

COMMENTARY

Incidental Papillary Microcarcinoma of the Thyroid

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Abstract

Papillary microcarcinoma (PMC) is a thyroid tumor measuring 10mm or less in maximum diameter and comprise up to 30% of all papillary thyroid cancers. Most of them are detected incidentally and defined as incidental papillary microcarcinoma (IPC \leq 10mm). The incidence of such incidental cancers found in surgical specimens of benign thyroid diseases is high. Although most PMC are incidental, all incidental papillary cancers cannot be classified as microcarcinoma, owing to their size that may be larger than 10mm. Not much is known about the biological behavior and clinical course of IPC \leq 10mm. There is an ongoing discussion among endocrinologists, endocrine surgeons and nuclear medicine specialists about the optimal therapeutic strategy for the patients with IPC \leq 10mm. Some investigators advocate in favor of not performing further treatment in addition to initial thyroid surgery, whereas others suggest an aggressive surgical approach followed by radioiodine ablation therapy. Randomized prospective trials of observation versus standard thyroid cancer care are required to high-lighten this dilemma.

Key Words: Thyroid cancer- papillary microcarcinoma- incidental papillary microcarcinoma- ultrasound- biopsy, fine-needle

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Introduction

Papillary thyroid cancer (PTC) is the most common epithelial thyroid tumor, accounting for more than 80% of all thyroid tumors (Udelsman, 1999). The recent prevalence of ultrasonography (US) screening and US-guided fine-needle aspiration biopsy (FNAB) have facilitated the frequent detection and diagnosis of PTC. Patients with PTC have an excellent prognosis with a 10-year survival rate 93% which is one of the best in the field of oncology (Hundahl et al., 1998). Significant historical factors predicting malignancy include a history of head and neck irradiation, total body irradiation for bone marrow transplantation, family history of thyroid carcinoma in a first-degree relative and exposure to fallout from Chernobyl under the age of 14 years (Curtis et al., 1997; Pacini et al., 1997). Among prognostic factors the most debated is tumor size and in many studies, it represents a factor which correlates with recurrence and mortality in PTC (Mazzaferri and Jhiang, 1994; Baudin et al., 1998). 131I ablative therapy following total thyroidectomy has been shown to improve survival and reduce recurrence in PTC \leq 10mm (Samaan et al., 1992; Mazzaferri and Jhiang, 1994). Papillary microcarcinoma (PMC) is a thyroid tumor measuring 10mm or less in maximum diameter and comprise up to 30% of all PTC (Sobin and Wittekind, 2002; Ito et al., 2004). Most PMC are not palpable and are detected incidentally by the studies performed for other purposes or by screening procedures

for thyroid diseases or by postoperative pathological examination of surgical specimens resected for benign diseases. Such tumors are defined as 'incidental'. This term refers to cancers that are not detectable before surgery. Most PMC are incidental, however, all incidental papillary carcinomas (IPC) cannot be classified as microcarcinoma, owing to their size that may be larger than 10mm. Although not much is known about the biological behavior and clinical course, IPCs are often considered of little clinical significance, depending on the fact that they are usually, but not always, small (\leq 10mm) and differentiated. Many patients have been treated by the endocrinologists for several years before undergoing surgery for a supposed benign disease. Since most of them are microcarcinomas, many authors prefer to use the term PMC as synonym of IPC- although not exactly true- and there is an ongoing discussion among endocrinologists, endocrine surgeons and nuclear medicine specialists about the optimal therapeutic strategy for the patients with IPC \leq 10mm (incidental papillary microcarcinoma).

Ultrasonography can accurately identify the location of the nodules and qualitatively evaluate them. It can detect nodules measuring 3-4 mm at minimum and the diameter of most IPC is even smaller. It appears to be the most useful tool for deciding which small nodules should undergo FNAB. It has been demonstrated that some echoic aspects such as hypoechogenicity, irregular margins and microcalcifications can identify the higher risk nodules (Papini et al., 2002). Other aspects suggesting malignancy

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can be increased vascularity and 'a taller than wide' aspect (Kim et al., 2002). The necessity of FNAB on small thyroid nodules, and particularly on nodules of less than 10mm, is a frequent matter of discussion (Topliss, 2004; Wang and Crapo, 1997). This uncertainty is supported by a few considerations; first is the high prevalence of small nodules, the second is the analysis of some autopsy series where papillary microcarcinoma are found in up to 36% of thyroids examined, suggesting that most of them never reach clinical significance and the third is the relatively indolent course of most PTC (Bondeson and Ljunberg, 1981; Franssila and Harach, 1986). Nevertheless, some reports of massive lymph node metastasis in some papillary microcarcinoma cases indicate the aggressiveness of some small sized cancers (Wada et al., 2003).

