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Program of early detection of pulmonary neoplasms by the computed tomography — preliminary Szczecin experience

Abstract

Introduction: Lung cancer (LC) remains one of the most serious epidemiological and clinical challenges both in the world and Poland. Results of LC therapy are far from satisfaction. One of the reasons of high LC mortality is its late detection. Currently, few centers in the world conduct LC screening programs based on low-dose spiral computed tomography (CT) of the chest. There have been no such programs in Poland up to date.

Material and methods: The program of LC early detection based on CT for citizens of Szczecin aged 55–65, who smoked at least 20 pack/years, was introduced on May 1st 2008 and was planned for 3 years. There were 3647 subjects examined till December 31st 2008. Algorithm of further action for detected lesions was based on the IELCAP and NELSON trial protocols.

Results: There were 25 malignancies detected, including 21 LC (17 females and 4 males) up to date (70% were in stage I TNM). In contrast — there was only 16.8% stage IA LC detected in the comparable group diagnosed on the symptoms basis. Fifty seven patients were treated surgically, of whom 16 underwent lobectomy or pneumonectomy coupled with radical mediastinal lymphadenectomy. There were 3 wedge resections and 2 segmentectomies performed, too. Perioperative mortality was 0%. There were 32 benign lesions of different clinical importance resected as well (tuberculoma, hamartoma, inflammatory, mycotic and sarcoidal lesions). In our group 1365 lesions were detected in 996 persons — they are followed up in accordance with the IELCAP algorithm.

Conclusions: Early LC detection program initiated in Szczecin resulted in significant increase of stage IA TNM detected patients subsequently treated radically. There was also a large number of small non malignant lesions detected.

Key words: lung cancer, early detection, preliminary results

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Introduction

Primary lung cancer (LC) remains one of the leading epidemiological problems both in Poland and many other countries [1–3]. Approximately 20 000 patients suffer from LC in Poland every year, but surgical resection is performed in 3200 cases only [4, 5]. Such low resection rate (16%) is caused predominantly by late detection of majority of the cases, in the disseminated phase of the disease. Long-term survival rate in LC depends mainly on the stage of the disease at the time of detection and therapy; it reaches 67% 5-years survival in stage I, but only 1–3% in stage IV [4, 6].

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The incidence rate for LC in Poland is the highest in Western Pomerania region among males (109.9/100 000) and close to the highest rate among females (33.5/100 000) immediately following Pomerania region (33.8/100 000) [5]. There are approximately 3200 LC resected in Poland annually of which 237 are performed in Thoracic Surgery Clinic of the Pomeranian Medical University in Szczecin in 2007. It results in the highest resection rate in Poland (237/1201 diagnosed LC) of 23.2% [4].

The LC screening trials based on conventional radiography or sputum cytology was proved as ineffective in few countries. Currently, there are many ongoing trials using low-dose computed tomography (CT) [7–14]. They are well advanced particularly in Japan. It results in the high rate of the patients treated surgically in stage I (up to 80%) in some of the Japanese centers [7, 13].

There have been no such trials in Poland up to date. City of Szczecin has decided to initiate such program based on the close cooperation of pulmonologists, radiologists, general practitioners (family doctors), thoracic surgeons and Mayors Office with intention to increase the number of early LC detections.

Material and methods

The Szczecin program was based on "International Early Lung Cancer Action Program" experience. Limited financial resources allowed the low-dose CT of the chest to be offered for appr. 4500 citizens only. After careful analysis of the Szczecin population, the program was targeted at citizens with an increased risk of LC (both males and females of age 55–65, current smokers or with Cl history of at least 20 pack/years). This range of age includes appr. 38 000 Szczecin citizens, so the expected accrual rate was 15%. The scheme of the program was designed (Fig. 1). All CT centers existing in town were connected via intranet to send the images online to the coordinating center, localized in the Regional Hospital for Lung Diseases in Szczecin Zdunowo. Regional Consultant for Radiology prepared guidelines for the low dose CT without any contrast. Patients were enrolled to the program by general practitioners (family doctors). The program has started on May 1st 2008. There were 400 people planned to enter the study each month. Due to the expected large number of small solitary pulmonary nodules of undefined, but probably relatively low clinical importance detected by CT, the algorithm indicating further steps was released on a basis of I-ELCAP and Nelson trial protocols [10, 13, 14]:

1. Nodules < 5 mm asymptomatic; CT 12 months later. If multiple — earlier pulmonologist consultation required.
2. Nodules 5–15 mm; asymptomatic — antibiotics for 14 days, CT 3 months later to assess the changes in shape or volume. If the growth observed — further pulmonologist consultation and diagnostics required, if regression or stable state — next CT 12 months later.
3. Nodules > 15 mm both asymptomatic and symptomatic — immediate pulmonologist consultation and diagnostics.
4. In the following years:
   a. every nodule with symptoms of growth — immediate pulmonary diagnostics;
   b. stable nodule — see point 1 and 2 (repeated antibiothics may be skipped).

Interim analysis of the program every 6 months was planned.

Results

There were 3647 Szczecin citizens (2150 females and 1497 males) examined between May 1st 2008 and December 31st 2008. One hundred sixty five nodules were detected in 966 people (Table 1) who were followed in accordance with the approved algorithm. Two hundred sixty five cases were hospitalized to perform profound invasive diagnostics. Lung cancer was suspected or confirmed (predominantly by thoracic fine needle aspiration biopsy) in 57 patients who were qualified subsequently for surgery. There were 25 malignancies including 21 primary LC (17 females, 4 males) detected in this group.

