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Assessing the probability of metastatic mediastinal lymph node involvement in patients with non-small cell lung cancer using convolutional neural networks on chest computed tomography

Alexey E. Shevtsov¹, Iaroslav D. Tominin¹, Vladislav D. Tominin¹, Vsevolod M. Malevanniy¹, Yury S. Esakov², Zurab G. Tukvadze², Andrey O. Nefedov³, Piotr K. Yablonskii³, Pavel V. Gavrilov³, Vadim V. Kozlov⁴, Mariya E. Blokhina⁵, Elena A. Nalivkina⁵, Victor A. Gomboleviskiy^{1,7}, Yuriy A. Vasilev⁶, Mariya N. Dugova¹, Valeria Yu. Chernina¹, Olga V. Omelyanskaya⁶, Roman V. Reshetnikov⁶, Ivan A. Blokhin⁶, Mikhail G. Belyaev¹

¹ IRA Labs, Moscow, Russia;

² Moscow City Clinical Oncological Hospital № 1, Moscow, Russia;

³ Saint-Petersburg State Research Institute of Phthisiopulmonology, Saint-Petersburg, Russia;

⁴ Novosibirsk Regional Clinical Oncology Dispensary, Novosibirsk, Russia;

⁵ AstraZeneca Pharmaceuticals LLC, Moscow, Russia;

⁶ Research and Practical Clinical Center for Diagnostics and Telemedicine Technologies, Moscow, Russia;

⁷ Sechenov First Moscow State Medical University, Moscow, Russia

ABSTRACT

BACKGROUND: Lung cancer is the second most common cancer worldwide, accounting for approximately 20% of all cancer-related deaths and having a <10% 5-year survival rate for very late-stage cases. For the prevalent non-small cell lung cancer (NSCLC), recent guidelines advise staging based on the 8th edition of the TNM classification, highlighting the importance of mediastinal lymph node involvement. While noninvasive methods are generally accurate, they often lack sensitivity, and invasive methods may not be suitable for all patients. Advances in deep learning present potential in solving such problems. However, most research focuses on algorithm development more than clinical relevance. Moreover, none of them addressed individual lymph node malignancies, limiting comprehensive analysis and interpretability and leaving clinicians without sufficient means to validate the results effectively.

AIM: To develop a local data-trained and validated algorithm for segmenting each mediastinal lymph node in chest computed tomography (CT) and assessing the probability of its involvement in metastasis.

MATERIALS AND METHODS: Initially, IASLC lymph node stations are segmented, providing a bounding box of the mediastinum for further processing. Next, the image is cropped to this box and passed through a second network to identify and mask all visible lymph nodes. Finally, each detected lymph node is extracted, stacked with its mask, and evaluated by a feed-forward network to determine malignancy probabilities.

RESULTS: The pipeline achieved an average recall and object Dice Score of 0.74 ± 0.01 and 0.53 ± 0.26 for the clinically relevant lymph node segmentation task. Further, it recorded a 0.73 ROC AUC for predicting a patient's N-stage, outperforming traditional size-based criteria.

CONCLUSION: The proposed algorithm enables new research algorithms to optimize the management of patients with nonenlarged intrathoracic lymph nodes, thus improving the quality of medical care for patients with cancer.

Keywords: lung cancer; lymph nodes; medical imaging; deep learning.

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Оценка вероятности метастатического поражения лимфатических узлов средостения у пациентов с немелкоклеточным раком лёгкого при использовании свёрточных нейронных сетей для интерпретации данных компьютерной томографии органов грудной клетки

А.Е. Шевцов¹, Я.Д. Томинин¹, В.Д. Томинин¹, В.М. Малеванный¹, Ю.С. Есаков², З.Г. Туквадзе², А.О. Нефёдов³, П.К. Яблонский³, П.В. Гаврилов³, В.В. Козлов⁴, М.Е. Блохина⁵, Е.А. Наливкина⁵, В.А. Гомболевский^{1,7}, Ю.А. Васильев⁶, М.Н. Дугова¹, В.Ю. Чернина¹, О.В. Омелянская⁶, Р.В. Решетников⁶, И.А. Блохин⁶, М.Г. Беляев¹

¹ «АЙРА Лабс», Москва, Россия;

² Городская клиническая онкологическая больница № 1, Москва, Россия;

³ Санкт-Петербургский научно-исследовательский институт фтизиопульмонологии, Санкт-Петербург, Россия;

⁴ Новосибирский государственный медицинский университет, Новосибирск, Россия;

⁵ «АстраЗенека Фармасытикалз», Москва, Россия;

⁶ Научно-практический клинический центр диагностики и телемедицинских технологий, Москва, Россия;

⁷ Первый Московский государственный медицинский университет имени И.М. Сеченова, Москва, Россия

АННОТАЦИЯ

Обоснование. Рак лёгкого — второй по распространённости тип рака во всём мире. На данное заболевание приходится приблизительно 20% всех случаев смерти от рака, а пятилетняя выживаемость на поздних стадиях — менее 10%. Для стадирования немелкоклеточного рака лёгкого, характеризующегося высокой распространённостью, в новейших клинических рекомендациях предлагают использовать классификацию TNM (8-е издание). Это подчёркивает значимость оценки поражения лимфатических узлов средостения. Неинвазивные методы обследования в целом обеспечивают точную оценку, однако часто обладают недостаточной чувствительностью, в то время как инвазивные — могут быть противопоказаны отдельным пациентам. Благодаря совершенствованию технологий глубокого обучения появилась возможность преодолеть эти сложности. Тем не менее в большинстве исследований по данному вопросу основное внимание уделяют разработке алгоритмов, а не клинической значимости результатов. Кроме того, ни в одном из таких исследований не оценивают поражение отдельных лимфатических узлов, что ограничивает возможности комплексного анализа и интерпретацию результатов, а также препятствует их эффективной валидации в клинической практике.

Цель — разработать валидированный алгоритм, обученный на внутренних данных, для сегментации отдельных лимфатических узлов средостения по данным компьютерной томографии органов грудной клетки, а также оценить вероятность их метастатического поражения.

Материалы и методы. Выполнение сегментации групп лимфатических узлов в соответствии с рекомендациями Международной ассоциации по изучению рака лёгкого, чтобы получить ограничивающий прямоугольник для области средостения с целью последующей обработки данных. Затем изображение кадрируют при использовании этого ограничивающего прямоугольника и обрабатывают с помощью второй сети для выявления всех визуализируемых лимфатических узлов и генерации масок. На заключительном этапе выделяют каждый визуализируемый лимфатический узел, применяют соответствующую маску и оценивают с использованием сети прямого распространения, чтобы определить вероятность метастатического поражения.

Результаты. В данной последовательности действий средний отклик и значение Dice Score объекта составили $0,74 \pm 0,01$ и $0,53 \pm 0,26$ соответственно для задачи клинически значимой сегментации лимфатических узлов. Кроме того, значение площади под ROC-кривой для прогнозирования степени поражения регионарных лимфатических узлов составило 0,73, что превосходит традиционные критерии, основанные на размере.

