Disease free interval and survival analysis after surgical treatment in patients with non-small-cell lung cancer

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DISEASE FREE INTERVAL AND SURVIVAL ANALYSIS AFTER SURGICAL TREATMENT IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

Diploma thesis

Academic year:

2021/2022

Mentor:

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Split, July 2022

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ABBREVIATIONS

CI − confidence interval

CT − computed tomography

CTLA4 − cytotoxic T lymphocyte associated protein 4

DFS − disease free survival

FDG − fluorodeoxyglucose

KBC − Klinički bolnički centar

LR − likelihood ratio

NSCLC − non-small-cell lung cancer

PD1 − programmed cell death protein 1

PET − positron emission tomography

PET CT – positron emission tomography and computed tomography

RATS − robot-assisted thoracic surgery

SCLC − small-cell lung cancer

SE − standard error

SIADH − syndrome of inappropriate antidiuretic hormone secretion

TNM − tumor, nodes and metastases

VATS − video-assisted thoracoscopic surgery

WMA − The World Medical Association

ACKNOWLEDGEMENTS

Firstly, I want to thank my mentor Assist. Prof. Dragan Krnić, who helped me through my diploma thesis and made it possible to end this important and big chapter of my life.

I also want to thank dr. Ivan Šimundža for his help and guidance.

Thank you to all professors of Medical University of Split for providing me with life long knowledge and prepared me for my future career and work with patients.

Thank you to all my colleagues who went through this 6 year journey with me and made it better and easier to survive.

Thank you to all my friends who were here for me in these stressful but amazing moments and for their enormous support and understanding.

Last but not least, thank you to my parents Marina and Drago. Without them my dream of becoming Doctor of Medicine would not come true. I dedicate this diploma thesis to them.

Hvala svima što su bili dio ove životne priče.

1. INTRODUCTION

1.1. Anatomy of the mediastinum

The mediastinum represents the central area of thoracic cavity and extends from the thoracic inlet to the diaphragm (1, 2). It is enclosed by mediastinal pleura and accommodates all the thoracic viscera and structures excluding the lungs (1).

The mediastinum is a region with extreme mobility because of hollow visceral structures inside it that are linked only by loose connective tissue and fat. This characteristic empowers mediastinum for the accommodation of movement and volume and pressure changes in the thoracic cavity (1).

Many important anatomical structures can be found in mediastinum such as heart, great vessles, trachea and essential nerves. Furthermore, mediastinum is considered clinically important because of various physical anomalies and pathologies. It can be divided into the superior, anterior, posterior and middle part (3).

The middle mediastinum accommodates heart and pericardium, the great vessels, the ascending aorta and aortic arch and the brachiocephalic veins. Its innervation emerges from the autonomic nervous system and phrenic nerves. Few pathologies that can occur in middle mediastinum are myocardial infarction, pericardial effusion and cardiac tamponade (3).

Anterior mediastinum is placed directly posterior to the sternum so it is prone to trauma to the anterior thorax (3). Superior mediastinum broadens from the superior thoracic aperture to the horizontal plane (1).

Furthermore, in posterior mediastinum trachea, esophagus, descending aorta and azygos vein can be found. It is surronded anteriorly by the pericardium and great vessels and posteriorly by the thoracic vertebral bodies (4).

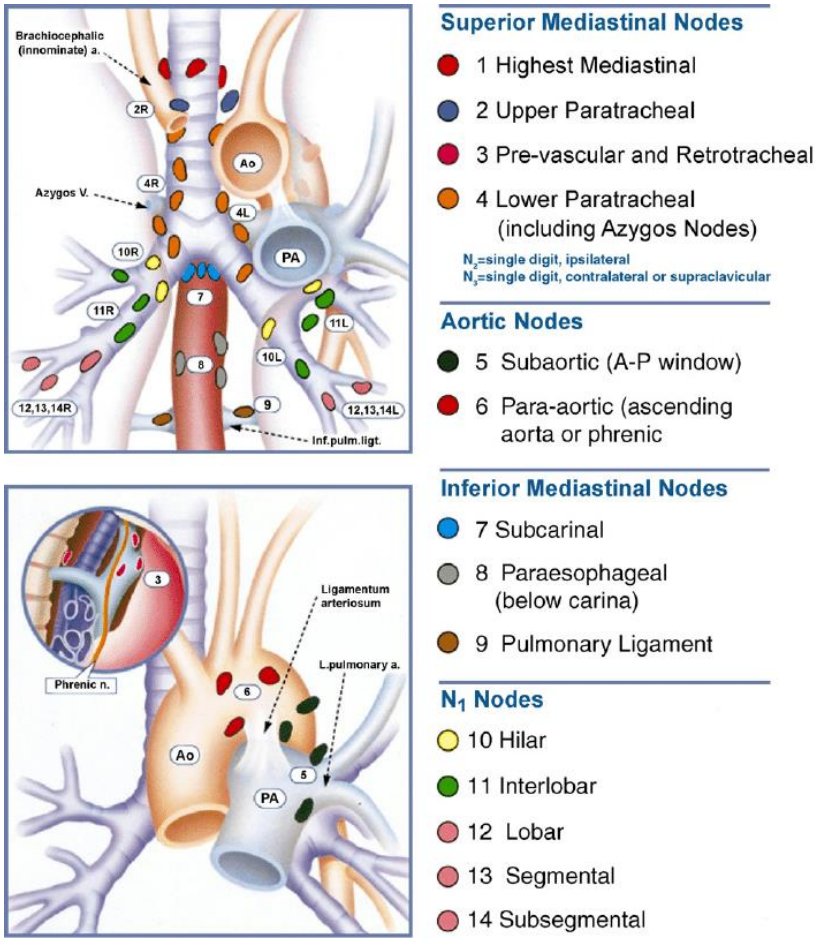

Figure 1. Regional lymph node stations for lung cancer staging.
Source: https://www.researchgate.net/figure/Regional-lymph-node-stations-for-lung-cancer-staging-2-with-kind-permission-from-Chest_fig1_240610201

1.2. Lung cancer

1.2.1. Epidemiology

Lung cancer represents the most common cancer globally. It is also the leading cause of cancer death in men and the second leading cause of cancer death in women after breast cancer (5).

Throughout the years an increase in the number of cases in developing countries has been noticed (6). In United States the 5-year survival rate for lung cancer is 15%. The median age of diagnosis is 70 years for both genders (7).

Considering the histologic type, the adenocarcinoma has become the most common histologic cancer type and its incidence has increased rapidly over the last few decades (5).

Lung cancer distribution also varies in different geographical locations. For example, low incidence rates are noticed in Middle and Western Asia while the highest incidence rates are present in Central and Eastern Europe and Eastern Asia (5). It has been noticed that African Americans and Native Hawaiians are at higher risk of lung cancer development than whites, Japanese Americans and Latinos (8).

1.2.2. Etiology

Today, we can define many risk factors for lung cancer development of which smoking is the major one (5). Longer duration of smoking and bigger number of cigarettes smoked per day increase the risk of lung cancer development (6). It is predicted that globally 80% of lung cancer cases in men and 50% in women each year are caused by smoking (5).

