Original Article

The clinico-pathological characteristics of surgically treated young women with NSCLC

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Background: Non-small cell lung cancer diagnosed in young patients is rare. Younger patients with lung cancer are mostly female and have a more advanced stage at initial diagnosis. To our knowledge, no studies have compared single-surgical treatment in different age groups among women. Our study aimed to elucidate the clinicopathological characteristics and the best strategies for surgically treating young women with non-small-cell lung cancer.

Methods: The data were collected retrospectively from the Polish Lung Cancer Study Group database. Women who were surgically treated for non-small-cell lung cancer between 2007 and 2020 were included in the study. The participants (n=11,460) were divided into two subgroups: aged ≤55 and >55 years.

Results: Statistically significant differences were found for grades IB, IIA, IIIA, and IIIB (22.8% *vs.* 24.5%, 5.3% *vs.* 7.5%, 19.3% *vs.* 15.8%, 5.8% *vs.* 3.2%, for younger and older women, respectively, all P<0.001). The univariate analysis showed a higher percentage of 5-year survival in the group of younger women than in older women (0.67 *vs.* 0.64, P=0.00076). Regarding the stage of advancement, statistically significant differences in survival were found for stages IA1, IA2, and IIIA (0.95 *vs.* 0.86, P=0.047; 0.88 *vs.* 0.79, P=0.003; 0.5 *vs.* 0.42, for younger and older women, respectively, all P=0.01). Postoperative complications were more common in older than younger women (27.6% *vs.* 23.1%, P<0.001). However, there were no statistically significant differences in the number of hospitalization days since surgery and postoperative 30-day mortality.

Conclusions: Younger women treated surgically were characterized by a lower percentage of comorbidities, were treated in a more advanced stage of the disease and had a lower percentage of postoperative complications, which, however, did not affect the hospitalization time. Despite the more advanced stage of the disease, survival in selected stages was much better than in the group of older women.

Keywords: Non-small cell lung cancer; lung cancer survival; surgical treatment; women

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Introduction

The World Health Organization estimates that cancer is the first or second leading cause of death before 70 years old. Looking at the reasons for cancer death, lung cancer remained the leading cause, with an estimated 1.8 million deaths globally (18%). Among women, lung cancer has increased in incidence over recent years and is a dominant cause of death in 25 countries, mainly in Northern America, Oceania, and Europe (1). After 5 years from diagnosis, survival ranges from only 10% to 20% globally (2). It is predominantly identified in the older population (the median age of diagnosis is 71). Non-small cell lung cancer (NSCLC) diagnosed in young patients is rare - according to estimates, the age-adjusted incidence rates in women <50 years is 2.9 and 2.6 in men (per 100,000) (3). Younger patients with lung cancer are the group with an increased likelihood of harboring a targetable genotype (4), are mostly female, have a greater frequency of adenocarcinoma (5,6), and have a more advanced stage at initial diagnosis (7). However young women seems beyoung suspicion of lung cancer, what is observed in clinical practice as well in screening programs.

Sex differences in survival concerning surgically treated patients with NSCLC are divergent. In many meta-analyses, women with NSCLC have better general survival than men (8-10). On the other hand, another study show no differences between the sexes (11), or there are studies that demonstrate that better survival in favor of women occurred significantly only in stage I (12,13). However, there are no studies of single surgical treatment in different age groups among women.

Therefore, we aimed to elucidate the clinicopathological characteristics and the best strategies for surgically treating young women with NSCLC compared to older patients. We present the following article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-443/rc).

Methods

Patients

The data were collected retrospectively from the Polish Lung Cancer Study Group (PLCSG) database. This database includes data from 30 thoracic surgery centers in Poland and includes information on every lung cancer surgery in Poland. The study included 11,460 women with NSCLC treated surgically between 2007 and 2020, aged 22 to 87 years (mean 65.5 years). In the available studies concerning surgical treatment for NSCLC in different age groups, the selected age of the analyzed younger patients varied from 40 to 66 years (7,9,11,14,15). Due to these differences in the age criterion, we chose 55 years as a cut-off point in our study and we selected two study groups. The age of 55 was the youngest age in which the group of young women was large enough to be statistically comparable with the rest of the group. The first group included younger women aged ≤55 years; 1574 participants aged 23 to 55 years (mean 51.1 years, median 52 years). The second group of 9,886 patients included older women aged >55 years (56 to 87 years, mean 66 years, median 65 years). Age distributions are graphically presented in *Figure 1*. Most patients from both groups were treated in academic hospitals, including a higher percentage of patients hospitalized in academic hospitals in the group of older women than younger (54.1% *vs.* 50.4%, P=0.00756). However, in other medical facilities, younger women were treated more often (49.6% *vs.* 45.9%). Unfortunately, we do not presented the data on the molecular alterations (EGFR, ALK and ROS1) in tumors that could influence the results because our study includes all years from 2007 when molecular alterations was not yet a standard procedure in resectable NSCLC.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The ethics committee of the National Research Institute of Chest Diseases, Warsaw, Poland, approved this study (No. 96/2021). All the patients signed an informed consent form to be included in the database.

