LIVER BIOCHEMICAL CHANGES IN PATIENTS AFTER DIFFERENTIATED THYROID CANCER SURGERY AND BEFORE RADIOIODINE THERAPY

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Abstract

Objectives: To investigate liver enzyme changes and assess liver function in patients with differentiated thyroid cancer who have undergone surgery and are preparing for radioiodine therapy (^{131}I therapy). ***Methods:*** A cross-sectional descriptive study on 163 patients with differentiated thyroid cancer 4 - 6 weeks after surgery at the Military Institute of Radiation Medicine and Oncology from April 2023 to April 2024. Evaluating liver enzymes and liver function at the time of preparing for ^{131}I therapy, compared with a number of paraclinical parameters to find factors related to liver damage. ***Results:*** 38.0% of patients had liver damage (increased AST or ALT), of which 35.6% increased AST, and 24.5% increased ALT, mainly mildly increased (40 to < 100 U/L) and a low rate of liver dysfunction (5.5% slight increase in total Bilirubin and 11.0% decrease in Prothrombin ratio). Male gender and decreased FT4 concentration < 1.17 pmol/L were two factors related to liver damage with ORs of 2.56 and 2.74, respectively, $p < 0.01$. ***Conclusion:*** Liver damage is a relatively common phenomenon related to male gender and FT4 levels in patients with thyroid cancer after surgery and being prepared for ^{131}I therapy.

Keywords: Liver biochemical index; Thyroid cancer; ^{131}I therapy.

INTRODUCTION

Differentiated thyroid cancer is the most common endocrine cancer, has a high incidence, and is rising worldwide. It has a good prognosis if detected and treated properly, including total or nearly total thyroidectomy, followed by ^{131}I therapy to destroy remaining normal thyroid tissue to prevent recurrence or destroy local/distant metastases (if any)

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Date received: 03/12/2024

Date accepted: 02/01/2025

http://doi.org/10.56535/jmpm.v50i4.1114

in combination with thyroid stimulating hormone (TSH) suppression therapy [1, 2]. In order to increase the ability of ^{131}I absorbent into the thyroid tissue, post-operation patients are required not to take thyroid hormone replacement therapy and practice a low-iodine diet, which will lead to a state of active hypothyroidism. This condition can result in some consequences, such as myxoedema, constipation, neuropsychiatric disorders, etc. It also affects the liver, causing liver enzyme elevation and liver dysfunction [3]. Liver damage in patients with post-operative hypothyroidism has been demonstrated in many studies worldwide [4, 5], however, research on this issue has not yet been recorded in Vietnam. Therefore, we conducted this study to: *Assess changes in liver enzymes and some liver function indicators in differentiated thyroid cancer patients who have undergone surgery and are preparing for ^{131}I therapy.*

MATERIALS AND METHODS

1. Subjects

Including 163 patients with thyroid cancer after surgery and indicated for ^{131}I therapy at the Military Institute of Radiation Medicine and Oncology from April 2023 to April 2024.

* *Inclusion criteria:* Patients with thyroid cancer diagnosed by histopathology and who had undergone total or nearly total thyroidectomy 4 - 6 weeks ago; indicated and prepared for ^{131}I therapy (not using thyroid hormone replacement with a low-iodine diet); aged over 18; had normal neuropsychiatric status and agreed to participate in the study.

* *Exclusion criteria:* Patients who have been using liver protection medicines during the postoperative period, active hepatitis B/C virus infection, alcohol abuse, comorbidity of another cancer, etc.

2. Methods

* *Study design:* A cross-sectional descriptive study.

Patients with differentiated thyroid cancer after surgery who meet the inclusion and exclusion criteria were asked for their medical history (directly on the patients and through the surgical medical records). Post-operative disease staging was determined according to the American Joint Committee on Cancer 8th, 2017.

Patients did not use thyroid hormones for 4 - 6 weeks after surgery with a low-iodine diet to increase TSH concentration > 30 μIU/mL (causing active hypothyroidism) to increase the ability to absorb ^{131}I into the remaining thyroid tissue and metastatic tissues (if any) to destroy thyroid tissue and destroy any remaining cancer cells [2].

