Thyroid microcarcinoma approach
A ten year experience

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AIM: To optimize thyroid microcarcinoma approach, through a retrospective examination of Authors’ experience and literature review.

MATERIALS: Characteristics, treatment and outcomes of patients affected with thyroid microcarcinoma were examined: among 1733 patients operated on for thyroid diseases at Endocrine Surgery Unit of San Paolo Hospital in Milan, from 2001 to 2011, 104 (6.0%) resulted affected with microcarcinoma. Twenty (19.2%) had pre-operative and 84 (80.8%) post-operative diagnosis, 11 with (N+) and 93 without (N0) lymph node metastasis. Eighty-five patients underwent total thyroidectomy, 11 (N+) total thyroidectomy with lymphoadenectomy and 8 lobectomy, 2 radicalized in thyroidectomy. All patients underwent Levo-thyroxine suppressive therapy, 25 (24.0%) 131I ablation. Differences between N0 and N+ patients were researched.

RESULTS: Neither recurrences nor death at a mean follow-up of 5.6 years. Tumour was multifocal and in thyroid with no other diseases in N+, in a greater rate than in N0 patients.

DISCUSSION: Microcarcinoma generally has an indolent course, but sometimes it presents with nodal metastasis. For this reason its treatment in literature is still largely debated.

CONCLUSION: In cases of pre-operative diagnosis of microcarcinoma without lymph node metastasis, we propose total thyroidectomy; otherwise, total thyroidectomy with lymphoadenectomy. In cases of post-operative diagnosis, after a partial resection, only selected cases on the basis of patients’ and tumour features require a completion total thyroidectomy. We propose Levo-thyroxine suppressive therapy to all patients, 131I ablation in cases of lymphatic metastasis and only in selected cases without metastasis, on the basis of patients’ and tumour aspects (age, sex, histological variant, multifocality).

KEY WORDS: Thyroid microcarcinoma, Thyroid papillary carcinoma, Thyroid differentiated carcinoma.

Introduction

The WHO defines thyroid microcarcinoma (TMC) as a differentiated thyroid tumour of 1 centimetre or less in greatest diameter 1. In the past, the diagnosis of TMC was more rare and always done on thyroid glands resected as affected by benign disease. At the present microcarcinoma is an increasing pre-operative diagnosis 2. This is due to the wide diffusion of neck ultrasound, which is able to detect small nodules and the use of ultrasound-guided FNAB, performed even on millimetric lesions (3 mm of diameter). Moreover pathologic examination of thyroids removed for benign diseases have resulted in increasing diagnosis of TMC, thanks to more accurate cytohistochemical tests. In autopsy studies on patients who have died because of a different disease, up to 35% examined subjects showed a microcarcinoma, suggesting that most of them have an indolent course 3,4. Tumour size has been demonstrated to be a major prog-
nostic factor for differentiated thyroid carcinoma (DTC) and people harbouring DTC less than 1.5 cm in greatest diameter showed a mortality rate comparable to normal population. Nevertheless some TMC is present with cervical lymph node metastasis. In the presence of a TMC, a crucial aspect is to predict whether it is going to be indolent or aggressive, with the possibility of developing local and distant metastasis. For this reason, treatment of TMC has become a dilemma and the question whether operating on these low-risk malignancies is mandatory or not is still a matter of debate. In general, a more aggressive attitude is shown by Authors worried about the malignant nature, that recall up to 11% loco-regional recurrences and some rare cases of distant metastases. Single Institution studies, both prospective and retrospective, share a wide range of behaviours: observation, thyroid lobectomy (TL), total thyroidectomy alone (TT), TT with lymph node dissection, with or without radioactive ablation by iodine (RAI) and/or suppressive therapy and, more recently, an approach regulated on clinical pathologic typing.

The aim of this paper is to review a retrospective series of operated TMC, in order to discuss an optimized and systematic approach of the management of this disease. A further purpose is to evaluate whether TMC with nodal involvement have different aspects than microcarcinoma without lymphatic metastasis. A review of the literature about these arguments is also carried out.

