

The Role of Videomediastinoscopy in Staging of Non-Small Cell Lung Cancer

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ABSTRACT

Lung cancer is the most frequent malignant disease and the leading cause of death from malignant diseases in the world and its incidence is increasing. At the time when diagnosis is established most patients have advanced disease and are not candidates for radical surgical treatment. Patients without distant metastases are subjected to various diagnostic methods to detect metastases in mediastinal lymph nodes that make up the path of lymph drainage from the lungs. The most reliable invasive diagnostic procedures for detecting metastases in mediastinal lymph nodes are videomediastinoscopy and endobronchial ultrasound with transtracheal puncture. In the absence of mediastinal lymph node metastases surgery is the treatment of choice. If mediastinal lymph nodes are positive for metastases multimodal treatment is implemented. At the Department of Thoracic Surgery, Zadar General Hospital, videomediastinoscopy for the staging of primary non-small cell lung cancer has been performed routinely since September 2009.

Key words: lung cancer; staging of lung cancer; surgical treatment of lung cancer; videomediastinoscopy, EBUS

Introduction

Lung cancer is the leading cause of death from malignant diseases worldwide and its incidence is increasing. In 2008, in the United States 215 000 people were diagnosed with lung cancer and 161 840 died. More people die annually from lung cancer than from breast, colon and prostate cancer together^{1,2}.

Five years survival rate in patients suffering from lung cancer is increasing slowly; in 1976, it was 11.9%, and in 2000, it was 15%. The main reason for the poor survival lies in the fact that 40% of patients have metastatic disease at the moment when diagnosis is established³.

In patients diagnosed with lung cancer it is necessary to carry out diagnostic evaluation to determine the stage of disease. Staging provides adequate information about the spread of the disease and it is crucial for determining the strategy of treatment and prognosis⁴. Staging is used for non – small cell lung cancer. For small cell lung cancer, which occurs in 10–15% of cases, invasive staging is not performed because this tumor has different biological features and is rarely subject of surgical treatment.

In the absence of distant metastases, involvement of mediastinal lymph nodes is the most important prognostic factor in patients with non-small cell lung cancer and mediastinal lymph node status determines the treatment strategy.

Primary surgical treatment of lung cancer with metastases to ipsilateral mediastinal lymph nodes (stage IIIA) gives poor results. Patients who were subjected to primary surgical treatment in stage IIIA have a five year survival rate of

7–14%⁵. Adjuvant chemotherapy often can not be completed because of poor general condition of patients who are recovering from surgery⁶.

Neoadjuvant Treatment

Chemotherapy, radiation or a combination of both methods are used as neoadjuvant treatment⁷. Neoadjuvant therapy offers several potential advantages. Theo-

retically, it acts on tumor cells before they produce resistant clones⁷. Patients can also receive full doses of drugs because they are not in postoperative recovery phase. In such conditions therapy often results in tumor reduction and eradication of the disease from mediastinal lymph nodes^{6–8}.

If neoadjuvant therapy eradicates the disease in lymph nodes (downstaging) or if there is no progression of disease, patients are rendered candidates for surgical treatment⁹. After implementation of neoadjuvant therapy and surgery, the five-year survival rate for patients with stage III A disease is about 25%^{6–9}.

Staging of Disease

The international system for staging of lung cancer is based on assessment of the extent of the primary tumor (T), the spread to the regional lymph nodes (N) and of the presence of distant metastasis (M). The combination of T, N and M is then used to determine the stage of disease (I–IV). The last revision of the TNM classification of lung cancer was in 2009¹⁰.

Status of mediastinal lymph nodes is the most important factor that determines treatment strategy. It is also used to evaluate efficiency of neoadjuvant therapy⁷.

For clinical work it is necessary to map lymph nodes in the mediastinum at nodal positions.

This kind of map was developed by Mountain and Dresler¹² and accepted by all relevant world organizations dealing with the treatment of lung cancer^{7,11,13}.

According to this map mediastinal lymph nodes are located in nine nodal positions while five other nodal positions are located in the lungs. Each nodal position is precisely defined anatomically.

There are several types of staging. The two principal ones are:

- clinical (non-invasive): cTNM
- pathological (invasive): pTNM

Noninvasive Staging

Clinical staging is based on history, physical examination, laboratory findings and radiological evaluation¹⁴.

Radiological Evaluation

All patients who are suspected to have lung cancer should have a chest X-ray. It serves as the basis for comparison with further scans.

Standard chest X-rays can reveal signs of advanced disease (eg. pleural effusion, secondary lesions in the lung parenchyma, destruction of the ribs and elevated diaphragm which indicates involvement of phrenic nerve)¹⁴.

Computed Tomography – CT

CT scan allows much better visualization of intrathoracic status. Besides determining tumor size, mediastinal and vascular invasion and involvement of airways, it can also suggest lymph node involvement. Disadvantages of CT staging are the inability to distinguish benign from malignant mediastinal lymphadenopathy and the inability to detect microscopic metastases. According to CT criteria, lymph node is suspicious to metastases if its short-

-axis diameter is greater than 10 mm. Sensitivity of this method is 57–70% and specificity of 59–82%¹⁴.

