

# Zgodnje odkrivanje metastaz v bezgavkah v vratu pri bolnicah z rakom dojke: vloga ultrazvoka in igelne biopsije

## Early detection of neck lymph node metastases in breast cancer patients: the role of ultrasound and fine needle biopsy

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### Izvleček

**Namen:** Namen raziskave je bil pridobiti razumevanje porazdelitve odkritih metastaz v vratu pri bolnicah z rakom dojke.

**Metode:** Skozi retrospektivno analizo smo identificirali 41 bolnic z rakom dojke ter analizirali klinično-patološke značilnosti bolnic in značilnosti potrjenih metastaz v vratu. Pregledali smo podatke bolnic, obravnavanih v naši ustanovi med leti 2010 do 2016, povzete iz medicinske dokumentacije. Diagnozo metastaz v vratu smo potrdili s tankoigelno biopsijo. Glede na prizade-

### Abstract

**Purpose:** To analyze the distribution and pattern of neck metastasis in breast cancer (BC) patients.

**Methods:** The clinicopathological characteristics of 41 patients with BC and confirmed neck metastasis (NM) treated at our institution between 2010 and 2016 were retrospectively analyzed by reviewing medical records. The diagnosis of NM was confirmed by fine needle aspiration cytology, and node localization was classified into six levels according to Robbins' classification. Statistical analysis was performed using

tost bezgavk so bile metastaze klasificirane v 6 ravni glede na Robinsonovo klasifikacijo. Statistično analizo smo opravili s pomočjo programa SPSS. Za analizo smo uporabili deskriptivno statistiko, Pearsonovo korelacijo in multidimenzionalno korespondenčno statistiko.

**Rezultati:** S pomočjo ultrazvoka vratu smo metastaze odkrili pri 34 bolnicah (85 %). 38 % bolnic je bilo asimptomatskih. V 17 % ni bilo tipnih nobenih bezgavk. Povprečni čas od diagnoze do razvoja metastaz je bil 5,8 let (razpon od 0 do 26 let). 53,7 % metastaz je bilo ugotovljeno na ravni V; IV. stopnja je bila vključena v 19,5 %. 9,8 % metastaz je bilo prisotnih na obeh ravneh. V 75 % so bile metastaze prisotne samo na eni ravni. Pomembna korelacija ( $p < 0,01$ ) je bila prisotna med: i) starostjo bolnice in časom od diagnoze do razvoja metastaz v vratu, ii) starostjo in stopnjo bolezni ter iii) stopnjo in videzom konglomeratov.

**Zaključek:** Metastaze v vratu se pri bolnicah z rakom dojke običajno kažejo poleg položaja v supraklavikularni loži, pa tudi na drugih ravneh. Zaznavanje zgodnjih okulturnih metastatskih bezgavk je mogoče z ultrazvočnim pregledom v kombinaciji s citološko punkcijo.

descriptive statistics, Pearson's correlation and multidimensional correspondence analysis. All statistical analyses were performed using SPSS.

**Results:** At the time of neck ultrasonography, 34 (85%) patients had developed distant metastases, 38% of the patients were asymptomatic, and 17% had no palpable nodes. The average time from BC diagnosis to the development of NM was 5.8 years (range, 0–26 years). Lymph node metastasis occurred at level V in 53.7% of patients and level IV in 19.5% of patients. Two-level involvement occurred in 9.8% and one-level involvement in 75% of patients. There were significant correlations ( $p < 0.01$ ) between patient age and time from diagnosis to development of NM, age and stage of the disease, and stage and appearance of conglomerates.

**Conclusion:** The most common site of NM from BC was next to the supraclavicular fossa, although they occurred at other levels. Ultrasonography combined with fine needle aspiration cytology is effective for the detection of early occult metastatic lymph nodes.

## INTRODUCTION

Breast cancer (BC) is the most common cancer in women worldwide. In Europe the average annual mortality is between 13 and 19/100,000 women (1,2). In Slovenia, the annual mortality rate per year is 17/100,000 women (3). Mortality rates have improved mainly because of advances in therapy rather than early detection (4). The prolonged life expectancy of women with BC is associated with a greater risk of distant metastasis. The most common sites of distant metastasis are the spine and pelvis (77%), liver (39%), and central nervous system (5).