Inclusion and exclusion criteria

The following patients were included in the study: women who underwent surgery between 2007 and 2020 for confirmed NSCLC and who underwent radical surgery (R0) with at least six nodes retrieved according to the European

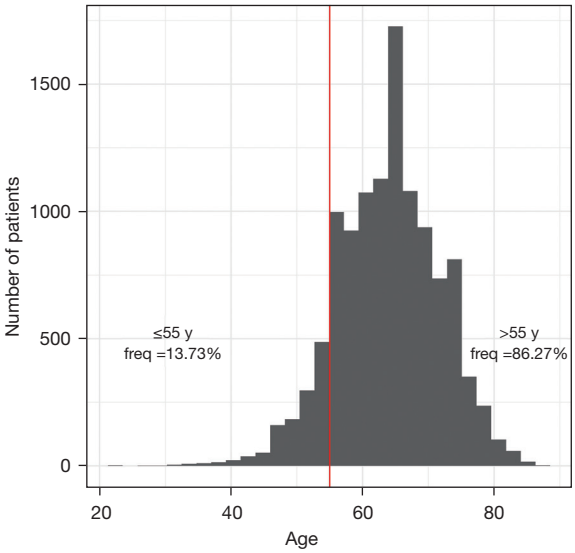

Figure 1 Patients' age distribution. freq, frequency; y, years.

Society of Thoracic Surgeons guidelines; and with complete data in the database. The following patients were excluded: women with nonradical resection (R1); those whose data were lost or incomplete; or those who failed to complete follow-up.

Preoperative staging

Before surgery, tumor staging in patients was assessed using the following tests: chest X-ray, computed tomography (CT), and/or magnetic resonance imaging. When hilar, mediastinal lymph nodes enlarged more than 10 mm were detected, patients underwent more invasive procedures (such as endobronchial ultrasound with guided transbronchial needle aspiration (EBUS/TBNA), endoscopic ultrasound fine-needle aspiration (EUS/FNA), mediastinoscopy, and mediastinotomy). Positron emission tomography (PET-CT) examination was not frequently performed in the initial years of the study period (only 23% of patients from 2008–2010 underwent this examination), but by the end of this study period, the majority of patients had PET-CT done before surgery.

Follow-up

The patients were consulted with a surgeon within the first 3 weeks after surgery. Additionally, they returned for follow-up examinations every 3–5 months for 5 years, at which they had a chest X-ray, CT, or PET-CT when it was required. The pattern of failures was assessed using follow-up imaging studies and data obtained from procedures such as bronchoscopy; endobronchial ultrasound-guided biopsy, endoscopic ultrasound fine-needle aspiration, transthoracic biopsy, mediastinoscopy, and mediastinotomy. Lymph node failure in the hilum or mediastinum was defined as a new or enlarging lymph node that showed excessive metabolism in PET-CT, or its short axis in the CT image was at least 10 mm. This was consistent with disease progression at the patient's subsequent follow-up. When follow-up data were lost from the PLCSG database, patient data were completed from the Polish National Personal Identity Number database.

Statistical analysis and propensity score matching (PSM)

The study patients were classified into one of two groups under 55 years of age and above and then compared with the presence or intensity of specific diagnostic factors. Continuous factors are summarised as the mean and standard deviation of the values of a given variable in both age groups. In addition, the median and range of accepted values are also given. The statistical significance of differences between the two groups was assessed by the Wilcoxon test. For categorical data, each category of variables was summarized as the percentage of occurrence in the patient sub-population, and the statistical significance of differences was assessed by the Chi-square test.

After propensity score matching, the study was conducted for both the original patient and the limited cohort. The matching method uses logistic regression and is adjusted for pathological T quality, stage, resection type, surgical approach, histopathological recognition, occurrence of mediastinoscopy, smoking history and comorbidities. Selected variables are summarised with the Kaplan-Meier estimator of the survival curve and differences are assessed by log-rank test. Every variable's predictive power and effect are estimated in the multivariate Cox model. Their selection was based on the backward selection. All chosen features are also statistically significant predictors in the univariate Cox model. To detect potential multicollinearity between features, the Generalized Variance Inflation factor (GVIF) is computed for every variable (Tables S1,S2). For all of them, GVIFs are less than 2, so we can assume that problem of collinearity does not apply in the multivariate Cox model. The Benjamini and Hochberg correction was applied for multiple testing and pairwise comparisons. Analysis was performed in R using the survival and survminer package,

the GVIFs were calculated using the car package.

Results

Population characteristics

The characteristics of the groups are presented in *Table 1*. The dominant histological type in both groups was adenocarcinoma, the percentage of which differed statistically in both groups: 74.3% in the group of younger women and 63.9% in the group of older women (P<0.001). The percentage of patients with squamous cell carcinoma was 25.7% and 36.1%, respectively (P<0.001). In both groups, the percentage of smokers was similar and amounted to, respectively, 64% and 63.7% (P=0.838). The predominant stage of advancement for the entire group of patients was IB (for younger and older women, 22.8% *vs.* 24.5%, P<0.001). Statistically insignificant differences were observed in grades IA1, IA2, IA3, and IIB (respectively for younger and older women, 2.3% *vs.* 2.3%, 14.7% *vs.* 15.1%, 12.0% *vs.* 13.0%, 17.7% *vs.* 18.5%). Statistically significant differences were found for grades IB, IIA, IIIA, IIIB (for younger and older women, respectively, 22.8% *vs.* 24.5%, 5.3% *vs.* 7.5%, 19.3% *vs.* 15.8%, 5.8% *vs.* 3.2%, P<0.001).

Comorbidities

A higher percentage of comorbidities was found in the group of older women. A significantly higher percentage concerned arterial hypertension (50.7% *vs.* 24.1%, P<0.001), chronic obstructive pulmonary disease (COPD) (20.2% *vs.* 14.6%, P<0.001), coronary artery disease (6.6% *vs.* 1.5%, P<0.001), cardiac infarction (4.0% *vs.* 1.0%, P<0.001), insulin-dependent diabetes (3.6% *vs.* 1.7%, P<0.001), cardiac insufficiency (2.2% *vs.* 0.5, P<0.001), and renal failure (0.9% *vs.* 0.4%, P<0.001). Detailed data on comorbidities are presented in the *Table 2*.

