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Simple Summary: Routine medical imaging, such as mammography (MMG) and ultrasound (US), used for preliminary breast cancer workup, have limited utility for radiation oncologists. We hypothesized that the inclusion of cross-sectional imaging (CT scan or PET-CT) completed in front of primary systemic therapy (PST) would improve clinical staging accuracy and facilitate customized postoperative radiation therapy planning. We quantified the value of cross-sectional imaging to MMG and US and find staging and radiation planning are altered by this additional procedure.

Abstract: The aim of the study was to compare the standard baseline imaging, with extended radiological staging. To assess our hypothesis, we performed a prospective, single-centre study which included 132 participants recruited between October 2015 and March 2020. Descriptive statistics, the Friedman and chi-squared tests were performed and $p < 0.05$ was considered significant. Patients were grouped into two cohorts, CT scan cohort (n=87) and PET-CT cohort (n=43). In the first group the originally determined disease stage changed in 36.8 % of cases, in second group in 51.2 %. The consistency between assessment of axillary lymph nodes by imaging (cN) and the postoperative pathology report (pN) was evaluated. In most cases, clinical and pathological evaluation of involved nodes was consistent, for CT scan the result was $\chi2(1) = 18.98$; $p < 0.001$, for PET-CT the result was $\chi2(1) = 6.41$; $p = 0.03$. Highly customized radiation therapy defined as dose boost within the involved lymph nodes, not covered by surgeon, was applied in nine patients. Conclusions: Cross-sectional imaging in patients with locally advanced high-risk breast cancer should be recommended.

Keywords: breast cancer; high-risk patients; primary systemic therapy; pre-treatment imaging; treatment individualization

1. Introduction

Currently, systemic therapy is administered upfront in majority of triple-negative breast cancer (TNBC) and Her2-positive cases, to achieve pathological complete remission (pCR). Irradiation is carried out after surgical treatment to improve local control and overall survival in early and advanced breast cancer [1]. When significant clinical response to systemic therapy is achieved, areas at highest risk of persistent disease will not be evident on the post-operative CT used for treatment planning. Standard imaging techniques for diagnosis and staging of breast cancer including

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mammography (MMG), ultrasound (US), and magnetic resonance imaging (MRI) have limited utility in personalizing radiation therapy (RT) because planning systems are mainly based on computed tomography (CT). MMG fails to show the lymph nodes clearly. It is more suitable for the evaluation of primary foci in the low mammographic density breasts of postmenopausal women than in the glandular breasts of younger patients [2,3], who are relatively frequently qualified for primary systemic therapy. Advanced RT techniques, such as intensity modulated radiation therapy (IMRT) require defining the desired dose to all target and non-target tissues on each slice of the planning CT. High-quality cross-sectional imaging that allows 3D visualisation, such as CT scan or positron emission tomography (PET-CT) are a necessary part of the procedure. Despite available data suggesting the utility of CT scan and PET-CT in breast cancer, they are not routinely performed [4–6]. Medical imaging before systemic therapy and surgery, followed by planning CT, offers numerous possibilities for RT customization, such as increased dose in the non-operated anatomical area, where the pathological lymph nodes were observed (e.g. supraclavicular region or internal mammary lymph nodes). Additionally, it can aid in diagnosing of oligometastatic disease and facilitate the application of stereotactic body radiation therapy (SBRT). Scans performed before cancer treatment and planning CT done after surgery could be compared or superimposed on each other, providing a tool for RT individualisation (Supplmental Figure 7), this procedure is called image fusion. In our study, the radiation immobilization device was used to position patients during imaging (Supplmental Figure 3). The aim of this single-center study was comparison of the standard baseline imaging with extended radiological staging, in patients initially qualified for preoperative systemic treatment; investigation of whether CT scan and PET-CT reliably visualize the primary focus in the breast and pathological lymph nodes in the axilla, assessment if the nodes, recognized as involved actually contained metastases (correlation between the postoperative pathological report and the imaging). We also analyzed whether extended radiological staging had an additional diagnostic value. The secondary objective was to investigate how often, after receiving an additional examination result, the multidisciplinary team (MDT) has modified the originally planned treatment strategy.

