillary thyroid cancers was associated with clinicopathological features of high-risk differentiated thyroid cancer, including older age, larger tumour size, extrathyroidal invasion, capsular invasion, and advanced disease stages.[80]

The presence of multiple mutations within the same papillary thyroid microcarcinoma (*BRAF* and *TERT* or multiple mutations) is rare and might predict a more aggressive disease.[80,81] However, this hypothesis needs to be confirmed in prospective clinical studies. A more comprehensive, integrated assessment of the genome by next-generation sequencing might identify a gene signature in aggressive papillary thyroid microcarcinoma.

Indications for fine needle aspiration

Thyroid nodules smaller than 1 cm in diameter that are highly suspected to be papillary thyroid microcarcinomas on the basis of neck ultrasonography that should be submitted to fine needle aspiration biopsy are those for which, if malignancy is confirmed, a resection will be preferred to active surveillance because of ultra-sonographic features suggesting a high risk of recurrence—ie, thyroid nodules with the presence of cervical lymph node metastases, extrathyroidal extension, or multiple foci. Thyroid incidentalomas detected by ^{18}F-FDG PET that are smaller than 1 cm in diameter and have ultrasound criteria of malignancy could also benefit from fine needle aspiration biopsy in rare cases in which the diagnosis of intrathyroid metastases affects the treatment of the other primary cancer. Additionally, suspicious subcentimetre nodules in subcapsular locations where even minor disease progression could be associated with complications (eg, adjacent to recurrent laryngeal nerve or trachea) should also be considered for biopsy.[82] The exclusion of patients with these nodules from active surveillance is mainly based on the absence of data, because these patients were not offered surveillance in the study by Ito and colleagues.[82] If active surveillance is chosen for these nodules, it should be done within the frame of prospective trials, since treatment de-escalation should be a prudent process. There is, however, a concern about the level and availability of expertise and experience needed to accurately recognise the presence of extrathyroid extension, multifocality, and at-risk nodules on neck ultrasonography because of their location. Otherwise, thyroid nodules smaller than 1 cm in size should not be submitted to fine needle aspiration biopsy. This recommendation is unanimous, and is considered a strong recommendation with moderate quality of evidence in the 2015 ATA guidelines.[55,83]

Initial treatment
Surgery

In patients with clinical lymph node metastases (cN1), surgery is the standard treatment. In most cases the clinical lymph nodes are located in the lateral compartment. A total thyroidectomy with therapeutic central and lateral lymph node dissection is then recommended because lateral neck metastases are present in 83% of patients with papillary thyroid microcarcinoma, central neck metastases in 96%, and skip metastases (lateral neck metastases without central neck metastases) in only 4%.[33,55] Because the effects of neck dissection on survival have not been clearly shown and because of the morbidity of surgery, even in high-volume centres, the extent of prophylactic central neck dissections done in conjunction with a therapeutic lateral neck dissection remains controversial. Some centres will recommend a bilateral prophylactic central neck dissection, others a unilateral, and less frequently no central prophylactic neck dissection at all. The same uncertainties exist regarding the prophylactic contralateral neck dissection.

In the absence of clinical lymph node involvement (cN0), the low risk of recurrence of papillary thyroid microcarcinoma has to be taken into account and balanced against the risk of permanent complications of total thyroidectomy and the possibility of salvage therapy in case of recurrence. The risk of recurrence is similar after lobectomy and total thyroidectomy in patients with unifocal papillary thyroid microcarcinoma without extrathyroid extension and cN0. Permanent complications of thyroid surgery include permanent hypoparathyroidism and recurrent nerve palsy and can be decreased if surgery is done by highly experienced surgeons.[84,85] However, even for operations done by experienced surgeons, the risk of permanent hypoparathyroidism and permanent recurrent nerve palsy is 1–3% following total thyroidectomy and prophylactic neck dissection, higher than following a total thyroidectomy alone or a lobectomy, for which it is less than 1%. The main advantage of a lobectomy is that it carries no risk of permanent hypocalcaemia, by contrast with a total thyroidectomy.[86]

