



Measurement of serum thyroglobulin is useful for the follow-up of papillary thyroid carcinoma patients treated with lobectomy



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Importance

- The value of serum **thyroglobulin/anti-thyroglobulin** (Tg/ATg) for **papillary thyroid carcinoma** (PTC) surveillance after **lobectomy** was investigated.

Objective

- To examine the association between **post-lobectomy serum Tg/ATg** and **PTC structural recurrence** and define applicable values for stratification.

Table 1. Study cohort characteristics.

Characteristic	ATg-negative group N (%)	ATg-positive group N (%)
Total	1050	401
Age		
<55 y	920(87.6)	356(88.8)
≥55 y	130(12.4)	45(11.2)
Sex		
Male	304(29.0)	32(8.0)
Female	746(71.0)	369(92.0)
Primary tumor size		
≤1 cm	631(60.1)	250(62.3)
1-2 cm	283(27.0)	101(25.2)
2-4 cm	120(11.4)	47(11.7)
>4 cm	16(1.5)	3(0.7)
Multifocality	184(17.5)	70(17.5)
Gross extrathyroidal extension	128(12.2)	32(8.0)
Hashimoto thyroiditis	76(7.24)	224(55.9)
Central neck dissection		
No	306(29.1)	73(18.2)
Yes	744(70.9)	328(81.8)
Lateral neck dissection		
No	867(82.6)	299(74.6)
Yes	183(17.4)	102(25.4)
ATA initial risk stratification		
Low	583(55.5)	238(59.4)
Intermediate	268(25.5)	104(25.9)
High	199(19.0)	59(14.7)
T stage		
T1	834(79.4)	336(83.8)
T2	85(8.1)	32(8.0)
T3	92(8.8)	20(5.0)
T4	39(3.7)	13(3.2)
N stage		
N0	582(55.4)	199(49.6)
N1a	265(25.2)	114(28.4)
N1b	203(19.3)	88(21.9)
TNM stage		
I	987(94.0)	380(94.8)
II	50(4.8)	19(4.7)
III	13(1.2)	2(0.5)

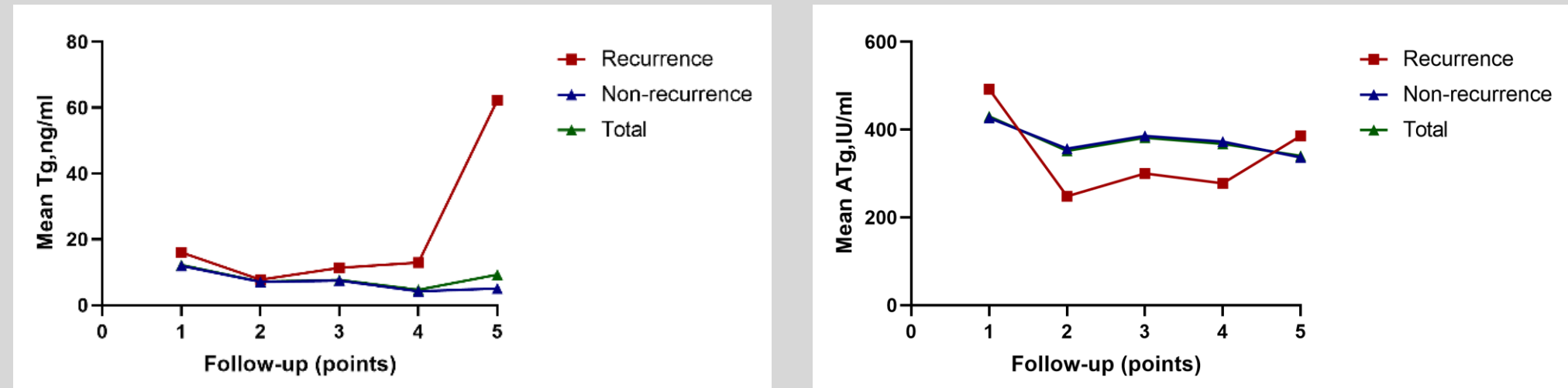


Figure 1. Mean Tg in the ATg-negative group (A) and ATg in the ATg-positive group (B) during follow-up.