Surgery and postoperative staging

In preoperative invasive diagnostics, the percentage of patients who underwent mediastinoscopy was higher in the group of younger women (5.1% *vs.* 3.3%, P<0.001). Minimally invasive surgical access [video-assisted thoracoscopic surgery (VATS)] was used more often than thoracotomy in the group of older women (25.8% *vs.* 15.7%, P<0.001). The most frequently performed surgery was upper lobectomy (in total 58.5%), less frequently was lower lobectomy (in total 33.7%) and pneumonectomy (in total 7.9%). A similar percentage of younger and older women underwent upper lobectomy (57.8% *vs.* 58.6%, P<0.001), while significant statistical differences were found in the case of lower lobectomy (28.8% *vs.* 34.5%, P<0.001) and pneumonectomy (13.4% *vs.* 7.0%, P<0.001). The most frequently observed pathological (pT) grade in the whole group was 2a (32.6%). There were no significant statistical differences between the two groups of women for pT grades 1a, 1b and 2a (younger and older women, 2.4% *vs.* 2.4%, 17.1% *vs.* 17.3%, 32.6% *vs.* 32.6%, P=0.114, respectively). The percentage of pT1c, pT2b, pT3, and pT4 patients differed statistically between the groups (younger and older women, respectively, 15.2% *vs.* 16.1%, 9.4% *vs.* 10.9%, 15.3% *vs.* 14.3%, 8.0% *vs.* 6.3%, P<0.001). No lymph node metastases were found among the patients in 65.2% of the examined patients. The percentage of pN0 patients in both groups was 59.3% and 66.1%, respectively (P<0.001). On the other hand, pN1 advancement was found in 13.0% and 12.3%, respectively (P<0.001). Statistically significant differences were shown for the pN2 grade. Metastases to mediastinal nodes in the younger and older women group were found in 14.7% and 10.0%, respectively (P<0.001). On the other hand, the percentage of patients with inadequate lymphadenectomy (pNX) was 13.0% and 11.6%, respectively, and was significantly higher in the younger group (P<0.001).

Postoperative morbidity and mortality

Postoperative complications occurred in 27.0% of women undergoing surgery, and they were more common in older than younger women (27.6% *vs.* 23.1%, P<0.001). Detailed data on complications are presented in *Table 3*. Statistically significant differences were found in relation to prolonged air leakage (4.5% *vs.* 7.1%, P<0.001), atrial arrhythmias requiring treatment (1.6% *vs.* 5.2%, P<0.001), respiratory complications (0.6% *vs.* 1.3%, P=0.0378), postoperative psychosis (0.3% *vs.* 0.8%, P=0.0252), pleural empyema without fistula (0.4% *vs.* 0.2%, P=0.031), and late bronchial fistula (0.4% *vs.* 0.2%, P=0.038). Patients' drains were cleared on average after 3.64 days, including faster in younger women (3.37 *vs.* 3.68, P<0.001). The average hospitalization time in the whole group was 12.2 days (median 10 days), and no statistically significant differences were found, as was the number of hospitalization days since surgery (mean 7.78 days, median 7 days). Postoperative 30-day mortality in the whole group was 0.7%, and no

Table 1 Female characteristics including PSM (propensity score matching) analysis

Characteristic	Original cohort				Matched cohort			
	≤55 years (N=1,574)	>55 years (N=9,886)	P value	Overall (N=11,460)	≤55 years (N=1,574)	>55 years (N=1,574)	P value	Overall (N=3,148)
Age, years								
Mean (SD)	51.1 (4.34)	66.0 (6.13)	<0.001	63.9 (7.82)	51.1 (4.34)	64.1 (6.00)	<0.001	57.6 (8.35)
Median [Min, Max]	52.0 [22.0, 55.0]	65.0 [56.0, 87.0]		64.0 [22.0, 87.0]	52.0 [22.0, 55.0]	64.0 [56.0, 86.0]		55.5 [22.0, 86.0]
Clinical stage			<0.001				0.202	
IA	558 (35.5%)	3,991 (40.4%)	<0.001	4,549 (39.7%)	558 (35.5%)	574 (36.5%)		1,132 (36.0%)
IB	545 (34.6%)	3,529 (35.7%)		4,074 (35.5%)	545 (34.6%)	507 (32.2%)		1,052 (33.4%)
IIA	50 (3.2%)	311 (3.1%)		361 (3.2%)	50 (3.2%)	36 (2.3%)		86 (2.7%)
IIB	229 (14.5%)	1,052 (10.6%)		1,281 (11.2%)	229 (14.5%)	264 (16.8%)		493 (15.7%)
IIIA	149 (9.5%)	743 (7.5%)		892 (7.8%)	149 (9.5%)	159 (10.1%)		308 (9.8%)
IIIB	33 (2.1%)	196 (2.0%)		229 (2.0%)	33 (2.1%)	23 (1.5%)		56 (1.8%)
IV	10 (0.6%)	64 (0.6%)		74 (0.6%)	10 (0.6%)	11 (0.7%)		21 (0.7%)
Pathological stage			<0.001				0.998	
IA1	36 (2.3%)	231 (2.3%)		267 (2.3%)	36 (2.3%)	39 (2.5%)		75 (2.4%)
IA2	232 (14.7%)	1,497 (15.1%)		1,729 (15.1%)	232 (14.7%)	241 (15.3%)		473 (15.0%)
IA3	189 (12.0%)	1,288 (13.0%)		1,477 (12.9%)	189 (12.0%)	184 (11.7%)		373 (11.8%)
IB	359 (22.8%)	2,426 (24.5%)		2,785 (24.3%)	359 (22.8%)	366 (23.3%)		725 (23.0%)
IIA	84 (5.3%)	743 (7.5%)		827 (7.2%)	84 (5.3%)	85 (5.4%)		169 (5.4%)
IIB	279 (17.7%)	1,824 (18.5%)		2,103 (18.4%)	279 (17.7%)	278 (17.7%)		557 (17.7%)
IIIA	304 (19.3%)	1,561 (15.8%)		1,865 (16.3%)	304 (19.3%)	290 (18.4%)		594 (18.9%)
IIIB	91 (5.8%)	316 (3.2%)		407 (3.6%)	91 (5.8%)	91 (5.8%)		182 (5.8%)
Smoking	1,008 (64.0%)	6,301 (63.7%)	0.838	7,309 (63.8%)	1,008 (64.0%)	1,006 (63.9%)	0.97	2,014 (64.0%)
pT descriptor			0.114				0.998	
1a	38 (2.4%)	242 (2.4%)		280 (2.4%)	38 (2.4%)	39 (2.5%)		77 (2.4%)
1b	269 (17.1%)	1,710 (17.3%)		1,979 (17.3%)	269 (17.1%)	275 (17.5%)		544 (17.3%)
1c	239 (15.2%)	1,591 (16.1%)		1,830 (16.0%)	239 (15.2%)	229 (14.5%)		468 (14.9%)
2a	513 (32.6%)	3,226 (32.6%)		3,739 (32.6%)	513 (32.6%)	519 (33.0%)		1,032 (32.8%)
2b	148 (9.4%)	1,076 (10.9%)		1,224 (10.7%)	148 (9.4%)	143 (9.1%)		291 (9.2%)
3	241 (15.3%)	1,415 (14.3%)		1,656 (14.5%)	241 (15.3%)	240 (15.2%)		481 (15.3%)
4	126 (8.0%)	626 (6.3%)		752 (6.6%)	126 (8.0%)	129 (8.2%)		255 (8.1%)