The occurrence of cervical lymph node metastasis in patients with BC is associated with poor prognosis. A study assessing the development of neck metastasis (NM) in the supraclavicular region in 2,658 patients (6) reported that only 4.3% of the patients developed metastasis. At that time in 2001, the factors associated with a higher probability of developing NM were age <40 years, tumor size >3 cm, high histological grade,

lymphovascular invasion, negative estrogen receptor status, synthetic phase fraction >4%, >4 positive axillary nodes, and involvement of axillary nodes at levels II and III.

Infraclavicular primaries commonly metastasize to the supraclavicular region and not to the neck (7). BC metastasis to the ipsilateral supraclavicular fossa is classified as loco-regional metastasis (N3c). Lymph nodes above the supraclavicular region are not mentioned, although they should be considered as distant metastases (7).

A study of NM in BC patients in the United Kingdom (UK) in 2012 showed considerable variation in the approach towards staging as well as treatment (8).

The aim of this study was to analyze the distribution and characteristics of NM in patients with BC and explore the value of ultrasonography and fine needle aspiration cytology for the early detection of occult nodes.

## METHODS

Patients with BC referred to the Department of Otorhinolaryngology & Maxillofacial Surgery of the University Medical Center Maribor between 2010 and 2016 were scanned for the presence of NM. Patients were referred to our department because of the presence of suspicious nodes on the neck or high levels of the breast carcinoma biomarker cancer antigen 15-3. The study included patients with a confirmed diagnosis of NM by fine needle biopsy.

Patients referred to the Department of Otorhinolaryngology & Maxillofacial Surgery were evaluated using ultrasonography, which is a commonly used first-line screening method (9). Partitioning the neck into six levels is a widely used method for determining the exact location of metastasis during head and neck surgery (10), and this technique was used in the present study.

### Patients and materials

Over a 7-year period, 1,349 patients with primary BC were treated at our institution. Approximately 3% of all BC patients treated at our institution at a given time were diagnosed with NM during follow-up. Patients were referred for head and neck examinations after undergoing screening at the Center for Diseases of the Breast. The examination was either a regular follow-up examination or an unscheduled examination in patients with deteriorating disease conditions. Ultrasonography and fine needle biopsy were performed in all patients. BC metastases were confirmed by cytological analysis.

The Voluson 730 ultrasound system (GE Healthcare; Boston, MA, USA) was used with a 5–10 MHz linear transducer. The location of metastases in the neck was classified according to Robbins (10) as follows: level I, submental and submandibular nodes; level II, upper jugular group of nodes; level III, middle jugular nodes; level IV, caudal jugular nodes; level V, nodes of the posterior neck triangle; and level VI, anterior neck compartment.

The distribution, size, and number of metastatic lymph nodes, the presence of conglomerates, and the presence of contralateral lymph node metastasis were evaluated. These features were determined by

ultrasonography.

Data analysis was performed using the SPSS statistical package version 20.0 (IBM, Armonk, NY, USA). Descriptive analysis and Pearson's correlation were used, and a p-value <0.05 was considered statistically significant. Multidimensional correspondence analysis (MCA) was used to assess the associations between node dimensions and number, the presence of conglomerates, the occurrence of collateral lymph node metastases, the distribution of nodes and stage. MCA is a multivariate statistical and visualization technique that is extremely useful for analyzing multiway contingency tables in cases showing correspondence between columns and rows. It is conceptually similar to principal component analysis, although it is used for categorical rather than continuous data. The MCA results are presented as "bi - plots." The proximity of items in a bi-plot represents the degree of association between them. Items positioned near each other show a greater association than items further away. Each bi-plot is characterized by two dimensions that can be identified during the analysis. The study was approved by the Institutional Review Board (approval No. UKC-MB-KME-46/14).

