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CASE REPORT
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Recurrent Thyroid Carcinoma in a Dog - Diagnosis by 18F-Fluorodeoxyglucose Positron Emission Tomography

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ABSTRACT

***Background*:** Thyroid tumor is a common endocrine tumor that accounts for up to 3.8% of all tumors in dogs. Most of them are malignant and usually nonfunctional in dogs. 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) is an imaging modality that detects intracellular accumulation of radioactive deoxyglucose administered in the body and is used in combination with computed tomography to provide functional information with exact anatomical localization. It is used in human medicine to detect residual or recurrent head and neck neoplasm after treatments, such as surgical resection. This report describes the first case of diagnosing recurrent thyroid carcinoma (TC) through FDG-PET in a dog.
***Case*:** A 9-year-old castrated male Maltese dog presented with a palpable mobile mass in the right ventral cervical region. Radiography and ultrasonography (US) showed a radiopaque mass adjacent to the trachea, and the right thyroid gland was enlarged on computed tomography. The surgically excised mass was encapsulated and measured to be 2.3 × 1.0 × 3.4 cm (width x length x height) in size. Histopathologically, the mass was diagnosed as differentiated follicular TC, and gross and vascular invasions were observed. To prevent recurrence, postoperative carboplatin chemotherapy was performed for 5 months. Two months after completion of chemotherapy, a nodule of approximately 7 mm in diameter was detected in the thyroidectomy bed by US. FDG-PET scanning was performed as an effective means of evaluating the malignancy, local recurrence, and metastasis of differentiated follicular TC. The nodule had the dimensions of 2.8 × 5.9 × 8.6 mm, a maximum standardized uptake value (SUV) of 8.49, and a mean SUV of 5.6. The results of FDG-PET suggested the recurrence of TC; therefore, the second chemotherapy protocol using toceranib was applied for 16 months. After initiation of the 2nd chemotherapy, follow-up examinations were conducted approximately every 4 months. On the 134th day, although the nodule was not palpated, its size was observed to have increased to 5.0 × 3.8 × 13.6 mm on cervical US on the 232nd day, showing heterogeneous and hypoechoic parenchyma. On the 405th day, the tumor was enlarged to a size of 13.4 × 12.9 × 22 mm and identified as a lobular, amorphous shape, and its heterogeneity was increased. Moreover, 2 pulmonary nodules with well-defined margins were found on radiography in the left caudal lung lobe (9 × 10 mm and 12 × 12 mm [width × length]); thus, lung metastasis was suspected. On the 536th day, anorexia and lethargy occurred, and the dog was lost to follow-up.
***Discussion*:** In the present case, local recurrence of TC was suspected based on cervical US. Although US was useful as a screening tool, additional examinations were necessary for evaluating local invasiveness, malignancy, and nodal/distant metastasis. FDG-PET can detect recurrence at an early stage because it can sense increased tumor metabolism through physiologic absorption of FDG, even before the beginning of anatomic change in the lesion. Therefore, FDG-PET can assist in treatment planning and provide better prognosis. In humans, focal FDG uptake and a high maximum SUV in the thyroid gland on FDG-PET were associated with a higher risk of cancer. Because there was no evidence of neoplasia except the thyroid lesion during the FDG-PET examination, the tumor showed an increasingly malignant pattern of the thyroid gland on US during the follow-up period, and the metastatic pulmonary nodules were identified on the 650th day after the thyroidectomy, the present case was diagnosed as recurrent TC. This report describes the use of FDG-PET for diagnosing local recurrence of TC, pointing to FDG-PET as a potential strategy to evaluate loco-regional recurrence and distant metastasis of TC.

Keywords: canine, FDG-PET, follicular thyroid carcinoma, metastasis, tumor, cancer.

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INTRODUCTION

Thyroid tumor is a common endocrine tumor that accounts for up to 3.8% of all tumors in dogs. Most of them are malignant and invade surrounding tissues as well. It is usually nonfunctional in dogs [20]. In humans, the loco-regional recurrence rate of thyroid tumor is known to be high (15-30%) in case of gross vascular invasion [12,17], which is associated with worse prognosis in well-differentiated follicular thyroid carcinoma (dFTC) patients [12,14]. According to a retrospective study with 156 dogs that experienced thyroidectomy, the loco-regional recurrence rate was 11.5%, and the metastatic rate was 8.3% as a post-surgical complication [26].

The monitoring tools for the diagnosis of local recurrence after thyroidectomy in dogs are cervical ultrasonography (US), US-guided fine needle aspiration (FNA), and computed tomography (CT) scans [18,26]. However, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) is also commonly used in human medicine [10,11,23]. FDG-PET is a modality that detects intracellular accumulation of radioactive deoxyglucose administered in the body and is used in combination with CT to provide functional information with exact anatomical localization [19]. In humans, FDG-PET is a powerful tool for detecting residual or recurrent head and neck neoplasm after treatments, such as surgical resection and radioiodine therapy [11]. However, to the authors' knowledge, the use of FDG-PET for the diagnosis of recurrent thyroid tumor following surgical resection has not yet been reported in small animals. Therefore, this report describes a case of recurrent TC diagnosed through FDG-PET and discusses its usefulness.