Another risk factor is outdoor and indoor air pollution which can be defined as environmental risk factors (5).

Furthermore, asbestos exposure was defined as the most common occupational risk factor. People with chronic obstructive pulmonary disease also have a higher chance of lung cancer development. Diets which contain low amounts of fruit and vegetables can be considered as risk factors too (7).

1.2.3. Histology

Lung cancer can be divided into small-cell lung cancer and non-small-cell lung cancer (9).

Small-cell lung cancer (SCLC) is extremely aggressive and almost always connected with smoking. It grows rapidly and metastatic disease is present in nearly 80% of patients at the time of diagnosis (9).

Non-small-cell lung cancer (NSCLC) makes up about 80 to 85% of lung cancer cases (10) and its behaviour depends on histologic subtype (9). The main subtypes are adenocarcinoma, squamous cell carcinoma and large cell carcinoma (10). Compared to SCLC 40% of patients present with metastatic disease outisde of the chest at the time of diagnosis (9).

Small-cell carcinoma and squamous cell carcinoma are most strongly connected with smoking although this connection can also be defined with adenocarcinoma (11).

1.2.3.1. Adenocarcinoma

Adenocarcinoma represents the most common type of lung cancer (12). It is also the most common subtype being diagnosed in non-smoker patients (13). Although the new strategies in its treatment were made it is still one of the most aggressive tumor types with its overall survival being less than 5 years (12).

Lung adenocarcinoma can be divided into 4 types: adenocarcinoma in situ, invasive adenocarcinoma, minimally invasive adenocarcinoma and variants of adenocarcinoma (13).

Their location is usually on the periphery but sometimes they can appear closer to the hilum. In comparasion to the other subtypes they grow slower and form smaller masses but metastases tend to appear at an early stage (11).

Tumor can spread locally to the pleura, diaphragm, pericardium or bronchi. Metastasis to the lymph nodes mostly occurs in peribronchial lymph nodes and then moves to mediastinal or subcarinal lymph nodes. Brain, bones and liver are the most common sites for distant metastasis (13).

1.2.3.2. Squamous cell carcinoma

Another subtype of non-small-cell lung cancer is squamous cell carcinoma and it makes up about 40% of all lung cancer (14). Generally, it has a poor clinical prognosis and is associated more with smoking than other types of NSCLC (14, 15).

Squamous cell cancer arises centrally in major bronchi and spreads to the local hilar lymph nodes (11).

World Health Organization divided squamous cell carcinoma into 4 variants: clear cell, small cell, basaloid and papillary (16). Keratinization, squamous pearl formation and intercellular bridges represent its histological hallmarks (17).

1.2.3.3. Large cell carcinoma

Large cell carcinoma is a subtype of NSCLC which makes up about 10 to 15% of all non-small-cell lung cancers (18). Its incidence is lower compared to other subtypes. At the time of diagnosis it appears quite large due to its rapid growth and non specific clinical signs (19).

It occurs more often in people with a history of cigarette smoking without gender predisposition (18).

This subtype of NSCLC is histologically marked by cells with large nuclei, moderate amounts of cytoplasm and prominent nucleoli (11).

1.2.3.4. Small cell lung cancer

Small-cell lung cancer occurs less often than other types of lung cancer (20) and represents 13% of all diagnosed cases of lung cancer around the world (20, 21). It is prone to rapid growth and tends to metastasize quite early to the regional lymph nodes and distant sites of which the most common are brain, liver, adrenal glands, bones and bone marrow (19, 22).

SCLC can be divided further into two subtypes: oat cell carcinoma and combined SCLC (19). Histologically, they occur as pale gray and centrally located masses (11).

The major risk factor for small cell lung cancer is cigarette smoking and risk increases with duration and intensity of smoking (21).

1.2.4. Clinical manifestations

At the time of diagnosis lung cancer patients are almost always symptomatic (23). Symptoms can be due to the local effects of the tumor, from regional and distant spread but also due to the effects that are not connected with metastases (24). Patients mostly present with more than one symptom and the possibility of lung cancer diagnosis is more certain when two or more symptoms are present (23).

Local effects of the tumor can result in cough and dyspnea. Chest pain is a common complaint, presented in almost 50% of patients. Regional spread of tumor can lead to hoarseness because of tumor enroachment on the recurrent laryngeal nerve (10). Symptoms and signs of extrathoracic spread, which occur in one third of patients, depend on the location (10, 25).

Paraneoplastic syndromes such as hypercalcemia, Cushing syndrom, syndrom of inappropriate antidiuretic hormone secretion (SIADH), Eaton Lamber syndrome may also be present in lung cancer patients (10). They emerge from ectopic production of hormones from the tumor or from the body's reaction to the tumor. Paraneoplastic syndrome has a higher incidence rate in patients with SCLC (23).

1.3. Diagnostic methods

1.3.1. X-ray

Chest x-ray has an important role in the initial investigation for lung cancer. Accessibility and low radiation dose represent its advantages (26).

A nodule or effusion on chest radiograph in asymptomatic patients may suggest the presence of lung cancer. While, in symptomatic patients it can support a suspicion of lung cancer (27).

Chest radiographs mostly show solitary nodules although an enlarged hilum, atelectasis, widened mediastinum, pleural thickening or effusion or tracheobronchial narrowing may also be present (13, 28). These findings can suggest the diagnosis of lung cancer but should always be followed up with computed tomography (CT) scans or combined Positron Emission Tomography and Computed Tomography (PET CT) scans (9). One especially important characteristic in the pulmonary lesion is calcification because specific patterns of calcification correspond to the high probability that the nodule is benign (27).

1.3.2. Computed tomography

If the chest radiograph turns out to be suspicious for malignant lesion, next step would be CT with contrast to complete the staging (29). In comparasion to chest radiographs, CT scans have higher sensitivity for detection of pulmonary nodules (30). They facilitate evaluation of the lesion, its location and its relation to nearby structures (31). CT can also be used as a tool for monitoring response to the treatment (29).

Recently, there have been advances in CT technology such as nodule perfusion analysis, dual energy applications, computer-aided detection, nodule volumetry which allowed even more detailed investigation for lung cancer (32).

1.3.3. Positron emission computed tomography (PET)

Positron emission computed tomography is a helpful noninvasive imaging technique which is based on the uptake and concentration of 2,3 - fluorodeoxyglucose (FDG) in lung cancer cells (22, 32). The technique is established on the accelerated glucose metabolism in the tumor cells and larger amount of glucose taken up by them (33). It appears to have more sensitivity and specificity for mediastinal nodal masses in comparasion to CT (34).

Further information that can be provided by integrated PET CT is: better delineation of the surrounding structures, more precise location of lesions, better characterization of the lesion as benign or malignant, detection of lesion firstly not seen on CT or PET. However, the disadvanatage of PET CT is that it is limited by lack of spatial resolution (32).

1.4. Staging

The Tumor, Node, Metastasis staging system represents universally approved system that is being used to identify extent of disease (27). Tumor (T) characterizes the size of the tumor. Node (N) defines if the cancer has spread to the lymph nodes. Metastasis (M) defines if the cancer has spread to a different part of body (35).