2. Materials and Methods

The study design was prospective, cross-sectional, and observational (the assignment of medical interventions was not at the discretion of the investigator). Data were collected from patients' medical records. Eligible patients were, aged ≥18 years, with an established diagnosis of invasive breast adenocarcinoma defined by punch biopsy. Assessment of histological grade, Immunohistochemistry (IHC) evaluation of; Estrogen receptor (ER), Progesterone receptor (PgR), Ki67 and Human epidermal growth factor receptor 2 (HER2) status was required in the histopathology report. If the Her2 score was borderline, a FISH test was performed. Patients with the following; Eastern Co-operative Oncology Group Performance Status 0/2, no distant metastases and no clinically significant renal failure were recruited. All participants were selected for systemic preoperative therapy by a MDT at the Breast Unit of the Lower Silesian Oncology, Pulmonology, and Haematology Center. After carrying out preliminary radiological staging according to the recommendations of the Polish Society of Clinical Oncology (bilateral MMG, breast US, and chest X-ray [CXR] regardless of the stage, abdominal cavity imaging by US and/or CT scan, and bone scintigraphy in CS III) [7], all eligible patients were offered an extended workup. Current Polish national recommendations suggest carrying out of additional imaging studies only as an option, routine inclusion of chest cross-sectional imaging (CT scan or PET-CT) prior to PST (primary systemic therapy) is not a common practice. Considering the estimated risk of spread of the neoplastic process, the decision to perform one of the imaging modalities was made by the MDT. High-risk patients underwent PET-CT; with no strict criteria for selecting additional imaging modality. Two cohorts of patients were analyzed separately: in the first, CT scan was performed, and in the second, PET-CT. All imaging and treatment results used in the study were considered a part of the patients' diagnostic and therapeutic scheme.

In total, 132 participants were recruited between October 2015 and March 2020. After detailed verification, two were excluded. In one case, surgical biopsy of the breast tumour, turned out to be

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tumorectomy, and the breast lesion could not be measured. In the other case, the assumed period of 2 weeks from the beginning of systemic therapy to the CT scan was exceeded. Further analyses included 130 participants (128 woman and two men). All PET-CT examinations were performed before treatment and a CT scan was allowed up to 2 weeks after starting systemic therapy, assuming that during this time, there would be no significant tumour shrinkage in most patients. The COVID-19 pandemic interrupted the recruitment process; participation required an additional clinic visit, which could increase the risk of coronavirus transmission. The last CT scan was performed on 12.03.2020, and the collection of COVID-19 statistics in Poland began approximately on 14.03.2020 (according to the COVID-19 Data Repository of the Center for Systems Science and Engineering [CSSE] at Johns Hopkins University, there were 35 COVID-19 cases in Poland at that time). Thus, it may be concluded that CT scan and PET-CT results are free from COVID-19 bias, concerning the lung parenchyma, as well as possible vaccination-related lymphadenopathy [8]. All scans were performed in the supine treatment position, were supervised by a radiation oncologist and experienced technicians, position was suited to the patient's anatomical structure. The prone position is not optimal if lymph node radiation is planned, and the current guidelines and contouring atlases, which are helpful in daily practice, refer to the supine position [9–11]. All CT scans were assessed by an experienced radiologist, and PET-CT by a nuclear medicine specialist. Tumour size measurements were also made by the above-mentioned professionals. CT was performed using an intravenous contrast agent and PET-CT using fluorodeoxyglucose (18F-FDG) as the radioactive tracer. The cross-sectional imaging result was attached to the patient's medical history and analyzed by MDT.