CASE

A 9-year-old castrated male Maltese dog presented with a palpable mobile mass in the right ventral cervical region. On physical examination, the mass was located at the level of the right side of the thyroid along the trachea, and the size of the mass was 3.4 × 3.6 cm (width [W] × length [L]). There were no other specific findings except for hyperthermia (39.4°C) and obvious clinical signs. In blood analysis, the dog had a mildly increased alkaline phosphatase level (144 IU/L; reference interval (RI) = 29-97 IU/L) and mild hypercholesterolemia (324 mg/dL, RI = 135-270 mg/dL). The total T4 concentration was normal (1.3 μg/dL; RI = 1.0-3.5 μg/dL). Radiography and US scans highlighted the possibility of a thyroid tumor (Figure 1A, B). In the FNA examination of the mass, loosely cohesive sheets of cells were observed as well as naked nuclei morphology, which is typical of endocrine cells (Figure 1C). In the CT exam, the right thyroid lobe was enlarged to a size of 2.3 × 1.9 × 3.4 cm (W × L × height [H]). The tumor had a moderately irregular, circular margin and was well-capsulated. Gross vascular invasion was observed, and there was no other evidence of lymph node or distant metastasis (Figure. 1D). The tumor was classified as T2aN0M0 stage according to the tumor-nodes-metastases classification [25].

Right thyroidectomy was performed due to the lack of metastases and the encapsulation and freely movable nature of the tumor. The removed tumor was sent for histopathology on the 15th day following initial presentation. In histopathology, neoplastic epithelial cells formed a few abnormally sized and shaped follicular structures, showing both follicular and compact cellular growth patterns. The cells with the compact cellular growth pattern appeared to be morphologically and functionally less differentiated than the cells that formed follicles. Therefore, the tumor was diagnosed as dFTC with the follicular-compact subtype. The surgical margin was complete, but the tumor was narrowly excised along the less than 1-mm thick capsule. The mitotic count was 4 in 10 per high-power fields, and vascular invasion was observed (Figure 2).

Because both macroscopic and microscopic vascular invasions were confirmed, the risk of recurrence was likely to be high. Therefore, the adjuvant chemotherapy protocol was performed with carboplatin[1] (300 mg/m^2/IV, once every month for 5 months). Two months after completion of chemotherapy, a nodule appeared in the right thyroidectomy bed; thus, the lesion was screened by US. A 7-mm size nodule was identified, and recurrence of the thyroid tumor was considered. However, in contrast to the typical features of thyroid cancer, which are inhomogeneous parenchyma, irregular margins, central vascularization, and micro-calcification [28], the nodule had a homogeneous parenchyma and a sharp margin without calcification, and the invasion into the surrounding tissues was unclear. In addition, US-guided FNA could not be performed because the nodule was relatively small, and there was a large blood vessel adjacent to the nodule.

Therefore, FDG-PET was performed to evaluate the recurrence of thyroid tumor, its malignancy, and

distant metastasis on the 245th day after thyroidectomy. FDG-PET was performed under general anesthesia as follows: after a 1-time injection of propofol[2] [4 mg/kg/IV] following midazolam[3] [0.2 mg/kg/IV/bolus] premedication, anesthesia was maintained with a mixture of isoflurane[4] and oxygen. Following induction, the dog was moved to the PET/CT suite (Discovery-72 STE)[5], where 25.16 MBq (0.14 mCi/kg) of FDG was administered intravenously. During the 60-min uptake time, whole-body CT scans were obtained, after which whole-body PET images were taken for 30 min in 6-bed positions (5 min each). Commercial medical imaging software[6] was used to analyze PET images. The region of interest (ROI) for the nodule was drawn manually and analyzed. Standardized uptake values (SUVs), which reflect tissue activity within a ROI, were calculated as the average tissue concentration of FDG using the following formula: (MBq/mL)/(total injected dose [MBq]/body weight [g]). The mean and maximum SUV (SUVmean and SUVmax) were calculated to quantitatively analyze FDG uptake.

