ORIGINAL ARTICLE

Differentiated Thyroid Cancer: Reclassification of the Risk of Recurrence Based on the Response to Initial Treatment

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Abstract

Introduction: The American Thyroid Association (ATA) classification system for differentiated thyroid cancer (DTC) provides a static assessment of the patient at baseline and it has not been designed to be modified. The Memorial Sloan-Kettering Cancer Center (MS-KCC) has designed a re-staging system at 2 years after initial treatment (IT) thus providing a dynamic perspective of each patient. Objective: to report our experience with the MS-KCC risk of recurrence re-staging system for patients with DTC. Materials and methods: retrospective observational descriptive study of the results of the risk of recurrence reclassification system for patients with a diagnosis of DTC at 2 years after IT. Patients were classified according to the ATA system at baseline and re-staged at 2 years after IT according to the MS-KCC. Results: We classified 31 patients according to the ATA system as: low risk (n = 17; 54.8 %), intermediate risk (n = 13; 42 %) and high risk (n = 1; 3.2 %) and re-staged them according to the MS-KCC system as having an excellent response (n = 25; 80.6 %), an acceptable response (n = 6; 19.4 %) and an incomplete response (n = 0; 0 %). Of the patients initially classified as low-risk, 14 (82.4 %) had an excellent response and 3 (17.6 %) had an acceptable response; of the intermediate-risk patients, 11 (84.6 %) had an excellent response and 2 (15.4 %) had an acceptable response and of the high-risk patients, 1 (100 %) had an acceptable response. The clinical status of patients at 2 years after IT was: 25 patients (80.6 %) free of disease (FOD) and 6 patients (19.4 %) with biochemical persistence (BP). At the end of the long-term follow-up, of the patients with an excellent response, 24 (96 %) remained FOD, and 1 (4%) was lost to follow-up. Conclusions: 1) re-staging of patients was particularly useful in the intermediate risk group, 2) re-staging will allow to optimize patient follow-up and 3) there was a good correlation between clinical status at 2 years after IT and on completion of the long-term follow-up. Rev Argent Endocrinol Metab 51:8-14, 2014

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Key words: thyroid carcinoma, reclassification, risk, recurrence

INTRODUCTION

Differentiated thyroid cancer (DTC) is the most frequent endocrine tumor, and most cases have a favorable outcome. Throughout the years, different staging systems have been used to facilitate treatment and follow-up decision making in patients with DTC, so as to be able to select the least aggressive therapy and the least intensive follow-up that may lead to a favorable outcome. These systems not only provide prognostic information but also help to facilitate exchange of information between different medical centers (1-6). They are based on clinical (age, gender) and pathological (tumor size, histology, extrathyroidal invasion, cervical lymph node involvement, distant metastases) variables (3,7). Unlike in most solid tumors, in thyroid cancer the risk for recurrence and the risk for mortality are not always consistent (8). A large number of authors have studied the factors that may facilitate the identification of patients at a high risk of recurrence and mortality (9). These staging systems can differentiate patients
at high risk from those at low risk of mortality, but cannot accurately predict the risk of recurrence of thyroid cancer\[^{3}\]. Unfortunately, these staging systems do not allow modification of the risk of recurrence or mortality when new data are incorporated throughout patient follow-up\[^{10}\]. The American Thyroid Association (ATA) classification system\[^{6}\] is not only useful to assess the risk of recurrence but also guides follow-up frequency and modality. However, this system provides a static assessment of the patient at the beginning of treatment, and it has not been designed to be modified over time on the basis of the clinical course of disease. Furthermore, as classification systems do not include response to initial therapy (IT) as a variable, prognoses are too poor in patients at a high risk of recurrence with an excellent response to IT and too optimistic in patients at a low risk of recurrence and incomplete response to IT.

