

# Thyroid Hormone Replacement Therapy in Patients with Various Types of Cancer

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## Abstract

Primary hypothyroidism is a common endocrine disorder that is effectively treated with L-thyroxine (T4) replacement. Preclinical and limited clinical evidence, however, indicates that T4 is a growth factor for a variety of cancers, acting at the thyroid hormone receptor on plasma membrane integrin  $\alpha\beta3$ . T4 is the primary ligand for this receptor, whereas 3,5,3'-triiodo-L-thyronine (T3) is the principal intracellular thyroid hormone analogue. The evidence is reviewed here that T4 is a proliferative for breast, lung, kidney and prostate cancers and for glioblastoma, regulates cancer cell respiration and is a pro-angiogenic factor in established tumors. The recommendation is made that T3 be considered alternative replacement treatment for patients with primary hypothyroidism who also have cancer.

**Keywords:** thyroid hormone receptors, integrin  $\alpha\beta3$ , breast cancer, lung cancer, glioblastoma, renal cell carcinoma

## 1. Introduction

Spontaneous primary hypothyroidism is a common disorder and prescriptions for L-thyroxine (T4) replacement therapy are among the five most commonly prescribed drugs in the U.S. [1]. The predictable absorbance of T4 from the human gastrointestinal tract and its relatively long half-life in the circulation enable once daily replacement dosing and high patient compliance. 3,5,3'-triiodo-L-thyronine (T3) is also prescribed as thyroid hormone replacement, but its relatively short biologic half-life means that more than once daily dosing is required for replacement.

Integrin  $\alpha\beta3$  is one of a family of plasma membrane proteins that are importantly involved in cell-to-cell and cell-extracellular matrix (ECM) protein interactions that are particularly relevant to tissue structure and function in cancer [2, 3].  $\alpha\beta3$  is generously expressed by cancer cells and contains a receptor for thyroid hormone at which nongenomic actions of thyroid hormone are initiated [4, 5]. There are no structural homologies between the thyroid hormone receptor site on  $\alpha\beta3$  and the nuclear thyroid hormone receptors (TRs) at which genomic actions of the hormone are initiated [4, 5]. The large panel of genomic actions of T3 that are critical to the function of normal cells in species with thyroid glands involve TRs. T4 is a prohormone for T3 and is not important within cells, except perhaps for regulation of the state of actin [5, 6].

At the cell surface receptor for thyroid hormone on  $\alpha\beta3$ , T4 is the principal ligand [7, 8] and has at physiological concentrations a set of actions that include cancer cell proliferation [4, 5], cancer cell defense pathways, e.g., anti-apoptosis [5], and the fostering of tumor-relevant angiogenesis [9, 10]. In nonmalignant cells, the T4 receptor on  $\alpha\beta3$  may have certain specific functions in neurons during development [11, 12], in phagocytosis [13] and in platelet aggregation [14]. Studies *in vitro* have disclosed that T4 stimulates the proliferation of breast cancer cells [15–17], lung cancer [18, 19] and kidney cancer [20] cells, glioblastoma cells [8, 21] and other tumor cells [22]. Pharmacologic blockade of T4 action at the integrin is feasible with tetraiodothyroacetic acid (tetrac) and modified forms of tetrac [7, 17, 20, 23–26] arrest tumor xenografts.

In patients with a variety of advanced solid tumors, elimination of endogenous T4 and substitution of exogenous T3 (“euthyroid hypothyroxinemia”) has also been shown to arrest tumor growth [27]. Other earlier studies of pharmacologic induction of mild hypothyroidism (decreased circulating host T4 without T3 replacement) may also improve survival in patients with glioblastoma [27] and renal cell carcinoma [28]. The aggressive behavior of certain cancers may also be ameliorated in the setting of spontaneous hypothyroidism [29].

In this chapter, we will extend our discussion of the possibility that clinical behaviors of a number of cancers are supported by endogenous T4 or exogenous T4 replacement in cancer patients who have concurrent hypothyroidism [16, 27, 29, 30]. In addition to the general principle that proliferation of many types of cancer cells is reduced by concurrent hypothyroidism, there are examples of highly specific roles that T4 may play in the behavior of certain tumors. In estrogen receptor-positive (ER<sup>+</sup>) cancer cells, T4 stimulates mitogen-activated protein kinase (MAPK)-dependent, specific phosphorylation of ER $\alpha$  in the absence of estrogen [15]. This may also apply to lung cancer cells that express ER. In the postmenopausal patient with such ER-expressing tumors, host T4 may substitute for host estrogen.