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	Original cohort				Matched cohort			
	≤55 years (N=1,574)	>55 years (N=9,886)	P value	Overall (N=11,460)	≤55 years (N=1,574)	>55 years (N=1,574)	P value	Overall (N=3,148)
pN descriptor			<0.001				0.394	
0	933 (59.3%)	6,537 (66.1%)		7,470 (65.2%)	933 (59.3%)	933 (59.3%)		1,866 (59.3%)
1	205 (13.0%)	1,214 (12.3%)		1,419 (12.4%)	205 (13.0%)	199 (12.6%)		404 (12.8%)
2	232 (14.7%)	984 (10.0%)		1,216 (10.6%)	232 (14.7%)	210 (13.3%)		442 (14.0%)
X	204 (13.0%)	1,151 (11.6%)		1,355 (11.8%)	204 (13.0%)	232 (14.7%)		436 (13.9%)
Histopatological recognition			<0.001				0.935	
Adenocarcinoma	1,169 (74.3%)	6,314 (63.9%)		7,483 (65.3%)	1,169 (74.3%)	1,166 (74.1%)		2,335 (74.2%)
Squamous cell carcinoma	405 (25.7%)	3,572 (36.1%)		3,977 (34.7%)	405 (25.7%)	408 (25.9%)		813 (25.8%)
Surgery			<0.001				0.779	
Lobectomy lower	453 (28.8%)	3,407 (34.5%)		3,860 (33.7%)	453 (28.8%)	469 (29.8%)		922 (29.3%)
Lobectomy upper	910 (57.8%)	5,790 (58.6%)		6,700 (58.5%)	910 (57.8%)	891 (56.6%)		1,801 (57.2%)
Pneumonectomy	211 (13.4%)	689 (7.0%)		900 (7.9%)	211 (13.4%)	214 (13.6%)		425 (13.5%)
Surgical approach			<0.001				0.854	
Thoracotomy	1,327 (84.3%)	7,334 (74.2%)		8,661 (75.6%)	1,327 (84.3%)	1,322 (84.0%)		2,649 (84.1%)
VATS	247 (15.7%)	2,552 (25.8%)		2,799 (24.4%)	247 (15.7%)	252 (16.0%)		499 (15.9%)
Mediastinoscopy	80 (5.1%)	331 (3.3%)	<0.001	411 (3.6%)	80 (5.1%)	70 (4.4%)	0.451	150 (4.8%)
Clinic center			0.00756				<0.001	
Academic	794 (50.4%)	5,348 (54.1%)		6,142 (53.6%)	794 (50.4%)	889 (56.5%)		1,683 (53.5%)
Other	780 (49.6%)	4,538 (45.9%)		5,318 (46.4%)	780 (49.6%)	685 (43.5%)		1,465 (46.5%)

SD, standard deviation; pT descriptor, postoperative tumor descriptor; pN descriptor, postoperative nodule descriptor; VATS, video-assisted thoracoscopic surgery.

statistically significant differences were found between the two groups.

Overall survival

Univariate analysis, including PSM

Follow-up in the whole group averaged 3363 days. The univariate analysis showed a higher percentage of 5-year survival in the group of younger women than in older women (0.67 *vs.* 0.64, P=0.00076). Moreover, in the PSM analysis the difference in 5-year survival percentage between groups was greater (0.67 *vs.* 0.59, P<0.0001, respective) (*Figure 2*). Regarding the type of resection, the 5-year survival rates were 0.67 for the upper lobectomy, 0.66 for the lower lobectomy, and 0.44 for the pneumonectomy. The survival depended on the presence of lymph node metastases. In the pN1 and pN2 cases, the survival in the group of younger women was greater (0.74 *vs.* 0.71, respectively, P<0.0001; 0.41 *vs.* 0.34, P<0.0001). In the case of inadequate lymphadenectomy (pNX), the mean survival was 0.61 and was close to pN1 (it was higher in younger women, 0.64 *vs.* 0.58, P<0.0001). Regarding the stage of advancement, statistically significant differences in survival were found for stages IA1, IA2, and IIIA (0.95 *vs.* 0.86, P=0.047; 0.88 *vs.* 0.79, P=0.003; 0.5 *vs.* 0.42, P=0.01). Detailed information concerning groups stage survivals post PSM are found in *Table 4* and Figure S1.