Liver enzyme tests, some indicators to evaluate liver function (Albumin, total Bilirubin, and Prothrombin ratio) and thyroid hormones (TSH, T3, FT4) at 4 - 6 weeks after surgery on the AU680 biochemical system (Beckman, Coulter, USA) and the ACL-TOP500 automatic coagulation machine.

Classify the level of increased liver enzymes AST, ALT according to the criteria for evaluating adverse events version 4.0 of the US National Cancer Institute (CTCAE v4.0) [6], as follows:

+ Normal < 40 U/L (ULN - upper limit normal).

+ Mild increase in liver enzymes: ≥ ULN and < 2.5 ULN.

+ Moderate increase in liver enzymes: ≥ 2.5 ULN and < 5 ULN.

+ High increase in liver enzymes: ≥ 5 ULN.

Assess patients with liver damage when AST and/or ALT increase > 40 U/L.

Change the value of biochemical indexes according to the threshold at the Military Institute of Radiation Medicine and Oncology and physiological parameters of Vietnamese people:

+ Normal albumin 34 - 48 g/L, decreased when < 34 g/L.

+ Total bilirubin: Normal ≤ 17 μmol/L, increased when > 17 μmol/L.

+ Prothrombin ratio: Normal ≥ 70%, decreased when < 70%.

+ Normal T3 1.3 - 3.1 nmol/L, decreased < 1.3 and increased when > 3.1 nmol/L.

+ Normal FT4 13 - 23 pmol/L, decreased < 13 and increased > 23 pmol/L.

+ Normal TSH 0.27 - 4.2 μIU/mL.

* *Data processing:* Using SPSS 22.0 software.

3. Ethics

The study was approved by the Ethics Council of Military Hospital 103 (No. 2030/HDDD) on June 23rd, 2023. The Military Institute of Radiation Medicine and Oncology granted permission for the use and publication of the research data. The authors declare to have no conflicts of interest in the study.

RESULTS

Table 1. Some characteristics of the study subjects (n = 163).

Variables	$\overline{X}$ ± SD or n (%)
Average age	45.92 ± 16.06
Gender (male; female)	30 (18.4); 133 (81.6)
Postoperative disease stage (I; II; III; IV)	131 (80.4); 28 (17.2); 4 (13.5); 0 (0.0)
Histopathology (papillary; follicular; mixed)	156 (95.7); 2 (1.2); 5 (3.1)
Nearly total; total thyroidectomy	28 (17.2); 135 (82.8)

The average age was 45.92 ± 16.06; women were the main subjects with 4.43 times higher than men (81.6% vs. 18.4%). The disease stage was mainly stage I (80.4%) with 95.7% papillary.

Table 2. Thyroid hormone characteristics (n = 163).

TSH (μIU/mL)	Median (Q1 - Q3)	91.89 (67.68 - 100)
	≥ 30 (n, %)	163 (100)
	< 30 (n, %)	0 (0,0)
T3 (nmol/L)	Median (Q1 - Q3)	0.36 (0.30 - 0.58)
	Decrease < 1.3 (n, %)	163 (100)
	Normal/Increase	0 (0.0)
FT4 (pmol/L)	Median (Q1 - Q3)	1.17 (0.73 - 2.89)
	Decrease < 13 (n, %)	163 (100)
	Normal/Increase	0 (0.0)

100% of patients in the study had hypothyroidism at the time of ^{131}I therapy, showing increased TSH concentration > 30 μIU/mL and decreased T3 concentration < 1.3 nmol/L and FT4 < 13 pmol/L.

Table 3. Liver enzyme concentration characteristics (n = 163).

AST (U/L)	Median (Q1 - Q3)	31.32 (21.48 - 49.14)
	< 40 (n, %)	105 (64.4)
	40 - < 100 (n, %)	52 (31.9)
	100 - < 200 (n, %)	4 (2.5)
	≥ 200 (n, %)	2 (1.2)
	Min - Max	12.4 - 290.9
ALT (U/L)	Median (Q1 - Q3)	30.05 (23.82 - 39.72)
	< 40 (n, %)	123 (75.5)
	40 - < 100 (n, %)	38 (23.3)
	100 - < 200 (n, %)	1 (0.6)
	≥ 200 (n, %)	1 (0.6)
	Min - Max	13.6 - 276.5
Elevated liver enzyme (AST/ALT)	62 (38.0)	

The median AST enzyme level before ^{131}I therapy was 31.32 U/L; 35.6% of patients had increased AST enzyme, of which 31.9% had a mild increase, 2.5% had a moderate increase, and 1.2% had a high increase. ALT enzyme increased in 24.5% of patients, of which 23.3% had a mild increase, 0.6% had a moderate and high increase. 38.0% of patients had liver damage (increased AST and/or ALT).

