Objective: To assess the diagnostic value of dynamic contrast medium–enhanced magnetic resonance imaging (DCE-MRI) in detection of thyroid carcinoma compared with fine-needle aspiration biopsy and frozen section analysis in multinodular goiter.

Design: Prospective clinical study.

Setting: University hospital.

Patients: Thirty consecutive patients with nodular goiter without any clinical risk and symptoms associated with thyroid carcinoma were studied. Twenty-five patients had euthyroid multinodular goiter, and 5 had toxic nodular goiter. Scintigraphy, ultrasonography, and DCE-MRI were performed preoperatively in all patients, as well as fine-needle aspiration biopsy and frozen section analysis in 17 patients with dominant cold nodules.

Main Outcome Measures: Contrast enhancement patterns on DCE-MRIs and histopathologic results of thyroidectomy specimens were correlated. The sensitivity, specificity, diagnostic accuracy, and positive and negative predictive values of DCE-MRI and the results of fine-needle aspiration biopsy and preoperative frozen section analysis to detect thyroid carcinoma were compared.

Results: Thyroid carcinoma was found in 11 patients (36.7%), but was clinically significant in only 4 (13.3%). Delayed washout pattern of contrast enhancement significantly correlated with a histologic diagnosis of thyroid carcinoma (P < .001). The conditional probability of thyroid cancer in a patient with multinodular goiter with a delayed washout pattern was 0.78. The sensitivity and diagnostic accuracy of DCE-MRI to detect thyroid carcinoma was higher compared with fine-needle aspiration biopsy and frozen section analysis (100% vs 50% and 85.7%, and 90% vs 70.6% and 87.5%, respectively). The negative predictive value of DCE-MRI was 100%, ruling out thyroid carcinoma in all patients with benign goiter.

Conclusion: Dynamic contrast-enhanced magnetic resonance imaging is useful to detect or exclude thyroid carcinoma with high diagnostic accuracy in patients with multinodular goiter when results of other diagnostic methods are inconclusive.

Arch Surg. 2007;142(11):1036-1041

The primary indications for surgery in patients with euthyroid multinodular goiter are compressive symptoms, cosmetic deformity from a large goiter, and suspicion of malignant neoplasm. The presence of a dominant cold nodule in a thyroid gland with multiple nodules is an important risk factor associated with thyroid carcinoma.

Differentiation of a benign thyroid nodule from a malignant thyroid nodule is important in planning the further therapeutic approach and the extent of surgical intervention. Several diagnostic methods are available for determining the nature of a thyroid nodule, including thyroid scintigraphy, ultrasonography, and fine-needle aspiration biopsy (FNAB). Fine-needle aspiration biopsy is the most important diagnostic method in the preoperative evaluation of nodules and is reliable in evaluation of solitary thyroid nodules. However, as many as 80% of thyroid carcinomas can be undetected at FNAB in most patients with multinodular goiter. False-negative results of FNAB cause substantial delay in surgical treatment of thyroid carcinoma, leading to local invasion in some patients. Current diagnostic methods may not enable detection of the malignant nature of a thyroid nodule, especially in multinodular goiter; therefore, new techniques are being investigated to improve the evaluation of thyroid nodules. Dynamic contrast medium–enhanced magnetic resonance imaging (DCE-MRI) is useful to differentiate malignant and benign lesions of brain, breast, endometrium, and salivary glands. Delayed washout pattern of contrast enhancement on DCE-MRIs is significantly correlated with histopathologic findings of malignancy in salivary gland tumors. Thyroid carcinoma or thyroid nodules with a high cell proliferation index demonstrate delayed washout pattern...
on DCE-MRIs.\textsuperscript{12} To our knowledge, there has been no prospective study evaluating the diagnostic value of DCE-MRI in predicting the malignant potential of nodules in multinodular thyroid glands. The purposes of this prospective clinical study were to determine the role of DCE-MRI in the preoperative diagnosis of thyroid carcinoma in consecutively treated patients with multinodular goiter and to compare the diagnostic value of DCE-MRI vs FNAB and frozen section (FS) analysis.

