BMI AND THE RISK OF AXILLARY FAT INFILTRATION IN PRIMARY CN0 BREAST CANCER PATIENTS – A SINGLE-CENTRE, SMALL-COHORT, RETROSPECTIVE ANALYSIS

BMI a ryzyko infiltracji tłuszczu pachowego u pacjentek z pierwotnym rakiem piersi cN0 – jednoośrodkowa analiza retrospektywna w małej kohorcie

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Abstract

Introduction and objective: The status of regional lymph nodes is one of the most important prognostic factors in breast cancer. Massive extracapsular extension of breast cancer metastasis carries a high risk of disease recurrence. A fairly high rate of false-negative clinical diagnoses of the N trait is observed during preoperative breast cancer staging. This may expose patients to prolonged therapeutic management. In this analysis, it was determined whether there is any correlation between body weight, BMI, age, and axillary fat infiltration in a population of patients who underwent both procedures – sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) – and were not originally suspected of having nodal metastases at all (cN0). **Material and methods:** A single-centre retrospective analysis of medical records was conducted in women treated between 2015 and 2019 for newly diagnosed cN0 breast cancer who ultimately underwent both procedures: SLNB followed by ALND as a separate procedure due to axillary node involvement confirmed on SLNB. A paired Student's t-test was used (confidence interval 95%). **Results:** A statistically significant association (p <0.001) between body weight and axillary fat infiltration was observed, but the linear correlation was not statistically significant. The second association – between age and axillary fat infiltration – was also statistically significant (p <0.001), while the linear correlation was not statistically significant. The association between BMI and nodal axillary fat infiltration was statistically significant (p <0.001), and unlike the previous two variables, the linear correlation was also statistically significant (p = 0.046); Pearson's correlation coefficient was r = +0.329, indicating a sufficient positive correlation. **Conclusions:** A statistically significant, sufficient, positive, linear correlation was found between BMI and nodal metastases with axillary fat involvement in women with breast cancer, initially staged as cN0.

Streszczenie

Wprowadzenie i cel: Status regionalnych węzłów chłonnych jest jednym z najważniejszych czynników prognostycznych w raku piersi. Masowe przejście przerzutu przez torebkę węzła chłonnego wiąże się z wysokim ryzykiem nawrotu choroby. Podczas diagnostyki przedoperacyjnej raka piersi obserwuje się dość wysoki wskaźnik fałszywie ujemnych rozpoznań cechy klinicznej N. Może to narażać pacjentów na przedłużone postępowanie terapeutyczne. Celem niniejszej analizy była ocena, czy istnieje jakakolwiek korelacja między masą ciała, BMI, wiekiem pacjentek a infiltracją nowotworową tłuszczu pachowego w populacji chorych, u których wykonano oba zabiegi – biopsję węzła wartowniczego (SLNB) oraz limfadenektomię pachową (ALND) – i u których pierwotnie nie podejrzewano obecności przerzutów do węzłów chłonnych (cN0). **Materiał i metody:** Przeprowadzono jednoośrodkową retrospektywną analizę dokumentacji medycznej kobiet leczonych w latach 2015–2019 z powodu nowo zdiagnozowanego raka piersi z cechą cN0, które ostatecznie przeszły obie procedury: najpierw SLNB, a następnie ALND (jako odrębny zabieg operacyjny) z powodu zajęcia pachowych węzłów chłonnych przez nowotwór. Zastosowano test t-Studenta dla par zależnych (przedział ufności 95%). **Wyniki:** Stwierdzono statystycznie istotny związek pomiędzy masą ciała a naciekaniem tłuszczu pachowego (p <0,001), jednak korelacja liniowa nie była istotna statystycznie. Również związek między wiekiem a infiltracją tłuszczu pachowego był istotny statystycznie (p <0,001), przy czym korelacja liniowa nie była istotna statystycznie. Związek między BMI a infiltracją tłuszczu pachowego był istotny statystycznie (p <0,001), a korelacja liniowa, w przeciwieństwie do dwóch poprzednich par, również była istotna statystycznie (p = 0,046). Współczynnik korelacji Pearsona wyniósł r = 0,329, co wskazuje na dodatnią i wystarczającą korelację. **Wnioski:** Stwierdzono statystycznie istotną, wystarczającą, dodatnią korelację liniową między BMI a obecnością przerzutów do węzłów chłonnych z zajęciem tłuszczu pachowego u kobiet z rakiem piersi, u których początkowo rozpoznano cechę cN0.