Design

- The study cohort was divided into **ATg-negative** (ATg ≤ 60 IU/ml) and **ATg-positive** groups (ATg > 60 IU/ml).
- Predictive classifiers of recurrence using random forest were established combining different variables related to serum Tg (ATg-negative patients) or ATg (ATg-positive patients), which included : **FTg**, **LTg**, **LTg-FTg**; **LTg/FTg**; **LTg-PTg**; **LTg/PTg**; **peak** (deviation was 20% higher than the larger one between FTg and LTg); **valley** (deviation was 20% lower than the smaller one between FTg and LTg); **high deviation** (difference of the highest deviation subtracting the larger one between FTg and LTg); **low deviation** (difference of the smaller one between FTg and LTg subtracting the smaller deviation); and **standard deviation** (SD). Similarly, the variables of the ATg-positive group replaced the Tg data with the ATg data.
- FTg** (FATg), **PTg** (PATg) and **LTg** (LATg), represented the first, penultimate and last Tg (ATg) levels measured in the first (first 6-12 months after surgery), penultimate and last follow-up, respectively; deviation was considered the remaining Tg (ATg) level that was out of range formed by FTg (FATg) and LTg (LATg).
- Cutoff values were determined with receiver operating characteristic curves.
- Kaplan-Meier curve and log-rank test were performed to compare recurrence-free survival (RFS) between different subgroups according to stratification by Tg/ATg to validate the differentiation ability of these serum markers.

Setting

- Single institute study in a referral cancer center.

Participants

- Inclusion criteria:** Patients who underwent lobectomy for PTC with adequate serum Tg/ATg data during 2000-2014.
- Exclusion criteria:** Patients with preoperative evidence of distant metastasis, positive surgical margins or incomplete Tg or ATg data, and elevated thyroid-stimulating hormone levels.

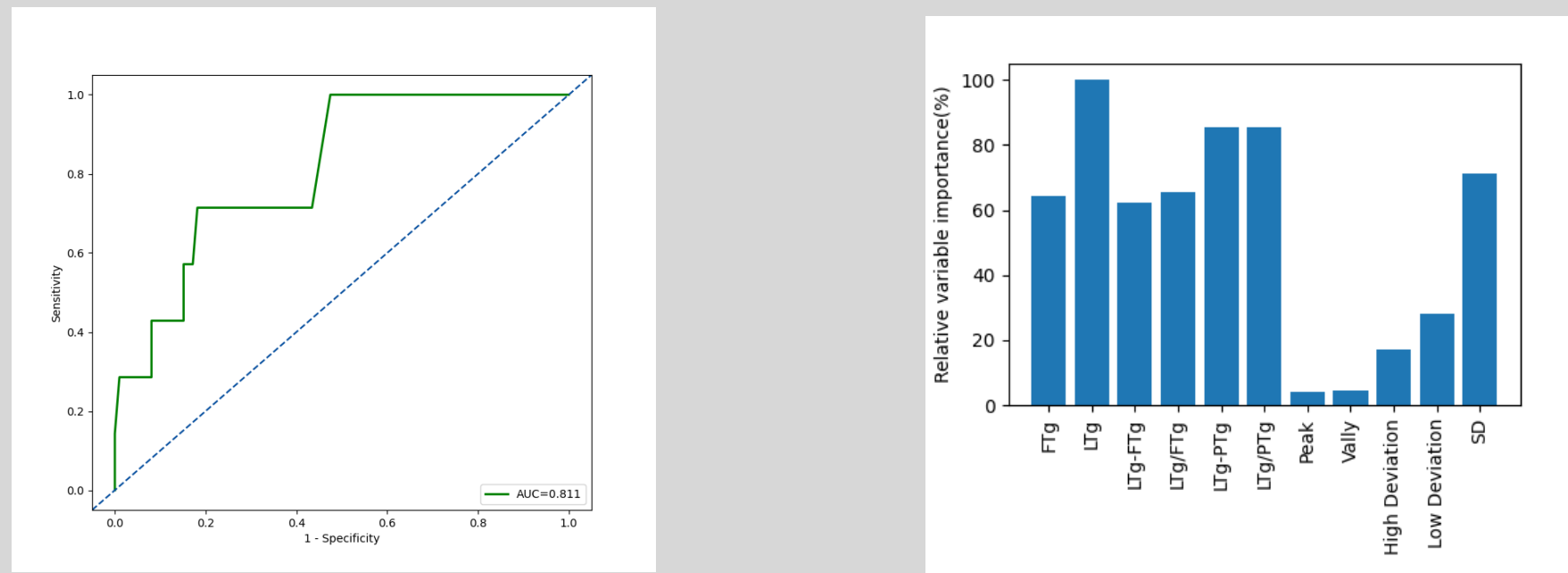


Figure 2. Differentiation of recurrence based on the classifier in the ATg-negative group. A, ROC curve of the classifier in the testing cohort. B, Relative importance of the variables in the classifier. Variable importance is represented as a percentage of the highest value.

