Original Article
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The Use of ^{18}F-FDG PET/CT in Patients with Recurrent Differentiated Thyroid Cancer

Rekürren Diferansiye Tiroid Kanserinde ^{18}F-FDG PET/BT'nin Katkısı

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Abstract

Objectives: ^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) is used to monitor the recurrence in thyroid cancer patients when there is suspicion of metastases. De-differentiated lesions become ^{18}F-FDG avid with a more aggressive clinical course. The aim of this study was to investigate the use of ^{18}F-FDG PET/CT in differentiated thyroid cancer.

Methods: Forty-six patients, either with a negative radioiodine scan or clinical progression and suspicions for metastases with differentiated thyroid cancer that were referred to our department for ^{18}F-FDG PET/CT scan and evaluated retrospectively. PET/CT findings were correlated with clinical and histopathological findings, serum thyroglobulin (Tg), and anti-Tg levels.

Results: Twenty-six patients (56.2%) were positive for recurrence in ^{18}F-FDG PET/CT images. Positive ^{18}F-FDG PET/CT findings were significantly correlated with the disease stage and Tg levels. Maximum standardized uptake value did not correlate with other findings or patients' profiles. The cut-off value for Tg was at 52.5 ng/mL having 73.08% sensitivity, 75% specificity, 79.17% positive predictive value, and 68.18% negative predictive value for ^{18}F-FDG PET/CT imaging.

Conclusion: ^{18}F-FDG PET/CT is useful for detecting recurrence in differentiated thyroid cancer. Increased Tg levels and stage of the disease were significantly correlated with ^{18}F-FDG positivity. ^{18}F-FDG positivity may also provide information about the de-differentiation process that may support the treatment plan.

Keywords: Thyroid cancer, ^{18}F-FDG PET/CT, SUV_{max}

Öz

Amaç: ^{18}Flor-florodeoksiglukoz (^{18}F-FDG) pozitron emisyon tomografi/bilgisayarlı tomografi (PET/BT) metastaz şüphesi bulunan tiroid kanseri hastalarında rekürrensi araştırmak için kullanılır. Özellikle de-diferansiye olan lezyonlar ^{18}F-FDG tutulumu göstermekte olup hastalığın klinik seyri daha agresif olarak izlenir. Bu çalışmada ^{18}F-FDG PET/BT'nin diferansiye tiroid kanserindeki katkısını araştırmayı amaçladık.

Yöntem: İyot-131 (I-131) tüm vücut tarama sintigrafisi negatif olarak saptanan ve/veya metastaz şüphesi uyandıran klinik olarak progrese diferansiye tiroid kanseri tanılı bölümümüzde ^{18}F-FDG PET/BT çekimi yapılan 46 hasta retrospektif olarak incelendi. ^{18}F-FDG PET/BT bulguları ile klinik ve histopatolojik özellikleri ile serum tiroglobulin (Tg) ve anti-Tg değerleri karşılaştırıldı.

Bulgular: Grupta bulunan 26 hastada (%56,2) ^{18}F-FDG PET/BT görüntülemesinde pozitif olarak değerlendirilen bulgular saptandı. Hastalık evresi ve Tg düzeyleri ile ^{18}F-FDG PET/BT pozitifliği arasında pozitif bir korelasyon bulundu. Lezyonların maksimum standart tutulum değeri (SUV_{maks}) ile anlamlı bir ilişki saptanmadı. Tg cut-off değeri 52,5 ng/mL olarak hesaplandı. Bu değer bazında ^{18}F-FDG PET/BT görüntüleme için %73,08 duyarlılık, %75 özgüllük, %79,17 pozitif prediktif değer ve %68,18 negatif prediktif değerler elde edildi.

Sonuç: ^{18}F-FDG PET/BT diferansiye tiroid kanserinde rekürrensi saptamada faydalı bir yöntem olarak değerlendirildi. Hastalığın evresi ve Tg değerleri ile PET görüntülemede elde edilen pozitif bulguları arasında anlamlı olarak korelasyon saptandı. Pozitif PET bulguları ile tümör dediferansiasyonu hakkında bilgi edinilmesi açısından tedavi planına katkısı bulunabileceği sonucuna varıldı.

