Support Vector Machines Model of Computed Tomography for Assessing Lymph Node Metastasis in Esophageal Cancer with Neoadjuvant Chemotherapy

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**Objective:** The aim of this study was to diagnose lymph node metastasis of esophageal cancer by support vector machines model based on computed tomography.

**Materials and Methods:** A total of 131 esophageal cancer patients with preoperative chemotherapy and radical surgery were included. Various indicators (tumor thickness, tumor length, tumor CT value, total number of lymph nodes, and long axis and short axis sizes of largest lymph node) on CT images before and after neoadjuvant chemotherapy were recorded. A support vector machines model based on these CT indicators was built to predict lymph node metastasis.

**Results:** Support vector machines model diagnosed lymph node metastasis better than preoperative short axis size of largest lymph node on CT. The area under the receiver operating characteristic curves were 0.887 and 0.785, respectively.

**Conclusions:** The support vector machine model of CT images can help diagnose lymph node metastasis in esophageal cancer with preoperative chemotherapy.

**Key Words:** support vector machine, computed tomography, esophageal cancer, lymph node metastasis

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The prognosis of patients with resectable esophageal cancer remains poor. The reported 5-year survival rates range from 20 to 36% after intentionally curative surgery.¹–³ Median survival is only 9–24 months in patients with surgical treatment.⁴–⁹ Prospective randomized trials demonstrated an improved survival after neoadjuvant therapy compared to surgery alone in patients with esophageal cancer. Some important studies include the CROSS trial, which analyzed neoadjuvant chemoradiation for patients with esophageal adenocarcinoma or squamous cell carcinoma, and the MAGIC and French trials analyzing neoadjuvant chemotherapy for adenocarcinoma.¹⁰–¹² Data from the RTOG9802 study suggested preoperative chemoradiaterapy increases complication incidence and mortality.¹³ Therefore, preoperative chemotherapy in treating esophageal carcinoma is gradually accepted by surgeons.

As reported by Worldwide Esophageal Cancer Collaboration, survival decreases with the presence of lymph node metastases (LNM).¹⁴ Indeed, the lymph node category was shown to be an independent prognostic factor in lymph node positive patients with resectable thoracic esophageal cancer.¹⁵ Imaging examinations are the most commonly used tools for lymph node status evaluation in esophageal cancer. Wakelin et al compared computed tomography (CT), laparoscopic ultrasound, and endoscopic ultrasound (EUS) in the preoperative staging of esophageal carcinoma; the accuracy of CT in diagnosing the stage of esophageal cancer was 17 of 29 (59%).¹⁶ These authors concluded that the nodal status remains the most difficult area to assess using all three modalities. The main hurdle appeared to be the differentiation between benign and malignant enlarged nodes, with lymph node size alone not being a good criterion for assessing malignancy.

In recent years, machine-learning methods have been used to predict complex biological problems. Support vector machines (SVMs) are supervised machine learning techniques widely used in pattern recognition and classification problems. An SVM algorithm performs a classification by constructing a multidimensional hyperplane that optimally discriminates between two classes, by maximizing the margin between two data clusters. This algorithm achieves high discriminative power by using special nonlinear functions called kernels to transform the input space into a multidimensional space.¹⁷ SVMs have been used in medical applications.¹⁸–²⁰ Given a set of training cases, each marked as belonging to one of two categories, a SVM training algorithm builds a model that predicts whether a new case falls into one category or the other.

Therefore, we used CT imaging data before and after neoadjuvant chemotherapy to establish a SVM mathematical model. In addition, the diagnostic power of the SVM method for differentiating LNM in patients with esophageal cancer was assessed. Because squamous cell carcinomas are significantly more common than adenocarcinomas and other malignant esophageal cancers in Asians, only patients with squamous cell carcinomas were evaluated in this study.

