Predictive value of stimulated postoperative thyroglobulin levels in patients with differentiated thyroid carcinoma

Chen-Ku Chih Hao MD, Cambronero-Morga Efraín MD
Endocrinology Department, Hospital San Juan de Dios, San José, Costa Rica. Email: chenku2409@gmail.com or ecambronero@icot.cr

Abstract

Objective: to determine the cutoff point of postoperative stimulated thyroglobulin which is able to predict local recurrence and distant metastasis

Materials and methods: 217 consecutive patients with differentiated thyroid carcinoma that underwent surgery at San Juan de Dios Hospital in San José, Costa Rica were included. Histological characteristics, stimulated thyroglobulin, antithyroglobulin antibodies levels and recurrence data were collected. Exclusion criteria were patients without postoperative stimulated thyroglobulin levels, positive antithyroglobulin levels, revision thryoidectomies or neck dissections. Patients received radioiodine ablation as mandated by local practice guidelines.

Results: 217 patients were included, 86.6% were female. 75.1% had total thyroidectomy, 17.1% total thyroidectomy plus neck dissection, 6.5% completion thyroidectomy and 1.4% subtotal thyroidectomy. 83.4% had classical papillary carcinoma, 6.5% follicular carcinoma and 9.6% had other variants. 68.2% had a TNM stage I, 12.4% stage II, 12.9% stage III, 6.5% stage IV. Mean age was 44.6 ± 12.86 years. 40.6% had a stimulated postoperative thyroglobulin of less than 2 ng/ml (group 1), 31.3% had between 2 and 10 ng/ml (group 2), 28.1% had more than 10 ng/ml (group 3). Recurrence rate was 5.7% in group 1 (4.18 years average of follow up, 100% of cases were locoregional), 5.9% in group 2 (3.84 years of follow up, 25% were distant), and 32.8% in group 3 (4.61 years of follow up, 30% were distant).

Conclusions: postoperative stimulated thyroglobulin levels of less than 10 ng/ml might predict a lower recurrence rate. Distant metastases were not associated with thyroglobulin levels of less than 2 ng/ml.

Introduction

Patients with well-differentiated thyroid cancer (WDTC) are a fairly heterogeneous group regarding surgery, I^{131} ablation therapy, and follow-up for recurrence determination.
For many years, validated thyroglobulin (Tg) levels have been regarded as a reliable marker for recurrence after treatment of well-differentiated thyroid cancer. Total thyroid tissue ablation also has been considered mandatory in order to make any Tg level interpretation reliable. Most attention has been placed on the thyroid hormone withdrawal (THW) or recombinant TSH stimulated Tg level after I^{131} ablation (6 to 12 months, at the time of the first diagnostic WBS) as a reliable tumor marker. However, some evidence has already been published on the prognostic significance of high initial values of the postoperative stimulated Tg level which, along with lymph node metastasis, have shown to be, on multivariable analysis, the two strongest predictors for recurrence.[1-3]
Recent reports[4-5] have shown that THW-stimulated Tg levels after total or near-total thyroidectomy and just before ablation and THW- stimulated Tg levels at the time of the first diagnostic WBS are equally reliable at predicting recurrence in patients with well differentiated thyroid cancer.
Although it is fairly clear that a low or very low postoperative stimulated serum Tg level may be associated with a lower risk of recurrence, we are far from defining a reliable cutoff level of serum Tg.
There are no definite guidelines or recommendations as to type of imaging or diagnostic algorithm to detect recurrence in patients with elevated postoperative thyroglobulin.
We have hypothesized that determination of validated THW stimulated Tg serum level (with TSH above 25-30 mU/L and negative anti-Tg levels) is a reliable tumor marker at predicting recurrence in patients with WDTC using a serum Tg cutoff of 2 ng/ml. The clinical implications of this hypothesis might include avoiding the use of I^{131} ablation and THW or recombinant TSH stimulated serum Tg determination, as well as the routine use of WBS as part of the follow-up recommendations in this group of patients. A more cost-effective approach and follow-up might also be evaluated.
The objective of this study is to determine the cutoff point of postoperative stimulated thyroglobulin which is able to predict local recurrence and distant metastasis

Materials and methods

Patients with differentiated thyroid carcinoma that underwent surgery between August 2005 and July 2011 and with at least one year follow up at San Juan de Dios Hospital in San José, Costa Rica were included. Surgery was performed by different surgeons, but all patients had total or near total thyroidectomy. Histological characteristics, stimulated Tg, antithyroglobulin antibodies levels and recurrence data were collected. Exclusion criteria included patients with microcarcinomas (less than 1 cm diameter), abscense of postoperative stimulated Tg levels, positive antithyroglobulin levels, revision thryoidectomies or revision neck dissections. Stimulated Tg levels were measured at least 2 weeks after surgery or right before ablation with I^{131} was given. Patients received I^{131} ablation as mandated by local practice guidelines (tumor greater than 2 cm in patients over 45 years old or greater than 4 cm at any age, presence of lymph node metastasis, distant metastasis, macroscopical extrathyroid invasion or high risk histologic variants).
Statistical analysis was performed using SPSS 20.0. Continuous variables were analyzed using T student test and categorical variables were analyzed using chi square test.