As a result, a hypermetabolic area was identified on the right thyroidectomy bed, and the size of the nodule was determined to be 2.8 × 5.9 × 8.6 mm. The SUVmax of the area was 8.49, and the SUVmean was 5.6, indicating the possibility of a malignant neoplasia. No regional lymph node or distant metastasis was found (Figure 3). Consequently, recurrence of the TC was strongly suspected because the tumor showed potential malignancy on FDG-PET, in the same location as that of the primary tumor, and also gross vascular invasion was confirmed in the previous histopathology of the primary tumor. The disease-free survival (DFS) was estimated to be 245 days after thyroidectomy. Since lymph nodes and distant metastasis were not observed, a second surgical resection was the primary treatment regimen offered, but the owner refused. However, several studies have confirmed the clinical benefit of toceranib, a tyrosine kinase inhibitor (TKI), for TC [21]. Accordingly, the secondary chemotherapy protocol using toceranib[7] [3 mg/kg, Peroral, every other day for 16 months] was applied since the time of recurrence.

After initiation of the 2nd chemotherapy, follow-up examinations were conducted approximately every 4 months. On the 134th day after the 2nd chemotherapy, although the nodule was not palpated, it was found to have expanded to a size of 5.0 × 3.8 × 13.6 mm on cervical US on the 232nd day, showing heterogeneous and hypoechoic parenchyma. On the 405th day, the tumor was enlarged to a size of 13.4 × 12.9 × 22 mm, and it was identified as a lobular, amorphous shape with an increased heterogeneity. Additionally, 2 pulmonary nodules with well-defined margins were found on radiography in the left caudal lung lobe (9 × 10 mm and 12 × 12 mm); thus, lung metastasis was suspected. On the 536th day, anorexia and lethargy occurred, and the dog was lost to follow-up.

DISCUSSION

Surgical excision has been recommended for freely movable, non-metastatic thyroid tumors. In a study, the incidence of gross and histologic vascular invasion in 156 TC dogs was reported to be approximately 34.6% and 43.6%, respectively [26]. Furthermore, macroscopic and histologic vascular invasions are thought to be negative predictors of DFS in dogs. It was found in a previous study that the median DFS for the no-macroscopic vascular invasion (n = 33) and no-histologic vascular invasion (n = 20) groups were 23 and 29 months, respectively [3]. In this dog, gross vascular invasion was confirmed by CT and at surgery, and histologic vascular invasion was also proven. Thus, the short DFS (245 days) at 1st recurrence after thyroidectomy could be influenced by both macroscopic and histologic vascular invasions in the present case.

Until now, the clinical benefits of chemotherapy in TC have not been well-established. In a previous study, there was no significant difference in the time of recurrence for the surgically resected dFTC group according to whether chemotherapy protocol was applied [4]. Conversely, the expression of multiple receptor tyrosine kinases, as well as activation of their downstream effector pathways, were revealed, and the clinical benefit of the TKI, toceranib, has been demonstrated in canine TC [21,29]. Clinical benefit was determined in dogs as either complete or partial response or stable disease at least 10 weeks while receiving toceranib. A total of 75% of dogs showed a clinical benefit when toceranib was used as an adjuvant chemotherapy [29]. In the current case, progression-free status was confirmed up to the 134th day, and progression was confirmed on the 232nd day after toceranib administration. Therefore, the outcome in the current case of a partial response for approximately 19 weeks was consistent with the previous study, suggesting that toceranib may be effective as a chemotherapeutic agent.