**MATERIALS AND METHODS**

**Patients**

This retrospective study was approved by the Ethics Committee of our hospital, with a waiver of requirement for informed consent. This study included patients with resectable thoracic esophageal cancer, lymph node metastasis, and primary tumors located in the thoracic esophagus. After excluding patients with other malignancies, patients with squamous cell carcinomas and esophageal adenocarcinomas were included. The patients included in this study were subject to preoperative chemotherapy with or without neoadjuvant chemotherapy for esophageal carcinoma.

**Imaging Analysis**

Imaging examinations were performed with the following modalities: computed tomography (CT), ultrasonography (US), and magnetic resonance imaging (MRI). The CT examinations were performed with 16-slice scanners, and the images were reconstructed at 0.625–1 mm intervals. The medical records were reviewed for the following imaging findings: tumor thickness, tumor length, lymph node area, longest axis, and shortest axis of the largest lymph node. These data were recorded and analyzed by the authors.

**Support Vector Machine (SVM) Model**

Support vector machines (SVMs) are supervised machine learning techniques widely used in pattern recognition and classification problems. An SVM algorithm performs a classification by constructing a multidimensional hyperplane that optimally discriminates between two classes, by maximizing the margin between two data clusters. This algorithm achieves high discriminative power by using special nonlinear functions called kernels to transform the input space into a multidimensional space. SVMs have been used in medical applications. Given a set of training cases, each marked as belonging to one of two categories, a SVM training algorithm builds a model that predicts whether a new case falls into one category or the other. Therefore, we used CT imaging data before and after neoadjuvant chemotherapy to establish a SVM mathematical model. In addition, the diagnostic power of the SVM method for differentiating LNM in patients with esophageal cancer was assessed. Because squamous cell carcinomas are significantly more common than adenocarcinomas and other malignant esophageal cancers in Asians, only patients with squamous cell carcinomas were evaluated in this study.

**Support Vector Machines Model**

Support vector machines model diagnosed lymph node metastasis better than preoperative short axis size of largest lymph node on CT. The area under the receiver operating characteristic curves were 0.887 and 0.785, respectively. Support vector machines model based on these CT indicators was built to predict lymph node metastasis. Support vector machines model diagnosed lymph node metastasis better than preoperative short axis size of largest lymph node on CT. The area under the receiver operating characteristic curves were 0.887 and 0.785, respectively. Support vector machines model based on these CT indicators was built to predict lymph node metastasis.
The clinical data were collected from the prospective database of our hospital. All patients in this database who had pathologically confirmed esophageal squamous cell carcinoma and received preoperative chemotherapy from January 2006 to January 2012 were included. All patients underwent gastroscopy to acquire pathological information, and received baseline and preoperative enhanced CT examinations.

Exclusion criteria were (a) pathologically proven adenocarcinoma, small cell carcinoma, mixed cancer, or other diseases; (b) other preoperative therapies (e.g., radiotherapy) simultaneously; (c) esophageal multiple primary carcinoma; (d) death within 30 days after surgery; (e) enhanced CT data before preoperative chemotherapy not obtained or images not interpretable; and (f) non-suitability for radical esophagectomy because of tumor progression or patient’s physical condition.

CT Protocol

MDCT was performed using a 64-detector row CT scanner (LightSpeed 64; GE Healthcare, Milwaukee, WI). Chest unenhanced CT scans were acquired with 0.625 mm collimation, 120–140 kVp, and 300–350 mAs. Subsequently, a total of 100 ml iopromide (Ultravist; Schering, Berlin, Germany) was administered intravenously via an 18-gauge angiographic catheter inserted into an antecubital vein, at 3 mL/sec with an automatic injector. Contrast-enhanced CT scans were performed at 60 seconds after iopromide injection. Sagittal and coronal reconstructions were carried out with contrast-enhanced images.

