Determining breast tumor size in mammogeraphy images by artificial intelligence

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**Abstract**

Breast cancer has been one of the main reasons of women’s death in the recent decade. For decreasing of resulting death estimation of this kind of cancer, premature recognized and treatment is a necessary point. After detection breast cancer treatment process is begin with determination extended scale of cancer in organs and choose the best measurment method and helping determination staging of the Tumor and Metastasis Sentinel lymph nodes by helping of common methods. Today, Offensive-biopsy method is used for determination staging of breast cancer that is risky, Time-consuming and Costly for a human. So this study is used to determine the staging of Tumor and Sentinel lymph nodes of breast cancer by using image Mammography from patients who are suffering by Convolution neural network. Used database in this study is 390 Mammography images of a woman suffered of breast cancer. In this research, at first Pre-processing method is done by deleting noise and development quality of Mammography of every patient by using Unsharp linear filter techniques and increased contrast of Histogram matching method. In Classification images of Tumor area in the form of manual method of the other parts of breast are separated by specialists. Afterward suggested networking Convolution layers is using of Tumor area try to determine the staging of cancer (Tumor measurement and Sentinel lymph Metastasis) in order to used the international descriptions Ajcc (American Joint Committee on Cancer) The outcome results are estimated by suggested networking function AUC 0.877. The results represents suitable function and high efficiency of this suggested pattern for determining staging of non-aggressive breast cancer is according to standard descriptions that will have an important role in premature treatment and increasing patient lifetime.

**Key words** : Mammography images, Sentinel lymph nodes, convolution neural network, breast cancer, Staging Cancer.

**Introduction**

Breast cancer is one of the leading causes of death in women worldwide. In 2020, two million and two hundred womenwere diagnosed with breast cancer worldwide, which resulted in the death of 685,000 of them [1]. Breast cancer patients will have problems if not diagnosed and treated in time [2]. Tumor size growth or involvement of the sentinel lymph nodes are the most important threat to people with this complication [3]. Increased tumor growth leads to increased spread of cancer in breast tissue and creates other risks for the health of a person and also the sentinel lymph nodes as the first reference source for the spread of this disease , so determining the size of the tumor and the extent of lymphatic system involvement is a valuable and important diagnostic factor in the treatment decisions [4,5]. presently determination of tumor size and extent of lymph node involvement in breast cancer patients is performed by determining the staging of the cancer [6]. Staging of the cancer is done to determine the progression of the tumor in breast tissue. The most common method of cancer staging is the The Classification of MalignantTumors (TNM) system [7]. The TNM system provides a complete staging according to the international definition of American Joint Committee on Cancer (AJCC) of cancer in a way that T represents the size of the tumor, N is the rate of lymph node transmission, and M the presence metastasis (spread to other tissues) in the body [8]. In the process of treating breastcancer patients, tumor staging, and sentinel lymph nodes are determined by biopsy [9]. According to the result, the doctor applies the best treatment option according to the patient's condition. [10] In this case,according to the importance of performing the process of determining the staging of breast cancer today, this process has problems such as invasive method, impossibility of tissue sampling in metastatic tumors and vital places of the body, time consuming and costly [11-13]. Therefore, determining the staging in the early stages of the disease andtimely treatment initiation and careis of considerable importanceespecially before tumor size increases and Lymphatic glands become involved and cancer spreads to other parts of the body non-invasively to reduce mortality and increase The survival of breast cancer patients [14-18].

Many studies have tried to predictthe staging of breast cancer non-invasively by applying mathematical methods based on lesions clinical data and cancerous masses of breast tissue [19-26] as well as the possibility of lymph node involvement [27-34]. In addition, tumor size, patient characteristics, or clinical data show that preliminary specificities of breast cancer tumors are effective in assessing lymph node involvement sentinel lymph node (SLN), Axillary lymph node (ALN) and staging of breast cancer [35-40]. while the effect of onset age, histological grade, molecular markers on SLN metastasis has not been reported on staging of breast cancer [40-44]. Several studies have been performed to determine staging (tumor, lymph node and metastasis) of breast cancer using biopsy and histopathology data as the most accurate method of staging, however this method is invasive and haspostoperative risks and complications and is time consuming [45-50]. Furthermore, only the use of clinical pathology data with AUC 0.66-0.74 has not been accurate and reliable enough in previous studies [51]. pathological some pathologic data cannot be available before operation, but preoperative knowledge of ALN status is important to determine appropriate treatment options [52].

