IDENTIFICATION OF A CUT-OFF FOR THE MACIS SCORE TO PREDICT THE PROGNOSIS OF DIFFERENTIATED THYROID CARCINOMA IN CHILDREN AND YOUNG ADULTS

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Abstract: Background. The metastases, age at diagnosis, completeness of resection, invasion, size of the tumor (MACIS) scoring system was developed to predict disease-specific survival in patients with differentiated thyroid carcinoma (DTC), mainly for adults, with a cut-off score of 6. The purpose of this study was to evaluate its ability to predict prognosis of DTC in children and young adults.

Methods. The medical records of 66 children and young adult (<21 years old) patients with DTC were reviewed retrospectively. Receiver operating characteristic (ROC) analysis was performed to determine the cut-off for predicting poor prognosis.

Results. Extrathyroidal invasion and regional lymph node metastasis were noted in 64% each, and distant metastases were found in 8%. The optimal cut-off for the MACIS score for poor prognosis was 4 (93% sensitivity, 67% specificity). The overall 10-year recurrence-free survival was better in patients with MACIS score <4 than score ≥4 (p < .05).

Conclusion. A MACIS score of more than 4 was associated with a poor prognosis. The incidence rate of thyroid cancer among children and adolescents below 19 years of age was 0.76 per 100,000 people and a total of 95 incident cases of thyroid cancer (men, 13; women, 82) were reported among 12.5 million people below 19 years of age in 2005. The incidence rate in this age group has remained stable between 2002 and 2005, even though there has been a rapid increase in the incidence rate of adult thyroid cancers, especially DTCs, during the same period.

In general, DTC in pediatric patients presents with more aggressive features. Local lymph node involvement at the time of diagnosis is found in about 40% to 80%, which is higher than in adult patients. Distant metastasis, almost always to the lungs, is observed in up to 20% of cases. However, the survival of patients with childhood DTC is good, as high as 90% to 99% after 20 years of follow-up. Nevertheless, 5% to 7% of patients with childhood DTC succumb to this disease, and almost all of these cases are associated with disease persistence or recurrence. On the other hand, some patients with childhood DTC have lethal treatment-related complications or secondary malignancies. Therefore, the risk and benefit of intensive treatment of patients with childhood DTC and young adults with DTC should be weighed and the risk evaluation for disease persistence and recurrence is thus important for managing these patients.

Hay et al designed a metastases, age at diagnosis, completeness of resection, invasion, size of the tumor (MACIS) scoring system to predict disease-specific survival in patients with PTC; the cut-off
score was set at 6 for a poor prognosis, based predominantly on adult patients. This system was originally designed for PTC. Powers et al. proposed that if a different cut-off value for the MACIS scoring system is used, this value might be used to predict disease recurrence and persistence in children and young adults with PTC. However, the statistical basis for their proposed cut-off was not specifically provided.

In this study, the cut-off value for the MACIS scoring system using receiver operating characteristic (ROC) analysis for predicting poor prognosis was determined in patients with childhood and young adult DTC.

PATIENTS AND METHODS

Patients. Sixty-six patients with DTC that were younger than 21 years of age at the time of diagnosis were included in this study. They were followed up from 1994 to 2007 at the thyroid cancer center of Samsung Medical Center, which is 1 of the largest tertiary referral hospitals in Korea. We retrospectively reviewed the medical records to collect clinical and pathological findings. Two experienced pathologists (Young Lyun Oh and Yoon-La Choi) reviewed and crosschecked all pathology specimens to confirm the diagnosis, characteristics of the tumor, and the extent of the disease. None of the patients had a medical history of radiation exposure to the neck before the diagnosis of thyroid cancer. Most of the patients underwent total thyroidectomy, and less than total thyroidectomy was selected for 20% of patients with small and intrathyroid carcinoma without gross nodal involvement. Central lymph node dissection was performed routinely when the patients underwent total thyroidectomy. Lateral lymph node dissection was done in the presence of radiologically or clinically documented lymph node diseases with compartment-based approach. Modified radical neck dissections were performed in patients with biopsy proven lateral neck disease.

Adjuvant radioactive iodine (RAI) treatment was performed in patients with any of the following criteria: a large tumor >1 cm, extrathyroidal or vascular invasion, lymph node invasion, multifocality, aggressive histology, and distant metastasis. The administered dose of RAI was adjusted according to the body weight (1.0–1.5 mCi/kg) and was increased up to 100 mCi in patients whose distant metastasis responded to the RAI therapy. This retrospective study was approved by the institutional review board of Samsung Medical Center.

