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A rationale for conservative management of microscopic papillary carcinoma of the thyroid gland: a clinicopathologic correlation of 90 cases

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Abstract Microscopic papillary carcinoma of the thyroid gland (MPC) measuring ≤ 1.0 cm in diameter has a generally benign outcome, but is often overtreated with additional surgery. Ninety cases of MPC and 77 cases of non-microscopic papillary carcinoma of the thyroid gland (non-MPC) from 1970 to 1980 were retrieved from the Endocrine Registry of the Armed Forces Institute of Pathology (AFIP), Washington, D.C. Histologic features and patient follow-up were analyzed. Twenty-one patients with MPC had multifocal disease within the affected thyroid lobe, while a further 15 had either bilateral or intraglandular spread. Four of 10 patients who had additional surgery were found to have additional foci of tumor. Fourteen patients with lymph node metastases at initial surgery had no subsequent nodal metastases. All patients were either alive without disease or had died of unrelated causes after an average follow-up period of 17.3 years. Of the 77 non-MPC patients, 13 developed lymph node metastases or local recurrences, and one died of metastatic disease. Sixty-four of these patients were alive without evidence of disease after an average follow-up of 22 years. Present findings show that while MPC may present with perithyroidal lymph node metastases (15.56%), patients do not develop clinical tumors in the remaining thyroid tissue. Our experience indicates that close clinical follow-up without additional surgery is the preferable management for patients with MPC.

Key words Microscopic papillary thyroid carcinoma · Diagnosis · Treatment · Prognosis

Introduction

The terms applied to microscopic papillary carcinoma of the thyroid gland are almost too numerous to mention, but whether correctly applied or not, have included “microscopic,” “occult,” “incidental,” “small,” “microcarcinoma,” “minute,” or “minuscule” carcinomas [8, 10, 11, 14, 16–18, 22, 24, 29]. These tumors measure less than or equal to 1.0 cm in maximum diameter and display the characteristic histomorphologic features of papillary carcinoma. Patients usually present with a variety of thyroid disorders such as adenomatoid nodules, follicular tumors, lymphocytic thyroiditis as well as parathyroid disorders, with the microscopic papillary carcinoma found incidentally in the resected thyroid specimen. In our study, 69 cases of incidental microscopic papillary carcinoma and 21 cases of clinically palpable tumors were included. Although a number of authors believe that a diagnosis of microscopic papillary carcinoma alone is a clinically insignificant diagnosis [13, 14, 17, 24, 35], additional surgical management remains controversial. We undertook this study to determine if age, sex, size (up to 1 cm), lymph node status or additional treatment for patients with microscopic papillary thyroid carcinoma had any bearing on patient outcome.

Material and methods

Ninety cases of microscopic papillary carcinoma (69 incidental and 21 clinically palpable) and 77 random cases of non-microscopic papillary carcinoma (control) of the thyroid gland, diagnosed between 1970 and 1980, were retrieved from the Endocrine Pathology Registry of the Armed Forces Institute of Pathology. The 90 cases were identified in a review of 4,942 primary thyroid neoplasms (1.82%) seen in consultation during this period. Forty-four of the microscopic papillary carcinoma cases were obtained from civilian sources, 44 from military hospitals and two from Veterans Administration hospitals. Twenty-five of the 77 non-microscopic papillary carcinoma cases were obtained from civilian sources and 52 from military hospitals.

Hematoxylin and eosin stained slides were available in all cases for review. Inclusion in the present study required that the papillary