Results

217 patients were identified and included in the present study. 86.6% were female and 13.4% males. 75.1% had total thyroidectomy, 17.1% total thyroidectomy plus neck dissection, 6.5% completion thyroidectomy and 1.4% subtotal thyroidectomy. 83.4% had classical papillary carcinoma, 6.5% follicular carcinoma and 9.6% had other variants. 68.2% had a TNM stage I, 12.4% stage II, 12.9% stage III, 6.5% stage IV. Mean age was 44.6 ± 12.86 years. Average follow up was 4.1 years (range 0-10).
Patients were categorized based on their postoperative stimulated thyroglobulin levels using THW protocol. 40.6% had a stimulated postoperative thyroglobulin of less than 2 ng/ml (group 1), 31.3% had between 2 and 10 ng/ml (group 2), 28.1% had more than 10 ng/ml (group 3). Recurrence rate was 5.7% in Group 1 (4.18 years average of follow up, 100% of cases were locoregional), 5.9% in Group 2 (3.84 years of follow up, 75% of cases were locoregional and 25% were distant), and 32.8% in Group 3 (4.61 years of follow up, 70% were locoregional and 30% were distant). Table 1 show demographic data in each group, recurrence rate and

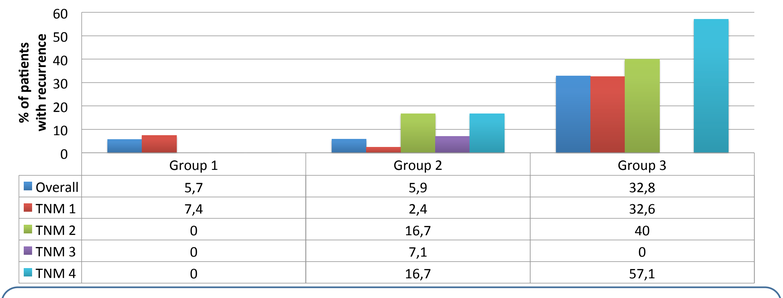
Table 1. General characteristics and recurrence rate and site.

	Group 1 (n=88)	Group 2 (n=68)	Group 3 (n=61)	P
Age ± SD	46.89 ± 11.51	45.35 ± 12.24	40.61 ± 14.54	0.011
% female	83.8%	86.9%	88.6%	0.68
% with neck dissection	12.5%	14.7%	26.2%	0.037
TNM stage 1	77.3%	61.8%	62.3%	
TNM stage 2	12.5%	8.8%	16.4%	
TNM stage 3	9.1%	20.6%	9.8%	
TNM stage 4	1.1%	8.8%	11.5%	0.459
% patients that received I^{131}	81.8%	76.5%	95%	0.024
Average I^{131} dose ± SD	65.56 ± 44.04	61.91 ± 46.14	87.83 ± 42.58	0.002
Recurrence rate	5.7%	5.9%	32.8%	<0.001
Recurrence site	100% locoregional	75% locoregional, 25% distant	70% locoregional, 30% distant	
Average follow up (years) ± SD	4.18 ± 2.03	3.84 ± 1.99	4.61 ± 1.45	0.069

Table 2. Recurrence rates in each group if radioiodine was given

Group	Received I^{131} ablation	Did not receive I^{131} ablation	p
Group 1	6.9%	0%	0.357
Group 2	1.9%	6.2%	0.363
Group 3	35.1%	0%	0.194

Graph 1. Recurrence rate in each group by TNM staging



Discussion

Stimulated postoperative Tg levels may be used as a surrogate marker for remnant normal thyroid tissue or microscopic metastasis. All patients had thyroidectomy, near total thyroidectomy or completion thyroidectomy, and in our practice, before radioiodine is given, all patients will have a neck ultrasound performed to evaluate the presence of remnant tissue. Therefore, in these patients, postoperative Tg more likely indicates the presence of microscopic persistent disease, so our finding that postoperative stimulated Tg levels greater than 10 ng/ml may predict a higher recurrence rate is not surprising.
However, baseline characteristics differ in the three evaluated groups. Patients in Group 3 had more advanced disease at presentation (11% had TNM stage 4), a higher percentage of patients had neck dissection and more patients received radioiodine ablation. Nonetheless, even in low risk patients (TNM stage 1), these patients also had a higher recurrence rate, supporting the hypothesis that these thyroglobulin levels reflect microscopic persistent disease. I^{131} treatment did not lower the recurrence rates significantly.
Although almost all patients in Group 3 received radioiodine ablation, recurrence rate was higher in this group. Average radioiodine dose was higher in these patients. A postoperative stimulated thyroglobulin level greater than 10 ng/ml may identify patients with more aggressive disease.
Recurrence rate was similar in Groups 1 and 2 but all recurrences in Group 1 were locoregional. A stimulated Tg level of less than 2 ng/ml predicts a low recurrence rate and all recurrence will be locoregional. A higher Tg level predicts a higher distant metastasis recurrence rate. Other series have reported different cutoff values for stimulated Tg. Rosario et al[7] reported that stimulated Tg levels below 1 combined with a negative ultrasound in low risk patients may help detect patients with a very low rate of recurrence after initial therapy. Sawka et al[8] showed that the lower the postoperative stimulated Tg level, the lower the probabilities of having a stimulated Tg greater than 2 ng/ml on follow up. Our study evaluated the presence of clinical recurrence and not only positive Tg on follow up. In the series by Kim et al[5], only 2% of patients with stimulated postoperative Tg of less than 2 ng/ml had clinical recurrence compared with 23% of those patients with a Tg level greater than 2. In contrast, our data showed a greater recurrence rate with a Tg level greater than 10 ng/ml, but not with greater than 2 ng/ml although there were differences in recurrence site.
We acknowledge that our data is retrospective in nature, which is a potential drawback. Likewise, the small number of patients and relatively short follow-up preclude us from obtaining definitive conclusions. Further studies need to be done in order to confirm our data.

Conclusions

Postoperative stimulated thyroglobulin levels of less than 10 ng/ml might predict a lower recurrence rate. Distant metastases were not associated with thyroglobulin levels of less than 2 ng/ml.

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