Anahtar kelimeler: Tiroid kanseri, ^{18}F-FDG PET/BT, SUV_{maks}

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Introduction

Differentiated thyroid cancers are slowly growing tumors with a good prognosis and relatively low mortality rates (1,2). The American Thyroid Association (ATA) defines the thyroglobulin (Tg) level of 0.2 ng/mL as acceptable after the ablation and/or radioiodine treatment. Routine follow-up is conducted by measuring serum Tg and anti-Tg levels, with a neck ultrasound (3). Whole-body scintigraphy with radioiodine is advisable when Tg serum levels are at the rise or on the occasion or suspicion of metastases. Residual disease or recurrence has been mostly detected in the thyroid bed or cervical lymph nodes (4). However, in the case of suspicion of residual disease or recurrence that could not be detected with the ultrasound, conventional imaging techniques are applied. Positron emission tomography/computed tomography (PET/CT) is helpful in restaging patients with increased Tg levels and a negative iodine whole-body scan (5,6). ATA guidelines suggest a serum Tg cut-off at 10 ng/mL to benefit from PET/CT imaging in metastatic cancers.

Whole-body iodine-131 (I-131) scan has high sensitivity and specificity for the detection of differentiated thyroid cancer. It is routinely used in searching for metastases or recurrence, as recommended in the ATA guidelines (7). However, spatial resolution might not be efficient in the case of small lesions (<1 cm). Additionally, thyroid cells may de-differentiate which leads to aggressive malignancy and loss of the iodine uptake during the follow-up. ^{18}Fluoride-fluorodeoxyglucose (^{18}F-FDG) PET/CT is useful for the detection of metastases, especially when cancer cells de-differentiate. While the iodine transport decrease in thyroid cancer cells, glucose metabolism increases and becomes more FDG avid; this is called the "flip-flop phenomenon" and serves as a sign of de-differentiation (8,9,10). Imaging techniques other than whole-body radioiodine scan are necessary in these cases. While ^{18}F-FDG avidity represents the aggressiveness of tumor cells, CT depicts metastatic lesions with negative ^{18}F-FDG uptake. This may benefit the tumors, where some of the metastases have a lower level of differentiation.

Maximum standardized uptake values (SUV_{max}) may provide a direction of the therapy, since the higher the values, the worse the prognosis (10). Recent studies have also emphasized the importance of ^{18}F-FDG PET/CT in patients with suspicions of recurrence and prior radioiodine treatment (11,12). Furthermore, ^{18}F-FDG PET/CT scan has an impact on disease management and prognosis (6). Nevertheless, PET/CT in routine imaging of thyroid cancer patients is not part of the recent guidelines' recommendations.

This study aimed to evaluate the use of ^{18}F-FDG PET/CT scans in differentiated thyroid cancer, in patients with suspicions of recurrence or metastases in our hospital. Moreover, we assessed the relation of SUV_{max} levels with clinical and pathological findings of the patients.

Materials and Methods

Patients with intermediate or high-risk differentiated thyroid cancer, who were referred to our department for radioiodine treatment between 2017 and 2020, have been analyzed retrospectively. Patients were either operated in our hospital or were following-up from the other clinics. A group of patients were referred to our department without previous routine follow-up. All patients had undergone thyroidectomy, with or without the central and lateral lymph node dissection, and radioiodine treatment. The I-131 treatment dosage was between 3700 (100 mCi) and 7400 MBq (200 mCi) by following the ATA guidelines' recommendations and risk assessment of the patient.

Six months after the treatment, when the thyroid stimulating hormone serum levels measurement had reached >30 ng/mL, Tg and anti-Tg levels were measured. Patients with suspicion or already discovered metastases with increasing levels of either Tg or anti-Tg after the radioiodine treatment were included in the study. Serum stimulated Tg and anti-Tg levels were measured. The risk stratification and suspicion for a recurrence or metastases are defined by the ATA guidelines. All the patients signed informed consent forms. University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee approved (number: 3112, date: 02.02.2021).

