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Case Report: Non-invasive [^{89}Zr]Zr-DFO-trastuzumab positron emission tomography in the multimodal characterisation of platinum-resistant high-grade serous ovarian cancer

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We report a case that combines several aspects of molecular diagnostics and clinical follow-up with innovative imaging of [^{89}Zr]Zr-DFO-trastuzumab positron emission computed tomography (PET/CT) to depict human epidermal growth factor receptor 2 (HER2)-targeted tracer uptake in several metastatic sites in advanced platinum-resistant high-grade serous ovarian cancer (HGSOC). A 74-year-old woman underwent this procedure, and PET/CT images were interpreted alongside conventional biomarkers [CA125 and immunohistochemistry (IHC)] and contrast-enhanced computed tomography (CE-CT). PET imaging revealed intense tracer uptake in the primary ovarian tumour site (SUVratio 13.8), with corresponding HER2 + expression (3+) observed on the IHC of the primary tumour. Moreover, moderate uptake was observed in abdominal wall metastases (SUVratio 3.6) and near-background uptake in hepatic lesions (SUVratio 1.6), consistent with image-suggestive spatial heterogeneity in HER2-targeted tracer uptake. CA125 measurements corroborated early biochemical response, with values declining from 676 to 254 U/mL after six weeks of trastuzumab deruxtecan (T-DXd) treatment as third-line therapy. Follow-up CE-CT showed qualitative regression of [^{89}Zr]Zr-DFO-trastuzumab-avid lesions, despite non-measurable disease by RECIST and a subsequent CE-CT imaging after 20 weeks demonstrated a mixed response pattern, without a clear relationship to pre-T-DXd [^{89}Zr]Zr-DFO-

trastuzumab uptake. This case study illustrates how integrating non-invasive [^{89}Zr]Zr-DFO-trastuzumab PET molecular imaging with conventional radiology, IHC, and biochemical markers within the clinical pathway may support individualised therapeutic decision-making.

KEYWORDS

[^{89}Zr]Zr-DFO-trastuzumab, case report, HER2 overexpression, high-grade serous ovarian cancer, multimodality

1 Introduction

Ovarian cancer is the seventh most common cancer among women and the eighth leading cause of cancer death worldwide, according to GLOBOCAN 2020 data (1). The five-year survival rate for ovarian cancer in Germany currently is at approximately 44%, but if detected early at stage I, this rate increases markedly to around 90%, underscoring the critical importance of early detection and improved therapeutic strategies (2).

Amongst all ovarian cancer types, high-grade serous (HGSOC) is the most prevalent histologic type and is typically diagnosed at an advanced stage due to vague, non-specific symptoms and lack of effective screening strategies, resulting in poor survival rates and frequent relapse (2–4). Traditional management employs serum biomarker cancer antigen 125 (CA125), the International Federation of Gynaecology and Obstetrics staging system (FIGO), tumour grade, and imaging modalities, including pelvic ultrasound, magnetic resonance imaging and Computed Tomography (CT) for disease evaluation (5–9). Moreover, molecular profiling has become an essential element in the personalised management of HGSOC. Recent advances using single-cell RNA sequencing and spatial transcriptomics revealed that HGSOC exhibits profound intra and intertumoural heterogeneity, with diverse gene expression patterns, tumour clones, and microenvironmental components varying even within single tumours. This heterogeneity underpins the frequent development of multidrug resistance and variable therapeutic responses, highlighting the necessity for comprehensive diagnostic approaches that can accurately characterise tumour biology and support individualised treatment planning (5, 7, 10, 11).

Among the promising molecular targets, folate receptor alpha (FRα) and human epidermal growth factor receptor 2 (HER2) have emerged as attractive candidates for the development of targeted therapies in HGSOC. High FRα expression has been identified in approximately 44% of high-grade serous ovarian carcinomas, whereas HER2 overexpression has been reported in a subset of ovarian tumours, with prevalence rates ranging from 6.6% to 39.5% (12). Trastuzumab deruxtecan (T-DXd), a monoclonal antibody-drug-conjugate targeting HER2, is a cornerstone of treatment in breast cancer (13–16) and has shown promise in ovarian cancer subsets, with an objective response rate of 45% in the DESTINY-PanTumor02 Phase II Trial for solid tumours with HER2 overexpression (17). An ongoing clinical trial, DESTINY-Ovarian01, is assessing T-DXd combined with Bevacizumab vs. Bevacizumab alone as first-line maintenance therapy in HER2-expressing ovarian cancer, including patients with a histologically confirmed diagnosis of epithelial high-grade ovarian cancer (18). Hence, accurate HER2 assessment is critical, as it can determine eligibility for HER2-targeted therapies.

