Detection of Medullary Thyroid Carcinoma and Regional Lymph Node Metastases by Magnetic Resonance Imaging

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Objectives: To evaluate the usefulness of magnetic resonance imaging in detecting primary medullary thyroid carcinoma (MTC) and regional metastasis to the lymph nodes, and to correlate magnetic resonance signal intensity to pathologic changes.

Materials and Methods: Magnetic resonance images in 14 patients with MTC (9 with primary disease, 5 with recurrent disease) were reviewed for signal intensities, tumor morphologic characteristics, and tumor invasion with spin-echo T1-weighted images (T1WIs), T2-weighted images (T2WIs), and gadolinium-enhanced T1WIs. Multiple regression analysis was used to examine the correlation between T2-weighted signal intensity and pathologic findings. Lymph nodes were evaluated based on signal and morphologic characteristics.

Results: Magnetic resonance imaging detected tumors in 9 (90%) of the 10 patients who had MTC in the thyroid gland. Extrathyroidal spread of the tumors was correctly predicted using this procedure. Most tumors were hypointense or markedly hypointense on T2WI. T2-weighted signal intensity of the tumor was associated with increased amyloid deposition and high tumor cellularity and low level of fibrosis (r = 0.91, P = .01). Lymph node metastasis was present in 35 (23%) of 168 surgically dissected nodes. The combined use of 4 criteria (nodule size, a minimum-maximum diameter ratio of 0.80 or greater, marked hypointensity on T2WI, and necrosis in the node) yielded a high detection accuracy (93%) for nodal metastasis, with 74% sensitivity and 98% specificity.

Conclusions: Magnetic resonance imaging is useful for detecting primary and recurrent MTC, and its signal intensity reflects the underlying pathologic changes.


Medullary thyroid carcinoma (MTC) accounts for 3.5% to 12% of all thyroid malignant neoplasms. The female-to-male ratio ranges from 1:1 to 1:1.3, and the mean age range at diagnosis is 44 to 52 years. The tumor occurs in either sporadic (74%-78% of all patients) or familial (22%-26%) form.1,4 The familial form is frequently associated with multiple endocrine neoplasia (MEN) II syndrome. Medullary thyroid carcinoma usually occurs as a component of MEN IIa syndrome, while it is uncommon in MEN IIb syndrome. Multiple endocrine neoplasia IIa syndrome is a multigang tumor condition characterized by the presence of MTC, adrenal pheochromocytoma, and hyperplasia of the parathyroid glands.

Medullary thyroid carcinoma tumors produce calcitonin, which serves as a specific tumor marker, while amyloid deposition within the stroma represents the pathologic hallmark for MTC. Measurement of plasma calcitonin levels is a sensitive tool for early diagnosis and postoperative follow-up. However, elevated plasma calcitonin concentrations may be found in the absence of a palpable tumor in patients who have undergone total thyroidectomy. In this situation, tumor detection by imaging is a very useful clinical diagnostic tool.

Although several studies have reported the diagnosis of MTC using ultrasonography and scintigraphy,2,7 and some investigators have described the magnetic resonance (MR) signal intensity in amyloid deposition,8-11 to our knowledge, no report has described the results of MR imaging (MRI) in a large series of patients with MTC. In the present study, we reviewed a group of 14 cases of MTC to evaluate the usefulness of MRI in the detection of thyroid tumors, tumor invasion, and lymph node metastasis. We also investigated the relationship between MR signal intensity and the underlying pathologic changes in MTC.
PATIENTS AND METHODS

Our study included 14 patients with MTC (10 women and 4 men), including 9 with primary disease and 5 with recurrent disease. Their ages ranged from 20 to 71 years (mean, 46 years). The sporadic form was found in 6 patients (43%) and the familial form in 8 (57%). All patients with primary disease were treated with total thyroidectomy combined with modified neck dissection. Of the 5 patients with recurrent disease, 1 was initially treated by partial thyroid lobectomy (because the histologic diagnosis was unknown at the time of surgery), followed at a later stage by total thyroidectomy combined with modified neck dissection for bilateral thyroid recurrent tumors. In the other 4 patients, total thyroidectomy was initially performed and was followed by a second operation for recurrent tumors.