Materials and Methods

In 1733 patients treated for thyroid diseases at the Endocrine Surgery Unit of San Paolo Hospital in Milan, from January 2001 to September 2011, 104 (6.0%) resulted affected with microcarcinoma. They were 85 females and 19 males with a mean age of 49.1 years (range 18-80 years). These patients were divided into two groups: a) those with pre-operative and b) those with post-operative diagnosis of TMC. Patients were further divided in two sub-groups: the ones with lymph node metastasis and the ones without lymph node metastasis, respectively named as N+ and N0.

Group a) consisted of 20 patients (19.2%), 14 females and 6 males, mean age 44.2 years (range 25-74 years), with pre-operative diagnosis of papillary carcinoma. Four patients resulted affected with a single sub-centimetric thyroid nodule, incidentally detected by an ultrasound neck examination, carried out for causes other than thyroid diseases. In all these four cases the lesion shows some aspects suggestive for malignancy. A further 5 patients showed a sub-centimetric nodule, suspicious at ultrasound examination during follow-up for non-functioning goitre or thyroiditis. All 9 patients underwent ultrasound-guided FNAB, with cytological evidence of papillary carcinoma. The other 11 patients had the diagnosis of TMC during the work up of a lateral neck swelling, resulting in a lymphatic metastasis by papillary thyroid carcinoma, in 2 cases after radical excision and in 7 cases after FNAb. Among these 11 patients, 2 were also affected with goitre, with clinical evidence of thyroid nodules, 6 had only ultrasound evidence of small thyroid nodules and 3 had neither clinical nor ultrasound thyroid nodules evidence.

Group b) consisted of 84 patients (80.8%), 71 females and 13 males, mean age 52.3 years (range 18-80 years), with post-operative histological diagnosis of TMC, previously unsuspected. Pre-operative diagnosis was of goitre in 53 (63.1%) subjects, of follicular neoplasm in 13 (15.5%), of goitre and thyroiditis in 7 (8.3%), of Plummer in 3 (3.6%), of Basedow in 2 (2.4%), of goitre associated to primary hyperparathyroidism in 3 (3.6%), of goitre associated to secondary hyperparathyroidism in 2 (2.4%) and of Plummer associated to primary hyperparathyroidism in 1 (1.1%). None of these patients had lymph node metastasis evidence (N0).

Subgroup N+ consisted of 11 (10.6%) patients and N0 of 93 (89.4%).

Surgical Procedures

All 9 patients with pre-operative diagnosis of MTC and no evidence of nodal metastasis (N0) underwent total thyroidectomy. All 11 patients with pre-operative diagnosis of lateral neck lymph node metastasis underwent total thyroidectomy with central neck (level VI) and functional mono-lateral cervical lymph node dissection (level II-V). In 84 patients with post-operative diagnosis of TMC, 76 (90.5%) had total thyroidectomy and 8 (9.5%) lobo-istmectomy. In 2 cases (25%) lobo-istmectomy was completed with controllateral lobectomy after definitive histology: one of these patients was a 36 years old male with tall cell variant of papillary micro carcinoma and the other a 38 years old woman with multifocal micro carcinoma.

Histological Features

In group a), all 9 patients with N0 resulted affected with papillary micro carcinoma: in 1 case the tumour was multifocal (11.1%), in 3 cases it was associated with thyroiditis and in 2 with nodular hyperplasia. In group a) N+, 10 patients resulted affected with papillary micro carcinoma and 1 with “diffusing sclerosis” variant of papillary carcinoma, multifocality was present in 7 cases (63.6%) and in 2 cases goitre was associated to microcarcinoma. In group b) 1 patient resulted affected with “tall cell” variant of papillary TMC and all the others with papillary micro carcinoma, that was multifocal in 12 cases (14.3%).

Post-operative treatment. All patients in group a) and b) were treated by Levo-Thyroxine (L-T4) TSH sup-
pressive therapy. In group a), only 1 patient without lymph node metastasis with multiple foci of microcarcinoma and all the 11 patients with lymph node metastasis underwent 131I RAI. In group b) 1 patient, a male with tall cell variant papillary carcinoma and 12 patients with multifocal microcarcinoma underwent 131I ablative therapy.

**Follow-Up**

Follow-up was carried out by clinical examination and neck ultrasound 6 and 12 months after the operation, then once a year, for all patients undergone lobectomy.