Table 1. TNM classification of lung cancer (36).

T (primary tumor)	
T0	No primary tumor
Tis	Carcinoma in situ (squamous or adenocarcinoma)
T1	Tumor ≤ 3 cm
T1mi	Minimally invasive adenocarcinoma
T1a	Superficial spreading tumor in central airway*
T1a	Tumor ≤ 1 cm
T1b	Tumor > 1 but ≤ 2 cm
T1c	Tumor > 2 but ≤ 3 cm
T2	Tumor > 3 but ≤ 5 cm or tumor involving: visceral pleura, main bronchus (not carina), atelectasis to hilum†
T2a	Tumor > 3 but ≤ 4 cm
T2b	Tumor > 4 but ≤ 5 cm
T3	Tumor > 5 but ≤ 7 cm or invading chest wall, pericardium, phrenic nerve; or separate tumor nodule(s) in the same lobe
T4	Tumor > 7 cm or tumor invading: mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, spine; or tumor nodule(s) in a different ipsilateral lobe
N (regional lymph nodes)	
N0	No regional node metastasis
N1	Metastasis in ipsilateral pulmonary or hilar nodes
N2	Metastasis in ipsilateral mediastinal or subcarinal nodes
N3	Metastasis in contralateral mediastinal, hilar, or supraclavicular nodes
M (distant metastasis)	
M0	No distant metastasis
M1a	Malignant pleural or pericardial effusion† or pleural or pericardial nodules or separate tumor nodule(s) in a contralateral lobe
M1b	Single extrathoracic metastasis
M1c	Multiple extrathoracic metastasis (1 > 1 organ)

*Superficial spreading tumor of any size but confined to the tracheal or bronchial wall. † Atelectasis or obstructive pneumonitis extending to hilum; such tumors are classified as T2a if > 3 and ≤ 4 cm, T2b if > 4 and ≤ 5 cm. † Pleural effusions are excluded that are cytologically negative, nonbloody, transudative and clinically judged not to be due to cancer.

1.5. Treatment of lung cancer

Options for treating lung cancer include surgery, radiation therapy, chemotherapy and targeted therapy (37).

1.5.1. Radiotherapy

Radiotherapy is one type of anti cancer treatment in which high energy x-rays eradicate cancer cells while avoiding normal cells. Radiation is given in smaller individual doses over a certain time period and it is mostly given from outside of the chest with machines called linear accelerators (38).

There is one additional option of applying radiotherapy called brachytherapy which is based on putting a small amount of radiation inside the lung (38). Brachytherapy is a minimally invasive therapeutic technique where radioactive source is embedded in or close by the tumor (39).

Recently, a special radiotherapeutic approach called stereotactic body radiotherapy has emerged as a treatment option for early stage inoperable NSCLC (40). It precisely distributes high dose x-rays to lung cancer cells without irradiating regional lymph nodes and normal tissue. It can be given as one treatment or as three or more fractions over a time period of 1-2 weeks (41).

Another improvement in radiotherapy is intensity modulated radiotherapy which uses intensity modulated beams (42).

1.5.2. Chemotherapy

Chemotherapy has been an important part of treatment in patients with non-small-cell lung cancer. It can be administered as adjuvant, neoadjuvant chemotherapy or as a part of bi or multimodality therapy (43).

Chemotherapy can produce significant side effects such as neuropathy, febrile neutropenia, constipation, vomitting, nausea, fatigue (43). Chemotherapy can also produce

effects on the bone marrow and lead to increased probability of infections, bruising or bleeding and fatigue (44). Its mortality ranges from 0,8 to 2 percent (43).

Since greater number of patients with non-small-cell lung cancer present with advanced stage of disease at diagnosis, surgery appears to be unsuitable for them (45). Because of this reason, combination of chemotherapy and surgery is a standard of care for resectable NSCLC (46). The first line chemotherapeutic agents given to patients with advanced stage NSCLC is platinum based doublet. Combination therapies based on platinum produce better response than the non-platinum ones (37). Lately, important discoveries have been made in the treatment of advanced NSCLC. An antivascular endothelial growth factor monoclonal antibody called Bevacizumab can be joined to platinum based chemotherapy. It has been shown to improve the end result of chemotherapy (45).

Adjuvant chemotherapy has proven to be a breakthrough in the treatment of NSCLC and became recommended treatment strategy for patients with metastases, tumors 4 cm or larger and extensive local invasion (47). Research has shown that the adjuvant chemotherapy and neoadjuvant chemotherapy enhance the possibility for cure in patients with stage 1b-3a lung cancers (48).

As for the SCLC, chemotherapy is still the first and second line option of treatment (49).

1.5.3. Surgery

Over the decades surgery has made a valuable impact as a curative option of treatment for lung cancer (50).

Surgical resection is most suitable for early stage 1 and 2 NSCLC and also an accepted choice of treatment in certain percentage of patients with stage 3B and stage 4 NSCLC (51). On the other side, in small-cell lung carcinoma surgery plays a smaller role. Since SCLC is aggressive and tends to metastasize early, surgical resection has a greater benefit as a part of multimodality treatment with chemotherapy and/or radiation when combined with chemotherapy/radiotherapy (52). Choice of treatment option is dependent on TNM clinical staging (51).

Surgical resection is considered treatment of choice for patients with stage 1A disease. As for patients with stage 1B adjuvant chemotherapy is combined with surgery. En bloc chest wall resection with ribs is done in patients with stage IIB (T3N0) in which chest wall invasion is present. Surgical treatment is not an option in patients with stage 3B or stage 4 NSCLC and for this subset of patients chemotherapy or chemoradiation is a treatment of choice. Surgical resection can also be applied to limited number of brain metastasis (52). Wedge resection, pneumonecomy, segmentectomy and lobectomy represent options of surgical treatment for lung cancer (51).

Surgical lobectomy is the choice for intraparenchymal lesion, while pneumonectomy is reserved for lesions that are centrally located. Segmentectomy and wedge resection should be applied in patients who are considered to be high risk surgical candidates and those with marginal lung function (52).

Two goals of surgical treatment can be defined. First one would be completely resected tumor together with its local lymphatic drainage and tumor staging that will be useful for perioperative treatment and prognosis (52). Complete and thorough surgery should ensure that none of metastatic cells have spread outside of the field of resection because this could lead to relapse (53). If relapse does happen after surgical resection it is mostly at distant sites. Systemic chemotherapy could be useful in this situation to reduce recurrence after surgical resection (54).

When we speak about type of surgical approach, open thoracotomy has been traditionally used for many years but lately video-assisted thoracoscopic surgical (VATS) lobectomy became more involved in surgical treatment (55). VATS makes up now more than 50% of lung cancer surgeries (54). Smaller incidence of pulmonary complications in VATS approach has a particular importance in elderly (53).

Another minimally invasive approach is the da Vinci Surgical System. It represents a telemanipulator system that is based on a console surgeon and bedside assistent (50). Hospital costs and duration of the procedure are longer than in VATS but it offers three dimensional visualization and possibility for rotational movement (53, 54).