Заключение. Предложенный алгоритм обеспечивает оптимизацию лечения пациентов без увеличения внутригрудных лимфатических узлов за счёт новых алгоритмов исследований, что повышает качество медицинского обслуживания пациентов с онкологическими заболеваниями.

Ключевые слова: рак лёгкого; лимфатические узлы; медицинская визуализация; глубокое обучение.

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使用卷积神经网络评估非小细胞肺癌患者纵隔淋巴结转移可能性的研究

Alexey E. Shevtsov¹, Iaroslav D. Tominin¹, Vladislav D. Tominin¹, Vsevolod M. Malevanniy¹, Yury S. Esakov², Zurab G. Tukvadze², Andrey O. Nefedov³, Piotr K. Yablonskii³, Pavel V. Gavrilov³, Vadim V. Kozlov⁴, Mariya E. Blokhina⁵, Elena A. Nalivkina⁵, Victor A. Gombolevskiy^{1,7}, Yuriy A. Vasilev⁶, Mariya N. Dugova¹, Valeria Yu. Chernina¹, Olga V. Omelyanskaya⁶, Roman V. Reshetnikov⁶, Ivan A. Blokhin⁶, Mikhail G. Belyaev¹

¹ IRA Labs, Moscow, Russia;

² Moscow City Clinical Oncological Hospital № 1, Moscow, Russia;

³ Saint-Petersburg State Research Institute of Phthisiopulmonology, Saint-Petersburg, Russia;

⁴ Novosibirsk Regional Clinical Oncology Dispensary, Novosibirsk, Russia;

⁵ AstraZeneca Pharmaceuticals LLC, Moscow, Russia;

⁶ Research and Practical Clinical Center for Diagnostics and Telemedicine Technologies, Moscow, Russia;

⁷ Sechenov First Moscow State Medical University, Moscow, Russia

摘要

背景。肺癌是全球第二大常见癌症，约占所有癌症死亡病例的 20%。其中晚期肺癌的五年生存率不足 10%。对于高发的 非小细胞肺癌（NSCLC），最新临床指南（TNM分类第8版）强调 纵隔淋巴结受累 的评估在分期中的重要性。非侵入性检查方法： 敏感性不足；侵入性检查方法： 某些患者可能存在禁忌；深度学习技术 的发展为克服上述挑战提供了新途径。然而，现有研究大多集中于 算法开发，忽略了 单个淋巴结受累评估的临床意义，限制了其在临床应用中的综合性和有效性。

目的。开发并验证一个基于内部数据训练的算法，通过 胸部CT图像 分割单个纵隔淋巴结，并评估其转移的可能性。

材料与方法。数据分割与处理：按照国际肺癌研究协会建议，对 淋巴结组 进行分割；获取纵隔区域的限制性矩形框，用于后续数据处理。深度学习技术应用：使用第一个神经网络对图像裁剪；使用第二个神经网络识别所有可视淋巴结并生成掩膜；在最后阶段，分离每个可视淋巴结，应用掩膜并利用前馈网络评估其转移的可能性。

结果。分割任务性能：平均响应值为 0.74 ± 0.01 ；Dice Score 为 0.53 ± 0.26 。预测淋巴结转移性能：ROC曲线下面积（AUC）为 0.73；该结果优于基于传统 大小标准 的评估方法。

结论。所提出的算法通过深度学习技术实现了对纵隔淋巴结转移可能性的自动评估，在无显著肿大的淋巴结患者中优化了治疗方案。该方法提升了 肿瘤患者医疗服务的质量，并为淋巴结评估提供了一种有效的非侵入性选择。

关键词：肺癌；淋巴结；医学影像；深度学习。

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BACKGROUND

Lung cancer is the second most prevalent cancer globally. In 2018, 2.1 million new lung cancer cases were reported, with 1.8 million deaths, representing approximately 20% of all cancer-related deaths [1]. The 5-year survival rate for early-stage lung cancer is 68%–92%. However, in advanced disease, it drops to <10%, accounting for 42% of lung cancer cases [2]. Thus, an early diagnosis and timely treatment are crucial for improving survival and lowering treatment costs.

Screening examinations are crucial for detecting early-stage lung cancer because they can identify the disease in asymptomatic high-risk patients. These examinations are recommended in patients aged over 50 years who are currently smoking or who have quit smoking within the last 15 years (smoking index ≥ 20) [3]. Low-dose *computed tomography* (CT) is used to screen for lung pathology because it has been proven effective in multiple randomized prospective studies [6–11]. However, this noninvasive technique, while associated with minimal risks, provides insufficient information.

It is recommended to utilize minimally invasive biopsies or noninvasive positron emission tomography with CT (PET/CT) to acquire initial results [4, 5]. For patients with confirmed lung cancer, staging is crucial for determining the degree of metastasis and selecting the best treatment strategy based on the cancer type.

Recent guidelines recommend using the TNM staging system (8th edition, 2017) for staging non-small cell lung cancer (NSCLC), the most prevalent lung cancer, where *T* indicates the primary tumor size and invasiveness, *N* the degree of spread to thoracic lymph nodes, and *M* represents distant metastasis [12]. This system enables the determination of disease stage based on clinical examination findings (typically prior to surgery, using noninvasive methods), histopathological findings, and repeated staging following treatment.

Since thoracic lymph node involvement is frequent in lung cancer, evaluating regional lymph node involvement is essential for staging the disease and selecting appropriate treatment approaches. Whether aggressive surgery or adjuvant therapy is employed in NSCLC patients depends on the extent of mediastinal lymph node involvement [4, 5]. There are currently two main types of treatment strategies for NSCLC patients:

- Perform PET/CT followed by diagnostic surgery [5, 13, 14];
- Perform diagnostic surgery irrespective of the PET/CT findings [4].

The *National Comprehensive Cancer Network* guidelines recommend *radical surgery* as a preferable therapeutic option in patients with early NSCLC, while *radiotherapy* or *chemotherapy* is considered appropriate for patients with advanced NSCLC [15].

Despite the wide range of approaches for detecting mediastinal lymph node involvement, it can be challenging

to confirm or rule out the presence of metastases. Studies performed by Roberts et al. [6] and Kanzaki et al. [17] reveal that compared to histological examination, which is considered the gold standard, the misdiagnosis and false-negative rates are higher when PET/CT is used for detecting lymph node involvement compared with histological examinations. Moreover, PET/CT is not accessible to most patients in remote areas [18]. Diagnostic surgeries, even minimally invasive ones, require anesthesia, which may be contraindicated in some patients. This necessitates the use of noninvasive, cost-effective techniques for predicting mediastinal lymph node involvement in patients with primary NSCLC.

Advancements in *deep learning* technologies make it possible to address these challenges [19]. Published studies have demonstrated encouraging outcomes for single or group lymph node segmentation [20–22]. However, most studies focus on algorithm development rather than on the clinical relevance of the findings. Moreover, to the best of our knowledge, no studies have assessed individual lymph node involvement, which limits the possibilities of integrating and independently validating the findings in clinical practice [23–25].

Determining the extent of lymph node involvement is crucial for administering effective treatment in patients with NSCLC. Clinicians employ two main groups of methods:

- Noninvasive: techniques that do not physically affect the patient's body;
- Invasive: diagnostic surgeries.