The age of the participants was similar in both cohorts, with a median of 51 and 50 years, respectively. A high-grade G3 histologic tumour was most common, and has been confirmed in 55.1% of cases in CT scan cohort and in 62.8% in PET-CT cohort, the G1 grade was observed in only one participant. High Ki67 expression prevailed and the median was 43.5 (7 — 90) in CT scan cohort and 52.5 (2 — 90) in PET-CT cohort (Table 1). Participants who qualified for PET-CT according to the opinion of MDT had a higher risk of cancer spread, and were in many cases originally non-operable, cT4 clinical tumour stage has been established in 39.5% patients in this group. In the CT scan cohort, the majority, 58.6% presented cT2 features. The most common subtype, based on the receptor profile and Ki67 rate, according to the St. Gallen surrogate classification for breast cancer [12], was the luminal-B-like, HER2 negative. Endocrine therapy as preoperative treatment was rare. Such management was applied in three patients in the PET-CT cohort, and in eight in the CT scan cohort. In 91.5 % of participants, PST was based on multi-drug chemotherapy. Anti-Her2 targeted therapy was administered when indicated. Optimal systemic therapy was selected by the MDT. The rate of pathologic complete response was rather low, slightly exceeding 22% in both the cohorts, due to a high representation of patients with T4 and N3 features and the dominant subtype being Luminal B (HER2-negative) [13].

Table 1. Patients baseline characteristics.

		CT scan cohort (n=87)	**PET-CT cohort (n=43)**
median age, years		51 (25 — 80)	50 (24 — 74)
sex	Women	85 (97.7%)	43 (100%)
	Men	2 (2.3%)	0
clinical tumour stage (cT)	cT1	3 (3.4%)	0
	cT2	51 (58.6%)	16 (37.2%)

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	cT3	25 (28.7%)	10 (23.3%)
	cT4	8 (9.2%)	17 (39.5%)
clinical nodal stage (cN)	cN0	24 (27.6%)	7 (16.3%)
	cN1	26 (29.9%)	8 (18.6%)
	cN2	26 (29.9%)	14 (32.6%)
	cN3	11 (12.6%)	14 (32.6%)
histologic grade	G1	0	1 (2.3 %)
	G2	37 (42.5%)	14 (32.6%)
	G3	48 (55.1%)	27 (62.8%)
	not established	2 (2.3%)	1 (2.3%)
median Ki67		43,5 (7 — 90)	52,5 (2 — 90)
St. Gallen surrogate classification for breast cancer	Luminal A-like	5 (5.7%)	4 (9.3%)
	Luminal B-like (HER2-negative)	34 (39.1%)	18 (41.9%)
	Luminal B-like (HER2-positive)	11 (12.6%)	9 (20.9%)
	HER2-positive (non-luminal)	8 (9.2%)	1 (2.3%)
	Triple-negative	29 (33.3%)	11 (25.6%)
definitive surgery		82 (94.3%)	35 (81.4%)
no surgery		5 (5.7%)	8 (18.6%)
pathologic complete response (pCR)		18 (22%)	8 (22.9%)
no pathologic complete response		64 (78%)	27 (77.1%)

histologic grade rated on Scarf-Bloom-Richardson Grading System, Nottingham Modification. Abbreviations: CT, computed tomography; PET-CT, positron emission tomography.

3. Results

3.1. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 25 software (IBM Corp., Armonk, N.Y., USA). Friedman test was used to evaluate the difference between largest dimension of the breast tumours in alternative medical imaging methods. Pairwise comparisons were performed using the post-hoc Dunn's test.

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The following descriptive statistics were considered: mean, standard deviation, median, minimum, maximum, and the first and third quartiles. Hereby the distribution of the analyzed variables was presented in detail. Pair collation was made based on the median. We compared the largest dimension of the largest breast tumour focus (T/mm), between the standard MMG, US, and CT scans, as well as between MMG, US, and PET-CT. Chi-squared test was applied to estimate distribution of the variables pN+ (involved axillary nodes based on the histopathology report) and cN+ (involved axillary nodes based on imaging). Consistency between the clinical assessment by imaging and the pathology report was estimated separately in CT scan cohort and PET-CT cohort. The rate of patients was calculated in terms of an additional diagnostic value of extended radiological staging, which resulted in a modification of the clinical stage or change in the management strategy. The level of statistical significance was set at $p<0.05$.

