

Epidemiology, diagnostics and long-term overall survival of patients with non-small cell lung cancer in the Brest Region

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Abstract

Introduction: Lung cancer has been the most common cancer in the world and in Belarus.

Aim of the research: To evaluate the epidemiology of non-small cell lung cancer and improvements in diagnostics and treatment for the past 11 years in the Brest Region of Belarus.

Material and methods: We conducted a retrospective analysis of statistical data (incidence rate, mortality) in the regional cancer registry of the Brest oncological clinic since 2000 and assessed survival for 652 adult patients with different stages of non-small-cell lung cancer (NSCLC) who underwent surgery in the Thoracic Surgery Department of Brest Regional Hospital in 2002–2010.

Results: Lung cancer continues to have the highest incidence rate among malignant neoplasms and because of its high fatality rate is a leading cause of cancer-related mortality in the Brest Region and Belarus. The chest radiography screening programme of lung cancer since 2000 and the implementation of computed tomography (CT)- and ultrasonography (USG)-guided needle biopsy and VATS LigaSure pulmonary wedge resection for the evaluation of solitary pulmonary nodules has allowed an increase of diagnostic rates and improved the histological confirmation rate of lung cancer in the Brest Region. Multivariate analysis indicates that male sex, age older than seventy and incomplete surgical resection are independent predictors of poor prognosis for postoperative long-term overall survival.

Conclusions: Today it is necessary to carry out low-dose spiral computerized diagnostics in the Brest Region, which would detect a greater proportion of asymptomatic lung cancers. Surgical resection remains the only consistent and successful option of a cure for patients with lung cancer.

Introduction

Lung cancer is the most common cancer in the world and 1.61 million new cases were estimated in 2008 [1]. In Belarus, its annual incidence rate is second only to that of breast cancer among the female population.

Aim of the research

The aim of this study is to evaluate the epidemiology of non-small cell lung cancer and improvements in diagnostics and treatment for the past eleven years in the Brest Region of Belarus.

Material and methods

We conducted a retrospective analysis of statistical data (incidence rate, mortality) in the regional cancer registry of Brest Oncological Clinic since 2000 and assessed survival for 652 adult patients with different stages of non-small-cell lung cancer (NSCLC) who un-

derwent surgery in the Thoracic Surgery Department of Brest Regional Hospital in 2002–2010; their mean age was 61.6 (23–84) years: 575 males (61.4 years) and 77 females (63.2 years).

In this retrospective study we also evaluated the use of Bard Magnum needle tools for cutting biopsy in 228 patients. In 183 patients with peripheral lung lesions transthoracic needle biopsy was performed under computed tomography (CT) (Figure 1) and 45 ultrasonography (USG) control using a needle of size 18G. Success rate, pneumothorax rate and total procedure time were compared in each method. Moreover, 22 patients with solitary pulmonary nodules (SPNs) diagnosed on screening chest radiographs, underwent video-assisted thoracoscopic electrothermal pulmonary wedge resection of lung tissue with nodules. Video-assisted thoracoscopic surgery (VATS) LigaSure resection and latex glue application to the cut parenchymal surface was applied (Figure 2).

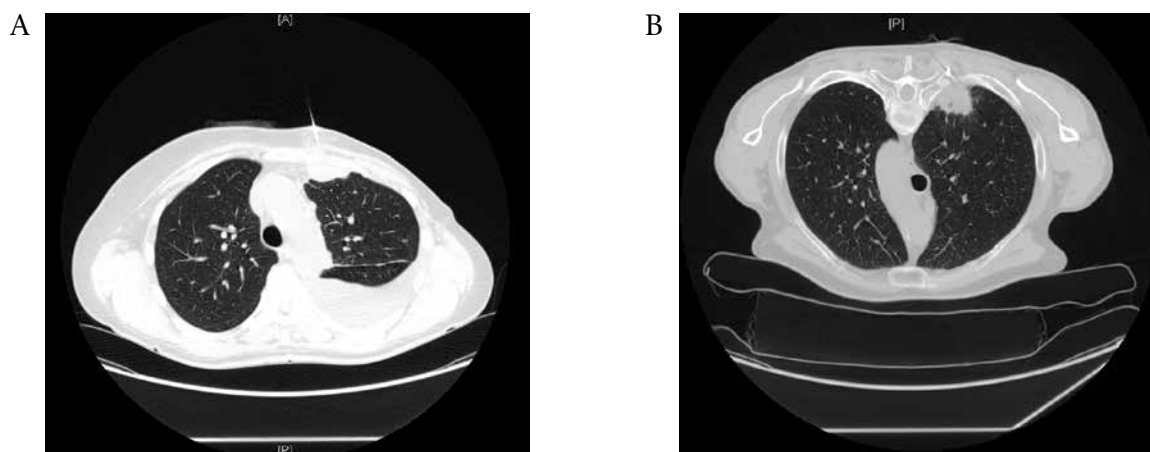


Figure 1. CT-guided transthoracic cutting needle biopsy of the left lung solid tumour (**A** – needle being introduced through thorax wall, **B** – cutting of tumour)