An Overview of the Reports Concerning IPC \leq 10mm of the Thyroid in Literature

Previous studies have demonstrated that the incidence of IPC found in surgical specimens of benign thyroid diseases is high (Miccoli et al., 2006; Lokey et al., 2005). The IPC \leq 10mm is pathologically detected in 27.4% of the specimens resected for benign thyroid diseases, such as; multinodular goiter and chronic thyroiditis (Carlini et al., 2005).

Detailed investigations regarding biological behavior of IPC are lacking in current medical literature and available studies exhibit conflicting results. In a trial (Miccoli et al., 2006) consisting of 998 consecutive patients that underwent surgery for unequivocally benign thyroid disease, incidental carcinoma was detected in 104 (10.4%) patients; 99 of them (95.2%) had IPC. Of the IPC group, 59 cases had the classical histological variant and rest of the cases presented with variants which represented more aggressive behavior; follicular (n=36), tall cell (n=2), oxyphilic (n=2). The IPC group and benign disease group exhibited similar age, time between diagnosis and operation, and estimated thyroid volume. The majority of the IPC cases were microcarcinomas (\leq 10mm); 58.6%. Twenty-five IPC cases (24.1%) had a tumor with a diameter of larger than 2cm. When considering the new TNM staging for thyroid carcinoma (Shah et al., 2002), 13 IPC patients (12.5%) were at stages higher than the first.

In their study, Barbaro and colleagues compared the incidental (\leq 10mm, n=12) and non-incidental (n=128) papillary thyroid cancers regarding prognostic factors; multi-focality, lymph node metastasis and extra-capsular invasion, in operation specimens (Barbaro et al., 2005). Before surgery, FNAB was performed on all nodules $>$ 10mm, and on hypoechoic nodules with irregular margins or microcalcification even if the size was $<$ 10mm. There were several different types of patients; those with papillary carcinoma diagnosed by FNAB before surgery, those with large goiter and with papillary carcinoma of small size diagnosed after histological examination, those with a highly suspicious appearing nodule that was not subjected to FNAB, and patients with real incidental PTC who did not exhibit any sign and symptom related with

malignancy prior to surgery. Multi-focality was found to be rare in incidental cancers (8.3% vs 56.8%) and lymph node metastasis or extra-capsular invasion was not detected. Most histological aggressive features could not be observed in IPC. However, non-IPC cases demonstrated incidences of these findings that increased with tumor size. The comparison between non-incidental cancer and true incidental cancer showed a striking difference for the prognostic factors suggesting that they represent different clinical entities.

Sampson and coworkers confirmed nodal metastasis in 2.8% of papillary carcinoma measuring less than 10mm. They suggested that not only PMC, but also IPC \leq 10mm could have node metastasis and/or multi-focality, although the incidence was somewhat lower in IPC (Sampson et al., 1971).

In a recent retrospective study (Roti et al., 2006), the investigators compared the clinical and histological characteristics of 243 patients with PMC; 191 cases with suspected cancer by FNAB prior to surgery and 52 with IPC \leq 10mm found in operation specimens resected for benign thyroid diseases. They detected similar biological behaviors, as well as clinical features; such as age, gender, history of familial thyroid cancer between the two groups. There has not been an agreement about the ideal therapeutic strategy of IPC \leq 10mm among endocrine surgeons, endocrinologists and nuclear medicine specialists. Some consider these small carcinomas to be a less aggressive subset of papillary thyroid cancers that require minimal treatment. Accordingly, Ito and associates reported that in 70% of 162 microcarcinoma patients under observation, the tumor size decreased or did not change at each follow-up (Ito et al., 2004). When IPC \leq 10mm is pathologically detected in surgical specimens resected for benign diseases, many endocrine surgeons traditionally prefer to follow the patients without additional surgery such as; completion total thyroidectomy and/or lymph node dissection. Nevertheless, in several patients, the clinical significance of these tumors cannot be ignored once a correct staging has been carried out. Some investigators report high incidences of metastasis and thus favor a surgical approach followed by radioiodine ablation therapy (Pellegriti et al., 2004).