Both approaches accomplish a similiar result with less side effects than in open lobectomy but patients who can not bare single lung ventilation are not candidates for these kind of techniques (51).

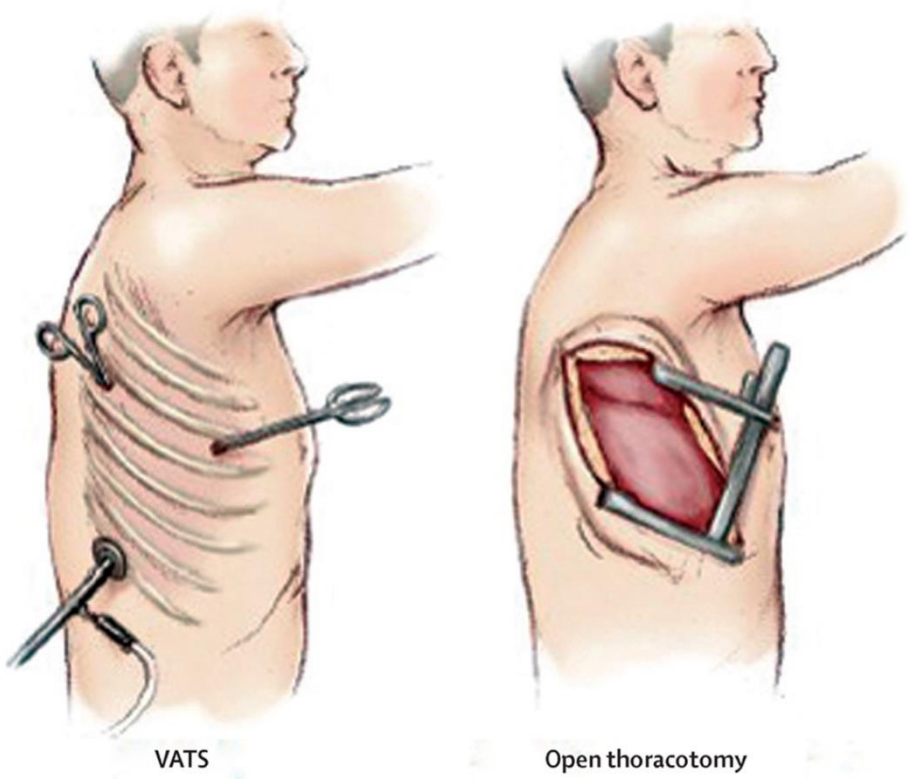

Figure 2. Comparative incisions for VATS and open thoracotomy.
Source: https://www.thelancet.com/journals/lanres/article/PIIS2213-2600%2816%2900024-2/fulltext

1.5.4. Immunotherapy

Interaction of cancer with immune system also has an effect on its growth and spread (56).

Recently, there has been an interest in immunotherapy as a treatment option for lung cancer. Immunotherapeutic agents which mark immune checkpoint pathways have shown to be beneficial and became integrated into the managment of advanced stage NSCLC (57).

Immune checkpoint inhibitors function by raising natural tumor killing response of body. Immune checkpoints represent surface proteins on T cells and other cells of immune system. They behave as negative regulators of immune activation by tumor antigens (57).

However, adverse effects of immunotherapy limit its widespread acceptance in the clinical practice (56). Immunotherapeutic agents can stimulate T cell attack on self antigens (57) which manifests as toxicities involving mostly skin, gastrointestinal system, thyroid and pituitary gland and lungs although they can affect any organ system (58). For example, one of

the serious side effects of cytotoxic T-lymphocyte-associated protein 4 (CTLA4) agent is colitis, while programmed cell death protein 1 (PD1) checkpoint blockade can lead to pneumonitis (56).

Immunotherapy has shown a significant benefit in patients with locally advanced NSCLC. Checkpoint inhibitors that are being used in advanced NSCLC are anti PD1 pembrolizumab and nivolumab, anti CTLA4 inhibitor ipilimumab and anti PD1 inhibitors atezolizumab. Pembrolizumab or atezolizumab being introduced as monotherapy are shown to be preferable over chemotherapy in tumors with positive PD1 expression (58). In situations where immune checkpoint inhibitors are used as neoadjuvant therapy better understanding of antitumor response has evolved (59).

The clinical evolution of immune checkpoint blockade has greatly alternated therapy strategies and prognosis for patients diagnosed with NSCLC (60).

1.6. Lymphadenectomy

Various recommendations are defined for the amount of removed lymph nodes. While some research groups recommend at least three mediastinal lymph node stations for precise staging others suggest dissection or sample of lymph nodes from stations 2R, 4R, 7, 10R and 11R for right sided tumors and stations 5, 6, 7, 10L and 11L for left sided tumors (61).

Mediastinal lymphadenectomy can be useful for staging and serve as a guidance tool in treatment. But it is still not known if mediastinal lymphadenectomy has an impact on outcome of a disease (61).

Mediastinal lymph node staging is an important part of treatment planning in lung cancer patients. The intention of mediastinal staging is to eliminate existence of malignancy in mediastinal lymph nodes. Mediastinal staging is established on CT and PET imaging. If mediastinal sampling is neccessary many techniques can be used such as: ultrasound-guided fine needle aspiration, endobronchial ultrasound guided transbronchial needle aspiration, video-assisted cervical mediastinoscopy (62).

2. OBJECTIVES

Aims:

1. Compare the length of survival without disease recurrence in relation to the type of surgical procedure and the histologic type of cancer.

2. Analyze the impact of surgical approach to the number of extirpated lymph nodes.

3. Analyze the impact of the number of extracted and positive lymph nodes on the mediastinal metastases occurence.

4. Compare disease free survival of patients with metastases in mediastinum and metastases at other locations.

Hypotheses:

The lenght of survival as well as the number of removed lymph nodes does not depend on the type of surgical procedure.

3. SUBJECTS AND METHODS

3.1. Patients

A total of 70 patients who were surgically treated for non-small-cell lung cancer at University Hospital Split in the period between 2012 and 2017 were included in original data sampling. The first surgery was recorded on 20th of December 2012 and the last one on 12th of September 2017.

3.2. Place of study

The research took place at the Department of Thoracic Surgery, University Hospital of Split, Croatia.

3.3. Data collection

Patient data was gathered from the archives of the Department of Surgery, Department of Radiology and Department of Pathology, University Hospital of Split. Data collected was the name, gender and age of each patient, his or her diagnosis, location of metastases, dates of surgeries, type of surgical approach, histologic type of lung cancer and number of isolated and affected lymph nodes.

3.4. Description of the Study

Subjects were grouped according to the histologic type of lung cancer, type of surgical approach, location of metastases and number of isolated and affected lymph nodes. The two types of surgical approach used were VATS and open thoracotomy. Locations of metastases were divided into 6 groups: no metastases present, mediastinum, lungs, brain, bones and intraabdominal.