Despite their high sensitivity and low rates of post-operative tumor grade changes, invasive techniques necessitate anesthesia and surgical intervention [14, 26]. This calls for more affordable and accessible noninvasive techniques.

Several studies have revealed that this technique has limitations when the short axis diameter is the only parameter for determining the histological status of lymph nodes based on CT or *magnetic resonance imaging* (MRI) findings [27–29]. For example, Brown et al. [27] reported that mesorectal MRI findings do not differentiate between histologically benign (2–10 mm) and malignant (3–15 mm) lymph nodes. The same problem arises in MRI of the head and neck, where the standard threshold of 10 mm yields a sensitivity and specificity of 0.88 and 0.39, respectively [28, 29]. However, additional morphological criteria such as irregular boundaries or mixed signal intensity raise the sensitivity to 0.85 (95% confidence interval [CI]: 0.74–0.92) and specificity to 0.97 (95% CI: 0.95–0.99). Although a recent study identified the classification accuracy for various combinations of criteria, it did not propose a standardized approach [30]. To address this issue, Elsholtz et al. [31] developed the *Node-RADS lymph node assessment system*. It assesses the visible lymph nodes based on their short axis diameter, texture, border, and shape, using five categories. Moreover, it considers other factors such as the anatomical site.

When used with PET, CT with contrast yields precise results. Significant differences ($p < 0.05$) in sensitivity and specificity were observed when ascertaining the degree of lymph node involvement using PET/CT compared to CT with contrast (0.78 and 0.92 vs. 0.56 and 0.73, respectively) [32]. However, this technique is expensive and not available to patients in remote areas [18].

Algorithmic Approach

Mediastinal lymph node segmentation and classification remain unexplored because of the lack of publicly available high-quality datasets. However, several studies have explored the algorithm components proposed in this paper.

Lymph Node Segmentation

Over the last 5–10 years, several approaches to volumetric medical image segmentation have emerged. Some architectures, such as *DeepMedic3D U-Net* or *V-Net*, provide credible results when assessing publicly available medical image sets [33–37]. The proposed pyramid convolutional neural networks are optimal for lymph node segmentation. Employing fourfold cross-validation, Iuga et al. [21] discovered that the detection rate for large lymph nodes was 0.77; however, the false positive rate was 10.3 per case [21]. Furthermore, this approach has low sensitivity (0.34) for lymph nodes measuring 5–10 mm, with a total Dice Score of 0.44.

Identification of Lymph Node Groups

Iuga et al. [21, 22] used a multiclass classification to analyze the distribution of mediastinal lymph nodes by group, building on their earlier work. Tops-1, -2, and -3 classifications demonstrated high accuracy values of 0.86, 0.94, and 0.96, respectively. Despite these findings, the proposed algorithm lacks sensitivity for critical lymph node groups and only partially meets the recommendations of Goldstraw et al. [2]. In contrast, Guo et al. [20] reported effective segmentation with a Dice score of 0.81 ± 0.06 . However, the authors did not ascertain the accuracy of the lymph node distribution and its influence on the extent of regional lymph node involvement.

Classification of lymph node involvement

Previous studies have proposed algorithms for the indirect analysis of mediastinal lymph node involvement using primary tumor image features, without indicating specific groups or individual lymph nodes [23–25]. This is partially due to the difficulties in acquiring precise reference labels. Determining the location of each lymph node on CT images after receiving the biomaterial can be challenging. In this scenario, the simplest solution was to assign labels to each lymph node, similar to the method employed for grading pulmonary nodules. Simple patch-based convolutional neural networks exhibit an area under the ROC curve (AUC) of 0.928 ± 0.027 for classification. Pretraining a convolutional autoencoder for picture fragment reconstruction and employing

an encoder as a basis for metastatic classification improves outcomes, with an AUC of 0.936 ± 0.009 [38]. However, using weak supervision, it is possible to establish a shared histological label for many lymph nodes from the same group. Dubost et al. [39] proposed the innovative concept of using a single label for training, with a prognostic map generation when receiving outputs. However, max-pooling can result in the loss of significant information for small targets, such as lymph nodes, limiting the efficacy of their histological status assessment.

AIM

To develop and validate a CT-based algorithm trained on internal data for individual mediastinal lymph node segmentation and to predict the probability of metastasis for each lymph node.

MATERIALS AND METHODS

Study Design

This was an observational, single-center, retrospective study.

Eligibility Criteria

Inclusion criteria:

- Histologically confirmed NSCLC;
- Availability of data acquired using contrast enhanced-chest CT (venous phase), slice thickness ≤ 1 mm;
- Presence of a two-month interval between the CT and surgery.

Non-inclusion criteria:

- Lack of data obtained through chest CT with contrast (venous phase) or lymph node biopsy;
- More than two months between the CT and surgery.

Exclusion criteria:

- CT artifacts preventing reliable assessment;
- Low diagnostic value of the biopsy findings.

Study Site

Patients who had undergone chest CT with contrast and thoracic lymph node biopsy were enrolled at the City Clinical Oncology Hospital No. 1 (Moscow).

Intervention

The proposed algorithm for lymph node segmentation and metastasis classification involves a three-stage process:

First stage: identification of lymph node groups and mediastinum segmentation in the region of interest are essential for determining the extent of regional lymph node involvement [12];

Second stage: cropping the input image and segmentation of all visible lymph nodes using a bounding box for the mediastinum;

Third stage: analyzing all identified lymph nodes using a feedforward network to determine the probability of metastasis.

The results provide information on lymph node involvement in specific groups, enabling evaluation of the degree of involvement based on the tumor site. *Subsection 3.1* addresses the segmentation of lymph node groups; *subsection 3.2* examines the segmentation of individual lymph nodes; and *subsection 3.3* discusses the classification of lymph node involvement.

Segmentation of the lymph node groups

In patients with NSCLC, the affected lymph nodes are located in a narrow range (mediastinal area). The anatomical and primary tumor sites dictate the extent of regional lymph node involvement [12]. The *International Association for the Study of Lung Cancer* (IASLC) guidelines recognize

ten lymph node groups in the mediastinum [40]. Lymph node groups near the trachea and bronchi are divided into left and right groups. No additional specialized classification system is used for the subcarinal lymph nodes. During diagnostic procedures, biopsies are not typically performed for Groups 1, 8, and 9 lymph nodes. Therefore, they were excluded from this study.

This study used a two-component *U-Net model* for the 3D segmentation of lymph node groups (Fig. 1) [41]. While the first component distinguished between the mediastinum and the background, the second component classified each voxel within the mediastinal mask to a specific lymph node group. Advanced deep learning technologies, such as *ResBlocks*, batch normalization, and the *ReLU activation function*, were used after each convolution, except for the data output [42–44].