In view of these data, thyroid lobectomy alone is a sufficient treatment for unifocal, intrathyroidal, and cN0 papillary thyroid microcarcinoma in the absence of previous head and neck radiation, familial thyroid carcinoma, and abnormalities of the contralateral thyroid lobe.[55] Furthermore, following lobectomy, not all patients will need levothyroxine treatment since overt hypothyroidism will occur in only 22% of cases.[87] Finally, quality of life is preserved in most, but not all, patients receiving levothyroxine treatment.[88] The drawback is that follow-up of patients might seem more convenient after a total thyroidectomy compared with a lobectomy. However, recent data show that serum thyroglobulin concentrations can be easily used to assess patient response after a lobectomy.[89]

Radioactive iodine

The question of whether to use radioactive iodine ablation following a diagnosis of papillary thyroid microcarcinoma only concerns patients who undergo total thyroidectomy. In patients with unifocal papillary

thyroid microcarcinoma and in the absence of lymph node metastases, there is no indication for postoperative remnant ablation as recommended by the 2009 and 2015 ATA guidelines and by the 2006 European guidelines.[55,57,90] In patients with multifocal tumours, a risk factor for recurrence, the ATA guidelines do not recommend routine radioactive iodine ablation. Finally, in patients with extrathyroid extension of papillary thyroid microcarcinoma—another risk factor for recurrence— the role of radioactive iodine ablation is controversial, and the benefit of this treatment on recurrence-free survival has not been shown.

Follow-up

The frequency of follow-up of patients with papillary thyroid microcarcinoma has to be adapted to the indolent course of the disease and to its low level of recurrence. Recurrence can be diagnosed by measurement of thyroglobulin concentration or neck ultrasonography. Following total thyroidectomy without radioactive iodine administration, serum thyroglobulin concentrations are dependent on the amount of thyroid residue left by the surgeon. In expert hands, serum thyroglobulin concentration is expected to be lower than 1 ng/mL in 96% of patients and lower than 2 ng/mL in all patients after total thyroidectomy.[91,92] Thyroglobulin antibodies, initially present in 10–20% of patients, are expected to decrease spontaneously.[92] Following lobectomy, thyroglobulin concentration, and trends in thyroglobulin concentrations and thyroglobulin antibodies over time, can be taken into account to define an excellent response, with a value of less than 30 ng/mL as a cutoff for thyroglobulin concentration.[89]

The remaining question is the frequency at which these examinations should be done. Unfortunately, prospective clinical data are not available. Thyroglobulin measurement and neck ultrasonography are done at 6–12 months after initial treatment. In the absence of abnormality, serum thyroglobulin measurement every 2–4 years seems reasonable, and in patients treated with lobectomy a neck ultrasonography every 4–5 years seems reasonable. Because of the absence of evidence, this follow-up strategy of surveillance is a proposition and can only be debated until further convincing data become available.