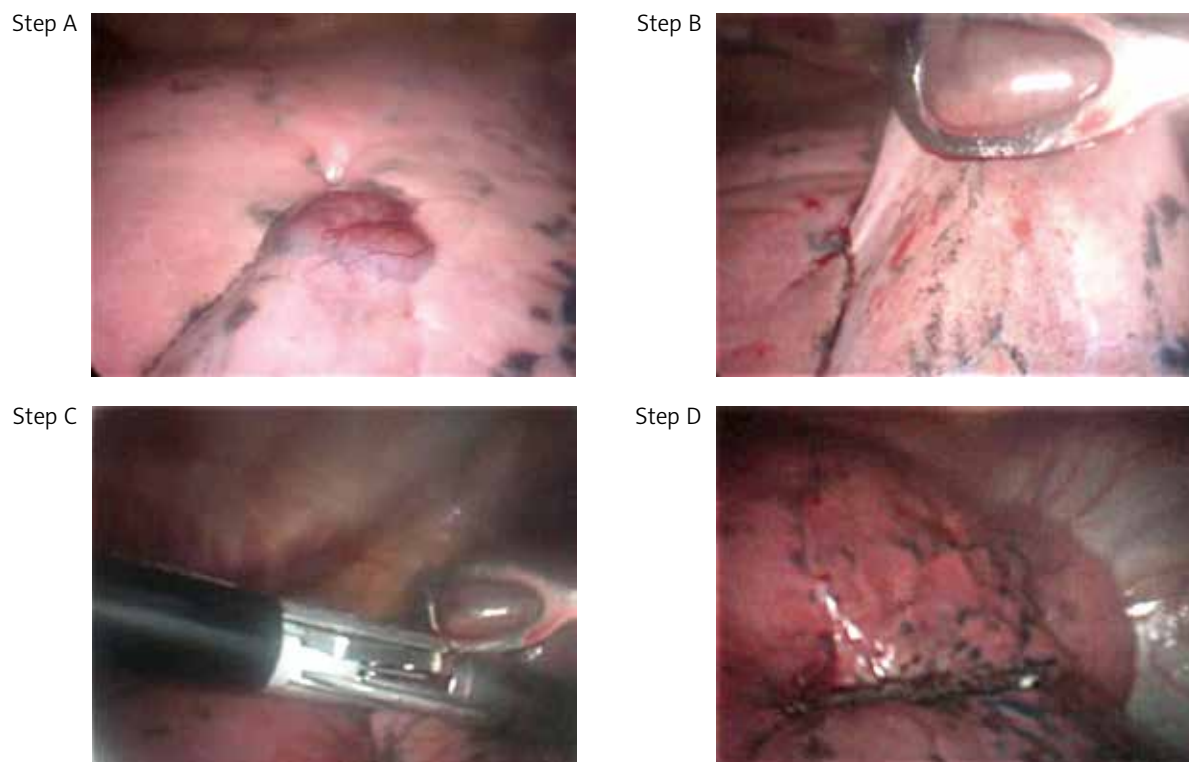


Figure 2. VATS LigaSure resection of lung metastasis

Patients with stage I and II NSCLC who were medically fit for conventional surgical resection underwent lobectomy or greater resection and lymph node dissection was performed for accurate pathologic staging. For patients with centrally or locally advanced NSCLC in whom a complete resection could be achieved with either operation technique, we used various types of lung resections in combination with trachea-bronchia-plastic, vascular-plastic operations

and operations on the pericardium. These reconstructive operations were aimed to save pulmonary lobes uninvolved by the neoplasm and to take advantage of opportunities of operative treatment in patients with poorer lung function, and poorer performance status.

Trachea-bronchia-plastic operations were as follows: wedge-shaped resections of the main bronchial tubes (Figure 3) and sleeve lobectomy (Figure 4), wedge-shaped resections of tracheal bifurcation in



Figure 3. Wedge-shaped resection of the main bronchial tube



Figure 4. Circular resection of the main bronchial tube



Figure 5. Wedge-shaped resection of bifurcation of trachea

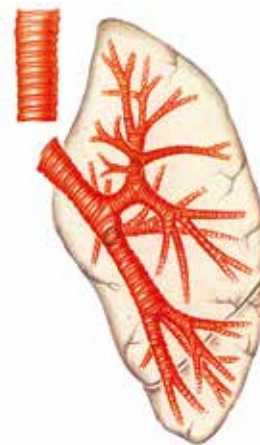


Figure 6. Circular resection of bifurcation of trachea

combination with bilobectomy or pneumonectomy (Figure 5), sleeve resections of tracheal bifurcation with pneumonectomy (Figure 6).

Vascular-plastic operations were performed in patients with central cancer of the left lung apex lobe when the tumour involved its segmental arteries. Apex lobectomy was done in combination with window-shaped resection of the left lung artery together with the initial segments of arteries (Figure 7). In 3 patients resection of the anterior wall of the left lung artery together with issues of all the apex lobe segmental arteries and subsequent reconstruction of the lung artery by a vascular seam were carried out.