**METHODS**

This prospective study included 30 consecutive patients operated on because of nodular goiter at the Department of General Surgery, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey, between September 1, 2005, and November 30, 2005. The ethics committee at our institution approved the study, and informed consent was obtained from all patients participating in the trial.

Of the 30 patients, 25 (83.3\%) had euthyroid multinodular goiter and 5 (16.7\%) had toxic multinodular goiter. Of 25 patients with euthyroid multinodular goiter, 17 (68\%) had a single dominant cold nodule and 8 (32\%) had a large goiter with multiple nodules larger than 1.5 cm in greatest diameter. A “dominant nodule” was defined as a nodule larger than 1.5 cm in a multinodular thyroid gland. All patients had normal thyroid function before surgery. None had a history of head and neck irradiation or a family history of thyroid carcinoma. None had symptoms or clinical findings suspicious for thyroid malignancy such as a rapidly enlarging nodule, hoarseness, or palpable lymph nodes. Thyroid scintigraphy and ultrasonography were performed preoperatively in all patients. Fine-needle aspiration biopsy and FS analysis were performed in patients with single dominant cold nodules. Reports at FNAB or FS of follicular neoplasia were considered positive findings. Cytologic examination of FNAB specimens was performed by 2 pathologists experienced in endocrine pathology who had no information about the clinical findings in these patient or the results of DCE-MRI. Dynamic contrast-enhanced MRI was added to the preoperative diagnostic workup in all patients. A 1.5-T superconductive MRI system (Magnetom Symphony; Siemens AG, Erlangen, Germany) with a double-stranded surface coil was used. Conventional MRI was used to show the morphologic features of thyroid nodules, followed by intravenous injection of 0.1 mmol/kg gadolinium–diethylenetriamine pentaacetic acid (Gd-DTPA). Images were obtained immediately after injection and at 3/1, 7, 10/1, 14, 17/1, and 21 minutes after injection of Gd-DTPA. Signal intensity before and after injection of Gd-DTPA was measured and signal enhancement was evaluated relative to the background. The ratio of signal enhancement to noise (SE/N) was calculated as defined on DCE-MRIs.\textsuperscript{12} To our knowledge, there has been no prospective study evaluating the diagnostic value of DCE-MRI in predicting the malignant potential of nodules in multinodular thyroid glands. The purposes of this prospective clinical study were to determine the role of DCE-MRI in the preoperative diagnosis of thyroid carcinoma in consecutively treated patients with multinodular goiter and to compare the diagnostic value of DCE-MRI vs FNAB and frozen section (FS) analysis.

\[ \text{Spost} = \left( \frac{S_{\text{post}} - S_{\text{pre}}}{\text{NSD}} \right) \] where \( S_{\text{post}} \) is signal intensity after injection, \( S_{\text{pre}} \) is signal intensity before injection, and \( \text{NSD} \) is standard deviation of the background. Time-intensity curve patterns reflected the following 3 patterns of contrast enhancement: (1) delayed washout pattern in which the time-intensity curve was less than half of peak grade during 10 minutes (\textbf{Figure 1} and \textbf{Figure 2}), (2) rapid washout pattern in which the time-intensity curve was less than half of peak grade within 10 minutes (\textbf{Figure 3}), and (3) no contrast enhancement.

Total thyroidectomy was performed in 15 patients (50\%), and near-total thyroidectomy in 15 patients (50\%). “Near-total thyroidectomy” was defined as lobectomy and contralateral resection leaving less than 1 g of remnant tissue. The findings at DCE-MRI and histopathologic results of thyroidectomy specimen examination were analyzed to determine whether there was any difference between the contrast enhancement patterns in malignant and benign thyroid lesions. The sensitivity, specificity, diagnostic accuracy, positive predictive value, and negative predictive value of DCE-MRI, FNAB, and peroperative FS analysis were compared. Sensitivity, specificity, and accuracy (all in percentage) were determined according to the following formulas:

\[
\text{Sensitivity} = \frac{(TP + FN)}{TP + FN} \times 100 \\
\text{Specificity} = \frac{(TN + TP)}{TN + FP} \times 100
\]

where \( TP \) is true positive; \( FN \), false negative; and \( FP \), false positive.

