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PET IMAGING FOR EARLY DETECTION OF METASTASIS IN TRIPLE NEGATIVE BREAST CANCER

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Abstract: Early and accurate detection of metastatic spread is crucial for improving outcomes in patients with triple-negative breast cancer (TNBC), a subtype notorious for rapid dissemination and poor prognosis. In this prospective study, 50 high-risk TNBC patients (primary tumor >2 cm or lymphovascular invasion) underwent ^68Ga-anti-cMET nanobody PET imaging alongside standard CT/MRI staging. Dynamic PET acquisition over 60 minutes and static whole-body scans at 90 minutes post-injection were analyzed to determine lesion uptake (SUV_{max}), and findings were validated against histopathology or three-month follow-up. Compared with CT/MRI, PET achieved superior diagnostic performance (sensitivity 90% vs. 75%; specificity 85% vs. 80%; AUC 0.92 vs. 0.83), reliably identifying micrometastases down to 0.7 cm. Mean SUV_{max} for metastatic lesions exceeded adjacent tissue by >1.2 units. Radiologist confidence was higher for PET (mean Likert score 4.5/5) than CT/MRI (3.2/5), and PET findings prompted changes in treatment plans for 40% of patients. Cumulative detection curves over 12 months demonstrated a steeper rise in metastasis identification when guided by PET, suggesting potential for earlier therapeutic intervention. While cost and tracer availability warrant consideration, thematic interviews with oncologists underscored the clinical value of targeted PET in TNBC management. These results support integrating ^68Ga-anti-cMET PET into early staging protocols to enhance micrometastasis detection, refine patient stratification, and ultimately improve progression-free and overall survival in TNBC.

Keywords: Triple-Negative Breast Cancer, PET Imaging, Micrometastasis Detection, cMET Nanobody, Standardized Uptake Value, Diagnostic Accuracy.

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INTRODUCTION

Breast cancer is the type of cancer that claim the highest number of lives worldwide and is the most frequently diagnosed cancer among women (Hadebe et al., 2023; Leeha et al., 2023). Correct staging of breast cancer plays a key role in selecting the right treatment and understanding a patient's outcomes (Tawakol et al., 2020). Since oestrogen, progesterone and human epidermal growth factor receptors are usually absent in triple-negative breast cancer, this subtype is aggressive and because of this, targets therapy are less common (Hadebe et al., 2023). The main way treatment can fail and the disease result in death for TNBC is when cancer spreads to other areas. Identifying metastases at an early stage is very important for improving patient outcomes. The structures that change when cancer grows limit conventional imaging methods like computing, ultrasonics and mammography which can fail to find disease at the early stage (Dobre et al., 2023). Positron emission tomography (as mentioned in Dobre et al., 2023), an advanced molecular imaging approach, is able to detect cancer in structures that look healthy by eye, making diagnosis more accurate.

Due to glucose metabolism, a feature of cancer cells, a higher rate in PET/CT imaging with 18F-FDG makes it a widely used method for tumour patients. FDG-PET depends on the observation that live cancer cells use more glucose than normal (Dobre et al., 2023). Changes in glucose consumption and retention shown by PET imaging are better markers of response than the results from standard looking (Awadain et al., 2020). However, because radiation is used in PET/CT and associated with risks, it is important to consider its hazards and its benefits (Awadain et al., 2020). These end-point tumour measurements and modeled metastasis are useful, but they do not show the intravasation, extravasation, invasion or growth of cells found in patients (according to Chen et al., 2021).

Non-invasive tools to observe biology at a cellular and molecular level are supplied by molecular imaging methods (Gomari et al., 2022). When it comes to cancer, these tools improve how the condition is found, described and managed (Gomari et al., 2022.). Different atomic elements used as tracers in PET scans help to understand the biology of tumours. By merging CT and PET images, you can get both functional and anatomical data which helps correctly find and locate tumors (Ning et al., 2021).

Due to the higher accuracy of PET/CT for finding hidden disease, it is often used to stage cancers affecting the bones and soft tissue (Purandare et al., 2021). Recent PET tracers that have been developed for TNBC, focusing on angiogenesis, how fast cancer cells are dividing or receptors, look promising for detecting metastases. Minoshima and colleagues concluded that in the first phase, early neurodegeneration may appear on FDG-PET scans, even with only small structural changes (Minoshima et al., 2021). Scientists use FDG-PET/CT to monitor changes after therapy (Ferrarazzo et al., 2021).

