



Occult Well Differentiated Thyroid Carcinoma Presenting as Cervical Node Disease

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Abstract. Records of 92 patients with differentiated thyroid carcinoma presenting as cervical adenopathy without a palpable mass were reviewed to identify prognostic factors and to evaluate therapy. Patients were treated between 1940 and 1990 and were observed for 3 to 48 years (median 18 years). Follow-up data were obtained by chart review, correspondence, and telephone contact. Among the group, 20 patients had unilateral and 72 bilateral thyroid lobectomy, with node dissection in 77. Thyroid hormone was used in 50 patients and radioactive iodine in 20. Patients were younger than the overall population of patients with differentiated thyroid carcinoma, with more men and more multifocal thyroid disease. Risk group defined by age and sex was the most important determinant of survival. All women 50 years of age or younger and all men 40 or younger (low risk group) survived independent of the type of initial operation or use of thyroid-stimulating hormone suppression or radioactive iodine. Of the low risk patients, 16% had recurrent disease but were treated successfully with surgery or radioactive iodine; 28% of the older patients (high risk) died of disease. A trend for better survival was noted in high risk patients undergoing bilateral thyroidectomy and in patients receiving thyroid suppression. Of the high risk patients, 26% had recurrent disease, with a 71% mortality rate. Age and sex are the primary determinants of survival. Therapy should be based on risk factors. Low risk patients should have conservative thyroid surgery and modified or limited node dissection. However, bilateral thyroid surgery may facilitate the use of radioactive iodine when required. Use of prophylactic radioactive iodine or thyroid suppression should be selective. For high risk patients, we suggest bilateral thyroidectomy, modified or limited node dissection, thyroid suppression, and radioactive iodine.

Among well differentiated carcinomas of the thyroid, some tumors, reported variously from 10% to 26% [1–3], present as a lateral neck mass with no palpable tumor in the thyroid. Historically, some of these tumors were called “lateral thyroid rests.” They are now recognized as cervical lymph node metastases of an occult primary tumor in the thyroid.

The prognosis and best management of patients whose disease presents this way are still controversial. As many as 90% of papillary thyroid carcinomas have microscopic involvement of the lymph nodes [4], but this factor may not necessarily affect survival or require lymph node dissection. Some authors [2] have identified thyroid carcinoma presenting as a neck mass as more aggressive disease; other authors [1] have pointed out that, in the young patient, lymph node metastases are not necessarily lethal. Opinions vary among authorities on the subject of management of both the thyroid disease

and the cervical lymph nodes [3]. The issue of the different risk groups, as defined by Cady and Rossi [5], is widely recognized to affect survival with thyroid carcinoma as a whole. The importance of these risk groups to this particular subset of patients with carcinoma of the thyroid is less widely acknowledged.

To identify factors that affect prognosis and to evaluate the effect of different therapies on survival, we reviewed records of patients who were seen with cervical lymphadenopathy as the manifestation of well differentiated carcinoma of the thyroid.

Patients and Methods

Of 885 patients with papillary or follicular carcinoma of the thyroid who have been observed from 1940 to 1990 at the Lahey Clinic, 92 had cervical adenopathy and no palpable thyroid mass on presentation. Their records had been reviewed for demographic data and clinical presentation, the nature of their surgical treatment, and subsequent therapy. They underwent follow-up studies from 3 to 48 years (follow-up time had both a mean and a median of 18 years) from the time of their operation for outcome, recurrent disease, and survival. Follow-up data were obtained by chart review, correspondence, and telephone contact.

Survival was calculated using the product-limit method of Kaplan and Meier using BMDP1L statistical software (BMDP1L Statistical Software, Los Angeles, CA, USA) [6]. Survival distribution between groups was compared using the Tarone-Ware test [7]. Probability was two-tailed, with $p < 0.05$ regarded as statistically significant.

Results

Patients with cervical lymphadenopathy on presentation tended to be younger (median age 34 years, range 5–73 years) than the group as a whole (median age 43 years, range 5–87 years). Male patients made up 46% of the group presenting with nodes compared with only 27% of thyroid carcinomas overall. The male patients were older, with a median age of 40 years, compared with the median age of female patients of 29 years.