Magnetic resonance imaging was performed before the latest surgery for both primary and recurrent diseases using a 1.5-T MR unit (Magnetom; Siemens, Erlangen, Germany) with either a 256 × 192 or a 256 × 256 acquisition matrix using a Helmholtz coil. Conventional spin-echo T1-weighted images (T1WIs) (repetition time [TR]/echo time [TE], 600-900/15) and spin-echo T2-weighted images (T2WIs) (TR/TE, 2000-2700/70) were obtained. Axial images were obtained in each patient from the top of the mandibular angle to the sternal notch or to the level of the aortic arch using the presaturation technique to eliminate flow artifacts. The slice thickness was 5 mm, with an intersection gap of 1.0 mm. T1-weighted images were also repeated immediately after a bolus intravenous dose of gadopentetate dimeglumine (Magnevist; Nihon Schering, Tokyo, Japan), 0.1 mmol/kg. Nonenhanced T1WIs and T2WIs were obtained in all 14 patients and gadolinium-enhanced T1WIs in 11. Magnetic resonance imaging was performed 3 to 18 days prior to surgery (mean, 7 days).

Magnetic resonance imaging images were reviewed retrospectively by 2 radiologists who were aware of the clinical condition and the presence of MTC. They independently evaluated MRI for tumor location, type (solitary, multiple, diffuse), presence or absence of tumor invasion into the surrounding structures and lymph node metastasis, and MR signal characteristics of the tumors. In addition, 1 of the radiologists measured the maximal and minimal diameters of the thyroid tumors. Final interpretations were determined by consensus. The diagnosis of nodal metastasis on MRI was based on nodal size, shape, and signal intensity. Based on the size criteria proposed by van den Brekel et al.,11 nodes with a minimal transverse diameter of 10 mm or larger or groups of 3 or more borderline lymph nodes with minimal transverse diameter of 8 mm or larger were considered metastatic. In addition to tumor size, the following criteria were also used for identifying metastatic lymph nodes: (1) presence of necrosis in the node, (2) ratio of the minimal to maximal diameter of the node of 0.8 or greater, and (3) markedly hyperintense node on T2WI, which was enhanced by gadopentetate on T1WI. In the next step, we assessed the diagnostic accuracy of each of the 4 criteria in predicting malignancy on MRI. We also examined the accuracy of the combined criteria of the size and ratio or all 4 factors together. The maximal and minimal transverse diameters of the node were measured by 1 radiologist on MRI. A precise schema of the surgical findings, including location and size of all dissected nodes and other relative anatomical landmarks (eg, relation to internal jugular vein, carotid artery, trachea, and cricoid cartilage), was documented from the surgical records. Pathologic results were superimposed on the same schema. Therefore, we were able to make a node-by-node comparison in all patients.

The MR signal intensity of the thyroid tumor was determined qualitatively on both T1WI and T2WI by comparing it with those of normal thyroid tissue and subcutaneous fat, whereas the MR signal intensity of the metastatic nodes was compared with those of adjacent skeletal muscle and subcutaneous fat. When the signal intensity of the thyroid tumor was higher than that of the normal thyroid tissue but equal to or lower than that of the fat, it was labeled as hyperintense. When the signal intensity of the node was higher than that of skeletal muscle but equal to or lower than that of fat, it was also labeled as hyperintense. When the signal intensities of the thyroid tumor and the node were higher than that of fat, they were labeled as markedly hyperintense. The degree of enhancement by gadopentetate was subjectively classified into 3 grades (ie, slight, moderate, and marked enhancement).