We also will review actions of T4 that appear to be relevant to chemoresistance and to radioresistance. The chemoresistance role played by T4 may involve (a) specific antagonism of chemotherapeutic drug-induced apoptosis in tumor cells or (b) enhanced export by tumor cells of cancer treatment agents [31]. Integrin  $\alpha\beta3$  is substantially involved in the induction of radioresistance in tumor cells [32–34], and the thyroid hormone receptor on  $\alpha\beta3$  controls the contribution of the integrin to radioresistance.

We conclude that for T4-treated patients with primary hypothyroidism who develop aggressive cancers, it is worthwhile to consider elimination of replacement T4 and management of hypothyroidism with T3.

## 2. Breast cancer

The published MD Anderson Cancer Center experience with breast cancer patients who develop spontaneous hypothyroidism is that the latter state changes the course of the cancer, i.e., the disease is less aggressive [29]. The survival of patients with end-stage metastatic breast cancer may be lengthened by induction of the state of euthyroid hypothyroxinemia [27]. Chemically modified tetrac that acts at the thyroid hormone receptor on  $\alpha\beta3$  significantly reduces breast cancer xenograft size in the nude mouse [24].

An extensive survey of survival pathway gene transcription in triple-negative human (MDA-MB-231) breast cancer cells revealed that the thyroid hormone receptor on  $\alpha\beta3$  differentially regulated expression of genes for anti-apoptotic X-linked inhibitor of apoptosis (XIAP), myeloid cell leukemia-1 (MCL-1), and for pro-apoptotic caspase-2 (CASP2) and BCL2L14 [26]. Acting in an anticancer mode, tetrac in this

study downregulated anti-apoptotic genes and increased expression of pro-apoptotic genes. The thyroid hormone receptor on integrin  $\alpha\beta3$  also affected breast cancer genes linked to angiogenesis. In addition, T4 and chemically modified tetrac (nano-diamino-tetrac, NDAT) stimulate and inhibit, respectively, programmed death ligand-1 (PD-L1) gene expression in cultured MDA-MB-231 breast cancer cells [17].

The observation 10 years ago that tetrac enhanced tumor cell uptake of doxorubicin, cisplatin and other chemotherapeutic agents suggested that a cell export system was regulated from integrin  $\alpha\beta3$  in breast cancer cells [35]. It was subsequently shown that activity of the p-glycoprotein (P-gp) plasma membrane efflux pump was regulated by thyroid hormone analogues that are acting at  $\alpha\beta3$  [31]. The implication of the observations is that T4 may act at the integrin to enhance P-gp action. Such an action may be desirable in healthy, nonmalignant cells for ridding the cells of toxic substances; in cancer cells, the action supports chemoresistance.

Radioresistance of certain cancer cells can be induced rapidly by X-radiation via a change in conformation of integrin  $\alpha\beta3$  [32, 33], but this has not yet been examined in breast cancer cells. The STAT3 [36] and NF- $\kappa$ B [37] signal transduction pathways appear to be involved in the development of radioresistance in breast cancer cells, and both of these signaling molecules are regulated via integrin  $\alpha\beta3$  and the thyroid hormone receptor [5, 38].

Taken individually and together, the breast cancer-focused actions of T4 that are initiated at the iodothyronine receptor on integrin  $\alpha\beta3$  are reason to consider in patients with breast cancer and primary hypothyroidism a modification of standard replacement therapy with T4. The alternative approaches are T3 replacement or reduction in T4 dosage that permits endogenous thyroid-stimulating hormone (TSH) elevation without symptoms of hypothyroidism.