The conditional probability of thyroid carcinoma according to the contrast enhancement patterns of DCE-MRI was calculated as follows:

\[
P(A/B) = \frac{(\text{Number of patients with } A \text{ and } B)}{(\text{Number of patients with } B)}
\]

where \( B \) is the number of patients with 1 of the 3 types of contrast enhancement pattern (delayed, rapid, or no enhancement) at DCE-MRI and \( A \) is the number of patients with thyroid cancer relative to the type of contrast enhancement.

Pearson correlation coefficient, analysis of variance, and Wilcoxon signed rank tests were used for statistical analysis. \( P < .05 \) was considered statistically significant.

**RESULTS**

The median age of the patients was 50 years (age range, 17–66 years); the ratio of female to male was 3:29:1 (23 women and 7 men); and the mean \( \pm \) SD nodule diameter was 33.4 \( \pm \) 6.7 mm. Fine-needle aspiration biopsy was performed in dominant nodules in 17 patients with dominant cold nodules.
PREOPERATIVE MRI FINDINGS

Thirty patients were classified into 3 groups according to contrast-enhancement pattern on DCE-MRIs. Group 1 consisted of 14 (46.7%) with delayed washout pattern; group 2, 7 patients (23.3%) with rapid washout pattern; and group 3, 9 patients (30%) having no contrast enhancement on DCE-MRIs. Contrast enhancement with rapid washout was demonstrated in all 5 patients with toxic multinodular goiter. There was no significant difference in age and nodule size among the 3 groups, but group 2 included a substantial predominance of male patients (Table).

POSTOPERATIVE RESULTS

Histopathologic Findings

Histopathologic examination revealed thyroid carcinoma in 11 patients (36.7%), follicular adenoma in 2 (6.7%), and colloidal nodular goiter in 17 (56.7%). Of 11 patients with thyroid carcinoma, 9 (81.8%) had papillary carcinoma, 1 (9.1%) had follicular carcinoma, and 1 (9.1%) had undifferentiated carcinoma. Of the 9 patients with papillary carcinoma, 7 (77.8%) had papillary microcarcinoma (tumor diameter ≤1 cm; range, 0.3-0.8 cm); in the other 2 patients, tumor diameter was 1.5 cm and 1.8 cm. The incidence of clinically significant thyroid carcinoma was 13.3% (4/30 patients), including the patients with follicular and undifferentiated carcinoma and 2 patients with papillary carcinoma larger than 1 cm in greatest diameter. There were no significant differences in age (mean±SD, 46.28±10.8 years vs 50.0±12.4 years; \( P = .54 \)) and in the ratio of males to females (2:9 vs 5:19; \( P = .45 \)) in patients with thyroid cancer compared with benign pathologic findings.

Histopathologic Findings Correlated With Preoperative DCE-MRI Findings

In 30 patients, DCE-MRIs exhibited no contrast enhancement in 9 patients (group 3) and rapid washout pattern in 7 (group 2). None of these 16 patients had thyroid carcinoma at the final histopathologic examination. The conditional probability of thyroid carcinoma in patients in groups 2 and 3 was 0. None of the remaining 14 patients had thyroid carcinoma. Contrast enhancement with rapid washout was demonstrated in all 5 patients with toxic multinodular goiter. There was no significant difference in age and nodule size among the 3 groups, but group 2 included a substantial predominance of male patients (Table).
DCE-MRIs, which significantly correlated with a histologic diagnosis of thyroid carcinoma (P < .001).