For patients N0, both with pre- and post-operative diagnosis, undergone total thyroidectomy, follow-up consisted of clinical examination, neck ultrasound (thyroid bed, central and lateral lymphatic compartment) and serum thyreoglobulin (TG) determination 6 and 12 months after the intervention. After the first year, the follow-up was based on clinical examination and serum TG level, with indication to neck ultrasound only in case of elevated TG values.

Patients with lymph nodes metastasis (N+), undergone total thyroidectomy and lymph nodes dissection, had clinical examination, TG dosage and neck ultrasound 6, 12 and 24 months after the operation, then clinical examination and TG dosage once a year. After the first 24 months, ultrasound has been indicated, only in case of elevated values of serum TG.

**Statistics.** Differences in clinical parameters were analyzed with a Fisher exact test or unpaired t test, as appropriate. SPSS software (version 10.0, Inc., Chicago, IL) was used in the data analyses. Significance levels were presented as P values. It was assumed that the observed differences were statistically significant at the P<0.05 level.

**Results**

We observed neither recurrences nor death for this pathology, after a mean follow-up of 5.6 years (range 0-10 years).

**Comparison between group a) and b).** (Table I). Mean age was 44.2 years (range 25-74 years; SD 14) in group a) and 50.3 years (range 25-74 years; SD 13.6) in group b). Male/female ratio was 6/4 in group a) and 13/71 in group b). TMC was multifocal in 8/20 (40%) patients in group a) and in 12/84 (14.3%) in group b). TMC was associated to other thyroid diseases in 7/20 (35%) cases (3 goitre and 4 thyroiditis) in group a) and in all patients in group b).

Multifocality was significantly more represented in group a) (p = 0.022), where the diagnosis of malignancy was made pre-operatively.

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**Table I - Comparison between patients with pre-operative (group a) and post-operative (group b) diagnosis of TMC.**

<table>
<thead>
<tr>
<th></th>
<th>Group a)</th>
<th>Group b)</th>
<th>Fisher’s exact test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female ratio</td>
<td>6/14</td>
<td>13/71</td>
<td>P = 0.19</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>44.2 (25-74)</td>
<td>52.3 (18-80)</td>
<td>P = 0.07</td>
</tr>
<tr>
<td>Multifocality</td>
<td>8/20</td>
<td>12/84</td>
<td>P = 0.022</td>
</tr>
<tr>
<td>Associated diseases</td>
<td>7/20</td>
<td>84/84</td>
<td>P &lt; 0.0001</td>
</tr>
</tbody>
</table>

**Table II - Comparison between patients with (N+) and without (N0) lymphatic metastasis.**

<table>
<thead>
<tr>
<th></th>
<th>N+</th>
<th>N0</th>
<th>Fisher’s exact test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female ratio</td>
<td>5/6</td>
<td>14/79</td>
<td>P = 0.027</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>42.7 (25-74)</td>
<td>49.0 (18-80)</td>
<td>P = 0.10</td>
</tr>
<tr>
<td>Multifocality</td>
<td>7/11</td>
<td>13/93</td>
<td>P = 0.0007</td>
</tr>
<tr>
<td>Associated diseases</td>
<td>2/11</td>
<td>89/93 (95.7%)</td>
<td>P &lt; 0.0001</td>
</tr>
</tbody>
</table>

Age distribution showed only a tendency to younger people in group a) (p = 0.07).

Association with other thyroid diseases was present in all group b) patients (100%), by definition and this distribution is obviously biased, meanwhile the presence of associated thyroid diseases was recorded in 7 group a) subjects (35%).

**Comparison between N+ and all N0 (both group a and b).** (Table II). Overall 93 patients without lymph nodes metastasis (N0) were recorded in this series of 104 subjects (89.4%). Mean age was 42.7 years (range 25-68 years SD 17.3) for N+ and 49.8 years (range 18-80 years SD 13.3) for N0. Male/female ratio was 5/6 for N+ and 14/79 for N0. TMC was multifocal in 7/11 patients (63.6%) in N+ and in 13/93 (14.4%) in N0. TMC was associated to other thyroid diseases in 2 cases (thyroiditis) in patients N+ (18.2%) and in 89 N0 (95.7%).

Among N+ patients, TMC showed multifocality in a larger number of cases than N0 (p = 0.0007).