### 3. Prostate cancer

An anti-thyroid agent, propylthiouracil (PTU), inhibited the growth of xenografts in nude mice of two human prostate cancer cell lines [39]. No direct effect of PTU on the tumor cells was found *in vitro*. PTU reduces circulating levels of both T4 and T3. In a study conducted in smokers, overt spontaneous hypothyroidism was associated with a decreased risk of prostate cancer, as was elevation of circulating TSH [40]. Increased TSH presumptively reflected patient-specific decreases within the normal range of circulating T4 and T3 (latent hypothyroidism). The authors speculated that the reduced risk of prostate cancer risk was related to decreased T4 action at integrin  $\alpha\beta3$ . In another study, latent hypothyroidism was a predictive marker of positive response in patients with prostate cancer undergoing a specific therapy (abiraterone acetate) [41].

Preclinical studies of iodothyronines in prostate cancer xenografts and of possible contributions of integrin  $\alpha\beta3$  to prostate cancer have not yet been reported. However,  $\alpha\beta3$  response to X-radiation has been examined in prostate cancer (PC3) cells *in vitro* [32]. Activation of the integrin was induced by radiation and this response was prevented by tetrac, implicating the thyroid hormone receptor on the integrin in the defensive response.

### 4. Lung cancer

Human non-small cell (NCI-H522) lung carcinoma cells and small cell (NCI-H510A) cancer cells proliferate *in vitro* in response to physiological concentrations of T4 and supraphysiological levels of T3 [19]. Tetrac inhibited these responses,

implicating the thyroid hormone receptor on integrin  $\alpha\beta3$  in the response. These cell lines express ER $\alpha$  As is the case in human breast cancer cells that express ER, the estrogen receptor is subject to activation/phosphorylation in the presence of T4. ER activation is associated with cancer cell proliferation quantitated by PCNA expression and thymidine incorporation. The specific ER $\alpha$  antagonist compound, ICI 162,770, diminished the activation by T4 of the estrogen receptor, as well as the stimulation of proliferation by T4. The growth of non-small cell (H1299) lung carcinoma xenografts is reversed by unmodified and chemically modified tetrac [23], consistent with a critical role for  $\alpha\beta3$  in the regulation of tumor growth.

More information available about T4 action on lung cancer is limited. Euthyroid hypothyroxinemia appears to slow the course of metastatic lung carcinoma [27].

## 5. Glioblastoma

In preclinical studies, T4 has been shown to be a growth factor for gliomas [21], and the actions of chemically modified tetrac molecules at the thyroid hormone receptor on integrin  $\alpha\beta3$  significantly increased transcription of a panel of pro-apoptotic genes (*p53*, *p21*, *PIG*, *BAD*) [7]. The latter results imply that T4 action at the integrin may undesirably either decrease or not affect expression of these genes. In a limited *in vitro* study, T3 restricted glioblastoma cell proliferation [42] and preclinical studies have also shown that NDAT—which limits access of T4 to its receptor on integrin  $\alpha\beta3$  on tumor cells—suppresses growth and is anti-angiogenic in glioblastoma xenografts [25].

In 2003, chemical induction of mild hypothyroidism with propylthiouracil (PTU) was shown in patients with recurrent, high-grade glioblastoma to be associated with significant prolongation of survival [43]. More recently, euthyroid hypothyroxinemia has significantly extended survival in patients with end-stage glioblastoma [27].

Induction of euthyroid hypothyroxinemia has been effective in prolonging survival of the few glioblastoma patients with end-stage disease in whom it has been tested [27].

## 6. Renal cell carcinoma

Among the side effects of chemotherapeutic tyrosine kinase inhibitors (TKIs) used in management of renal cell carcinoma (RCC) is induction of preclinical primary hypothyroidism. The “preclinical” state is an elevation of circulating TSH with normal range serum T4 and T3 concentrations. An extensive clinical literature documents that response of metastatic RCC to TKIs sorafenib and sunitinib is importantly enhanced when drug-induced hypothyroidism complicates tumor management [28, 30, 44–48]. TKIs may cause hypothyroidism in up to 40% of treated patients. The therapeutic response to the recognition of drug-induced preclinical primary hypothyroidism in RCC patients was administration of exogenous T4 to the point of returning host TSH to the normal range. In the noncancerous patient with preclinical hypothyroidism, the American Thyroid Association has endorsed a strategy of replacement thyroid hormone as needed to prevent symptoms of hypothyroidism and maintain serum TSH below 10 mIU/mL [49]. This approach may be adequate to take advantage of the TKI support that preclinical hypothyroidism provides with reduction in circulating T4 within the normal range.