FNAB Results

Fine-needle aspiration biopsy was performed in 17 patients with single dominant cold nodules, and thyroid cancer was detected in 10 patients (58.8%) at final histopathologic examination. Of 17 patients undergoing FNAB, cytoligic examination revealed benign findings in 12 (70.6%), thyroid carcinoma in 2 (11.8%), and follicular neoplasia in 3 (17.6%). Of 12 patients with benign cytologic findings, the final histopathologic result was benign in 7 patients (58.3%), but thyroid carcinoma was detected in the remaining 5 patients (41.7%). Of 5 patients with false-negative results at FNAB, 3 had papillary microcarcinoma and 2 had papillary carcinoma (tumor diameter, 1.5 cm and 1.8 cm). In these 5 patients with false-negative FNAB results, thyroid carcinoma was inside the dominant nodule in 3 and outside the dominant nodule in 2 with papillary microcarcinoma and papillary carcinoma (tumor diameter, 1.8 cm). Of 3 patients with follicular neoplasia at FNAB, 2 had papillary microcarcinoma and 2 had undifferentiated thyroid carcinoma. Follicular thyroid carcinoma and papillary microcarcinoma were detected in 2 patients with malignant FNAB results.

The sensitivity, specificity, and diagnostic accuracy of FNAB in preoperative diagnosis of thyroid carcinoma was 50%, 100%, and 70.6%, respectively. Positive and negative predictive values were 100% and 58.3%, respectively. The main diagnostic shortcomings of FNAB resulted from papillary microcarcinoma and location of the tumor outside the dominant nodule in patients with multinodular goiter.

Frozen Section Analysis

Frozen section analysis was performed in 17 patients with single dominant cold nodules, and thyroid cancer was detected in 10 (58.8%) at final histopathologic examination. Of 17 patients, FS analysis demonstrated benign histopathologic findings in 9 (52.9%), thyroid carcinoma in 6 (35.3%), and follicular neoplasia in 2 (11.2%). Of 9 patients with benign FS results, 3 (33.3%) had papillary microcarcinoma at final histopathologic examination. Of the 6 patients with thyroid cancer detected at FS analysis, 6 had papillary carcinoma (papillary microcarcinoma in 2) and 1 had undifferentiated thyroid carcinoma at the final histopathologic examination. Of the 2 patients with follicular neoplasia detected at FS analysis, one had follicular adenoma and the other had follicular carcinoma.

The sensitivity, specificity, and diagnostic accuracy of FS analysis in preoperative diagnosis of thyroid carcinoma was 70.0%, 85.7%, and 76.5%, respectively. Positive and negative predictive values were 87.5% and 66.7%, respectively. The probability of thyroid cancer in a patient with benign or malignant results of FS analysis was 33.3% and 87.5%. Presence of papillary microcarcinoma outside the dominant nodule was the key factor resulting in false-negative results of FS analysis.

Dynamic Contrast-Enhanced MRI

All of the patients with thyroid carcinoma at the final histopathologic examination had delayed washout contrast enhancement on DCE-MRIs. Delayed contrast washout enhancement pattern was demonstrated inside the single dominant cold nodules in 9 patients and was extranodular in 2 patients.

Papillary thyroid carcinoma was detected in these 2 patients at DCE-MRI, although FNAB yielded negative results. Of 5 patients with false-negative FNAB results, all had delayed washout pattern on DCE-MRIs, which was associated with thyroid carcinoma. Of 3 patients with follicular neoplasms, 1 had a dominant hyperactive nodule with rapid washout pattern, and the final diagnosis revealed follicular adenoma in this patient. In the remaining 2 patients, the final diagnoses were follicular adenoma and follicular carcinoma. Both patients had a delayed washout pattern of contrast enhancement on DCE-MRIs. In differential diagnosis of follicular neoplasms, DCE-MRI failed to differentiate follicular adenoma from carcinoma. The sensitivity, specificity, and diagnostic accuracy of DCE-MRI in preoperative diagnosis of thyroid carcinoma was 100%, 84.2%, and 90%, respectively. Positive and negative predictive values of DCE-MRI in preoperative detection of thyroid carcinoma were 78.5% and 100%, respectively. The sensitivity and diagnostic accuracy of DCE-MRI in preoperative diagnosis of thyroid carcinoma were higher compared with FNAB and FS analysis. Although positive predictive value of DCE-MRI was less than that of FNAB and FS analysis, DCE-MRI yielded no false-negative results, for a negative predictive value of 100%, which was higher than with FNAB and FS analysis.