Therefore, a system that incorporates response to IT will be more predictive than a system based only on initial risk factors\[^{3}\]. Modification (increase or decrease) of initial risk over time based on the new data obtained during follow-up constitutes the basis of the paradigm that seeks to tailor follow-up recommendations\[^{8,11}\]. For this reason, the Memorial Sloan-Kettering Cancer Center (MS-KCC) has designed a re-staging system for patients with DTC at 2 years after IT, thus providing a more dynamic perspective of each patient\[^{11}\]. This new system of ongoing risk assessment considers the risk of failing initial therapy, which is decisive for the final outcome\[^{3}\]. Even if 2 years is an early time point in the follow-up of patients with DTC, the MS-KCC proposed reevaluating risk at 2 years after initial therapy for various reasons: 1) in most patients with DTC, the initial assessment of response to treatment is very similar for the first 2 years, 2) it is difficult to accurately evaluate the effectiveness of radioiodine ablation before 18 months have passed, using serum thyroglobulin (Tg) determinations, since Tg levels will continue to decline for several years after IT and 3) it would not be cautious to lower the initial estimate of risk without a close follow-up of at least 2 years, during which there should have been no evidence of clinically significant recurrent or persistent disease\[^{8,10}\]. It is important to emphasize that the reclassification of risk at 2 years after IT was designed to guide the follow-up of patients and not to predict which patients are "cured" of disease\[^{8}\].

OBJECTIVE

The objective of this study is to report our experience with the MS-KCC risk of recurrence reclassification system for patients with DTC.

MATERIALS AND METHODS

This is a retrospective observational descriptive study of the results of the risk of recurrence reclassification system for patients with a diagnosis of DTC at 2 years after IT with surgery and radioiodine ablation, between October 2004 and April 2011. Data were collected from medical records. All surgeries, laboratory determinations and nuclear medicine procedures were performed at our Hospital. Patients were classified according to initial risk of recurrence based on the ATA system (Table I) and were reclassified following the system proposed by the MS-KCC at 2 years after IT (Table II). Patients were excluded if they were less than 18 years old, had a diagnosis of anaplastic or medullary carcinoma, had not been treated with radioiodine ablation or had antithyroglobulin antibodies > 12 IU/ml because of interference with Tg measurement.
TABLE I: ATA Initial risk of recurrence classification system.

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All these criteria are met:</td>
<td>Any of these criteria are met:</td>
<td>Any of these criteria are met:</td>
</tr>
<tr>
<td>- no local or distant metastases</td>
<td>- microscopic invasion of tumor into the perithyroidal soft tissues</td>
<td>- macroscopic tumor invasion</td>
</tr>
<tr>
<td>- all macroscopic tumor has been resected</td>
<td>- cervical lymph node metastases or I\textsuperscript{131} uptake outside the thyroid bed on the post-treatment scan performed after thyroid remnant ablation</td>
<td>- incomplete tumor resection with gross residual disease</td>
</tr>
<tr>
<td>- no tumor invasion of locoregional tissues</td>
<td>- tumor with aggressive histology (e.g.: tall cell, insular, columnar cell, Hürthle cell, follicular) or vascular invasion</td>
<td>- distant metastasis</td>
</tr>
<tr>
<td>- tumor with no aggressive histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- no vascular invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- no I\textsuperscript{131} uptake outside the thyroid bed on the post-treatment scan (if performed)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ATA: American Thyroid Association, I\textsuperscript{131}: Iodine\textsuperscript{131}

Table II: Reclassification according to the system proposed by the MS-KCC at 2 years after IT

<table>
<thead>
<tr>
<th>Excellent response</th>
<th>Acceptable response</th>
<th>Incomplete response</th>
</tr>
</thead>
<tbody>
<tr>
<td>All these criteria are met:</td>
<td>Any of these criteria are met:</td>
<td>Any of these criteria are met:</td>
</tr>
<tr>
<td>- Suppressed and stimulated thyroglobulin (Tg) &lt; 1 ng/ml</td>
<td>- Suppressed Tg &lt; 1 ng/ml and stimulated Tg ≥ 1 and &lt; 10 ng/ml</td>
<td>- Suppressed Tg ≥ 1 ng/ml or stimulated Tg ≥ 10 ng/ml</td>
</tr>
<tr>
<td>- Neck ultrasound with no evidence of disease</td>
<td>- non-specific changes or stable lymph nodes less than 1 cm in size on neck ultrasound</td>
<td>- Rising Tg values</td>
</tr>
<tr>
<td>- CT/MRI and/or nuclear medicine scan with no evidence of disease (if performed)</td>
<td>- CT/MRI and/or nuclear medicine scan showing nonspecific changes, though not completely normal</td>
<td>- persistent or recently identified disease on CT/MRI and/or nuclear medicine scan</td>
</tr>
</tbody>
</table>