In recent years, Computer-aided design (CAD) computer diagnostic systems have played an important role in early detection and non-invasive diseases worldwide, leading to reduced mortality andtreatment costsand increased life expectancy [53]. In this diagnostic method, different image processing techniques are applied to radiological data based on artificial intelligence, especially machine learning which have been widely used in the early and non-invasive diagnosis of breast cancer [54,55]. Today, one of the common algorithms ofmachine learning is the Convolutional Neural Network (CNN), [56,57] this processing technique can automatically extract a large number of quantitative image properties from medical images, whichdetermining the features are very important for distinguishing and predicting images [58,59]. While CNN has been used to classify the disease status and predict therapeutic responses based on diagnostic images of the primary breast tumor [61.60].

In the past, a study has been performedaimed at determining staging (T) using breast-based thermographic images based on deep learning techniques, which has had a better performance among the applied techniques of Inception- V3 [62]. In addition, breast thermography has some limitations like the lack of access to hospitals and false diagnosis in the early stages of breast cancer. In the previous study, deep features extracted from magnetic resonance imaging (MRI) with Diffusion-weighted imaging (DWI) was used to predict breast cancer SLN metastasis that ultimately delivered an AUC 0.852 [63]. However, MRI was time consuming and expensive and DWI is not common in routine clinical MRI breast examinations in many hospitals.

Currently, mammography imaging is to diagnose breast cancerous lesions and massesas a standard detector based on guidelines of the World Cancer Society [64-67]. Mammographic images are considered suitable for assessing cancer masses and lesions in breast tissue for early detectiondue to its high sensitivity in detection and ease of public access and cheapness.Some previous studies also showed that the features of deep learning based on convolutional neural network, mammographic imaging potentially improves the function of determining cancerous lesions and lymph node involvement [68-74].

However, the efficacy of mammography has not been examinedin determining tumor staging and sentinel lymph nodes in breastcancer patients. We hypothesized that the deep features resulting from mammography staging can be used to determine tumor staging and lymph nodes of the SLN before surgery in breast cancer patients. In this regard, a study has been suggested aimed at determining staging (tumor status and sentinel lymph nodes) patients with breast cancer in the early stages of treatment using mammography images based on the application of CNN algorithms according to the international definitions of AJCC. Finally, the function of the proposed system in determining the staging of the tumor and the sentinel lymph nodesis possible non-invasively. It also can be helpful at initial diagnosis and in determining appropriate and timely treatment as well as increasing the life expectancy of breast cancer patients. To our knowledge, this is the first time that such a classification is made using mammographic images of the breast.

Based on the relevant research to determine the stage of breast cancer of the tumor and the lymph nodes of the sentinel in 6 Final stages (Table 1)**.**

Table 1- Details of the studied staging [75,76].

|  |  |
| --- | --- |
| Status details | stage |
| Stage I describes invasive breast cancer (cancer cells are breaking through to or invading normal surrounding breast tissue) Stage I is divided into subcategories known as IA and IB. | **Stage I** |
| the tumor measures up to 2 centimeters (cm) and  the cancer has not spread outside the breast; no lymph nodes are involved. | **stage IA** |
| there is no tumor in the breast; instead, small groups of cancer cells — larger than 0.2 millimeter (mm) but not larger than 2 mm — are found in the lymph nodes or  there is a tumor in the breast that is no larger than 2 cm, and there are small groups of cancer cells — larger than 0.2 mm but not larger than 2 mm — in the lymph nodes | **stage IB** |
| Stage 2 breast cancer is a fairly common stage of breast cancer diagnosis. Stage 2 tumors are at least 1 centimeter (cm) in size and have spread to lymph nodes.1 Treatment usually includes surgery (either a lumpectomy or mastectomy), and adjuvant chemotherapy is often recommended. | **stage II** |
| no tumor can be found in the breast, but cancer (larger than 2 millimeters [mm]) is found in 1 to 3 axillary lymph nodes (the lymph nodes under the arm) or in the lymph nodes near the breast bone (found during a sentinel node biopsy) or  the tumor measures 2 centimeters (cm) or smaller and has spread to the axillary lymph nodes or  the tumor is larger than 2 cm but not larger than 5 cm and has not spread to the axillary lymph nodes | **stage IIA** |
| the tumor is larger than 2 cm but no larger than 5 centimeters; small groups of breast cancer cells — larger than 0.2 mm but not larger than 2 mm — are found in the lymph nodes or  the tumor is larger than 2 cm but no larger than 5 cm; cancer has spread to 1 to 3 axillary lymph nodes or to lymph nodes near the breastbone (found during a sentinel node biopsy) or  the tumor is larger than 5 cm but has not spread to the axillary lymph nodes | **stage IIB** |