Age distribution was not significantly different between the two groups.

Associated diseases were more often represented among the N0 patients: this finding could be affected by a selection bias in a small series.

**Discussion**

Different circumstances may lead to the discovery of a thyroid microcarcinoma: the accidental disclosure of an unsuspected thyroid nodule during an ultrasound neck
examination, with positive cytology after Fine Needle Aspiration biopsy (FNAb), the discovery of neck lymph node or distant thyroid metastases, for which the thyroid origin has been shown by positive FNAb and surgery for benign thyroid disease. In the first two situations the diagnosis of TMC is pre-operative, in the last one it is post-operative. These different modes of diagnosis may reflect different populations regarding TMC behaviour, as well as different medical approaches.

Thyroid nodules less than 1 cm. in their main dimension are often discovered accidentally during imaging studies of the cervical organs, which are being carried out for other reasons, because in the majority they are not palpable. Sometimes they have been termed incidentalomas, although this term originally referred to unsuspected adrenal masses. Whether to treat incidental TMC is debated, because of the low mortality and its usually slow growth rate. On the basis of statistical evidence from autopsy series, Ito et al. found that the prevalence of latent TMC, measuring 3.0-9.9 mm in autopsy specimens, have been reported to range from 0.5 to 5.2%, whereas the prevalence of clinically evident thyroid papillary carcinoma is one thousand times less frequent, accounting for 1.9 to 11.7 per 100000 females. This difference suggests that thyroid micro carcinoma grows slowly and seldom becomes a threatening clinical entity: Ito et al. concluded that TMC could be candidates for observation regardless of patients' background and clinical features. If there were subsequent signs of progression, such as tumour enlargement and novel nodal metastasis, it would not be too late to perform surgical treatment. Behind any statistical evidence, in our opinion, the patient's anxiety due to the knowledge of harbouring a malignant lesion is a significant argument in favour of surgery. In our experience 8.7% of all treated micro carcinomas, were nodules less than 1 cm. accidentally discovered during imaging studies of the neck. In all these cases we performed total thyroidectomy. In literature, the kind of operation for diagnosis of TMC is pre-operative, in the last one it is post-operative. These different modes of diagnosis may reflect different populations regarding TMC behaviour, as well as different medical approaches.

For treatment of microcarcinoma detected pre-operative-ly by the presence of neck nodal metastasis, 10.6% in our series, there is a clear general agreement: the recommended operation is a total thyroidectomy, associat-
ted with central and lateral cervical lymph node dissec-
tion, followed by suppressive therapy and RAI. An unsolved question is whether microcarcinoma, which pre-

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sents with nodal metastasis, may be considered the same kind of tumour of microcarcinoma without metastasis. In our series we noted some differences between patients N+ and N0: tumour was multifocal, with multiple microscopic cancer foci, not detectable at ultrasound and in thyroid with no other diseases, in N+ in a greater rate than in N0 patients. The number is too small to conclude that the two groups are significantly different, but it may be a hint to further investigation in a larger series.

Moreover this data may support the trend to total thyroidectomy, when the diagnosis of microcarcinoma is made pre-operatively, especially in thyroid without other diseases, both because of the risk of multifocality and because of the apparent greater aggressiveness of MTC with this characteristics.

The more frequent situation still remains papillary cancer < 1 cm, diagnosed by the Pathologist after thyroid resection, which has been carried out for benign diseases, 80.8% cases in our series. The main problem arises when the diagnosis of TMC is after a partial thyroidectomy. What may be indicated to do? Is it always necessary to complete the thyroidectomy or partial thyroid resection may be considered adequate? In these cases there is also not agreement in literature. We believe, according to other Authors, that radicalization is necessary only in selected cases. We radicalized 2 of 8 patients (25.0%) with post-operative diagnosis of TMC, because of adjunctive risk factors: histological type (tall cell variant) and sex (male) in one case and multifocality in the other one. Even in these cases a question would arise whether post-operative \(^{131}\)I ablation or suppression therapy should be done and the arguments are the same as discussed for patients with pre-operative diagnosis of TMC, without evidence of lymph node metastasis: we always administrate suppressive therapy and RAI only in selected cases, as mentioned before.