The relevance of the thyroid hormone receptor on integrin  $\alpha\beta3$  to RCC has been shown in xenograft studies in the nude mouse [20]. Tetrac and chemically modified tetrac significantly reduced xenograft volume and xenograft vascularity in 20-day studies.

The clinical and preclinical information available on RCC documents the importance of thyroid hormone to RCC. When drug-induced or spontaneous early hypothyroidism complicates the course of RCC, substantial decision-making surrounds when and with what hormone the hypothyroid state should be addressed.

## 7. Pancreatic carcinoma

Pancreatic cancer is an aggressive tumor locally and metastasizes regionally and systemically with sufficient frequency to have a very unsatisfactory 5-year survival. The relevance of thyroid hormone to tumor behavior has been shown in xenograft studies [50]. Unmodified and chemically modified tetrac in 15-day studies reduced xenograft size by up to 50% and reduced graft vascularity. Tumor gene expression studies showed that chemically modified tetrac acted via  $\alpha\beta3$  to reduce epidermal growth factor receptor (EGFR) gene and anti-apoptotic XIAP gene transcription and to increase expression of pro-apoptotic p53 and anti-angiogenic thrombospondin 1. The implication of these results is that T4—whose binding to  $\alpha\beta3$  is inhibited by tetrac—may play an important tumor support role in this form of cancer.

In contrast to RCC, there is not a significant literature on chemotherapeutic drug-induced hypothyroidism in patients with pancreatic carcinoma. Induction of euthyroid hypothyroxinemia appears to slow the course of advanced pancreatic cancer [27].

## 8. Discussion

At the cancer cell surface receptor for thyroid hormone on the extracellular domain of integrin  $\alpha\beta3$ , T4 is an active hormone, supporting a variety of critical tumor cell functions [5, 10, 26]. In contrast, T4 within normal cells and cancer cells can serve as a prohormone source for T3. T4 is the standard of care for management of hypothyroidism [49].

A small minority of hypothyroid patients coincidentally have an experience with cancer of various types, as pointed out above. The behavior of the tumors is reported in most clinical studies of this combination of diseases to be less aggressive. But interpretation of the data is sometimes difficult because a distinction may not be made between T4-treated and untreated spontaneous hypothyroid states and the appearance or behavior of the cancer. However, substantial information is now available about the link of hypothyroid state to tumor behavior in those patients in whom hypothyroidism is a side effect of chemotherapy, e.g., TKI use in RCC patients [28, 47, 51], or the clinical use of euthyroid hypothyroxinemia in patients with advanced cancers [27].

A body of preclinical evidence also exists to indicate that T4 stimulates proliferation of a variety of tumors, and this effect is initiated at a plasma membrane receptor for thyroid hormone that is generously expressed in cancer cells [5]. At this receptor site, T4 is also anti-apoptotic [5] and supports tumor-relevant angiogenesis [5]. The integrin may also be involved in tumor cell radioresistance [32, 33].

Against this background, we raise the issue of whether prescription of T4 replacement in hypothyroid patients with concurrent cancer should be routine. T3 is not active at physiological concentrations at the integrin receptor for thyroid hormone

and we have shown that T3 can be substituted for endogenous T4 in euthyroid patients with cancer with a result of improved survival and, in some cases, reduction in tumor size. Thus, we feel that the use of T3 replacement can be endorsed in patients with spontaneous or TKI-induced hypothyroidism and cancer. A disadvantage is that T3 must be administered more than once daily because of its short half-life.

A particularly interesting example of the complexity of the relationships of thyroid hormone and cancer is the capacity of T4 to activate ER $\alpha$  in ER-positive breast cancer cells in the absence of estrogen [15]. In addition, T4 is able to promote trafficking of ER from cytoplasm to nucleus [52]. Thus, ER in breast cancer of the postmenopausal euthyroid woman remains a functional component of the tumor.

The setting of thyroid cancer and concomitant hypothyroidism management is not included in the sections above in this review but has been discussed elsewhere by the current authors [53]. Hypothyroidism in the setting of thyroid cancer may of course be a consequence of radiation therapy of the tumor. Exogenous T4 may be administered in patients with thyroid cancers to suppress endogenous thyrotropin (TSH) that may support thyroid tumor cell proliferation. What we have recommended in the context of thyroid cancer and hypothyroidism or T4-suppression of endogenous TSH with T4 and intractable tumor behavior is that the use of T3 be considered [53] as, respectively, hormone replacement or vehicle to suppress host TSH.