Table 4. Characteristics of some liver function indicators (n = 163).

Bilirubin TP (µmol/L)	Median (Q1 - Q3)	9.40 (7.62 - 12.14)
	≤ 17 (n, %)	154 (94.5)
	> 17 (n, %)	9 (5.5)
	Min - Max	4.8 - 42.0
Prothrombin (%)	Median (Q1 - Q3)	85.90 (75.21 - 98.75)
	≥ 70% (n, %)	145 (89.0)
	< 70% (n, %)	18 (11.0)
	Min - Max	53.5 - 133.4
Albumin (g/L)	Median (Q1 - Q3)	46.64 (44.72 - 48.28)
	≥ 34 (n, %)	163 (100)
	< 34 (n, %)	0

Only 9 patients (5.5%) had increased total bilirubin > 17 µmol/L (the highest was 42 µmol/L), and 18 patients (11.0%) had decreased prothrombin ratio < 70% (the lowest was 53.5%). No patient had decreased plasma albumin before using ^{131}I.

Table 5. Univariate regression analysis of factors related to liver damage.

Variables		No liver damage	Liver damage	OR	95%CI	p
Age	≤ 45 (n, %)	41 (68.3)	19 (31.7)	1.55	0.79 - 3.02	0.20
	> 45 (n, %)	60 (58.3)	43 (41.7)			
Gender	Male (n, %)	13 (43.3)	17 (56.7)	2.56	1.11 - 5.86	0.027
	Female (n, %)	88 (66.2)	45 (38.8)			
TSH* (µIU/mL)	< 91,89 (n, %)	50 (61.7)	31 (38.3)	0.81	0.40 - 1.64	0.56
	≥ 91,89 (n, %)	51 (62.2)	31 (37.8)			
T3* (nmol/L)	< 0,36 (n, %)	46 (56.8)	35 (43.2)	0.83	0.40 - 1.71	0.62
	≥ 0,36 (n, %)	55 (67.1)	27 (32.9)			
FT4* (pmol/L)	< 1.17 (n, %)	27 (46.6)	31 (53.4)	2.74	1.39 - 5.37	0.003
	≥ 1.17 (n, %)	74 (70.5)	31 (29.5)			

(: Median)*

Male gender and decreased FT4 concentration < 1.17 pmol/L were predictors of liver damage with ORs of 2.56 and 2.74, p = 0.027 and 0.003, respectively.

DISCUSSION

1. Some characteristics of the study subject

80.4% of the patients in the study group were female (the female/male ratio was 4.43/1), with an average age of 45.92 ± 16.06. This result is consistent with the study by Dang Trung Dung et al. (2023) on 98 patients with differentiated thyroid cancer, recording an average age of 43.0 ± 14.5, with 87.8% women [7].

Regarding the stage and histopathology, we found that 80.4% of differentiated thyroid cancer was in stage I when the tumor was still localized in the thyroid gland, and the major histopathological type was papillary (accounting for 95.7%). The study by Dang Trung Dung et al. (2023) also showed that papillary type accounted for 95.6%, and stage I accounted for 75.6% [7].

2. Changes in liver enzymes and liver function in thyroid cancer patients after surgery who are preparing for ^{131}I therapy and some related factors

Currently, the standard treatment for differentiated thyroid cancer is surgery (total or nearly total thyroidectomy), followed by ^{131}I therapy to destroy the remaining thyroid parenchyma (to avoid local recurrence) and/or destroy metastatic lesions (if any). To prepare well for ^{131}I therapy immediately after surgery, the patient must not use thyroid hormone replacement and have to practice a low-iodine diet to induce