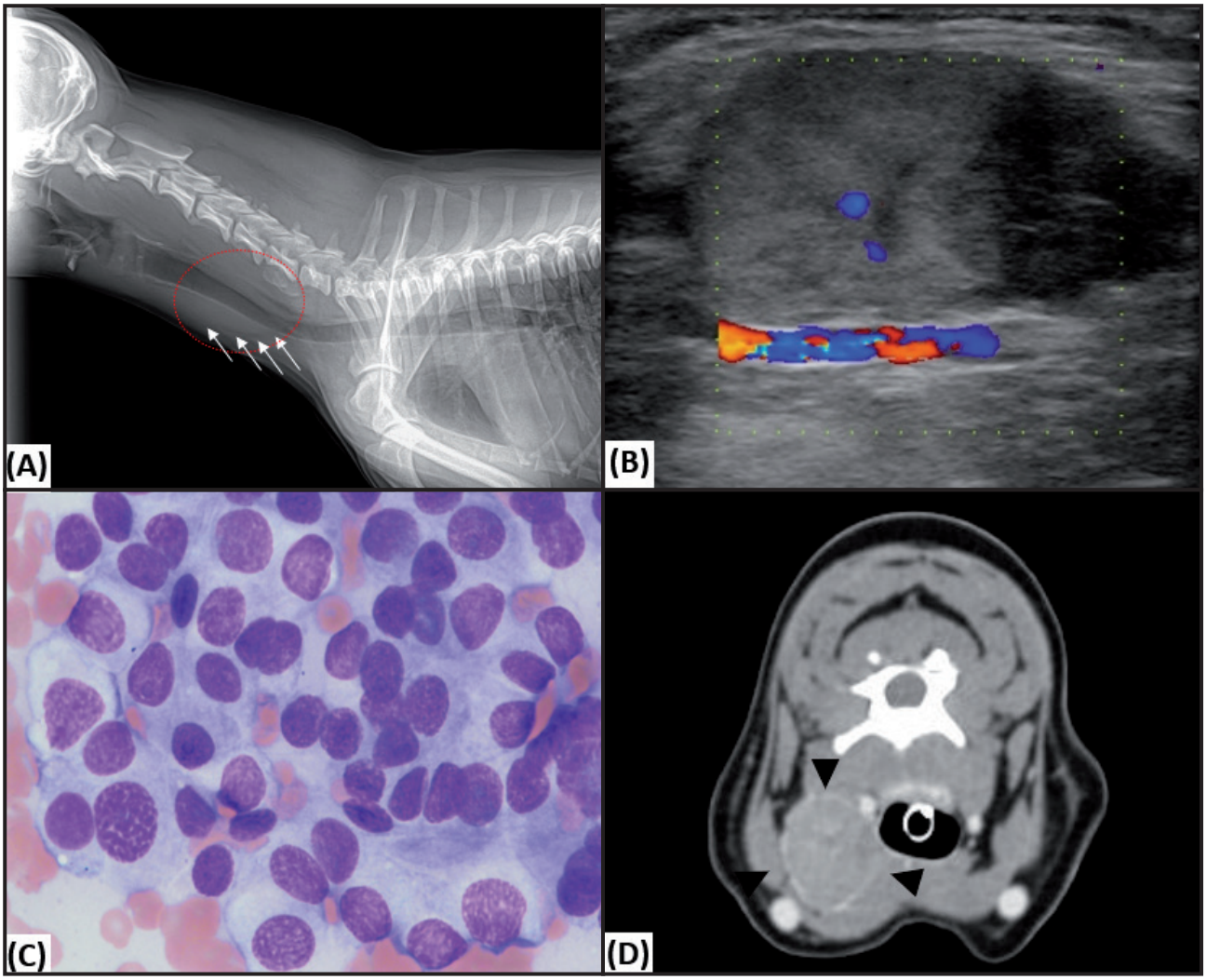

Figure 1. Radiographic (A), ultrasonographic (B), cytological (C), and computed tomography (D) findings of the thyroid mass in a dog. A- An ill-defined oval shape mass is located at the C4-C6 level (arrows). B- The right thyroid gland appears enlarged and has heterogeneous echogenicity with central vascularization. C- Loosely cohesive cell groups and various malignant cytological findings, such as anisokaryosis, anisocytosis, multinucleated figure, and increased N:C ratio, are observed. D- Rim and parenchymal contrast enhancement (arrowheads) is observed in post-contrast CT scan.

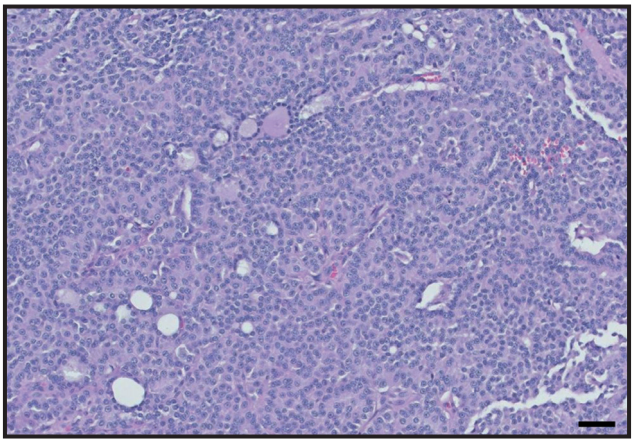

Figure 2. Histopathologic section of the follicular thyroid carcinoma in a dog. Neoplastic epithelial cells are seen forming a few abnormally sized and shaped follicular structures containing intraluminal amorphous eosinophilic material [H&E; Bar = 50 μm].

In human medicine, cervical US, US-guided FNA, and ^{131}I-whole body scintigraphy (WBS) are imaging modalities used in routine follow-up tests after thyroidectomy. US and FNA are strongly recommended as diagnostic procedures for the follow-up of patients with differentiated TC (DTC) [10]. In a previous study, US showed a specificity of 95.3% for detecting recurrence [10]. In an appraisal of studies, the overall sensitivity and specificity of FNA in thyroid lesions were reportedly 83% and 92%, respectively [13]. Currently, a negative result does not exclude malignancy, and a biopsy of the mass should be performed when a malignant lesion is suspected. ^{131}I-WBS is useful for identifying tumors of thyroid origin [20]. However, in 20-30% of patients