## RESULTS

### Patient characteristics

The study included 41 patients with cytologically confirmed NM. The average age of BC patients at the time of NM diagnosis was 54.9 years (range, 38–81 years). The primary BC was invasive ductal carcinoma in 29 (70.7%) patients, invasive lobular carcinoma in 2 (4.9%), invasive ductal and lobular carcinoma in 3 (7.3%), invasive ductal and inflammatory carcinoma in 1 (2.4%), and invasive micropapillary carcinoma in 1 (2.4%) patient. Five (12.2%) patients had no exact histologic diagnosis and were diagnosed by cytological evaluation at an advanced disease stage. In these cases, histological samples were not obtained by surgery. The primary treatment in 31 (75.6%) patients was surgery combined with postoperative chemotherapy,

radiotherapy, and/or hormonal therapy according to established guidelines. Three (7.3%) patients underwent neoadjuvant chemotherapy followed by surgery. Among the surgically treated patients, mastectomy was performed in 22 and breast conserving surgery in 11 women. Axillary lymph node dissection was performed in 26 patients and sentinel node biopsy in two. Four patients (9.8%) were treated with chemotherapy only and two (4.9%) with hormone therapy only. Exact information on primary treatment could not be obtained for one patient who was treated in a different institution.

### Metastasis evaluation

At the time of the otorhinolaryngological examination, 34 of 41 patients (85%) had developed distant metastases. Of these patients (n = 34), 29 developed metastasis at multiple sites. The locations of the distant metastases were as follows: bones (73.5%), liver (35.3%), lung (32.4%), pleura (17.6%), central nervous system (14.7%), skin (8.8%), mediastinum (8.8%), and peritoneum (2.9%).

### BC neck dissemination

Pathological lymph nodes were characterized as solitary or conglomerate-forming according to ultrasonography. Solitary pathological lymph nodes were round as determined by sonography, hypoechoic, without clear boundaries from the surrounding tissue, and with pathologic peripheral or central vascularization. The average maximal diameter of solitary pathological lymph nodes was 16.2 mm (range, 3–28 mm). The average time from the diagnosis of BC to the diagnosis of NM was 5.8 years (range, 0–26 years). A proportion of 38% of patients were asymptomatic. No nodes were palpable in 17% of patients.

### Neck node characteristics

In 43.9% of cases, metastatic nodes were smaller than 10 mm, and 26.8% were larger than 20 mm (Table 1). Conglomerates of metastatic nodes were present in 11 patients (26.8%). One solitary metastatic node was present in 19.5% of patients; two nodes were observed in 26.8%; three in 12.2%; four in 12.5%, and five or more in 29.3% of the patients. The majority of metastatic nodes (53.7%) were in level V, which included supraclavicular metastases; 19.5% of patients had metastatic nodes in level IV and 9.8% had metastases in two levels. One patient had metastasis in level I, which is within the submandibular region (Table 1). Metastases in only one level were detected in 75.6% of the patients, and in two levels in 9.8% of

**Table 1:** Patient neck node metastasis characteristics

Size of metastatic nodes in breast cancer patients		
Size	No.	%
< 1 cm	18	43.9
1-2 cm	12	29.3
> 2 cm	11	26.8
Metastatically involved neck levels in breast cancer patients		
Level	No. of patients	%
I	1	2.4
IV	8	19.5
V	22	53.7
IV+V	4	9.8
3 levels	2	4.9
4 levels	4	9.8
Number of metastatically involved neck levels in patients with breast cancer		
Number of levels	No. of patients	%
1	31	75.6
2	4	9.8
3	2	4.9
4	4	9.8