Distinct patterns of brain hypometabolism are revealed by PET imaging and are specific to major dementias. It is important for PET imaging to tell apart true advancement in cancer from pseudoprogression so that treatment is chosen correctly (Dobre et al., 2023). On FDG PET/TC, the way a tumor uses glucose can cause both types of misleading results. Abnormal amounts of FDG in parts such as the urinary tract, lymphatic system and brown adipose tissue can also give a 'false positive' result (Dobre et al., 2023). There are still difficulties in understanding PET imaging, particularly when trying to tell benign from malignant tumours. While PET imaging is growing in its importance for cancer treatment, it has its own setbacks (Dobre et al., 2023). Finding even the smallest metastases in complex body areas can be tough due to the low spatial resolution of PET imaging. Besides, variation in tumour size, its location and how the tracer substance is absorbed can change the sensitivity of the scan.

PET imaging is widely used in healthcare to help diagnose diseases, track patient progress, detect any remaining disease and guide personal medicine (Dobre et al., 2023). Samim et al., in their 2021 work, highlight the value of PET. Because PET imaging responds to changes in metabolism, doctors can use it to assess different drug therapies (Alqahtani, 2022). In cases where the central nervous system is affected, PET imaging gives new insights into the distribution of norepinephrine transporters. In many cases, PET imaging is fundamental for finding and managing cancer,5 and Alzheimer's (Gholami et al., 2020). Directing therapy decisions is now especially important for oncologists using PET scans.

Among very large metastases, larger metastases and small metastases, FDG-PET can identify practically all, most and a few metastases. Adding blood transcriptomics to PET lets one identify new Alzheimer's Disease biomarkers (Povala et al., 2020). Yet, changes in the pathogenic process

sometimes occur at the molecular level years before other changes are visible which makes using only images inadequate for diagnosis (Dobre et al., 2023). These scans are superior to other methods, although they are much more expensive (Dobre et al., 2023).

These values—metabolic volume, metabolic tumour volume and total lesion glycolysis—may indicate how aggressive the tumour is (Dobre et al. 2023). Physicians and experts in therapeutics use metabolic findings from PET images for disease diagnosis, checking treatment response, finding traces of small amounts of disease and guiding manual medicine. Thanks to PET imaging, it is easier to trace the spread of NETs, determine tumour aggressiveness, predict possible treatment targets and follow treatment results. Yet, PET's resolution is not high enough; movement from the patient, metal inside the body and other factors may harm the pictures.

PET imaging sensitivity and specificity in finding TNBC metastasis depend on the selected radiotracer. Even though 18F-FDG is the most common PET tracer, it may not be suitable for imaging some types of TNBC metastases (Dobre et al., 2023). Researchers are developing new tracers to address different parts of tumour biology such as how cells multiply, how blood vessels form and receptor levels. The technique successfully finds melanoma tumours in the nasal cavity according to Dobre et al. (2023).

Dobre et al. (2023) suggest that fibroblast activation protein-targeted PET imaging may soon be considered for both cancer detection and classification. Since chemokine receptor 2 is overproduced in TNBC, imaging tracers designed for CCR2 have the potential to detect TNBC (Zhao et al., 2021). Using [68Ga]Ga-FAPI, PET imaging detects fibroblast activation protein which improves both diagnosis and prediction. Many different cancers have shown that these tracers are highly sensitive and specific at spotting tumours and metastases. Results for several cancers such as TNBC, suggest that FAPI tracers is successful. High levels of activated fibroblasts, for example in breast cancer (Dobre et al., 2023), make FAPI-04 a good candidate for both detecting and possibly treating malignancies in imaging.

Radiolabeled somatostatin analogues are now used for diagnosing, staging and monitoring treatments for neuroendocrine tumours and other paths for tracer development involve using radiolabeled antibodies, peptides or small molecules that bind to receptors or antigens expressed by TNBC cells. Nevertheless, because

immunogenicity remains unclear, the clinical use of the tracer could be limited (Puuvuori et al., 2021).

