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REVIEW ARTICLE

# Prediction of pathological response after neoadjuvant chemotherapy using baseline FDG PET heterogeneity features in breast cancer

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## ABSTRACT

Complete pathological response to neoadjuvant systemic treatment (NAST) in some subtypes of breast cancer (BC) has been used as a surrogate of long-term outcome. The possibility of predicting BC pathological response to NAST based on the baseline 18F-Fluorodeoxyglucose positron emission tomography (FDG PET), without the need of an interim study, is a focus of recent discussion. This review summarises the characteristics and results of the available studies regarding the potential impact of heterogeneity features of the primary tumour burden on baseline FDG PET in predicting pathological response to NAST in BC patients. Literature search was conducted on PubMed database and relevant data from each selected study were collected. A total of 13 studies were eligible for inclusion, all of them published over the last 5 years. Eight out of 13 analysed studies indicated an association between FDG PET-based tumour uptake heterogeneity features and prediction of response to NAST. When features associated with predicting response to NAST were derived, these varied between studies. Therefore, definitive reproducible findings across series were difficult to establish. This lack of consensus may reflect the heterogeneity and low number of included series. The clinical relevance of this topic justifies further investigation about the predictive role of baseline FDG PET.

## INTRODUCTION

Breast cancer (BC) is the most common cancer type among females throughout the world. It is also the leading cause of female cancer deaths in almost all countries, with some exceptions where it stands second to lung cancer. Despite the increasing incidence of BC in the later decades, its mortality has been declining in high-income countries, as a result of screening, early diagnosis and improved treatment strategies.[1]

Neoadjuvant systemic therapy (NAST) is an option for early and locally advanced BC, enabling tumour size reduction, expanding the surgical indications and facilitating breast-conserving surgery. The decision on NAST is based on the predicted sensitivity to particular treatment types, the benefit from their use and an individual's risk of relapse.[2] NAST approach is preferred in subtypes highly sensitive to chemotherapy, such as triple-negative and HER2-enriched, in tumours >2 cm and/or axillary lymph nodes involved.[2] In BC, a pathological complete response (pCR) after NAST, defined as the absence of remaining invasive cancer in the breast (irrespective of carcinoma *in situ*) and axillary nodes on pathological examination of the post-treatment surgical excision specimens (ypT0/TispN0), has been used as a surrogate of long-term outcomes and is a relevant prognostic factor.[3–5] The strongest association between pCR and long-term outcomes has been described for triple-negative, luminal high-grade and HER2-positive hormone receptor-negative subtypes.[3] The presence of residual tumour burden after NAST has been associated with higher risk of relapse.[4] However, NAST is not bereft of side-effects, in particular neutropaenia, cardiac toxicity, pulmonary toxicity and neurotoxicity[6]; thus, an accurate selection of the patients that might benefit from it would reduce unnecessary toxicities and the costs associated with inadequate treatment strategies.[7]

MRI has been considered the gold-standard for locoregional breast tumour assessment and prediction of response in BC, usually after a fixed number of treatment cycles of NAST.[8,9]

Recently, research has turned towards the prediction of response to NAST based solely on the pre-treatment MRI, using dynamic contrast-enhanced (DCE) *T1* weighted sequence in the majority of the studies,[8] but no sufficient data have yet been attained to fulfil this purpose with accuracy.[8] Since aggressive tumours tend to have heterogeneous contrast uptake distribution, due to heterogeneous vascularisation and angiogenesis, heterogeneity-based DCE-MRI features are emerging as potential predictors of response to NAST.[9]

$^{18}$F-Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) is important in BC because it significantly impacts clinical management, not only in the initial systemic staging of patients (from TNM stages IIB to IV),[10] but also for monitoring treatment response and follow-up (in the suspicion of recurrence or equivocal findings on other imaging modalities).