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## References

- [1] Fuentes AV, Pineda MD, Venkata KCN. Comprehension of top 200 prescribed drugs in the US as a resource for pharmacy teaching, training and practice. *Pharmacy (Basel)*. 2018;**6**:43. DOI: 10.3390/pharmacy6020043
- [2] Seguin L, Desgrosellier JS, Weis SM, Cheresch DA. Integrins and cancer: Regulators of cancer stemness, metastasis, and drug resistance. *Trends in Cell Biology*. 2015;**25**:234-240. DOI: 10.1016/j.tcb.2014.12.006
- [3] Desgrosellier JS, Cheresch DA. Integrins in cancer: Biological implications and therapeutic opportunities. *Nature Reviews Cancer*. 2010;**10**:9-22. DOI: 10.1038/nrc2748
- [4] Cheng SY, Leonard JL, Davis PJ. Molecular aspects of thyroid hormone actions. *Endocrine Reviews*. 2010;**31**:139-170. DOI: 10.1210/er.2009-0007
- [5] Lin HY, Chin YT, Yang YC, Lai HY, Wang-Peng J, Liu LF, et al. Thyroid hormone, cancer, and apoptosis. *Comprehensive Physiology*. 2016;**6**:1221-1237. DOI: 10.1002/cphy.c150035
- [6] Farwell AP, Leonard JL. Extranuclear actions of thyroid hormone in the brain. In: Porterfield SP, Hendrich CE, editors. *Recent Research Developments in Neuroendocrinology—Thyroid Hormone and Brain Maturation*. Trivandrum, India: Research Signpost; 1997. pp. 113-130
- [7] Lin HY, Landersdorfer CB, London D, Meng R, Lim CU, Lin C, et al. Pharmacodynamic modeling of anti-cancer activity of tetraiodothyroacetic acid in a perfused cell culture system. *PLoS Computational Biology*. 2011;**7**:e1001073. DOI: 10.1371/journal.pcbi.1001073
- [8] Lin HY, Sun M, Tang HY, Lin C, Luidens MK, Mousa SA, et al. L-Thyroxine vs. 3,5,3'-triiodo-L-thyronine and cell proliferation: Activation of mitogen-activated protein kinase and phosphatidylinositol 3-kinase. *American Journal of Physiology. Cell Physiology*. 2009;**296**:C980-C991. DOI: 10.1152/ajpcell.00305.2008
- [9] Davis PJ, Sudha T, Lin HY, Mousa SA. Thyroid hormone, hormone analogs, and angiogenesis. *Comprehensive Physiology*. 2015;**6**:353-362. DOI: 10.1002/cphy.c150011
- [10] Mousa SA, Lin HY, Tang HY, Hercbergs A, Luidens MK, Davis PJ. Modulation of angiogenesis by thyroid hormone and hormone analogues: Implications for cancer management. *Angiogenesis*. 2014;**17**:463-469. DOI: 10.1007/s10456-014-9418-5
- [11] Yonkers MA, Ribera AB. Sensory neuron sodium current requires nongenomic actions of thyroid hormone during development. *Journal of Neurophysiology*. 2008;**100**:2719-2725. DOI: 10.1152/jn.90801.2008
- [12] Yonkers MA, Ribera AB. Molecular components underlying nongenomic thyroid hormone signaling in embryonic zebrafish neurons. *Neural Development*. 2009;**4**:20. DOI: 10.1186/1749-8104-4-20
- [13] Chen Y, Sjolinder M, Wang X, Altenbacher G, Hagner M, Berglund P, et al. Thyroid hormone enhances nitric oxide-mediated bacterial clearance and promotes survival after meningococcal infection. *PLoS ONE*. 2012;**7**:e41445. DOI: 10.1371/journal.pone.0041445
- [14] Mousa SS, Davis FB, Davis PJ, Mousa SA. Human platelet aggregation and degranulation is

induced in vitro by L-thyroxine, but not by 3,5,3'-triiodo-L-thyronine or diiodothyropropionic acid (DITPA). *Clinical and Applied Thrombosis/Hemostasis*. 2010;**16**:288-293. DOI: 10.1177/1076029609348315