Pathologic findings in the group with nodes on presentation included 93% papillary or mixed papillary and follicular, with 7% follicular tumors. In the larger group of 885 patients with well differentiated carcinoma, 75% were papillary and 25% were follicu-

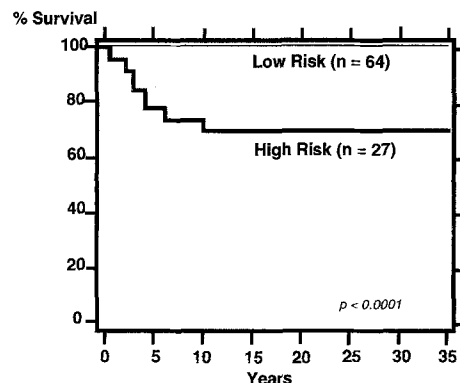


Fig. 1. Adjusted survival: high risk versus low risk.

lar lesions. Of the 92 patients comprising this study, 25% had multiple foci of tumor in the thyroid compared with only 13% of the 885 patients in the overall group having multifocal disease ($p = 0.005$). The rates of major capsular invasion were 44% and 36%, respectively; and rates of blood vessel invasion were 38% and 33%, respectively.

The groups were stratified into risk group according to age, metastases to distant sites other than lymph nodes, extent of primary tumor, and size larger than 5 cm (AMES criteria) [5]; women aged 50 years or less and men aged 40 years or less were in the low risk group ($n = 64$), and patients who were older at the time of diagnosis were in the high risk group ($n = 27$). Because all of the patients presented with *occult* primary carcinoma, making distant metastases, extent, and size less relevant in this group, the risk groups in this sample were defined primarily only by age and sex. The risk group was by far the most important determinant of survival (Fig. 1), with all low risk patients alive at 10 years, whereas only 60% of the women and 72% of the men in the older higher risk group survived ($p < 0.0001$ and 0.01, respectively). No deaths from disease occurred after 10 years postoperation. Two patients in the low risk group were alive with disease at 5 and 7 years after operation. One patient had metastasis to the lung on presentation, and the other had a minimally elevated thyroglobulin level as the only evidence of persistent disease.

Regardless of risk group, survival was not significantly affected by several other tumor characteristics. Patients with predominantly papillary carcinoma had an 89% ten-year survival compared with 100% survival for patients with mixed papillary and follicular carcinoma and 100% survival for patients with follicular carcinoma ($p = 0.4454$). Major capsular invasion was associated with a 92% ten-year survival compared with a 91% survival without major invasion. The number of nodes involved did not affect survival: 90% of patients with four or fewer positive nodes survived 10 years compared with 95% of patients with more than four positive nodes.

When the effect of different therapies was studied, no statistical difference was found on survival taking the group as a whole, although a trend was apparent for better survival for patients having bilateral thyroid surgery. The trend in the whole group toward better survival after bilateral surgery is explored further later; it was exclusively the result of better survival in the high risk group. This finding correlates with the findings of other authors [8, 9]. Unilateral lobectomy (20 patients) was associated with an 85% ten-year survival compared with 94% survival for patients having bilateral surgery (71 patients; $p = 0.1614$). Before 1980 bilateral surgery was usually

bilateral subtotal resection; since 1980 bilateral surgery has more often been ipsilateral total resection with contralateral subtotal lobectomy.

Neck dissection has become less radical in recent years. Before 1960 lymphadenectomy consisted of radical neck dissection in 84% of patients. Recently, the trend is to less aggressive surgery, with modified radical or limited neck dissections performed in 85% of patients since 1980. The type of node dissection was not associated with any alteration in survival. Radical neck dissection ($n = 41$) was associated with a 97.5% survival, modified dissection ($n = 23$) 85.6% survival, and limited dissection ($n = 13$) 100% survival, with a p value of 0.077 (no significant difference).

Complications have become less common in recent years. Temporary recurrent nerve paralysis occurred in two patients and permanent cord paralysis in five patients (5%), all but one of these five complications being in patients who had had surgery before 1960. Prolonged hypocalcemia occurred in one patient from 1954. Horner syndrome developed in one patient after neck dissection in 1982, and one patient who had surgery in 1950 had postoperative bleeding severe enough to require tracheostomy. Of the eight patients with significant complications (cord paralysis, severe bleeding, or late hypocalcemia), all had had bilateral procedures. Five complications were in low risk patients and three in high risk patients. No complications occurred in the seven patients who had had unilateral total and contralateral subtotal thyroidectomy, all of whom had surgery in 1983 or later. Seromas developed in two patients (2%), and one patient had a wound infection. Clinical hypothyroidism (myxedema) developed in three patients in the low risk group and in one patient in the high risk group. No operative deaths occurred.