The fact that FDG PET studies reflect the glycolytic metabolism of tumours has increased the expectation related to the information about glycolytic intratumoral heterogeneity that can be obtained. Recent research has suggested that FDG PET parameters reflecting intratumoral metabolic heterogeneity (IMH) can play a role in predicting response to therapy and providing prognostic information in several types of cancer.[11–14]

The intensity of FDG uptake in the primary BC has already been shown to correlate with histopathological markers (an increase in FDG uptake was associated with higher tumour grade, negativity for oestrogen receptors, triple-negative status and p53 mutation)[15] and prognosis (patients with higher FDG uptake demonstrated poorer survival).[16,17] In addition, the decrease in tracer uptake between baseline and interim FDG PET (performed during the treatment cycles) has been reported as predictive of pCR in BC treated with NAST.[18] Recent studies have demonstrated that highly heterogeneous breast tumours on baseline FDG PET present more aggressive molecular phenotypes and have a worse response to therapy.[11,19–22] The possibility of predicting response to NAST based on imaging features of the breast tumour burden on the baseline FDG PET, without the need of an interim FDG PET study, would allow for an earlier prognosis prediction and subsequent earlier strategy decisions, thus avoiding unnecessary side-effects of NAST and reducing treatment costs.

In this paper, we reviewed the available literature about the relation between intratumoral heterogeneity-based features of the primary BC on baseline FDG PET and the response to NAST. We included both IMH and FDG uptake texture-based features to reflect uptake heterogeneity. We summarised the characteristics and results of the reviewed studies, seeking to uncover what remains to be further explored.

## METHODS

PubMed database was used for selection of original papers comparing heterogeneity-based features on baseline FDG PET and response to NAST in BC patients. Combinations of the terms "pet", "fdg", "breast", "neoadjuvant", "prediction", "metabolic heterogeneity", "texture features" and "radiomics" were utilised in the literature search. After reviewing the titles and abstracts of the retrieved articles, the full-text papers were analysed to assess their eligibility for inclusion. The inclusion criteria were the following: (1) English written, (2) original research papers comparing metabolic or texture-based features of the primary tumour burden on baseline FDG PET (including at least one feature reflecting IMH or texture) and response to NAST. The exclusion criteria were the following: (1) review articles and meta-analyses; (2) studies including only baseline FDG PET features not directly related to heterogeneity [*e.g. metabolic tumour volume (MTV), maximum standardised uptake value (SUVmax), SUVmean, SUVpeak*]; (3) articles comparing baseline FDG PET features with long-term outcomes but not with response to NAST; (4) articles evaluating interim FDG PET response to NAST (instead of baseline FDG PET prediction of response to NAST). No beginning date restriction was used. Literature search was last updated in December/2022.

For each eligible article, information described in Table 1 was collected.

## RESULTS

### Literature search

Thirteen papers were finally eligible for inclusion, with publication dates between 2017 and 2022. The result is shown in Figure 1.

### Study types and populations

The majority of the groups performed retrospective studies[4,11,20–26] enrolling between 38 and 435 patients (average: 161 patients). Four papers reported prospective studies, enrolling between 20 and 168 patients (average: 80 patients).[19,27–29] All but one study[29] were non-interventional. Roy et al[29] performed a co-clinical study using animal models, but only the clinical arm was considered in this review.

### Clinicopathological and demographic characteristics

The following characteristics were collected by the authors of the analysed papers: age[4,11,20–27]; menopausal state[4,25]; tumour grade[4,20,21,23–29]; clinical TNM stage[11,19–22,24,26–29]; tumour size[4,11,19,20,23–29]; type of chemotherapy[4,11,19–22,24,26–29]; histological type[4,11,19,23–27]; Ki67 index[4,11,19,21–26,28]; oestrogen receptors[4,11,19–23,25,26,28]; progesterone and HER2 receptors.[4,11,19–23,26–28] Lemarignier et al[27] included only patients with oestrogen-positive tumours. Bouron at al[24] and Roy et al[29] included only patients with triple-negative BC. Most studies included patients with TNM Stage II-III (tumour size larger than 2 cm), BC of no special type (NST) and chemotherapy regimens based on anthracycline and/or taxane and/or anti-HER2 agents. More information about clinicopathological and demographic characteristics is provided in Supplementary Material 1 (Table 1).