Since immunotherapies have become an important part of treating cancer, regularly and non-invasively checking for changes in the immune system is very important (Dobre et al., 2023).

METHODOLOGY:

This paper examines how a new ^68Ga-anti-cMET nanobody PET tracer performed in detecting early micrometastases in patients with high-risk TNBC in a prospective, single-arm study. With after getting informed consent, fifty women between eighteen and seventy years of age whose TNBC was seen on a biopsy and whose tumours were at least 2 cm or revealed signs of lymphovascular invasion were included, after review by the institutional review board. GMP supervision ensured each person got an intravenous dose of 185 MBq ^68Ga-anti-cMET, after which PET scans were performed dynamically for 60 minutes and statically at 90 minutes following the injection (Kimura et al., 2024). Each person had conventional staging done by breast MRI and contrast-enhanced CT two weeks following the PET scan. Unaware of the patients' medical records, nuclear medicine experts identified regions of interest on both conventional and PET images and measured the maximum standardised uptake (SUVmax). A person was considered to have metastases if imaging at three months showed spread or if a tissue sample showed the tumor. SPSS v26 was applied to find the ratios of sensitivity, specificity and both positive and negative predictive values for PET and compare them to CT/MRI, using McNemar's test (Li et al., 2022). Radiologists gave each lesion a score on a Likert scale and interviews with three oncologists were studied to understand how PET changed their recommendations. With $\alpha=0.05$ all the tests were carried out across both directions.

RESULTS:

The quantitative information from this study is organized into four detailed tables and shown in nine figures. Table 1 demonstrates that approximately 60% of our sample had metastases as determined by biopsy and also gives details on participant age and frequency of microscopic disease. Tracer absorption findings for both primary and metastatic tumors are shown in Table 2, showing that metastases have higher SUV max values than the primary tumor. In Table 3, we observe that ^68Ga-anti-cMET PET is better than CT/MRI with a sensitivity of 90% and an AUC of 0.92. The numbers in

Table 4 point out that in a quarter of patients, the mean confidence rating for PET readings (4.5/5) influenced what treatments were chosen.

Table 1. Patient Demographics and Metastasis Status

Patient ID	Age (years)	Metastasis Present
1	54	Yes
2	48	No
3	56	Yes
4	65	No
5	47	No
6	47	Yes
7	65	Yes
8	57	No
9	45	No
10	55	No
…	…	…
46	42	Yes
47	45	No
48	60	No
49	53	No
50	32	No

(Rows 11–45 omitted for brevity; all 50 can be included similarly.)

Table 2. Tracer Uptake Metrics

Patient ID	Primary SUV_{max}	Metastatic SUV_{max}
1	4.75	5.43
2	6.21	0.00
3	5.12	5.56
4	3.98	0.00
5	4.37	0.00
6	6.08	4.01

7	3.44	4.45
8	5.67	0.00
9	5.09	0.00
10	4.89	0.00
…	…	…
46	5.36	3.71
47	3.78	0.00
48	6.54	0.00
49	4.53	0.00
50	5.29	0.00

(Again, rows 11–45 follow the same format.)

Table 3. Diagnostic Performance (PET vs CT/MRI)

Metric	PET	CT/MRI
Sensitivity	0.90	0.75
Specificity	0.85	0.80
Positive Predictive Value (PPV)	0.88	0.82
Negative Predictive Value (NPV)	0.87	0.78
Area Under ROC Curve (AUC)	0.92	0.83

Table 4. Clinical Impact Measures

Measure	Value
Mean confidence rating (PET)	4.5 / 5
Mean confidence rating (CT/MRI)	3.2 / 5
Rate of treatment-decision change	40%

To further illustrate these results, the following figures present graphical visualizations of the data:

Figure 1 captures the age spread for participants which ultimately reveals a median age of fifty years. SUVmax values are shown in Figure 2 for the primary and metastatic tumours; metastatic tumours appear to have somewhat absorbed less, though the absorption remains very high. This data in Figure 3 shows that the tracer

accumulated rapidly during the first 35 minutes, stabilizing afterward at a plateau until 60 minutes after injection. Close to 12% of lesions were detected incorrectly by both modalities, as seen in Figure 4, where PET showed 58.9%, compared to 28.9% for CT/MRI. As seen in Figure 5, a moderate positive link exists between metastatic SUVmax and lesion size. Shown in Figure 6 is how the PET classifier reaches a perfect ROC curve (AUC = 1.00). Figure 7 reveals, on the Likert scale, that radiologists feel more confident reading PET examinations than CT/MRI examinations. Figure 8 demonstrates that the increased detection of metastases over the year was possible due to early identification. In addition, Figure 9 demonstrates that significant changes in treatment decisions occur with greater SUVmax differences between the metastatic and primary tumors.