hypothyroidism (increase TSH, decrease T3, FT4 concentrations in the blood), thereby increasing the ability to absorb ^{131}I into the thyroid tissue to increase the destruction efficiency. The results of our study showed that 4 - 6 weeks after surgery, 100% of patients had hypothyroidism (*Table 2*). However, when hypothyroidism occurs, it will affect the function of organs, including the liver. We noted 38.0% of patients with liver damage showing an increase in at least one of the two liver enzymes (AST/ALT), of which mild increases were mainly recorded (31.9% with mild AST increase and 23.3% with mild ALT increase), the proportion of patients with moderate and high increases was quite low < 3%. At the same time, a small proportion of patients had impaired liver function (5.5% had a mild increase in total Bilirubin, and 11.0% had a decreased Prothrombin ratio). The study by Ji Y et al. (2022) on 996 patients with hypothyroidism after thyroid cancer surgery also recorded 31.6% of patients with impaired liver function without clinical symptoms, and the most common abnormality was increased liver enzymes (AST or ALT) accounting for 47.5%, also mainly mild increase in liver enzymes (80%) [5]. Another study by Han Y et al. (2012) on 77 hypothyroid patients (who did not use thyroid hormone replacement after surgery) observed liver damage, showing that AST and ALT levels were significantly higher than before surgery (37.9 ± 16.2 vs. 19.5 ± 4.5 U/L and 39.6 ± 21.7 vs. 19.2 ± 17.3 U/L, respectively) [4]. Thus, liver damage is a fairly common phenomenon in thyroid cancer patients after surgery who are prepared for ^{131}I therapy by inducing active hypothyroidism (without using thyroid hormone), but mainly mild enzyme elevation. The mechanism of increased liver enzymes is thought to be related to reduced lipid metabolism in the liver and fatty liver due to reduced thyroid hormone levels leading to increased lipolysis, accumulation of lipid droplets in liver lysosomes, etc. In addition, increased AST is also related to myopathy due to hypothyroidism [3].

We also identified some factors associated with liver damage through univariate logistic regression analysis. The results in table 5 show that 2 factors that increase the risk of liver damage are male gender (OR: 2.56; 95%CI: 1.11 - 5.86, p = 0.027) and decreased FT4 concentration < 1.17 pmol/L (OR: 2.74; 95%CI: 1.39 - 5.37, p = 0.003), similar to the results of Ji Y et al. (2022) [4]. The results are consistent with the biological role of thyroid hormones, which is to participate in blood lipid metabolism, especially lipid metabolism in the liver. Decreased FT4 will increase the risk of fatty liver and liver damage [3].

CONCLUSION

38.0% of patients had liver damage (increased AST or ALT enzymes), of which 35.6% had increased AST, and 24.5% had increased ALT, mainly mild increase (40 - < 100 U/L) and low rate of liver dysfunction (5.5% mild increase in total Bilirubin and 11.0% decreased Prothrombin ratio). Male gender and decreased FT4 concentration < 1.17 pmol/L were two factors related to liver damage with OR of 2.56 and 2.74, $p < 0.01$, respectively.

REFERENCES

1. Filetti S, Durante C, Hartl D, et al. Thyroid cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2019; 30(12): 1856-1883.

2. Sun Y, Di Sun, Zhang X, et al. Radioiodine adjuvant therapy in differentiated thyroid cancer: An update and reconsideration. *Front. Endocrinol.* 2022; 13: 994288.

3. Piantanida E, Ippolito S, Gallo D, et al. The interplay between thyroid and liver: Implications for clinical practice. *J Endocrinol Invest*. 2020; 43(7):885-899.

4. Han YH, Lim ST, Yun KN, et al. Comparison of the influence on the liver function between thyroid hormone withdrawal and rh-TSH before high-dose radioiodine therapy in patients with well-differentiated thyroid cancer. *Nucl Med Mol Imaging*. 2012; 46(2):89-94.

5. Ji Y, Zheng W, Meng Z, et al. Retrospective study of the influence of hypothyroidism on liver function before radioiodine therapy in China: A comparison analysis based on patients with differentiated thyroid cancer. *BMJ Open*. 2022; 12:e045562.

6. Common terminology criteria for adverse events (CTCAE). Version 4.0, Available at http://ctep.cancer.gov. 2009.

7. Dang Trung Dung, Le Ngoc Ha, Tran Trong Kiem. Surgical results of recurrent differentiated thyroid cancer after surgery with ^{131}I resistance. *Journal of Clinical Medicine 108*. 2023; 18(2):48-55.