3.5. Compliance with ethical standards

Plan of this study is in accordance with the Patient protection Act (NN 169/04, 37/08) and General Data Protection Regulation implementation Act (NN 42/18), and regulations of Code of Medical Ethichs and Deontology (NN 55/08), 139/15) and the rules of World Medical Association (WMA) Declaration of Helsinki 1964-2013 which states Code. The study protocol was approved by the Ethics Review Bord of University Hospital of Split with reference No. 2181-147/01/06/M.S.-22-02.

3.6. Statistical analysis

Statistical analysis was done by SPSS20. Statistical significance of differences of categorical demographic and clinical characteristics was calculated by the χ^2 test. As Shapiro Wilk test indicated statistically significant deviations from normal distribution for all numeric variables, the median and the interquartile range were used. Analysis of statistical significance of differences in quantitative variables was calculated by Mann-Whitney test. Quantitative variables were expressed as median and interquartile range. Disease free survival (DFS) was calculated according to Kaplan-Meier curve and differences between curves were evaluated with Log-rank test. Statistical significance was set to $P<0.05$ and confidence intervals (CI) were given at the 95%.

4. RESULTS

A total of 70 patients were included in this study with a median of age of 65 years (Q1-Q3: 60-70; min-max: 49-84 years) operated in the University Hospital Split, Department of Surgery who met the set up criteria between 2012 to 2017.

From the total number of patients, 45 were male (65%) with a median of age of 66 years (Q1-Q3: 60-71; min-max: 50-84 years) and 25 patients were female (36%) with a median of age of 64 years (Q1-Q3: 57-69; min-max: 49-76 years).

There was no statistically significant difference between males and females according to age (*P*=0.211).

Two surgical approaches were used:

- Thoracotomy in 25 (36%) of cases and
- VATS in 45 (64%) of cases

In Table 2 demographic characteristics of patients according to the type of surgery are shown.

Table 2. Demographic characteristics of patients according to the type of surgery.

Type of surgery		Thoracotomy (n=25)	VATS (n=45)	*P*
Gender; n (%)				0.457*
	Male	18 (72)	27 (60)	
	Female	7 (28)	18 (40)	
Age (years)	Median (Q1-Q3; min-max)	66 (60-71; 49-76)	64 (60-70; 50-84)	0.736†

*Chi square test; †Mann-Whitney test
VATS − video-assisted thoracoscopic surgery

The types of surgery (thoracotomy and VATS) were well balanced in terms of gender (*P*=0.457) and age (*P*=0.736).

In Table 3 distribution of patohistological characteristics in patients operated at University Hospital Split is shown.

Table 3. Distribution of patohistological characteristics.

Histologic type; n (%)		
	adenocarcinoma	47 (67)
	squamous cell	20 (29)
	giant-cell carcinoma	3 (4)
Number of affected lymph nodes; n (%)		
	0	52 (74.3)
	1	14 (20)
	2	1 (1.4)
	4	2 (2.9)
	5	1 (1.4)
Number of isolated lymph nodes		
Median (Q1-Q3; min-max)	5 (3-8; 0-18)	

Remark: in five patients there were no isolated lymph nodes.

In Table 4 distribution of metastases according to the location is shown.

Table 4. Number (%) of patients according to the location of metastases.

Localization of metastases	n (%)
none	13 (18.6)
mediastinum	11 (15.7)
lungs	29 (41.4)
brain	6 (8.6)
bones	4 (5.7)
intraabdominal	7 (10)

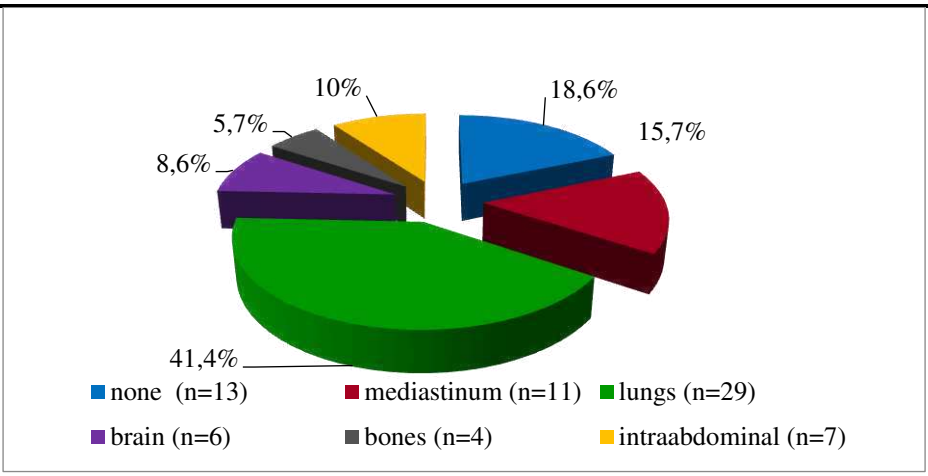

Figure 3. Distribution of patients according to the location of metastases.

In Table 5 association between patohistological characteristics and type of surgery is presented.

Table 5. Association of patohistological characteristics with type of surgery.

Type of surgery		Thoracotomy	VATS	*P*
Histologic type n (%)				0.261*
	adenocarcinoma	15 (60)	32 (76)	
	squamous cell	10 (40)	10 (24)	
Number of affected lymph nodes n (%)				0.237*
	0	16 (64)	36 (80)	
	≥1	9 (36)	9 (20)	
Number of isolated lymph nodes	Median (Q1-Q3; min-max)	5.5 (3-12; 0-18)	4 (3-7; 0-18)	0.194†

*Chi square test; †Mann-Whitney test
VATS – video-assisted thoracoscopic surgery

There was no statistically significant association between number of affected lymph nodes and type of surgery (*P*=0.237).

There was no statistically significant association between number of isolated lymph nodes and type of surgery (*P*=0.194).

Table 6 shows distribution of metastases according to the number of affected lymph nodes.

Table 6. Distribution of metastases according to the number of affected lymph nodes.

	Number of Affected lymph nodes				
Metastases	0	1	2	4	5
none	10	3	0	0	0
mediastinum	7	2	0	2	0
lungs	24	5	0	0	0
brain	4	0	1	0	1
bones	3	1	0	0	0
intraabdominal	4	3	0	0	0

Table 7 shows an association between number of affected lymph nodes and location of metastases.

Table 7. Association between affected lymph nodes and location of metastases.

		Meta2gr		Total
		mediastinum	other	
Affected lymph nodes; n (%)				
	None	7 (63.6)	35 (76.1)	42 (73.7)
	yes (≥1 lymph node)	4 (36.4)	11 (23.9)	15 (26.3)
	total	11 (100)	46 (100)	57 (100)

There is no statistically significant association between affected lymph nodes and location of metastases (mediastinum, other) (P=0.645).

In Table 8 association between isolated lymph nodes and location of metastases is presented.

Table 8. Association between isolated lymph nodes and location of metastases.

		Location of metastases		Total
		mediastinum	other	
Isolated lymph nodes; n (%)				
	<5 lymph nodes	6 (54.5)	21 (46.7)	27 (48.2)
	≥5 lymph nodes	5 (45.5)	24 (53.3)	29 (51.8)
	total	11 (100)	45 (100)	56 (100)

There is no statistically significant association between number of isolated lymph nodes and location of metastases (mediastinum, other) (*P*=0.895).

