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Observational Study

Factors predicting upstaging from clinical N0 to pN2a/N3a in breast cancer patients

Oda G *et al.* Factors of multiple ALN metastases

Goshi Oda, Tsuyoshi Nakagawa, Hiroki Mori, Iichiro Onishi, Tomoyuki Fujioka, Mio Mori, Kazunori Kubota, Ryoichi Hanazawa, Akihiro Hirakawa, Toshiaki Ishikawa, Kentaro Okamoto, Hiroyuki Uetakeszsz

Abstract

BACKGROUND

With sentinel node metastasis⁹ in breast cancer (BC) patients, axillary lymph node (ALN) dissection is often omitted from cases with breast-conserving surgery. Omission of¹⁴ lymph node dissection reduces the invasiveness of surgery to the patient, but it also obscures the number of metastases to non-sentinel nodes. The possibility of finding ≥ 4 lymph nodes (pN2a/pN3a) preoperatively is important given the ramifications for postoperative treatment.

AIM

To search for clinicopathological factors that predicts upstaging from N0 to pN2a/n3a.

METHODS

Patients who were sentinel lymph node (SLN)-positive and underwent ALN dissection between September 2007 and August 2018 were selected by retrospective chart review. All patients had BC diagnosed preoperatively as N0 with axillary evaluation by

⁵ fluorodeoxyglucose (FDG) positron emission tomography/computed tomography and ultrasound (US) examination. When suspicious FDG accumulation was found in ALN, the presence of metastasis was reevaluated by second US. We examined predictors of upstaging from N0 to pN2a/pN3a.

RESULTS

Among 135 patients, we identified 1-3 ALNs (pN1) in 113 patients and ³⁴ ALNs (pN2a/pN3a) in 22 patients. Multivariate analysis identified the total number of SLN metastasis, the maximal diameter of metastasis in the SLN (SLNDmax), and FDG accumulation of ALN as predictors of upstaging to pN2a/pN3a.

CONCLUSION

We identified factors involved in upstaging from N0 to pN2a/pN3a. The SLNDmax and number of SLN metastasis are predictors of ≥ 4 ALNs (pN2a/pN3a) and predictors of metastasis to non-sentinel nodes, which have been reported in the past. Attention should be given to axillary accumulations of FDG, even when faint.

¹¹ **Key Words:** Breast cancer; Axillary lymph node metastasis; Positron emission tomography/computed tomography; Sentinel lymph node; Predictive factors of lymphnode metastasis; Standardized uptake value max; Diameter of sentinel lymphnode metastasis

²⁵ Oda G, Nakagawa T, Mori H, Onishi I, ²⁹ Fujioka T, Mori M, Kubota K, Hanazawa R, Hirakawa A, Ishikawa T, Okamoto K, Uetake H. Factors predicting upstaging from clinical N0 to pN2a/N3a ²⁹ in breast cancer patients. *World J Clin Oncol* 2022; In press

¹⁶ **Core Tip:** This is the first report to include the results of preoperative positron emission tomography/computed tomography (PET/CT) and ²⁰ to examine results related to the upstaging of pN2a/N3a (more than 4 axillary lymph node metastases) in breast cancer

(BC) patients. Specifically, 135 patients who were sentinel lymph node (SLN)-positive and underwent ALN dissection were selected by retrospective chart review, all of whom had BC diagnosed preoperatively as N0 with axillary evaluation by fluorodeoxyglucose (FDG) PET/CT and ultrasound. Our results suggest that the size and number of SLN metastases were still important factors. And, attention should be given to axillary accumulations of FDG, even when faint.