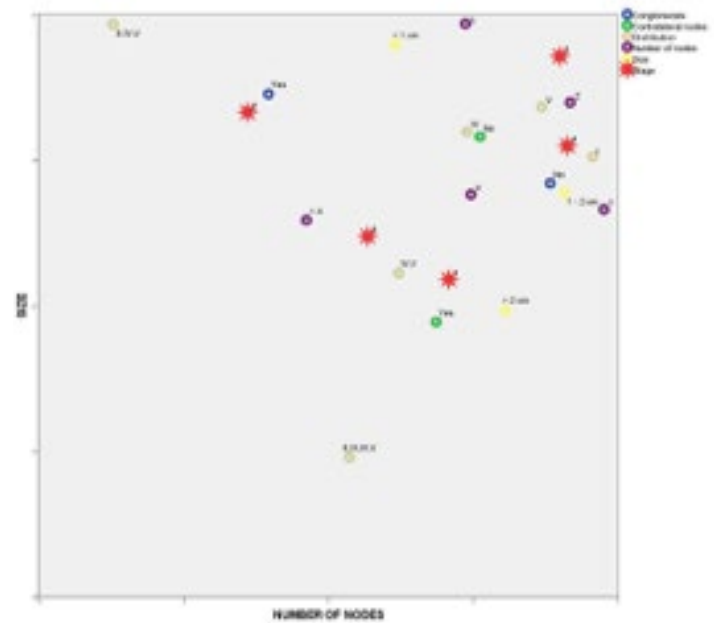
patients (Table 1). In 12.2% of the patients, metastases were detected on the contralateral side of the neck.

**Correlation between patient characteristics and risk for NM**

There was a moderate positive correlation between patient age and onset of metastasis ( $r = 0.345, p < 0.05$ ). There was a moderate negative correlation between patient age and disease stage ( $r = -0.358, p < 0.01$ ) and a significant negative correlation between onset of the NM and disease stage ( $r = -0.538, p < 0.01$ ). There was a small but statistically significant correlation between stage and the appearance of conglomerates ( $r = 0.037, p < 0.01$ ) and a negative correlation between age and contralateral node involvement ( $r = -0.108, p < 0.05$ ). Time from first BC diagnosis to NM diagnosis and involvement of contralateral nodes was also statistically significant ( $r = -0.194, p < 0.01$ ) (Table 2). All other variables were not significantly correlated.

**Multidimensional analysis and effect of staging on risk for NM**

The associations between node dimensions and number, the presence of conglomerates, and the occurrence of contralateral lymph node metastasis



**Figure 1.** Bi-plot of associations between the dimensions of the nodes (size), their number (number of nodes), presence of conglomerates (conglomerate), appearance of contralateral lymph node metastases (contralateral nodes), the distribution of nodes distribution) and Stage (IA=1, IIA=2, IIB=3, IIIA=4, IIIC=5).

**Table 2:** Pearson's correlation coefficients ( $r$ ) between variables in patients with breast cancer ( $N = 41$ ). \* $p < 0.05$ , \*\* $p < 0.01$ . Age – age of the patient at the time of primary disease; Time – time from first treatment to the development of neck metastases; Stage – stage at the first presentation (TNM); No. levels – number of metastatically involved neck levels; Level – certain level in the neck; Size – size of the lymph node; Congl – presence of conglomerates; Contra – involvement of contralateral lymph nodes; No. nodes – number of metastatic lymph nodes in the neck.

	Age	Time	Stage	No. levels	Level	Size	Congl	Contra	No. nodes
Age	1	.345*	-.358**	.222	.204	.162	-.030*	-.108*	.043
Time	.345*	1	-.538**	-.43	.077	.037*	-.110	-.194**	-.178
Stage	-.358**	-.538**	1	.202	-.240	-.107	-.037**	.196	-.152

were analyzed using MCA (optimal scaling). The results of the analysis are shown in a bi-plot in Figure 1.

The results showed that primary disease stage had an effect on patients with the following characteristics:

in patients diagnosed with stage IA BC, the presence of contralateral nodes and node size  $> 2$  cm in regions IV and V were associated with the risk of NM. In stage IIA, NM was strongly associated with the presence of conglomerates. In patients with stage IIB disease, a minimum of two nodes and region V involvement

were associated with an increased risk of NM. Stage IIIA was associated with the presence of NM in the absence of conglomerates, but in patients with nodes 1–2 cm and one or two nodes in region IV or V. Stage IIIB was strongly associated with NM in patients with more than four nodes involving regions IV and V.