Imaging Techniques

Ultrasound for residual disease or abnormal lymph node on the neck region was performed. Whole-body scan was performed 48-72 hours after administering the 185 MBq (5 mci) I-131 for the patients with increasing levels of either Tg or anti-Tg. A Mediso dual-head camera was used for whole-body scintigraphy and single photon emission computed tomography/CT images when detailed images are required. Finally, ^{18}F-FDG PET/CT scan was performed on the patients with either a negative I-131 scan or clinical signs of disease progression after the iodine treatment. Patients with already known metastases and increased levels of either Tg or anti-Tg were also included and screened with ^{18}F-FDG PET/CT scan.

FDG PET/CT protocol had the following parameters: 45-60 mins after receiving approximately 111-370 Mbq (3-10 mci) of ^{18}F-FDG with patient having an empty

bladder, underwent a head to mid-thigh whole-body CT scan (130 kV, 50-80 mAs, thickness slice of 3 mm) and followed by a PET scan (GE Healthcare, Wisconsin, USA). Neither oral nor intravenous contrast was used in any of the patients. A region of interest was drawn around the metastases to measure the SUV_{max}. Lesions with an abnormal anatomical shape and higher SUV_{max} levels than the background were accepted as PET-positive for recurrence or metastases. Biopsy confirmation was not achieved in all the patients.

Statistical Analysis

All data were analyzed on SPSS software for Windows (v17.0; IBM, Armonk, NY, USA). Individual and aggregate data were summarized using descriptive statistics including the mean, standard deviations, medians (min-max), frequency distributions, and percentages. The normality of the data distribution was verified by the histogram graphs and the Kolmogorov-Smirnov test. For the variables that were not normally distributed, the Mann-Whitney U and Kruskal-Wallis tests were applied to compare between groups. The correlation was analyzed with Spearman's Rho tests. Receiver operating characteristic (ROC) analysis was used to determine the cut-off levels of Tg and anti-Tg. P values of <0.05 were considered statistically significant.

Results

Forty-six patients with a mean age of 47.65±15.82 were included in our study (Table 1). Seventeen of the patients were male. The patients were categorized according to the type of cancer. Papillary thyroid cancer (PTC) corresponded to 76.09% (n=35), follicular thyroid cancer (FTC) to 6.52% (n=3), and mixed type of differentiated thyroid cancer to 17.39% (n=8). Two of the PTC patients had tall cell variant and one had an oncocytic variant. Two of the mixed type patients had tall cell variant tumors. According to the classification of the American Joint Committee of Cancer and the TNM guidelines, 27 patients were stage-I, nine patients were stage-II, and four patients were stage-IV (13). Twenty-six patients (56.2%) had at least one lesion with a SUV_{max} >2.5, were grouped as recurrent or metastatic disease, and consequently accepted as PET-positive group. In the PET-positive group, 12 patients had local recurrence findings, and 14 patients had lesions positive for metastatic lymph nodes in the cervical region. Furthermore, five patients had lesions in the mediastinum, five had lung lesions, and three had bone lesions compatible with the metastases (Figure 1).

The mean Tg levels were 240.36±372.75 ng/mL (range between 0.04 and 11.000 ng/mL), and the mean anti-Tg levels were 37.87±237.37 ng/mL (range between 0.9 and 1.611 ng/mL). Tg and anti-Tg levels of all patients were categorized into two groups as PET-positive and negative. Tg levels were detected significantly higher in PET-positive patients (101.3 ng/mL) than in PET-negative patients (19.4 ng/mL; p=0.001, Table 2). The cut-off value of Tg levels for PET-positive patients was at 52.5 ng/mL, as calculated by the ROC analysis (Figure 2). With this cut-off value for Tg, 73.08% sensitivity, 75% specificity, 79.17% positive predictive value, and 68.18% negative predictive value were achieved in the PET-positive patients. Eight of the total number of patients had increased anti-Tg levels, of which two had ^{18}F-FDG-positive lesions. However, there was either no significant relation or no meaningful cut-off value for the anti-Tg levels, probably due to the smaller sample size.

The comparison between PET-positive disease and the TNM stage of the patients showed significant differences between stage-I and stage-II or stage-IV patients. Stages-II and-IV disease had significantly higher ^{18}F-FDG positivity in PET/CT images (p=0.049, Table 3).

