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Unprecedented radioiodine uptake in metastatic thyroid cancer without thyroidectomy

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► *Case report*

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ABSTRACT

Background: We report an unusual case of metastatic thyroid carcinoma in an 80-year-old man without prior thyroidectomy, deviating from standard diagnostic and therapeutic protocols. ***Case Presentation:*** The patient presented with a rapidly growing buccal mass. Pathology confirmed metastatic follicular thyroid carcinoma. Despite no prior thyroid surgery, whole-body ^{131}I scintigraphy demonstrated extensive radioiodine-avid lesions involving the thyroid, buccal region, chest, abdomen, and skeletal sites. Radioiodine imaging was performed without thyroid hormone withdrawal or TSH stimulation. ***Materials and Methods:*** The patient underwent 18F-FDG PET/CT and ^{131}I SPECT/CT. Imaging revealed concordant metastatic disease, with SPECT/CT confirming iodine uptake in the thyroid gland and multiple bone lesions. ***Results:*** A "flip-flop" phenomenon was observed, showing discordance between FDG uptake and radioiodine avidity. Low serum TSH may have influenced heterogeneous iodine uptake in metastatic lesions and reduced thyroid gland uptake. ***Conclusion:*** This case challenges the conventional assumption that effective radioiodine uptake in metastatic thyroid cancer requires prior thyroidectomy and TSH stimulation. It highlights atypical iodine biodistribution and the complexity of metastatic thyroid cancer biology, underscoring the need for further investigation into non-standard clinical scenarios.

INTRODUCTION

Metastatic differentiated thyroid cancer (DTC) generally demonstrates effective radioactive iodine (RAI) uptake only after total or subtotal thyroidectomy, which minimizes competitive iodine accumulation by normal thyroid tissue and enhances the visualization and therapeutic targeting of metastatic lesions [1, 2]. The diagnostic and therapeutic efficacy of RAI is largely dependent on the expression and functional activity of the sodium/iodide symporter (NIS), a membrane transporter responsible for iodine uptake in thyroid follicular cells [3]. However, compared with normal thyroid tissue, thyroid cancer cells typically exhibit reduced NIS expression and impaired iodine-handling capacity, resulting in significantly decreased RAI avidity [3, 4]. Furthermore, tumor dedifferentiation during disease progression may lead to complete loss of iodine uptake ability, accompanied by increased glucose metabolism detectable on FDG-PET imaging, a phenomenon commonly referred to as the "flip-flop phenomenon" [5].

For these reasons, current clinical guidelines consider total or subtotal thyroidectomy a prerequisite before diagnostic or therapeutic RAI administration [1, 2]. Removal of the primary thyroid gland not only eliminates the competitive "sink effect" of normal thyroid tissue but also facilitates endogenous thyroid-stimulating hormone (TSH) elevation, thereby enhancing iodine uptake in residual or metastatic lesions [6]. Consequently, the detection of distant metastatic lesions in patients with an intact thyroid gland is exceedingly rare, as radioiodine is usually concentrated predominantly within the cervical thyroid tissue, obscuring distant metastatic foci on scintigraphy imaging [7].

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Herein, we report a clinically significant case involving an 80-year-old patient with unresectable thyroid cancer and widespread metastatic disease who demonstrated intense RAI uptake in both the intact thyroid gland and multiple disseminated metastatic lesions involving the oral cavity, thorax, and abdomen, despite not undergoing thyroidectomy, thyroid hormone withdrawal, or recombinant human TSH (rhTSH) stimulation. More remarkably, the patient exhibited profoundly suppressed serum TSH levels (<0.03 μIU/mL), a condition generally considered unfavorable for radioiodine accumulation. Nevertheless, the metastatic lesions retained sufficient iodine avidity to successfully compete with the intact thyroid gland for RAI uptake.

To our knowledge, robust metastatic radioiodine accumulation in the absence of prior thyroidectomy and under suppressed TSH conditions is exceptionally uncommon [8]. This observation challenges the conventional assumption that elevated TSH levels and surgical thyroid removal are mandatory prerequisites for effective RAI imaging and targeting of metastatic thyroid cancer [1, 2]. The current case therefore suggests a unique biological behavior characterized by preserved (or potentially enhanced) iodine-handling machinery within metastatic tumor cells.

From a mechanistic perspective, this unusual uptake pattern may reflect preserved differentiation status and sustained membrane localization of NIS within metastatic lesions [3, 4]. Alternatively, molecular alterations associated with tumor redifferentiation may contribute to restoration of iodine avidity. Recent studies have demonstrated that targeted therapies, particularly RET and NTRK inhibitors, may induce re-expression of thyroid-specific genes and restore radioiodine uptake in previously RAI-refractory metastatic thyroid cancer [9,10]. Although no such therapy was administered in the present case, the findings raise important questions regarding the molecular mechanisms governing iodine metabolism and tumor differentiation in advanced thyroid cancer.