### Primary endpoint for assessing response to NAST

The studies compared parameters from baseline FDG PET with response to NAST. According with the majority of the authors,

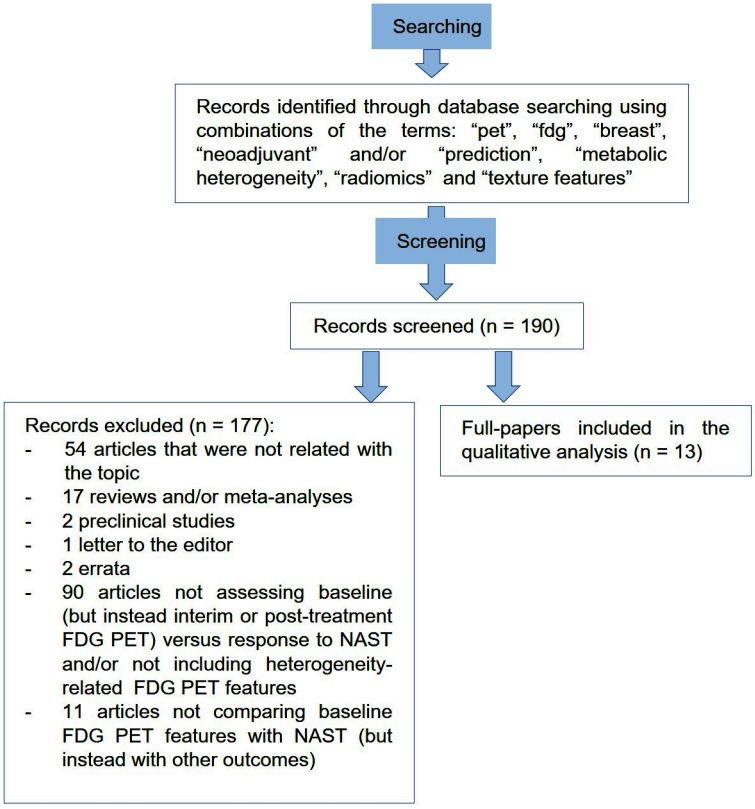
Table 1. Collected parameters in each selected paper

| Parameters | Type of information |
|---|---|
| Study type | Retrospective or prospective |
| Study population | Number of included patients |
| Clinicopathological and demographic characteristics | Age; menopausal state; tumour grade; clinical TNM stage; tumour size; type of chemotherapy; histological type; Ki67 index; oestrogen, progesterone and HER2 receptors |
| Primary endpoint for assessing response to NAST | pCR or partial response |
| PET scanner and scanning parameters | PET equipment; acquisition parameters; reconstruction algorithm |
| Segmentation | Target lesions of the tumour burden included in segmentation (primary tumour only or inclusion of suspicious axillary lymph nodes); segmentation method (manual, automatic or semi-automatic); segmentation criteria in cases of multifocal tumour; segmentation method/software |
| Heterogeneity features | Analysed IMH features and/or texture features; impact on prediction of response to NAST; correlation with prognostic markers; software used for features computation |

IMH, intratumoral metabolic heterogeneity ; NAST, neoadjuvant systemic therapy; PET, positron emission tomography;pCR, pathological complete response.

patients were considered as responders when pCR (ypT0/pN0 or ypT0/TispN0) was achieved and non-responders when pCR was not achieved.[4,11,21–23,25–27] In one study, pCR *vs* non-pCR was considered according with Sataloff scale.[24] Apart from analysing the impact of baseline FDG PET in predicting pCR,[27] one study also considered as responders the patients with either pCR or partial response,[27] defined as >50% therapeutic effect in the breast and no invaded lymph nodes or evidence of a therapeutic effect in the lymph nodes (Sataloff scale),[30,31] the remaining patients being considered as non-responders. Another study used Sataloff classification for considering patients with pCR or partial response *vs* non-responders.[20] Other studies considered

Figure 1. Flowchart explaining the selection of the included studies. FDG, 18F-Fluorodeoxyglucose; NAST, neoadjuvant systemic therapy; PET, positron emission tomography



a response to NAST based on the reduction in cellularity of the primary tumour,[19,28] following the specifications of a previous publication[32] attending to Miller and Payne system, maintaining a binary response (complete or nearly complete response *vs* other tumour regression grades).

### PET scanners and scanning parameters

In two studies,[25,29] the PET component was acquired on a PET/MRI scanner. The others performed PET/CT acquisitions on one[11,19,20,22,26–28] or more than one PET/CT scanners.[4,21,23,24] In most studies, imaging started 60 min after radiopharmaceutical injection[4,11,20–26,28] and PET images were reconstructed using iterative algorithms.[4,11,20–27] More details about PET scanners and scanning parameters is provided in Supplementary Material 1 (Table 2).