In the PSM analysis for the pT feature, statistically

Table 2 Comorbidities in women including PSM (propensity score matching) analysis

Comorbidities	Original cohort				Matched cohort			
	≤55 years old (N=1,574)	>55 years old (N=9,886)	P value	Overall (N=11,460)	≤55 years old (N=1,574)	>55 years old (N=1,574)	P value	Overall (N=3,148)
Arterial hypertension	379 (24.1%)	5,014 (50.7%)	<0.001	5,393 (47.1%)	379 (24.1%)	369 (23.4%)	0.706	748 (23.8%)
COPD	230 (14.6%)	1,996 (20.2%)	<0.001	2,226 (19.4%)	230 (14.6%)	229 (14.5%)	1	459 (14.6%)
Coronary disease	24 (1.5%)	654 (6.6%)	<0.001	678 (5.9%)	24 (1.5%)	27 (1.7%)	0.778	51 (1.6%)
Cardiac infraction	16 (1.0%)	395 (4.0%)	<0.001	411 (3.6%)	16 (1.0%)	16 (1.0%)	1	32 (1.0%)
Insulin-dependent diabetes	26 (1.7%)	355 (3.6%)	<0.001	381 (3.3%)	26 (1.7%)	19 (1.2%)	0.368	45 (1.4%)
Illability of circulatory system	8 (0.5%)	214 (2.2%)	<0.001	222 (1.9%)	8 (0.5%)	8 (0.5%)	1	16 (0.5%)
Kidney failure	6 (0.4%)	91 (0.9%)	0.0433	97 (0.8%)	6 (0.4%)	6 (0.4%)	1	12 (0.4%)
Nervous system diseases	13 (0.8%)	73 (0.7%)	0.829	86 (0.8%)	13 (0.8%)	8 (0.5%)	0.381	21 (0.7%)

COPD, chronic obstructive pulmonary disease.

Table 3 Complications of lung cancer surgical treatment in women

Type of complication	≤55 years (N=1,574)	>55 years (N=9,886)	P value	Overall (N=11,460)
Total number	364 (23.1%)	2730 (27.6%)	<0.001	3,094 (27.0%)
Intra or postoperative blood transfusion	129 (8.2%)	758 (7.7%)	0.498	887 (7.7%)
Prolonged air leak	71 (4.5%)	705 (7.1%)	<0.001	776 (6.8%)
Atrial arrhythmias requiring treatment	25 (1.6%)	519 (5.2%)	<0.001	544 (4.7%)
Atelectasis requiring bronchoscopy	50 (3.2%)	300 (3.0%)	0.822	350 (3.1%)
Residual air chamber	40 (2.5%)	248 (2.5%)	1	288 (2.5%)
Other respiratory complications	10 (0.6%)	127 (1.3%)	0.0378	137 (1.2%)
Pneumonia	10 (0.6%)	121 (1.2%)	0.0558	131 (1.1%)
Pleural hematoma requires reoperation	13 (0.8%)	75 (0.8%)	0.898	88 (0.8%)
Postoperative psychosis	4 (0.3%)	80 (0.8%)	0.0252	84 (0.7%)
Haemorrhage requiring reoperation	9 (0.6%)	61 (0.6%)	0.968	70 (0.6%)
Other cardiovascular complications	3 (0.2%)	60 (0.6%)	0.0586	63 (0.5%)
Infection of the surgical wound	11 (0.7%)	42 (0.4%)	0.198	53 (0.5%)
Prolonged intubation	6 (0.4%)	44 (0.4%)	0.88	50 (0.4%)
Ventricular arrhythmias requiring treatment	4 (0.3%)	41 (0.4%)	0.466	45 (0.4%)
Prolonged intubation above 48 hours	4 (0.3%)	36 (0.4%)	0.647	40 (0.3%)
Reintubation	6 (0.4%)	32 (0.3%)	0.895	38 (0.3%)
ARDS	2 (0.1%)	30 (0.3%)	0.33	32 (0.3%)
Tracheostomy	2 (0.1%)	29 (0.3%)	0.358	31 (0.3%)
Chylothorax treated with drainage or conservatively	5 (0.3%)	18 (0.2%)	0.416	23 (0.2%)

Table 3 (*continued*)

Table 3 (*continued*)