Active surveillance: an alternative to surgery

Active surveillance is a strategy initially used in the setting of low-risk localised prostate cancer. It is an approach with a curative intent in which active treatment is delayed until the cancer shows significant progression to avoid (or at least delay) side-effects of treatment.[93] This strategy can only be used in patients with indolent malignancies. Active surveillance is a new management strategy in oncology for both physicians and patients. As a result, both need to be made aware of and educated about the approach, and physicians need to gain experience of it, especially since patients are heavily influenced by physicians in their decision of whether or
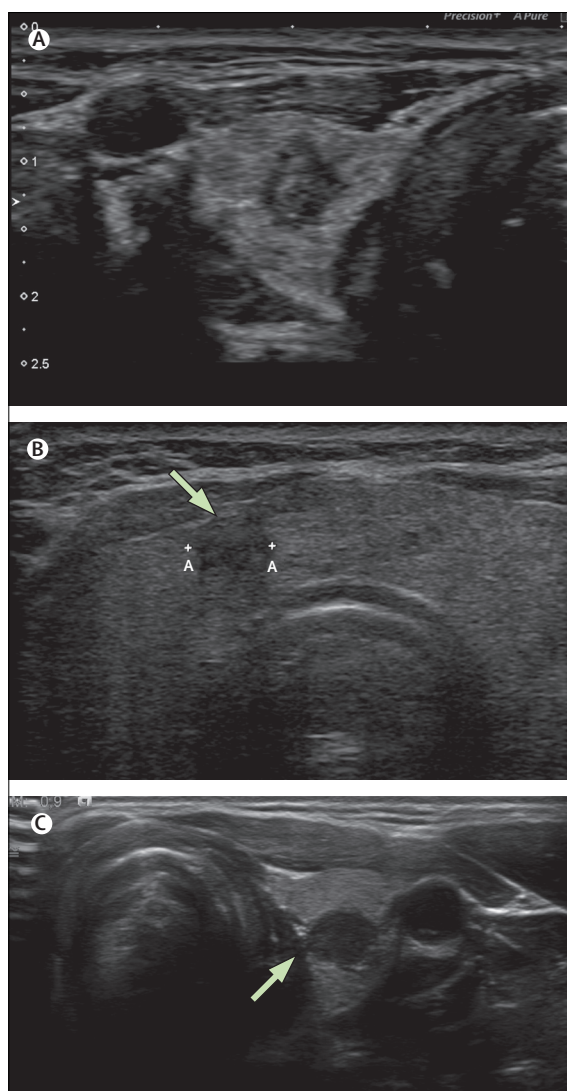

Figure 1: **Ultrasound images of patients with papillary thyroid microcarcinoma showing suitability for active surveillance**
(A) Suitable for active surveillance because the papillary thyroid microcarcinoma is confined to the thyroid parenchyma. (B) Not suitable for active surveillance because of location close to the thyroid capsule (arrow); the limits of the thyroid microcarcinoma are shown by the two As. (C) Not suitable for active surveillance because of location close to the trachea (arrow is pointing to the thyroid capsule close to the trachea).

not to opt for active surveillance.[94] Furthermore, the effects of anxiety created by the diagnosis of cancer without receiving active treatment need to be assessed and investigated, and might change with time.[95] Although the general concept that very low-risk thyroid cancer can be safely observed without immediate treatment is slowly being accepted by patients and physicians, much more experience will be required before this approach will be widely applied in routine clinical practice.

Patients with papillary thyroid microcarcinoma who meet the following criteria are good candidates for active

surveillance: tumour size of 1 cm or less, confined to the thyroid parenchyma, not adjacent to the thyroid capsule, or in the absence of abnormal cervical lymph nodes or recurrent nerve palsy (figure 1).[96,97] Many factors can affect the decision for or against active surveillance.[96] These factors include patient characteristics such as age, family history of thyroid cancer, compliance with follow-up, and willingness to defer immediate surgery (figure 2); and characteristics of the multidisciplinary team such as the experience of the clinician treating the thyroid cancer and the quality of neck ultrasonography.[96] However, the level of clinician experience is difficult to assess because criteria to define relevant expertise are not available.