**Materials and Methods**

**Data**

The license of the data of this study has been approved by the ethics committee of University of Medical Sciences of Dezful -Iran.( [IR.DUMS.REC.1400.022](http://ethics.research.ac.ir/IR.DUMS.REC.1400.022)).

The study only included retrospective analysis of anonymous patient data, and therefore did not require informed patient consent. A retrospective study of female breast cancer patients being treated between January 2018 and December 2020 was selected for this study from a pathology database including mammographic images and clinical and pathology data at the Cancer Center of Dezful - Iran.

Inclusion criteria in this study were: (1) histologically confirmed primary breast cancer, (2) pre-treatment mammography images, (3) SLN and ALN biopsy, (4) confirmed SLN metastasis results after pathobiology operation.

Exclusion criteria were (1) tumor area smaller than 100 pixels in mammographic images (2) Incomplete pathology clinical data (3) Neoadjuvant treatment (chemotherapy) before mammography examination and biopsy surgery. (4) Non-mass lesions (calcification, high tissue density and image distortion).

Finally, 390 patients with breast cancer were included in this study. The studied patients were divided into two groups in terms of time. Patients treated between January 2016 and April 2020 were assigned to a training group (n = 273) and patients treated between May 2020 and December 2020 were assigned to a validation group (n = 117). How to select a patient is listed in Table 2.

Pathological variables were collected from medical records, including age, tumor location, staging based on AJCC, pathological type, HER2 status, PR status, and ER status.

**Data collection and preprocessing**

All mammographic images were obtained from the Selenia Dimensions Hologic. Meanwhile, the craniocaudal (CC) projections and mediolateral oblique (MLO) have 4 images per patient. Due to the nature of mammographic images that fall into the category of noisy images, preprocessing operations are very important to improve the quality and detail of the studied images. At this stage, the images were first changed from colored to gray in the preprocessing process. In the first step, by applying Unsharp linear filter, the noise reduced and resolution of the images were improved. In order to improve the image quality, the contrast enhancement technique with Contrast-Limited Adaptive Histogram Equalization (CLAHE) was applied to the studied data using MATLAB software.Finally, after applying the preprocessing techniques, the images were changed from gray to colored again, because colored images have a lot of functionality and useful information about the texture under study, which the characteristics of colored images can be very useful in determining the staging.

**ROI**

At this stage, the division of the studied images was done manually by a radiologist (10 years of experience) due to the importance of primary tumor information in determining staging. In this process, the site of the primary tumor was isolated from other areas of breast tissue. Also, the second radiologist (12 years of experience) examined all the sites of the primary tumor that had been manually removed by the first radiologist. The dispute over the isolated sites was resolved between the two radiologists and a final agreement was reached.