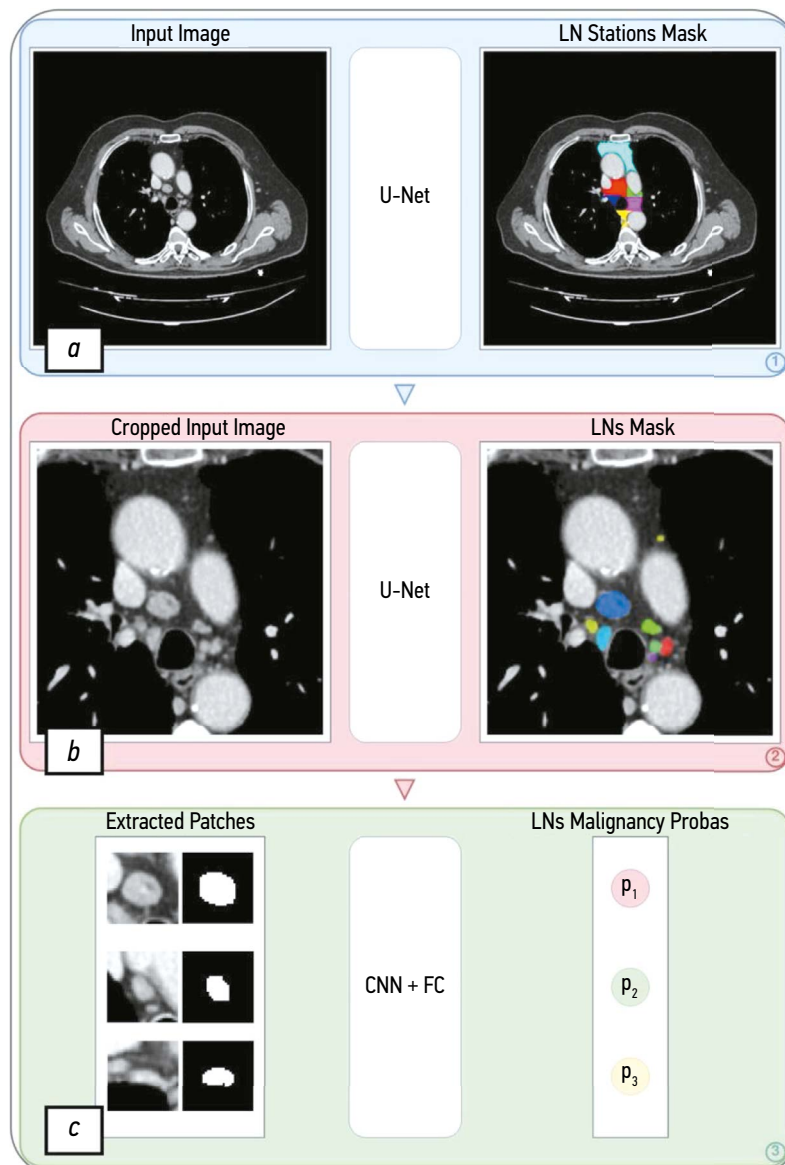


Fig. 1. Three-stage algorithm for lymph node segmentation and metastasis classification: *a*, segmentation of lymph node groups; *b*, image coding based on the bounding box and processing using a second network; *c*, marking each identified lymph node, applying the respective mask, and assessment through a feedforward network. LN, lymph node.

Lymph node segmentation

To preserve computing resources during the second stage, the region of interest should be marked employing the bounding box for the mediastinum obtained in the first stage. If the size in the axial view exceeds 128 pixels, filling is used to achieve the minimal size of 128 pixels.

During this stage, the architecture was comparable to the one used for the segmentation of the lymph node groups. However, it offers a pooled binary data output for a lymph node segmentation prognostic map with more channels and fewer levels (see Fig. 1). This design is adapted to individual lymph nodes that are substantially smaller than the groups; thus, a large receptive field is not required. The design provides for additional characteristics that boost segmentation accuracy.

Classification of lymph node involvement

In weak supervision, a metastasis label is assigned to a lymph node group, and the probability of metastasis for each lymph node is predicted. Lymph nodes are marked on 32×32 image fragments for study purposes. They are merged with respective masks to combine all identified objects in a single dataset. Data is processed using convolutional neural networks with a five-level *ResNet architecture*, followed by max-pooling to minimize spatial dimensions [42]. During the final stage, data is analyzed using the sigmoid and fully connected layers to assess the probability of metastasis for each lymph node.

This is further complicated by the fact that in contrast to benign lymph nodes, metastases might be present or absent in malignant lymph node groups. Thus, a benign lymph node group has no affected lymph nodes, whereas a malignant group must have at least one. To satisfy this requirement, a unique loss function is used. The binary cross-entropy loss function was used for training to assess the probability of metastasis in all benign group lymph nodes. For lymph nodes with metastasis, training is only performed if the prognostic data indicates that is all lymph nodes in this region are benign (see Fig. 1). This method has both advantages and disadvantages.

EXPERIMENT

Data

The publicly available dataset exhibited several limitations [45]:

- It contains inadequate information on the diagnosis and histological status of the mediastinal lymph nodes;
- The groups are not specified, and the annotation only includes lymph nodes with a short axis diameter of >10 mm;
- Contrast-enhanced CT images were likely obtained during the arterial rather than the venous phase.

Thus, a private dataset for 60 patients with confirmed NSCLC who underwent diagnostic surgery to assess specific lymph node groups was used.

The following inclusion criteria were applied to the dataset:

- presence of CT images acquired during the venous contrast phase, which allows the most effective differentiation between the lymph nodes and surrounding structures (particularly blood vessels);
- diagnostic surgery performed within two months after the previous examination, which included the venous phase contrast-enhanced CT images;
- contrast-enhanced CT slice thickness of <1 mm, with eight image series selected for annotation.

Lymph node groups

The same radiologist annotated the lymph node groups, meticulously adhering to the IASLC guidelines for generating prognostic maps for the mediastinum [40]. The annotation protocol required that large blood vessels, such as the aorta, pulmonary trunk, and azygos vein, as well as the esophagus, be differentiated from the lymph node groups (Fig. 2).

Lymph nodes

Two radiologists annotated the mediastinal lymph nodes and assigned binary masks to all the identifiable lymph nodes. If the boundaries between several lymph nodes were uncertain, a single mask was assigned.

Degree of lymph node involvement

Lymph node group involvement was determined based on the outcomes of *video-assisted mediastinoscopic lymphadenectomy* (VAMLA) [14]. A biopsy of the dissected lymph nodes was performed to establish their status. During the final stage, each group was assigned one of the three labels based on the histological examination findings:

- *No data* for lymph node groups that were not resected;
- *benign*;
- *malignant*.

The statistics for the training dataset are presented in Table 1.

Training

All experiments were performed using a standard pre-processing method, with input images amplified to a fixed voxel spacing (1, 1, 1). The CT images were scaled at 0–1 HU for intensity and set to the soft tissue window level (160–240 HU) for window level. Goncharov et al. [46] used a pretrained neural network to crop the input image to match the lung area, then adjusted it to fit the mediastinal area. Given the small dataset, high amplification was used during training, including 10° and 90° rotation, random shifts, and vertical and horizontal flip (Fig. 3).