INTRODUCTION

³⁰ Sentinel lymph node (SLN) biopsy is usually performed in N0 cases. If SLN biopsy yields a positive result, an axillary lymph node (ALN) dissection is performed. ⁷ However, since the publication of findings from the American College of Surgeons Oncology Group (ACOSOG) Z-0011 trial, many cancer centers have been omitting ALN dissection from breast-conserving surgeries^[1]. The problem with omitting axillary dissection is that the number of non-SLN metastases cannot be ascertained, which may lead to over or under-treatment with adjuvant chemotherapy and radiation therapy. For example, patients with pN2a [4-9 ALN metastases (ALNMs)] or pN3a (³10ALNMs) need to be irradiated to not only the residual breast, but also the supraclavicular region after breast-conserving surgery. However, without knowing the number of metastases, no accurate decision on the need for irradiation can be made. Post-mastectomy radiation (PMRT) is also required for pN2a/N3a patients. Some reports have noted that PMRT after reconstruction impairs conformity^[2-4]. Further analyses have shown that direct implants and autologous tissue reconstruction have fewer complications from PMRT^[5,6]. The ability to predict the necessity of postoperative irradiation before surgery would affect surgical planning, including reconstructive surgery. A variety of factors and nomograms have been reported to allow preoperative prediction of the presence or absence of ALNMs^[7-9], but few reports have examined factors predicting the presence of ³⁴ ALNMs. Preoperative ¹⁷ fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) is reportedly excellent for predicting metastasis preoperatively and may have influenced the prediction of ALNMs in the present study. Although many papers have described predictors of non-SLN metastasis, few have rigorously assessed ALNM preoperatively using PET/CT. In this study, ⁵ all patients were evaluated preoperatively by PET/CT, and cases with false-negative results on other imaging modalities were excluded. ⁵ This is the first report to include the results of preoperative PET/CT and to examine results related to the upstaging of pN2a/N3a.

¹² MATERIALS AND METHODS

Patients

A retrospective chart review was conducted for patients who were SLN-positive and underwent ALND between September 2007 and August 2018. All patients had breast cancer (BC) diagnosed preoperatively as N0 with axillary evaluation by PET/CT and ultrasound (US) examination. This study was conducted with approval from the institutional review board and with the informed consent of each patient. Axillary dissection was performed in all patients with SLN metastasis > 2 mm in diameter. In the case of total mastectomy, axillary dissection was performed for metastases > 0.2 mm in diameter. A flow chart of the eligible/included patients is shown in Figure 1.

About ultrasound examination

A EUB-7500 scanner with a EUP-L54MA 9.75-MHz linear probe (Hitachi Medical Systems, Tokyo, Japan) or Aplio XG scanner with a PLT-805AT 8.0-MHz linear probe (Toshiba Medical Systems, Tochigi, Japan) was used for US examinations. If ultrasound or PET/CT findings were suspicious for metastatic lymph nodes, cytology was performed.

Protocol for FDG-PET/CT

All patients were intravenously administered ^{18}F -FDG (3.7 MBq/kg; 0.1 mCi/kg) after a minimum 4-h fasting period. Next, whole-body images were routinely obtained using a PET/CT system (Aquiduo; Toshiba Medical Systems, Tokyo, Japan). In addition, CT was performed using the following parameters: pitch factor, 0.938; gantry rotation time, 0.5 s; table time, 30 mm/s; auto-exposure control (SD20), 120 kVp; and slice thickness, 2.0 mm. Notably, contrast media were not used for CT examinations. Approximately 60 min after ^{18}F -FDG administration, whole-body PET was performed using the following parameters: emission time per bed, 2 min; bed positions, 7-8; slice thickness, 3.375 mm; and matrix, 128×128 .

Data analysis of FDG-PET/CT

¹In the present study, ¹⁸F-FDG-PET/CT findings at each examination were assessed using a consensus reading by two breast radiologists (T.F. with 14 years of experience in breast imaging; M.M. with 10 years of experience in breast imaging). We performed visual analysis of primary lesions and ALNs without defining a cut-off value. Of note, lesions with an ¹⁸F-FDG uptake value higher than that of the background tissue were defined as FDG-positive.

²*Immunohistochemical examination*

All specimens were analyzed by pathologists from our institution, and specimens were considered estrogen receptor (ER) positive on immunohistochemistry (IHC) for staining rates higher than 10%. For human epidermal growth factor receptor 2 (HER2) values, and IHC result of 3+ was defined as BC with strong, complete membrane staining observed in at least 10% of tumor cells. For HER2 overexpression of 2+, gene amplification with fluorescence in situ hybridization was performed in this study.