Currently, HER2 measurement relies primarily on immunohistochemistry (IHC) and fluorescence *in situ* hybridisation (FISH) performed on biopsy specimens. However, these methods sample only limited tumour regions and may not account for spatial variability in HER2 expression across metastatic sites. This limitation can lead to suboptimal therapy selection (10, 19). Advances in the field of nuclear medicine have introduced immuno-Positron Emission Tomography (PET) imaging with radiolabelled antibodies such as [^{89}Zr]Zr-trastuzumab, offering a non-invasive, whole-body, semi-quantitative assessment of HER2 in breast and gastro-oesophageal cancers (20–23). For example, the ZEPHIR trial combined PET molecular imaging [[^{89}Zr]Zr-trastuzumab for HER2 expression assessment, [^{18}F]fluorodeoxyglucose (FDG) for metabolism] with transcriptomic profiling in advanced HER2-positive breast cancer patients receiving trastuzumab emtansine (T-DM1). This study revealed that lesions with low [^{89}Zr]Zr-trastuzumab uptake were enriched for genes involved in extracellular matrix organisation and glycosylphosphatidylinositol synthesis, and these lesions were less likely to show metabolic responses to T-DM1, whereas immune-related processes were associated with high [^{89}Zr]Zr-trastuzumab uptake and metabolic response (22). In a pilot study of patients with oesophagogastric cancer, [^{89}Zr]Zr-trastuzumab PET was evaluated alongside [18F]FDG PET and CT. Although [^{89}Zr]Zr-trastuzumab PET detected fewer lesions overall than CT or [^{18}F]FDG PET, it provided complementary HER2-targeted lesion-level information, including detection of a right cerebellar metastasis (SUV 2.6) that was not visualised by [^{18}F]FDG PET and was confirmed by brain MRI (20). Beyond breast and oesophagogastric cancer, [^{89}Zr]Zr-trastuzumab have been explored preclinically in ovarian cancer and clinically in patients with gastric cancer (24–26).

Collectively, this case report provides an early clinical example of how [^{89}Zr]Zr-DFO-trastuzumab PET imaging can be integrated with radiological assessment, immunohistochemistry and biochemical markers within the platinum-resistant HGSOC pathway to support multimodal, individualised clinical assessment.

2 Case description

2.1 Patient history

A 74-year-old woman presented with advanced-stage HGSOC (FIGO IIIC) with HER2 3 + overexpression by IHC. First-line treatment was primary systemic treatment with 6 cycles of carboplatin and paclitaxel chemotherapy from 09/2024 to 12/2024. Severe pre-existing hypertension precluded Bevacizumab therapy, and due to extensive disease burden, debulking surgery

was not performed. The patient had no germline BRCA mutation, and no FRα over-expression could be found. Disease progression developed immediately after first-line therapy. Due to the platinum-resistant situation, PEG-liposomal doxorubicin was administered from 02/2025 to 05/2025 for 3 cycles. Under this second-line treatment, the patient had transfusion-requiring vaginal bleeding caused by the pelvic mass. Radiation therapy of the vaginal stump was done. Rising CA-125 levels and clinical deterioration prompted reassessment of therapeutic options. Due to HER2 overexpression (with gastric score), [^{89}Zr]Zr-DFO-trastuzumab PET/CT was undertaken (March 2025). An activity of 31.7 MBq was administered intravenously (containing 50 mg Ontruzant), and imaging was acquired at 72 h p.i. The patient underwent whole-body PET/CT on a Siemens Biograph Vision 600 PET/CT (Siemens Healthineers, Erlangen, Germany) system. HER2-targeted therapy was considered. T-DXd was administered to the patient once every three weeks at a dose of 5.4 mg/kg since the end of 05/2025. Three contrast-enhanced CT scans were performed - one before treatment initiation, and two after starting T-DXd therapy (at 8 and 20 weeks after treatment) to further evaluate the anatomical extent of disease and response to therapy.

A summary of the events is represented in Figure 1.

The patient gave informed consent to participate in the procedure, and the competent ethics committee approved the retrospective data analysis (BO-EK-438112024).