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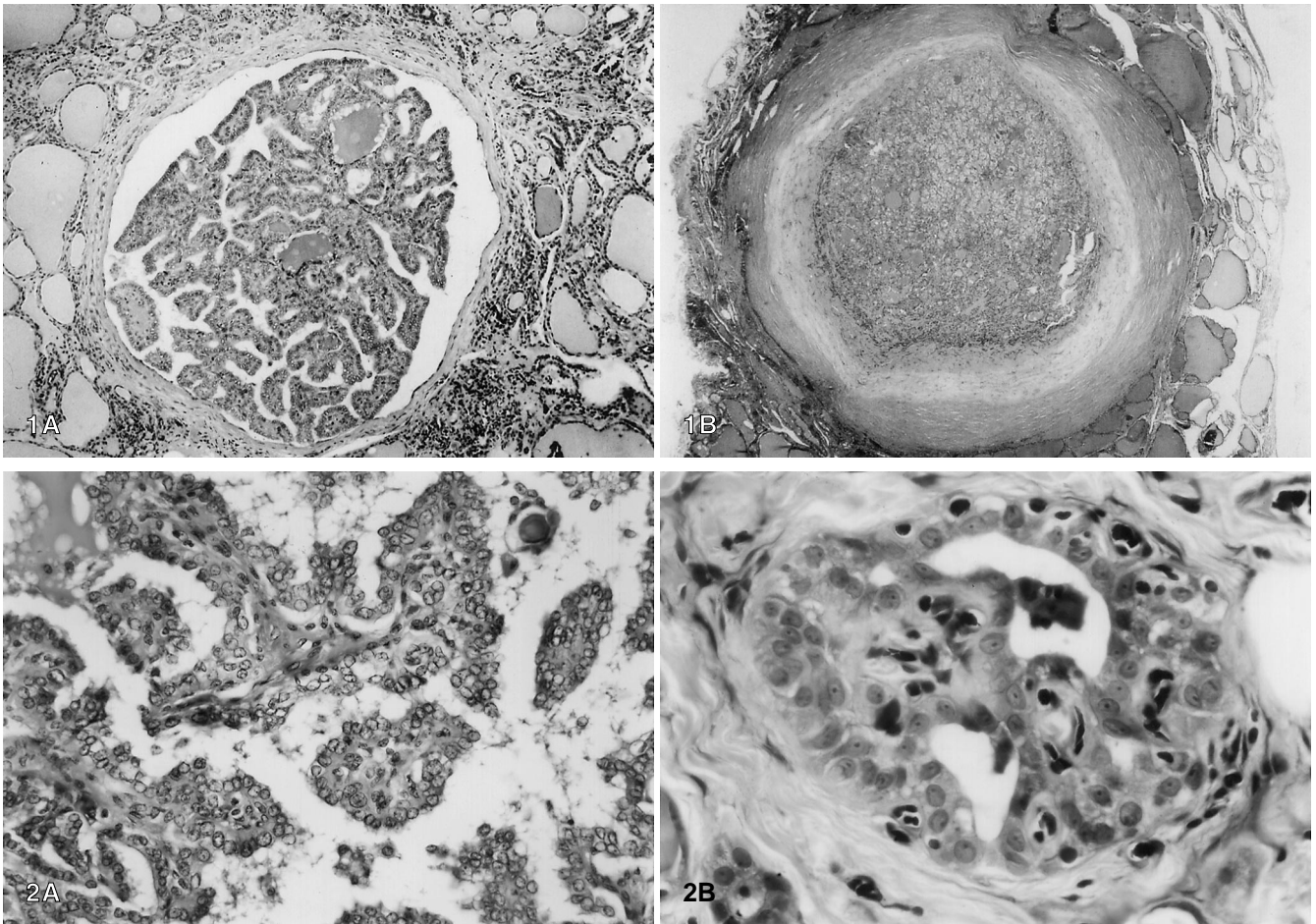


Fig. 1 **A** Well-circumscribed, microscopic papillary carcinoma with characteristic papillae ($\times 150$). **B** Encapsulated microscopic papillary carcinoma demonstrating a well-defined, thick capsule ($\times 30$)

Fig. 2 **A** Papillae lined by overlapping cells with irregular nuclear outlines, nuclear overlapping, and nuclear chromatin clearing ($\times 300$). **B** High-power magnification demonstrating nuclear irregularity, "ground glass" nuclear chromatin and disordered polarity in a papillary carcinoma ($\times 400$)

carcinomas measure less than or equal to 1.0 cm in maximum dimension (either by gross description or by microscopy) (Fig. 1 A,B). All cases were measured with a micrometer to ensure consistency. All cases demonstrated the histomorphologic features of papillary carcinoma [4, 12, 15, 29, 30, 34], as illustrated in Figs. 1 and 2.