Keywords: breast cancer; axillary fat infiltration; BMI and breast cancer; lymph node metastasis

Słowa kluczowe: rak piersi; naciek tłuszczu pachowego; BMI a rak piersi; przerzuty do węzłów chłonnych

DOI 10.53301/lw/210967

Received: 26.07.2025

Accepted: 16.09.2025

Published: 15.09.2026

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Introduction

A fairly high rate of false-negative clinical N staging occurs during preoperative breast cancer diagnosis. This may expose patients to prolonged therapeutic management and involve malpractice claims, particularly directed at radiologists. According to Whang et al., the most frequent cause of medical malpractice claims in the United States related to procedures performed by radiologists involves errors made during breast cancer diagnosis [1].

The diagnostic procedure in breast cancer staging requires radiological examinations of the breast and regional lymphatic system (mammography (MMG) and ultrasound (US)), in addition to physical examination. Magnetic resonance imaging (MRI) is also used in selected cases, especially in younger patients.

Regional lymph nodes metastatic status remains one of the most important prognostic factors. Massive extracapsular extension of breast cancer metastasis carries a high risk of disease recurrence [2].

During the reviewed period, the available randomised trial data were insufficient to recommend omitting completion axillary lymph node dissection (ALND) in T1/T2 breast cancer with fewer than three involved sentinel lymph nodes (SLNs) in patients undergoing lumpectomy and whole-breast irradiation. Longer follow-up was then necessary to confirm that omitting ALND was safe and that distant outcomes were equivalent in patients with luminal A breast cancer presenting with more advanced disease, e.g. in patients with T2 tumours and two positive SLNs [3].

The subjectivity of ultrasound and physical examination is their main disadvantage. US, which plays a significant role in assessing axillary lymph node status, demonstrates 77% sensitivity and 80% specificity [4]. Other authors report a specificity of 95% in vivo, with only 36% sensitivity [5]. A sensitivity below 40% may raise doubts about the clinical utility of US in breast cancer staging.

Axillary lymph nodes metastatic involvement may be very subtle [6].

The criteria for suspecting a metastatic lymph node are:
- the longest dimension greater than 1 cm or more than 5 mm in the short axis,
- asymmetry compared with the contralateral side (both in the number of lymph nodes and in size, even if within normal limits),
- loss or blurring of the nodal margin,
- infiltration of axillary fat,
- thickening of the cortical layer of more than 3 mm,
- obliteration of the fatty hilum,
- significant enlargement, especially when the node assumes a spherical shape [6, 7].

A preserved nodal hilum has limited prognostic value. The tumour and the visible interstice in the hilum are, on the other hand, late signs of massive metastatic lymph node involvement [8].

In 2016, researchers published a paper describing 5,142 cN0 patients who underwent 5,262 sentinel lymph node biopsy (SLNB) procedures. Overall, 28% of the patients had body mass index (BMI) >30 kg/m^2. Larger tumour size, younger age, multifocality, lymphovascular invasion, and high nuclear grade were the most common predictors of SLN positivity. They found no correlation (p = 0.6) between increased BMI and an increased likelihood of SLN metastasis. There was a 4% overall burden of axillary metastases in cN0 patients. Physical examination, according to the authors, is both appropriate and sufficient for preoperative axillary staging regardless of patient BMI [9].

In a retrospective study of 188 women who underwent screening mammography, the length and width of the lymph node, as well as the size of the hilum in the largest visible axillary node, were measured. The authors of this study found a significant association between increased BMI and the dimensions of axillary lymph nodes (caused by fatty infiltration), independent of age or breast density [10].

Conversely, the absence of suspicious changes on mammography, ultrasound, or MRI does not exclude the presence of lymph node metastases – especially micrometastases (i.e. metastases smaller than 2 mm) [11].

In this analysis, it was determined whether there is any correlation between body weight, BMI, patient age, and axillary fat infiltration in a cohort of patients who underwent both procedures – SLNB and ALND – and who were not originally suspected of having nodal metastases at all (cN0). The research hypothesis investigates whether an association exists between body weight, BMI, or age of cN0 breast cancer patients and axillary fat infiltrating lymph node metastases.

Material and methods

A retrospective analysis of medical records was conducted among female patients with cN0 breast cancer treated at the St. John of Dukla Oncology Centre in Lublin, Poland. There were 37 women operated on between 2015

and 2019 for newly diagnosed cN0 breast cancer who underwent both procedures: SLNB followed by ALND as a separate procedure due to axillary node involvement found on SLNB. Micrometastases were not considered.

The axillary nodes were initially assessed as clinically non-suspicious – cN0. Clinical staging was determined by physical examination, mammography, and ultrasound only.