Segmentation of lymph node groups

The first stage involved training with 30,000 iterations using the *Adam optimizer*, including mixed precision and gradient scaling. The first component was binary cross-entropy with adaptive foreground voxel reweighting. For the second

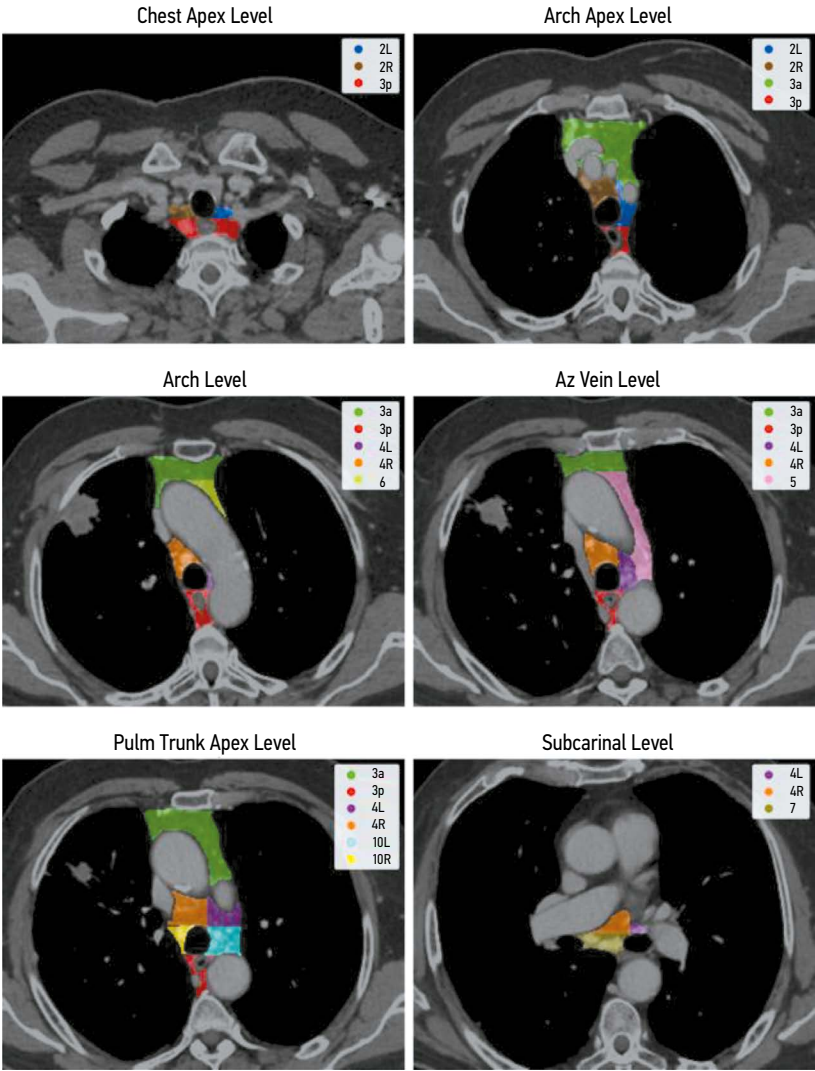


Fig. 2. Example of lymph node group annotation at different mediastinal levels.

Table 1. Training dataset: biopsy findings for the lymph node groups

Lymph node groups	Benign	Malignant	No data
Right low cervical, supraclavicular, and sternal notch nodes	0	0	8
Left low cervical, supraclavicular, and sternal notch nodes	0	0	8
Right upper paratracheal nodes	5	2	1
Left upper paratracheal nodes	3	0	5
Prevascular nodes	0	0	8
Prevertebral (retrotracheal) nodes	0	0	8
Right lower paratracheal nodes	6	2	0
Left lower paratracheal nodes	8	0	0
Subaortic nodes	0	1	7
Paraaortic nodes	0	1	7
Subcarinal nodes	6	1	1
Paraesophageal nodes	0	0	8
Pulmonary ligament nodes	1	0	7
Right hilar nodes	2	2	4
Left hilar nodes	2	1	5

Note. Regional lymph node classification according to the *International Association for the Study of Lung Cancer (IASLC)* guidelines.

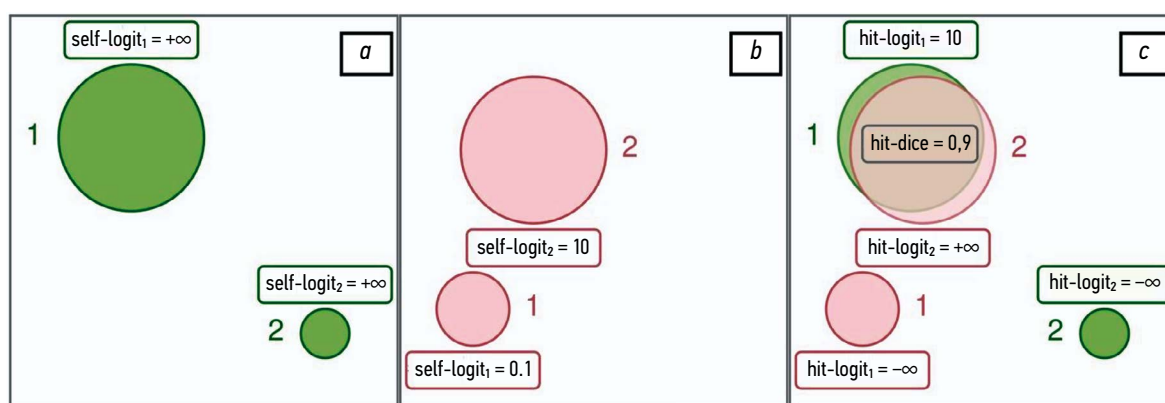


Fig. 3. Example of assigning the assessed statistical parameters to different connected components of the sample mask (a) and the respective logit mask (b); self-logit and hit-logit, personal statistics for each connected component; hit-dice, shared parameters for a pair of connected components with a positive value (c).

component, cross-entropy was employed. Throughout the training, the learning rate remained consistent at 0.003.

Lymph node segmentation

In the second stage, training was performed with 70,000 iterations using the *Adam optimizer*, incorporating mixed precision and gradient scaling. Like the first stage, the second stage was aimed at minimizing the binary cross-entropy and adaptive foreground voxel reweighting. The learning rate was 10^{-3} at the beginning of training and gradually decreased by 3, 3, 2, and 2 times during 5,000, 15,000, 50,000, and 60,000 iterations, respectively.

Classification of lymph node involvement

The classification network was trained with 40,000 iterations using the *Adam optimizer*, with loss minimization using positive class example reweighting (coefficient 100). The learning rate was 3×10^{-5} at the beginning of the training and remained constant throughout the training.

Parameters

To assess the first stage, the accuracy of assigning lymph nodes to respective groups was ascertained, as conventional segmentation parameters were of little relevance in this case. Moreover, prognoses based on the final outcome were assessed for the third stage. Patients with and without metastases had their regional lymph node involvement levels evaluated using the AUC.

FROC method

The *FROC method* developed by Van Ginneken et al. [36] was used to assess the quality of lymph node detection. The FROC curve represents the relationship between the model response to the object (*Y-axis*) and the average false positive rate in the image (*X-axis*).