Clinical data included material in the files of the AFIP, supplemented by a review of available clinical records, including admitting history and physical examinations, operative reports, surgical pathology reports and specific questionnaires. Tumor size was compared to additional treatment performed (surgery, radiation or chemotherapy), recurrences, lymph node status and each patient's long-term outcome. Multifocal disease was defined by the presence of more than one focus of papillary carcinoma within the thyroid gland, each of which was encapsulated or infiltrative and contained dense fibrous connective tissue bands within the substance of the tumor (Figs. 1 B, 3). Intraglandular spread was defined as tumor foci identified within lymphatic channels along the fibrovascular septa of the thyroid parenchyma. Psammoma bodies (concentrically laminated calcified concretions around infarcted papillae, or mummified papillae) were also interpreted as evidence of intraglandular spread.

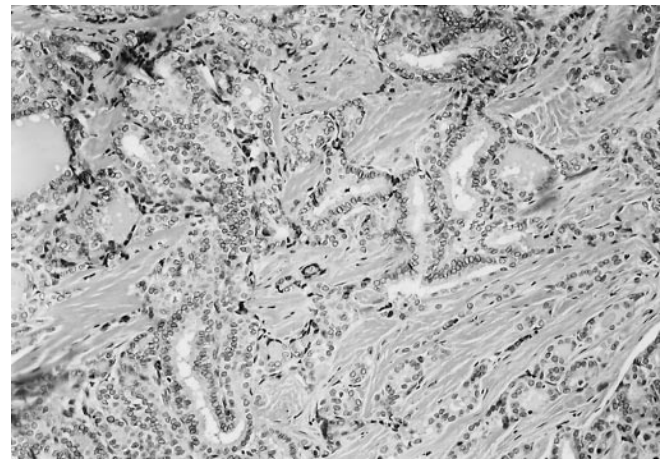


Fig. 3 A microscopic papillary carcinoma demonstrating dense fibrous connective tissue ($\times 300$)

Results

Clinical follow-up was possible in 62 of the 90 microscopic papillary carcinoma cases, including both microscopic-incidentally and microscopic-clinically palpable, while follow-up was obtained in all of the non-microscopic cases. Sixty-five of the microscopic papillary car-

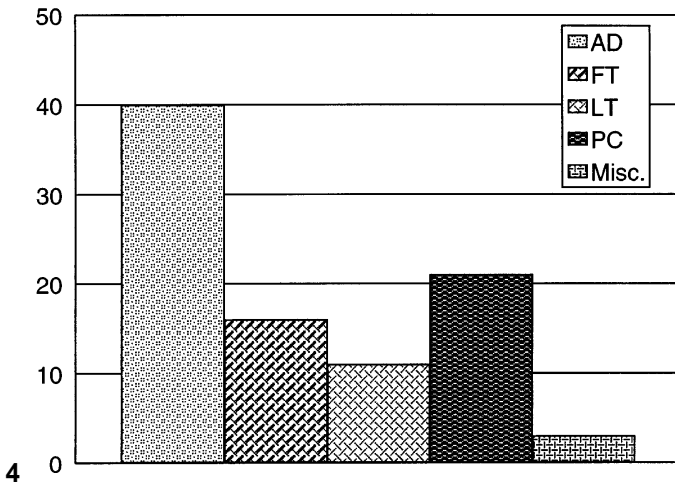


Fig. 4 Indications for initial surgery of patients with microscopic papillary carcinoma [AD adenomatoid nodule, FT follicular tumor, LT lymphocytic thyroiditis, PC papillary carcinoma, Misc parathyroid disorders ($n = 2$) and medullary carcinoma ($n = 1$)]

cinomas occurred in females and 25 in males, yielding a gender ratio of F:M 2.6:1. Ages ranged from 16 to 68, with an average age at presentation of 43 years. Forty-three of the non-microscopic papillary carcinomas occurred in females and 34 in males. Ages of these latter patients ranged from 12 to 68, with an average age at presentation of 35 years.

The majority of the microscopic papillary carcinomas were identified post-operatively as an incidental finding in patients who required thyroid surgery for other disorders (Fig. 4). Pathology in these cases included adenomatoid nodules ($n = 40$), follicular adenomas ($n = 7$), follicular carcinomas ($n = 9$), lymphocytic thyroiditis ($n = 11$), parathyroid disease ($n = 2$) and medullary carcinoma ($n = 1$). The remaining patients presented with a single, clinically palpable, small nodule (< 1 cm) that was usually discovered on routine physical examination rather than with radiographic imaging studies or laboratory abnormalities.