2.2 Therapy outcome

T-DXd therapy was well tolerated after 3 cycles, with no grade $\geq$ 3 adverse events or interstitial lung disease. A sharp decline in CA-125 from 676.0 to 254.0 U/mL was observed within six weeks. Therapy is still ongoing and currently in the 8th cycle. CA-125 remained stable just before the 8th cycle started (267.0 U/mL).

2.3 HER2 expression as determined by immunohistochemistry findings

The patient had HER2-positive primary malignancy (score of 3+) according to the Rüschoff et al. score for gastric cancer (27). The tumour cells showed strong, partly complete, partly incomplete, membrane-bound immunoreactivity for the HER2neu protein in approximately 15% of cases, and moderate, partly complete, partly incomplete, in approximately 70% of cases, as represented in Figure 2. Figure 2A shows the histological features of the primary HGSOC tumour using H&E staining, illustrating the dense cellular infiltrates with marked nuclear pleomorphism and atypia, consistent with the aggressive nature of high-grade serous cancer. HER2 immunohistochemical staining demonstrated heterogeneous membrane expression in the tumour cells, with approximately 15% showing strong, complete or basolateral membrane staining (score 3+) and about

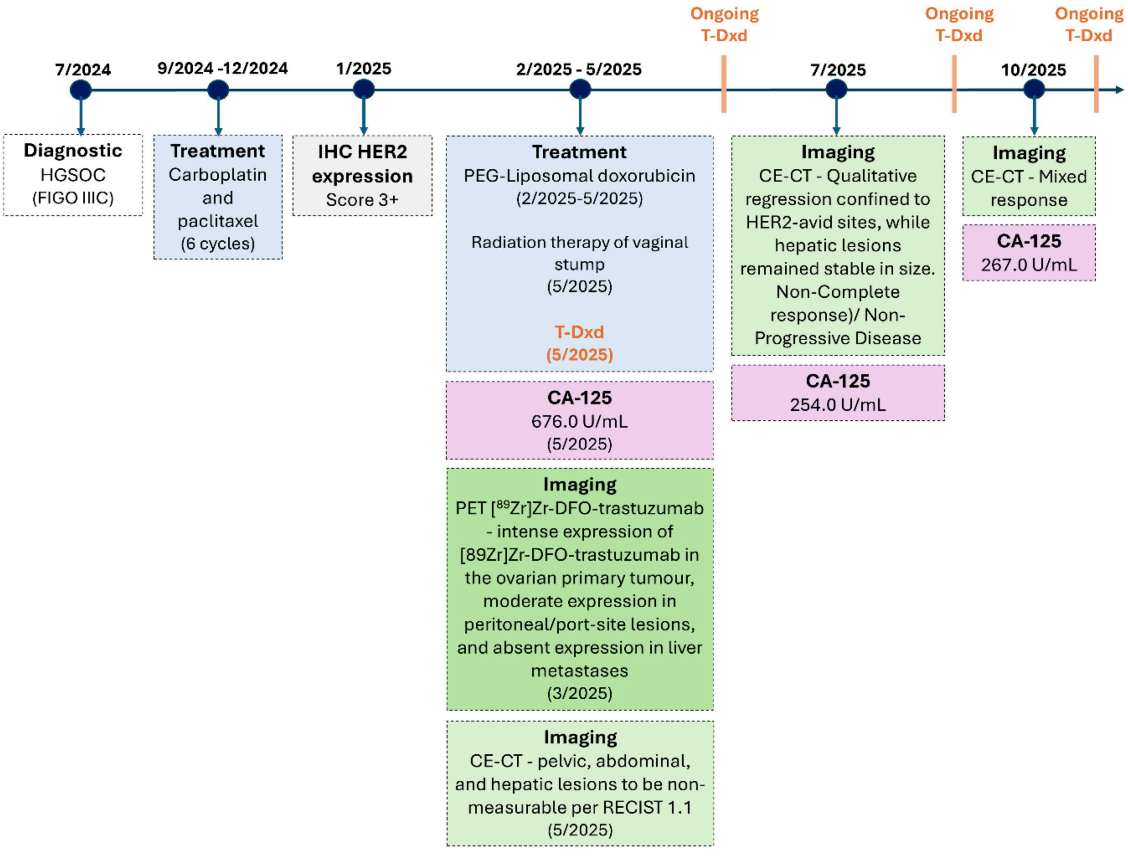


FIGURE 1
Treatment timeline of the patient. The timeline illustrates the chronology of events relevant to this case report between diagnostic and follow-up CE-CT at 20 weeks post T-Dxd initiation.