### Image-based tumour segmentation

When information about the target of FDG PET segmentation was available, only the primary BC was segmented,[4,11,20,23,25–29] with only one exception,[24] where regional lymph nodes were also segmented, although no heterogeneity features were extracted from them.

An automatic or semi-automatic segmentation algorithm was used in the majority of the cases, including either threshold-based methods,[4,11,19,20,23,24,26–28] flood fill-based[21] or GrowCut-based algorithms,[22] the latter followed by manual adjustment. Functional tumour volumes were manually drawn by Roy et al.[29] In the study of Umutlu et al,[25] lesions were annotated on post-contrast subtracted images (from PET/MRI) using a semi-automatic method. Additional information concerning segmentation method/software is given in Supplementary Material 1 (Table 2).

When information about unifocal *vs* multifocal disease was available and patients with multifocal disease were included,[4,24,28] the segmentation method for multifocal tumours included more than one lesion identified on the FDG PET images[4] or was restricted to the lesion with the highest FDG uptake.[24,28]

### Analysed heterogeneity and texture-related features and their impact in predicting pathological response to NAST

The results about the potential role of IMH features in the prediction of response to NAST are summarised in Table 2. From the IMH features reported in the reviewed literature,[11,20,22,23,26,28,29] an association with prediction of response to NAST was suggested for coefficient of variation,[11] skewness,[11] QRobust mean absolute deviation[29] and kurtosis.[26] The other analysed IMH features (in particular entropy, range, standard deviation, uniformity, variance and SUVmean/SUVmax ratio) were not considered to be associated with response to NAST in any study.

Table 3 shows the results of the analysis of texture-based features in the prediction of response to NAST. From the reviewed literature, the majority of the studies (Ha et al,[11] Molina-García et al,[19] Yoon et al,[20] Lee et al,[21] Li et al,[22] Roy et al,[29] Umutlu et al[25] and Yang et al[26]) suggested FDG PET texture-based features may predict response to NAST. However, none of the predictive texture-based features was the same in these studies. In other three studies,[4,24,27] texture-based features did not show a significant association with NAST response prediction.

Of note, in the study of Lee et al,[21] gradient skewness and gradient kurtosis were considered to be independent prognostic factors for response to NAST in HER2-negative patients but not in HER2-positive patients (in whom anti-HER2 antibody treatment was an independent prognostic factor for response to NAST). The other studies did not report any correlation that could be influenced by any specific type of NAST.

### Correlation between intratumoral FDG uptake heterogeneity or texture features and prognostic markers

Some studies found a correlation between IMH or texture-based features and prognostic markers, namely Ki67 index,[11,22,23,28] oestrogen receptors,[22,23,28] molecular subtype,[19,22,23,28] T stage[22,27] and AJCC clinical stage (eighth edition).[27] However, contradictory results were found in terms of higher heterogeneity *vs* worse prognostic markers (*i.e.* higher Ki67, more aggressive molecular subtypes namely triple-negative and HER2-enriched tumours, higher T and AJCC clinical stage) across the studies. The other reviewed articles compared heterogeneity-related features with response to NAST but not with other prognostic markers.

### What remains to be further explored

#### *Image feature extraction*

Despite the growing interest in applications of radiomics in the field of nuclear medicine, some concerns exist regarding the lack of robustness of many of the currently used features.[33–35] In fact, the reproducibility of some second-order features (which are obtained by calculating the statistical inter-relationships between neighbour voxels)[36] and higher-order features (which are obtained by statistical methods after applying filters or mathematical transforms to the images) is dependent on the different acquisition modes, reconstruction[33,34,37] and post-processing parameters. It was previously determined that, in cervical cancer tumours, for a spatial resolution of 4 mm and 64 $mm^3$ voxel size, about 700 total voxels (45 $cm^3$) were required to give 95% certainty that the global intensity distribution on PET imaging had been sufficiently sampled for reliability of common statistical comparisons of individual tumour intensity distributions.[38] In BC, Soussan et al[15] suggested a MTV cut-off of 5 $cm^3$ for reliable texture analysis. The same difficulties do not apply for CT or MRI, whose equipment allow the performance of acquisitions with spatial resolution under 1 mm. Thus, texture analysis can be more advisable for CT and MRI, provided that the acquisitions are standardised and harmonised between equipment.