Table 1. Patient characteristics

Clinicopathologic features	**n**
Age (mean ± SD)	47.65±15.82
Sex	
Male	17
Female	29
Tumor type	
Papillary thyroid cancer	
- Classic type	35
- Mixed type	8
Folicular carcinoma	3
PET/CT findings	
^{18}F-FDG-positive	26
^{18}F-FDG negative	20
Previous treatment dose of I-131	
3.7 GBq (100 mCi)	13
5.6 GBq (150 mCi)	23
7.4 GBq (200 mCi)	10
Serum thyroglobulin level (ng/mL) (mean ± SD)	240.36±372.75
Serum anti-thyroglobulin level (ng/mL) (mean ± SD)	37.87±237.37
Serum thyroid stimulating hormone (mIU/mL) (mean ± SD)	71.3±14.11
Size of primary tumor (cm) (mean ± SD)	2.83±1.87
Localization of recurrence/metastases	
Local	12
Neck	14
Mediastinum	5
Lung	5
Bone	3

SD: Standard deviation, PET/CT: Positron emission tomography/computed tomography, ^{18}F-FDG: ^{18}Fluoride-fluorodeoxyglucose, I-131: Iodine-131

Table 2. Mean and median values of ^{18}F-FDG PET/CT positive and negative patients

	^{18}F-FDG PET		p
	Positive	Negative	
	Mean ± SD	Mean ± SD	
Age	51.35±16.35	42.85±14.08	0.063
Serum Tg level (ng/mL)	339.55±417.29	111.41±262.65	**0.001**
Serum anti-Tg level (ng/mL)	65.91±315.49	1.43±2.20	0.375
Size of primary tumor (cm)	2.97±1.93	2.63±1.83	0.519

SD: Standard deviation, PET/CT: Positron emission tomography/computed tomography, ^{18}F-FDG: ^{18}Fluoride-fluorodeoxyglucose, Tg: Thyroglobulin

Gender, age, and tumor type did not exhibit a significant effect on PET/CT positivity. SUV_{max} data also correlated with the clinical and pathological findings of the patients. The mean SUV_{max} value for the recurrent or metastatic lesions in PET/CT scan was 7.65±5.99 (2.5-25.3). The highest SUV_{max} was 25.3 in one patient with FTC. However, it did not have any correlation with the prognostic factors or patients' characteristics.

Discussion

^{18}F-FDG PET/CT scan is useful in staging and following-up most of the cancer types, yet the evidence of the benefits in thyroid cancer is limited. Even the cost-effectiveness relationship of PET/CT imaging in differentiated thyroid

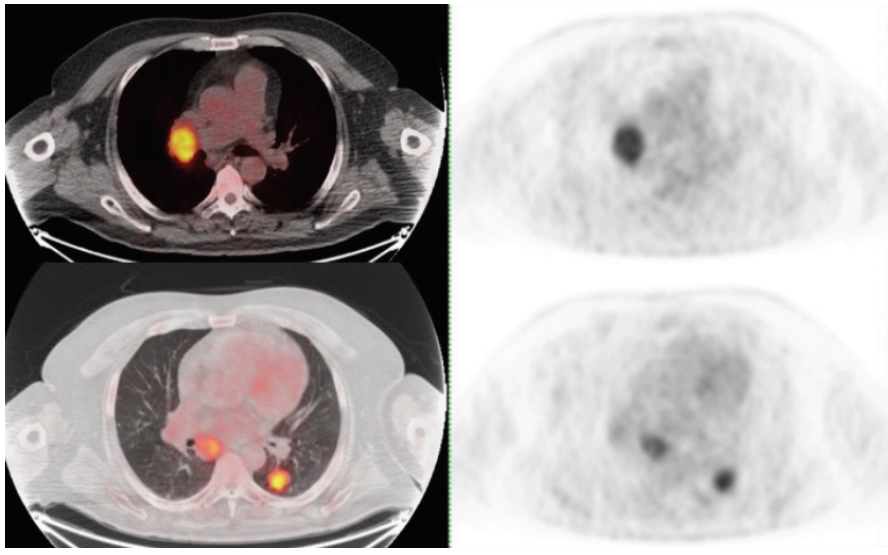

Figure 1. A 56-year-old man with classic type papillary thyroid cancer, previously received 200 mCi I-131 treatment. He was referred for clinical progression. Lesions with high ^{18}F-FDG uptake were found in the mediastinum and lung parenchyma (Tg: 1.853 ng/mL, anti-Tg: 0.9 ng/mL)
I-131: Iodine-131, ^{18}F-FDG: ^{18}Fluoride-fluorodeoxyglucose, Tg: Thyroglobulin