Histopathologic examination and evaluation was conducted by a pathologist in a blinded fashion. All specimens were stained with hematoxylin-eosin and Congo red. Evaluation of the tumor included the presence or absence of calcification, necrosis, and hemorrhage, and the density of tumor cells, amyloid deposition, and fibrosis. The latter 3 factors were semiquantitatively graded into low, moderate, and high. To examine the relationship between MR signal intensity of thyroid tumors and pathologic findings, T1-weighted signal intensities of the tumors were correlated with the histopathologic findings in 10 patients using stepwise multiple regression analysis. In this model, the grade of T1-weighted signal intensity was used as the dependent variable, and 3 histopathologic findings (ie, degree of tumor cellularity, amount of amyloid deposition, and extent of fibrosis) as the independent variables. \( P < .05 \) was considered significant.
The MR signal intensity of MTC is shown for all patients (Table 2). Hyperintense and markedly hyperintense signal intensities were found in 11 (78.6%) of the 14 tumors. Gadopentetate-enhanced images confirmed these signal intensity patterns. A slight to marked enhancement was found in 5 of 7 tumors relative to the residual thyroid gland. One isointense tumor was identified based on the surrounding rim, which appeared hypointense compared with the thyroid tissue on enhanced T1WI. Thus, the sensitivity of detecting thyroid tumors was 50% for nonenhanced T1WI, 80% for T2WI, and 86% for enhanced T1WI. The use of a combination of these 3 pulse sequences resulted in accurate diagnosis in 9 (90%) of the 10 thyroid tumors. In the present series, 2 tumors were isointense on all pulse sequences. In 1 of these patients, histopathologic studies showed the presence of a small amount of amyloid deposit and tumor cells and broad fibrous bands forming nearly half of the tumor. In the other patient, the tumor showed infiltrative growth pattern and tumor cells and amyloid deposits scattered within the normal thyroid tissues.

Table 3 summarizes the histopathologic findings in MTC. Calcification, necrosis, and hemorrhage within the tumors were found in 9 (64%) of the 14 tumors. Eight of these tumors showed an inhomogeneous composition on MRI. Stepwise multiple regression analysis was done using T2-weighted signal intensities in 10 thyroid tumors as dependent variables and 3 histopathologic findings as independent variables, and the following statistically significant model was obtained ($r = 0.91$, $P < .01$):

$$T_2\text{-Weighted Signal Intensity} = 0.16 + 0.84 \times \text{Tumor Cellularity} + 0.69 \times \text{Amyloid Deposits} - 0.48 \times \text{Fibrosis}$$

This suggested that T2-weighted signal intensity correlated positively with tumor cellularity and amyloid deposits but negatively with fibrosis (Figure 1 and Figure 2).

In our series, a total of 168 cervical and mediastinal lymph nodes were dissected and examined histopathologically. Of these, 38 nodes (23%) in 9 patients...
were metastatic. Fifty-six (35%) of the 168 nodes were identified on MRI, and their size ranged from 3 to 29 mm (mean ± SD, 7.1 ± 4.8 mm); the signal intensity of most nodes was similar to that of thyroid tumors. Table 4 shows the sensitivity and specificity of each diagnostic criterion in detecting metastatic lymph nodes on MRI. The presence of necrosis in the node, marked hyperintensity on T2WI, and the size of the lymph node on MRI were associated with poor sensitivity but high specificity. The sensitivity of MRI in detecting metastatic lymph nodes markedly improved when the diameter of the node was 10 mm or larger (or ≥8 mm in groups of 3 or more borderline lymph nodes) with a ratio of minimum-maximum diameter of 0.8 or greater (Table 4). When the 2 criteria were used in combination, 28 (74%) of 38 positive nodes in 8 patients (89%) were correctly identified. The addition of necrosis and marked hyperintensity to the above 2 criteria did not change the diagnostic accuracy (Figure 3). There were 10 false-negative nodes in 4 patients with primary disease. Among these 4 patients, the lymph nodes were too small in size and ratio in 3 (whereas metastasis was identified in other nodes), and nodes were not indistinguishable from the adjacent primary thyroid tumors in 1.

Table 3. Histopathologic Findings in Medullary Thyroid Carcinoma*

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<th>Patient No.</th>
<th>Cellularity</th>
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*+ indicates low level; ++, moderate level; +++ high level.