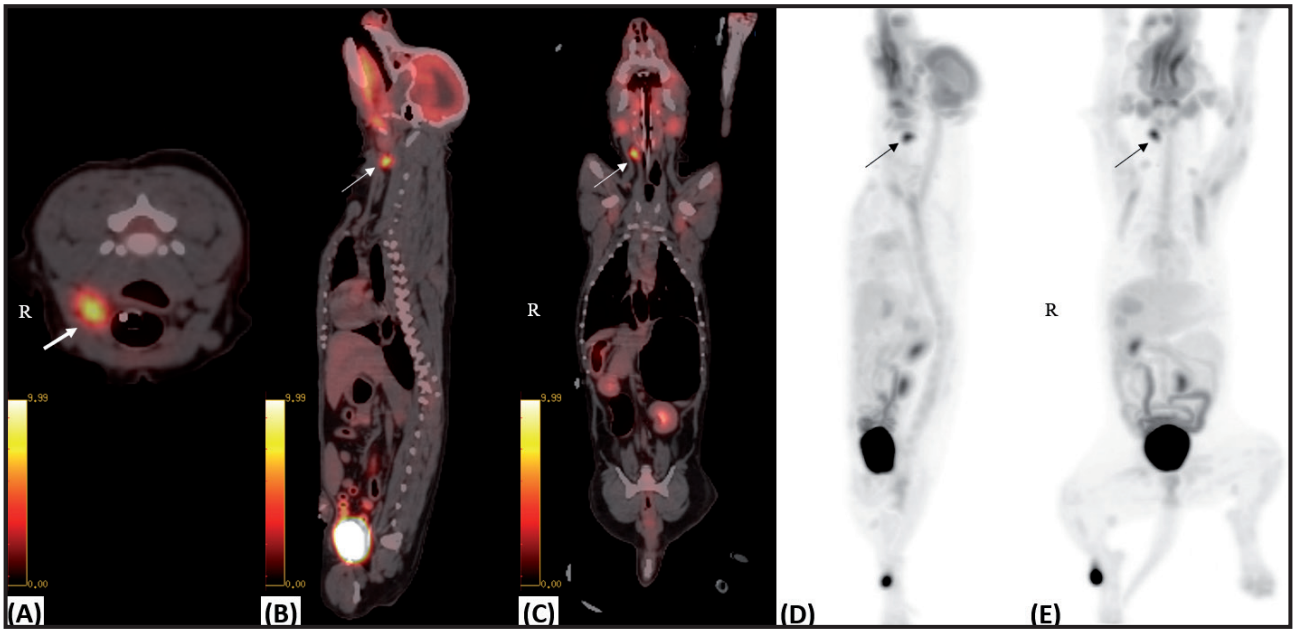

Figure 3. Recurrent thyroid nodule diagnosed in a dog with FDG-PET. A, B & C- Fused PET/CT images using FDG. The hypermetabolic area (white arrows) showing the elevated uptake of FDG (SUVmax 8.49 and SUVmean 5.6) and is found located in the right thyroidectomy bed. A- Transverse plane. B- Sagittal plane. C- Dorsal plane. D & E- Maximum intensity projection (MIP) images using FDG. The images reveal a hypermetabolic lesion (black arrows) in the right thyroidectomy bed [R: Right, L: Left].

with recurrent DTC, TC cells are unable of concentrating iodine, resulting in a negative iodine uptake [10, 27]. Therefore, ^{131}I-WBS presents limitations in detecting local recurrence or distant metastasis.

Most human TCs are DTCs of follicular cell origin, which are mainly composed of the papillary and follicular types, as in this case [30]. In general, FDG--PET is utilized for the follow-up of all DTC patients with suspected recurrence and/or metastasis when there are pathologically elevated serum thyroglobulin levels but no abnormal ^{131}I-WBS uptake [10,23]. In such cases, the sensitivity for detecting recurrent or metastatic lesions through FDG-PET is known to be 71-94%; hence, it is recommended as a diagnostic method for recurrent papillary carcinoma [6]. In addition, when FDG-PET was used in combination with US, it was demonstrated that the sensitivity, specificity, and accuracy in diagnosing cervical nodal metastasis was increased to 81.5%, 95.6%, and 87.3%, respectively [15].

In veterinary medicine, local recurrence was reported to be diagnosed by US, US-guided FNA, and CT in previous cases [18,26]. In the present case as well, local recurrence was suspected through US. However, in the early stage of recurrence, the malignant findings were insufficient for diagnosis, invasion into surrounding tissues was undefinable on US, and US-guided FNA could not be performed due to the nodule's small size and proximity to a large vessel. US has been shown to be less sensitive and specific than CT for assessing invasiveness and verifying thyroid origin [31]. Therefore, although US examination of the neck was useful as a screening tool, additional examinations were necessary for evaluating local invasiveness, malignancy, and nodal/distant metastasis. Meanwhile, the ^{131}I-WBS test was also considered to confirm thyroid origin. However, the original tumor in the present case was of the less-differentiated, follicular-compact type of dFTC. In other words, ^{131}I--WBS was an ineffective diagnostic approach since it could lead to incorrect results due to the insufficient radioiodine absorption by thyroid tissue [7].