The FROC curves were plotted employing a sample mask for the entire image (Fig. 3a) and the respective logit map, which was converted to binary form using the threshold of 0 to obtain a logit mask (Fig. 3b). Both masks were then divided into interconnected components. Each connected component was assigned three statistical parameters:

- *self-logit*: maximum logit value within the connected component; is set to infinity if the connected component is within the sample mask;
- *hit-dice*: maximum Dice score between the selected connected component and another mask (Fig. 3c);
- *hit-logit*: the same statistical parameter as *self-logit*; however, it is derived from a connected component within another mask that matches the first mask in terms of the *hit-dice* value; is set to negative infinity if *hit-dice* = 0.

These statistical parameters enable the *hit-logit* value to be used plot an FROC curve by selecting different *l* thresholds. Moreover, the *hit-dice* value was considered when the curve points were obtained to check the hit condition. The hit condition for two connected components was considered to be met if the *hit-dice* value was positive. Thus, for the selected *l* threshold:

- The *false positive value* was defined as the number of connected components within a logit mask with a *self-logit* $> l$ threshold, but with *hit-dice* = 0;
- The *true positive value* was defined as the number of connected components within a sample mask with *hit-logit* $> l$ threshold and *hit-dice* > 0 ;
- The *false negative value* was defined as the number of connected components within a sample mask with a *self-logit* $\leq l$ threshold or *hit-dice* = 0.

In experiments, we used *l* thresholds in the range of 0.1 to *max-logit*, where the *max-logit* value is the maximum logit value for the control sample of the predictions.

In contrast to traditional approaches for plotting such curves, this approach ensures uniformity because each connected component within a prognostic mask appears in full or does not appear at all, preventing the separation or merging of the connected components. Given the limited accuracy of the floating point calculations, we used a logit value search instead of using a classical probability search. It allows plotting curves for the whole range, because large logit values can be found with greater accuracy than large probabilities, which are usually rounded to 1.

Table 2. Lymph node detection rates for groups based on the short axis diameter

Group	Mean response	Dice score
d > 0 mm	0.48 ± 0.01	0.53 ± 0.24
d > 5 mm	0.74 ± 0.01	0.53 ± 0.26
d > 10 mm	0.95 ± 0.01	0.56 ± 0.26

Note. d, short axis diameter.

Mean response

The FROC method yields comprehensive analysis results; however, their interpretation can be challenging. We used an additional parameter to simplify and integrate the data derived from the FROC curves. This paper presents the mean values for false positive points in the range of 0 to 5, with an increment of 0.01. Because it identifies a crucial clinical characteristic—the number of detected lesions per case—this method establishes the detection efficacy and functions as the primary quality criterion in this investigation.

Dice Score of an object

The *Dice* score is the most frequently employed approach for analyzing segmentation [37]. However, applying its average value for multiple objects in several images may cause small objects to be obscured by large ones, which is a significant drawback. This paper reveals the average Dice score for an object:

$$objDSC_{(1)} = \sum_{i=1}^N \left(\frac{1}{M} \sum_{j=1}^M \frac{2 \cdot |Y_j \cap \hat{Y}_j|}{|Y_j| + |\hat{Y}_j|} \right)$$

where *N* is the number of images in the control sample; *M* is the number of lesions within the sample mask; *Y_j* is the set

Table 3. Patient status by the degree of regional lymph node involvement for the maximum short axis diameter; predicted probability of metastasis

Patient	Lymph node involvement	Maximum d, mm	Maximum p-value
0	0	11	0.29
1	0	14	0.41
2	+	38	1.00
3	+	14	0.54
4	+	14	0.54
5	0	21	0.83
6	+	15	0.61
7	+	11	0.96

Note. Lymph nodes selected by diameter can differ from the lymph nodes with the highest probability of metastasis. d, short axis diameter.

of voxels associated with the *j*-th connected component within this mask; and *Y[^]_j* is the respective connected component for the prognostic mask with the greatest hit rate for the Dice Score (DSC).

RESULTS

Lymph Node Segmentation

In the second stage, the parameters for different size ranges are presented:

- All lymph nodes;
- Lymph nodes >5 mm in size: clinically significant according to the guidelines;
- Lymph nodes >10 mm in size: are used as a baseline parameter of potential metastasis [31].

The results are presented in Table 2 and Table 3.

Despite the low detection rate in the first group, the convolutional neural networks demonstrated optimal sensitivity for the highest risk (last) group, as evidenced by a low false positive rate (three per case) (Fig. 4, 5).

Classification of Lymph Node Involvement

The metastasis classification outcomes are consistent with those obtained using a simplified approach, where

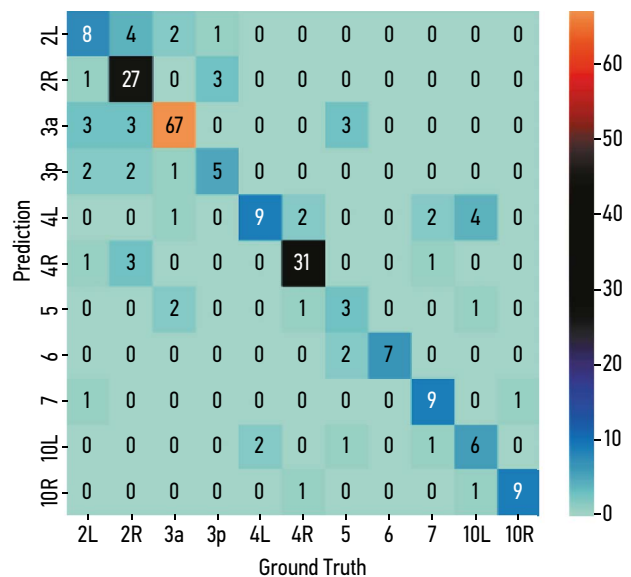


Fig. 4. Accuracy of assigning lymph nodes to groups in accordance with the International Association for the Study of Lung Cancer (IASLC) guidelines.

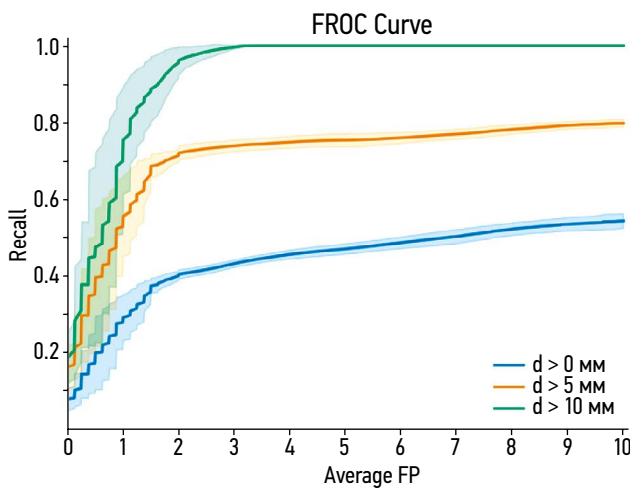


Fig. 5. Detection results during lymph node segmentation. FP, false positive; d, short axis diameter.

a lymph node with the greatest short axis diameter was considered a marker of metastasis. Using a threshold of 10 mm, this straightforward criterion produced three false positive findings. However, the proposed algorithm is more effective than this approach (Fig. 6) because it provided a larger AUC compared to the simplified approach (0.73 vs. 0.53). The Node-RADS classification indicates that lymph nodes with a short axis diameter of >30 mm be definitely considered as lymph nodes with metastasis. The only error was detected in *patient 5*: the selected lymph node had a very high probability of metastasis (Fig. 7).