Exposures

- Lobectomy

Main outcomes

- The association between post-lobectomy serum Tg/ATg and PTC structural recurrence.

Results

- A total of 1451 (1050 ATg-negative and 401 ATg-positive) patients were selected (Table 1). With a median follow-up of 72.0 (range, 14-135) months and 71.7 (range, 12-124) months, 66 (6.3%) and 26 (6.5%) patients in the ATg-negative group and ATg-positive group experienced recurrence, including 9 and 1 distant metastasis, respectively.
- The overall trend in the serum Tg of patients with recurrence was relatively stable and rose sharply before recurrence but decreased in patients without recurrence (Figure 1A). The serum ATg of patients with recurrence showed a downward trend and slightly rose before recurrence, but patients without recurrence showed an overall downward trend (Figure 1B).
- The established classifier of serum Tg (n=1050) showed a favorable association with recurrence (AUC=0.81) (Figure.2A). LTg and its difference/ratio with PTg had the best predictive value, followed by SD, FTg and its difference/ratio with LTg (Figure.2B).
- The optimal cutoff values of the first Tg (FTg, measured 6-12 months after lobectomy) was 5.3 (Fig.3A). Kaplan-Meier curves showed that patients with elevated FTg had significantly compromised RFS rates compared with patients with normal FTg in all ATg-negative patients, low-risk patients and intermediate- to high-risk patients (n=1050, 583 and 467, all P<0.05) (Fig.3B, Fig.3C).

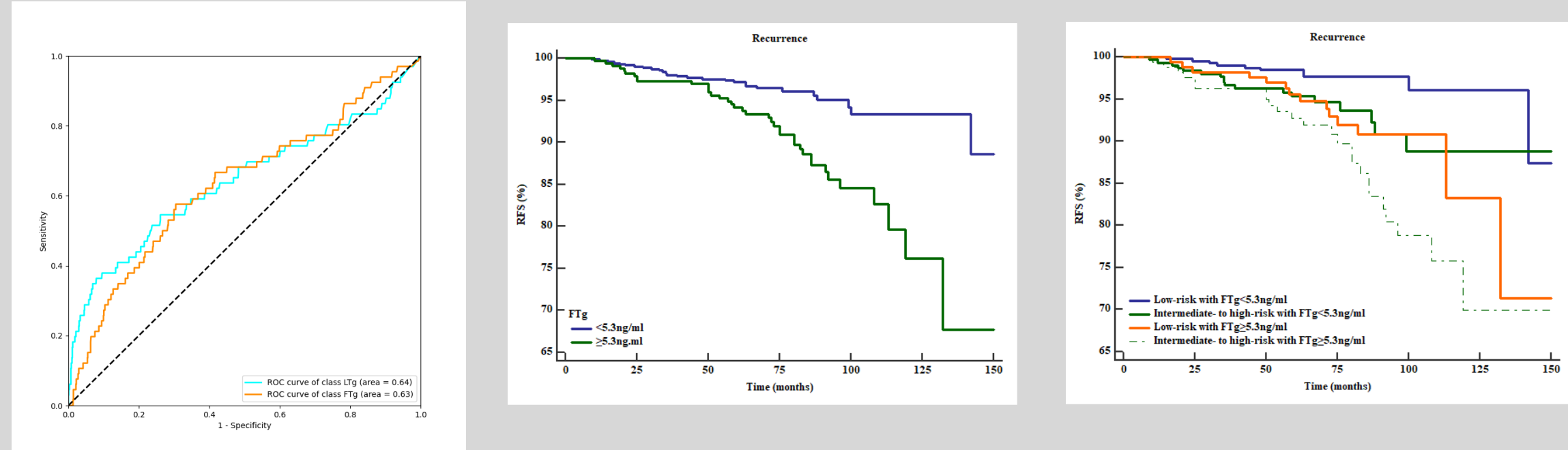


Figure 3. Evaluation of prognostic performance in the overall cohort. A, ROC curves for FTg- and LTg-based prediction of recurrence. B, Kaplan-Meier curves for recurrence in the FTg≥5.3 ng/ml and FTg<5.3 ng/ml groups. C, Kaplan-Meier curves for recurrence based on FTg (5.3 ng/ml as cutoff) at different ATA initial risk stratifications.