A very recent study (Ito et al., 2007), inquiring the disease-free survival (DFS) of 317 IPC \leq 10mm patients and 1,674 cases with PTC detected preoperatively, demonstrated that IPC \leq 10mm had an excellent prognosis with 5-year and 10-year DFS rates; being 99.7% and 96.6%, respectively. All 317 IPC \leq 10mm were pathologically diagnosed as well-differentiated carcinomas without extra-thyroidal extension. Fifty-four of them (17%) had total or near total thyroidectomy, 148 (46.7%) had subtotal thyroidectomy and 115 (36.3%) had lobectomy, partial lobectomy and isthmectomy. Further surgery was performed in none of the patients. Fourteen IPC \leq 10mm cases (3.8%) were confirmed as multi-focal. Only 7 of them (2.2%) exhibited recurrence and all but one recurred in locoregional organs. The IPC \leq 10mm were observed to have node metastasis and/or multi-focality, although the incidence was somehow lower. The authors concluded that IPC \leq 10mm was associated with good

prognosis and further surgery, such as completion total thyroidectomy or lymph node dissection was not necessary.

In another study, the clinical behavior and outcome of papillary thyroid cancers smaller than 1.5cm in diameter (n=299) were examined retrospectively (Pellegriti et al, 2004).

The investigators compared 148 cases of non-incidental carcinomas with 151 IPC. Only 7 patients with IPC did not undergo completion thyroidectomy, the rest of the cases in both groups had near-total thyroidectomy. At presentation, incidental papillary cancers significantly differed from non-incidental cancers regarding multifocality; 24.5% vs 39.2%, extra-thyroidal invasion; 10.6% vs 25.7%, lymph node metastasis; 15.9% vs 44.6%. Vascular invasion and distant metastasis were observed at similar ratios within the groups. Patients (n=43) with residual cervical uptake greater than 3% at WBS (with a diagnostic dose of 5mCi ¹³¹I) and negative neck US were subjected to ablative doses of radioactive iodine (30mCi ¹³¹I) and, cases with distant metastasis (n=91) underwent post-surgical treatment with radioiodine with a dose of 100mCi. Seventy-seven patients (25.7%) showed evidence of persisting/relapsing disease during follow-up (12.2 to 252.4 months, median 45.2 months). Depending on these findings, the authors suggested near-total thyroidectomy as first line treatment, followed by radioiodine ablation therapy for papillary thyroid carcinomas <15mm.

In a prospective study (Cappelli et al., 2007) with a median follow-up time of 102 months, the investigators performed radioiodine ablation therapy to all cases with PTC (n=484) independent of tumor size after total thyroidectomy. Removal of regional lymph nodes was performed if metastasis was detected intra-operatively. Cases with PMC (n=102, 21.1%, mean tumor size; 7.8mm) exhibited similar clinicopathological features with the PTC >10mm cases. At the end of a mean follow-up of 74 months, one out of 8 PMC cases were detected to have an unfavorable outcome and 58.5% of them had local lymph node metastasis, although only one fifth of them were affected at presentation. The authors of this study suggested performing a total thyroidectomy followed by radioiodine ablation therapy in PTC independent of the tumor size.

Very recently, Ito and Miyauchi proposed a new therapeutic strategy for IPC ≤ 10mm. As IPC ≤ 10mm with ultrasonographically detectable nodal metastasis were more likely to recur in regional lymph nodes, they recommended therapeutic neck dissection and total thyroidectomy for such cases and careful observation without further surgery for the ones without lymph node involvement (Ito and Miyauchi, 2007).

Conclusion

Incidental papillary microcarcinoma of the thyroid is a dilemma in modern clinical thyroidology. Regarding this entity, the term 'incidental' refers to cancers that exhibit no sign related with malignancy prior to the surgical procedure. They are detected by the studies performed for other reasons or by screening procedures for thyroid

diseases or by postoperative pathological examination of surgical specimens resected for benign diseases. The affected patients have usually been treated by endocrinologists for many years before undergoing surgery for a supposed benign disease. Since there are conflicting reports regarding the clinical and biological features of IPC ≤ 10mm, the optimum therapeutic strategy has not been defined until now. There is an ongoing discussion among endocrinologists, endocrine surgeons and nuclear medicine specialists. Some advocate in favor of not performing further treatment in addition to initial surgery (Ito et al., 2007), whereas others suggest an aggressive surgical approach followed by radioiodine ablation therapy (Pellegriti et al., 2004; Cappelli et al., 2007). A new therapeutic approach has also been proposed recently in favor of performing invasive surgical treatment for the IPC ≤ 10mm cases who have lymph node metastasis (Ito and Miyauchi, 2007). The optimum therapeutic strategy needs to be determined for IPC ≤ 10mm. However, it seems not possible to gather this information without a randomized prospective trial of observation versus standard thyroid cancer care. The ethical aspects of such a trial are uncertain and needs further data concerning the most optimal treatment strategy with careful selection of patients among a heterogeneous group of clinical presentations.

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