## DISCUSSION

Tumor cell dissemination occurs shortly after primary tumor vascularization (11). The ability of cells to lie dormant explains why metastases appear many years after the treatment of the primary tumor (12). The incidence of NM of 3% in the present study is comparable to that previously reported at 4% (13). BC can metastasize to different head and neck regions, although the most common site is the supraclavicular fossa (14–16). A recent study (17) explored patterns of metastasis to the head and neck region and demonstrated extreme variability in the clinical and pathological features of BC metastasis. In the present study, the average time from primary diagnosis to the detection of NM was 5.8 years (range, 0–26 years). A study by Gondim et al. (17) reported a period of 10.9 years (range 1–33 years) for the detection of metastasis. This difference can be attributed to differences in methodology, as the present study focused exclusively on NM, whereas the study by Gondim assessed metastasis to both the head and neck regions.

In 44% of patients with BC, metastatic lymph nodes were smaller than 10 mm. This suggests that cases suspicious for metastatic disease need to be evaluated carefully to identify small sonographically detectable nodes. Sonography needs to be considered in patients with BC who are at a high risk for developing NM because metastatic lymph nodes are not always detected by palpation alone. In the present study, palpation failed to detect metastatic nodes in 17% of cases. In patients with BC at a high risk of metastasis, even a 4-mm node needs to be considered suspicious, and ultrasound-guided fine needle aspiration cytology should be performed. Ultrasound alone is only up to 70% accurate in finding occult metastases, and its

accuracy increases to 89% when combined with fine needle aspiration cytology (18). Obtaining sufficient material for aspiration cytology is frequently difficult in small nodes. In these cases, the procedure should be repeated unless the lymph node is negative or in cases in which there is no clinical benefit in obtaining an exact diagnosis.

NM are often thought to arise within the supraclavicular fossa only (1,6). This was not the case in the patients included in this study. Although level V was the most commonly involved region, metastatic nodes were detected in level IV, as well as in two or more levels in a comparatively large number of patients. One patient had metastases in level I. In almost one third of the patients, metastatic nodes appeared in conglomerates, which is a typical sign of malignancy (1,6). However, metastases were solitary in 20% of patients, and 46% of patients had only one or two metastatic nodes. The onset of metastatic disease in the neck was correlated with patient age and disease stage. Higher stages were associated with metastases in regions IV and V. Elderly patients had fewer conglomerates and metastases in the contralateral side of the neck. This is consistent with research findings that distant metastasis (regardless of type) is less frequent in older patients than in young patients (19).

The proximity of stages IIB and IIIA in the bi-plot reflected their similarity (both showed region V involvement and were characterized by the presence of two nodes, and weak associations with the absence of contralateral nodes and region I were detected in both stages). The proximity and similarity between stages IA and IIIB was surprising. Both stages were associated with region V involvement; however, stage IIIB was also strongly associated with the presence of more than four nodes.

By the time they underwent ultrasound examination, 85% of the patients had already developed distant metastases. NM development was associated with the occurrence of other distant metastases. In these patients, early detection of asymptomatic NM is probably not clinically meaningful. However, NM may be the primary site of disease recurrence in some patients, and early diagnosis and treatment may be of value in selected

patients in this group.

In the 7th edition of the TNM classification, NM are mentioned as N3c in the ipsilateral supraclavicular fossa (20). Our study showed that in addition to the supraclavicular fossa (part of neck level V), metastases also appeared in other levels (19.5% in neck level IV). These are currently staged as distant metastases in the TNM classification.

## STUDY LIMITATIONS

This study had methodological limitations such as its retrospective nature and the restriction of available data to that collected during active patient follow-up. In addition, the patient group analyzed (n = 41) was small, although the number is consistent with the general incidence of NM in BC. To the best of our knowledge, this is the largest analysis of NM in BC patients currently available.

## CONCLUSIONS

Metastasis of BC to the neck may involve other regions in addition to the supraclavicular fossa. Nodes can be very small at initial presentation and were solitary in 20% of the patients. Neck palpation should be combined with ultrasonography of the neck and fine needle aspiration cytology in patients at high risk of NM to improve the early detection of occult nodes. Author contributions: JR, BL, and PB evaluated data from the ENT point of view, performed critical data analysis, and critically revised the manuscript draft. PK performed data analysis and interpreted data in terms of the current knowledge. DA, AD, NFD, MS, and IT collected available gynecological and oncological patient data and evaluated the data in terms of the current body of knowledge. All authors participated in the drafting and critical manuscript evaluation.

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