- The optimal cutoff value of the last Tg (LTg, measured most recently) was 11.0 ng/ml. Elevated LTg patients had significantly higher recurrence rates than normal LTg patients (23.5% vs. 4.4%, P<0.05) (Table 2).

Table 2. Predictive performance of LTg (11.0 ng/ml as the cutoff) in the overall cohort.

	LTg		Total
	LTg≥11.0 ng/ml	LTg<11.0 ng/ml	
Recurrence	24	42	66
No recurrence	78	906	984
Total	102	948	1050

- The established classifier of serum Tg (n=401) showed a favorable association with recurrence (AUC=0.72) (Fig.4A). Further evaluation was not performed considering the unfavorable predictive value according to the AUC. The relative importance of a variable for separating patients with recurrence from patients without recurrence is shown in Figure 4B.

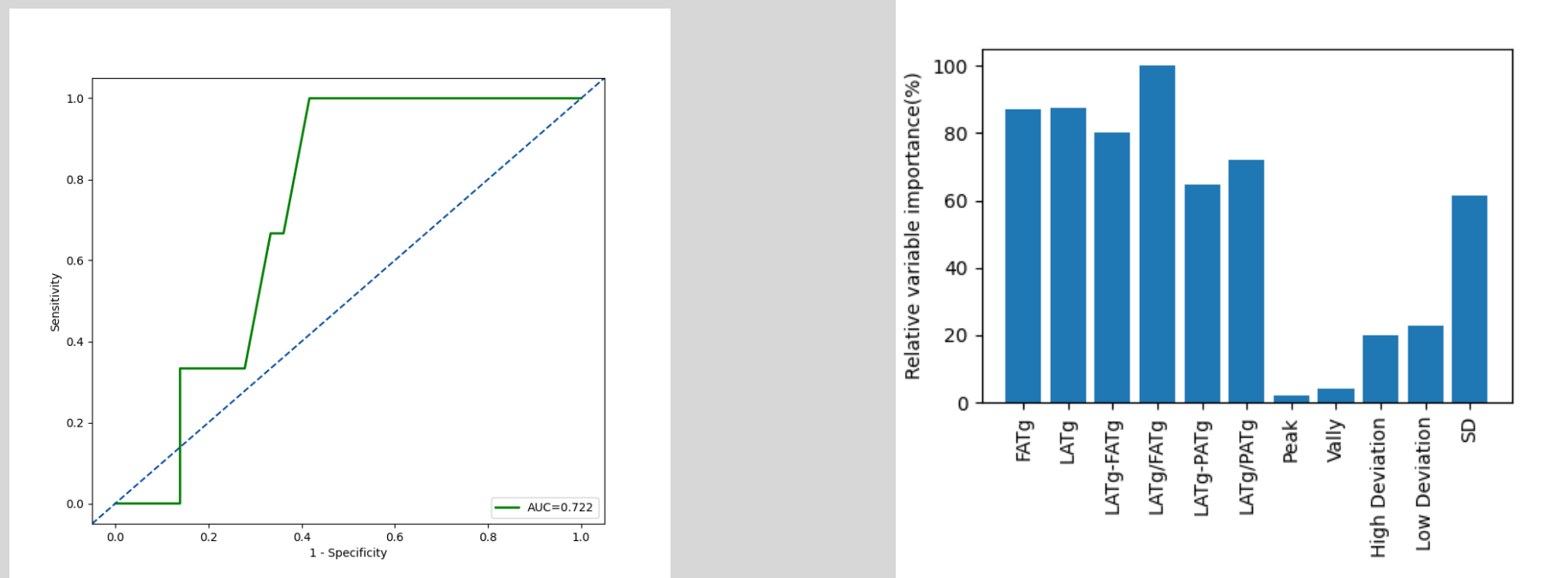


Figure 4. Differentiation of recurrence based on the classifier in the ATg-positive group. A, ROC curve of the classifier in the testing cohort. B, Relative importance of the variables in the classifier. Variable importance is represented as a percentage of the highest value.

Conclusions

Post-lobectomy serum Tg has favorable value for recurrence risk stratification in PTC patients, and reasonable thresholds could differentiate patients well during follow-up.

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