Table 9 shows number of affected and isolated lymph nodes in relation to the location of metastases.

Table 9. Median (Q1-Q3; min-max) number of affected and isolated lymph nodes in relation to the location of metastases (mediastinum, other).

	Metastases		
	mediastinum	other	*P**
Affected lymph nodes	0 (0-1; 0-4)	0 (0-0; 0-5)	0.519
Isolated lymph nodes	4 (2-8; 0-14)	5 (4-5; 0-18)	

*Mann-Whitney test

There is no statistically significant difference between number of affected lymph nodes (*P*=0.312) and number of isolated lymph nodes (*P*=0.519) between patients with metastases in mediastinum and metastases at other locations.

In Table 10 association between location of metastases divided into four groups and affected lymph nodes (0; ≥1) is shown.

Table 10. Distribution of association between location of metastases (none, mediastinum, lungs, other) and affected lymph nodes (0; ≥1).

	Affected lymph nodes n (%)		
Metastases	no	≥1	*P**
			0.456
none	10 (19.2)	3 (16.7)	
mediastinum	7 (13.5)	4 (22.2)	
lungs	24 (46.2)	5 (27.8)	
brain, bones, intraabdominal	11 (21.2)	6 (33.3)	

*Chi square test

There was no statistically significant association between number of affected lymph nodes and location of metastases (*P*=0.456).

In Table 11 analysis of DFS with Log-rank test is presented based on variables that were investigated.

Table 11. Analysis of DFS with Log-rank test based on investigated variables.

Variable	Average DFS (months)	SE	95% CI	Median	LR	*P*
Gender					0.26	0.610
male (n=45)	42	5	32-53	33		
female (n=25)	35	6	24-46	28		
Histologic type					0.162	0.688
Adenocarcinoma (n=47)	37	4.5	28-46	29		
squamous cell (n=20)	40	8	24-56	24		
Affected lymph nodes					0.215	0.643
0 (n=52)	39.6	5	30-49	28		
≥1 (n=18)	41	7	27-56	45		
Isolated lymph nodes					0.457	0.499
<5 (n=32)	37	6	25-48	24		
≥5 (n=37)	41	5	30-52	33		
Metastases					10.2	0.006
none (n=13)	**					
mediastinum (n=12)	14	4	7-21	10		
lungs (n=29)	31	3	24-37	29		
brain, bones, intraabdominal (n=17)	26	4	17-35	22		
Type of surgery					0.399	0.527
Thoracotomy (n=25)	44	8	29-60	28		
VATS (n=45)	35	4	27-42	29		
Age					0.042	0.838
≤65 (n=37)	38	4.5	29-46	31		
>65 (n=33)	42	7	28-55	22		
Overall DFS	40	4	32-49	28		

*log-rank test

DFS − disease free survival; VATS − video-assisted thoracoscopic surgery; LR − likelihood ratio; SE − standard error; CI − confidence interval

Remark: isolated lymph nodes (n=5), and age (65 years) were divided into two groups based on the median.

There was no statistically significant difference of DFS between males and females (*P*=0.610); between histologic types (adenocarcinoma and squamous cell carcinoma) (*P*=0.688); in relation to affected lymph nodes (0; ≥1) (*P*=0.643); in relation to isolated lymph nodes (<5; ≥5) (*P*=0.499); in relation to the type of surgery (*P*=0.527); in relation to age groups (*P*=0.838).

Disease free survival was estimated by using Kaplan-Meier curve. There was statistically significant difference of DFS among localizations of metastases. Average value of DFS in patients with metastases in the mediastinum was 17 months shorter than in patients with metastases in the lungs and 12 months shorter than in patients with metastases in other localizations. The patients without metastases were excluded (n=13) from the DFS analysis by Kaplan-Meier curve. The reason was that no one was censored. All of them were without metastases until the end of the study (31.12.2021). The average time of follow up for this group is 78 ± 18 months, the median of follow up is 76 months (minimum follow up-maximum follow up: 52-108 months).

In Table 12 variables that were investigated in group of patients without metastases are shown.

Table 12. Investigated variables in group of patients without metastases.

Variable	n
Gender	
males	9
females	4
Histologic type	
adenocarcinoma	6
squamous cell	5
giant-cell	2
Affected lymph nodes	
0	10
1	3
Isolated lymph nodes	
<5	5
≥5	8
Type of surgery	
Thoracotomy	5
VATS	8