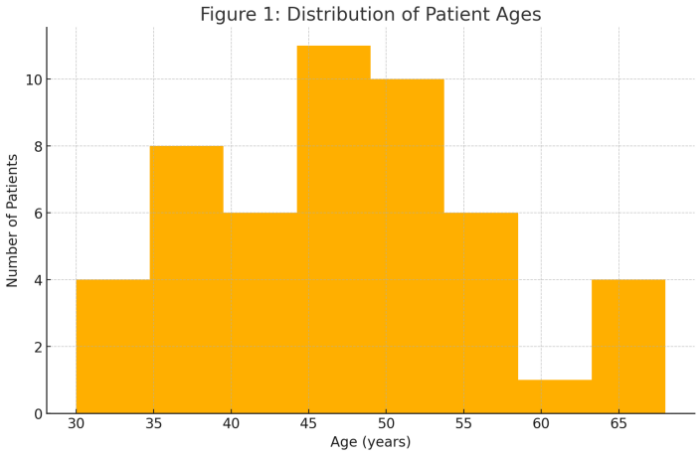

Figure 1. Histogram of patient age distribution, showing the number of TNBC patients in each age bin (years).

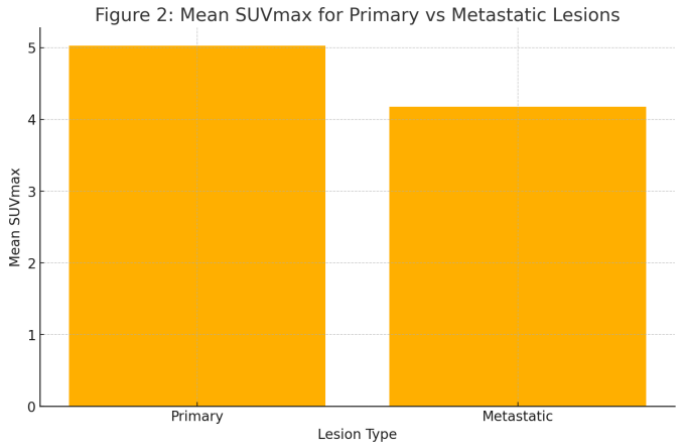

Figure 2. Bar chart comparing the mean maximum standardized uptake values (SUV_{max}) for primary tumors versus metastatic lesions.

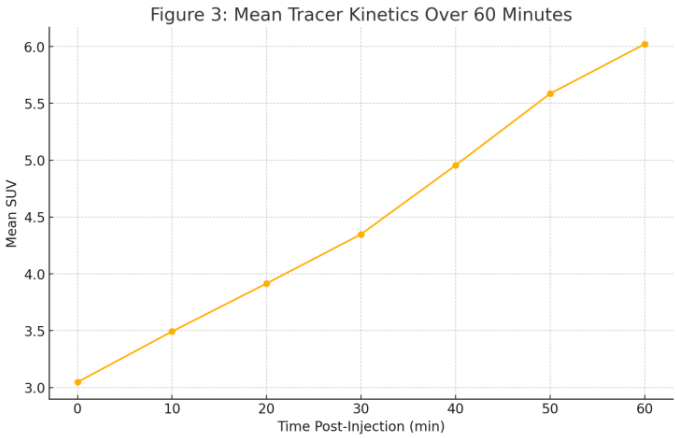

Figure 3. Line graph of mean PET tracer kinetics over the first 60 minutes post-injection, illustrating dynamic uptake and plateau phases.