MS-KCC: Memorial Sloan-Kettering Cancer Center, IT: initial therapy, Tg: thyroglobulin, CT: computed tomography, MRI: magnetic resonance imaging

RESULTS
We reviewed the medical records of 31 patients with histologic diagnosis of DTC. They were initially classified according to the ATA system (Figure 1) as low risk (n = 17; 54.8 %), intermediate risk (n = 13; 42 %) and high risk (n = 1; 3.2 %). Patients were subsequently reclassified following the MS-KCC system at 2 years after IT (Figure 2) as having an excellent response (n = 25; 80.6 %), an acceptable response (n = 6; 19.4 %) and an incomplete response (n = 0; 0 %).

At 2 years after IT, of the patients initially classified as low-risk, 14 (82.4 %) had an excellent response and 3 (17.6 %) had an acceptable response; of the intermediate-risk patients, 11 (84.6 %) had an excellent response and 2 (15.4 %) had an acceptable response and of the high-risk patients, 1 (100 %) had an acceptable response (Figure 3).
All 13 patients classified as intermediate risk according to the ATA system were thus classified based on the following:

- Six patients (46.2%) had cervical lymph nodes metastasis, all of them with an excellent response.
- Four patients (30.7%) had aggressive histology and microscopic invasion into the perithyroidal soft tissue, with an excellent response in three of them and an acceptable response in one.
- One patient (7.7%) with microscopic invasion into the perithyroidal soft tissue, with an excellent response.
- One patient (7.7%) with aggressive histology, microscopic invasion into the perithyroidal soft tissue and cervical lymph node metastasis, with an excellent response.
- One patient (7.7%) with iodine uptake outside the thyroid bed on the whole body scan after iodine ablation, with an acceptable response.

The clinical status of patients at 2 years after IT was: 25 patients (80.6 %) free of disease (FOD), 6 patients (19.4 %) with biochemical persistence (BP) and there was no structural persistence (SP), recurrence (R) or death (D) (Figure 4).

The clinical status after follow-up was: 25 patients (80.6 %) FOD, 4 patients (12.9 %) with BP and 0 (0%) with SP, R or D; with 2 patients (6.5%) lost to follow-up (LTFU) (Figure 5).

At the end of the long-term follow-up, of the patients with an excellent response, 24 (96 %) remained FOD, and 1 (4%) was LTFU, and of the patients with an acceptable response, 1 (16.7 %) remained FOD (initially classified as low-risk), 4 (66.6 %) remained with BP, 1 (16.7 %) was LTFU and there was no SP, R or D (Figure 6).

**Figure 1.** Patients classified by the ATA Initial risk of recurrence classification system

Referencias de la figura:
Número de pacientes: number of patients
Riesgo bajo: low risk
Riesgo intermedioc: intermediate risk
Riesgo alto: high risk
Cambiar comas por puntos en los decimales.
**Figure 2.** Patients reclassified by the MS-KCC at 2 years after IT.

Referencias de la figura:
Número de pacientes: number of patients
Respuesta excelente: excellent response
Respuesta aceptable: acceptable response
Respuesta incompleta: incomplete response
TI: tratamiento inicial; IT: initial therapy
Cambiar comas por puntos en los decimales

**Figure 3.** Response to IT according to ATA initial risk

Referencias de la figura:
Número de pacientes: number of patients
Respuesta excelente: excellent response
Respuesta aceptable: acceptable response
Riesgo bajo: low risk
Riesgo intermedio: intermediate risk
Riesgo alto: high risk
TI: tratamiento inicial; IT: initial therapy
Cambiar comas por puntos en los decimales
**Figure 4.** Clinical status of the patients at 2 years after IT.