An additional difficulty that can compromise even more FDG PET radiomics in BC is related with the deformability of the breasts and their positioning during PET acquisition. This limitation can be partly overcome with the breast dedicated PET systems (FDG bdPET), where the patient lies in prone position. However, patient positioning in these FDG bdPET equipment can be another challenge in females with large or very small

Table 2. Prediction of pathological response to NAST in BC based on first-order FDG PET imaging features reflecting IMH

| | Number of patients | IMH features | | Was an association between IMH first-order FDG PET features and response to NAST suggested in the paper? |
|---|---|---|---|---|
| | | Associated with pathological response to NAST | Not associated with pathological response to NAST | |
| Gallivanone et al 2017[23] | 38 | *None* | Entropy, Kurtosis, Range, Skewness, SD, Uniformity, Variance | No |
| Ha et al 2017[11] | 73 | CoV, Skewness | Variance, SD, Kurtosis, Entropy | Yes |
| Galán et al 2019[28] | 62 | *None* | CoV, SUVmean/SUVmax ratio | No |
| Yoon et al 2019[20] | 83 | *None* | Entropy, Kurtosis, Skewness, SD, Variance | No |
| Li et al 2020[22] | 100 | *None* | Entropy, Kurtosis, Range, Skewness, Uniformity, Variance | No |
| Roy et al 2022[29] | 20 (all triple-negative) | QRobust mean absolute deviation[a] | >15 features | Yes |
| Yang et al 2022[26] | 124 | Kurtosis | Probably >12 features | Yes |

BC, breast cancer; CoV, coefficient of variation; FDG, 18F-Fluorodeoxyglucose; IMH, intratumoral metabolic heterogeneity; NAST, neoadjuvant systemic therapy; PET, positron emission tomography;SD, standard deviation.
[a]The only first-order IMH feature included in the four top features that constituted the radiomic signature used for prediction.

breasts. Moreover, the evaluation of tumours close to the chest wall can be compromised, because posterior tissues are difficult to include due to positioning the relatively bulky detectors and need for coincidence detection on PET.[39] Despite these limitations, the higher resolution of FDG bdPET, as well as its higher tumour tissue fraction (the ratio of BC tissue size to the total field of view) relative to the conventional whole-body FDG PET highlights the spatial and signal intensity heterogeneity of the tumour volume of interest in FDG dbPET.[40] This makes the exploitation of IMH a desirable target for research with FDG bdPET, as it can eventually reduce tumour-sampling bias[41] and have a role in pre-treatment prediction of pathologic response to NAST.

Due to the difficulties in exploring texture-based features applied to PET (in particular in breast tumours), the exploration of imaging features reflecting a more "global heterogeneity" could be beneficial. First-order characteristics (*e.g.* SUV-based entropy, kurtosis, skewness, standard deviation, uniformity, variance, coefficient of variation) are more stable and thus more reliable than the second- and higher-order features when applied to PET imaging, since they use statistical moments of the intensity histogram of the image[42] and do not contain information about the relative position of the pixels with respect to each other.[33] As such, further research focusing on them and applied to a sample as homogeneous as possible could help exploring the potential predictive role of baseline FDG PET.

Regarding the radiomics approach, data are required to first train and then evaluate the model (train and test), in order to create robust algorithms.[43] This strategy was adopted in some of the studies included in this review.[21,22,25,26,29] Also, the use of harmonisation programs [*e.g. European Association of Nuclear Medicine Research Ltd. (EARL) certification for PET scanners and Image Biomarker Standardisation Initiative (IBSI)*[44] *for Radiomics analysis*] is recommended to make PET imaging and radiomics models as reliable and reproducible as possible across centres.[43]

### *Axillary lymph nodes*

Regional lymph node status is one of the strongest predictors of long-term prognosis in primary BC.[2] A better survival was