Pneumonectomy combined with resection of the pericardium was performed in lung cancer patients with present locally advanced disease which was revealed at the time of operations. Pericardium defects were sewn or covered with patches of parietal pleura if the postresection aperture was more than 3 cm × 4 cm.

In patients with NSCLC who had bulky N2 disease a combination of platinum-based chemotherapy and radiotherapy was applied.

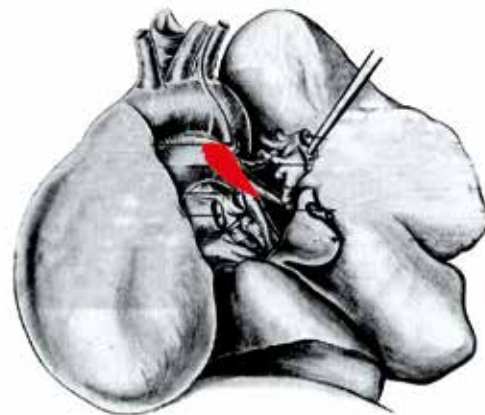


Figure 7. Window-shaped resection of the left lung artery wall with the issues of the apex lobe segmental arteries

Statistical analysis

The descriptive statistics were summarized as mean for the continuous variables (\pm standard error from the mean) and as frequencies and percent-

ages for the categorical variables in Microsoft Excel for Window. Kaplan-Meier survival curves (Statistica 7) were used to visually compare the overall survival (OS), which was defined as the time from the date of surgery to the last date of follow-up for patients who remained alive or to the date of death, for subjects grouped by gender, radical surgery and according to tumour-node metastasis (TNM) classification stages. Log-rank tests and the Cox proportional hazards regression model were used to assess the influence of various risk factors on survival time. All differences were considered significant at a *p* value less than 0.05.

Results

The annual number of new cases of lung cancer among the population in the Brest region was 638 in 2000 and 546 in 2011, taking into account the average 580 new cancer diagnoses annually (average 513 among males and 67 among females). According to the regional registry the lung cancer crude incidence rate among the population of the region (about 1.4 million) was 41.5 ± 2.5 , the same ($p = 0.42$) as in Belarus:

43.6 ± 2.0 (Figure 8). Also the lung cancer incidence rate has no tendency to reduction, and still is number one in the structure of cancer morbidity among the Brest region population (11%) and especially among the male population (21%).

Within 2001–2011 the female/male ratio in lung cancer incidence was 1/8 and the average incidence per 100 000 among the male population was 77.4 ± 6.7 and among females 9.4 ± 1.3 (Figure 9).

For the past years in the whole (both sexes) population lung cancer mortality (33.9 ± 1.6) has shown a small tendency to decrease from 36.7 (2001) to 31.8 per 100 000 (2011) (Figure 10) and the male population death rate also has decreased by about 11% from 70.2 in 2001 to 62.2/100 000 in 2011 with the mean rate of 65.2 ± 3.2 (Figure 11). However, men have had 10 times as high death rates from lung cancer ($65.2 \pm 3.2/100\ 000$) as women ($6.4 \pm 0.6/100\ 000$) and the gender difference in mortality has not changed for the past decade (Figure 11).

For the past decade the efficiency of diagnostics of lung cancer has considerably increased by means of

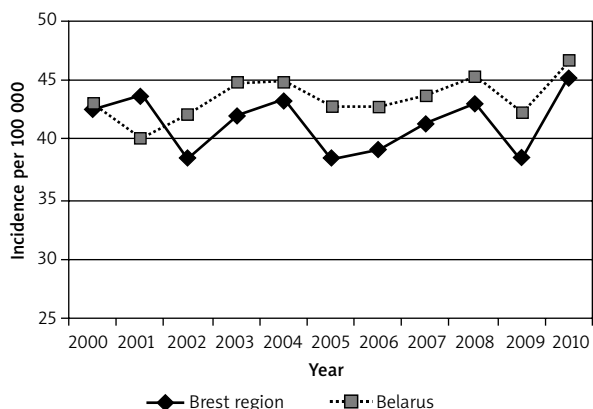


Figure 8. Lung cancer incidence per 100 000 in Brest region and Republic of Belarus

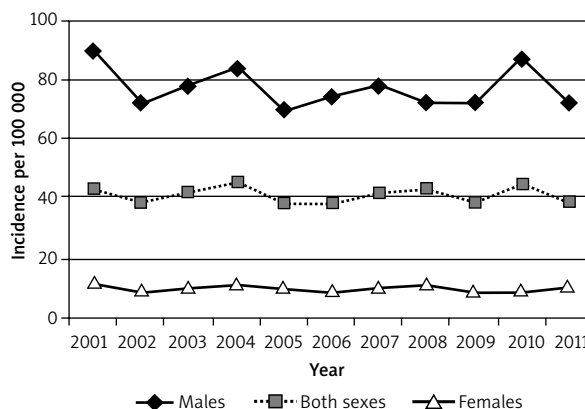


Figure 9. Lung cancer gender differences for incidence rate in Brest region within 2001–2011