Therefore, in the present case, FDG-PET was used for the diagnosis of recurrent thyroid tumor, complementing other diagnostic methods. FDG-PET can detect recurrence at an early stage because it can sense increased tumor metabolism and physiologic absorption of FDG, even before the beginning of anatomic change in the lesion. A human study reported that the sensitivities of CT alone and FDG-PET/CT were 73% and 96%, and the specificities were 71% and 100%, respectively, indicating that FDG-PET/CT considerably enhanced diagnostic accuracy in recurrent iodine-negative DTC patients [9]. Additionally, FDG-PET/CT reduces the uncertainty of ^{131}I-WBS [6,10,11]. As a result, FDG-PET can more accurately

detect tumor recurrence, assist in treatment planning, and provide better prognosis.

As a glucose analog, FDG is the most widely used PET tracer in oncology. The physiologic thyroid uptake of FDG is homogeneous and low in both humans and dogs; therefore, it is generally not visualized in FDG-PET. The SUVmean of the normal thyroid gland is known to be 1.31 ± 0.3 in humans and has not been established in dogs [5,24]. In a previous study, focal uptake (i.e., focally increased ^{18}F-FDG uptake) was highly correlated with malignancy compared with diffuse uptake (i.e., ^{18}F-FDG uptake in the whole thyroid gland), and the mean SUVmax of malignant thyroid lesions was significantly higher than that of benign lesions (6.64 ± 4.12 vs. 3.35 ± 1.69) [2]. In another study, when diagnosing malignant tumors, if the cutoff SUVmax of the thyroid lesion were 7 and 9, the specificities were 90.9% and 97.7%, and the positive predictive values were 60.0% and 75.0%, respectively [1]. Consequently, focal FDG uptake on FDG-PET and a high SUVmax were associated with a higher risk of cancer.

Therefore, FDG-PET may be useful in diagnosing the recurrence of TC. A few cases have been reported regarding the diagnosis of TC using FDG-PET in veterinary fields [8,16,22], but these cases identified primary thyroid tumors. In 1 of these cases, TC was discovered incidentally, and in the other 2 cases, FDG-PET/MRI or FDG-PET/CT was used to diagnose the primary TC.

There are some limitations in this case report. First, because of its small size, the recurrent lesion was not investigated by cytology, and it was not analyzed by histopathology due to the owner's rejection of invasive procedures. If FNA or surgical biopsy had been performed, the origin of the mass could have been clearly identified. Second, follow-up FDG-PET was not performed; thus, the treatment response of the 2nd chemotherapy was evaluated by only cervical US. However, because there was no evidence of neoplasia other than the thyroid lesion at the time of FDG--PET examination, the tumor showed an increasingly malignant pattern of the thyroid gland on US during the follow-up period, and the metastatic pulmonary nodules were identified on the 650th day after thyroidectomy, the tumor was assumed to be a recurrent TC.

In conclusion, the present case suggests the usefulness of diagnosing local recurrence of TC through FDG-PET. FDG-PET may thus be considered as a strategy to evaluate loco-regional recurrence and distant metastasis of TC.

MANUFACTURERS

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REFERENCES

1 Anil G., Hegde A. & Chong F.H.V. 2011. Thyroid Nodules: Risk Stratification for Malignancy with Ultrasound and Guided Biopsy. *Cancer Imaging*. 11: 209223. DOI: 10.1102/1470-7330.2011.00302.

2 Bae J.S., Chae B.J., Park W.C., Kim J.S., Kim S.H., Jung S.S. & Song B.J. 2009. Incidental Thyroid Lesions Detected by FDG-PET/CT: Prevalence and Risk of Thyroid Cancer. *World Journal of Surgical Oncology*. 7(1): 63. DOI:10.1186/1477-7819-7-63

3 Campos M., Ducatelle R., Rutteman G., Kooistra H.S., Duchateau L., de Rooster H., Peremans K. & Daminet S. 2014. Clinical, Pathologic, and Immunohistochemical Prognostic Factors in Dogs with Thyroid Carcinoma. *Journal of Veterinary Internal Medicine*. 28(6): 1805-1813. DOI:10.1111/jvim.12436

4 Castillo V., Pessina P., Hall P., Blatter M.C., Miceli D., Arias E.S. & Vidal P. 2016. Post-Surgical Treatment of Thyroid Carcinoma in Dogs with Retinoic Acid 9 Cis Improves Patient Outcome. *Open Veterinary Journal*. 6(1): 6-14. DOI:10.4314/ovj.v6i1.2

5 Chae Y., Yun T., Koo Y., Lee D., Kim H., Yang M.P. & Kang B.T. 2021. Characteristics of Physiological 18F-Fluoro-2-Deoxy-D-Glucose Uptake and Comparison Between Cats and Dogs with Positron Emission Tomography. *Frontiers in Veterinary Science*. 8: 708237. DOI:10.3389/fvets.2021.708237