[15] Tang HY, Lin HY, Zhang S, Davis FB, Davis PJ. Thyroid hormone causes mitogen-activated protein kinase-dependent phosphorylation of the nuclear estrogen receptor. *Endocrinology*. 2004;**145**:3265-3272. DOI: 10.1210/en.2004-0308

[16] Hercbergs A, Mousa SA, Leinung M, Lin HY, Davis PJ. Thyroid hormone in the clinic and breast cancer. *Hormones & Cancer*. 2018;**9**:139-143. DOI: 10.1007/s12672-018-0326-9

[17] Lin HY, Chin YT, Nana AW, Shih YJ, Lai HY, Tang HY, et al. Actions of L-thyroxine and Nano-diamino-tetrac (Nanotetrac) on PD-L1 in cancer cells. *Steroids*. 2016;**114**:59-67. DOI: 10.1016/j.steroids.2016.05.006

[18] Davis PJ, Davis FB, Mousa SA, Luidens MK, Lin HY. Membrane receptor for thyroid hormone: Physiologic and pharmacologic implications. *Annual Review of Pharmacology and Toxicology*. 2011;**51**:99-115. DOI: 10.1146/annurev-pharmtox-010510-100512

[19] Meng R, Tang HY, Westfall J, London D, Cao JH, Mousa SA, et al. Crosstalk between integrin  $\alpha\beta3$  and estrogen receptor- $\alpha$  is involved in thyroid hormone-induced proliferation in human lung carcinoma cells. *PLoS ONE*. 2011;**6**:e27547. DOI: 10.1371/journal.pone.0027547

[20] Yalcin M, Bharali DJ, Lansing L, Dyskin E, Mousa SS, Hercbergs A, et al. Tetraiodothyroacetic acid (tetrac) and tetrac nanoparticles inhibit growth of human renal cell carcinoma xenografts. *Anticancer Research*. 2009;**29**:3825-3831

[21] Davis FB, Tang HY, Shih A, Keating T, Lansing L, Hercbergs A, et al. Acting via a cell surface receptor, thyroid hormone is a growth factor for glioma cells. *Cancer Research*. 2006;**66**:7270-7275. DOI: 10.1158/0008-5472.CAN-05-4365

[22] Fabian ID, Rosner M, Fabian I, Vishnevskia-Dai V, Zloto O, Shinderman Maman E, et al. Low thyroid hormone levels improve survival in murine model for ocular melanoma. *Oncotarget*. 2015;**6**:11038-11046. DOI: 10.18632/oncotarget.3566

[23] Mousa SA, Yalcin M, Bharali DJ, Meng R, Tang HY, Lin HY, et al. Tetraiodothyroacetic acid and its nanoformulation inhibit thyroid hormone stimulation of non-small cell lung cancer cells in vitro and its growth in xenografts. *Lung Cancer*. 2012;**76**:39-45. DOI: 10.1016/j.lungcan.2011.10.003

[24] Bharali DJ, Yalcin M, Davis PJ, Mousa SA. Tetraiodothyroacetic acid-conjugated PLGA nanoparticles: A nanomedicine approach to treat drug-resistant breast cancer. *Nanomedicine (London, England)*. 2013;**8**:1943-1954. DOI: 10.2217/nnm.12.200

[25] Sudha T, Bharali DJ, Sell S, Darwish NHE, Davis PJ, Mousa SA. Nanoparticulate tetrac inhibits growth and vascularity of glioblastoma xenografts. *Hormones & Cancer*. 2017;**8**:157-165. DOI: 10.1007/s12672-017-0293-6

[26] Glinskii AB, Glinsky GV, Lin HY, Tang HY, Sun M, Davis FB, et al. Modification of survival pathway gene expression in human breast cancer cells by tetraiodothyroacetic acid (tetrac). *Cell Cycle*. 2009;**8**:3562-3570. DOI: 10.4161/cc.8.21.9963

[27] Hercbergs A, Johnson RE, Ashur-Fabian O, Garfield DH, Davis PJ.

