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Association between serum 25(OH)D and clinicopathologic outcome in PTC using the AJCC 8th edition

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Background/Aims: Previous study have suggested that preoperative lower serum 25-hydroxy (OH) vitamin D is associated with poor prognosis in female patients with papillary thyroid cancer (PTC). The updated 2017 American joint committee on cancer (AJCC) TNM staging system have adopted the 8th TNM classification system. Mostly stages were down-staged to avoid unnecessary over treatment and potential complications. The aim of the this study was to investigate comparison of 25(OH) vitamin D levels are associated with poor clinicopathologic characteristics in the 7th and 8th editions of the AJCC TNM staging for female patient with PTC. **Methods:** This cross-sectional retrospective study enrolled 548 female patients who underwent a total thyroidectomy for PTC from June 1, 2012 to May 31, 2013. 25(OH) vitamin D levels were measured in blood sample before two weeks prior to surgery. Patients were categorized into four quartiles by preoperative serum 25(OH) vitamin D levels. We re-staged patient with PTC by applied the 7th and 8th editions of the AJCC staging system and compared associations between two staging systems. **Results:** Applying the 7th and 8th editions of the AJCC staging system, preoperative serum 25(OH) vitamin D levels was significantly lower in patient with a tumor size of >1cm(p=0.010) and lymph node metastasis (LNM, p=0.013). Patients applied the 7th TNM classification system of the AJCC in the second quartile had a greater occurrence of T stage 3-4 (odds ratio (OR) 2.03; 95% confidence interval (CI) 1.19-3.44; p=0.009) than those in the fourth quartile. Multivariate analysis showed that patients in the second quartile had a greater occurrence of T stage 3-4 (OR 1.89; 95% CI 1.08-3.30; p=0.026) than those in the fourth quartile. But the association between vitamin D quartile and T stage 3-4 was not significant after applied the 8th editions of the AJCC staging system. **Conclusions:** Our study revealed that poor clinicopathologic features in PTC divided by 8th edition of AJCC staging were not associated lower serum levels of 25(OH) vitamin D. The reason for this result is thought to be most stage were down-staged in the 8th edition compared to the 7th edition.

Table 1. Odds ratios and confidence intervals for prognostic factor and thyroid cancer stage in study patients grouped according to quartiles of adjusted serum 25(OH) vitamin D

Characteristics	Quartile 1		Quartile 2		Quartile 3		Quartile 4
	OR[95% CI]	p-value	OR[95% CI]	p-value	OR[95% CI]	p-value	
T stage 3-4 (7^{th})	1.31[0.76-2.27]	0.331	2.03[1.19-3.44]	0.009	1.27[0.73-2.10]	0.402	1(ref.)
T stage 3-4 (8^{th})	23,932,949.95 [0.00-0.00]	0.996	48,585,687.88 [0.00-0.00]	0.996	23,932,949.95 [0.00-0.00]	0.996	1(ref.)
LNM	1.73[1.01-2.95]	0.045	2.03[1.19-3.44]	0.009	1.27[0.73-2.19]	0.402	1(ref.)
Stage Ⅲ-Ⅳ (7^{th})	1.48[0.88-2.51]	0.143	1.53[0.91-2.59]	0.112	1.08[0.63-1.86]	0.782	1(ref.)
Stage Ⅲ-Ⅳ (8^{th})	1.00[0.00-0.00]	1.000	23,932,961.62 [0.00-0.00]	0.996	1.00[0.00-0.00]	1.000	1(ref.)
ETE	1.35[0.79-2.32]	0.273	1.95[1.13-3.29]	0.013	1.26[0.73-2.17]	0.406	1(ref.)
LVI	1.91[0.68-5.31]	0.217	2.29[0.84-6.21]	0.104	1.91[0.86-5.31]	0.217	1(ref.)
BRAF ^{V600E}	1.16[0.72-1.87]	0.542	1.39[0.86-2.26]	0.178	0.89[0.55-1.43]	0.628	1(ref.)