Homogeneity of variance was evaluated by Levene's test; statistical significance was assessed at a 95% confidence interval (CI) using a paired Student's t-test; and internal consistency was evaluated using Cronbach's alpha test. GNU PSPP ver. 2.0.0-g5b54d1 statistical software was used.

The mean age of patients was 56.1 years; median age: 44 years; mean body weight: 72.2 kg; median body weight: 73 kg; mean BMI: 28.2 (kg/m^2); and median BMI was 28 (kg/m^2) (Tab. 1).

The number of women with metastases to the adipose tissue surrounding a sentinel lymph node with node diameter = <10 mm was 9 (24.3%); and with node dimension >10 mm it was also 9 (24.3%). There were 6 (16.2%) women with metastases to perinodal adipose tissue (excluding micrometastases) revealed during the ALND procedure (Tab. 2).

As many as 26 (70.2%) women did not have any further metastases identified on ALND.

Statistical analysis for the body weight and axillary infiltration pair yielded: homogeneity of variance using Levene's test = 0.28, p = 0.597; paired t-test: p <0.001; Pearson's correlation r = +0.315, p = 0.058.

For the age and lymph axillary infiltration pair: Levene's test = 1.59, p = 0.215; paired t-test: p <0.001; Pearson's correlation r = −0.103; p = 0.543.

Finally, for the BMI and axillary infiltration pair: Levene's test = 0.27, p = 0.681; paired t-test: p <0.001; and Pearson's correlation r = +0.329, p = 0.046 (Fig. 1).

Scale reliability measured using Cronbach's alpha was 0.75 (N = 6 items).

A comprehensive summary of the statistics is presented in Table 3.

Results

The tests showed a statistical significance (p <0.001) between body weight and axillary fat infiltration, but the linear correlation (moderate and positive) was not statistically significant.

The second association – between age and axillary fat infiltration – also demonstrated statistical significance (p <0.001), but the linear correlation was weak, negative – and not statistically significant.

Evaluating the paired t-test for dependent pairs revealed that the association between BMI and nodal axillary fat infiltration was also statistically significant (p <0.001) and, importantly, the linear correlation was statistically significant here (p = 0.046); Pearson r = +0.329 (sufficient and positive).

Discussion

The aim of this study was to evaluate potential correlations between body weight, BMI, age of women with

Table 1. Patient characteristics

Number of cases	Mean age (y)	Median age (y)	Mean body weight (kg)	Median body weight (kg)	Mean Body Mass Index (BMI) (kg/m^2)	Median BMI (kg/m^2)
37	56.1	44	72.2	73	28.2	28

Table 2. Number of patients with metastases to the perinodal adipose tissue of the sentinel lymph node

Sentinel Lymph Node (SLN) dimension =<10mm (excluding micrometastases)	SLN dimension >10mm (excluding micrometastases)	Lymph nodes after Axillary Lymph Node Dissection (ALND), no sentinel dimension data in pathological report (excluding micrometastases)	Lymph nodes after Axillary Lymph Node Dissection (ALND), no sentinel dimension data in pathological report) (micrometastases)	No metastases found after ALND
9	9	6	5	26
24.3%	24.3%	16.2%	13.5%	70.2%

Table 3. Results of statistical analyses

Variable pair		
Body weight-axillary infiltration	**Age-axillary infiltration**	**BMI-axillary infiltration**
Paired Student's t-test		
***p* <0.001**	***p* <0.001**	***p* <0.001**
Pearson's linear correlation		
R = +0.315 (p = 0.058)	R = −0.103 (p = 0.543)	**R = +0.329 (p = 0.046)**