VATS − video-assisted thoracoscopic surgery

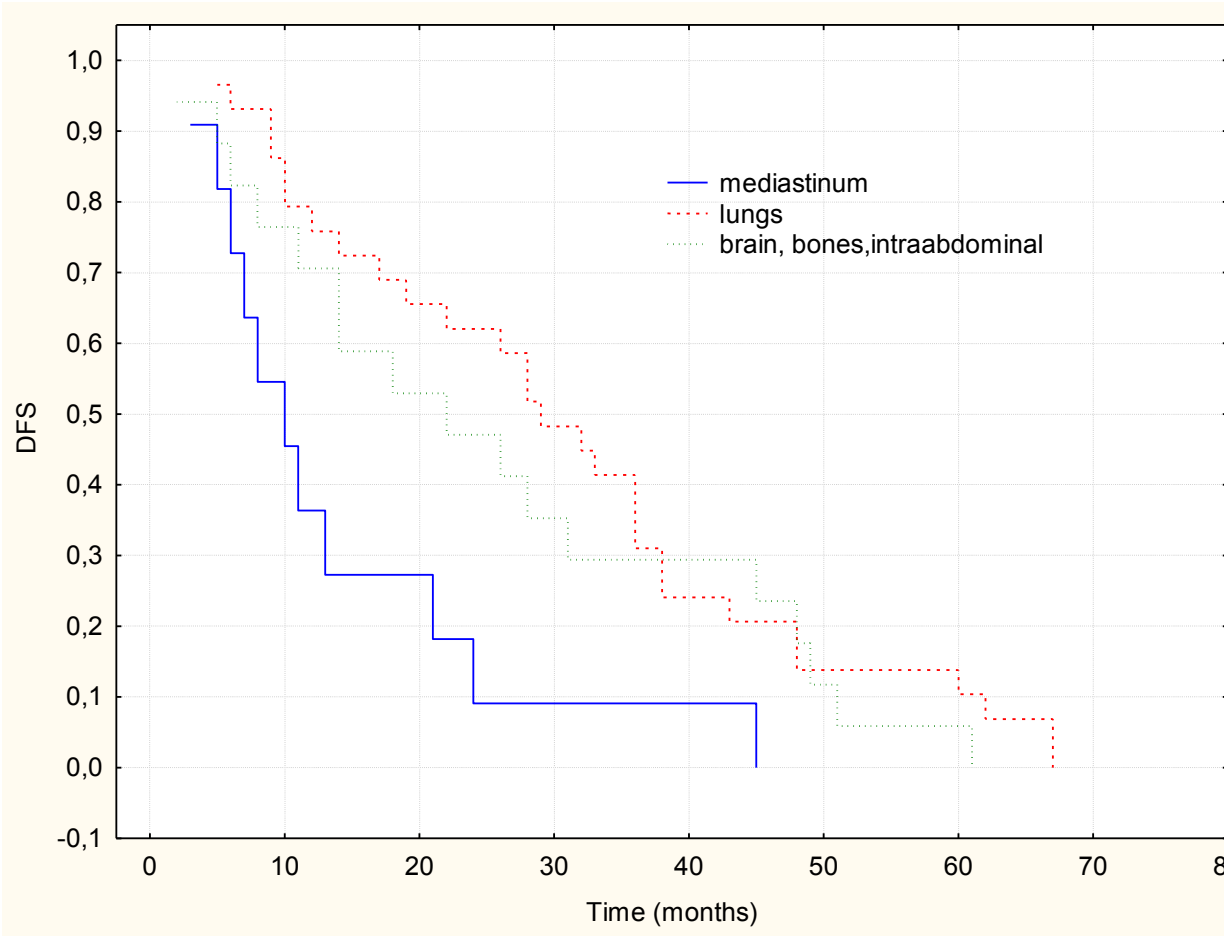

Figure 4. DFS in relation to the metastases (mediastinum, lungs, brain, bones, intraabdominal).

5. DISCUSSION

Lung cancer represents one of the most common cancers globally and is the main cause of death related to cancer (5). Adenocarcinoma has exceeded squamous cell carcinoma as histologic type of lung cancer and is considered to be the most common histologic type of lung cancer (7). Our results were similiar to this data. From total number of patients 67% was adenocarcinoma while the rest were squamous cell carcinoma (29%) and giant-cell carcinoma (4%). Incidence of lung cancer differs among men and women. In males lung cancer is known to be the most common cancer being diagnosed, while for the women it takes 4th place among malignancies (6). In our study 65% of patients were male and 36% were female which corresponds to the world statistics.

Type of surgical approach for lung cancer is determined by the location of the tumor (52). Open thoracotomy has been traditional approach but lately less invasive strategies are being used such as video-assisted thoracoscopic surgical (VATS) lobectomy. Enormous number of research reports has demonstrated shorter time of recovery, less incisional pain and shorter duration of chest drainage following VATS surgery compared to open thoracotomy (55). VATS surgical approach is extensively preferred over an open approach and more widely used today (50). This fact can be seen from the statistical data in our study. Thoracotomy was used in 25 (36%) of cases of surgeries while VATS was used in 45 (64%) of cases. In our study we did not investigate duration of recovery and chest tube drainage nor the severity of incisional pain but we analyzed the association between type of surgical approach and number of affected and isolated lymph nodes.

Lymphadenectomy is an essential part of surgical treatment for early stage lung cancer (61). Ismail *et. al.* have proved in their study that uniportal VATS enables an efficient and safe radical lymphadenectomy when compared to other minimally invasive therapeutic techniques (63). The study of Zhang *et. al.* did not find any difference between type of surgical approach (VATS and open thoracotomy) on the amount of lymphadenectomy (64). In the results we got there was no statistically significant association between number of affected (P=0.237) and isolated lymph nodes (P=0.194) and type of surgical approach. As our hypothesis states we did not manage to establish any dependence of number of removed lymph nodes on the type of surgical procedure.

Furthermore, in our results we did not get any statistically significant difference of DFS and type of surgery (P=0.527) which supports our hypothesis. In retrospective study of Wu *et. al.* impact of VATS and robot-assisted thoracic surgery (RATS) surgical approach on disease free survival was investigated and they concluded that RATS group had a longer disease free

survival than the VATS group (*P*=0.03) (65). On the other hand like in our study, the analysis of Hernandez Vaquero *et. al.* came to the conclusion that disease free survival between VATS and open lobectomy is similiar between the groups (66).

As for the metastases, the most common sites for extrathoracic spread in lung cancer are bones, liver, adrenal glands, lymph nodes, brain and spinal cord (25). Rihiimaki *et. al.* have established in their study that most frequently metastatic sites were nervous system (39%), bones (34%), liver (20%), respiratory system (18%) and adrenal gland (8%) (67). On the other hand, in our study the highest number of metastases was noted in lungs (41.4%) and the smallest number in bones (5.7%). We payed special attention on metastases in mediastinum where 15.7% of them was marked. Additionally, in 18.6% of patients there were no metastases present.

Study of Zuo *et. al.* implicated that histologic type of lung cancer had no statistically significant connection with DFS in NSCLC (68). Similarly, in our study we concluded that there was no statistically significant difference of DFS between adenocarcinoma and squamous cell carcinoma (*P*=0.527) which was the first aim of our research. Like in the study of Zuo *et. al.* our study also did not prove statistically significant difference of DFS in relation to age (*P*=0.838).

Positive lymph node number has been presented as strong component for prognosis of NSCLC. Lymph node ratio indicates distribution of positive lymph nodes in the number of extracted lymph nodes. Zhou *et. al*. determined that patients with lower lymph node ratio had better survival in terms of DFS (69). On the contrary, in our study we found no statistically significant difference of DFS in relation to affected (*P*=0.643) and isolated lymph nodes (*P*=0.499).

Choi *et. al.* concluded in their study that number of metastases to mediastinal lymph nodes is one of essential factors for prognosis. They proved that metastasis to more than one mediastinal lymph nodes is a significant prognostic factor (70). From the results in our study average value of disease free survival in patients with metastases in mediastinum was shorter than in patients with metastases at other locations.

When we talk about age, age of lung cancer diagnosis is mostly 71 years, it rarely occurs before the age of 20 (13). In our study median of age was 66 years for males and 64 years for females. We did not find any statistically significant difference among genders according to age (*P*=0.211).

One of the aims of our study was to analyze the impact of the number of extracted and positive lymph nodes on the mediastinal metastases occurence. Metastases in mediastinum were marked in 11 out of 70 patients in our sample, specifically 15.7%. Firstly, we compared the number of affected lymph nodes to the occurence of metastases in mediastinum and other locations (lungs, bones, intraabdominal, brain). The P value turned out to be 0.645 and we concluded that there is no statistically significant association between affected lymph nodes and location of metastases. Similiar to this we also compared association between number of isolated lymph nodes and location of metastases in mediastinum and other locations and found no statistically significant connection (P=0.895).

Bria *et. al*. discovered a significant influence of removed lymph nodes on overall survival, while Jonnalagadda *et. al*. concluded that the amount of involved lymph nodes had a significant impact but the number of removed lymph nodes did not (71). On the other hand, Riquet *et. al.* came to the conclusion that number of lymph nodes mediastinally and intrapulmonary varies from patient to patient and has no significant impact on survival (71). In our study we did not establish a difference of DFS in relation to the affected (P=0.643) and isolated (P=0.499) lymph nodes.

The main limitations of this study were the retrospective collection of patient's data and a small sample of patients since the study was conducted in only one hospital center.