**Proposed model of deep learning**

In this study, we have applied a proposed convolution neural network model. Convolution neural networks have a unique efficiency in extracting features of images automatically, which has increased the productivity of this study. The general architecture of the proposed network is shown in the figure.1. First, all the images of the original tumor that were manually isolated to convert the size of the images and improve the processing were all converted to 64 x 64, and applied as network input. In this structure, the proposed network consists of 4 layers of convolution, which at each step the amount of automatic extraction of features increases. In the first layer, 64-filters convolution with 3 \* 3 dimensions, in the second layer, 128 filters with 3 \* 3 dimensions, in the third layer, 265 filters with 3 \* 3 dimensions, and in the fourth layer, 512 filters with 3 \* 3 dimensions exist. All convolution layers are activated via the non-linear RLUE function. After each layer of convolution and activation function of RLUE, the Max Pooling layer with dimensions of 2 \* 2 and step 2 has been used in order to prevent over-fitting of the network. Three fully connected layers are then used, The fully connected layer acts as a normal neural network. The dimensions of the first fully connected layer were 4096 Features, the second layer was 1000 Features And the third layer was 6 Features. Then, in the final layer, the SOFT MAX function is used to classify and increase the detection accuracy.

Also, in order to optimize the training of the proposed model, the Stochastic gradient descent (SDG) algorithm with a rate of 0.01 has been used to move in the direction of updating the teachable parameters of the proposed network model. In fact, the random reduction gradient gives us an algorithm to obtain the minimum value of a function in several iteration loops and the values ​​for which the minimum function takes its value. In the iteration loop for the training and review stage, the amount of network weights in each iteration is MINI-Batch -Size 273. In fact, when the proposed model intends to train the input, from the total of all data images, only 273 images in each iteration loop should be trained. Weights are adjusted and updated according to this criterion in practically every network update. Finally, the number of dataset training processes in the proposed Epoch model is 200 times. When you train all the datasets 200 times, this has been a suitable rate with high network performance.

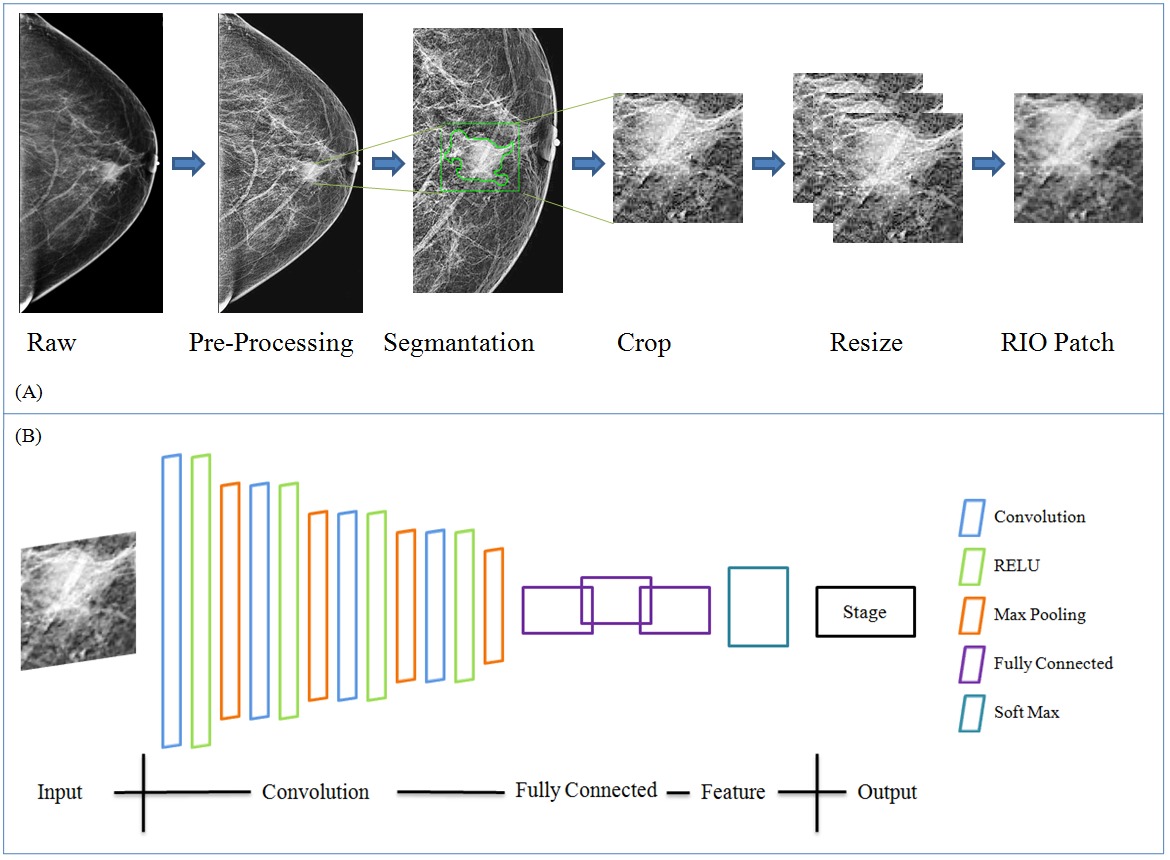


Figure.1. Proposed method. A) Steps of preparing data. B) The structure of the proposed model.