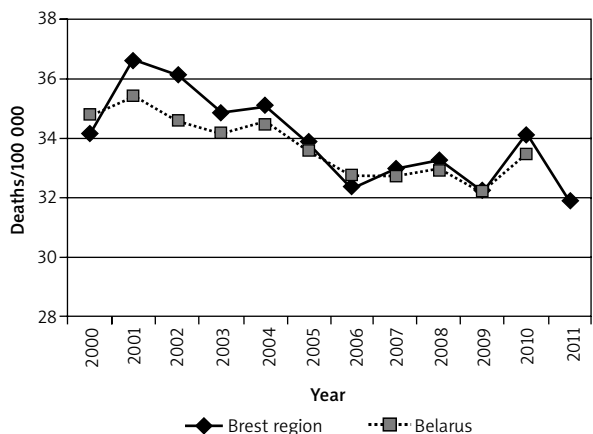


Figure 10. Lung cancer mortality per 100 000 in Brest region and Republic of Belarus

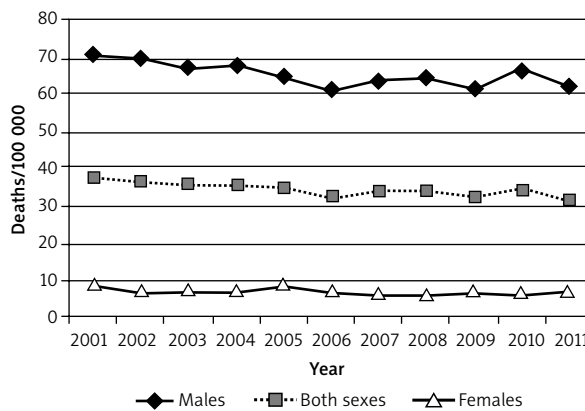


Figure 11. Mortality gender differences in Brest region within 2001–2011

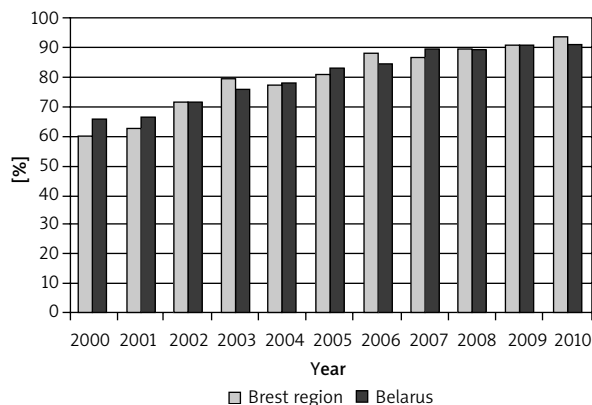


Figure 12. Histological confirmation rate of lung cancer

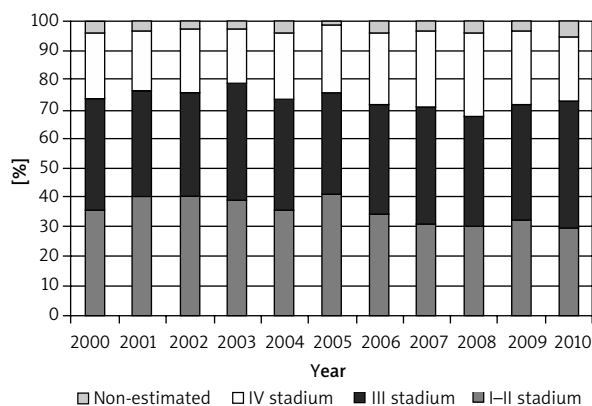


Figure 14. Stage distribution of lung cancer among Brest cohort

radiological screening. In 2001 only 22% of patients with lung cancer were revealed with the help of preventive diagnostics, whereas in 2011 this parameter achieved about 54%. The implementation of minimally invasive diagnostic technologies has allowed the histological confirmation rate of lung cancer to be increased significantly from 60% in 2000 to 93% in 2010 (Figure 12). However, the performance of biopsies was impossible for sizes of pulmonary nodules less than 10 mm, which is connected with the limits of sensitivity of diagnostic methods used in the procedure. Success rates of CT-guided transthoracic cutting-needle biopsy (TCNB) of pulmonary nodules were higher (99%) than those using ultrasound-assisted transthoracic biopsy (96.8%), which is connected with the complexity of the location of pulmonary nodules and the effect of attenuation and dispersion of the ultrasonic signal in the air environment. Histological results of CT- and USG-guided biopsies are distributed as follows: the malignant nature of disease was revealed in 205 (90%) cases; tuberculoma and limited pleural fibrosis was diagnosed in 18 (8% of cases) and in 5 patients (2%) the central form of ma-



Figure 13. CT images of patient treatment with VATS LigaSure tumour resection and latex glue application (A – before operation, B – second postoperative day without any air leak)

lignant pleural mesothelioma was established. Small pneumothorax after transthoracic biopsy occurred in 3 patients older than 55 years and 3 patients had insignificant haemoptysis. All complications were resolved in a conservative way. Among 22 cases with SPNs who underwent LigaSure diagnostic surgery the operation time was 48 min, haemorrhage volume 60 ml, average chest drain duration 3.5 days, and hospital stay 5.7 days. All patients who underwent VATS resection of SPNs by tissue-sealing technique using the LigaSure system and glue applications to the parenchymal fusion lines did not have any air leaks, even those who had bronchial stubs about 3 mm in diameter, as presented in Figure 13. There were no late complications after an average follow-up of 10 months either.