Type of complication	≤55 years (N=1,574)	>55 years (N=9,886)	P value	Overall (N=11,460)
Pleural empyema without fistula	7 (0.4%)	15 (0.2%)	0.031	22 (0.2%)
Stroke or other CNS complication	3 (0.2%)	18 (0.2%)	1	21 (0.2%)
Pulmonary embolism	2 (0.1%)	17 (0.2%)	0.942	19 (0.2%)
Urinary tract infection	3 (0.2%)	16 (0.2%)	1	19 (0.2%)
Late bronchial fistula (after 6 days)	6 (0.4%)	12 (0.1%)	0.038	18 (0.2%)
Myocardial infarction	0 (0%)	18 (0.2%)	0.177	18 (0.2%)
Early bronchial fistula	1 (0.1%)	14 (0.1%)	0.674	15 (0.1%)
Recurrent laryngeal nerve paralysis	1 (0.1%)	12 (0.1%)	0.818	13 (0.1%)
Deep vein thrombosis	0 (0%)	4 (0.0%)	0.943	4 (0.0%)
Intraoperative death	0 (0%)	1 (0.0%)	1	1 (0.0%)
Day of drain removal				
Mean (SD)	3.37 (2.00)	3.68 (2.45)	<0.001	3.64 (2.40)
Median [Min, Max]	3.00 [0, 18.0]	3.00 [0, 26.0]		3.00 [0, 26.0]
Days of hospitalization				
Mean (SD)	12.5 (13.0)	12.2 (11.9)	0.891	12.2 (12.1)
Median [Min, Max]	10.0 [0, 238]	10.0 [0, 337]		10.0 [0, 337]
Number of days from surgery to discharge				
Mean (SD)	8.09 (10.6)	7.73 (7.30)	0.497	7.78 (7.84)
Median [Min, Max]	7.00 [0, 233]	7.00 [0, 310]		7.00 [0, 310]
Death during the hospitalization after surgery	7 (0.4%)	74 (0.7%)	0.24	81 (0.7%)
Death in the first 24 hours after surgery	7 (0.4%)	74 (0.7%)	0.24	81 (0.7%)

ARDS, acute respiratory distress syndrome; CNS, central nervous system; SD, standard deviation.

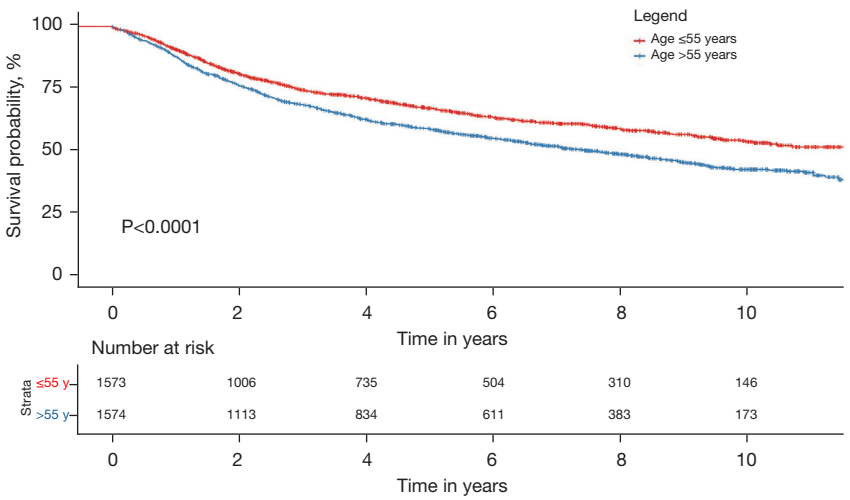

Figure 2 5-year survivals of the patients.

Table 4 The 5-year survival rates in stage subgroups after propensity-score matching

Stage	5-year		P value
	≤55 years, OSR (95% CI)	>55 years, OSR (95% CI)	
IA1	0.95 (0.87, 1)	0.95 (0.87, 1)	0.19
IA2	0.88 (0.83, 0.94)	0.76 (0.71, 0.82)	0.0037
IA3	0.77 (0.7, 0.84)	0.72 (0.66, 0.79)	0.11
IB	0.74 (0.7, 0.8)	0.72 (0.68, 0.77)	0.061
IIA	0.7 (0.59, 0.82)	0.54 (0.44, 0.67)	0.16
IIB	0.64 (0.58, 0.71)	0.53 (0.48, 0.60)	0.018
IIIA	0.5 (0.44, 0.57)	0.32 (0.26, 0.38)	<0.0001
IIIB	0.29 (0.2, 0.42)	0.22 (0.14, 0.34)	0.50

CI, confidence interval; OSR, overall survival rate.

significant differences between the group of younger and older women were found for the pT1b grade (0.84 *vs.* 0.74, P=0.015), pT2a (0.68 *vs.* 0.62, P=0.002) pT3 (0.57 *vs.* 0.42, P=0.005) and pT4 (0.50 *vs.* 0.37, P=0.034). In the case of the type of resections, PSM showed differences between the groups concerning the lower lobectomy (0.72 *vs.* 0.62, P=0.00031) the upper lobectomy (0.7 *vs.* 0.63, P=0.00035) and pneumonectomy (0.48 *vs.* 0.37, P=0.029). Regarding the histological type, statistically significant differences were found for adenocarcinoma (0.69 *vs.* 0.60, P<0.0001) and squamous cell carcinoma (0.64 *vs.* 0.56, P=0.0023). In the PSM analysis, in the case of operative access, younger women showed better survival in the VATS group (0.86 *vs.* 0.72, P=0.0053) and the thoracotomy group (0.65 *vs.* 0.57, P<0.0001).

Multivariable analysis

The statistically significant independent prognostic factors were as follows: insulin-dependent diabetes (HR 1.981; 95% CI: 1.308–3.002), pneumonectomy (HR 1.374; 95% CI: 1.153–1.638), VATS approach (HR 0.695, 95% CI: 0.546–0.883), pN2 (HR 1.444; 95% CI: 1.155–1.806), pNX (HR 1.355; 95% CI: 1.143–1.607), stages IA3 (HR 2.862, 95% CI: 1.168–7.014), IB (HR 2.843, 95%CI 1.171–6.902), IIA (HR 4.052, 95% CI: 1.632–10.059), IIB (HR 4.317, 95% CI: 1.769–10.538), IIIA (HR 5.988 95% CI: 2.444–14.669), IIIB (HR 8.128, 95% CI: 3.248–20.340) and age over 55 years (HR 1.497; 95% CI: 1.335–1.680). All data from the multivariable analysis are presented in *Table 5*.