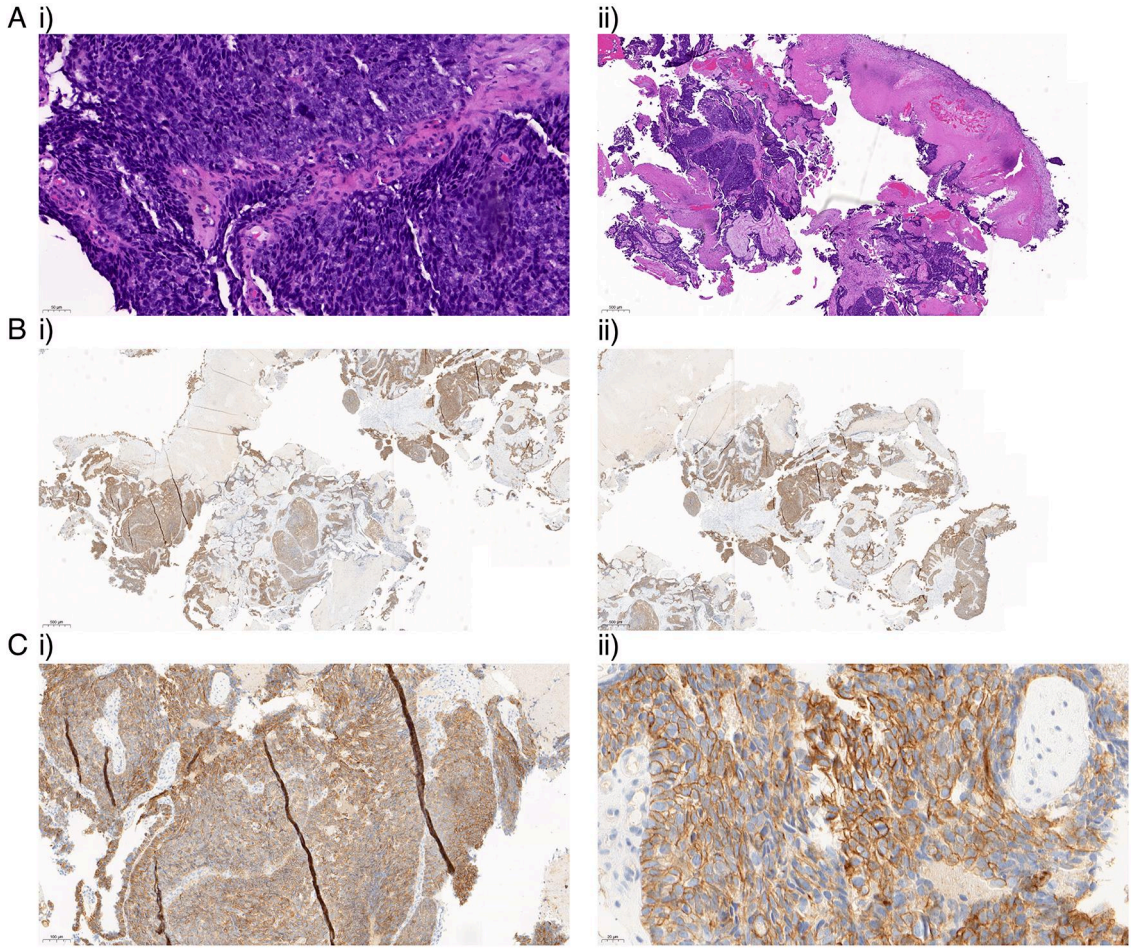


FIGURE 2
IHC of the superficial carcinoma infiltrates of the corpus uteri **(A)** i) Low magnification (2x) overview of superficial uterine infiltrates of HGSOC stained with H&E; ii) higher magnification (20×) highlighting cellular infiltrates with marked nuclear pleomorphism, H&E stain; **(B)** i) Low magnification (2×) overview of HER2 IHC staining in HGSOC (clone 4B5, ventana; ii) moderate to strong membrane HER2 staining at 2× magnification; **(C)** i) HER2 staining of HGSOC at 10 × magnification (4B5, ventana) ii) higher magnification (40x) showing moderate to strong membrane staining of HER2. Scale bar represents 500 µm in 2×, 50 µm in 20 × and 20 µm in 40 × magnification.

70% exhibiting moderate, incomplete or complete membrane staining (score 2+), as visualised in Figure 2B and C.