The median follow-up was 59 months (range, approximately 16–166 months). Four patients were lost to follow-up and none of them had recurrence during their follow-up periods (range, approximately 35–94 months). They were considered as being free of recurrence in the recurrence-free survival analysis.

Criteria for Remission, Persistence, and Recurrence of Differentiated Thyroid Carcinoma. Remission was defined as follows: (1) negative ¹³¹I uptake outside the thyroid bed, (2) no other clinical evidence of residual disease, and (3) an undetectable thyroid-stimulating hormone–stimulated thyroglobulin (Tg) level or a thyroid-stimulating hormone–stimulated Tg level of <2 ng/mL with absence of Tg autoantibodies if total thyroidectomy and RAI remnant ablation were performed.

Recurrence was defined as the appearance of new disease, confirmed either by any imaging modality or a biopsy, in patients that had been in remission for at least 1 year. Patients that never entered remission were not considered as having persistent diseases.

DTC was classified as “aggressive” if a patient had (1) local invasion, (2) distant metastasis, (3) recurrent disease, and/or (4) persistent disease. “Indolent” DTC was defined if all of the above-mentioned “aggressive” features were absent.

MACIS Scoring System. The MACIS score was calculated according to Hay et al.’s report: a score of 3.1 (if age ≤39 years old) or 0.08 × age (if age ≥40 years old), +0.3 × tumor size (in cm), +1 (if incompletely resected), +1 (if locally invasive), and +3 (if distant metastases present).

Statistics. Statistical analyses were performed using SPSS software, version 17.0, for Windows (SPSS, Chicago, IL). Descriptive statistics were used to delineate demographic and clinical/pathological characteristics. Differences between the 2 groups (PTC vs FTC; indolent PTC vs aggressive PTC) were tested by the Wilcoxon rank sum test for continuous variables and the chi-square test for categorical variables. Differences among the 3 groups that were defined according to age at the time of diagnosis (<15 years vs 15 to <18 years vs 18–21 years) were assessed with the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables. ROC analyses were used to determine the cut-off value for predicting a poor prognosis. Recurrence-free survival was calculated by the Kaplan–Meier survival analysis, and groups that were defined according to the newly proposed cut-off value of the MACIS scoring system were compared using the log-rank test. The p values < .05 were considered statistically significant.

RESULTS

Clinical/pathological Characteristics of the Patients. Among the 66 patients with DTC, 57 patients had PTC and 9 patients had FTC. The clinical/pathological characteristics of the 66 patients with...
DTC are described in Table 1. DTC was more common in female patients (p < .05), but the difference in frequency between men and women was less evident in patients with FTC. The mean (SD) tumor size of the patients with DTC was 2.4 (1.4) cm; the FTC tumors were larger than PTC tumors (3.7 [1.4] cm versus 2.2 [1.3] cm, p < .05). Extrathyroidal invasion, lymph node metastasis, and distant metastasis were found in 42 of 57 patients (74%), and 9 of 57 patients (9%) with FTC. These aggressive features were not observed in patients with FTC. Fourteen of 42 patients (one third) with extrathyroidal extension had gross invasion. Among 42 patients with central lymph node metastasis, 17 of 42 patients (40%) showed microscopic lymph node metastasis.

Fifteen of 42 patients with central lymph node metastasis had lateral lymph node metastasis. All distant metastases were located to the lungs and occurred only in patients with PTC. Total thyroidectomy was performed in 53 patients with DTC (80%); 49 patients with PTC, 4 patients with FTC). Another 13 patients underwent subtotal thyroidectomy or hemithyroidectomy. Central lymph node dissection was performed in 48 patients with DTC (73%) and lateral lymph node dissection was carried out in 18 patients (27%). Postoperative adjuvant RAI treatment was performed in 51 patients (77%). There were no significant differences in the frequency and dose of RAI between patients with PTC and FTC.

Comparisons of Clinical/pathological Characteristics among the Different Age Groups. After grouping patients with PTC into 3 groups according to age at diagnosis (children, age <15 years; adolescents, 15≤ age <18 years; young adults, 18≤ age <21 years), their clinical and pathological characteristics were compared (Table 2). There were no statistically significant differences among the age groups in terms of clinical/pathological characteristics or treatment-related factors.