6 **Choi M.Y., Chung J.K., Lee H.Y., So Y., Park D.J., Jeong J.M., Lee D.S., Lee M.C. & Cho B.Y. 2006.** The Clinical Impact Of18f-FDG PET in Papillary Thyroid Carcinoma with a Negative 131I Whole Body Scan: A Single-Center Study of 108 Patients. *Annals of Nuclear Medicine*. 20(8): 547-552. DOI:10.1007/BF03026819

7 **Dionigi G., Fama' F., Pignata S.A., Pino A., Pontin A., Caruso E., Fu Y., Li S., Mazzeo C., Sun H. & Baldari S. 2020.** Usefulness of PET-CT Scan in Recurrent Thyroid Cancer. *World Journal of Otorhinolaryngology - Head and Neck Surgery*. 6(3): 182-187. DOI:10.1016/j.wjorl.2020.02.008

8 **Frank I., Mann K. & Duerr F. 2019.** Fluorine-18-Fluoro-2-Deoxy-D-Glucose PET-CT Aids in Detection of Soft-Tissue Injuries for Dogs with Thoracic or Pelvic Limb Lameness. *Veterinary Radiology & Ultrasound*. 60(5): 575-85. DOI:10.1111/vru.12790

9 **Freudenberg L.S., Frilling A., Kühl H., Müller S.P., Jentzen W., Bockisch A. & Antoch G. 2007.** Dual-Modality FDG-PET/CT in Follow-Up of Patients with Recurrent Iodine-Negative Differentiated Thyroid Cancer. *European Radiol*ogy. 17(12): 3139-3147. DOI:10.1007/s00330-007-0682-2

10 **Frilling A., Görges R., Tecklenborg K., Gaßmann P., Bockhorn M., Clausen M. & Broelsch C.E. 2000.** Value of Preoperative Diagnostic Modalities in Patients with Recurrent Thyroid Carcinoma. *Surgery*. 128(6): 1067-1074. DOI:10.1067/msy.2000.110771

11 **Fukui M.B., Blodgett T.M., Snyderman C.H., Johnson J.J., Myers E.N., Townsend D.W. & Meltzer C.C. 2005.** Combined PET-CT in the Head and Neck: Part 2. Diagnostic Uses and Pitfalls of Oncologic Imaging. *RadioGraphics*. 25(4): 913-930. DOI:10.1148/rg.254045136

12 **Gardner R.E., Tuttle R.M., Burman K.D., Haddady S., Truman C., Sparling Y.H., Wartofsky L., Sessions R.B. & Ringel M.D. 2000.** Prognostic Importance of Vascular Invasion in Papillary Thyroid Carcinoma. *Archives of Oto-rhinolaryngology - Head & Neck Surgery*. 126(3): 309-312. DOI:10.1001/archotol.126.3.309

13 **Gharib H. 1993.** Fine-Needle Aspiration Biopsy of the Thyroid: An Appraisal. *Annals of Internal Medicine*. 118(4): 282-289. DOI:10.7326/0003-4819-118-4-199302150-00007

14 **Haugen B.R., Alexander E.K., Bible K.C., Doherty G.M., Mandel S.J., Nikiforov Y.E., Randolph G.W., Sawka A.M., Schuff K.G., Sherman S.I. & Ann S. 2016.** 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 26(1): 1-133. DOI:10.1089/thy.2015.0020

15 **Joo Y.H., Yun C.H., Cho J.H., Sun D.I., Yoo I.R. & Jung S.R. 2008.** Utility of FDG PET/CT Scans on Nodal staging in Patients with Papillary Thyroid Cancer. *Journal of Korean Thyroid Association*. 1(2).

16 **Kang B.T., An D., Kim H.W., Jin Y., Son Y.D., Jung D.I., Kang J.H., Yang M.P., Sur J.H. & Lee S.R. 2018.** Primary Brain Involvement of Disseminated Histiocytic Sarcoma in a Rottweiler Dog – Histopathology, 18F-Fluorodeoxyglucose Positron Emission Tomography and 7 T-Magnetic Resonance Imaging Findings: A Case Report. *Veterinarni Medicina*. 62(11): 604-613. DOI:10.17221/8/2017-VETMED

17 **Lang W., Choritz H & Hundeshagen H. 1986.** Risk Factors in Follicular Thyroid Carcinomas. A Retrospective Follow-Up Study Covering a 14-Year Period with Emphasis on Morphological Findings. *American Journal of Surgical Pathology*. 10(4): 246-255. DOI:10.1097/00000478-198604000-00003