2.4 [^{89}Zr]Zr-DFO-trastuzumab PET findings

[^{89}Zr]Zr-DFO-trastuzumab PET (Figure 3) and fused PET/CT images (Figure 4, I) revealed accumulation of the radiotracer in sites of physiological distribution such as blood pool, liver, spleen, bone marrow, heart and kidneys. The images represented in Figure 4 also revealed intense tracer accumulation in the pelvic tumour [(Figure 4, row Ic) SUVratio 13.8], colocalising with the dominant ovarian lesion on previous imaging, which underwent biopsy and demonstrated an IHC score of 3+ (Figure 2). Port-site metastases (abdominal wall) (Figure 4, row Ib) also showed uptake (SUVratio 3.6) clearly above background, indicating a targetable profile despite lower intensity than the primary mass. By contrast, the dominant hepatic metastasis in segment VI (Figure 4, row Ia) exhibited a photopenic core with only minimal peripheral uptake (SUVratio 1.6), markedly below liver background (SUVratio 4.2). Additional subcapsular and perihepatic lesions were likewise non-avid.

Overall, findings indicated marked inter-lesional differences in [^{89}Zr]Zr-DFO-trastuzumab uptake, with intense tracer accumulation in the ovarian primary tumour, moderate uptake in peritoneal/port-site lesions and near-background uptake in hepatic lesions against high physiological liver background. Except for the primary tumour, none of the lesions were biopsied to assess HER2 expression; therefore, these findings should be interpreted as imaging-suggestive spatial heterogeneity in HER2-targeted tracer uptake rather than histologically confirmed metastatic HER2 expression heterogeneity. During injection and the following imaging period no side effect of [^{89}Zr]Zr-DFO-trastuzumab were evident or reported by the patient.

2.5 CE-CT findings

CE-CT at baseline (Figure 4, II–VI) showed pelvic, mesenteric, and hepatic lesions to be non-measurable per RECIST 1.1 owing

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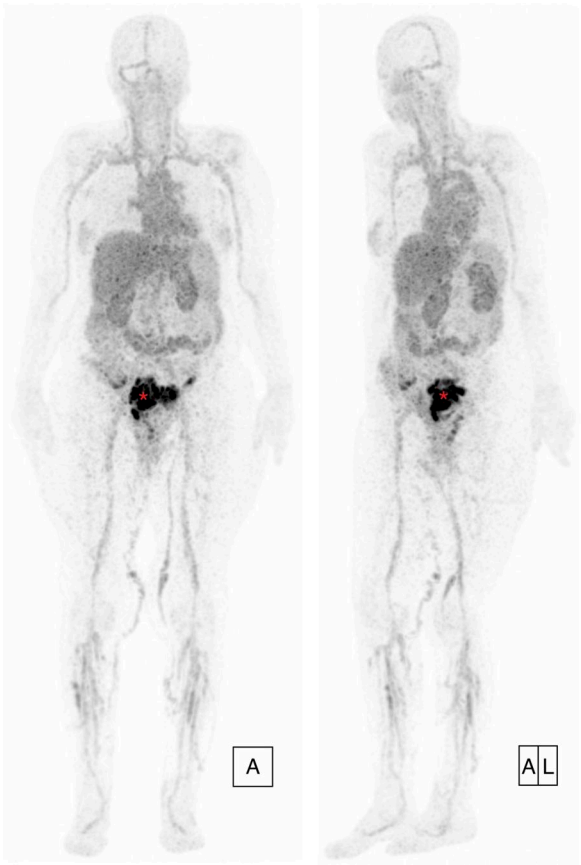


FIGURE 3
[^{89}Zr]Zr-DFO-trastuzumab immuno-PET maximum-intensity projections, anterior (A) and left anterior oblique (LAO, 45°), 72 h after i.v. administration of 31.7 MBq of [^{89}Zr]Zr-DFO-trastuzumab. The red asterisk marks the intensely tracer-avid pelvic/ovarian mass. No discrete hepatic uptake is visible on MIP. Subtle peritoneal implants are below MIP conspicuity.

to indistinct borders. At 8 weeks, follow-up CE-CT showed qualitative regression confined to [^{89}Zr]Zr-DFO-trastuzumab-avid sites. Because these lesions were non-measurable, the non-target response was classified as Non-Complete Response (Non-CR)/ Non-Progressive Disease (Non-PD), while hepatic lesions remained stable in size. Subsequent imaging after 20 weeks demonstrated a mixed response pattern (Figure 4, IV). The pelvic mass showed nodular enlargement consistent with progressive ovarian carcinoma. In contrast, hepatic lesions in segment VI and peritoneal/port-site metastases showed regression with reduced hepatic capsular involvement, although a mild increase in ascites was noted. Under RECIST 1.1 criteria, the unequivocal progression of pelvic disease led to classification as PD despite regression in other non-target sites.