Unfortunately, despite successes in morphological verification the proportion of potentially operable NSCLC at an early stage (stage I–II) remains at the level of $35.3 \pm 4.4\%$, the group treated with surgery alone or surgery combined with chemotherapy, radiation therapy or both is $38.1 \pm 2.6\%$ (stage III), and the group for palliative chemotherapy and palliative nursing is $23.1 \pm 3.0\%$ and $3.5 \pm 1.1\%$ respectively (Figure 14).

In the Brest region lung cancer cohort with a 1-year mortality rate after diagnosis confirmation is presented in Figure 15. The chart shows that the percentage of mortality of NSCLC patients who were diagnosed

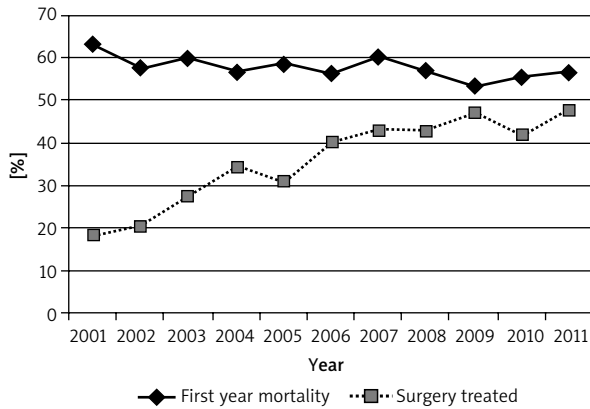


Figure 15. First-year mortality rate of lung cancer patients and percent of surgically treated patients

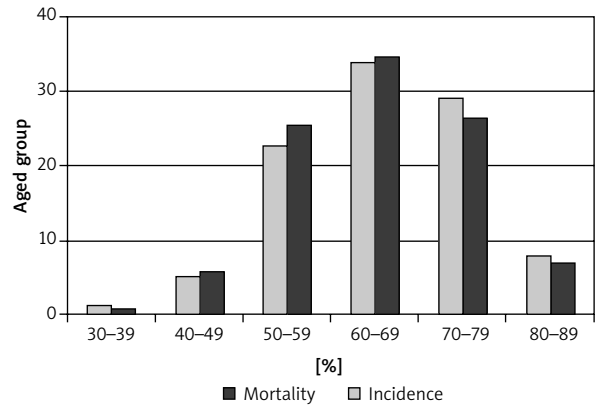


Figure 16. Age-dependent lung cancer mortality and incidence

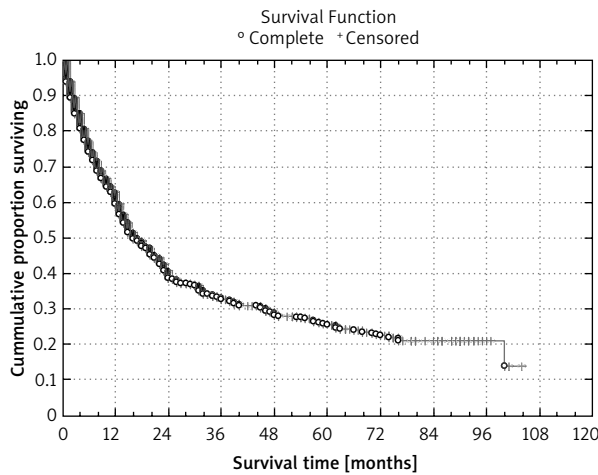


Figure 17. Cumulative survival after surgical treatment

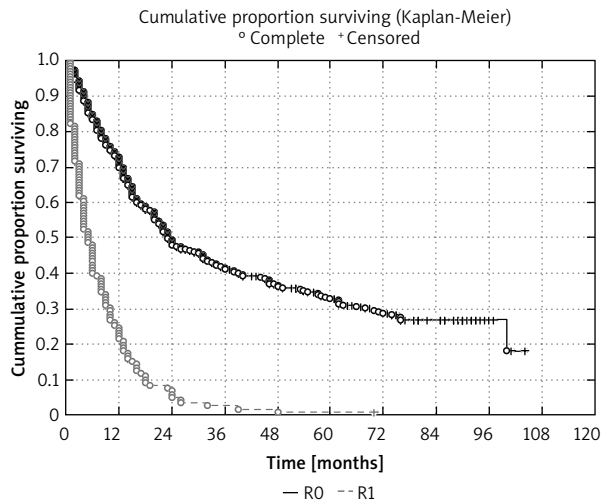


Figure 18. Differences in survival after radical (R0) and non-radical (R1) surgical treatment of NSCLC

between 2001 and 2011 (57.7 ± 2.6) had a small tendency to decrease, as more than 63% of patients died within the first year in 2001 and about 56% in 2011. This tendency correlates ($r = -0,68; p = 0.022346$) with the increasing percentage of patients undergoing surgical treatment.