Medically induced euthyroid hypothyroxinemia may extend survival in compassionate need cancer patients: An observational study. *The Oncologist*. 2015;**20**:72-76. DOI: 10.1634/theoncologist.2014-0308

[28] Schmidinger M, Vogl UM, Bojic M, Lamm W, Heinzl H, Haitel A, et al. Hypothyroidism in patients with renal cell carcinoma: Blessing or curse? *Cancer*. 2011;**117**:534-544. DOI: 10.1002/cncr.25422

[29] Cristofanilli M, Yamamura Y, Kau SW, Bevers T, Strom S, Patangan M, et al. Thyroid hormone and breast carcinoma. Primary hypothyroidism is associated with a reduced incidence of primary breast carcinoma. *Cancer*. 2005;**103**:1122-1128. DOI: 10.1002/cncr.20881

[30] Riesenbeck LM, Bierer S, Hoffmeister I, Kopke T, Papavassilis P, Hertle L, et al. Hypothyroidism correlates with a better prognosis in metastatic renal cancer patients treated with sorafenib or sunitinib. *World Journal of Urology*. 2011;**29**:807-813. DOI: 10.1007/s00345-010-0627-2

[31] Davis PJ, Incerpi S, Lin HY, Tang HY, Sudha T, Mousa SA. Thyroid hormone and P-glycoprotein in tumor cells. *BioMed Research International*. 2015;**2015**:168427. DOI: 10.1155/2015/168427

[32] Leith JT, Hercbegs A, Kenney S, Mousa SA, Davis PJ. Activation of tumor cell integrin  $\alpha\beta 3$  by radiation and reversal of activation by chemically modified tetraiodothyroacetic acid (tetrac). *Endocrine Research*. 2018;**43**:215-219. DOI: 10.1080/07435800.2018.1456550

[33] Leith JT, Mousa SA, Hercbegs A, Lin HY, Davis PJ. Radioresistance of cancer cells, integrin  $\alpha\beta 3$  and thyroid hormone. *Oncotarget*.

2018;**9**:37069-37075. DOI: 10.18632/oncotarget.26434

[34] Leith JT, Davis PJ, Mousa SA, Hercbegs AA. In vitro effects of tetraiodothyroacetic acid combined with X-irradiation on basal cell carcinoma cells. *Cell Cycle*. 2017;**16**:367-373. DOI: 10.1080/15384101.2016.1269044

[35] Rebbaa A, Chu F, Davis FB, Davis PJ, Mousa SA. Novel function of the thyroid hormone analog tetraiodothyroacetic acid: A cancer chemosensitizing and anti-cancer agent. *Angiogenesis*. 2008;**11**:269-276. DOI: 10.1007/s10456-008-9110-8

[36] Kim JS, Kim HA, Seong MK, Seol H, Oh JS, Kim EK, et al. STAT3-survivin signaling mediates a poor response to radiotherapy in HER2-positive breast cancers. *Oncotarget*. 2016;**7**:7055-7065. DOI: 10.18632/oncotarget.6855

[37] Veuger SJ, Hunter JE, Durkacz BW. Ionizing radiation-induced NF- $\kappa$ B activation requires PARP-1 function to confer radioresistance. *Oncogene*. 2009;**28**:832-842. DOI: 10.1038/onc.2008.439

[38] Zhao Y, Tan Y, Meng T, Liu X, Zhu Y, Hong Y, et al. Simultaneous targeting therapy for lung metastasis and breast tumor by blocking the NF- $\kappa$ B signaling pathway using celastrol-loaded micelles. *Drug Delivery*. 2018;**25**:341-352. DOI: 10.1080/10717544.2018.1425778

[39] Theodossiou C, Schwarzenberger P. Propylthiouracil reduces xenograft tumor growth in an athymic nude mouse prostate cancer model. *The American Journal of the Medical Sciences*. 2000;**319**:96-99

[40] Mondul AM, Weinstein SJ, Bosworth T, Remaley AT, Virtamo J, Albanes D. Circulating thyroxine, thyroid-stimulating hormone, and hypothyroid status and the risk of prostate cancer. *PLoS ONE*.