Integrated Positron Emission Tomography – Computed Tomography (PET-CT)

This method can detect occult disease. Lung cancer cells have an increased metabolism and therefore receive increased Fluoro-Deoxy-Glucose (FDG). By PET criteria lymph node is considered metastatic if its metabolic activity is increased 1.5 times compared to baseline. This method has a sensitivity of 90%. Despite this high sensitivity histological confirmation of metastases is required due to its low specificity. Inflammation and infection can give false positive results which can result in upstaging¹⁵.

Invasive Staging

There are controversies about the definition of pathological staging. Some believe that the pathological stage of disease can be established only after surgical exploration of hemithorax and mediastinum.

Others accept that the pathological stage can be determined based on tissue samples obtained by invasive diagnostic methods⁷.

Videomediastinoscopy

Because of high sensitivity (90%), low percentage of false negative results (10%) and rare complications, videomediastinoscopy is recommended by the European Society of Thoracic Surgeons (ESTS), as the »gold standard« for invasive staging of lung cancer¹¹.

It is performed under general anesthesia. The patient is placed in supine position with the neck extended. The incision is made transversely 1 cm above the jugulum. After the incision of the pretracheal fascia an optical-working instrument – videomediastinoscope (Richard Wolf, Germany) is introduced. With bimanual technique of preparation the upper mediastinum lymph nodes are exposed.

By cervical videomediastinoscopy following nodal positions can be sampled: high mediastinal lymph nodes (group 1), left and right upper paratracheal (group 2L and 2R), left and right lower paratracheal (group 4L and 4R) and subcarinal lymph nodes (group 7).

There are no internationally accepted recommendations considering the number of nodal stations that should be retrieved during cervical mediastinoscopy.

American Association of Thoracic Surgeons (ATS) recommends that all available nodal positions should be sampled. It includes lymph nodes at nodal positions 2L, 2R, 4L, 4R, 7, 10 L and 10 R (left and right tracheobronchial). The recommendation is to perform left parasternal mediastinotomy for lymph node sampling at nodal positions 5 and 6 (subaortal and anterior mediastinal) in patients with cancer of left lung¹¹.

Working Group of the European Association of Thoracic Surgeons (ESTS) states that there are two standards for mediastinoscopy:

- sampling of lymph nodes from nodal positions 2L, 2R, 4L, 4R and 7 should be performed.

- for routine clinical practice lower standard can be accepted which includes sampling of lymph nodes at nodal positions 4L, 4R, and 7.

In patients with left lung cancer it is necessary to sample lymph nodes in positions 5 and 6 (subaortal and anterior mediastinal)¹¹.

In these cases, cervical approach is complemented with Chamberlain's anterior mediastinotomy or VATS or extended mediastinoscopy is performed within the plane of the dissection in the area in front of the aortic arch and its branches¹⁴.

The advantage of mediastinoscopy compared to fine-needle aspiration biopsy (FNA), is that it can gain more complete insight into the status of lymph nodes in mediastinum including the contralateral side. This may be significant in patients with metastases in lymph nodes of one nodal station. It allows differentiation of extra and intracapsular metastasis and it also allows differentiation of nodal metastasis and direct tumor invasion¹⁶.

Complications of videomediastinoscopy are bleeding from large mediastinal blood vessels, pneumothorax, recurrent laryngeal nerve injury, injury of the esophagus and trachea and bronchial injury. Complications occur very rarely (2%). Most severe complications resulting in death occur in 0.008% of cases^{7,15}.

The sensitivity of cervical mediastinoscopy ranges from 72 to 89%. The reason for suboptimal sensitivity of cervical videomediastinoscopy lies in the fact that some nodal positions (5, 6, the posterior parts of group 7, 8, and 9) are not reachable with videomediastinoscopy¹¹.

In 2007. Kuzdzal et al. compared standard mediastinoscopy to extended transcervical mediastinal lymphadenectomy (VAMLA) and demonstrated increased sensitivity in detecting metastases to mediastinal lymph nodes using VAMLA. It is a technique of extended dissection of mediastinal lymph nodes and requires special instruments. VAMLA has a sensitivity of 94% and specificity of 100%¹⁷.

These preliminary data suggest that VAMLA combined with R0 resection could have a positive therapeutic effect. Besides somewhat more intensive postoperative pain incidence of complications is not higher when compared to standard cervical videomediastinoscopy.

In patients with left lung cancer more aggressive TEMLA (transcervical extended mediastinal lymphadenectomy) can be performed. This technique requires elevation sternum, dissection is done in front of the aortic arch, and lymph nodes of nodal groups 1, 2L, 2R, 3, 4L, 4R, 5, 6, 7 and 8 are reachable^{18,19}.

Anterior Mediastinotomy by Chamberlain

Predilective lymph nodes for metastatic cancer of the left upper lobe are those at nodal position 5 (subaortal). With the incision in the second or third intercostal space these lymph nodes can be accessed. This method is usually performed in addition to mediastinoscopy for cancer of the left upper lobe¹⁵.