The age-dependent structure (%) of lung cancer mortality is shown in Figure 16, which also completely displays the histogram of incidence in different age groups. The peak in lung cancer mortality and incidence still occurs for the age category from 60 to 70, despite the tendency to an increasing number of younger lung cancer patients.

Cumulative overall survival after surgical treatment and survival rate differences depending on radicalism of operations (R0 – complete resection, R1 – non-radical operation) are presented in Figures 17 and 18. The 5-year (60-month) survival was about 27% among all operated patients and about 35% for patients after complete resection. The 2-year (24-month) survival was five times as low as in the patients who underwent non-radical operations (9% vs. 49%). The median sur-

vival of all surgery patients was 24.5 months, 28.6 months in the R0 group and only 8.0 months in R1 ($p < 0.001$). The examination of the unadjusted hazard rate shows that for non-radically operated patients the risk of mortality was 3.4 ($p < 0.05$), which is more pronounced than after complete tumour resection.

Kaplan-Meier postoperative overall survival curves for lung cancer patients according to TNM stages and to gender differences are shown in Figure 19 and Figure 20 respectively.

There were overall differences in the cumulative survival between the TNM staged groups I–VI and both sexes. The average length of survival of the patients who had advanced TNM stages (III – 16.0 and IV – 10.3 months) was significantly shorter ($p < 0.05$ for each stage) than in the groups who had a limited disease after the surgery (I – 37.0 and II – 24.2 months). The survival difference between men and women was also significant ($p < 0.001$), as the mean length of male survival was 23.5 and 31.8 months for women. Both

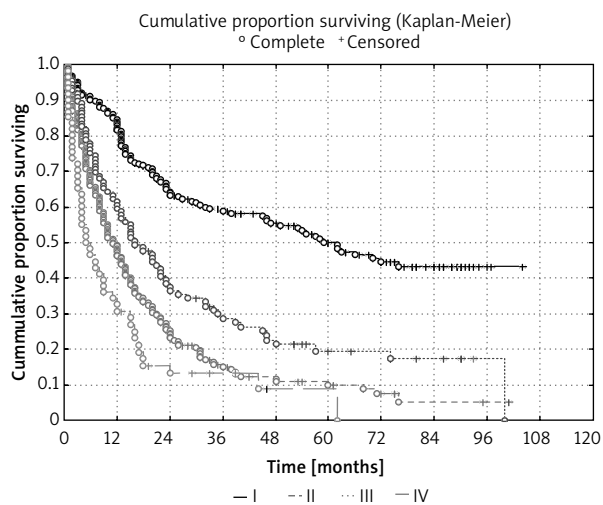


Figure 19. Stage-dependent cumulative survival rate among surgically treated patients