18 **Latifi M., Skinner O.T., Spoldi E., Ackerman L., Souza C.H., Yoon J., Vinayak A., Tuohy J.L., Wallace M.L., Dornbusch J.A. & Selmic L.E. 2021.** Outcome and Postoperative Complications in 73 Dogs with Thyroid Carcinoma with Gross Vascular Invasion Managed with Thyroidectomy. *Veterinary and Comparative Oncology*. 19(4): 685-696. DOI:10.1111/vco.12739

19 **Lawrence J., Rohren E. & Provenzale J. 2010.** PET/CT Today and Tomorrow in Veterinary Cancer Diagnosis and Monitoring: Fundamentals, Early Results and Future Perspectives. *Veterinary and Comparative Oncology*. 8(3): 163-187. DOI:10.1111/j.1476-5829.2010.00218.x

20 **Liptak J.M. 2007.** Canine Thyroid Carcinoma. *Clinical Techniques in Small Animal Practice*. 22(2): 75-81. DOI:10.1053/j.ctsap.2007.03.007

21 **London C., Mathie T., Stingle N., Clifford C., Haney S., Klein M.K., Beaver L., Vickery K., Vail D.M., Hershey B. & Ettinger S. 2012.** Preliminary Evidence for Biologic Activity of Toceranib Phosphate (Palladia®) in Solid Tumours. *Veterinary and Comparative Oncology*. 10(3): 194-205. DOI:10.1111/j.1476-5829.2011.00275.x

22 **Mattoon J.S. & Bryan J.N. 2013.** The Future of Imaging in Veterinary Oncology: Learning from Human Medicine. *The Veterinary Journal*. 197(3): 541-552. DOI:10.1016/j.tvjl.2013.05.022

23 **Mirallié E., Guillan T., Bridji B., Resche I., Rousseau C., Ansquer C., Bodet-Milin C., Curtet C., Carnaille B., Murat A. & Charbonnel B. 2007.** Therapeutic Impact of 18FDG-PET/CT in the Management of Iodine-Negative Recurrence of Differentiated Thyroid Carcinoma. *Surgery*. 142(6): 952-958. DOI:10.1016/j.surg.2007.09.015

24 **Nakamoto Y., Tatsumi M., Hammoud D., Cohade C., Osman M.M. & Wahl R.L. 2005.** Normal FDG Distribution Patterns in the Head and Neck: PET/CT Evaluation. *Radiology*. 234(3): 879-885. DOI:10.1148/radiol.2343030301

25 **Owen L.N. & World Health Organization. 1980.** *TNM Classification of Tumours in Domestic Animals*. Veterinary Public Health Unit & WHO Collaborating Center for Comparative Oncology. 53p. Available at: <https://apps.who.int/iris/handle/10665/68618>

26 **Reagan J.K., Selmic L.E., Fallon C., Sutton B., Lafferty M., Ben-Aderet D., Culp W.T., Liptak J.M., Duffy D., Simons M. & Boston S. 2019.** Complications and Outcomes Associated with Unilateral Thyroidectomy in Dogs with Naturally Occurring Thyroid Tumors: 156 Cases (2003–2015). *Journal of the American Veterinary Medical Association*. 255(8): 926-932. DOI:10.2460/javma.255.8.926

27 **Rouxel A., Hejblum G., Bernier M.O., Boëlle P.Y., Ménégaux F., Mansour G., Hoang C., Aurengo A. & Leenhardt L. 2004.** Prognostic Factors Associated with the Survival of Patients Developing Loco-Regional Recurrences of Differentiated Thyroid Carcinomas. *The Journal of Clinical Endocrinology and Metabolism*. 89(11): 5362-5368. DOI:10.1210/jc.2003-032004

28 **Scopa C. 2004.** Histopathology of Thyroid Tumors. An Overview. *Hormones*. 3(2): 100-110. DOI:10.14310/horm.2002.11118

29 **Sheppard-Olivares S., Bello N.M., Wood E., Szivek A., Biller B., Hocker S. & Wouda R.M. 2020.** Toceranib Phosphate in the Treatment of Canine Thyroid Carcinoma: 42 Cases (2009–2018). *Veterinary and Comparative Oncology*. 18(4): 519-527. DOI:10.1111/vco.12571

30 **Stangierski A., Woliński K., Czepczyński R., Czarnywojtek A., Lodyga M., Wyszomirska A., Janicka-Jedyńska M., Bączyk M. & Ruchała M. 2014.** The Usefulness of Standardized Uptake Value in Differentiation between Benign and Malignant Thyroid Lesions Detected Incidentally in 18F-FDG PET/CT Examination. *PLoS ONE*. 9(10): e109612. DOI:10.1371/journal.pone.0109612

31 **Taeymans O., Penninck D.G. & Peters R.M. 2013.** Comparison between Clinical, Ultrasound, CT, MRI, and Pathology Findings in Dogs Presented for Suspected Thyroid Carcinoma. *Veterinary Radiology & Ultrasound*. 54(1): 61-70. DOI:10.1111/j.1740-8261.2012.01966.x