Table 1. Clinical/pathological characteristics of 66 childhood and young adult patients with DTC less than 21 years of age.

<table>
<thead>
<tr>
<th></th>
<th>All DTC (n = 66)</th>
<th>PTC (n = 57)</th>
<th>FTC (n = 9)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>17.3 (2.9)</td>
<td>17.5 (2.7)</td>
<td>16.5 (3.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Gender, female, n (%)</td>
<td>59 (89)</td>
<td>53 (93)</td>
<td>6 (67)</td>
<td>.048</td>
</tr>
<tr>
<td>Tumor size, mean (SD), cm</td>
<td>2.4 (1.4)</td>
<td>2.2 (1.3)</td>
<td>3.7 (1.4)</td>
<td>.012</td>
</tr>
<tr>
<td>Extrathyroidal invasion, microscopic, n (%)</td>
<td>42 (64)</td>
<td>42 (74)</td>
<td>0</td>
<td>.001</td>
</tr>
<tr>
<td>Extrathyroidal invasion, gross, n (%)</td>
<td>14 (21)</td>
<td>14 (25)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>LN metastasis, central, n (%)</td>
<td>42 (64)</td>
<td>42 (74)</td>
<td>0</td>
<td>.001</td>
</tr>
<tr>
<td>LN metastasis, lateral, n (%)</td>
<td>15 (23)</td>
<td>15 (26)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Resection margin positivity, n (%)</td>
<td>11 (17)</td>
<td>10 (18)</td>
<td>1 (11)</td>
<td>NS</td>
</tr>
<tr>
<td>Multicentric, n (%)</td>
<td>12 (18)</td>
<td>12 (21)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Distant metastasis, n (%)</td>
<td>5 (8)</td>
<td>5 (9)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>MACIS score, mean (SD)</td>
<td>4.4 (1.4)</td>
<td>4.4 (1.5)</td>
<td>4.3 (0.7)</td>
<td>NS</td>
</tr>
<tr>
<td>RAI treatment, frequency, mean (SD)</td>
<td>2.37 (1.3)</td>
<td>2.4 (1.3)</td>
<td>2.0 (1.4)</td>
<td>.02</td>
</tr>
<tr>
<td>RAI dose, cumulative, mCi, mean (SD)</td>
<td>173.1 (136.1)</td>
<td>173.8 (139.1)</td>
<td>165 (107.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: DTC, differentiated thyroid carcinoma; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; NS, not significant; LN, lymph node, MACIS, metastases, patient age, completeness of resection, local invasion, and tumor size; RAI, radioactive iodine.

Note: p values between PTC versus FTC.

Table 2. Clinical/pathological characteristics of three groups according to age at diagnosis in 66 patients with DTC less than 21 years of age.

<table>
<thead>
<tr>
<th></th>
<th>Age &lt;15 y (n = 13)</th>
<th>15 ≤ Age &lt;18 (n = 18)</th>
<th>18 ≤ Age &lt;21 (n = 35)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, female, n (%)</td>
<td>11 (85)</td>
<td>18 (100)</td>
<td>30 (86)</td>
<td>NS</td>
</tr>
<tr>
<td>Pathology, PTC, n (%)</td>
<td>10 (77)</td>
<td>16 (89)</td>
<td>31 (89)</td>
<td>NS</td>
</tr>
<tr>
<td>Tumor size, mean (SD), cm</td>
<td>2.3 (1.0)</td>
<td>2.1 (1.3)</td>
<td>2.6 (1.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Extrathyroidal invasion, microscopic, n (%)</td>
<td>7 (54)</td>
<td>13 (72)</td>
<td>22 (63)</td>
<td>NS</td>
</tr>
<tr>
<td>Extrathyroidal invasion, gross, n (%)</td>
<td>2 (15)</td>
<td>4 (22)</td>
<td>8 (23)</td>
<td>NS</td>
</tr>
<tr>
<td>LN metastasis, central, n (%)</td>
<td>8 (62)</td>
<td>13 (72)</td>
<td>21 (60)</td>
<td>NS</td>
</tr>
<tr>
<td>LN metastasis, lateral, n (%)</td>
<td>2 (15)</td>
<td>6 (33)</td>
<td>7 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>Multicentric, n (%)</td>
<td>2 (15)</td>
<td>6 (33)</td>
<td>4 (11)</td>
<td>NS</td>
</tr>
<tr>
<td>Distant metastasis, n (%)</td>
<td>1 (8)</td>
<td>1 (6)</td>
<td>3 (9)</td>
<td>NS</td>
</tr>
<tr>
<td>MACIS score, mean (SD)</td>
<td>4.4 (1.2)</td>
<td>4.3 (1.5)</td>
<td>4.5 (1.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Total thyroidectomy, n (%)</td>
<td>8 (62)</td>
<td>15 (83)</td>
<td>30 (86)</td>
<td>NS</td>
</tr>
<tr>
<td>RAI treatment, n (%)</td>
<td>8 (62)</td>
<td>14 (78)</td>
<td>29 (83)</td>
<td>NS</td>
</tr>
<tr>
<td>RAI treatment, frequency, mean (SD)</td>
<td>2.8 (1.1)</td>
<td>2.3 (1.5)</td>
<td>2.2 (1.4)</td>
<td>NS</td>
</tr>
<tr>
<td>RAI dose, cumulative, mCi, mean (SD)</td>
<td>131.2 (80.4)</td>
<td>156.4 (104.9)</td>
<td>192.7 (159.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: DTC, differentiated thyroid carcinoma; NS, not significant; PTC, papillary thyroid carcinoma; LN, lymph node, MACIS, metastases, patient age, completeness of resection, local invasion, and tumor size; RAI, radioactive iodine.