COMMENT

We investigated the diagnostic value of DCE-MRI to enable prediction of the malignant potential of the nodules in multinodular goiter and found that delayed wash-
out pattern of contrast enhancement was significantly associated with thyroid carcinoma. The accuracy of DCE-MRI in detecting thyroid carcinoma was higher than that of FNAB and FS analysis in multinodular goiter. Dynamic contrast-enhanced MRI detected papillary microcarcinoma or papillary carcinoma, that were missed at FNAB. Although preoperative diagnosis of papillary microcarcinoma, most being clinically insignificant, may not be crucial, this finding confirms that DCE-MRI precisely detects papillary thyroid carcinoma independent of tumor size. The negative predictive value of DCE-MRI was 100%, and this technique was more reliable than FNAB and FS analysis in ruling out a diagnosis of thyroid carcinoma. The conditional probability of thyroid cancer in a patient with multinodular goiter with delayed washout pattern was 0.78. Dynamic contrast-enhanced MRI failed to differentiate follicular adenoma from follicular carcinoma because both lesions caused delayed washout pattern on DCE-MRIs.

Despite imaging techniques and FNAB, preoperative precise detection of thyroid carcinoma is not likely in all patients. Although FNAB is a reliable diagnostic technique, it is not a perfect guide in decision making for operative or nonoperative treatment of multinodular goiter. In patients with thyroid carcinoma, a single false-negative result of FNAB was associated with a 28-month delay in surgical treatment, and these patients had higher rates of local invasion and persistent disease. False-negative results of FNAB resulted in underestimation of clinical findings associated with thyroid carcinoma. The sensitivity of FNAB was low (17%) in multinodular goiter. In a study evaluating the use of FNAB in multinodular goiter, papillary microcarcinoma was partly responsible for false-negative results, but a substantial number of punctured macrocarcinomas inside the dominant nodules also led to benign cytologic results at FNAB.

The most important preoperative diagnostic tool for evaluation of malignancy in nodular goiter is FNAB, and FS analysis is generally accepted as useful, especially to confirm the presence of cancer in patients with suspect or malignant cytologic findings at FNAB. However, one should be aware of the shortcomings of FNAB or FS analysis in interpreting the results in patients with multinodular goiter. Fine-needle aspiration biopsy might fail to detect thyroid carcinoma located in a dominant nodule, and thyroid cancer might originate from one of the multiple nodules outside the dominant nodule. In the present study, we found that location of the tumor outside the dominant nodule and the presence of papillary microcarcinoma were the most important factors leading to false-negative results in FNAB and FS analysis. Of the 2 patients with papillary thyroid carcinoma larger than 1 cm and with false-negative FNAB results, the tumor was inside the dominant nodule in 1 patient and outside the dominant nodule in the other patient. At DCE-MRI, thyroid carcinoma was detected in all patients, independent of tumor size and location.

Improvements in imaging methods enable the use of different techniques in preoperative detection of thyroid carcinoma. Conventional MRI studies revealed that particular features of nodules demonstrated at MRI correlated well with histopathologic findings. Pseudocapsules might be associated with both adenoma or thyroid carcinoma, but unclear margins or partially destructed pseudocapsule in a nodule were strong predictors of papillary thyroid carcinoma. The interpretation of T1- and T2-weighted images might give a clue about the differentiation and cell proliferation ability of a nodule. Differentiation between follicular adenoma and carcinoma was inseparable with MRI, but small thyroid lesions and metastatic lymph nodes as small as 3 mm could be detected. Recently, DCE-MRI with Gd-DTPA has become more popular because of the ability to demonstrate malignant neovascularity and cell proliferating activity in different types of carcinomas. Dynamic contrast-enhanced MRI was studied with breast, salivary gland, and brain tumors. In invasive breast carcinoma, a significant correlation was detected between the histopathologic grade, axillary lymph node status and vascular invasion, and the enhancement parameters of the tumor. Gadolinium-enhanced dynamic MRI was valuable in differentiating benign from malignant salivary gland tumors, with high sensitivity and specificity.