The exact size of each tumor was recorded and calculated from the glass slides, and divided into groups of 2 mm intervals, ranging from 0.1 mm to 10 mm according to gender (Fig. 5). The difference in anatomic location according to gender was not appreciably significant.

Twenty-one patients had multifocal microscopic papillary carcinoma within the lobe initially excised and examined, while another 15 patients had bilateral multifocal tumors or intraglandular spread. The diagnosis of multifocality was made more difficult when additional sections were embedded, making it impossible to determine if the presence of a small focus represented an unsubmitted portion of a previously embedded tumor. However, if the tumor was in the contralateral lobe, surrounded by a fibrous capsule, or demonstrated infiltration, it was presumed to be a second primary rather than intraglandular spread.

After the diagnosis of microscopic papillary carcinoma was rendered, 10 of the 62 patients with microscopic papillary carcinoma in whom follow-up was obtained had un-

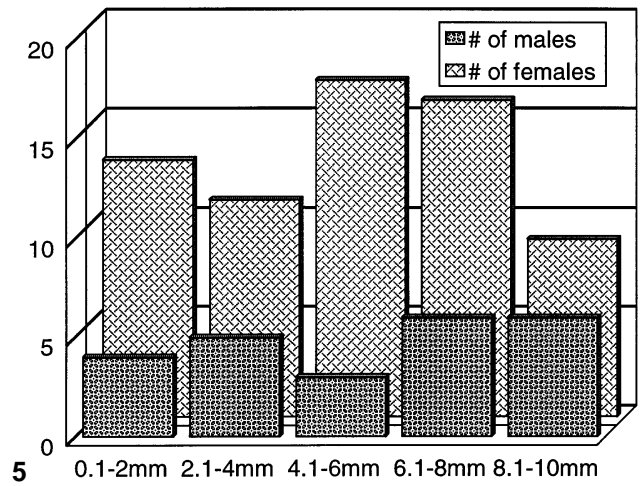


Fig. 5 Number of cases of microscopic papillary carcinoma by size and gender

dergone additional surgery, including completion/contralateral lobectomy ($n = 6$), subtotal thyroidectomy ($n = 1$), and total thyroidectomy ($n = 3$). Four of these patients demonstrated additional foci of microscopic papillary carcinoma in the tissue removed.

Two patients with microscopic papillary carcinoma initially presented with palpable, clinically suspected lymph node metastases, while a total of 14 of 90 patients demonstrated microscopic foci of metastatic papillary carcinoma to perithyroidal (cervical) lymph nodes at the time of initial surgery. None of the patients during the follow-up period developed any additional lymph node metastases. All patients with microscopic papillary carcinoma in whom follow-up was obtained ($n = 62$) were either alive without evidence of disease or recurrence ($n = 50$) or had died of other causes ($n = 12$), an average of 17.3 years after initial presentations. As shown in Table 1, survival did not depend on the size separation of tumors or lymph node metastases. Regardless of the type of initial or subsequent treatment, or whether there was lymph node metastases, there was no statistically significant difference in the outcome of the patient survival (Table 2).

As a matter of comparison, 63 of 77 patients (81.1%) with non-microscopic papillary carcinoma (control group)

Table 1 Survival of patients with microscopic versus non-microscopic papillary carcinoma

	Number	Average survival (years)
Microscopic carcinoma	76	15.1
Microscopic carcinoma with lymph node metastases	14	19.1
Non-microscopic carcinoma	12	19.9
Non-microscopic carcinoma with lymph node metastases	63	22.1
Non-microscopic carcinoma with distant metastases	2	12

Table 2 Survival of patients with microscopic papillary thyroid carcinoma

	Treatment	Number	Average survival (years)
Microscopic papillary carcinoma	Biopsy, lobectomy or subtotal thyroidectomy alone	45	16.3
	Total thyroidectomy only	12	16.5
	Additional therapy: Surgery	7	16.7
	Chemo/XRT	6	20.4
	Combination	0	n/a
	Treatment	Number	Average survival (years)
Microscopic papillary carcinoma with lymph node metastases	Biopsy, lobectomy or subtotal thyroidectomy alone	6	15.86
	Total thyroidectomy only	3	21
	Additional therapy: Surgery	2	20
	Chemo/XRT	2	20.5
	Combination	1	24