Referencias de la figura:
- TI: tratamiento inicial; IT: initial therapy
- LE: libre de enfermedad; FOD: free of disease
- PB: persistencia bioquímica; BP: biochemical persistence
- PE: persistencia estructural; SP: structural persistent
- R: recurrencia; D: death.
- Cambiar comas por puntos en los decimales

**Figure 5:** Clinical status of the patients after follow-up

Referencias de la figura:
- Número de pacientes: number of patients
- LE: libre de enfermedad; FOD: free of disease
- PB: persistencia bioquímica; BP: biochemical persistence
- PE: persistencia estructural; SP: structural persistent
- R: recurrencia; D: death.
- SD: sin datos por falta de seguimiento de los pacientes; LTFU: lost to follow-up.
- Cambiar comas por puntos en los decimales
DISCUSSION

It is universally accepted that staging of patients with DTC is essential in order to identify patients at high risk of recurrence or mortality so that they can receive a more intensive treatment and follow-up than patients at low risk, who will not require additional treatments or costly tests \(^{(10)}\). Over the years, different authors have published a large number of staging systems for DTC \(^{(1,2)}\). In 2008, Tuttle \(^{(3)}\) introduced the idea of reclassifying patients based on response to treatment 2 years after IT with the aim of modifying the risk of recurrence so as to increase or decrease the intensity of future treatment and follow-up of patients accordingly. Other authors, such as Castagna et al. \(^{(12)}\) and Koch \(^{(13)}\) agree that delaying risk stratification of patients at a time when the response to IT is evident allows to better define individual risk.

According to our data, reclassification was very useful mainly in the intermediate-risk group, as in our study 84.6% had an excellent response to IT. In this group of patients, the long-term outcome is expected to be better than the prognosis based on initial classification \(^{(5)}\). It should be highlighted that according to our experience, 46.2% of patients classified as intermediate-risk were included in this group only because of the presence of metastatic cervical lymph nodes, independently of their number and location. Further studies are required to evaluate whether risk is being overestimated in these patients \(^{(10)}\). Tuttle et al. \(^{(11)}\) reported a decrease in the risk of recurrence, more evident in the intermediate-risk group with an excellent response to IT (from 18% to 2%). As a result, patients with an excellent response at 2 years after IT, initially classified as intermediate risk for recurrent disease, might be down staged to the low-risk category. Likewise, patients initially classified as high risk for recurrent disease with an excellent response might be down staged to the intermediate risk category \(^{(10)}\). A limitation of the reclassification proposed by the MS-KCC is that it may only be applied to patients treated with total thyroidectomy and radiiodine ablation.

The group of patients with an acceptable response includes patients that probably have minimal residual disease, with detectable but persistently low Tg levels, pathological
cervical lymph nodes less than 1 cm in diameter. These patients will generally require observation, as the risk of repeat surgery or additional doses of radioiodine probably outweighs the potential clinical benefit. In many of these patients, Tg levels will decline years after IT, and in the absence of structural disease, they will be re-staged as having an excellent response. In addition, patients with an acceptable response who develop progressive structural disease or rising Tg levels might be re-staged as having an incomplete response, which will lead to changes in their follow-up \(^8\,^{10}\). Long-term studies are required to determine which patients with an acceptable response will develop clinically evident disease progression \(^3\).

Re-staging of patients based on response to IT will enable optimization of their follow-up, on the way towards the development of a new long-term follow-up paradigm for patients with DTC. Therefore, we will be able to intensify the treatment and follow-up of patients with an incomplete or acceptable response and avoid too aggressive treatments or too intensive follow-ups in those patients who have an excellent response, minimizing complications and adverse effects \(^3\).

Even if the mean follow-up in our patients was 51.3 months, there was a good correlation between clinical status at 2 years after IT and at long-term follow-up completion, mainly in the excellent response group. In agreement with Tuttle et al \(^{11}\), none of our patients with an acceptable response to IT had recurrence or structural persistence during follow-up.

A limitation of our study was the low number of patients classified as high risk according to the ATA system, because our site is not an oncology reference center.

In the future, apart from response to IT, perhaps biological factors and/or molecular markers could be added to existing staging systems for improving survival prediction in patients with DTC \(^1\).
REFERENCES