Image Analysis

Baseline and preoperative CT images were analyzed using the picture archiving communication system (PACS) by two independent radiologists blinded to patients’ clinical history. The following CT indicators were measured:

- Tumor length: longest diameter obtained from the sagittal CT image.
- Tumor thickness: lesion thickness obtained from the axial CT image.
- Tumor CT value: region of interest (ROI) placed on the lesion with maximum cross-section at the cross-sectional CT image.
- Total LN number: number of all visible regional lymph nodes on chest CT image.
- Long axis size of largest regional LN (LSDL): long axis diameter of the largest regional lymph node in the axial CT image.
- Short axis size of largest regional LN (SSDL): diameter perpendicular to the long axis of the largest regional lymph node in the axial CT image.

The average results from the two radiologists were used for continuous variable analysis. Changes of CT image indicators between baseline and preoperative CT were assessed.

Statistical Analysis

LNM Assessment

All patients were divided into positive-LNM and negative-LNM groups, respectively. Node metastasis was confirmed by postoperative pathological results. A univariate statistical analysis with the SPSS software version 17.0 (SPSS Inc., Chicago, IL) was performed to evaluate the differences in various imaging indicators between the positive-LNM and negative-LNM groups. Group comparison was carried out by independent-samples T test. P < 0.05 was considered statistically significant.

The CT indicators significantly different between positive-LNM and negative-LNM groups were selected to build the SVM model. Receiver operating characteristic (ROC) curves were used to evaluate these indicators in diagnosing LNM. The MedCalc software version 11.2 (MedCalc; MedCalc Software, Ghent, Belgium) was used to generate and compare the ROC curves.

Least Squares Support Vector Machine (SVM)

Least squares support vector machine (LS-SVM) was proposed by Suykens and Vandewalle. Compared with other SVMs, LS-SVM utilizes quadratic sum of the slack variables as the penalty factor which ensures that LS-SVM can obtain a small training error. Specifically, LS-SVM minimizes the follow optimization problem, that is:

\[
\min_{w,b,e} \left\{ \frac{1}{2} w^T w + \gamma \sum_{i=1}^{N} e_i^2 \right\}, \quad \text{s.t.} \quad y_i(w^T \phi(x_i) + b) = 1 - e_i, \quad i = 1, ..., N
\]

where \( x_i \) is the \( i \)-th training sample, \( y_i \in \{-1, 1\} \) is the label of \( x_i \), \( \phi \) is a feature map which maps \( x_i \) to the feature space, \( w \) is the weight parameter vector, \( b \) is the bias parameter, \( e_i \) is \( i \)-th slack variable and \( \gamma = (e_1, ..., e_N)^T \), \( y \) is a tuning parameter which makes a trade-off between the slack variable penalty and the margin. The Lagrangian function of Eq. (1) is

\[
L = \frac{1}{2} w^T w + \sum_{i=1}^{N} e_i, \quad \sum_{i=1}^{N} \alpha_i \left[ y_i(w^T \phi(x_i) + b) + e_i \right] = 0
\]

where \( \alpha_i \) is \( i \)-th Lagrange multiplier (\( i = 1, ..., N \)). According to the optimal conditions, we have

\[
\alpha_i = \gamma e_i
\]

and

\[
y_i = w^T \phi(x_i) + b + e_i, \quad i = 1, ..., N.
\]

By eliminating \( w \) and \( e \), we can obtain the system of linear equations

\[
\begin{bmatrix}
0 & I^T \\
1 & \Omega + \frac{1}{\gamma} I
\end{bmatrix} \alpha = \begin{bmatrix}
0 \\
0
\end{bmatrix}
\]

where \( \alpha = (\alpha_1, ..., \alpha_N)^T \), \( y = (y_1, ..., y_N)^T \), \( I = (1, ..., 1)^T \) is a length-\( N \) vector, \( I \) is \( N \times N \) identity matrix, and \( \Omega = (\phi(x_1)^T \phi(x_1))_{N \times N} \) is Gram matrix. Solving Eq. (7), we obtain the solution \( b \) and \( \alpha \). Then the optimal weight parameter vector \( w \) can be computed by Eq. (3) and \( e_i \) by Eq. (5). For a testing sample \( x \), its label can be estimated by

\[
sign(y) = sign(w^T \phi(x) + b)
\]