Table 3 Survival of patients with non-microscopic papillary thyroid carcinoma

	Treatment	Number	Average survival (years)
Non-microscopic papillary carcinoma	Biopsy, lobectomy or subtotal thyroidectomy alone	4	19
	Total thyroidectomy only	4	23
	Additional therapy: Surgery	2	22
	Chemo/XRT	1	19
	Combination	1	17
	Treatment	Number	Average survival (years)
Non-microscopic papillary carcinoma with lymph node metastases	Biopsy, lobectomy or subtotal thyroidectomy alone	12	19.5
	Total thyroidectomy only	14	22.6
	Additional therapy: Surgery	7	22.3
	Chemo/XRT	14	21.1
	Combination	19	22.8

presented with perithyroidal (cervical) lymph node metastases at the time of initial surgery, most of which were clinically palpable rather than just detected histologically. Thirteen patients went on to develop additional lymph node metastases or local recurrence within 1 to 11 years after initial surgery. There is a statistically significant difference in recurrent lymph node metastases when the microscopic category is compared with the non-microscopic category ($P = 0.0001$).

Only 1 of 77 patients with non-microscopic papillary carcinoma of the thyroid (control group) died of metastatic disease, while 12 died of unrelated causes without evidence of thyroid disease. The remaining 64 patients were alive without evidence of disease at last follow-up, an average of 22 years after initial clinical presentation (Tables 1, 3).

Discussion

A host of names has been given to microscopic papillary carcinoma of the thyroid gland, which are generally characterized by tumors measuring less than or equal to 1.0 cm in maximum diameter [8, 10, 11, 14, 16–18, 22, 24, 29].

Although all of the terms utilized literally identify microscopic or incidental papillary carcinoma of the thyroid gland, no standardization of the nomenclature has been presented, with many of the terms representing individual bias. In our study we considered all tumors measuring less than or equal to 1.0 cm as microscopic, whether incidentally discovered on histologic examination or found by physical examination. Our results and conclusions are based on this hypothesis, as there was no difference in clinical outcome. Therefore, we propose the use of the term “microscopic, incidental” for tumors not clinically suspected, but identified histologically and measuring ≤ 1.0 cm in greatest dimension. In contrast, the term “microscopic, clinically palpable” should be applied to tumors measuring ≤ 1.0 cm in their greatest dimension when identified clinically.

Patients with microscopic papillary thyroid carcinoma usually present with a radioisotopically cold, slowly enlarging nodule or with diffuse enlargement of the gland, both of which are non-specific findings in thyroid disease. These changes clinically represent a wide variety of thyroid disorders histologically, including, but not limited to adenomatoid nodules, follicular tumors (both adenomas and carcinomas), various forms

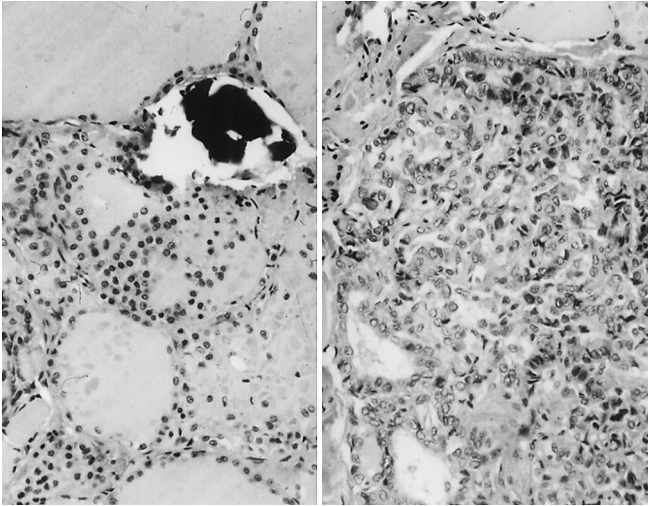


Fig. 6 Psammoma body seen as a concentrically laminated calcific body indicating intraglandular spread (*left*), with a characteristic microscopic papillary carcinoma located separately (*right*) in the lobe ($\times 300$)

of thyroiditis, medullary carcinoma and intrathyroidal parathyroid disorders (presenting as a “false” cold nodule on radioactive iodine scan). However, given a size limitation of ≤ 1.0 cm, the microscopic papillary carcinoma may also be the presenting clinical finding or the dominant histologic observation, thereby not representing an “incidental” finding.