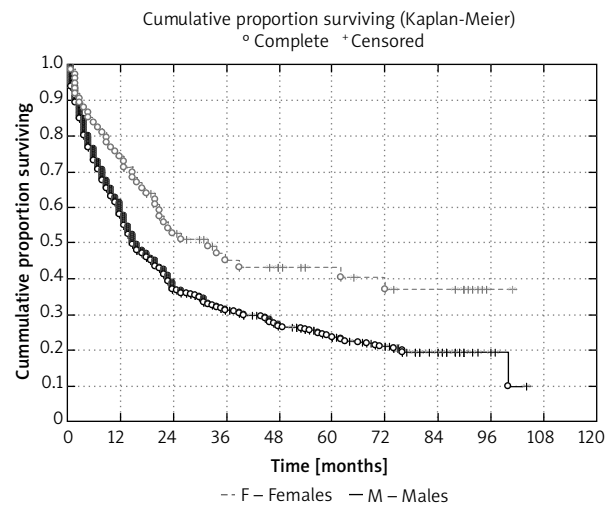


Figure 20. Gender differences of survival rate among surgically treated patients

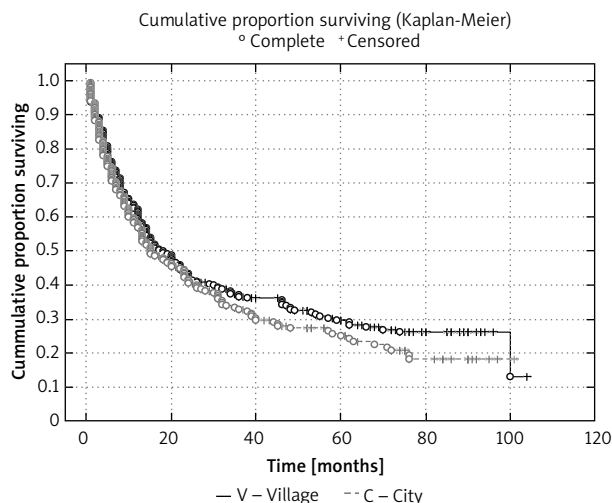


Figure 21. Urban differences of survival rate among surgically treated patients

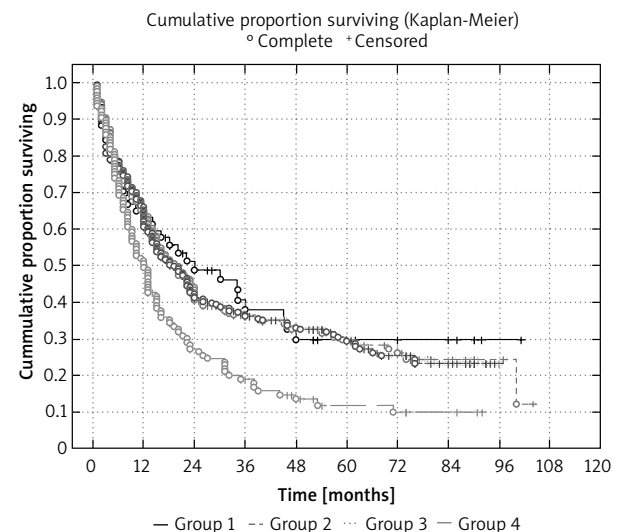


Figure 22. Age-dependent differences of survival rate among surgically treated patients (group 1 – < 50 years old, group 2 – 50–59, group 3 – 60–69, group 4 – > 70)

tumour stages and gender factors exhibited an influence on death risk. Male patients demonstrated considerably higher death hazards than female ones (hazard ratio (HR): 0.54, $p = 0.0003$). An increasing TNM pathological stage was also associated with an increasing risk of mortality for more advanced cancer (HR: 1.37, $p < 0.001$). Postoperative mean survival for lung cancer patients living in urban and rural areas was 22.2 and 26.6 months respectively, but the urban factor exhibited a lack of proportionality in hazard ratios (HR: 1.08, $p = 0.42$) and the findings suggest that the place of residence (rural or urban) was not an important determinant (log-rank test, $p = 0.21$) of the overall survival in surgery patients (Figure 21). When the surgery patients were divided into four groups according to age (Figure 22), there was a significant difference

($p < 0.05$) comparing the first three groups to the fourth group (over 70 years old). Moreover, the age of more than 70 years old was an independent prognostic factor for a worse survival prognosis (HR: 1.4, $p = 0.019$).

Discussion

In the Brest region as well as in Belarus for the past decade the lung cancer incidence and death rate of the population have decreased only by approximately 11%, which is possibly caused by the absence of a significant reduction of exposure to cancerogenic factors such as smoking [2], low level of physical activity [3], excessive consumption of alcohol [4] and other

unhealthy dietary predilections, air pollution [5] and exposure to specific occupational or environmental toxicants [6], leading to an increased risk of lung and other cancers. The NSCLC incidence rate and mortality of the population in the Brest region and Belarus (RB) are the same as those in the Europe Region (EURO): age-standardized rates per 100 000 in RB/EURO are 25.5 vs. 28.2 (incidence) and 22.7 vs. 24.1 (mortality) for both sexes, whereas the ratio RB/EURO of these indicators was negative for Belarusian men (59.3 vs. 48.1 for incidence, 56.5 vs. 42.0 for mortality) and positive for Belarusian women (4.7 vs. 12.7, 3.7 vs. 10.3 respectively). Thus, lung cancer is the leading cause of mortality of all cancers, both in Belarus and in EURO [7] because of its high fatality rate (the ratio of mortality to incidence was 0.86 in EURO, 0.82 \pm 0.05 in the Brest Region and 0.78 \pm 0.05, $p = 0.016$ in Belarus).

In females, incidence rates are generally lower, but, worldwide, lung cancer is now the fourth most frequent cancer of women (516 000 cases, 8.5% of all cancers) and the second most common cause of death from cancer (427 000 deaths, 12.8% of the total) [7].

The reduction of the first year mortality in the Brest Region NSCLC cohort may be explained by the increase of the number of patients who underwent the combination of platinum-based chemotherapy and radiotherapy from 7% in 2001 to 15% in 2011 as well as the increase of surgical treatment from 19% to 48% respectively. It is also supported by other authors that surgical treatment was associated with improved survival for both localized and regional advanced diseases [8].

The age peak in the incidence rate of 60–70 year-olds and gender differences in overall survival after the operation have been confirmed by a European multicentre study showing that a lifetime smoker has an incidence risk some 20–30 times as high as that of a non-smoker, the relative risk of lung cancer for cigarette-smoking men is 57.9 for squamous/small cell carcinoma and 8.0 for adenocarcinoma, and 18.1 and 4.1 respectively for smoking women [9]. The same age peak and gender differences in lung cancer mortality have been confirmed by other studies which show that with the decrease in the prevalence of smoking, lung cancer has become more frequent among former than current smokers [10]. Among 575 men of our surgically treated cohort in the Brest region there were 90% current tobacco smoking, 7% former smokers, and only 3% were non-smokers. Only 12% of 77 operated women were current and former smoking ones. The current literature is equivocal. While several studies report smoking to be a predictor of poor prognosis, others have found no such association. One study reports smoking to be a negative prognostic factor only in men, whereas another finds an association only in women [11].