Data analysis

Differences in proportions of categorical data were tested using Fisher's exact probability test. Unless otherwise indicated, significant differences among mean values of numerical data were analyzed using Mann-Whitney test. Relationships between the size of SLN metastases and the number of ALNMs were measured using Spearman rank correlation analysis, which can have a magnitude ranging from 0 to 1, with 0 denoting no correlation at all and 1 denoting complete correlation. Predictors of upstaging to pN2a/pN3a were determined by univariate and multivariate logistic regression analyses. Values of $P < 0.05$ were regarded as statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interfaces for R (The R Foundation for Statistical Computing, Vienna, Austria)^[10]. More precisely, EZR is a modified version of R Commander designed to add statistical functions frequently used in biostatistics.

RESULTS

Demographic and clinical characteristics of study subjects

We retrospectively analyzed 135 BC patients who were SLN-positive and had undergone ALN dissection. FDG-PET/CT was performed in all cases preoperatively. The detailed clinicopathological characteristics of subjects are summarized in Table 1. Among these, 113 patients showed 1-3 ALNMs (pN1) and 22 patients had 34 ALNMs (pN2a/pN3a). FDG accumulation in ALNs was found on PET/CT in 19 cases (14.1%). The mean standardized uptake value (SUV) max was 1.48 (range, 0.8-2.0). Preoperative PET/CT showed accumulation in the ALNs, and second-look US was performed in cases where metastasis could not be ruled out. The mean number of excised SLNs was 1.6 (range, 1-5) and the mean number of SLN metastasis was 1.2 (range, 1-3). The median maximal diameter of metastasis in the SLN (SLNDmax) was 3 mm. The correlation between the SLNDmax and the number of ALNMs is shown in Figure 2. A strong correlation was identified between SLNDmax and the number of ALNMs ($P < 0.001$). We measured the cut-off value for the SLNDmax from the receiver operating characteristic (ROC) curve and the cut-off value for upstaging from N0 to pN2a/pN3a was set at 5 mm (area under the curve: 0.873; 95%CI: 0.808–0.931) (Figure 3). Table 2 shows a comparison between pN1 and pN2a/pN3a.

Univariate logistic regression analysis of risk factors associated with upstaging

To search for risk factors for upstaging to pN2a/N3a, univariate and multivariate analyses were performed for associations with clinicopathological factors in two groups of pN1 and pN2a/N3a cases. Invasive diameter at the primary site, number of SLN metastasis, FDG accumulation in ALNs, and SLNDmax were associated with upstaging to pN2a/pN3a, but age, ER status, HER 2 status, tumor grade, and SUVmax at the primary site were not (Table 3).

Multivariate logistic regression analysis of risk factors associated with upstaging

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Multivariate logistic regression analysis of clinicopathologic factors was used to examine risk factors for upstaging to pN2a/pN3a. The number of SLN metastasis, SLNDmax, and FDG accumulation in ALNs were associated with upstaging (Table 3).

DISCUSSION

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The ACOSOG Z-0011 trial concluded that ALN dissection is not always necessary for women undergoing breast-conserving surgery with 1-2 positive SLNs^[1]. However, the overall number of ALNMs represents crucial clinical information. Although avoidance of ALN dissection reduces the degree of surgical invasiveness of a procedure, the number of ALNMs cannot be ascertained. If more than 4 metastatic lymph nodes are present, radiation to the breast or chest wall as well as to the supraclavicular area is necessary^[11]. Thus, not knowing the number of ALNMs may lead to over-or under-treatment with radiation therapy postoperatively. The presence or absence of postoperative radiation may also affect the choice of reconstructive technique. Radiation during the insertion of an expander is associated with a greater risk of complications, while radiation after implant placement or to autologous tissue is reported to have fewer complications^[2,3]. Pre- and postoperative prediction of the number of ALNMs affects not only the optimal extent of axillary dissection, but also the choice of radiotherapy and, indirectly, reconstruction methods. In the present study, we searched for predictors of upstaging from clinical N0 to pN2a/pN3a using factors identified pre- or intraoperatively, including FDG-PET/CT. This imaging modality is generally considered useful in searching for ALNMs^[12]. However, few reports have specified whether preoperative PET/CT was performed when examining factors predicting non-SLN metastasis. As a result of examining various factors for upstaging, we extracted SLNDmax, mild accumulation of FDG in the axilla, and the number of SLN metastasis. The SLNDmax and the number of SLN metastasis have been reported in the past as predictors of metastasis to non-SLNs^[13-16]. This is the first study to show that these factors are also important in upstaging from N0 to pN2a/pN3a. Various cut-offs for the SLNDmax have been reported as a predictor of non-SLN metastasis, and we used ROC