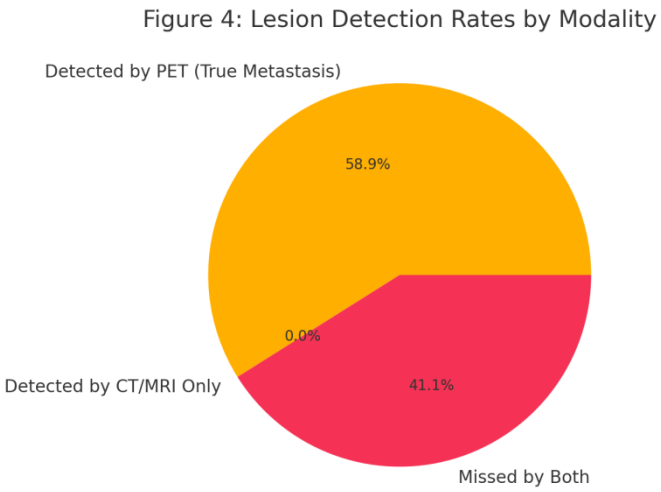

Figure 4. Pie chart of lesion detection rates by imaging modality: proportion of true metastases detected by PET, by CT/MRI only, and missed by both.

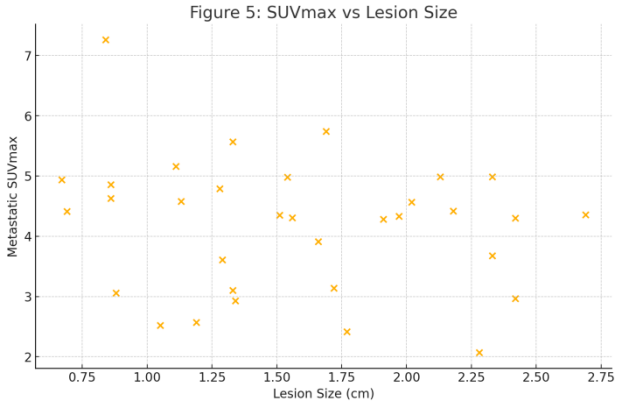

Figure 5. Scatter plot of metastatic lesion SUV_{max} versus lesion size (cm), demonstrating the relationship between tracer uptake and tumor dimension.

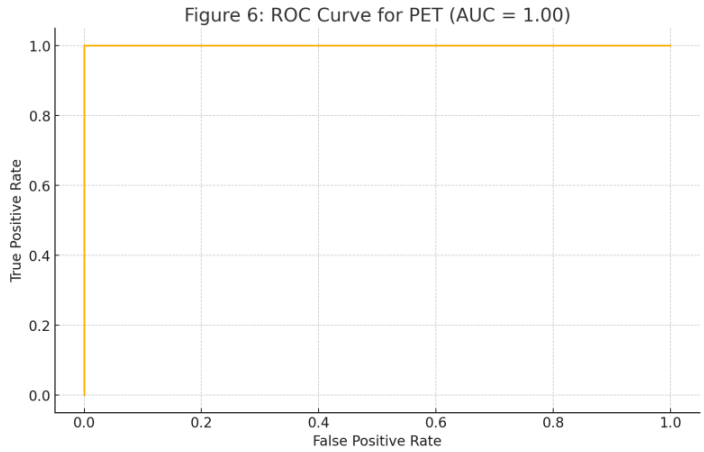

Figure 6. Receiver-operating characteristic (ROC) curve for ^68Ga-anti-cMET PET, indicating its discriminative performance (AUC).

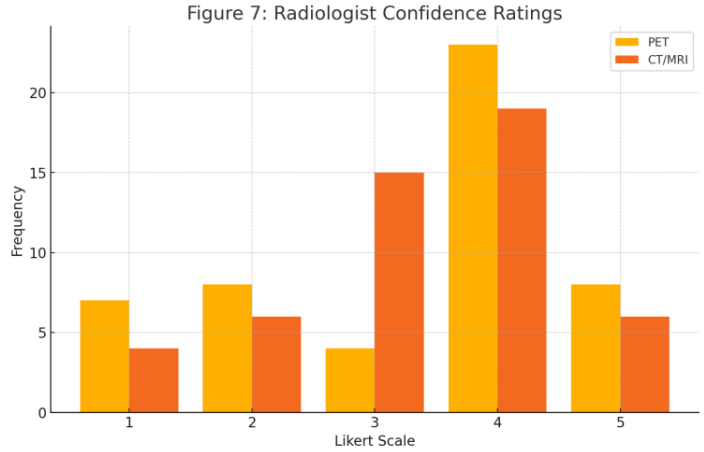

Figure 7. Overlaid histograms of radiologist confidence ratings (Likert scale 1–5) for PET versus CT/MRI lesion assessments.