The use of radioactive iodine or thyroid medication preoperatively was also not associated with a significant difference in survival of the group as a whole. Ten-year survival was 93% without radioactive iodine and 84% with radioactive iodine treatment ($p = 0.6729$). Postoperative thyroid hormone replacement had a slight but not significant association with greater survival (96% versus 87% without thyroid hormone; $p = 0.1660$). The group of patients treated with radioactive iodine, thyroid medication, or both appeared to be similar in terms of the extent of the primary tumor, age, and ratio of high risk or low risk patients to patients untreated. Forty-one patients received thyroid replacement, and fifty-one patients did not. Of the patients who received medication, 70% were in the low risk group, with a median age of 27 years for women and 37 years for men. Of patients who did not receive medication, 63% were in the low risk group, with a median age of 32 years for women and 40 years for men. Of course, patients with total or subtotal thyroidectomy might require replacement therapy as a separate issue from thyroid hormone for suppression of thyroid-stimulating hormone.

Twenty patients received radioactive iodine, and 72 did not; 75% of patients who received radioactive iodine were in the low risk group, and 72% of patients who did not receive radioactive iodine were in the low risk group. The median age was 26 years for women and 37 years for men in the treated group versus 29 years for women and 40 years for men in the untreated group.

We then considered the effect of various therapies on the different risk groups. The low risk group, as mentioned, had 100% survival at 10 and 20 years, 14 of these patients had unilateral lobectomy, and 50 patients had bilateral procedures. Of these 64 patients, 10 had recurrent disease, 7 of whom had local (nodal)

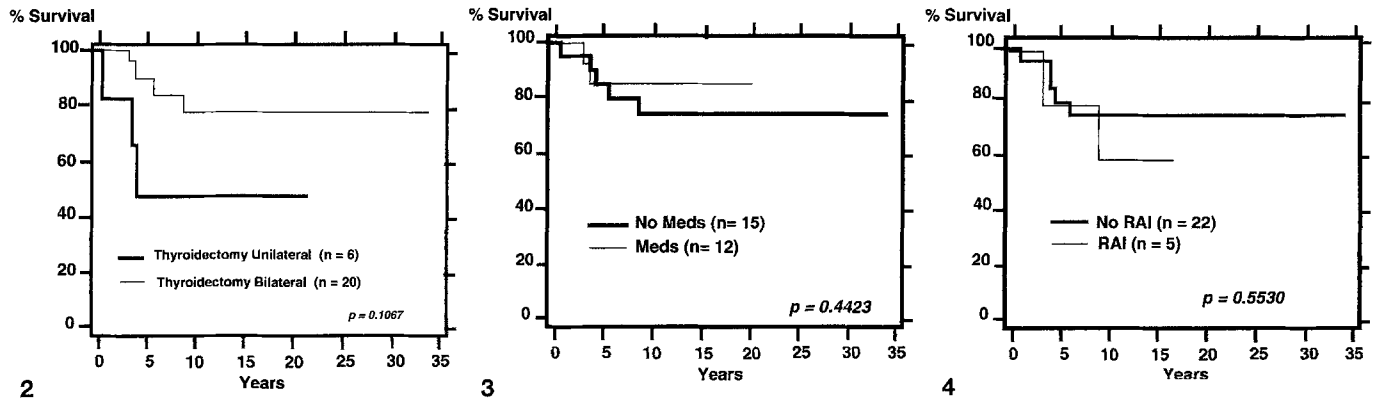


Fig. 2. Adjusted survival: high risk by extent of thyroid surgery.
 Fig. 3. Adjusted survival: high risk and thyroid suppression.
 Fig. 4. Adjusted survival: high risk and use of radioactive iodine.

disease that was treated surgically. Three patients had distant recurrent disease, all to the lung, and all were treated successfully with radioactive iodine.