Table 3. Prediction of pathological response to NAST in BC based on FDG PET imaging texture-based features

| | Number of patients | Texture matrices | Texture-based features | | Was an sssociation between PET texture-based features and response to NAST suggested in the paper? |
|---|---|---|---|---|---|
| | | | Associated with pathological response to NAST | Not associated with pathological response to NAST | |
| Lemarignier et al 2017[27] | 171 (all oestrogen-positive) | GLCM | *None* | Contrast, Entropy, Homogeneity, Energy | No |
| Ha et al 2017[11] | 73 | GLCM | Normalised entropy, Normalised homogeneity | 56 features | Yes |
| | | GLRM, GLNIDM, TSM, TFC, TFCCM, NGLDM | *None* | | |
| | | GLSZM | Zone percentage | | |
| Molina-García et al 2018[19] | 68 | GLCM | *None* | Contrast, Entropy, Homogeneity, Dissimilarity, Uniformity | Yes |
| | | RLM | LGRE, LRHGE, RLNU | LRE, SRE, HGRE, SRLGE, SRHGE, LRLGE, GLNU, Run percentage | |
| Antunovic et al 2019[4] | 79 | NGLDM | *None* | Coarseness | No |
| | | GLZLM | *None* | GLNU | |
| Yoon et al 2019[20] | 83 | NGLDM | Number non-uniformity | Second moment, Entropy, Small number emphasis, Large number emphasis | Yes |
| | | GLCM, VAM, NIDM, ISZM, NGLCM, TSM | *None* | 41 features | |
| Lee et al 2019[21] | 435 | Absolute gradient | Gradient skewness[a], Gradient kurtosis[a] | Probably >20 features | Yes |
| | | RLM, GLCM | Difference variance | | |
| Li et al 2020[22] | 100 | GLRLM | Run length variance[b] | 15 features | Yes |
| | | GLSZM | Zone size variance[b] | 15 features | |
| | | GLCM, GLDZM, NGTDM | *None* | 41 features | |

(Continued)

Table 3. (Continued)

| | Number of patients | Texture matrices | Texture-based features | | Was an sssociation between PET texture-based features and response to NAST suggested in the paper? |
|---|---|---|---|---|---|
| | | | Associated with pathological response to NAST | Not associated with pathological response to NAST | |
| Bouron et al 2021[24] | 74 (all triple-negative) | GLCM, GLRLM, NGLDM, GLZLM | *None* | Homogeneity, Entropy, SRE, LRE, LGZE, HGZE | No |
| Roy et al 2022[29] | 20 (all triple-negative) | GLDZM | GLNUN[c], SDLGLE[c], LGDE[c] | 10 features | Yes |
| | | GLSZM, GLCM, NGLDM, NGTDM, GLRLM | *None* | >40 features | |
| Umutlu et al 2022[25] | 73 | GLCM | Autocorrelation, Second InfCorr | >70 features | Yes |
| | | NGLDM | LDHGE | | |
| | | NGTDM | Busyness | | |
| | | SZM | SZHGLE | | |
| Yang et al 2022[26] | 124 | GLDM | GLV, GLNU | All available in the LIFEx software for PET (1316 features in total), except the three indicated in the cells on the left | Yes |
| | | GLSZM | Large area emphasis | | |

BC, breast cancer; FDG, 18F-Fluorodeoxyglucose; GLCM, grey-level co-occurrence matrix; GLDM, grey-level dependence matrix; GLDZM, grey-level distance zone matrix; GLNIDM, grey-level neighbourhood intensity-difference matrix; GLNU, grey-level non-uniformity; GLNUN, grey-level non-uniformity normalised; GLRLM, grey-level run length matrix; GLSZM, grey-level size zone matrix; GLV, grey-level variance; GLZLM, grey-level zone length matrix; HGRE, high grey-level run emphasis; HGZE, high grey-level zone emphasis; ISZM, intensity size zone matrix; LDHGE, large dependence high grey-level emphasis; LGDE, low grey dependence emphasis; LGRE, low grey-level run emphasis; LGZE, low grey-level zone emphasis; LRE, long-run emphasis; LRHGE, long run high grey-level emphasis; LRLGE, long run low grey-level emphasis; NAST, neoadjuvant systemic therapy; NGLCM, normalised GLCM; NGLDM, neighbouring grey-level dependence matrix; NGTDM, neighbourhood grey tone difference matrix; NIDM, neighbourhood intensity difference matrix; PET, positron emission tomography; RLM, run-length matrix; RLNU, run-length non-uniformity; SDLGLE, small dependence low grey-level emphasis; SRE, short-run emphasis; SRHGE, short run high grey-level emphasis; SRLGE, short run low grey-level emphasis; SZHGLE, small zone high grey-level emphasis; SZM, size zone matrix; TFC, texture feature coding; TFCCM, texture feature coding co-occurrence matrix; TSM, texture spectrum matrix; VAM, voxel-alignment matrix.