Table 3. Detailed data of ^{18}F-FDG PET/CT positive and negative patients' group

		^{18}F-FDG PET				p
		Positive		Negative		
		n	%	n	%	
Sex	Male	10	(58.82)	7	(41.18)	0.809
	Female	16	(55.17)	13	(44.83)	
Tumor type	Classic type	21	(60.02)	14	(39.98)	0.125
	Folicular C	3	(100)	0	(0)	
	Mixed type	2	(25.00)	6	(75.00)	
Stage	1	12	(44.44)	15	(55.56)	**0.049**
	2	8	(88.89)	1	(11.11)	
	4	3	(75.00)	1	(25.00)	

^{18}F-FDG: ^{18}Fluoride-fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography

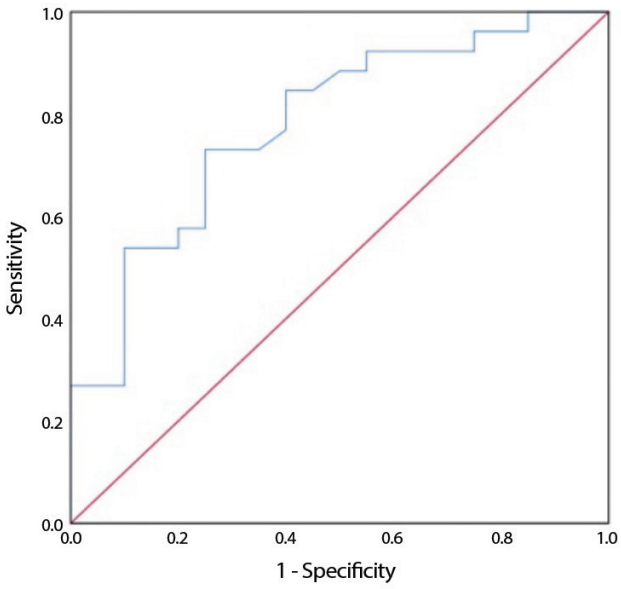

Figure 2. ROC curve of Tg serum levels
ROC: Receiver operating characteristic, Tg: Thyroglobulin

cancer is still being discussed. ^{18}F-FDG uptake represents de-differentiation, and the "flip-flop" phenomenon serves as a sign of worse prognosis (10).

The results from our study indicate that the TNM stage of the disease may lead to specific follow-up for patients who could benefit from the PET/CT. ^{18}F-FDG positivity is significantly higher in patients with stage-II and -IV, consistent with the aggressive potentiality of the disease. The other prognostic factors like age, gender, type, or size of the tumor did not have a significant relation to PET positivity.

The group of ^{18}F-FDG-positive lesions in PET/CT scan had a significantly higher median of Tg levels than the ^{18}F-FDG negative group (101.3 ng/mL vs. 19.4 ng/mL; p=0.001). The cut-off Tg value in the present study was higher than that indicated by the guidelines and that of other studies (7,14,15,16). We believe it resulted from the low number of patients participating in our study, and/or the high mean of Tg levels (240.36±372.75; median: 59.65). Some of the patients that presented to our department were not routinely followed up, so they had already developed metastatic pathologies before they underwent the PET/CT scan.