DISCUSSION

The proposed *loss function* exhibits both advantages and disadvantages. It allows a convolutional neural network to independently determine the relationship between lymph nodes classified as malignant groups, using prior experience

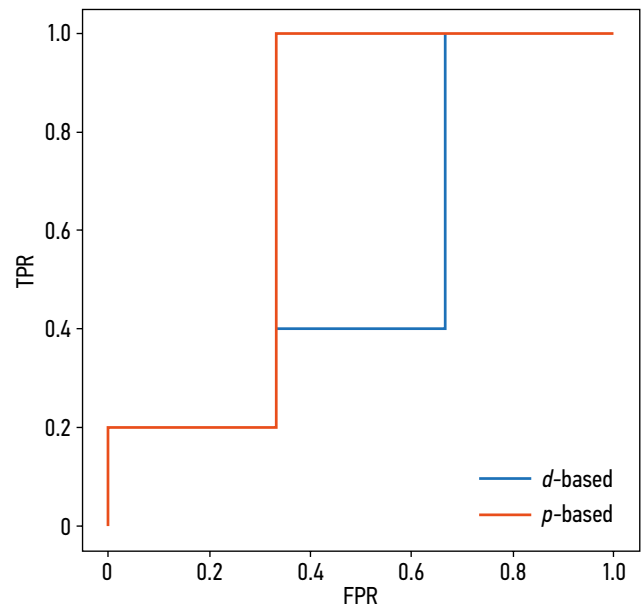


Fig. 6. Comparison of baseline criteria derived from the short axis diameter for predicting patient status regarding the degree of regional lymph node involvement and the proposed algorithm. TPR, true positive rate; FPR, false positive rate; SAD, short axis diameter.

to make modifications. Conversely, it is limited in its capacity to assign respective probabilities to positive class examples because specific information for each lymph node in the malignant group is unavailable. This training method can improve sensitivity but can also increase the false positive rate.

The clinical classification of lymph node locations places stringent requirements on the method. However, its main disadvantage is the *small dataset*, which lacks examples of different lymph nodes with and without metastasis. This is primarily due to the labor- and time-intensive process of establishing the boundaries of the lymph node groups

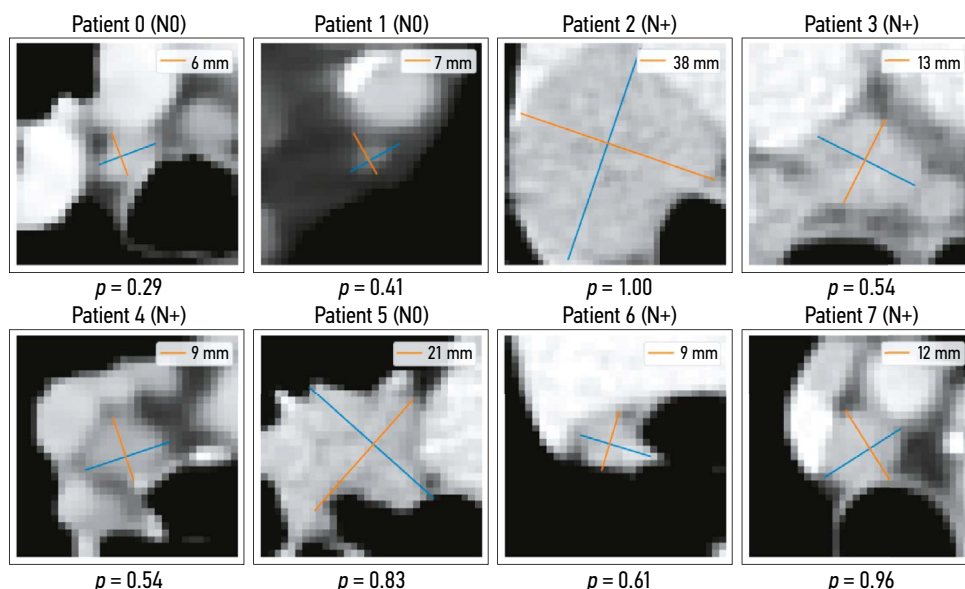


Fig. 7. Lymph nodes with the highest probability of metastasis for each patient. N0, no metastasis; N+, metastasis.

and individual lymph nodes from scratch. For one patient, mapping lymph node groups and individual lymph nodes takes approximately 1 hour and 2–3 hours, respectively. Ambiguous human anatomy criteria further complicate the process, making it unfeasible to establish broad guidelines. Thus, it is essential to augment the efficacy of the algorithm parameters by expanding the training dataset by including new cases of lymph node involvement without enlargement and enlarged lymph nodes without metastasis for each group of thoracic lymph nodes.

Multiphase CT images can significantly boost the capability to determine the degree of lymph node involvement by providing detailed information on each lymph node with and without intravenous contrast enhancement. The venous contrast phase is especially valuable [25]. However, the potential benefits of multiphase CT, including the native (without contrast), arterial, venous, and delayed intravenous contrast phases, are poorly understood. Their assessment can provide further insight into the mechanism of contrast uptake and distribution in the lymph nodes.

CONCLUSION

This paper presents a three-stage algorithm for lymph node segmentation and metastasis classification in patients with NSCLC. Training was conducted using the histological confirmation results for the lymph node groups. The proposed algorithm has an overall response of 0.74 ± 0.01 and a Dice score of 0.53 ± 0.26 for the segmentation of clinically significant lymph nodes (with a short axis diameter of 5 mm). It also has an AUC of 0.73 for predicting patient status regarding the degree of regional lymph node involvement. Thus, the proposed three-stage algorithm is superior to the conventional size-based methods. In enlarged lymph nodes (with a short axis diameter of 10 mm), segmentation was more effective, with an overall response of 0.95 and a Dice score of 0.56. This provides an opportunity for future studies to improve the quality of cancer therapy and the treatment of patients without thoracic lymph node enlargement.

Moreover, the proposed algorithm can be incorporated into the current management protocol for patients with confirmed NSCLC as a transitional step between the initial

diagnosis and PET/CT. This algorithm has several potential applications. If the algorithm predicts a low probability of mediastinal lymph node involvement, radical surgery can be considered immediately, eliminating the need for PET/CT and diagnostic surgery. In contrast, if there is a high chance of metastasis, radical surgery is not recommended. In this case, neoadjuvant chemotherapy can be considered without the need for PET/CT and diagnostic surgery. It is anticipated that this algorithm will be more affordable and accessible to patients, even if its accuracy is on par with PET/CT.