LS-SVM can easily be extended to \( K \)-class \((K > 2)\) classification problem by one-versus-one strategy.
RESULTS

A total of 131 patients (102 males and 29 females; mean age of 58.0 years, ranging from 42 to 75 years) were included in the study (Fig. 1). There were 51 cases with lymph node metastasis and 80 without. The clinicopathological features of the patients are detailed in Table 1. The majority of patients (97%; 127/131) received a platinum-based two-drug combination, mainly paclitaxel (175 mg/m²), IV, d1 Q21; the remaining patients received nedaplatin (80 mg/m²) combined with paclitaxel. A total of one to four chemotherapy cycles were administered before surgery at 3–6 weeks after neoadjuvant chemotherapy.

In the univariate analysis, preoperative tumor thickness, preoperative long axis and short axis sizes of largest lymph node, total numbers of lymph nodes in baseline and preoperative CT, and change of tumor thickness in second CT showed statistically significant differences between the LNM positive and negative groups (Table 2). Of these six CT indicators, preoperative short axis size of largest lymph node yielded the highest power for diagnosing LNM in ROC curves (Table 3, Fig. 2), with an area under curve (AUC) of 0.705.

After the random sampling by the SPSS statistical software, 66 cases were randomly selected to constitute the training sample. The remaining 50% of cases formed the testing sample. The training sample was used to establish the LS-SVM model. Finally, the ability of the model to predict LNM in the testing sample was evaluated by ROC curves. ROC curves can be created automatically by the MATLAB software.

TABLE 1. Patient Characteristics

| Characteristics | Number | Percent |
|-----------------|--------|---------|
| Sex             |        |         |
| Male            | 102    | 77.9%   |
| Female          | 29     | 22.1%   |
| Age (median, range) | 58 (42–75) |
| Location       |        |         |
| Upper 1/3      | 35     | 26.7%   |
| Middle 1/3     | 55     | 42.0%   |
| Lower 1/3      | 41     | 31.3%   |
| Surgical method |        |         |
| Transhiatal    | 17     | 13.0%   |
| Modified McKown| 98     | 74.8%   |
| Modified Ivor-Lewis | 10   | 7.6%    |
| Modified Sweet | 6      | 4.6%    |

FIGURE 1. Flow chart of the study.
these biological behavior factors should be taken into account in comprehensively predicting LNM.

Other machine-learning methods have been used in medical studies. The mainly used method is artificial neural network (ANN), which is considered an appropriate tool for medical data analysis. Bollschweiler et al applied a single-layer perceptron, an ANN, to predict lymph node metastasis in esophageal cancer, with an accuracy of 79%. However, the ANN has some disadvantages: (1) the model is prone to overfitting, (2) it requires lengthy development and optimization time, and (3) it is more difficult to use in the field because of computational requirements. Considering the above reasons, this study instead selected the SVM model, which could produce lower prediction error compared with classifiers based on other methods like artificial neural networks. Few reports are available regarding the application of SVM in esophageal cancer lymph node metastasis. In this preliminary study, the results indicated that the SVM model has better diagnostic capability for LNM than the traditional LN size criteria, with AUC achieving a good diagnostic power. With further improvement, SVM may become an effective tool in predicting lymph node staging in esophageal cancer.