2012;7:e47730. DOI: 10.1371/journal.pone.0047730

[41] Heidegger I, Nagele U, Pircher A, Pichler R, Horninger W, Bektic J. Latent hypothyreosis as a clinical biomarker for therapy response under abiraterone acetate therapy. *Anticancer Research*. 2014;**34**:307-311

[42] Liappas A, Mourouzis I, Zisakis A, Economou K, Lea RW, Pantos C. Cell-type-dependent thyroid hormone effects on glioma tumor cell lines. *Journal of Thyroid Research*. 2011;**2011**:856050. DOI: 10.4061/2011/856050

[43] Hercbergs AA, Goyal LK, Suh JH, Lee S, Reddy CA, Cohen BH, et al. Propylthiouracil-induced chemical hypothyroidism with high-dose tamoxifen prolongs survival in recurrent high grade glioma: A phase I/II study. *Anticancer Research*. 2003;**23**:617-626

[44] Buda-Nowak A, Kucharz J, Dumnicka P, Kuzniewski M, Herman RM, Zygulska AL, et al. Sunitinib-induced hypothyroidism predicts progression-free survival in metastatic renal cell carcinoma patients. *Medical Oncology*. 2017;**34**:68. DOI: 10.1007/s12032-017-0928-z

[45] Song Y, Du C, Zhang W, Sun Y, Yang L, Cui C, et al. A study on the association between hyperlipidemia and hypothyroidism and the response to TKIs in metastatic renal cell carcinoma. *Asia-Pacific Journal of Clinical Oncology*. 2016;**12**:174-180. DOI: 10.1111/ajco.12473

[46] Bozkurt O, Karaca H, Hacibekiroglu I, Kaplan MA, Duzkopru Y, Uysal M, et al. Is sunitinib-induced hypothyroidism a predictive clinical marker for better response in metastatic renal cell carcinoma patients? *Journal of*

*Chemotherapy*. 2016;**28**:230-234. DOI: 10.1179/1973947815Y.0000000039

[47] Bailey EB, Tantravahi SK, Poole A, Agarwal AM, Straubhar AM, Batten JA, et al. Correlation of degree of hypothyroidism with survival outcomes in patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor receptor tyrosine kinase inhibitors. *Clinical Genitourinary Cancer*. 2015;**13**:e131-e137. DOI: 10.1016/j.clgc.2014.11.002

[48] Kappers MH, van Esch JH, Smedts FM, de Krijger RR, Eechoute K, Mathijssen RH, et al. Sunitinib-induced hypothyroidism is due to induction of type 3 deiodinase activity and thyroidal capillary regression. *Journal of Clinical Endocrinology and Metabolism*. 2011;**96**:3087-3094. DOI: 10.1210/jc.2011-1172

[49] Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, et al. Guidelines for the treatment of hypothyroidism: Prepared by the american thyroid association task force on thyroid hormone replacement. *Thyroid*. 2014;**24**:1670-1751. DOI: 10.1089/thy.2014.0028

[50] Yalcin M, Lin HY, Sudha T, Bharali DJ, Meng R, Tang HY, et al. Response of human pancreatic cancer cell xenografts to tetraiodothyroacetic acid nanoparticles. *Hormones & Cancer*. 2013;**4**:176-185. DOI: 10.1007/s12672-013-0137-y

[51] Bilen MA, Patel A, Hess KR, Munoz J, Busaidy NL, Wheler JJ, et al. Association between new-onset hypothyroidism and clinical response in patients treated with tyrosine kinase inhibitor therapy in phase I clinical trials. *Cancer Chemotherapy and Pharmacology*. 2016;**78**:167-171. DOI: 10.1007/s00280-016-3073-z

[52] Hsieh MT, Wang LM, Changou CA, Chin YT, Yang YSH, Lai HY, et al. Crosstalk between integrin  $\alpha v \beta 3$  and ER $\alpha$  contributes to thyroid hormone-induced proliferation of ovarian cancer cells. *Oncotarget*. 2017;**8**:24237-24249. DOI: 10.18632/oncotarget.10757

[53] Davis PJ, Hercbergs A, Luidens MK, Lin HY. Recurrence of differentiated thyroid carcinoma during full TSH suppression: Is the tumor now thyroid hormone dependent? *Hormones & Cancer*. 2015;**6**:7-12. DOI: 10.1007/s12672-014-0204-z