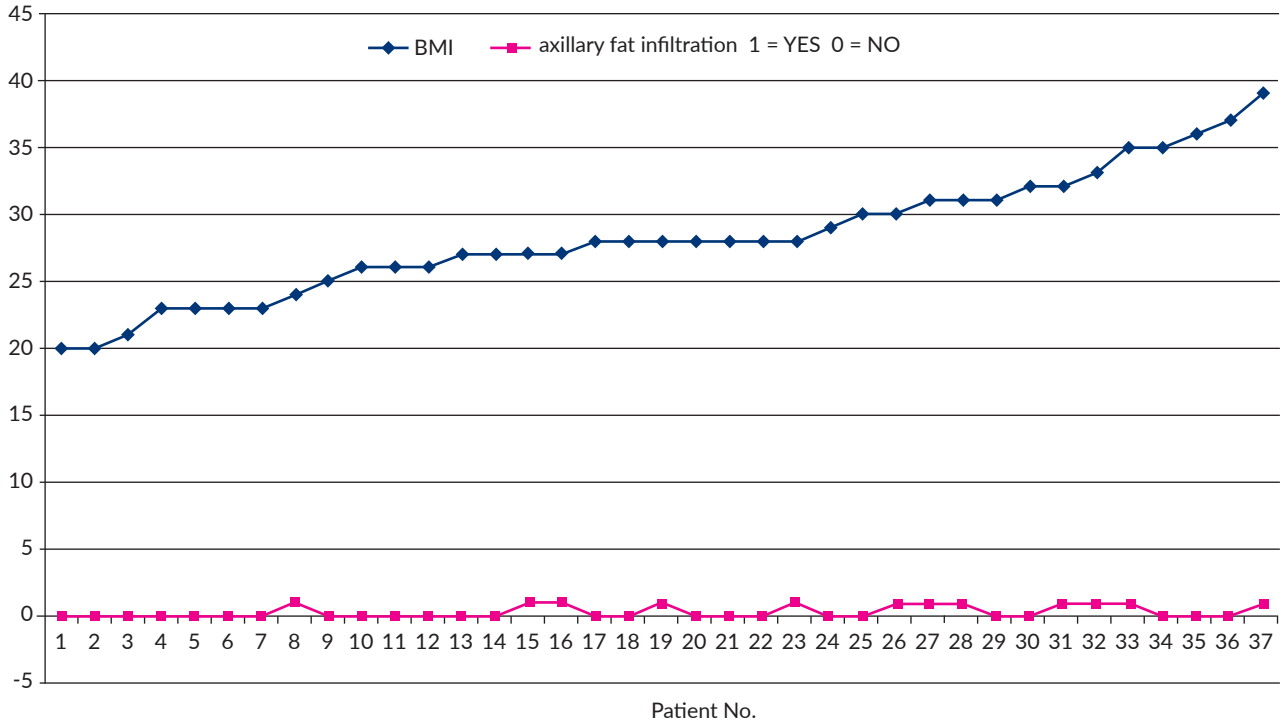

Figure 1. BMI-axillary fat infiltration

breast cancer, and axillary fat infiltration in a cohort of patients who underwent both procedures – SLNB and ALND – and were initially classified as cN0. A paired t-test (CI = 95%) was conducted for related variables (all features were measured across the same 37 patients). The test detected statistically significant relationships between body weight, BMI, age, and axillary fat infiltration ($p < 0.001$).

Linear Pearson correlations for the "weight-infiltration" and "age-infiltration" pairs were not statistically significant. However, for the "BMI-infiltration" pair, the Pearson linear correlation ($r = +0.329$) was statistically significant ($p = 0.046$), demonstrating a sufficient, positive relationship.

This means a higher likelihood of nodal metastases with axillary fat involvement along with increasing BMI.

The main limitation of the present analysis is the small sample (37 patients) derived from a single centre, and its retrospective design.

Prior scientific studies show that enlargement of the fatty hilum on MRI is associated with a high likelihood of nodal metastasis in obese women with breast cancer, regardless of BMI and tumour characteristics [12]. Whether this warrants broader utilisation of MRI in the routine staging of obese patients remains controversial. Other studies do not support this strategy. For example, a large (2,084 patients with invasive breast cancer) study shows that MRI prediction had lower accuracy in overweight women (65.1%) than in normal-weight (67.8%) and underweight women (76.1%) [13].

Furthermore, some studies on the value of ultrasound in detecting axillary lymph node metastases depending on BMI in breast cancer patients indicate that axillary ultrasound (AUS) is a valuable method in diagnosing the condition of axillary lymph nodes ($p < 0.0001$). However, the specificity ($p = 0.001$) and accuracy ($p = 0.008$) of AUS were better in overweight ($p = 0.007$) and obese ($p = 0.02$) patients than in individuals with normal BMI [14].

It can be concluded that AUS is a dependable method for detecting axillary metastases; however, it requires substantial experience on the part of the radiologist to avoid false-negative evaluations.

Conclusions

There is a statistically significant, sufficient, positive linear correlation between BMI and lymph node metastases with axillary fat involvement in women with breast cancer, initially diagnosed as cN0. The linear correlations between age, body weight, and axillary fat metastatic involvement were identified but did not reach statistical significance.

The primary limitation of this study was the small, retrospective sample from a single centre: 37 patients who underwent both procedures: SLNB followed by ALND as a separate procedure due to axillary node involvement (initially cN0 staging on AUS and mammography). It is necessary to verify these findings in a larger, prospective, multi-centre study.

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