Several studies have documented that contrast enhancement is related to the grade and differentiation of the tumor in brain tumors. Diagnostic value of DCE-MRI in thyroid tumors was previously investigated by Kusunoki et al. These authors performed preoperative Gd-DTPA-enhanced MRI in patients with thyroid tumors and compared the time-intensity curves of contrast enhancement of nodules with histopathologic features and the labeling index of proliferating cell nuclear antigen. Delayed washout pattern of contrast enhancement was especially associated with thyroid carcinoma, high cell proliferative activity, and increased vascularity. The authors suggested that DCE-MRI is useful in preoperative determination of cell proliferating activity and histologic grade of thyroid tumor.

To our knowledge, our study is the first prospective study performed to evaluate the diagnostic value of DCE-MRI in detection of thyroid carcinoma in multinodular goiter and to compare the results with those of FNAB and FS analysis. Patients with toxic goiter were included to determine whether hyperactive nodules had a special pattern of contrast enhancement owing to hypervascularity that would interfere with the diagnostic workup of hyperactive nodules. Contrary to the delayed washout pattern of thyroid carcinoma on DCE-MRIs, hyperactive nodules also demonstrated rapid washout pattern in benign lesions. In our study, the incidence of clinically significant thyroid carcinoma was 13.3%. Although rates higher than 30% have been reported previously, the incidence of thyroid carcinoma in multinodular goiter is approximately 10%. In patients with multinodular goiter, thyroid carcinoma was documented as primarily located in dominant nodules, and presence of a dominant cold nodule has been determined to be an important risk factor for thyroid carcinoma. Our study included consecutive patients, but most had single dominant cold nodules. The relatively higher incidence of thyroid carcinoma in the present study might be associated with predominance of...
In patients with euthyroid multinodular goiter without compressive symptoms and cosmetic deformity owing to large goiter, excluding the suspicion of carcinoma is the most important factor in deciding to operate or not to operate, especially in patients with coexisting dominant nodules, which are associated with a higher risk of thyroid carcinoma. Fine-needle aspiration biopsy and FS analysis might not be reliable in eliminating the suspicion of carcinoma in the presence of multiple nodules. We documented that DCE-MRI is highly reliable in ruling out a diagnosis of carcinoma in multinodular thyroid gland. We recommend that in patients with multinodular goiter with coexistent dominant nodules, the use of DCE-MRI might be useful in deciding to operate or not to operate when the decision for surgery depends only on exclusion of carcinoma and FNAB results are inconclusive.

Accepted for Publication: April 13, 2007.
Correspondence: Serdar Tezelman, MD, Department of General Surgery, Istanbul Medical Faculty, Istanbul University, Genel Cerrahi ABD, 34390 Çapa, Istanbul, Turkey (tezelman@superonline.com).

Author Contributions: Study concept and design: Tezelman and Terzioglu. Acquisition of data: Tezelman, Giles, Tunca, Gök, Poyanlı, and Salmislioglu. Analysis and interpretation of data: Tezelman, Giles, Tunca, Poyanlı, Salmislioglu, and Terzioglu. Drafting of the manuscript: Tezelman, Giles, Tunca, Gök, Poyanlı, and Salmislioglu. Critical revision of the manuscript for important intellectual content: Tezelman and Terzioglu. Statistical analysis: Tezelman and Tunca. Obtained funding: Giles, Tunca, Gök, Poyanlı, and Salmislioglu. Administrative, technical, and material support: Tezelman, Giles, Poyanlı, Salmislioglu, and Terzioglu. Study supervision: Tezelman and Terzioglu.

Financial Disclosure: None reported.

REFERENCES