Conclusion

From the discussion above, treatment of TMC shows a variety of behaviours due to the lack of larger prospective multicentric trials. Although long-term observation is a suggestive item, in our opinion it still needs confirmation. TMC, which presents with nodal involvement, seems to show some differences versus TMC without metastasis, even if this data needs further confirmation, in larger series. To summarize, we adopt therapeutic schedule as follows.

In patients with pre-operative diagnosis of microcarcinoma, with no evidence of nodal metastasis, we perform: total thyroidectomy, always with post-operative L-T4 TSH suppressive therapy and \(^{131}\)I ablation only in selected cases, with the adjunctive risk factors discussed above: patients’ characteristics (age and sex) and tumour aspects (histology and multifocality).

In patients with pre-operative diagnosis of cervical lymph nodes metastasis we perform: total thyroidectomy, central neck and functional cervical lymph nodes dissection, always followed by L-T4 TSH suppressive therapy and \(^{131}\)I ablation.

In patients with post-operative diagnosis of microcarcinoma, who underwent total thyroidectomy we perform: always post-operative L-T4 suppressive therapy and \(^{131}\)I ablation only in selected cases (with the adjunctive risk factors discussed above). In cases of partial thyroidectomy: always L-T4 TSH suppressive therapy and radicalization only in patients with adjunctive risk factors discussed above. For all patients who undergo radicalization, always L-T4 TSH suppressive therapy and \(^{131}\)I ablation only in selected cases, on the basis of patients’ characteristics (age and sex) and tumour aspects (histology and multifocality).

Obiettivo: Il microcarcinoma della tiroide è un tumore differenziato con diametro inferiore o uguale a 1 centimetro, il cui trattamento è attualmente ancora largamente dibattuto. Lo scopo del lavoro è ottimizzare l’approccio a tale neoplasia, attraverso la revisione della casistica degli Autori e della letteratura.

Metodi: Fra 1733 pazienti operati per tireopatie, presso l’Unità di Chirurgia Endocrina dell’Ospedale San Paolo di Milano, dal 2001 al 2011, 104 (6.0%) sono risultati affetti da microcarcinoma. Di questi, sono stati esaminati caratteristiche, trattamento e risultati a distanza. Si è trattato di 85 femmine e 19 maschi, età media 49.1 anni, 20 con diagnosi pre-operatoria e 84 post-operatoria, 11 con (N+) e 93 senza (N0) metastasi linfonodali. Osservavano pazienti sono stati sottoposti a tiroidectomia totale, 11 (N+) a tiroidectomia totale con linfadenectomia e 8 a lobectomia, 2 radicalizzati in tiroidectomia totale dopo l’esame istologico. Tutti sono stati trattati con Levotiroxina a dosaggio TSH soppressivo, 25 (24%) con radioablazione con \(^{131}\)I. Sono state inoltre ricercate eventuali differenze fra pazienti con metastasi linfonodali (N+) e senza (N0).

Risultati: Non sono stati osservati decessi legati alla patologia in esame, ne recidive ad un follow-up medio di 5.6 anni. Il tumore è risultato multifocale e in tiroide sana in una percentuale maggiore nei pazienti con metastasi linfonodali (N+) rispetto a quelli senza (N0).

Discussione: Nella casistica presentata, come in letteratura, il microcarcinoma tiroideo sembra una neoplasia con una buona prognosi, sia in presenza che in assenza di metastasi linfonodali alla diagnosi. La possibilità che un microcarcinoma possa dare metastasi, lascia comunque ancora ampi dubbi sul reale comportamento biologico di questo tumore. Questo fa sì che in letteratura ci sia una certa variabilità nei trattamenti proposti. Si passa dai Autori che propongono il semplice follow-up cli-
Comunque per i pazienti in cui la diagnosi di microcarcinoma sia pre-operatoria, a diversi trattamenti chirurgici, dalla lobectomia, alla tiroidectomia totale senza o con linfadenectomia.

CONCLUSIONI: Sulla base dell’esperienza presentata, in caso di diagnosi pre-operatoria di microcarcinoma, senza metastasi linfonodali, proponiamo la tiroidectomia totale, altrimenti la tiroidectomia totale con linfadenectomia.