Of the 14 patients in the low risk group who had unilateral operations, two patients had recurrent disease. One lesion was in the cervical lymph nodes and was treated successfully surgically. The other recurrent lesion was pulmonary and was treated successfully with radioactive iodine. It appears unlikely that either instance of recurrent disease would have been prevented with a bilateral procedure initially. The bilateral operation could have facilitated the use of radioactive iodine therapy in two patients (14%). Its prevention by routine use of radioactive iodine is controversial. No patient in either the high risk or low-risk group had recurrent disease in the thyroid gland or thyroid bed. Radioactive iodine may still be used if needed after a less than total thyroidectomy. The thyroid remnant is ablated first, then the recurrent disease.

The high risk group displayed some trend toward better results with more aggressive surgery, although none was statistically significant. As with the entire group, patients who were treated with radioactive iodine, thyroid medication, or both appear similar to the untreated patients. Those who had unilateral surgery (removal of a nodule, which was only performed before 1960, or unilateral lobectomy) had a 50% ten-year survival compared with a 79% ten-year survival for patients having bilateral surgery (bilateral subtotal, bilateral total, or ipsilateral total and contralateral subtotal; $p = 0.107$) (Fig. 2). Seven patients without node dissection had a 10-year survival of 57% compared with 89% for the 28 patients having thyroidectomy with node dissection ($p = 0.0814$). However, of the seven patients without node dissection, one patient had pulmonary metastases at presentation; bilateral thyroidectomy was performed, and the patient died of disease after 3 years. The two other patients without node dissection who died of disease were treated before 1950 and had biopsy only. One received radioactive iodine and died at 4 years. The other patient died at 3 years.

When medical treatment was considered, survival with thyroid-stimulating hormone suppression with thyroid medication in the high risk group was 65% without treatment versus 82% with treatment ($p = 0.44$) (Fig. 3). Of patients who received radioactive iodine 60% survived 10 years, whereas 75% survived without treatment ($p = 0.55$) (Fig. 4). However, patient selection in this retrospective group is uncertain.

Recurrence of disease in the high risk group, contrasted with

the low risk group, was a grave prognostic sign associated with a 70% mortality rate. Seven patients in the high risk group had recurrent disease. Five patients had initially had bilateral thyroidectomy, and two had had unilateral thyroid procedures. In these seven patients, there were three local recurrences (soft tissue, thyroid bed, or both), three nodal recurrences, and three distant metastases (lung). The three patients with distant disease (lung) were treated with radioactive iodine. Of these seven patients, five died of disease, one died without disease, and one whose recurrent lung lesion was treated with radioactive iodine is alive and apparently well 15 years after operation.

Comment

Well differentiated thyroid carcinoma remains a controversial topic, especially with regard to how aggressive its optimal surgical treatment should be. One element contributing to the confusion is the heterogeneous nature of these tumors, with sharp differentiation in prognosis by age, sex, and tumor size [5]. Another element is that their behavior is unusual for a malignant lesion in that metastases to lymph nodes, at least from papillary carcinoma, are frequent [4, 10, 11] but clinically not an indicator of poor prognosis in this and other studies [5, 12]. This point has been questioned by some authors [13].

In a review of our experience with the subset of patients who had cervical lymphadenopathy and occult thyroid disease on presentation, we saw both of these characteristics of the disease. The low risk group did well despite differences in surgical treatment over a 50-year span and despite postoperative medical intervention or the lack thereof. The high risk group, however, with an otherwise similar presentation, had a much worse prognosis. It was in this high-risk group that differences in treatment appeared to have an effect on how the patients fared, although this difference did not reach statistical significance, perhaps because of our small sample size. Also because of the retrospective nature of the study, some questions about patient selection for specific therapies must remain.

The importance of risk groups in predicting outcome of patients with papillary or follicular thyroid carcinoma has been recognized for some time [5, 12, 14]; women less than 50 years of age and men less than 40 years of age have a much better prognosis than older patients of either sex. Other important variables—the size of the

primary tumor and extraglandular extension—were not distinguishing factors in our group of all occult tumors. Many other prognostic scores, such as the AGES system of the Mayo Clinic [15], show a strong relation of age to prognosis.

When the AMES risk groups were outlined by Cady and Rossi [5] in 1988, the intended application was to select a conservative surgical approach in the low risk patient at the time of surgery. However, there continue to be many advocates for total thyroidectomy for all thyroid carcinomas [3, 16] despite the fact that “total” thyroidectomy may in fact leave thyroid tissue detectable on thyroid scans postoperatively [16]; and in the experience of the occasional thyroid surgeon, the risk of total thyroidectomy may be considerably higher than for subtotal or unilateral thyroidectomy.