**Evaluation of the performance of the proposed model and Statistical Analysis**

The K-fold 5 validation method was used to evaluate the validity of the proposed algorithm. In other words, we divided the whole data into five parts and in each implementation of the algorithm, we applied 4 parts of the data as training data and one part as validation data to the introduced classifier. Also in this study, 70% of the data was allocated to training and 30% was allocated to validation. The performance of the proposed network was evaluated in the training and validation group, and the ROC performance curve was used for more accurate evaluation and fit. In this AUC assessment, sensitivity, specificity and accuracy were examined for both training and validation groups. Also, the confidence curve was plotted with a value of 0.5 between both favorable and unfavorable network performance conditions.

The relationships between the criteria of sensitivity, specificity and accuracy are expressed in Equations (1-3) determining the staging of the tumor and the metastasis of the sentinel lymph nodes.

|  |  |
| --- | --- |
| (1) |  |
| (2) |  |
| (3) |  |

Comparison of clinical pathology characteristics between educational groups and validation were performed using T-test and Chi-square tests. All statistical analysis were performed using R software (version 3.5.2). The R packages implemented included "rms"، "rmda"، "pROC"، "mRMRe"، "ResourceSelection" "caret" "glmnet", "psych", "Hmisc", "survival", "survminer", "grid", "Lattice", "Formula", "ggplot2", "nomogramEx", "tidyverse", "dplyr" and "tidyr". A two-tailed p < 0.05 was considered to be statistically significant.

**Results**

**Patient Characteristics**

In this study, a total of 390 patients' information was used to analyze the data. In the training set and validation, sentinel lymph node metastatic involvement of 1 to 3 nodes was 76.9% and 76.7%, respectively. In total, out of 390 patients, 300 had metastatic sentinel lymph node involvement and 390 had a tumor size greater than 1 mm. There was no significant difference between age, tumor location, staging based on AJCC, pathological type, HER2, PR and ER status of tumor size and involvement of the number of lymph nodes in both groups. Details of data used in training and validation sets have been shown in Table 2.

TABLE.2. Characteristics of Patients in the Primary and the Validation Cohort.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | |  | | Characteristic |
| *P*-value | The Validation Cohort | The Primary Cohort | All retrospective patients |  |
|  | (n=117) | (n=273) | (n=390) |
| 0.323 | 61.6 13.7 | 60.52 13.2 | 59.9 13.5 | Age,Mean SD(years) |
| 0.082 |  | | | Tumor Location (%) |
|  | 11 (9.5) | 24 (8.8) | 35 (9) | Upper inner quadrant |
|  | 30 (25.5) | 71 (26) | 101 (26) | Lower inner quadrant |
|  | 15 (13) | 36 (13.2) | 51 (13) | Lower outer quadrant |
|  | 61 (52) | 142 (52) | 203 (52) | Upper outer quadrant |
| 0.050 |  |  |  | Ajcc Tumor Stage (%) |
|  | 14 (12) | 33 (12.1) | 47 (12) | I |
|  | 13 (11.3) | 30 (11) | 43 (11) | IA |
|  | 2 (1.8) | 6 (2.2) | 8 (2) | IB |
|  | 5 (3.5) | 11 (4) | 16 (4) | II |
|  | 51 (43.8) | 120 (44) | 171 (44) | IIA |
|  | 32 (27.6) | 73 (26.7) | 105 (27) | IIB |
| 0.339 |  | | | Histological type (%) |
|  | 93 (79.4) | 217 (79.5) | 310 (79.5) | Ductal Carcinoma |
|  | 24 (20.6) | 56 (20.5) | 80 (20.5) | Lobular Carcinoma |
| 0.314 |  | | | HER2 Status (%) |
|  | 91 (77.8) | 211 (77.3) | 302 (77.5) | Negative |
|  | 26 (22.2) | 62 (22.7) | 88 (22.5) | Positive |
| 0.282 |  | | | PR Status (%) |
|  | 31 (26) | 72 (26.2) | 103 (26.3) | Negative |
|  | 86 (74) | 201 (73.8) | 287 (73.7) | Positive |
| 0.212 |  | | | ER Status (%) |
|  | 39 (33) | 90 (33) | 129 (33) | Negative |
|  | 78 (67) | 183 (67) | 261 (67) | Positive |