However, most of the more than 1.4 million lung cancer deaths that occur annually worldwide are caused by tobacco smoking [1], and smoking cessation and healthy life style should be the basis of the prevention strategy for reduction of lung cancer incidence and morbidity [12] especially for the male population so that it may improve prognostic outcomes even in surgery patients with lung cancer [13].

The negative impact of age on overall survival may be explained by a worse functional status and important preoperative comorbidities of the oldest patients. Ryu *et al.* suggest that aging (over 68 years old) is an important determinant of overall survival in patients with adenocarcinoma [14] and should be considered in classifying the patients into groups of higher or lower risks for death. Birim *et al.* with both univariate and multivariate analysis showed that male gender, age, comorbidity, clinical and pathological stage, and type of resection were significantly associated with impaired survival [15].

Differentiation of benign from malignant solitary pulmonary nodules (SPNs) with a non-invasive method such as CT, magnetic resonance imaging (MRI), or positron emission tomography (PET) with fluorine 18-labelled fluorodeoxyglucose (FDG PET) has been considered an important goal of diagnostic radiology [16]. The FDG PET has greater sensitivity for the detection of metabolically active malignant disease and can lead to changes in initial staging and treatment plans for NSCLC when used in combination with conventional work-up [17]. However, currently and for the foreseeable future, peripheral pulmonary nodules are difficult to reach bronchoscopically, so we have tried, by the use of imaging techniques such as ultrasound and computed tomography, to reach these nodules with the needle cutting core biopsy for exact histological diagnosis. Moreover, our results indicate that the sealing capacity of VATS LigaSure resection plus latex glue is adequate even with a large cut surface of lung tissue including bronchi larger than 3 mm in diameter. We support Shigemura and others' point of view that the electrothermal bipolar tissue sealing system is suitable for lysis of pleural adhesions, bullectomies, and lung wedge resections and may be a valid alternative to staplers, particularly in the thoroscopic setting [18]. It is known that minimal-access surgical procedures expand the applicability of surgical resection to patients with marginal operability. Video-assisted lobectomy, which is offered by a growing number of surgical centres, can provide a less invasive method of accomplishing the same oncological resection with a similar long-term survival rate [19, 20], thereby allowing some patients who were not candidates for standard thoracotomy because of comorbidity to undergo resection. As the age of the general population increases, so too does the mean age of patients referred for surgical resection of lung cancer [21]. As

today techniques for limited or less invasive resections have become available, patients in their ninth decade are increasingly undergoing successful surgical resection of their lung cancers with meaningful long-term survival.

Since 2009 video-assisted LigaSure thoracic operations have been used by us and they are also an alternative to open thoracotomy for elder patients with stage I NSCLC who are considered appropriate candidates for thoracoscopic anatomic lung resection (segmentectomy or lobectomy). Moreover, surgery for lung cancer is prominent in diagnosis, staging, curative treatment, and palliative care [22]. Staging remains integral and essential for management of patients with lung cancer and is paramount because the prognostic information it provides is invaluable in determining appropriate treatment.

The treatment of NSCLC is surgery for early stages, chemotherapy with concurrent radiation for some locally advanced cancers, and palliative chemotherapy for metastatic disease.

Conclusions

Lung cancer continues to have the highest incidence rate among malignant neoplasms and because of its high fatality rate (the ratio of mortality to incidence is 0.86) is a leading cause of cancer-related mortality in the Brest Region and Belarus. The chest radiography screening programme of lung cancer since 2000 has allowed a 2-fold increase of diagnostic rates in the Brest Region, but now it is necessary to carry out low-dose spiral computerized diagnostics, which is currently proposed as a much more sensitive screening tool and would detect a greater proportion of asymptomatic lung cancers. The implementation of CT- and USG-guided needle biopsy and VATS LigaSure pulmonary wedge resection for the evaluation of solitary pulmonary nodules has significantly improved the histological confirmation rate of lung cancer recently. The VATS LigaSure method with glue application is eligible for pulmonary wedge resection for different diagnostics of malignant and benign peripheral pulmonary lesions, as it is a safe method, easy to use, having a minimal rate of complications. Multivariate analysis indicates that male sex, age older than seventy, and incomplete surgical resection are independent predictors of poor prognosis for postoperative long-term overall survival. There is also a strong monotonic effect of TNM stages on overall survival that continues for years after surgery – the more advanced the stage, the worse is the cumulative survival at every time point. Surgical resection remains the only consistent and successful option of a cure for patients with lung cancer, so radical surgical resection is the most important factor in long-term survival.

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