In our subset of patients, no difference was seen in the low risk group by type of operation. All the low risk patients did well with either unilateral lobectomy (14 patients) or bilateral subtotal or total procedures (50 patients). In the high risk group, however, a trend toward better outcome was observed with more extensive thyroid surgery.

In consideration of node dissection, over the past 50 years the trend has been away from radical and toward limited or modified neck dissection. More radical surgery does not appear to improve prognosis and is associated with more complications [14, 17].

Other studies [2, 18, 19] that have looked at the treatment of patients with metastases to lymph nodes have suggested that extension of disease in itself was a marker for more aggressive disease. Fewer studies have made reference to age-defined and sex-defined risk groups; one study [20] found that all deaths occurred in patients diagnosed after the age of 40 years (not broken down by sex), and another study [14] found no difference in survival between risk groups. By contrast, our study found considerable differentiation in tumor behavior for the high risk group by age and sex. Obvious cervical lymph node metastases were not an indicator of aggressive disease in women less than 50 years of age and in men less than 40 years of age.

Despite evidence that microscopic lymph node metastases are not clinically important, especially in terms of survival [4, 5, 12], many surgeons [1, 10, 11, 18, 19, 21] continue to call for elective lymph node dissection for microscopic nodal disease. Our study, which did not include patients with only microscopic lymph node metastases, would not support an aggressive approach to the lymph nodes at least in the low risk patient. We would not advocate prophylactic lymph node dissection without obvious disease.

Postoperative medical treatment of patients with papillary and follicular thyroid carcinoma has consisted of thyroid replacement with thyroid-stimulating hormone suppression, radioactive iodine therapy, or both, each of which we have used more extensively in recent years. As with surgery, the use or not of both medical therapies had no effect on the low risk patient, who did well regardless of treatment. In the high risk patient again the use of thyroid replacement tended to improve prognosis, although again this figure did not reach statistical significance, perhaps because of sample size. We did not see any effect on prognosis with the use of radioactive iodine in the high risk patient; the one high risk patient whose recurrence was treated successfully with radioactive iodine, however, illustrates that this therapy may find useful application in individual cases.

The prognosis of patients with occult thyroid carcinoma presenting as cervical adenopathy depends primarily on the risk group at presentation as defined by age and sex, with all low risk

patients surviving. It is only in the high risk patients that more aggressive surgical or medical treatment appears to be warranted and in our study showed a tendency to be reflected in a better outcome. We advocate modified neck dissection and currently perform near-total or total thyroidectomy for high risk patients when it can be performed safely. We avoid unnecessary routine extensive surgical procedures in the low risk group. Ipsilateral lobectomy probably suffices, although in most instances we add contralateral subtotal lobectomy, which facilitates the management of recurrent disease with radioactive iodine. Total thyroidectomy may not increase survival, except possibly in the high risk group, and therefore the occasional thyroid surgeon may favor subtotal or even a unilateral procedure in the low risk patient if it is safer in his or her experience. Routine use of radioactive iodine in the low risk patient is not warranted. We continue to use thyroid replacement, especially in the high risk patient, until additional information is available, both for thyroid-stimulating hormone suppression and replacement of thyroid hormone after removal of the gland. Therapeutic use of radioactive iodine has been effective in managing recurrent and metastatic disease.