3.2. Tumour size measurements

The largest dimension of the breast tumours was compared in millimetres (T/mm) using alternative medical imaging methods (Table 2). In case of multifocal tumours, the largest lesion was taken into account. Friedman test was used to evaluate the difference. No statistically significant differences were observed between the median dimensions evaluated using CT scan and MMG. In PET-CT cohort, the measurement of the focus in the breast was made in low-dose CT (LDCT), which is a component of the PET-CT scan. When dimensions evaluated in PET-CT ware compared with US and MMG, there was no statistically significant difference in the size likewise. Only the dimensions evaluated in US turned out to be statistically significantly smaller ($p = 0.02$) than those evaluated in CT scan. It should be emphasised that US and MMG was performed before the diagnosis was confirmed by biopsy, whereas CT scan was performed after the initial workup and MDT meeting. Disease progression over a period of several weeks may be suspected in some patients.

***Table* 2.** Largest contiguous dimension of a tumour focus in alternative imaging methods.

CT scan cohort	**M**	**Me**	**SD**	**Min**	**Max**	**Q1**	**Q3**
T/mm MMG	40.79	37.5	21.88	10	130	25	51.25
T/mm US	38.51	38	13.95	11	75	29	46
T/mm CT scan	43.48	40	19.2	13	115	30	54
PET-CT cohort							
T/mm MMG	44.78	35	26.93	12	100	27	55
T/mm US	44.72	40	21.93	14	100	27	56
T/mm PET-CT	46.32	37.5	26.43	12	120	29.75	56

Abbreviations: US, ultrasound; MMG, mammography; CT, computed tomography; SD standard deviation.

3.3. Baseline lymph node evaluation

Unambiguous results of lymph node assessment prevailed in all imaging techniques; these were further analysed (Table 3).

Table 3. An unequivocal result was the one in which the nodes were recognized as pathological (cN+) or not involved (cN-). Results that reported suspicious or enlarged nodes were reckoned as dubious.

no pathologic complete response	**CT scan cohort (n=64)**
unequivocal lymph node evaluation by CT scan	60 (94%)
dubious lymph node evaluation by CT scan	4 (6%)
unequivocal lymph node evaluation by US	59 (92%)
dubious lymph node evaluation by US	5 (8%)

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no pathologic complete response	PET-CT cohort (n=27)
unequivocal lymph node evaluation by PET-CT	26 (96 %)
dubious lymph node evaluation by PET-CT	1 (4%)
unequivocal lymph node evaluation by US	26 (96%)
dubious lymph node evaluation by US	1 (4%)

Abbreviations: CT, computed tomography; PET-CT, positron emission tomography; US, ultrasound.

3.4. Consistency between the clinical assessment (cN) with the postoperative pathology report (pN)

Following the exclusion of unoperated patients and those reaching pCR, the consistency between the clinical assessment of axillary lymph nodes (cN) by CT scan and US with the postoperative pathology report (pN) was evaluated (Table 4). This analysis is reliable because of the large cohort of participants with only a partial response, respectively 64 in CT scan cohort and 27 in PET-CT cohort. In 95.3 % of node positive cases, there was consistency between microscopic and CT scan evaluations. In only two cases (4.7 %), lymph nodes were assessed on CT scan as not involved, yet contained metastases. Similar results were obtained on comparing the clinical evaluation of lymph nodes by US and the pathology report. It may be assumed that the diagnostic values of CT scan and US are similar in terms of lymph node assessment. In 92.5 % of node positive cases, pathology reports and lymph node evaluations in US were consistent; however, in three cases (7.5%), lymph nodes were assessed as not involved, yet contained metastases (Table 4). Chi-squared test confirmed consistency between the clinical assessment by imaging and the pathology report, for CT scan the result was $\chi 2(1) = 18.98$; $p < 0.001$.

Table 4. The consistency between clinical assessment of axillary lymph nodes (cN) by baseline CT scan, US, and the postoperative pathology report (pN). Only patients with no pathologic complete response and unequivocal lymph node evaluation by imaging were included in this analysis, refer to the Table 3.

Imaging vs pathology report	cN evaluated by CT scan			
	cN-(n=11)		cN+ (n=49)	
	n	%	n	%
pN- (n=17)	9	52.9	8	47.1
pN+ (n=43)	2	4.7	41	95.3
	cN evaluated by US			
	cN- (n=16)		cN+ (n=43)	
pN- (n=19)	13	68.4	6	31.6
pN+ (n=40)	3	7.5	37	92.5

Abbreviations: CT, computed tomography; PET-CT, positron emission tomography; US, ultrasound.