**Evaluation of the proposed network model**

Finally, 4096 features were extracted from mammographic images of each patient, and 6 related features are selected according to the relationship between tumor size determination and lymph node metastasis. Based on these selected features, we have proposed a 6-stage grid that describes the status of tumor size and sentinel lymph node metastasis. Performance evaluation of the proposed convolution neural network staging was AUC 0.919 CI (0.852,0.971) for training group and AUC 0.877 CI (0.805,0.949) for validation group which were shown in Figure.2 and Table.3.

According to the purpose of the study on determining the stage of breast cancer tumor and the metastasis of the sentinel lymph nodes, the predictive function of the proposed convolution neural network (AUC, sensitivity, specificity and accuracy) is mentioned in the Table.3.

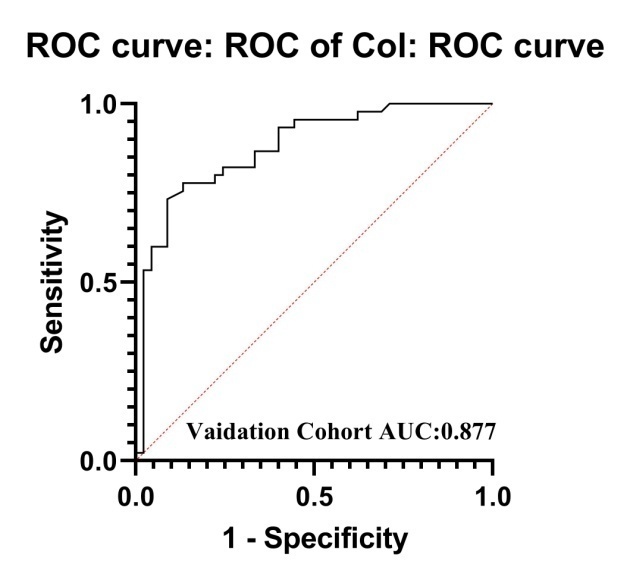
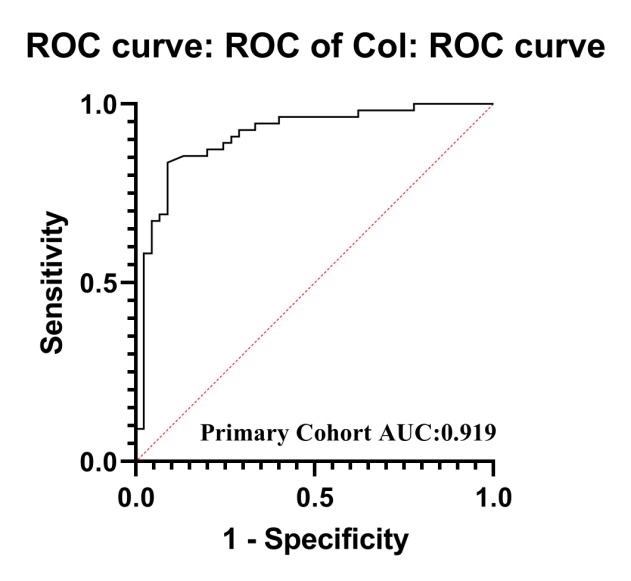


Fig 2.Evaluation of the proposed network performance to determine the stage of the tumor size and metastasis of the sentinel lymph nodes**.**

A-ROC curve proposed model for training dataset , B- ROC curve proposed model for validation dataset.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| *P Value* | Accuracy | Specificity | Sensitivity | AUC (95% CI) | Cohort | **signature** |
| <0.001 | 0.796 | 0.601 | 0.963 | 0.919 (0.852,0.971) | **Primary** | **Deep learning signature (for TNM Stage )** |
| <0.001 | 0.758 | 0.550 | 0.934 | 0.877 (0.805,0.949) | **Validation** |

Table.3. The results of the proposed network model.