Résumé

Les dossiers de 92 patients ayant un cancer de la thyroïde différencié révélé par une adénopathie sans tumeur thyroïdienne palpable ont été analysés afin d'identifier des facteurs pronostiques et une attitude thérapeutique. Parmi des patients traités entre 1940 et 1990, la durée de surveillance a varié entre 3 et 48 ans (médian 18 ans). Le suivi a été obtenu par analyse retrospective des dossiers par correspondance et par téléphone. Vingt patients ont eu une lobectomie unilatérale, 72, une thyroïdectomie bilatérale, associée à un curage chez 77. L'hormonothérapie a été utilisée chez 50 patients, et l'iode radioactif chez 20. Comparés à la population générale des patients ayant un cancer bien différencié de la thyroïde, ces patients étaient plus jeunes, avec plus d'hommes et plus de maladie multifocale. L'âge et le sexe étaient les éléments déterminants les plus importants pour définir la population à risque. Les femmes de 50 ans ou plus jeunes et tous les hommes de 40 ans ou moins (groupe à risque peu élevé) ont survécu indépendamment du type d'intervention initiale ou de la thérapie hormonale ou radioactive. Parmi ces patients, 16% avaient une récurrence mais celle-ci a pu être traitée avec succès soit par la chirurgie soit par l'iode radioactif. 28% des patients plus âgés (risque élevé) sont décédés de leur maladie. Parmi ces patients à risque élevé, on note une meilleure survie lorsqu'ils ont eu une thyroïdectomie bilatérale, et quand ils ont reçu une thérapie suppressive. 26% de ces patients ont eu une récurrence avec une mortalité de 71%. L'âge et le sexe étaient déterminants dans la survie. Nous recommandons une attitude thérapeutique basée sur ces données. Chez le patient à risque peu élevé, on peut pratiquer une chirurgie conservatrice avec une lymphadénectomie limitée ou modifiée. La thyroïdectomie bilatérale peut, cependant, être indiquée pour faciliter l'utilisation de l'iode radioactif lorsqu'elle est indiquée. Chez le patient à risque, nous suggérons de pratiquer une thyroïdectomie bilatérale, un curage limité ou modifié, une thérapie hormonosuppressive et l'iode radioactif.

Resumen

Se revisaron las historias clínicas de 92 pacientes con carcinoma diferenciado de tiroides que se presentaron como adenopatía cervi-

cal sin masas palpables a fin de identificar factores de pronóstico y de evaluar la terapia. Los pacientes fueron tratados en el período entre 1940 y 1990 y fueron observados por 3 a 48 años (media, 18 años). Los datos de seguimiento se obtuvieron mediante revisión de la historia, correspondencia y contacto telefónico. En 20 pacientes se practicó lobectomía unilateral, 72 tiroidectomía bilateral y en 77 disección ganglionar. Se utilizó hormona tiroidea en 50 pacientes y yodo radioactivo en 20. Los pacientes de esta serie aparecieron más jóvenes, con mayor incidencia de hombres y más predominio de enfermedad multifocal, en comparación con la población general de pacientes con carcinoma diferenciado de tiroides. El grupo de riesgo definido por edad y sexo, fue el factor determinante de sobrevida de mayor importancia. Todas las mujeres de 50 años de edad o menores y todos los hombres de 40 años o menores, que constituyen el grupo de bajo riesgo, sobrevivieron en forma independiente del tipo de operación inicial o del régimen de supresión de la hormona tiroide-estimulante o del uso del yodo radioactivo. De los pacientes de bajo riesgo, 16% presentaron enfermedad recurrente pero fueron tratados exitosamente con cirugía o con yodo radioactivo; 28% de los pacientes de mayor edad, o sea el grupo de alto riesgo, murieron por causa de la enfermedad. Se observó una tendencia hacia mejor sobrevida en los pacientes de alto riesgo que fueron sometidos a tiroidectomía bilateral y en los pacientes recibieron supresión tiroidea. De los pacientes de alto riesgo, el 26% tuvo enfermedad recurrente con una mortalidad de 71%. La edad y el sexo son los factores determinantes primarios de sobrevida y la terapia debe ser basada en los factores de riesgo. Los pacientes de bajo riesgo deben ser sometidos a cirugía tiroidea conservadora y a disección ganglionar modificada o limitada. Sin embargo, la tiroidectomía bilateral puede facilitar el uso del yodo radioactivo en los casos en que éste sea necesario. El uso del yodo radioactivo profiláctico o de la supresión tiroidea debe ser selectivo. Para los pacientes de alto riesgo, sugerimos tiroidectomía bilateral, disección ganglionar modificada o limitada, supresión tiroidea y yodo radioactivo.

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Invited Commentary

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This paper by Sanders and Rossi addresses an important clinical situation, which is how patients presenting with lymph node metastases should be managed. The authors conclude

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that high risk patients should be treated by "bilateral" thyroidectomy, modified or limited node dissection, thyroid suppression, and radioactive iodine ablation, whereas low risk patients should be treated by "conservative" thyroid surgery and modified or limited node dissection. They add that bilateral thyroid surgery may facilitate the use of radioactive iodine when required.

The paper is an excellent retrospective study of 92 patients (64 patients were considered to be in a low risk category and 28 were at high risk based on the AMES classification) [1]. Their selection