Our study has some limitations. First, although a relatively large sample size was used, this was a single-center retrospective study. Further prospective studies are warranted to confirm the diagnostic power of the SVM model. In addition, the majority of patients were male (77.9%). Gender factors may influence the external validity of these findings. Finally, the AUC obtained for the LS-SVM model in the testing sample was relatively lower

TABLE 2. The Results of Univariate Statistical Analysis for CT Indicators of Baseline and Preoperative CT

|                | LNM (+)       | LNM (-)       | T value | P      |
|----------------|---------------|---------------|---------|--------|
| Baseline CT    |               |               |         |        |
| Tumor thickness (mm) | 17.6 + 6.2    | 17.2 + 6.1    | 0.369   | 0.713  |
| Tumor length (mm)  | 7.7 + 2.3     | 7.3 + 3.3     | 0.742   | 0.460  |
| Tumor CT value (HU) | 60.1 + 16.6   | 62.0 + 17.6   | 0.603   | 0.548  |
| LSLN (mm)       | 20.5 + 9.2    | 17.8 + 10.0   | 1.592   | 0.114  |
| SSLN (mm)       | 13.9 + 7.5    | 11.9 + 8.7    | 1.415   | 0.159  |
| No. of lymph nodes | 6.4 + 3.8     | 4.8 + 3.0     | 2.792   | 0.006  |
| Preoperative CT  |               |               |         |        |
| Tumor thickness (mm) | 13.2 + 6.5    | 10.5 + 4.5    | 2.572   | 0.012  |
| Tumor length (mm)  | 5.6 + 2.2     | 5.0 + 2.6     | 1.471   | 0.144  |
| Tumor CT value (HU) | 51.7 + 17.0   | 49.0 + 16.5   | 0.933   | 0.353  |
| LSLN (mm)       | 16.6 + 6.0    | 13.4 + 5.9    | 3.0     | 0.003  |
| SSLN (mm)       | 11.4 + 5.3    | 8.0 + 4.4     | 3.946   | <0.001 |
| No. of lymph nodes | 7.9 + 4.6     | 5.5 + 3.6     | 3.356   | 0.001  |
| Change after chemotherapy |               |               |         |        |
| Tumor thickness change (mm) | 4.4 + 4.6     | 6.7 + 4.9     | 2.651   | 0.009  |
| Tumor length change (mm)  | 2.0 + 1.7     | 2.3 + 2.4     | 0.655   | 0.513  |
| Tumor CT value change (HU) | 8.4 + 15.5    | 13.0 + 14.5   | 1.738   | 0.085  |
| LSLN change (mm) | 3.9 + 5.7     | 4.4 + 6.3     | 0.406   | 0.686  |
| SSLN change (mm) | 2.6 + 4.6     | 3.8 + 6.1     | 1.267   | 0.208  |
| No. of lymph node change | 1.5 + 1.9     | 0.7 + 1.6     | 2.565   | 0.012  |

LSLN indicates long axis size of maximum lymph node; SSLN, short axis size of maximum lymph node.

*The value of the data was means ± standard deviation. The P value was from independent-samples T test.

TABLE 3. AUC of CT Indicators

| Indicator                  | AUC  | SE     | 95% CI   |
|----------------------------|------|--------|----------|
| Thickness on pCT           | 0.620| 0.0505 | 0.531 to 0.703 |
| LSLN on pCT                | 0.666| 0.0485 | 0.579 to 0.746 |
| SSLN on pCT                | 0.705| 0.0466 | 0.619 to 0.782 |
| Number of LN on pCT        | 0.669| 0.0484 | 0.581 to 0.749 |
| Number of LN on bCT        | 0.636| 0.0505 | 0.547 to 0.718 |
| Thickness change           | 0.634| 0.0496 | 0.545 to 0.716 |

bCT indicates baseline CT; pCT, preoperative CT; LSLN, long axis size of maximum lymph node; SSLN, short axis size of maximum lymph node.

FIGURE 2. Receiver operating characteristic (ROC) curve for lymph node metastasis with six CT indicators. The highest AUC of these six CT indicators was 0.705 which was performed by the short axis size of maximum lymph node (SSLN) of preoperative CT. Figure 2 can be viewed online in color at www.jcat.org.
compared with the training sample value. This indicates a need for improvement of the model’s ability to assess new cases.

CONCLUSIONS
The least squares support vector machine model based on CT images can help diagnose lymph node metastasis in esophageal cancer with preoperative chemotherapy.

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