[a]In HER2-negative patients.

[b]In combination with CT features.

[c]The three texture-based features included in the four top features that constituted the radiomic signature used for prediction.

demonstrated in patients experiencing a pCR in both breast and axilla than those with breast-only[3,45] or axilla-only pCR.[45] Hence, in the models for prediction of response to NAST, it is desirable that the endpoint includes the response of both the primary BC and axillary lymph nodes (in clinically node-positive patients). It could also be appropriated to include the suspicious axillary lymph nodes in the segmentation of the tumour burden (unless they are too small for reliable texture analysis), thus incorporating imaging features of the axilla in the NAST response prediction models.

### *Tumour microenvironment*

Intratumoral heterogeneity, meaning the existence of tumour cells with different genotypes and phenotypes within the same tumour, is regarded as a major factor in tumour progression and resistance to therapy.[22] A topic that has recently attracted considerable attention in regard of tumorigenesis and metabolic heterogeneity is the tumour microenvironment, which is orchestrated by cancer-associated fibroblasts (CAFs).[46] According to the "reverse Warburg effect" model, epithelial tumour cells induce the Warburg effect (aerobic glycolysis) in neighbour

stromal fibroblasts, which, in turn, produce energy-rich metabolites (namely pyruvate) that can be driven to the mitochondrial Krebs cycle in the surrounding tumour cells.[47] This metabolic reprogramming may impact on IMH, due to different rates of glucose consumption in the same tumour microenvironment. The complexity and spectra heterogeneity of CAFs has hampered the development of CAF-directed therapies. What remains to be further explored is which of the expressed enzymes and which of the molecules produced by CAFs have a pro-tumour effect in the several types of cancer, including in BC, such that novel therapeutics against these factors can be developed. In addition, a possible association between metabolic heterogeneity-related variables on FDG PET and specific pro-tumour CAF biomarkers in BC deserves future research.

### *Limitations of the study*

This review has some limitations. Firstly, the low number of studies fulfilling the inclusion criteria. The fact of being a qualitative review, with no quantitative meta-analytic data, is also a limitation. In addition, we did not have access to the full database that gave rise to the analysed research papers, which could have resulted in some missing data in this review. Moreover, some confounding factors may have contributed to the non-consensual nature of the results, namely: the lack of standardisation of acquisition and reconstruction protocols; the varied approaches to image data analysis; the variability of the definition, implementation and semantic grouping of some quantitative FDG PET imaging features between studies, scanners and software, which can affect the interpretation and comparison of the results in the analysed literature[48,49]; the biodiversity of BC subtypes, influencing the response to NAST; the different chemotherapy regimens between the studies; and factors affecting FDG uptake that may not be referred in the included papers (*e.g.* surrounding inflammatory activity may interfere with tumour segmentation). Regarding the texture-based features, their variability highly depends on the algorithm implementation and image reconstruction protocols. In addition, FDG PET texture-based features do not make sense in very small lesions, since the low number of voxels do not allow to extract significant textural information. Also, they depend on the shape, thus positioning the breast differently will produce different texture-based features.

## CONCLUSION

We reviewed the current literature concerning the prediction of pathological response to NAST based on heterogeneity-related features of BC on the baseline FDG PET. Eight out of 13 analysed studies suggested a possible relation between some heterogeneity-reflecting variables and pathological response to NAST. Nevertheless, since features associated with prediction of response to NAST in a study were not confirmed by other studies, more robust evidence about this potential relationship is necessary. This lack of consensus may reflect the heterogeneity and low number of included series. The clinical relevance of this topic justifies, however, further investigation and continuing research about the predictive role of baseline FDG PET.

## AUTHOR CONFLICTS OF INTEREST

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