2.6 Outcome

With stable CA-125 levels and imaging demonstrating overall disease control, continuation of therapy was recommended in agreement with multidisciplinary tumour board consensus.

3 Discussion

HGSOC remains one of the most challenging gynaecologic malignancies due to its aggressive nature, frequent late-stage diagnosis, and intra- and inter-tumour heterogeneity, which limits the effectiveness of standard therapies (6, 28, 29). This patient's clinical situation highlights several challenges inherent in managing advanced HGSOC, including the development of platinum resistance, a major contributor to poor prognosis. The absence of germline BRCA mutations and FRα over-expression further underscores the heterogeneous molecular landscape that complicates therapeutic decision-making. Nevertheless, the confirmed HER2 3 + overexpression by IHC identified a potential opportunity for targeted therapy, offering a precision medicine approach in a setting with limited standard treatment options.

In this report, we present a case of [^{89}Zr]Zr-DFO-trastuzumab immuno-PET imaging in HGSOC, which may provide complementary whole-body spatial information on HER2-targeted tracer uptake and thereby partly address the spatial limitations of conventional single-site IHC. The results of the PET imaging study revealed the presence of HER2 tracer uptake in the primary ovarian tumour, with concomitant HER2 + expression observed on the IHC analysis. Moderate uptake was observed in the abdominal wall metastasis, whereas hepatic lesions showed near-background tracer conspicuity. This finding should not be equated with absent HER2 expression, because physiological liver activity, antibody biodistribution and hepatic antibody catabolism can reduce lesion-to-background contrast and limit the detectability of liver metastases with [^{89}Zr]Zr-DFO-trastuzumab PET. For example, Dehdashti et al. demonstrated that most hepatic lesions, both HER2-positive and HER2-negative, showed uptake similar to normal liver tissue, rendering them difficult to distinguish from the background (30). Moreover, Dijkers et al. reported that known liver lesions were visualised by [^{89}Zr]Zr-trastuzumab in only four of seven patients (31). Together with the intense uptake observed in the primary tumour, these inter-lesional differences support image-suggestive spatial heterogeneity in HER2-targeted tracer uptake, while not establishing histologically confirmed metastatic HER2 expression heterogeneity. Such intra- and intertumoural spatial heterogeneity in HER2-targeted tracer uptake and HER2 expression has been observed in breast cancer using [^{89}Zr]Zr-trastuzumab PET (24, 32, 33). For example, Gebhart et al. found intra-patient heterogeneity in 46% of patients with metastatic breast cancer (32).

The current German guideline for ovarian cancer does not routinely recommend HER2 testing as a diagnostic or prognostic marker in ovarian cancer, or specifically in HGSOC, because phase III data and the European Medicines Agency (EMA) approval for HER2-targeted therapies are missing (7). However, HER2 testing is acknowledged and recommended in mucinous ovarian carcinoma to identify candidates for HER2-targeted therapies. The clinical outcome in our patient supported the value of integrating IHC for HER2 testing in HGSOC, which revealed a score of 3 + in the primary tumour site with intense tracer accumulation in the [^{89}Zr]Zr-trastuzumab PET (SUVratio 13.8). Hence, an important point to consider is the relationship between the uptake intensity of