OR: Odds ratio, CI: Confidence interval, LNM: Lymph node metastasis, ETE: Extrathyroidal extension, LVI: Lymphovascular invasion

Table 2. Multivariate analysis of prognostic factors and the thyroid cancer stage

characteristics	Model 1		Model 2	
	OR[95%CI]	p-value	OR [95%CI]	p-value
T stage 3-4 (7^{th})				
Quartile 1	1.36[0.79-2.36]	0.271	1.24[0.68-2.24]	0.483
Quartile 2	2.07[1.21-3.52]	0.007	1.89[1.08-3.30]	0.026
Quartile 3	1.32[0.76-2.29]	0.330	1.21[0.69-2.14]	1.506
Quartile 4	1 (reference)		1 (reference)	
T stage 3-4 (8^{th})				
Quartile 1	25,684,408[0.00-0.00]	0.996	19,114,442[0.00-0.00]	0.996
Quartile 2	45,300,083[0.00-0.00]	0.996	44,561,812[0.00-0.00]	0.996
Quartile 3	26,013,841[0.00-0.00]	0.996	21,624,023[0.00-0.00]	0.996
Quartile 4	1 (reference)		1 (reference)	
LNM				
Quartile 1	1.67[0.98-2.87]	0.060	1.47[0.82-2.64]	0.191
Quartile 2	2.00[1.18-3.41]	0.010	1.88[1.08-3.28]	0.026
Quartile 3	1.22[0.70-2.12]	0.481	1.20[0.68-2.12]	0.526
Quartile 4	1 (reference)		1 (reference)	
ETE				
Quartile 1	1.40[0.82-2.42]	0.221	1.26[0.70-2.27]	0.447
Quartile 2	1.98[1.17-3.36]	0.011	1.81[1.04-3.14]	0.037
Quartile 3	1.31[0.76-2.26]	0.334	1.22[0.69-2.13]	0.495
Quartile 4	1 (reference)		1 (reference)	

Model 1 was adjusted for age; model 2 was adjusted for the variables in model 1 plus BMI, seasonal differences, and TSH

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Ineffective therapeutic plasma exchange for intractable Graves' disease

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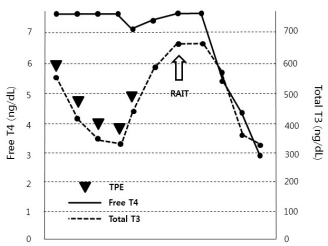
Graves' disease can be treated with any of the three following modalities: anti-thyroid drugs (ATDs), radioactive iodine therapy (RAIT), or thyroidectomy. Among the three effective and relatively safe therapies, ATDs are most frequently chosen as initial treatment in Asia and Europe. However, some patients suffer from side effects of ATDs including agranulocytosis, hepatic damage, or poor responsiveness to medical treatment. The successful use of therapeutic plasma exchange (TPE) for uncontrolled thyrotoxicosis has been described in only a few reports, however the optimum role of TPE is not established in intractable Graves' disease. We describe a case of a 33-year-old male with methimazole-induced agranulocytosis who did not respond to conventional medical treatment (Lugol's solution, steroid, lithium, and propranolol). When he was referred to our institution, the patient suffered from palpitations, weight loss, and heat intolerance. Graves' disease was confirmed based on clinical and laboratory findings: total triiodothyronine (TT3), 553 ng/dL (80–200 ng/dL), free thyroxine (FT4), >7.77 ng/dL (0.93–1.70 ng/dL), and thyroid stimulating hormone (TSH), 0.01 mIU/L (0.27–4.20 mIU/L). Thyroid ultrasonography showed a large goiter with increased vascularity. TPE was discussed for the management of thyrotoxicosis before definitive treatment. Five sessions of TPE were performed via right jugular vein catheterization. After the first three TPE sessions, total triiodothyronine decreased 40% from baseline but rebounded during the following two sessions; in our patient, the procedure was ineffective for controlling thyrotoxicosis and he was achieved euthyroid status after radioactive iodine therapy (Table 1 and Fig. 1). In this report, we described the lack of sustained response of TPE for intractable Graves' disease, although most studies showed biochemical and clinical improvement with TPE, which can be an alternative procedure for uncontrolled thyrotoxicosis. Thus, clinicians need to expect the effect of TPE based on the severity of thyrotoxicosis and determine the number and frequency of TPE sessions for successful response.

Fig. 1. Changes in thyroid function after therapeutic plasma exchange and radioactive iodine therapy.



TPE, therapeutic plasma exchange; RAIT, radioactive iodine therapy