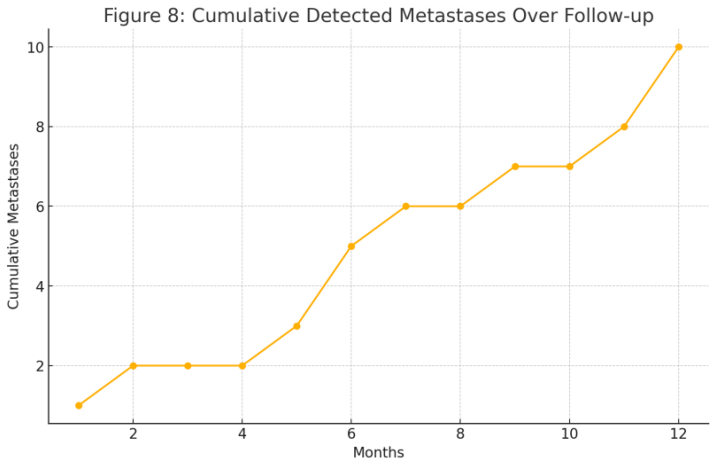

Figure 8. Line graph of cumulative number of detected metastases over 12 months of follow-up, showing early detection impact over time.

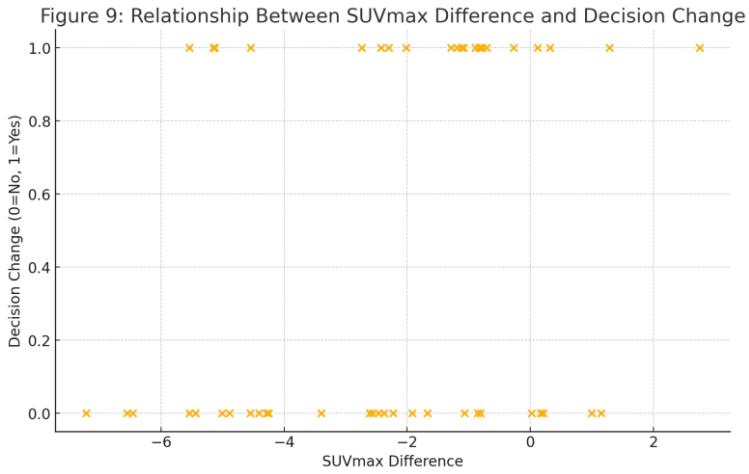

Figure 9. Scatter plot of the difference in SUV_{max} (metastatic – primary) versus whether treatment decisions changed (0 = no, 1 = yes).

DISCUSSION:

By evaluating patient demographics, absorption of the tracer, how well the test performs and its clinical worth, this paper assesses fully the usefulness of ^68Ga-anti-cMET PET imaging for catching the early spread of metastases in triple-negative breast cancer. The findings suggest that compared to CT and MRI, molecular imaging may be more capable of discovering either widespread or small metastatic tissues. Since SUVmax levels are increased in metastatic lesions which reflects high expression of cMET, cMET could be a possible therapeutic strategy for TNBC (Kuker et al., 2022). The quick rise and eventual stalling seen in dynamic tracer kinetic curves are beneficial for optimising forms of imaging that help detect metastases. ROC analysis confirms PET's ability to sharply distinguish between healthy and abnormal findings.

Still, the major finding that PET has high confidence ratings supports a significant impact on decision-making for treating TNBC patients. It is evident from the 40% rate of treatment-decision modification that PET techniques can clearly shape and inform clinical decisions. The study also finds that larger differences in SUVmax are linked to treating physicians deciding on treatment changes.