From a theranostic standpoint, this rare presentation expands current understanding of radioiodine physiology in metastatic thyroid cancer and may provide novel insights into personalized RAI -based diagnostic and therapeutic strategies, particularly for patients with advanced disease who are poor surgical candidates or have unresectable metastatic burden. The ability of metastatic lesions to maintain substantial radioiodine avidity despite the presence of an intact thyroid gland and suppressed TSH levels suggests that selected tumors may retain clinically meaningful responsiveness to RAI even before surgical intervention.

Case report

We describe an unusual case of disseminated metastatic thyroid carcinoma in an 80-year-old man who presented with rapid enlargement of a left buccal mass over a two-month period. Histopathological examination of the biopsied lesion confirmed metastatic follicular thyroid carcinoma. Serial imaging studies, including neck computed tomography (CT), demonstrated a left lower buccal lesion with adjacent mandibular bone destruction, a calcified right thyroid mass with cervical spine involvement, a left scapular osseous lesion, and multiple pulmonary metastases. The patient was subsequently referred to our hospital for further evaluation with ^{18}F fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT).

FDG PET/CT images were acquired using a GE HealthCare Discovery MI DR PET/CT scanner. PET images were reconstructed iteratively using the ordered subset expectation maximization (OSEM) algorithm with CT-based attenuation correction. The reconstructed images were reviewed on the Xeleris Functional Imaging Workstation (GE HealthCare, Waukesha, Wisconsin, USA).

FDG PET/CT revealed multiple FDG-avid lesions involving the lungs, left buccal region, right humerus, spine, and pelvic bones (figure 1). To evaluate the feasibility of radioiodine-targeted therapy, radioiodine (RAI) scintigraphy was performed following oral administration of 3 mCi (117 MBq) of ^{131}I sodium iodide supplied by Global Medical Solutions (SPECT Pharmacy, Kaohsiung, Taiwan). RAI scintigraphy and SPECT/CT imaging were performed using a Discovery NM/CT 670 SPECT/CT scanner (GE HealthCare, Waukesha, Wisconsin, USA). The 24-hour whole-body images demonstrated intense radioiodine uptake not only within the thyroid region but also at multiple metastatic sites, including the left buccal region, chest, and abdomen (figure 2). Subsequent SPECT/CT imaging further localized the RAI accumulation to the thyroid bed and bulky metastatic lesions involving the destructed left mandibular bone, L1 vertebral body, and left ilium, as correlated with the reference CT images (figure 3). Notably, the distribution of radioiodine uptake did not completely correspond to the FDG-avid lesions identified on the prior PET/CT study.

Laboratory investigations revealed suppressed thyroid-stimulating hormone levels (TSH < 0.03 μIU/mL) and markedly elevated serum thyroglobulin levels (35,109.80 ng/mL). Despite subsequent therapy, the patient expired four months later.

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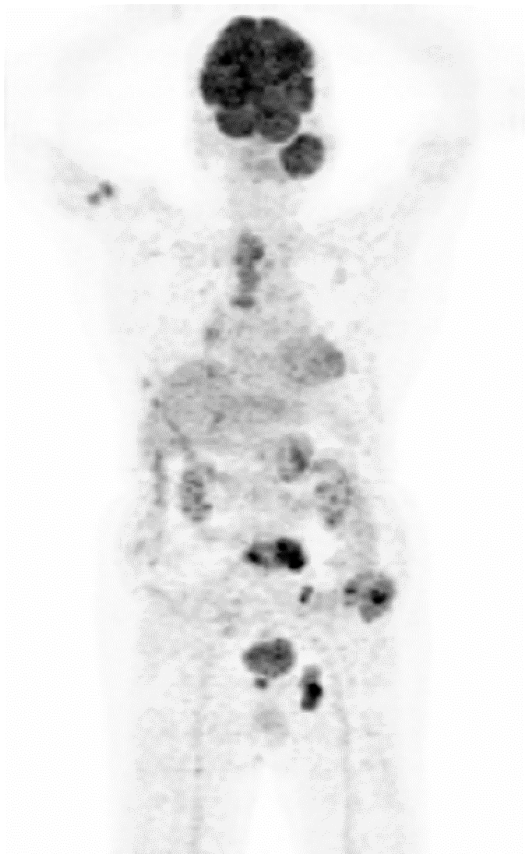


Figure 1. Maximum intensity projection images from Fluorodeoxyglucose 18F PET/CT demonstrated multiple FDG-avid lesions in the lungs, left buccal region, right humerus, spine, and pelvic bones.