So far, all studies of active surveillance in patients with papillary thyroid microcarcinoma have been done in Japan.[43,82,97,98,100] The active surveillance programme consisted of serial neck ultrasonography every 6–12 months. Significant progression of the primary tumour was defined as an increase in size of 3 mm or more, or identification of locoregional or distant metastases. The first report on a cohort of 340 patients managed with active surveillance showed that 22 (6%) patients with papillary thyroid microcarcinoma had an increase in tumour size (≥3 mm) at 5 years and 54 (16%) had an increase at 10 years.[82] Only seven (1%) patients developed locoregional lymph node metastases.[82] No patients developed distant metastases, and no disease-specific deaths were reported.[82] The update of this prospective cohort study included 1235 patients with papillary thyroid microcarcinoma followed up for more than 1·5 years (mean follow-up 5 years).[100] Consistent with the initial findings, 58 (5%) patients showed an increase in tumour size during follow-up (ie, an increase of ≥3 mm or a tumour size of ≥12 mm), 19 (2%) had locoregional lymph node metastases (mostly located in the lateral compartment), and no patients developed distant metastases (table 3).[100] All patients who underwent surgery at the time of progression had a favourable outcome, similar to the outcome seen in patients who had immediate surgery. Furthermore, patients undergoing active surveillance had a lower frequency of unfavourable events such as permanent hypoparathyroidism than those who had immediate surgery (0·8% vs 1·6%, respectively; p=0·0001).[43] Finally, no thyroid cancer-related deaths were reported in patients under active surveillance or in patients treated with surgery during the same time period at the same institution.

Age is the only identified risk factor for disease progression, with younger patients (aged <40 years) being more likely to progress than older patients (table 3).[100] Tumour size, multiple foci, sex, thyroid-stimulating hormone concentration, and family history were not significant prognostic factors for progression.[100] Disease progression was noted in four of nine patients with papillary thyroid microcarcinoma under observation during pregnancy.[101] However, an updated assessment showed disease progression in only four (8%) of 50 patients with papillary thyroid microcarcinoma examined before and after a full-term pregnancy.[102] Findings from a recent study suggested that changes in ultrasonographic pattern during follow-up might predict progression, with consolidation of calcification and loss of vascularity during follow-up being significant indicators for non-progressive disease.[103]

These data suggest that a long-term active surveillance management approach might be more effective and appropriate in older patients than in younger patients. However, younger patients could also opt for an active surveillance approach for deferral of surgical intervention to a more convenient time. The drawback of active surveillance is its acceptance by patients. Indeed, half of patients from the centre that initiated the approach in thyroid cancer and promoted it through a prospective trial chose immediate surgery rather than surveillance.[43]

Other than age, there is no identified predictor of progression of papillary thyroid microcarcinoma during active surveillance. Whether the molecular profiling of papillary thyroid microcarcinoma can be useful to decide whether active surveillance can be offered is a question that needs to be answered. A large genomic analysis might be more pertinent than an analysis focusing on *BRAF* and *TERT* mutations. In view of the indolent natural history of papillary thyroid microcarcinomas, the question of the cost-effectiveness of active surveillance will also have to be addressed.
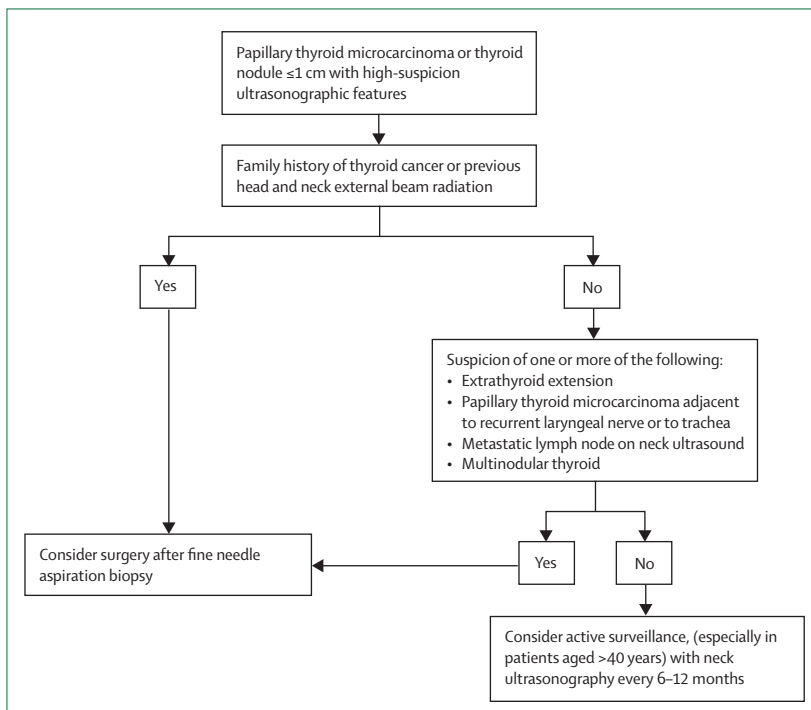