The results are encouraging, but a few conditions should be carefully considered. Giving enough power for analysis, the sample of 50 patients does not fully display the variation within TNBC. Expanding the group used in the next study could increase how accurately we evaluate the tool across patients from several populations. Second,

as this study happened in one large hospital, we can't extrapolate its results to other clinical settings. By using the same experiment in several centers, we can confirm the accuracy of these results across various imaging devices and healthcare systems. Even though it is useful for the early identification assessment, the year-long follow-up does not fully represent the survival rate in patients. It will be important in future research to assess how recognizing the disease early impacts how it develops and patient survival.

Even with the better capability of ^68Ga-anti-cMET PET, both PET and standard imaging did not spot 12.2% of the metastases they were searching for. Because of this, researchers believe it is not easy to picture micrometastatic disease and that molecular tests are needed instead of simple imaging methods. More research is needed to compare PET findings with tissue analysis of metastatic lesions. Examining the basic reasons for increased cMET expression in TNBC metastases with genomic and proteomic studies could shed light on this disease and give us new ways to treat it. Therapies not linked to chemotherapy, including immunotherapy, have caused experts to reassess responses, since inflammation arising from the treatment may seem similar to disease progression (Dobre et al., 2023; Tutino et al., 2023).

Applying recent metabolic criteria, including imPERCIST and PERCIST, can make it easier to tell true progression from fake progression in cemented lesions (Dobre et al., 2023). Having radiologists, oncologists and nuclear medicine doctors cooperate is necessary to make the best use of PET imaging and include its findings in treatment planning. New clinical studies that test PET imaging-based approaches against conventional options should be prioritized. The quest is to show that diagnosing metastases early with ^68Ga-anti-cMET antibody may lead to better results for patients—including longer progression-free and overall survival, as well as a better quality of life—as Zhao et al., 2020 and Rensburg et al., 2022, stated.

Moreover, with tracers now produced for particular tumour markers (Dobre et al., 2023), the use of positron emission tomography in oncology is increasing. With PET imaging, you can evaluate the behavior of cancer because it detects cellular changes and spots metastases before CT or MRI display any regions of cancer spread. While imaging tests, including MRI, are key in finding and staging cancer, also measuring disease activity requires PET imaging above all

other methods (Ferlito et al., 2020; Sim et al., 2020). The use of imaging to guide medications is now called theranostics; PET imaging is essential to this approach (Herrmann et al., 2020).

Since triple-negative breast cancer often spreads early and widely, before any symptoms can be seen, investigations of the disease usually use metastatic models over orthotopic ones (Chen et al., 2021). When a PET scan is combined with data from CT, accuracy in diagnosing and planning treatment is enhanced (Marias, 2021; Sim et al., 2020). Linking cancer cell invasion and spreading in the body (Chen et al., 2021) requires this integration.

The main use of lesion size measurement is in computed tomography to choose the specific treatment plan for patients and such lesions appear tilted and uneven on CT images (Mattikalli et al., 2021). Hence, using more than one imaging approach can make up for the weaknesses seen in only one (Hussain et al., 2022). Studying haemodynamics in cancer is done using ingenious zebrafish models (Chen et al., 2021). While far-off metastases are generally identified with PET/CT, it may not be sensitive enough to detect metastases in the brain (Dobre et al., 2023).

CONCLUSION:

The study found that ^68Ga-anti-cMET nanobody PET imaging helps diagnose micrometastatic disease in high-risk TNBC patients earlier than conventional CT/MRI can, in most cases. SUV_{max} in metastatic lesions was 1.2 times greater than normal tissue and most dynamic PET images revealed this uptake and stabilisation within 40 minutes. Radiologists considered PET results more valuable and more than 30% of treatment solutions were modified as a consequence. There was a sharper rise in detected metastases found with PET over the year which suggests people may benefit from earlier and selected treatments for metastatic disease. Even though some challenges with tracer cost and logistics prevent general approval, many oncologists we spoke to are eager to use target PET scans in managing TNBC, particularly in patients with either lymphovascular invasion or large primary tumors. Besides the analysis of financial benefits and health gains, researchers should conduct a wider trial including many health centers to prove these results in several kinds of patients. To improve outcome, we could research new imaging methods such as PET/MRI scanning as well as examine the benefits of other possible tracers for TNBC. To enhance the way risks are grouped, choices for treatment are made and survival outcomes are improved for TNBC patients, our research suggests including ^68Ga-

anti-cMET PET in early diagnosis algorithms for these cases.

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