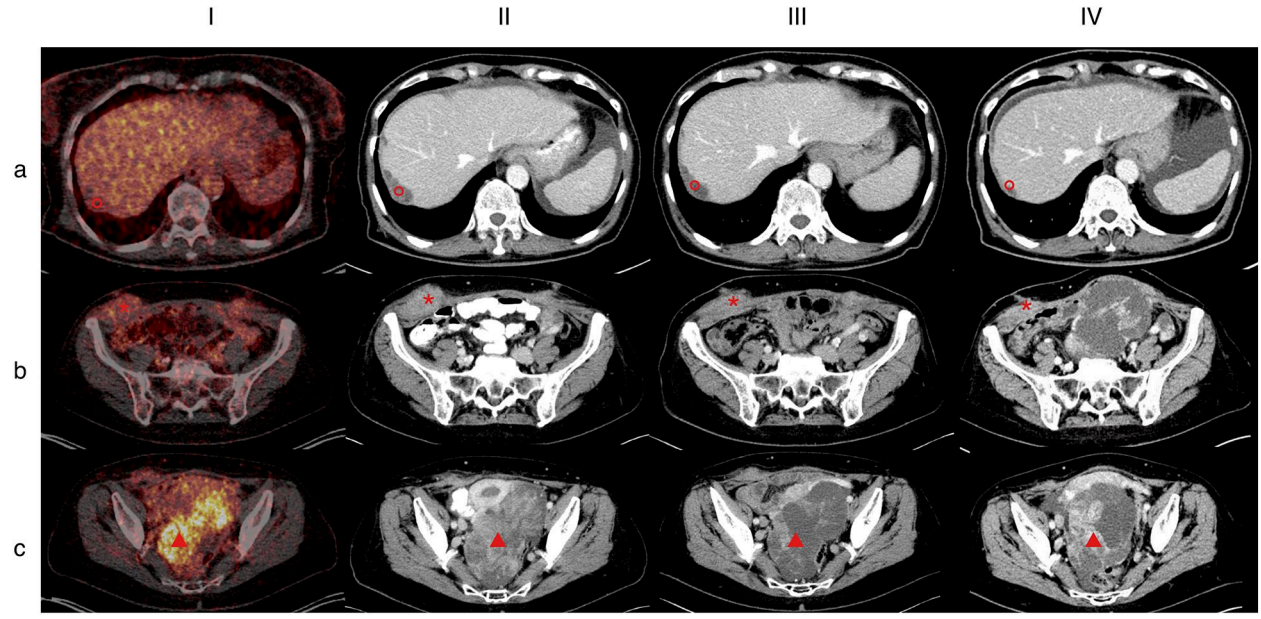


FIGURE 4
Seventy-four-year-old woman with high-grade serous ovarian cancer. Transaxial images shown at three anatomic levels (rows): **(a)** liver, **(b)** right abdominal wall/peritoneum, **(c)** pelvis. Columns depict: **(I)** [^{89}Zr]Zr-DFO-trastuzumab PET/CT fusion (72 h p.i.), **(II)** pre-T-DXd CE-CT, **(III)** follow-up CE-CT after three cycles of T-DXd, and **(IV)** follow-up CE-CT after seven cycles of T-DXd. Symbols indicate lesions: ○ subcapsular hepatic metastasis in segment VII; * port-site metastasis along a prior trocar tract; ▲ pelvic/ovarian mass. SUVratio was defined as lesion SUVmax divided by mean SUV in the psoas major muscle, which served as the physiological reference background. The psoas major muscle was selected as a reproducible non-target reference tissue because blood pool activity and liver uptake may be affected by the prolonged circulation time, biodistribution and physiological hepatic uptake or catabolism of radiolabelled monoclonal antibodies. Lesions were visually classified as [^{89}Zr]Zr-DFO-trastuzumab-avid (visible/high uptake) or non-avid (background/near-background activity).

[^{89}Zr]Zr-trastuzumab and the IHC scores, which has been reported in literature to be inconsistent, with PET uptake sometimes observed in lesions classified as HER2-low or even negative by biopsy, highlighting the complexity of HER2 biology (24, 33). As IHC was not performed on the peritoneal/port-site metastases and hepatic lesions, which demonstrated lower [^{89}Zr]Zr-DFO-trastuzumab uptake in comparison to the primary site, their HER2 expression status remains undetermined. From a quantitative perspective, no validated SUVratio threshold currently exists to define HER2 positivity by [^{89}Zr]Zr-DFO-trastuzumab PET in HGSOC. Therefore, SUVratio values were interpreted descriptively and exploratorily, together with visual assessment, anatomical imaging and IHC. Consequently, the observed inter-lesional uptake pattern should be interpreted as imaging-suggestive spatial heterogeneity in HER2-targeted tracer uptake rather than as histologically confirmed metastatic HER2 expression heterogeneity.