ADDITIONAL INFORMATION

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AUTHORS' INFO

*** Victor A. Gombolevskiy**, MD, Cand. Sci. (Medicine);
address: 30 Bolshoy Boulevard, 121205, Moscow;
ORCID: 0000-0003-1816-1315;
eLibrary SPIN: 6810-3279;
e-mail: v.gomboleviskiy@ira-labs.com

Alexey E. Shevtsov;
ORCID: 0000-0003-3085-4325;
e-mail: a.shevtsov@ira-labs.com

Iaroslav D. Tominin;
ORCID: 0000-0002-7210-7208;
e-mail: ia.tominin@ira-labs.com

Vladislav D. Tominin;
ORCID: 0000-0001-5678-3452;
e-mail: v.tominin@ira-labs.com

Vsevolod M. Malevanniy;
ORCID: 0009-0005-8804-2102;
e-mail: v.malevanniy@ira-labs.com

Yury S. Esakov, MD, Cand. Sci. (Medicine);
ORCID: 0000-0002-5933-924X;
eLibrary SPIN: 8424-0756;
e-mail: lungosurgery@mail.ru

Zurab G. Tukvadze, MD;
ORCID: 0000-0002-4550-6107;
e-mail: tukvadze.z.med@gmail.com

Andrei O. Nefedov, MD, Cand. Sci. (Medicine);
ORCID: 0000-0001-6228-182X;
eLibrary SPIN: 2365-9458;
e-mail: herurg78@mail.ru

Petr K. Yablonskiy, MD, Dr. Sci. (Medicine), Professor;
ORCID: 0000-0003-4385-9643;
eLibrary SPIN: 3433-2624;
e-mail: glhirurgb2@mail.ru

Pavel V. Gavrilov, MD, Cand. Sci. (Medicine);
ORCID: 0000-0003-3251-4084;
eLibrary SPIN: 7824-5374;
e-mail: pbniifrentgen@mail.ru

Vadim V. Kozlov, MD, Cand. Sci. (Medicine);
ORCID: 0000-0003-3211-5139;
eLibrary SPIN: 8045-4286;
e-mail: vadimkozlov80@mail.ru

Maria E. Blokhina, MD;
ORCID: 0009-0002-9008-9485;
e-mail: mariya.blokhina@astrazeneca.com

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ОБ АВТОРАХ

*** Гомболевский Виктор Александрович**, канд. мед. наук;
адрес: Россия, 121205, Москва, Большой б-р, 30 стр. 1;
ORCID: 0000-0003-1816-1315;
eLibrary SPIN: 6810-3279;
e-mail: v.gomboleviskiy@ira-labs.com

Шевцов Алексей Евгеньевич;
ORCID: 0000-0003-3085-4325;
e-mail: a.shevtsov@ira-labs.com

Томинин Ярослав Дмитриевич;
ORCID: 0000-0002-7210-7208;
e-mail: ia.tominin@ira-labs.com

Томинин Владислав Дмитриевич;
ORCID: 0000-0001-5678-3452;
e-mail: v.tominin@ira-labs.com

Малеванный Всеволод Михайлович;
ORCID: 0009-0005-8804-2102;
e-mail: v.malevanniy@ira-labs.com

Есаков Юрий Сергеевич, канд. мед. наук;
ORCID: 0000-0002-5933-924X;
eLibrary SPIN: 8424-0756;
e-mail: lungosurgery@mail.ru

Туквадзе Зураб Георгиевич;
ORCID: 0000-0002-4550-6107;
e-mail: tukvadze.z.med@gmail.com

Нефёдов Андрей Олегович, канд. мед. наук;
ORCID: 0000-0001-6228-182X;
eLibrary SPIN: 2365-9458;
e-mail: herurg78@mail.ru

Яблонский Петр Казимирович, д-р мед. наук, профессор;
ORCID: 0000-0003-4385-9643;
eLibrary SPIN: 3433-2624;
e-mail: glhirurgb2@mail.ru

Гаврилов Павел Владимирович, канд. мед. наук;
ORCID: 0000-0003-3251-4084;
eLibrary SPIN: 7824-5374;
e-mail: pbniifrentgen@mail.ru

Козлов Вадим Викторович, канд. мед. наук;
ORCID: 0000-0003-3211-5139;
eLibrary SPIN: 8045-4286;
e-mail: vadimkozlov80@mail.ru

Блохина Мария Евгеньевна;
ORCID: 0009-0002-9008-9485;
e-mail: mariya.blokhina@astrazeneca.com

Elena A. Nalivkina;

ORCID: 0009-0003-5412-9643;

e-mail: elena.nalivkina@astrazeneca.com

Yuryi A. Vasilev, MD, Dr. Sci. (Medicine);

ORCID: 0000-0002-5283-5961;

eLibrary SPIN: 4458-5608;

e-mail: VasilevYA1@zdrav.mos.ru

Mariya N. Dugova, MD;

ORCID: 0009-0004-5586-8015;

e-mail: m.dugova@ira-labs.com

Valeria Yu. Chernina, MD;

ORCID: 0000-0002-0302-293X;

eLibrary SPIN: 8896-8051;

e-mail: v.chernina@ira-labs.com

Olga V. Omelyanskaya;

ORCID: 0000-0002-0245-4431;

eLibrary SPIN: 8948-6152;

e-mail: OmelyanskayaOV@zdrav.mos.ru

Roman VI. Reshetnikov, Cand. Sci. (Physics and Mathematics);

ORCID: 0000-0002-9661-0254;

eLibrary SPIN: 8592-0558;

e-mail: reshetnikov@fbb.msu.ru

Ivan A. Blokhin, MD, Cand. Sci. (Medicine);

ORCID: 0000-0002-2681-9378;

eLibrary SPIN: 3306-1387;

e-mail: BlokhinIA@zdrav.mos.ru

Mikhail G. Belyaev, Cand. Sci. (Physics and Mathematics);

ORCID: 0000-0001-9906-6453;

eLibrary SPIN: 2406-1772;

e-mail: belyaevmichel@gmail.com

Наливкина Елена Александровна;

ORCID: 0009-0003-5412-9643;

e-mail: elena.nalivkina@astrazeneca.com

Васильев Юрий Александрович, д-р мед. наук;

ORCID: 0000-0002-5283-5961;

eLibrary SPIN: 4458-5608;

e-mail: VasilevYA1@zdrav.mos.ru

Дугова Мария Николаевна;

ORCID: 0009-0004-5586-8015;

e-mail: m.dugova@ira-labs.com

Чернина Валерия Юрьевна;

ORCID: 0000-0002-0302-293X;

eLibrary SPIN: 8896-8051;

e-mail: v.chernina@ira-labs.com

Омелянская Ольга Васильевна;

ORCID: 0000-0002-0245-4431;

eLibrary SPIN: 8948-6152;

e-mail: OmelyanskayaOV@zdrav.mos.ru

Решетников Роман Владимирович, канд. физ.-мат. наук;

ORCID: 0000-0002-9661-0254;

eLibrary SPIN: 8592-0558;

e-mail: reshetnikov@fbb.msu.ru

Блохин Иван Андреевич, канд. мед. наук;

ORCID: 0000-0002-2681-9378;

eLibrary SPIN: 3306-1387;

e-mail: BlokhinIA@zdrav.mos.ru

Беляев Михаил Геннадьевич, канд. физ.-мат. наук;

ORCID: 0000-0001-9906-6453;

eLibrary SPIN: 2406-1772;

e-mail: belyaevmichel@gmail.com

* Corresponding author / Автор, ответственный за переписку