SUV_{max} values significantly did not correlate with the other clinical findings or characteristics of the patients. Nevertheless, SUV_{max} values provide important information about the de-differentiation degree. Other groups have reported a correlation between high SUV_{max} and worse prognosis in PTC patients (17). As a result of de-differentiation of tumor cells, the glucose transporter-1 increases and affects the increase in ^{18}F-FDG uptake (18). Robbins et al. (19) demonstrated that SUV_{max} affected positively both the prognosis and the survival of the patients. ^{18}F-FDG-positive lesions indicate higher aggressiveness correlated with the value of the SUV_{max} (20). Furthermore, another study has demonstrated that a SUV_{max} >10 is related to shorter locoregional disease-free survival (21). The two patients with aggressive variant (tall cell) PTC in our study had ^{18}F-FDG-positive metastatic lesions. They had Tg levels of 1.522 ng/mL, 35 ng/mL, and SUV_{max} values of 12.9, 5.8, respectively. Both patients had local recurrence while one of them, with the highest Tg and SUV_{max} levels, additionally presented with lung metastases. These findings are compatible with the literature, but further correlations are necessary with more patients in aggressive differentiated thyroid cancers. More observational studies for detecting or staging thyroid cancers with ^{18}F-FDG PET/CT in the initial phases of the disease also provide valuable information for the treatment decision (22). Furthermore, the challenge of treatment for the patients with simultaneous iodine positivity and ^{18}F-FDG positivity should be taken into consideration (23). We also had a patient with both iodine-positive and negative metastases. Intense ^{18}F-FDG uptake was detected in de-differentiated metastatic lesions, as seen in PET/CT images (Figure 3). Therapy management is a challenge in such cases and the treatment decision, including tyrosine kinase as an option, should be made in accordance with oncology.

Study Limitations

This study had some limitations. ^{18}F-FDG negative patients could not be discussed in detail, due to the lack of follow-up data. Some of the initial clinical data were not available because of the referrals from different hospitals for the radioiodine treatment. Hence, the correlations with other conventional imaging techniques were not applicable.

Conclusion

^{18}F-FDG PET/CT may be useful in detecting recurrence for differentiated thyroid cancer patients. Tg levels and the initial stage of the disease are significantly correlated with FDG positivity. It may also provide information about the de-differentiation process which supports the treatment plan.

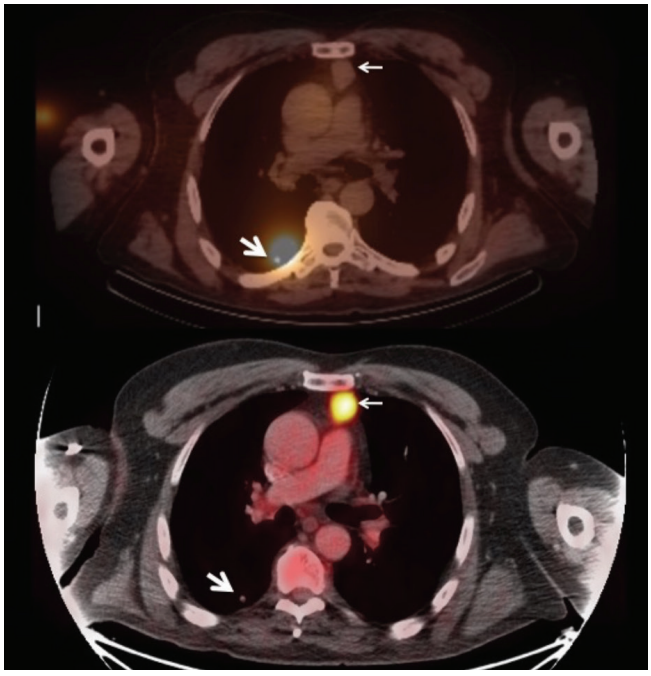

Figure 3. A 64-year-old woman with mixed type of differentiated thyroid cancer (classic and follicular type) had increased Tg levels (167 ng/mL) after radioiodine treatment. The upper row demonstrates SPECT/CT image of positive I-131 for metastatic lung lesion in the posterior part of the upper right lobe, whereas no uptake in the lymph node of the anterior mediastinum. The lower row shows intense ^{18}F-FDG uptake in the same mediastinal lymph node in PET/CT images, later histopathologically proven as metastases

Tg: Thyroglobulin, SPECT: Single photon emission computed tomography, CT: Computed tomography, I-131: Iodine-131, PET: Positron emission tomography, ^{18}F-FDG: ^{18}Fluoride-fluorodeoxyglucose

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee approved (number: 3112, date: 02.02.2021).

Informed Consent: All the patients signed informed consent forms.

Peer-review: Externally and internally peer-reviewed.

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