Figure 1. Primary medullary thyroid carcinoma of the sporadic form in a 26-year-old woman (case 2). The tumor (arrowheads) appeared isointense relative to the thyroid on nonenhanced T1-weighted images (A) (repetition time [TR]/echo time [TE], 900/15), as markedly hyperintense areas on T2-weighted images (B) (TR/TE, 2000/70), and as markedly hyperintense areas on gadolinium-enhanced T1-weighted images (C) (TR/TE, 900/15). D, Histopathologic findings, showing a large amount of amyloid and a small amount of tumor cells and fibrosis (hematoxylin-eosin, original magnification ×20).
Recurrent tumors were found in both lobes of the thyroid gland in 1 patient who had a partial thyroid lobectomy. Of the remaining 4 patients who had total thyroidectomy, recurrent tumors were found in the cervical nodes in 1, in the mediastinal nodes in 2, and in both the cervical and mediastinal nodes in 1. Magnetic resonance imaging detected metastatic lymph nodes in all of these patients. The enlarged nodes appeared either as a coalesced mass or as multiple separated masses. The tumors appeared as isointense in 2 patients and hyperintense in another 2 on T1WI, while they appeared hyperintense in 3 patients and markedly hyperintense on T2WI in 1. The images of all metastatic lymph nodes were moderately or markedly enhanced following intravenous administration of gadopentetate (Figure 2).

The reported 5- and 10-year adjusted survival rate ranges for patients with MTC are 67% to 78% and 47% to 61%, respectively.3,4 Radiotherapy and chemotherapy are generally ineffective for primary MTC; surgery remains the most effective mode of treatment.1,2 Therefore, prior to surgery, it is important to accurately localize the thyroid tumor, evaluate tumor invasion into the surrounding structures, and detect lymph node metastases using imaging modalities to predict prognosis and determine treatment policy. In our study, MRI showed a high level of accuracy in localization of tumors in the thyroid gland (90%) and in determining tumor invasion and detecting lymph node metastasis (93%).

In this series, most of the MTC appeared as isointense to hyperintense areas on nonenhanced T1WI, slightly to markedly enhanced with gadopentetate on T1WI, and hyperintense to markedly hyperintense areas on T2WI. According to previous studies and based on our own experience, these MR features are not specific to MTC.13-15 Therefore, we believe that the diagnosis of MTC is only possible when MRI is combined with the clinical evidence of elevated plasma calcitonin levels. However, the presence of a markedly hyperintense T2WI would suggest the presence of MTC.

Several studies have described the MR findings of systemic or local amyloidosis, although the findings are controversial.8-11 Our results showed that T2-weighted signal intensities were correlated with increased tumor cellularity and amyloid deposition, whereas increased fibrous tissue within the tumor decreased the signal intensity. Approximately 90% of the amyloid is composed of fibrillar protein with a b-pleated structure of a diverse chemical composition.16 Such diversity in chemical composition may be the underlying reason for various T2-weighted signal intensities reported for amyloid deposits. Since the tumor content of amyloid was a positive prognostic factor in patients with MTC,3 T2-weighted signal characteristics may also be useful in providing prognostic information.

Keiser et al17 reported that the cellular types of MTC were more frequently detected in a younger age group and were associated with less lymph node metastasis during surgery. However, the relationship between tumor cellularity and clinical prognosis has not yet been clarified.3,4 In our study, tumor cellularity did not correlate with the degree of enhancement with gadopentetate, and all tumors with high cellularity showed moderate to marked enhancement. These findings suggest that high cellularity did not necessarily reduce the extracellular space but rather increased the extracellular space, probably because of the associated edema and increased vascular space.3,18 This mechanism may explain the high T2-weighted signal intensity in highly cellular MTC described in the present study. In this regard, the fibrous tissue is known to have a very short T2 relaxation time and low density of water protons, and it therefore reduces the T2-weighted signal intensity.19,20