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curves in our search. As a result, the predictor for upstaging from N0 to pN2a/pN3a was set at 5 mm. If the number of SLN metastasis is large (that is, two or more) or the diameter of metastasis is large (more than 5 mm), or if FDG accumulation in the axilla is mild even if no metastases have been confirmed, irradiation to the chest wall and supraclavicular region may need to be considered even in cases where axillary dissection has been omitted. PET/CT is often performed preoperatively for different cancers. On the other hand, findings from this modality are reportedly less significant for low-stage BC, given the low likelihood of distant metastasis. Some reports have suggested that SUV at the primary site may offer a useful predictor of metastasis to non-SLNs^[17]. Ueda *et al*^[18] evaluated ALNMs using PET/CT and reported low sensitivity but high specificity. In the present study, we found PET/CT to be useful in predicting multiple ALNMs, but the positive predictive value was not particularly high (57.9%). Many questions remain unanswered, such as the optimal cut-off value for integrated SUV, the influence of the histological type of the primary tumor, and the suitable timing of biopsy.

Further accumulation and analysis of cases are needed. Institutions that aggressively omit axillary dissection should be aware of the dangers of remaining ignorant of the number of ALNMs when multiple risk factors are identified pre- or intraoperatively.

CONCLUSION

The present study investigated factors predictive of upstaging from clinical N0 to pN2a/pN3a. Factors such as the number of metastases and SLNDmax, which have previously been reported as predictors of metastasis to non-SLNs, were also useful in predicting upstaging to pN2a/pN3a and emphasized the utility of FDG-PET/CT. The only factor that predicts preoperatively, but not intraoperatively, is the result of FDG-PET/CT.

ARTICLE HIGHLIGHTS

Research background

With sentinel node metastasis⁹ in breast cancer (BC) patients, axillary lymph node (ALN) dissection is often omitted from cases with breast-conserving surgery. Omission of¹⁴ lymph node dissection reduces the invasiveness of surgery to the patient, but it also obscures the number of metastases to non-sentinel nodes.

Research motivation

The possibility of finding ≥ 4 lymph nodes (pN2a/pN3a) preoperatively is important given the ramifications for postoperative treatment.

Research objectives

The purpose of this study is to search for clinicopathological factors that predict upstaging from N0 to pN2a/N3a.

Research methods

Patients who were SLN-positive and underwent ALN dissection between September 2007 and August 2018 were selected by retrospective chart review. All patients had BC diagnosed preoperatively as N0 with axillary evaluation by⁵ fluorodeoxyglucose (FDG) positron emission tomography/computed tomography and ultrasound (US) examination. When suspicious FDG accumulation was found in ALN, the presence of metastasis was reevaluated by second US. We examined predictors of upstaging from N0 to pN2a/pN3a.

Research results

Among 135 patients, we identified 1-3 ALNs (pN1) in 113 patients and ³⁴ ALNs (pN2a/pN3a) in 22 patients. Multivariate analysis identified the total number of SLN metastasis, the maximal diameter of metastasis in the SLN (SLNDmax), and FDG accumulation of ALN as predictors of upstaging to pN2a/pN3a.

Research conclusions

We identified factors involved in upstaging from N0 to pN2a/pN3a. The SLNDmax and number of SLN metastasis are predictors of ≥ 4 ALNs (pN2a/pN3a) and predictors of metastasis to non-sentinel nodes, which have been reported in the past. Attention should be given to axillary accumulations of FDG, even when faint.

Research perspectives

It is somewhat possible to predict upstaging to pN2a/pN3a by searching for clinicopathological factors

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