In caso di diagnosi post-operatoria, dopo resezione tiroidea parziale, proponiamo il completamento in tiroidectomia totale solo in casi selezionati, sulla base delle caratteristiche del paziente e del tumore. Sottoponiamo a terapia soppressiva con levotiroxina tutti i pazienti, a trattamento radiometabolico quelli con metastasi linfonodali. In assenza di secondarismi linfonodali la terapia radiometabolica viene indicata in casi selezionati, in funzione di età, sesso, variante istologica e multifocalità del tumore.

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Commento e Commentary

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L’incidenza del carcinoma tiroideo si è progressivamente accresciuta nel corso degli ultimi decenni sia per un reale aumento di questa patologia sia per il miglioramento della diagnosi clinica e strumentale. L’introduzione di apparecchi per ecografia ad alta risoluzione coniugata alla valutazione citologica ecoguidata ha contribuito all’accertamento diagnostico della lesione definita microcarcinoma, neoplasia inferiore ad un centimetro di diametro, di riscontro spesso incidentale all’esame del collo.

L’importanza clinica di questa patologia è legata oltre che al sempre più frequente riscontro soprattutto al suo comportamento biologico, poiché se è vero che presenta nella maggioranza dei casi una prognosi eccellente, che giustifica atteggiamenti terapeutici meno aggressivi, numerose sono le esperienze con prognosi più severa per ricorrente morbilità e a volte mortalità che ne mettono in discussione il significato clinico ed il trattamento1. Molti studi sono stati indirizzati alla caratterizzazione clinica ed istopatologica del microcarcinoma al fine di individuare i “fattori prognostici” associati alle recidive e proporre per questi casi ad alto rischio linee guida per un più idoneo trattamento. Lo studio di L. De Pasquale et al. è di particolare interesse e i dati presentati confermano l’importanza della metastasi linfonodale all’atto della diagnosi, quale fattore di rischio di recidiva locale e a distanza. I risultati di una nostra esperienza, a riguardo, hanno individuato quali importanti fattori di rischio oltre al coinvolgimento linfonodale anche alcune caratteristiche istopatologiche, quali la struttura solida e la mancanza di capsula della lesione2.

Concordiamo con gli A.A. che in tutti i pazienti con diagnosi pre-operatoria di microcarcinoma l’intervento di elezione debba essere la tiroidectomia totale con linfektemia centrale e laterocervicale di necessità. La lobectomia ed il trattamento radio-ablativo sono indicati in casi selezionati3.

Importante nel follow-up è controllare la terapia sostitutiva/soppressiva ed identificare precocemente la comparsa di recidive locali o a distanza della malattia, che compaiono elettivamente nel collo ed in tempi anche molto tardi.

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The incidence of papillary thyroid cancer (PTC) overall has increased over the past several decades. It is estimated that in recent years, as the use of high-quality ultrasonography and fine-needle aspiration biopsy US guided have increased, suspect sub-centimetric nodules are more often discovered and papillary microcarcinomas (PMGs) are being identified with greater frequency. PMGs are also frequently identified incidentally at surgery for benign thyroid disorders. Despite the overall excellent prognosis for patients with PMG, however, recurrent or persistent disease after surgery is surprisingly common and a small subgroup of PMGs have the potential to behave aggressively and metastasize early, resulting in increased morbidity and mortality. Many authors have investigated independent factors associated with recurrence in an effort to define therapeutic guidelines. The interesting study of L. De Pasquale et al. reports the experience of their centre and represents a further contribution in confirming that lymph node metastases at presentation and extent of surgery may be identified as determinant risk factors. In a retrospective study we focused our attention on the histologic features as the absence of the capsule and the solid pattern of the lesion as predictive factors of poor outcome. We agree with the authors that the treatment of patients with PMG should be no different from the treatment of the patients with conventional PTC, and total thyroidectomy should be the surgery of choice. The routine therapeutic lymph node dissection at the time of thyroidectomy is warranted in patients with positive neck nodes at presentation. Prophylactic central lymph node dissection is not recommended in clinical negative neck. Consideration for RAI therapy must be undertaken if poor prognostic factors are present. Lobeectomy may be sufficient therapy in selected cases.

Patients with PMG require minimal, but long-term monitoring and higher priority should be placed on follow-up with neck ultrasonography because 95.5% of recurrences first appear in the neck.

REFERENCES