VATS (Video assisted thoracoscopic surgery)

Video-assisted thoracoscopic surgery can be used for sampling of mediastinal lymph nodes. It is limited to evaluating only one side of the mediastinum. Because of low sensitivity (50%) it is rarely used for the evaluation of mediastinal lymph nodes^{21,22}.

Flexible Bronchoscopy

It is an endoscopic method for visualization of bronchial tree and sampling using endobronchial biopsy, sampling brush and bronchial lavage.

Blind Transbronchial Fine Needle Aspiration Cytology (TBNA)

It is also known as Wang's method. It is commonly used for sampling of subcarinal lymph nodes (group 7). The sensitivity of this method is about 70% with 30% false negative results¹⁵.

Endobronchial Ultrasound with Transbronchial Biopsy (EBUS-TBNA)

To perform this method a flexible bronchoscope equipped with convex ultrasound probe is used in order to enable visualisation of lymph nodes before the needle biopsy. Nowadays, besides invasive mediastinoscopy, it is the most relevant method for mediastinal lymph node staging. The issue whether this method is as reliable as videomediastinoscopy for invasive staging is not solved yet. There is also controversy about the claims that it is less invasive because in over 60% of cases EBUS-TBNA is performed under general anesthesia. Otherwise it is difficult to collect adequate samples because patients are restless, the procedure is very uncomfortable and the materials taken with a small diameter needle may result in an inadequate intake of the sample and produce false negative results¹⁵. In the meta-analysis published by Adams et al. sensitivity of this method is 70 – 88%²⁰. In the evaluation of 17 studies on EBUS-TBNA method conducted by the American College of Chest Physician (ACCP), it showed 24% false negative results¹⁵.

Due to its suboptimal negative predictive value, the ACCP recommends if EBUS-TBNA findings are non malignant, mediastinoscopy should be performed to confirm them¹⁴.

Esophageal Endoscopic Ultrasound with Needle Biopsy (EUS-FNA)

This technique is limited by poor access to the upper mediastinal lymph nodes, which are the most common sites for metastases in lymph nodes. It is still useful in the evaluation of lower mediastinal lymph nodes (nodal positions 8 and 9) and can therefore be combined with EBUS and mediastinoscopy¹⁵. Needle biopsy of mediastinal lymph nodes through the esophageal wall can be done with minimal risk of infection.

Conclusion

For an optimal therapeutic approach to patients suffering from lung cancer it is necessary to determine the stage of disease. In the absence of distant metastases, mediastinal lymph node status is crucial in the therapeutic strategy. Status of lymph nodes determined by non-invasive staging requires histological confirmation.

For invasive staging videomediastinoscopy and EBUS-TBNA have by far the highest sensitivity and the lowest percentage of false negative results. Recommendation of medical associations involved in treatment of lung cancer (ACCP, ESTS, AATS) is to use videomediastinoscopy or EBUS-TBNA for staging of patients with discretely increased mediastinal lymph nodes. In case of negative EBUS-TBNA findings, mediastinoscopy should be performed to confirm these findings.

In patients whose lymph nodes are not enlarged videomediastinoscopy is preferred method because of its

greater sensitivity and lower percentage of false negative results, although EBUS-TBNA comes to mind if confirmation of the negative result with videomediastinoscopy is planned.

In patients with clinical N2 disease videomediastinoscopy is preferred method to exclude N3 disease. Given the high percentage of false negative results of EBUS-TBNA if lymph nodes are not enlarged N3 disease can be overlooked in 24% cases using this method.

And last but not least, there is the issue of costs of both methods. Equipment for videomediastinoscopy is significantly less expensive than one for EBUS which is, in terms of county hospitals, extremely important item.

From the foregoing it is evident that videomediastinoscopy is a method of choice for invasive staging of the primary non – small cell lung cancer.

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ULOGA VIDEOMEDIJASTINOSKOPIJE U ODREĐIVANJU STADIJA PRIMARNOG NE-SITNOSTANIČNOG RAKA PLUĆA

SAŽETAK

Rak pluća je najčešća maligna bolest i vodeći uzrok smrti od malignih bolesti u svijetu a njegova incidencija je u porastu. U trenutku postavljanja dijagnoze većina bolesnika ima uznapredovalu bolest i nisu kandidati za radikalno kirurško liječenje. Bolesnici koji nemaju udaljene metastaze podvrgavaju se brojnim dijagnostičkim metodama u svrhu otkrivanja metastaza u limfnim čvorovima medijastinuma koji čine drenažni put limfe iz pluća. Za otkrivanje metastaza u limfnim čvorovima medijastinuma izvodi se više invazivnih dijagnostičkih procedura od kojih su najpouzdanije videomediastinoskopija i endobronhijalni ultrazvuk sa transtrahealnom punkcijom. Kirurško liječenje je terapija izbora u odsustvu metastaza u limfnim čvorovima medijastinuma, dok se u suprotnom provodi multimodalno liječenje. Na Odsjeku torakalne kirurgije Opće bolnice Zadar videomediastinoskopija se radi u svrhu određivanja stadija primarnog ne-sitnostaničnog raka pluća rutinski od rujna 2009. godine.