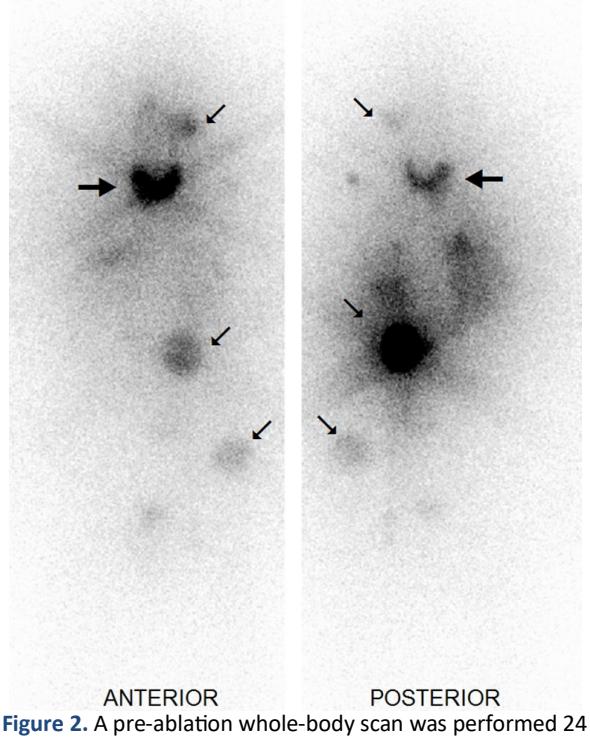


Figure 2. A pre-ablation whole-body scan was performed 24 hours after oral administration of 3 mCi (117 MBq) of 131I sodium iodide, without thyroid hormone withdrawal or recombinant human TSH (rhTSH) stimulation. Surprisingly, in addition to thyroid uptake, markedly increased radioactivity was observed at multiple sites in the left buccal region, chest, and abdomen on the 24-hour images.

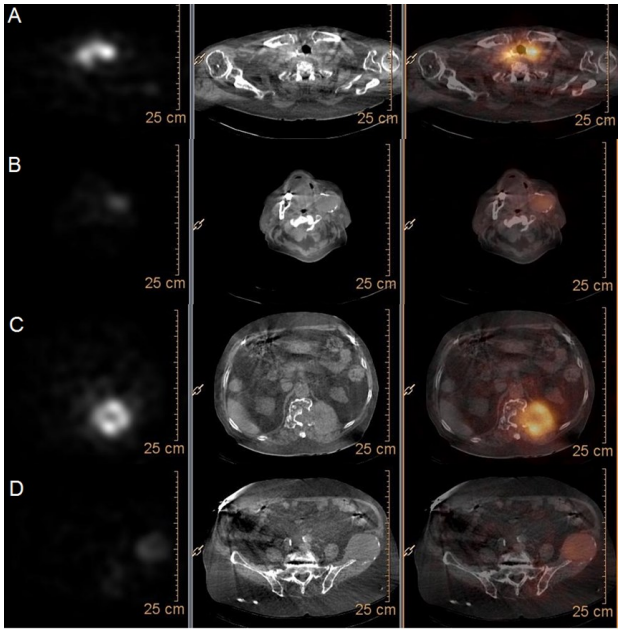


Figure 3. The SPECT/CT study revealed radioiodine accumulation predominantly in the thyroid bed and within bulky tumors involving destructed bony structures of the left mandible, L1 vertebral body, and left ilium on the corresponding CT images (A–D, respectively). These radioactive foci did not completely correspond to the lesions identified on the previous FDG PET/CT study. In thyroid cancer, FDG uptake and radioiodine avidity typically demonstrate an inverse relationship, known as the "flip-flop" phenomenon, which is largely dependent on the degree of tumor differentiation.

DISCUSSION

The visualization of RAI uptake in metastatic DTC is generally achieved only after total or subtotal thyroidectomy because the intact thyroid gland acts as a dominant "sink" for iodine accumulation through the NIS system [11-13]. Consequently, current clinical guidelines recommend thyroidectomy before diagnostic or therapeutic RAI administration to eliminate competitive iodine uptake by normal thyroid tissue and to enhance visualization of metastatic lesions [11, 12]. Therefore, the detection of disseminated metastatic lesions on ^{131}I scintigraphy without prior thyroidectomy is considered highly unconventional and rarely reported in the literature [14-16].

In the present case, an 80-year-old male with metastatic follicular thyroid carcinoma demonstrated extensive RAI accumulation in multiple metastatic lesions involving the buccal region, thorax, and abdomen despite the presence of an intact primary thyroid tumor. This unusual imaging pattern challenges the traditional concept that thyroidectomy is a prerequisite for effective RAI imaging of metastatic disease. Unlike previously reported cases, our patient exhibited immediate and widespread metastatic RAI uptake without thyroid hormone withdrawal or rhTSH stimulation. Okuyama *et al.* described a rare case of papillary thyroid carcinoma

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in which pulmonary metastases regressed after a single administration of RAI without thyroidectomy; however, the disease later underwent anaplastic transformation [17]. Compared with previous reports, the current case demonstrated more extensive metastatic dissemination and unusually strong iodine avidity despite persistent native thyroid tissue.