6. CONCLUSIONS

1. Number of removed lymph nodes does not depend on the type of surgical approach.

2. Disease free survival in patients with metastases in mediastinum is shorter than with metastases at other locations.

3. Length of survival without recurrence of disease is not related to the type of surgical approach.

4. Length of survival without recurrence of disease is not related to the histologic type of lung cancer.

5. Number of extirpated lymph nodes does not depend on the type of surgical approach.

6. Number of extracted and positive lymph nodes does not depend on mediastinal metastases occurence.

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8. ENGLISH SUMMARY

Objectives: The aim of this study was to determine the length of survival without disease recurrence in relation to the type of surgical procedure and histologic type of lung cancer, to analyze the impact of surgical approach on number of extirpated lymph nodes, to analyze the impact of number of extracted and positive lymph nodes on the mediastinal metastases occurence.

Subjects and Methods: From December 2012 until September 2017, 70 patients (45 males, 25 females) who underwent surgery for the treatment of non-small-cell lung cancer at the Department of Surgery, University Hospital of Split, were included in the retrospective study. Patients were divided according to the type of surgical approach, histologic type of lung cancer, location of metastases and number of affected and isolated lymph nodes.

Results: Between 2012 and 2017, 70 patients were treated surgically for non-small-cell lung cancer either by VATS or open thoracotomy approach. The median age of patients was 65 years. The most frequently diagnosed histologic type was adenocarcinoma (n=47). Lungs were the most common site for metastatic spread. When analyzing the impact of surgical approach on number of affected and isolated lymph nodes there was no statistical difference (P=0.237), (P=0.194). There was no difference between number of affected and isolated lymph nodes with location of metastases (P=0.645, P=0.895). Disease free survival was 17 months shorter in patients with metastases in mediastinum than in patients with metastases in the lungs and 12 months shorter than in patients with metastases in other locations. There was no significant difference of disease free survival between genders (P=0.610), histologic types (P=0.688), age groups (P=0.838), type of surgical approach (P=0.527) and number of affected (P=0.643) and isolated (P=0.499) lymph nodes.

Conclusion: Type of surgical approach does not have an impact on number of removed lymph nodes and disease free survival.

9. CROATIAN SUMMARY

Naslov: Prognoza bolesti nakon operacijskog liječenja karcinoma pluća u Kliničkom bolničkom centru (KBC) Split.

Ciljevi: Cilj ovog istraživanja bio je odrediti duljinu preživljenja bez povrata bolesti s obzirom na tip kirurškog pristupa i histološki tip karcinoma pluća, analizirati utjecaj kirurškog pristupa na broj ekstirpiranih limfnih čvorova te analizirati utjecaj broja pozitivnih i izvađenih limfnih čvorova na pojavu metastaza u medijastinumu.

Ispitanici i metode: Od prosinca 2012 do rujna 2017, 70 ispitanika (45 muškaraca, 25 žena) koji su kirurški liječeni zbog nesitnostaničnog karcinoma pluća na Klinici za kirurgiju, KBC-a Split, bili su uključeni u ovu retrospektivnu studiju. Ispitanici su bili podijeljeni u skupine s obzirom na tip kirurškog pristupa, histološki tip karcinoma pluća, lokaciju metastaze i broj zahvaćenih i izoliranih limfnih čvorova.

Rezultati: Između 2012 i 2017.godine, 70 ispitanika je kirurški liječeno zbog nesitnostaničnog karcinoma pluća VATS pristupom ili pristupom otvorene torakotomije. Medijan životne dobi ispitanika bio je 65 godina. Najčešće dijagnosticirani histološki tip bio je adenokarcinom (n=47). Najčešća lokacija metastaza bila su pluća. Analizirajući utjecaj kirurškog pristupa na broj zahvaćenih i izoliranih limfnih čvorova nije bilo statistički značajne razlike (P=0.237, P=0.194). Između broja zahvaćenih i izoliranih limfnih čvorova te lokacija metastaza nije bilo statistički značajne razlike (P=0.645, P=0.895). Duljina preživljenja je bila 17 mjeseci kraća kod ispitanika s metastazama u medijastinumu za razliku od ispitanika s metastazama na plućima te 12 mjeseci kraća za razliku od pacijenata s metastazama na drugim lokacijama. Nije bilo statistički značajne razlike u duljini preživljenja između spola (P=0.610), histološkog tipa (P=0.688), dobi (P=0.838), tipa kirurškog pristupa (P=0.527) i broja zahvaćenih (P=0.643) i izoliranih (P=0.499) limfnih čvorova.

Zaključak: Tip kirurškog pristupa nema utjecaj na broj uklonjenih limfnih čvorova i duljinu preživljenja.

10. CURRICULUM VITAE

Personal Data:

Name and Surname: Katarina Boko

Date of Birth: 20.11.1997.

Citizenship: Croatian

Education:

10.2016-09.2022	University of Split School of Medicine, Split, Croatia
	Doctor of Medicine
09.2012-06.2016	Gymnasium Marko Marulić , Split, Croatia
09.2006-06.2012	Elementary School Sućidar, Split, Croatia

Languages

Croatian	Mother Tongue
English	C2
German	B1

11. SUPPLEMENT

KBC Split

KLINIČKI BOLNIČKI CENTAR SPLIT
ETIČKO POVJERENSTVO

Klasa: 500-03/22-01/111
Ur.broj: 2181-147/01/06/M.S.-22-02

Split, 29.06.2022.

IZVOD
IZ ZAPISNIKA SJEDNICE ETIČKOG POVJERENSTVA KBC SPLIT 12/2022

7.

Doc.dr.sc. Dragan Krnić, dr.med. iz Klinike za kirurgiju KBC-a Split uputio je Etičkom povjerenstvu zamolbu za odobrenje provedbe istraživanja:

" Prognoza bolesti nakon operacijskog liječenja karcinoma pluća u KBC Split"

Istraživanje za potrebe diplomskog rada će se provesti u Klinici za kirurgiju KBC-a Split, Kliničkom zavodu za patologiju, sudsku medicinu i citologiju i Kliničkom zavodu za dijagnostičku i intervencijsku radiologiju KBC-a Split.
Suradnica u istraživanju je Katarina Boko, studentica.
Nakon razmatranja zamolbe, donesen je sljedeći

Zaključak

Iz priložene dokumentacije razvidno je da je Plan istraživanja usklađen s odredbama o zaštiti prava i osobnih podataka ispitanika iz Zakona o zaštiti prava pacijenata (NN169/04, 37/08) i Zakona o provedbi Opće uredbe o zaštiti podataka (NN 42/18), te odredbama Kodeksa liječničke etike i deontologije (NN55/08, 139/15) i pravilima Helsinške deklaracije WMA 1964-2013 na koje upućuje Kodeks.

Etičko povjerenstvo je suglasno i odobrava provođenje istraživanja.

PREDSJEDNIK ETIČKOG POVJERENSTVA
KLINIČKOG BOLNIČKOG CENTRA SPLIT
PROF. DR. SC. MARIJAN SARAGA

KLINIČKI BOLNIČKI CENTAR SPLIT
Etičko povjerenstvo