Mirror analysis was performed in the PET-CT cohort (Table 5). The clinical stage of the patients who qualified for PET-CT was more advanced. Noteworthily, there was no discordance between the nodes assessed, as not involved by PET-CT, and the postoperative pathology report. Although this cohort was smaller, the result of Chi-squared test confirmed consistency between the clinical assessment by imaging and the pathology report and for PET-CT was $\chi 2(1) = 6.41$; $p = 0.03$. All analyzed histopathological reports were postoperative and in patients after systemic treatment. It can

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be assumed that in some cases nodal pCR with simultaneous lack of pCR in the primary focus occurred. It is recognized that node-only pCR is present about twice as often as breast-only pCR [14]. A small percentage of patients may also experience disease progression during systemic therapy. For this reason, the calculation of false negative and false positive rates of axillary status was abandoned.

Table 5. The consistency between clinical assessment of axillary lymph nodes (cN) by baseline PET-CT, US, and the postoperative pathology report (pN). Only patients with no pathologic complete response and unequivocal lymph node evaluation by imaging were included in this analysis, refer to the Table 3.

Imaging vs pathology report	**cN evaluated by PET-CT**			
	cN- (n=3)		cN+ (n=23)	
	n	%	n	%
pN- (n= 9)	3	33.3	6	66.7
pN+ (n=17)	0	0	17	100
cN evaluated by US				
	cN- (n=5)		cN+ (n=21)	
pN- (n=8)	5	62.5	3	37.5
pN+ (n=18)	0	0	18	100

Abbreviations: CT, computed tomography; PET-CT, positron emission tomography; US, ultrasound.

3.5. Added value of extended radiological staging.

We also analysed whether CT scan or PET-CT have an additional diagnostic value, compared to that of the standard initial workup. The results confirmed that in 49.4 % of the participants, clinically significant information could be obtained from CT scan. Internal mammary lymph node involvement was detected in six patients. In two cases, the supraclavicular lymph nodes were found outside the anatomical boundaries suggested by the ESTRO guidelines for the delineation of lymph nodal areas. In one participant, the CT scan revealed a previously undiagnosed heart pathology (blood clot in the left atrium). Involved lymph nodes in the mediastinum were found in one participant (M1 feature). In ten cases, CT scan suggested satellite foci within the involved breast and in five pectoral muscle infiltration. In the PET-CT cohort, one-fourth of the cases ended with modification of the originally planned treatment strategy, and in 51.2 % of cases, the originally determined disease stage changed. PET-CT confirmed multifocal spread of the neoplastic process in seven patients and was helpful in diagnosing oligometastatic disease in two participants (Table 6).

Table 6. Impact of the CT scan and PET-CT on the multidisciplinary team's decision. Modification of the management strategy was understood as withdrawal of surgery or personalized radiation therapy (e.g., boost within the internal mammary lymph nodes or stereotactic body radiation therapy [SBRT] in oligometastatic disease).

CT scan cohort (n=87)	**n**	**%**
management strategy modification	9	10.3
clinical stage shift	32	36.8
other clinically significant findings	2	2.3
no added value of extended radiological staging	44	50.6
PET-CT cohort (n=43)	**n**	**%**
management strategy modification	11	25.6

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clinical stage shift	22	51.2
no added value of extended radiological staging	10	23.3

Abbreviations: CT, computed tomography; PET-CT, positron emission tomography.