Figure 2: Decision tree for treatment of patients with papillary thyroid microcarcinoma

	Increase in tumour size by 3 mm or more		Appearance of lymph node metastases		Progression to clinical disease*	
	5 years	10 years	5 years	10 years	5 years	10 years
<40 years	45 (9·1%)	11 (12·1%)	49 (5·2%)	13 (16·1%)	48 (9·5%)	13 (22·5%)
40–59 years	225 (5·0%)	82 (9·1%)	229 (1·4%)	87 (2·3%)	229 (4·0%)	87 (4·9%)
≥60 years	157 (4·0%)	36 (4·0%)	160 (0·5%)	36 (0·5%)	157 (2·2%)	36 (2·5%)

Data are number of patients at risk (incidence [%]). *Progression to clinician disease defined by a tumour size reaching 12 mm or larger.

Table 3: Patients with progression of papillary thyroid microcarcinoma by age group[100]

All data for active surveillance have been obtained in Japan and confirmation by prospective trials in North America and Europe are needed. However, on the basis of these data and a careful consideration of the risks versus benefits of immediate surgical intervention in papillary thyroid microcarcinoma, the authors of the 2015 ATA guidelines note that, although surgery is generally recommended for cytologically confirmed thyroid cancer, an active surveillance management approach "can be considered" as an alternative to immediate surgery in patients with very low-risk tumours, such as papillary microcarcinomas without other known high-risk clinical, cytological, or molecular (if assessed) features.[55] An effective active surveillance management plan requires careful patient selection, meticulous neck ultrasound follow-up, and a shared treatment philosophy between the patient and all members of the disease management team. The optimum patient for active surveillance is an older patient (>40 years) with a unifocal papillary microcarcinoma with no ultrasound evidence of extrathyroidal extension or cervical lymph node involvement in the setting of an otherwise normal thyroid ultrasound, and who is willing to return at 6–12-month intervals for serial ultrasound examinations over many years.

Local destruction: an alternative to surgery?

Radiofrequency ablation, ethanol injection, and laser ablation were first developed for the treatment of distant metastases from thyroid cancer, locoregional recurrences of thyroid cancer, and benign nodules.[104,105] Treatment of papillary thyroid microcarcinomas with these techniques has been little studied. Recent reports of needle track tumour seeding after radiofrequency ablation of a thyroid cancer and incomplete destruction of a thyroid cancer should lead to a prospective assessment of these techniques.[106,107] A feasibility study in three patients treated with laser ablation followed by surgery was recently reported.[108] The primary papillary thyroid microcarcinomas were destroyed, leaving the problems of multifocality and perithyroid metastatic lymph nodes. These results emphasise the question of whether papillary thyroid microcarcinomas need treatment or not.

Conclusions

To address recent concerns regarding overdiagnosis and overtreatment of papillary thyroid microcarcinomas, an

active surveillance approach in which active treatment is delayed until the cancer shows signs of substantial progression should be considered in selected patients. Criteria for selection include the absence of clinical lymph node metastases, absence of ultrasound signs of extrathyroid extension, and location of the nodule distant from the recurrent laryngeal nerve or trachea. Available data suggest the safety of active surveillance, but further prospective data from the USA and Europe are needed. The drawbacks of active surveillance are its poor acceptance by patients and the need for frequent follow-up. A renaming of the term papillary thyroid microcarcinoma to indolent lesion of epithelial origin will not solve all problems because we will still need to identify the few lesions that will progress and need surgery. In this context, genomic analysis should be investigated for its ability to determine which patients with papillary thyroid microcarcinoma require surgery and those who do not need follow-up.

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