Medullary thyroid carcinoma spreads early to the regional lymph nodes. Some authors believe that once lymph node metastasis occurs, surgery becomes an in-

Figure 2. Recurrent medullary thyroid carcinoma of the familial form in a 54-year-old woman (case 12). Multiple metastatic nodes presented in the superior and anterior mediastinum (arrowheads). Tumors appeared isointense relative to the adjacent muscles on T1-weighted images (A) (repetition time [TR]/echo time [TE], 900/15) and hyperintense relative to adjacent subcutaneous fat on T2-weighted images (B) (TR/TE, 2000/70). C, Gadopentetate dimeglumine resulted in marked enhancement in the tumors.
effective treatment option. However, other studies have shown that repeated operations to remove nodal metastases may allow complete resolution of the disease. Nonetheless, in patients with occult recurrent MTC, discovery of tumors by palpation is difficult, if not impeded, because of the scar tissue caused by prior operation, whereas the lymph nodes in the superior mediastinum are far beyond palpation. Gorman et al reported that ultrasonography was useful in detecting metastatic cervical lymph nodes in 12 of 12 patients with MTC. Based on these results, we believe that ultrasonography should be used as the first diagnostic procedure for detecting thyroid tumors and metastatic cervical nodes because it is inexpensive and can serve as a guide for biopsy at the time of examination. However, the usefulness of ultrasonography is limited, as it is difficult to detect tumors in the superior mediastinum. In comparison, several groups have reported the usefulness of MRI in detecting recurrent thyroid tumors and the superiority of this procedure to thallium 201 scintigraphy.

Our study showed that signal intensity on T2WI was correlated positively with amyloid deposition in thyroid tumors. Furthermore, we also showed that the signal intensity of metastatic lymph nodes is similar to that of thyroid tumors. These results suggest that it is possible to assess hyperintense lymph nodes on T2WI to indicate regional metastasis of MTC tumors. Although our results showed that this criterion had low sensitivity, the specificity was nevertheless 100%, similar to the criterion of necrosis in the nodes. The combination of size and ratio criteria provided the best sensitivity, but the presence of a markedly hyperintense lymph node on T2WI...
or features consistent with necrosis in the node strongly indicate the presence of regional metastasis in MTC.

The accuracy of MRI in detecting metastatic lymph nodes in our study (93%) was higher than reported in the literature (75%-88%). This difference was probably caused by differences in the patient populations and the diagnostic criteria used in these studies. The results of our analysis suggest that using a combination of 4 criteria (i.e., size of the node, ratio of the minimal-to-maximal diameter ≥0.80, presence of necrosis in the node, and markedly hyperintense node on T2WI) is more appropriate than using a single criterion alone for the diagnosis of metastatic lymph nodes. Although 10 nodules were false-negative using these criteria, MRI detected 74% (n = 28) of the metastatic nodes in 89% (n = 8) of the patients who had metastatic disease. The positive nodes that were undetected by MRI were all microscopic metastases or nodes that had adhered to the primary tumor. Furthermore, these nodes were found in patients who had undergone initial surgery and were located in the planned surgical field. Microscopic metastases are unavoidable; hence, MRI cannot be used to exclude the presence of such metastases. Therefore, standard neck dissection is necessary during initial surgery. However, when there are positive nodes detected by MRI outside the surgical field, more extensive surgery or sampling from these nodes is required, and the extent of surgical resection may need to be modified. Moreover, as indicated in previous reports, most recurrent tumors were found in the lymph nodes in the neck or superior mediastinal region. Interestingly, all recurrent tumors were correctly diagnosed with MRI in the present study. Therefore, we believe MRI is a promising procedure for both detecting primary thyroid tumors and the follow-up of patients with MTC. It will indicate the need for prompt, adequate surgery and possibly provide an improved prognosis.

Magnetic resonance imaging is a promising procedure for the detection of primary or recurrent MTC tumors as well as tumor invasion. Our results also show that MR signal intensity reflects underlying pathologic changes in these tumors.

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