Biochemical markers (CA-125) demonstrated an early, pronounced reduction (from 676 to 254 U/mL at six weeks), while follow-up CE-CT confirmed regression in [^{89}Zr]Zr-DFO-trastuzumab-avid lesions. However, a subsequent CE-CT after 20 weeks revealed a mixed response pattern, illustrating the complexity of HGSOC. Because [^{89}Zr]Zr-DFO-trastuzumab PET/CT was performed after initiation of PEG-liposomal doxorubicin and before T-DXd, the scan should be regarded as pre-T-DXd imaging rather than as a treatment-naive baseline assessment; potential effects of preceding therapy on tumour viability, perfusion and HER2-targeted tracer uptake, as well as delayed effects on subsequent follow-up findings, cannot be excluded. In this context, pre-T-DXd [^{89}Zr]Zr-DFO-trastuzumab uptake should be interpreted as descriptive spatial uptake information rather than as evidence of response prediction, particularly because disease was largely non-measurable by RECIST 1.1 and follow-up demonstrated a mixed response pattern. While RECIST evaluation was hampered by the non-measurable nature of pelvic, mesenteric, and hepatic disease, multimodal imaging [combining CE-CT and (^{89}Zr)Zr-trastuzumab PET/CT] afforded a multidimensional assessment of disease and therapeutic response. Nevertheless, it is important to highlight that the use of RECIST 1.1 in HGSOC is inherently limited. Many disease manifestations in HGSOC, such as ascites, are classified as non-measurable; hence, size changes in these lesions are not quantified in the same manner as target lesions under RECIST 1.1 (34). Yaseen et al. reported that in patients with pathologically confirmed advanced ovarian cancer (FIGO III–IV), 68% had three or more non-target lesions, with ascites being the most prevalent (88%), followed by peritoneal (73%), omental (68%), and pleural effusions (32%), thereby limiting the capacity to quantify treatment efficacy (35). Moreover, in a single-institution retrospective analysis of 105 epithelial ovarian cancer patients, evaluation of carcinomatosis involving the small and large bowel mesentery was especially difficult, with 57 and 43 patients' lesions regarded as "not evaluable" on CT, and diffuse mesenteric involvement accounted for almost 80% of residual tumours in patients undergoing cytoreduction (36).

Several important limitations must be considered, both in the context of this single-patient case report and in the existing literature. This study reports on a single patient. Hence, larger

cohorts are required to validate clinical utility and evaluate clinical endpoints, such as progression-free survival and overall survival, as well as other biomarkers (e.g., CDH6) (37). Furthermore, the lack of defined tumour borders posed challenges in quantitative analyses.

It is worth noting that the HER2 patient score was provided based on gastric cancer scoring criteria (27). This is of particular relevance, because there are no universally accepted ovarian cancer-specific HER2 scoring guidelines. Therefore, this highlights the importance of developing dedicated, disease-specific HER2 scoring criteria to optimise diagnosis and therapeutic decision-making.

Looking forward, the application of [^{89}Zr]Zr-DFO-trastuzumab in a larger patient population in HGSOC will require standardised quantitative thresholds, automated analytic workflows, and validation in larger, multi-institutional cohorts. Surveys assessing the impact of multimodal imaging on clinical decision-making could further guide implementation. Moreover, the application of our approach could potentially be expanded to other diseases, especially considering the recent FDA approval of T-DXd in a tumour-agnostic indication for HER2 3 + solid tumours (38). In summary, this proof-of-concept case suggests that [^{89}Zr]Zr-DFO-trastuzumab PET/CT may provide complementary whole-body spatial information when integrated with IHC, CE-CT and CA-125 in platinum-resistant HGSOC. These findings are hypothesis-generating and require prospective validation.

Data availability statement

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Ethics Committee at the Technical University of Dresden (Approval number: BO-EK-438112024). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JF: Data curation, Formal analysis, Writing – original draft. RW: Data curation, Conceptualization, Supervision, Writing – original draft, Formal analysis. RA: Methodology, Conceptualization, Writing – review & editing. AF: Writing – review & editing, Methodology. KZ: Writing – review & editing, Methodology. TK: Writing – review & editing, Methodology. MK: Methodology, Writing – review & editing. KK: Methodology, Writing – review & editing. OK: Writing – review & editing, Methodology. JK: Writing – review & editing, Methodology. PW: Conceptualization, Supervision, Writing – review & editing. MM: Conceptualization, Supervision, Writing – review & editing. TL: Supervision, Writing – review & editing, Conceptualization.

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Conflict of interest

TL and PW have honoraria for scientific lectures from AstraZeneca and Daiichi Sankyo, and they participated in clinical trials of both companies.

The remaining author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnume.2026.1832138/full#supplementary-material.

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