4. Discussion

In malignancies that are highly sensitive to systemic therapy, such as nasopharyngeal cancer, it is difficult to imagine modern RT planning without performing precise imaging before chemotherapy [15,16]. A thorough understanding of the original scope of the disease is required to determine the appropriate volume of irradiation. The effectiveness of systemic therapy is increasing in patients with breast cancer. Regarding HER2 positive and TNBC subtypes, pCR may be expected in nearly half of the treated population, even in patients with locally advanced disease[17,18]. The NCCN guidelines recommend an increased RT dose to the involved lymph nodes outside the surgeons' reach [19]. However, there are no suggestions on how to diagnose such clinical situations systematically. PET-CT is highly precise in evaluating breast cancer nodal involvement and was the basis of an anatomical atlas created in 2018 [20]. A study published in 2012 demonstrated that a preoperative CT scan may facilitate and increase the precision of boost planning in the tumour bed [21]. Recent experience in innovative imaging modalities, such as PET-prostate-specific membrane antigen (PSMA) in prostate cancer, has led to the assumption that in some cases, nodal metastases are outside the typical location covered in the current contouring guidelines [22]. In terms of the radiation dose in breast cancer, hypofractionated schedules are considered state-of-the-art [23]. However, significantly less attention has been paid to the complete radiation dose. Reportedly, an increased dose to the tumour bed doubles the local effectiveness of RT, yet the boost practice varies greatly in different cancer centers [24–26]. For the majority of neoplasms, a hard-to-question paradigm in which local control depends on the total dose seems true. Modern irradiation techniques enable safe and precise application of high doses. It has been proven in a small group of breast cancer patients, that IMRT is effective enough to be considered as optional radical treatment, in those who do not want to undergo surgery [27]. Data concerning increased doses in areas other than the tumour bed are scarce, but using a total dose higher than 60 Gy to involved lymph nodes improves local control [28–30]. Particular attention should be paid to the internal mammary and supraclavicular nodes, because these are not routinely covered by surgical procedures [31]. In the 130 patients in this study, a boost dose within the involved but unoperated lymph nodes was applied in nine patients, most often 63 Gy in 28 fractions. Boost to the internal mammary lymph nodes was applied in five patients, and in four patients, to the pathological lymph nodes within the part of the axilla not covered by the surgeon. Oligometastatic disease was diagnosed in two patients, and SBRT was carried out.

In the future, we may modify the dose, apart from the tumour bed boost, depending on the risk of anatomical area involvement. Such an approach is implemented in daily practice in RT for head and neck cancers, where one RT plan often involves three different doses to various areas: a gross disease dose to the volume of direct cancer infiltration, a high-risk subclinical disease dose to the areas that are the most common recurrence sites, and a low-risk dose to the elective lymph node areas [32]. Similar methods may be used in the future for breast cancer in cases where high-quality imaging techniques are available.

This study has some limitations. The number of participants recruited was too small to analyze the impact of personalized RT on the progression-free survival (PFS) and overall survival (OS). This study was not a randomized but an observational trial; PET-CT was performed preferentially in the group of patients with an unfavorable prognosis. Therefore, it was not possible to compare the two additional imaging modalities. Despite these limitations, the results are encouraging.

5. Conclusions

The study results prove that both CT and PET-CT enable a detailed assessment of the location and size of the primary tumour in the breast and of the pathological lymph nodes. Contrary to MRI, which is most often performed in the prone position which significantly affects the anatomical conditions, both CT scan and PET-CT may be performed in the same position (therapeutic position) as that of the planning CT. The majority of recommendations suggest performing CT or PET-CT in cases of suspected spread of the disease [33,34]. However, considering the capabilities of modern RT, routine and accurate imaging should be performed in a systematic way. In our opinion, a patient's selection by a MDT for systemic preoperative therapy, separates those who may benefit clinically from extended radiological staging.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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Informed Consent Statement: Written informed consent was obtained from all the participants.

Data Availability Statement: Data is unavailable due to privacy or ethical restrictions. Data were collected from patients' medical records.

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Abbreviations

CT scan (computed tomography scan, performed using intravenous contrast agent), **CXR** (chest X-ray), **IMRT** (intensity modulated radiation therapy), **LDCT** (low-dose computed tomography), **MBC** (metastatic breast cancer), **MDT** (multidisciplinary team), **MMG** (mammography), **MRI** (magnetic resonance imaging), **NCCN** (National Comprehensive Cancer Network), **OS** (overall survival), **pCR** (pathologic complete response), **PET-CT** (positron emission tomography), **PFS** (progression-free survival), **planning CT** (non-contrast-enhanced computer tomography, performed in supine treatment position), **PST** (primary systemic therapy), **RT**(radiation therapy), **TNBC** (triple-negative breast cancer), **US** (ultrasound), **18F-FDG** (fluorodeoxyglucose).

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