Table 5 Multivariable proportional hazards (Cox) regression analyses after propensity score matching

Variable	HR	95% CI	P value
COPD	1.126	0.963–1.316	0.13
Insulin-dependent diabetes	1.981	1.308–3.002	0.001
Upper lobectomy	1.036	0.906–1.184	0.602
Pneumonectomy	1.374	1.153–1.638	<0.001
VATS	0.695	0.546–0.883	0.003
pN1	1.146	0.935–1.405	0.188
pN2	1.444	1.155–1.806	0.001
pNX	1.355	1.143–1.607	<0.001
IA2	1.980	0.807–4.862	0.136
IA3	2.862	1.168–7.014	0.022
IB	2.843	1.171–6.902	0.021
IIA	4.052	1.632–10.059	0.003
IIB	4.317	1.769–10.538	0.001
IIIA	5.988	2.444–14.669	<0.001
IIIB	8.128	3.248–20.340	<0.001
Age over 55 years	1.497	1.335–1.680	<0.001

COPD, chronic obstructive pulmonary disease; pN, postoperative nodule; pT, postoperative tumor.

Discussion

Surgical treatment of NSCLC remains the best radical curative method. The differences in surgical outcomes in women with NSCLC according to age are rarely the subject of clinical studies. Here we present the precise clinical analysis of a large group of young women who underwent lung cancer resection. Our results show that lung cancer affects young women on a large scale and differs in many aspects compared to older patients. Our present study fits the current interest in the problem of lung cancer among women and seems to be a valuable supplement to our previous works (16,17).

Most of the publications present material covering both women treated surgically, and women treated with chemotherapy and radiotherapy. In addition, in the part of the studies where there is a distinction between age groups, the entire population of treated patients, including women and men, is analyzed. There are no studies detailing only surgical treatment in different age groups among women.

This rationale behind our retrospective studies targeting risk factors and outcomes among younger and older women undergoing surgery.

The survival studies concerning young people with NSCLC varied. Some of them demonstrated higher survival in younger patients compared with older (18-21). Others rate the survival to be comparable (6,15), whereas others show that the survival rate in younger groups was worse (14,22).

Over the last decade, there has been an increase in the incidence of lung cancer among women, which is one of the most common types of cancer, along with breast cancer and colorectal cancer. In terms of age, there is a downward trend in the age groups 30–39 (–5.31/100,000), 40–49 (–6.27/100,000), and 80–89 (–3.78/100,000) (23). For comparison, there is a decrease in the incidence in all age groups in men, with the greatest decrease in the 40–49 age group. The most important reason for the observed changes is a significant decrease in the percentage of smokers, especially among men, and an increase in the number of NSCLC cases in the group of young, never non-smoking women.

Smoking is known to be one of the most important risk factors for the development of NSCLC. This study found a high proportion of smokers among women in both age groups. In Poland, there is decreasing tendency to smoke among both sexes. However, a higher proportion of smokers is noted among people aged 45–64 years, both females and males (28.3% *vs.* 30.4%). Never smokers are the most numerous in the group aged 20–44 years, with the domination of females (69.4 % *vs.* 51.5% in men) (24). According to the data from the literature, in the younger group, the percentage of smoking patients diagnosed with NSCLC is 75% (5). Only in the study by Galves-Nino *et al.* this percentage was significantly lower and amounted to only 14.4%, which indicates a significant influence of environmental factors on the development of lung cancer (14). In our study, the percentage of smoking in both the younger and older groups was similar to the global data and amounted to 64.0% and 63.7%, respectively, with no statistical difference between the two groups. This prompts a reflection on the necessity of smoking cessation programs targeted at young women.

The histological type of lung cancer belongs to prognostic factors of importance and some sense to predictive ones. There is evidence that adenocarcinoma is the predominant histological type among women. As demonstrated by Fu *et al.*, adenocarcinoma (44.7%) was predominant in women, followed by small cell carcinoma (22.6%) and squamous cell carcinoma (21.4%) (25). In our study, the dominant histological type in both age groups was adenocarcinoma (74.3% and 63.9%, respectively), but in the group of elderly people, a significantly higher percentage of squamous cell carcinoma was found (36.1% *vs.* 25.7%). Similar results were presented by Subramanian *et al.*: the percentage of adenocarcinoma in the group of younger patients was significantly higher than in the group of older people (57.5% *vs.* 45.2%, P<0.0001), whereas squamous cell carcinoma was substantially less prevalent in the younger group compared to the older group (12.5% *vs.* 26.4%; P<0.0001) (26).

A greater percentage of elderly people was treated in academic centers (54.1% *vs.* 50.4%, P=0.007), which can be explained by better preparation for treating patients with multiple comorbidities, where the risk of postoperative complications is higher. It was supported by Arnold *et al.*, who showed that the percentage of comorbidities was significantly higher in the group of older patients than in younger patients (76% *vs.* 58%, P<0.0001) (27). The presence of comorbidities, the percentage of which was higher in the elderly group, significantly influenced the long-term results. These included insulin-dependent diabetes, previous myocardial infarction, coronary artery disease, cardiovascular disorders, renal failure, arterial hypertension, and COPD. It is assumed that in women, the rate of COPD is 5.6% of the total population and is closely related to cigarette smoking (28). There is growing evidence suggesting that females are more susceptible to developing COPD because exposition to the same dose of smoking causes a higher probability of airflow obstruction in women than in men (29). A higher risk of developing NSCLC before age 55 has been shown in women with COPD (HR =1.67) (30).