Microscopic papillary carcinoma has been subgrouped according to its growth pattern, including encapsulated, circumscribed (lacking a well-formed capsule) and occult non-encapsulated, infiltrative sclerosing carcinoma [7, 20, 29], illustrated in Figs. 1 and 3. The sensitivity in detecting these papillary carcinomas is perhaps increased by not only an awareness of the entity, but also a greater reliance on combined cytomorphologic features and growth patterns [24, 32]. The characteristic features of dense fibrosis, psammoma bodies (Fig. 6), papillae or elongated follicles lined by enlarged cells with an increased nuclear to cytoplasmic ratio, nuclei which are irregular in size, shape and placement within the cell, nuclear chromatin clearing, nuclear chromatin condensation along the nuclear membranes, nuclear overlapping, nuclear grooves (Fig. 2 A, B) and intranuclear cytoplasmic inclusions can all be seen to a variable degree in each of the tumors, whether measuring less than 1 mm or up to 1.0 cm in greatest dimension.

While the autopsy literature yields a prevalence rate for microscopic papillary carcinoma ranging from 5.6 to 35.6% [2, 3, 9, 13, 19, 21, 25, 28, 36], surgical pathology studies seem to yield a slightly lower rate of 1% to 26% [23, 24, 26, 31], which includes our rate of 1.82% of primary thyroid tumors examined in consultation cases. We believe our incidence rate is within the limits of the probable frequency of microscopic papillary carcinoma in surgical pathology material of the thyroid gland.

The proper management of microscopic papillary carcinoma remains controversial. Allowing for obvious ex-

ceptions related to tumor size, tumor growth pattern (encapsulated or widely invasive), age (older) and sex (male) of the patient, nearly all papillary carcinomas (non-microscopic) have an excellent clinical prognosis. Our findings for microscopic papillary carcinomas replicate those in the literature, with patients generally following a benign clinical course irrespective of the local or regional lymph node status at the time of initial surgery [17, 33]. All of the patients in our study with microscopic papillary carcinoma were either alive without evidence of disease ($n = 50$) or had died of unrelated causes ($n = 12$) during an average period of follow-up of 17.3 years, in spite of the presence of lymph node metastases at initial surgery in 15.6%.

Many authors have suggested that certain cytomorphologic features, lymph node or distant metastases, multifocality and intraglandular spread of microscopic papillary carcinoma of the thyroid may result in a more aggressive biologic behavior, suggesting more aggressive surgical or adjuvant management [1, 5, 6, 24, 26, 27, 37]. However, in these studies, the overall number of patients, size of the tumor, length of follow-up and a lack of a control group may perhaps overstate the biologic severity of microscopic papillary carcinoma. None of our patients died of their disease or developed additional lymph node metastases, even though some of the patients (15.56%) had lymph node metastases at initial surgery and others (37.9%) demonstrated multifocal disease or intraglandular spread. Our patients had a uniformly excellent outcome, irrespective of the initial or subsequent treatment (subtotal thyroidectomy, total thyroidectomy, radiation therapy, and/or chemotherapy), confirming the reports of others that additional therapy is probably unnecessary [8, 17].

There was no statistically significant difference between the survival of microscopic papillary carcinoma patients and those with non-microscopic papillary carcinoma. Even though we had a bias in the non-microscopic papillary carcinoma control group of a high number of patients with lymph node metastases (83.1%), only one patient died of their disease 1 year after initial presentation.

In our opinion, due to the low probability of lymph node metastases (15.6% at presentation) and the extraordinarily low probability of local recurrences (as reflected by none in our series) or mortality (also none in our series) in all excised microscopic papillary carcinomas measuring ≤ 1.0 cm in greatest dimension (both clinically palpable and incidental), we recommend that no additional therapy should be given. In these cases close clinical follow-up should be adequate with any further treatment predicated on changes found during this follow-up.

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