**Conclusion**

In this study, we developed a convolutional neural network-based deep learning algorithm to determine tumor staging and metastasis to sentinel lymph nodes before invasive surgery based on mammographic images. The performance of the proposed model was performed on validation data (n = 117) with AUC 0.877 CI (0.805,0.949). The results show that mammographic imaging-based deep learning features can be a suitable and non-invasive method for staging tumor size and SLN metastasis before surgery.

In recent years, many advances have been made in the field of image processing (classification, detection and segmentation, etc.), and deep learning engineering techniques have worked well on medical images [77,78]. In a previous study, ultrasound imaging features based on ultrasound images assessed the condition of the sentinel lymph nodes with AUC 0.846. [79] However, these ultrasound-based studies have had some drawbacks, such as the number of different types of ultrasound imaging and the importance of physician experience. [79-82]. In one study, the evaluation of lymph nodes using in-depth learning based on MRI images was associated with promising results. This study had limited and single samples of T1 modality and two-dimensional images. [83] Therefore, the efficiency of the features extracted from MRI images was not sufficient to determine the assessment of the condition of the mammary lymph nodes. [83,84] In our present study, the deep learning extracted features were from the primary tumor area and a proposed model has been suggested considering the nature of the tumor area. In this regard, it showed a good performance in determining tumor staging and sentinel lymph node metastasis with an AUC of 0.877 in the validation group. In addition, the results show that the proposed model can help low-risk patients to avoid unnecessary invasive biopsy of the sentinel lymph nodes. In most previous studies, the predictive features of SLN metastases and tumor diagnosis were based on MRI and ultrasound images. (79-84). This study is based on the mammography imagery that Gold Standard is the diagnosis of breast cancer and is increasingly available and used in practice all over the world. Preoperative mammography examination can assess not only the size of the tumor area, breast tissue lesions, and regional lymph nodes (axillary, internal breast), but also helps with clinical staging and the implementation of an appropriate treatment plan. Also, the ease of access and cheapness and diagnosis of the gold standard of breast cancer, mammography in the diagnosis and evaluation of breast tissue diseases has been more appropriate than ultrasound MRI imaging. In this study, we examined only the clinical features of the pathology that can be obtained from the pathological results of preoperative biopsy. However, no clinical pathological factors associated with the determination of tumor staging and breast SLN metastasis were found in our study. Therefore, the performance of our proposed convolutional neural network deep learning model (AUC 0.887) was to determine tumor staging and sentinel lymph node metastasis. In this research, retrospective data of the Dezful hospital have been used, with the application of engineering techniques in the preprocessing process, the detail and quality of the images have been improved, which has made the performance of the proposed model more better. Also, by using RGB images and increasing the detail of the images, appropriate information has been extracted from the studied images. Finally, the proposed model was able to determine the tumor staging and metastasis of the breast SLN with an AUC 0.887. The positive points of this study include the use of hospital data, appropriate preprocessing, color images containing real information and staging of tumor and SLN metastasis referring to only the primary tumor area in the breast tissue. Our study also had limitations, First, mammogram images were performed manually to divide the images. The automatic segmentation process can have a positive effect on the performance of the proposed system. Second, the images are retrospectively collected. This can cause bias. Third, our study examined only mammographic images. In the future, other imaging modalities or information combinations may be used for further research. Finally, in this study, we propose a deep learning model based on convolutional neural network based on mammographic images, which has a suitable function for determining tumor staging and SLN metastasis. This proposed method can be used as a potential non-invasive tool to determine tumor staging and SLN metastasis in breast cancer in people suspected of having the complication, and to avoid unnecessary surgery. This study can also be very useful in determining the appropriate treatment plan for early diagnosis and treatment, which reduces the cost and increases the survival of patients with this complication.

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