Analysing TNM classification, clear differences were found in the stage of the disease between both groups. In our study, younger women showed a significantly higher percentage of pN1 and pN2 (13.0% *vs.* 12.3% and 14.7% *vs.* 10.0%, respectively). A higher percentage of young patients than older was diagnosed with stage IIIA and IIIB disease (19.3% *vs.* 15.8% and 5.8% *vs.* 3.2%, P<0.001). Similar observations were presented by Lienert *et al.* (31). In their study, the percentage of younger females in the advanced stage of the disease was significantly higher than in the group of older women and amounted to 73% and 49%, respectively. Similarly, in the work of Arnold *et al.*, in the group of younger people compared to older, the percentage of patients with positive mediastinal nodes was

higher (60% *vs.* 51%, P<0.0001) with stage III (35% *vs.* 31%, P<0.0001) and IV (39% *vs.* 31%, P<0.0001) (27). One of the potential explanations for the above-described fact is the belief that there is a lower risk of cancer among younger people and greater neglect of symptoms. The second probable explanation is the greater biological aggressiveness of the tumor in younger people and the shortening of the time from the onset of symptoms to the development of advanced disease. Concerning preoperative diagnosis, a higher percentage of younger women underwent mediastinoscopy (5.1% *vs.* 3.3%, P<0.001), which is understandable considering the higher percentage of pN1 and pN2 in this group. In the group of younger women, VATS was used less frequently (15.7% *vs.* 25.8%, P<0.001) and pneumonectomy were performed more often (13.4% *vs.* 7.0%, P<0.001). Both facts can be explained by a higher degree of disease advancement, necessitating more extensive resections.

The rate of postoperative complications was higher in the older women than in younger women (27.6% *vs.* 23.1%, P<0.001), which is understandable given the higher percentage of comorbidities. However, this mortality was comparable in both groups (0.4% *vs.* 0.7%, P=0.24). There was also no statistically significant difference in the number of days of hospitalization in both groups. The 5-year survival rates were significantly higher in the group of younger women and amounted to 0.67 and 0.64, respectively (P=0.0007). Taking into account the stage of advancement, the PSM analysis showed significantly better survival in the group of younger women with stage IA2 (0.88 *vs.* 0.76, P=0.0037), IIB (0.64 *vs.* 0.53, P=0.018) and IIIA (0.5 *vs.* 0.32, P<0.0001). No significant differences were found in other stages of advancement. The differences in survival in different histological types were found. Younger women with adenocarcinoma and squamous cell carcinoma after PSM had better survival than the older ones.

Also, the type of resection influenced survival. In the case of all resection type, late results favored younger women.. The better long-term results in the group of younger women despite more advanced disease can be explained by the reducing effect of a smaller number of comorbidities and more aggressive surgical treatment. In the literature, data on differences in survival between younger and older patients are not unequivocal. In the study by Shi *et al.*, 1-, 3-, and 5-year survival in the group of younger people were 68.58%, 36.86% and 27.14%, respectively, and were worse than in the group of older people (75.11%, 41.83% and 30.82%, respectively) (22). Similar conclusions were reached by Galvez-Nino *et al.* (14). On the other hand, Hsu *et al.* did not show statistically significant differences between both age groups (32). At the other end of the spectrum, many studies show a better prognosis in young patients. Lienert *et al.* found that the survival in young women with stage I-IIIA NSCLC treated with surgery was 2,238 days and was significantly better than in the group of older women >45 years, where it was only 609 days (31). In some publications, the results vary depending on the stage of advancement. In the study by Arnold *et al.*, better 5-year survival was found in younger patients in stages I and II and similar in patients in stages III and IV (27). Similarly, in our study, better results in the younger population were obtained in selected stages: IA1, IA2, and IIIA, which proves that the distribution of clinical parameters varies within individual stages (e.g., greater comorbidities in older stage I patients). Multivariable analysis showed that comorbidities, pneumonectomy, thoracotomy, advanced disease, and age over 55 are significant poor prognostic factors in the study group.

Our study has some limitations. One limitation is the study's retrospective nature, which may bias the evaluation of the results. The use of the PSM method does not eliminate all potential errors in interpreting the results. We do not presented the data on the molecular alterations in tumors that could influence the results because our study includes all years from 2007 and recently molecular diagnosis of adenocarcinoma is recommended also in resectable NSCLC. The retrospective character of the study did not allow us to collect information about the socioeconomic status of the patient and their family history of cancers.

Conclusions

The occurrence of NSCLC among young women and the most effective treatment i.e. tumor resection is noteworthy. The women younger than 55 years old are treated surgically in a more advanced stage of the disease. The predominant histological type of NSCLC is adenocarcinoma. The more invasive preoperative procedures were performed in this group of patients. Young women with NSCLC had significant lower percentage of comorbidities, a lower percentage of postoperative complications. However mortality in both groups was comparable (0.4% *vs.* 0.7%, P=0.24) what prompts us to the same careful care for young women as for older. Despite the more advanced stage of the disease, basing on PSM analysis survival was much better in younger than in older women only in selected stages of

NSCLC (IA2, IIB, IIIA) whereas no significant differences were found in other stages of advancement. In Poland the opportunity of treatment is equal despite age. Our results do not show significant differences in terms of access to academic centers in both groups. To improve the survival of young women with NSCLC we should take into account lung cancer in differential diagnosis in early stages, enable faster diagnostic path for young patients and be aware of the need for aggressive diagnostics in younger women knowing that they have more often advanced disease at the time of diagnosis and modernize anti-smoking programs.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-443/rc

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-443/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-443/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The ethics committee of the National Research Institute of Chest Diseases, Warsaw, Poland, approved this study (No. 96/2021). All the patients signed an informed consent form to be included in the database.

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