Note: p values between 3 groups.
Comparisons between “Indolent” and “Aggressive” Differentiated Thyroid Carcinomas. Among the 66 patients with DTC, 46 patients (70%) were classified as having indolent disease. All 9 patients with FTC seemed to have indolent disease. The remaining 20 patients with DTC (30%) had aggressive disease, and all of them had PTC. Patients with aggressive disease had larger tumors and more frequent extrathyroidal invasion, cervical lymph node metastasis, resection margin positivity, and distant metastasis ($p < .01$; Table 3). The mean MACIS score (mean [SD]) was significantly higher in patients with aggressive disease than in patients with indolent disease (5.9 [1.8] vs 3.8 [0.6], $p < .05$). Furthermore, 95% of patients with aggressive DTC had a MACIS score $\geq 4$ compared to 24% of patients with indolent DTC ($p < .05$).

Receiver Operating Characteristic Analysis to Identify the MACIS Score Cut-off for Differentiated Thyroid Cancer with a Poor Prognosis in Children and Young Adults. ROC analysis was used to identify the cut-off value of the MACIS scoring system for detecting young patients with DTC with a poor prognosis (persistence and recurrence of thyroid carcinoma). The area under the ROC curve, representing values associated with a poor prognosis, was 0.845 (95% confidence interval, 0.72–0.97; $p < .001$). The optimal cut-off value of the MACIS system for classifying young patients with DTC with a poor prognosis was a MACIS score $\geq 4.0$, with a sensitivity of 93%, a specificity of 67%, a positive predictive value of 43%, and a negative predictive value of 97% (Figure 1). The diagnostic value of an MACIS score $\geq 4$ for detecting each poor prognostic feature are listed in Table 4.

Recurrence-free survival was calculated by Kaplan–Meier survival analysis according to the newly proposed cut-off (MACIS score $\geq 4.0$; Figure 2). The median follow-up period was 59 months (range, approximately 16–166 months). During follow-up, 8 patients had disease recurrences; however, there was no disease-specific mortality. The overall 10-year recurrence-free survival of patients with DTC was 67.5%; it was significantly worse in patients with an MACIS score $\geq 4.0$ than in those with an MACIS score $< 4.0$ (54.9% vs 80.0%; $p < .05$).