Another remarkable feature of this case was the significant RAI uptake under profound TSH suppression (TSH < 0.03 μIU/mL). Conventionally, elevated serum TSH levels (>30 μIU/mL) induced by thyroid hormone withdrawal or rhTSH administration are considered essential for maximizing iodine uptake in metastatic lesions [11, 18]. Nevertheless, the metastatic lesions in this patient retained robust ^{131}I avidity despite undetectable TSH levels, suggesting autonomous or highly preserved NIS expression within the tumor cells. In addition, the markedly elevated serum thyroglobulin level (35,109.80 ng/mL) indicated an extraordinarily large burden of functional thyroid cancer tissue, which may have contributed to sufficient competitive iodine uptake by metastatic lesions even in a low-TSH environment.

The coexistence of heterogeneous tumor differentiation states may further explain the atypical imaging findings observed in this patient. The so-called "flip-flop phenomenon," characterized by an inverse relationship between FDG uptake and radioiodine avidity, has long been recognized in metastatic thyroid cancer [19, 20]. Well-differentiated thyroid cancer cells generally maintain NIS expression and demonstrate strong RAI uptake, whereas poorly differentiated cells progressively lose iodine-concentrating ability and instead exhibit increased glucose metabolism detectable on FDG-PET imaging [21, 22]. Feine *et al.* first demonstrated this inverse relationship between ^{131}I and FDG uptake in metastatic thyroid cancer lesions [20]. Similarly, Wang *et al.* analyzed 222 patients undergoing both ^{131}I scintigraphy and FDG-PET and reported that well-differentiated tumors were preferentially visualized by RAI imaging, whereas poorly differentiated lesions showed stronger FDG uptake [21].

In our patient, the findings from SPECT/CT and FDG-PET imaging were not completely concordant, suggesting substantial inter-lesional and intra-lesional heterogeneity. We propose that both differentiated and dedifferentiated thyroid cancer cell populations coexisted within the metastatic lesions. The preserved RAI uptake observed in some lesions may reflect retained NIS activity in well-differentiated tumor components, whereas discordant FDG uptake likely represented dedifferentiated cellular populations with increased glycolytic metabolism. Such tumor heterogeneity may explain the simultaneous presence of strong metastatic iodine uptake and aggressive systemic disease progression.

This case also raises important biological questions regarding the mechanisms underlying preserved radioiodine avidity in metastatic disease despite suppressed TSH levels. Recent molecular studies have demonstrated that restoration of iodine uptake may occur through re-differentiation pathways involving MAPK inhibition, RET fusion blockade, or NTRK-targeted therapy [23-25]. Although our patient did not receive targeted therapy, the unexpectedly high metastatic iodine avidity suggests the possibility of intrinsically preserved thyroid differentiation pathways or heterogeneous molecular alterations affecting NIS regulation.

In conclusion, this case provides rare evidence that RAI scintigraphy may successfully detect disseminated metastatic thyroid cancer even in the absence of thyroidectomy or TSH stimulation. The coexistence of extensive metastatic RAI uptake, suppressed TSH levels, and heterogeneous FDG-PET findings highlights the biological complexity and heterogeneity of advanced thyroid cancer. These findings challenge the conventional paradigm that thyroidectomy and TSH elevation are absolute prerequisites for effective RAI imaging and may provide a potential diagnostic and therapeutic alternative for elderly or surgically ineligible patients with advanced metastatic thyroid carcinoma. Unfortunately, the patient died four months later, precluding longitudinal follow-up studies and leaving unresolved questions regarding the long-term biological and therapeutic implications of this rare presentation.

CONCLUSION

This unique case demonstrates unexpected radioiodine accumulation in distant metastatic differentiated thyroid cancer without prior thyroidectomy. It highlights the heterogeneous behavior of thyroid cancer and suggests a potential role for radioiodine scintigraphy in detecting metastatic disease even in patients with an intact thyroid gland. Further studies are needed to clarify the underlying mechanisms and clinical implications of this rare phenomenon.

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could inappropriately influence this work. All individuals who made significant contributions to this study and the manuscript are included in the author list.

***Ethical considerations*:** This case report describes a single patient and is based solely on data obtained during routine clinical care. No additional research-related interventions were performed. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

***Author contributions*:** Each author's contribution to this study is acknowledged. Y-W.C. and C-C.C., designed the study, conducted the investigations, and performed image analysis. Y-F.H. and C-Y.L., contributed to the clinical studies. Y-C.T., played a key role in editing and preparing the manuscript.

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