**DISCUSSION**

In the present study, we determined that a cut-off value on the MACIS scoring system of 4.0, rather than the value of 6.0 used for adult patients, allowed good prediction of a poor prognosis of DTC in childhood and young adult patients less than 21 years of age.
The MACIS scoring system was designed and has been used to predict disease-specific mortality since 1993. Hay et al. reported a 20-year cause-specific survival of 99% for patients of all ages with an MACIS score of <6. This scoring system has been repeatedly validated in adult patients with DTC. However, few attempts have been made to validate this scoring system in childhood and young adult patients. Powers et al. reported that the MACIS scores correlate well with the response to initial therapy in children and adolescents, and they proposed an MACIS score cut-off value of >4.25 for detecting patients that would fail to enter remission after the initial therapy, with acceptable diagnostic parameters (sensitivity 83%; specificity 73%). In a subsequent report by Powers et al. they decreased the cut-off value to 4.0 for identifying high risk and aggressive cases of recurrent and persistent DTC in childhood and adolescent patients. In the present study, 66 childhood and young adult patients with DTC less than 21 years of age at the time of diagnosis were analyzed to determine the cut-off value of the MACIS score for a poor prognosis by ROC analysis. We confirmed that an MACIS score cut-off value >4.0 was useful for predicting a poor prognosis with comparable diagnostic sensitivity and specificity in young patients with DTC. The sensitivity of the new cut-off for poor prognosis is 93%; the specificity is 67%; negative predictive value (NPV) is 97% but positive predictive value (PPV) is only 43%. Given that PPV does depend on the prevalence of the disease and the sensitivity and the specificity, the low PPV might result from the relatively low prevalence of disease persistence and disease recurrence of DTC among these study patients. However, considering that the purpose of the new cut-off is to differentiate young patients with poor prognosis so that the proper managements can be given without unnecessary treatment-related complications, these diagnostic values have some implications on managements. The NPV is as high as 97% and thus we can avoid unnecessary aggressive treatment in patients with an MACIS score of less than 4. Although the sensitivity is high, the PPV is around 50%, thus half of the patients with MACIS score ≥4 will have disease recurrence or persistence. Therefore, we should be alert in managing this group of patients. Until more precise and accurate models to stratify risks of persistent and recurrent diseases are available in the future, we can cautiously use the new cut-off of MACIS score in managing these young patients with DTC.

When the clinical/pathological characteristics of patients with DTC were compared according to 3 age groups, pre-puberty (age <15 years), adolescents (15 ≤ age <18 years), and young adults (18 ≤ age <21 years), no significant differences among the 3 age groups was found (Table 2). Lazar et al. reported that pre-pubertal patients with DTC were more likely to have extrathyroidal invasion, lymph node metastasis, and lung metastasis than patients of pubertal age. They classified 27 patients with DTC less than 17 years of age as either pre-pubertal (n = 10) or pubertal (n = 17) using Tanner staging, and their median age at diagnosis were 9 years old and 14 years old, respectively. The difference between the results of the present study and those of Lazar et al. might result from the difference in the characteristics of the enrolled patients. Patients in the study reported by Lazar et al. had familial malignant syndromes and previous exposure to external irradiation, both of which led to early detection of DTC at a pubertal age. In the present study, by contrast, the patients were a relatively homogenous group without a history of familial malignant syndrome or irradiation. In addition, there were only 3 patients less than 10 years of age in the present study. Recently, Machens et al. reported that PTC in children and adolescents does not differ in growth pattern and metastatic behavior, which is quite in agreement with our study. Therefore, large prospective studies are needed to validate the scoring system and to develop an age-specific cut-off value.
needed to investigate the differences in the clinical/pathological characteristics according to age. Even though the results failed to demonstrate the difference in clinical/pathological features among the age groups, the findings confirmed the frequent extrathyroidal invasion, cervical lymph node metastasis, and distant metastasis in patients with childhood and young adult DTC that have been observed in previous reports.10,25–26

There are some limitations in this study. First, the validation study was not conducted prospectively. Because this study was conducted in 1 institution with a limited number of patients (n = 66), we could not divide the modeling group and the validation group like the original study by Hay et al's15 study with a large number of patients (n = 1799). Thus, wide dissemination of the results of this study which propose different cut-off values for these age group needs further validation with a larger number of patients. Second, the follow-up period was relatively short (median, 59 months) when compared to the 20-year follow-up by Hay et al's15 report on the MACIS scoring system to predict cancer-specific mortality. There was no mortality in the follow-up period of this study, which reflects good prognosis in this age group. Considering that the new cut-off proposed in this study is not to predict cancer-specific mortality but to predict risks of disease recurrence and persistence and that these events occur earlier in the disease course than cancer-related mortality, this might partly justify the short follow-up period of this study. However, studies of longer follow-up with a larger number of patients to validate the new MACIS cut-off in this age group are warranted in the future.

In conclusion, a cut-off value of 4.0 rather than 6.0, which is used for adult MACIS scoring, can predict poor outcomes in childhood and young adult patients with DTC.

REFERENCES