Lobectomy with systematic mediastinal lymph nodes dissection was performed in 16 cases (right upper lobe — 6, right lower lobe — 4, middle lobe — 2, left upper lobe — 2, left lower lobe — 2). Preoperative confirmation of LC in this subgroup was difficult due to small size of the resected lesions. Seventy percent of the excised LC were in the stage I (80% of stage I was finally staged IA — it accounted for 62% of all resected lesions). In comparison, the IA rate in the matched group detected on a basis of symptoms and treated surgically in 2005 was 16.8%. All patients treated radically underwent systematic mediastinal lymphadenectomy. There were no early postoperative deaths. Three metastatic tumors were resected as well (2 — kidneys, 1 — large bowel) and 1 pleural mesothelioma was diagnosed, too. There were 32 resections due to benign lesions (4 tuberculomas, 5 hamartomas, 5 inflammatory lesions, 5 lesions typical for silicosis, 4 intrapulmonary lymph nodes, 2 lipo-

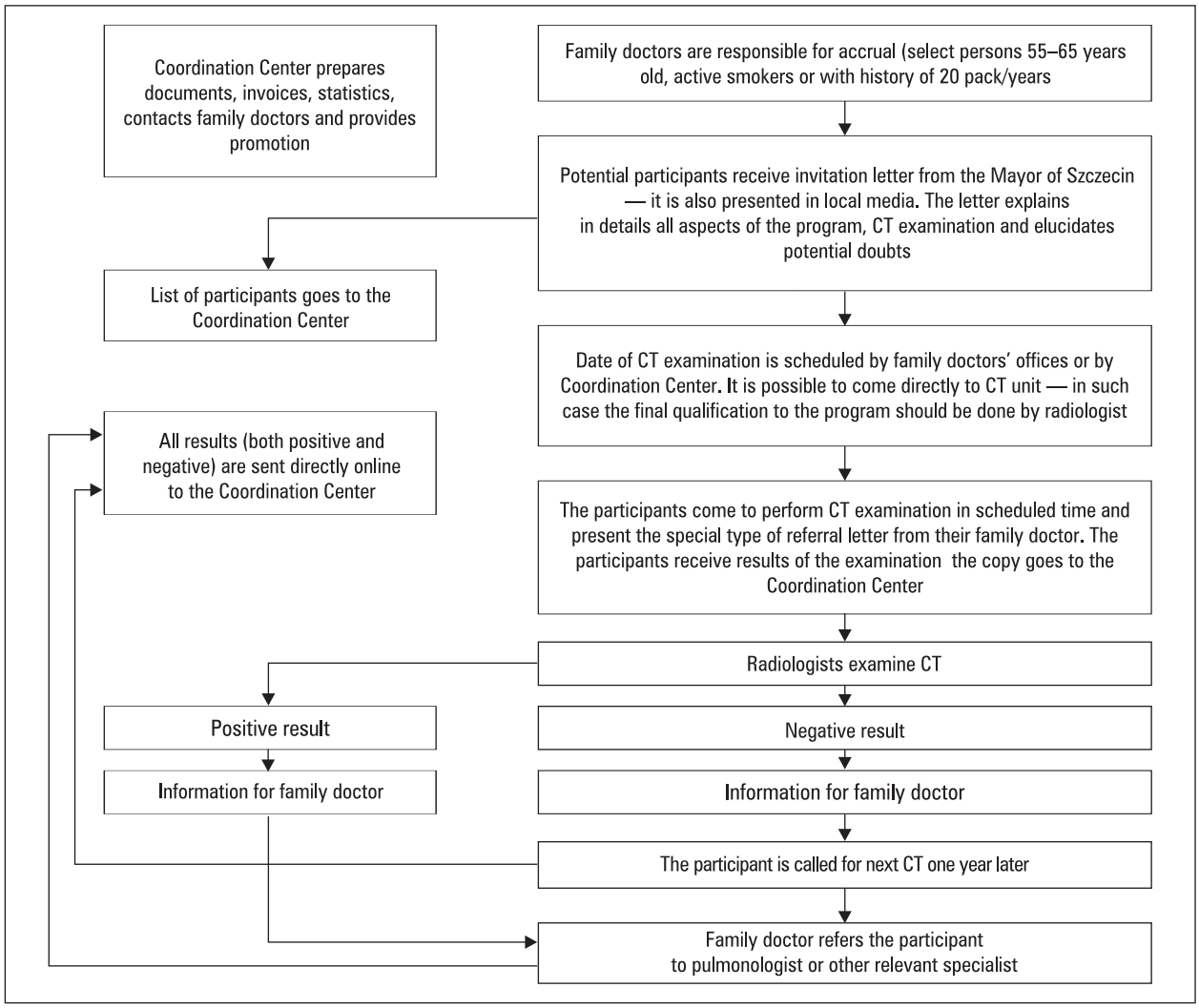

Figure 1. Functional scheme of the early lung cancer detection program in Szczecin

Table 1. Size of the detected lesions

Type of detected lesion	No
< 5 mm asymptomatic	440
< 5 mm multiple asymptomatic	314
5–15 mm asymptomatic	346
5–15 mm multiple asymptomatic	152
> 15 mm asymptomatic	100
> 15 mm symptomatic	13
All	1365

mas, 2 adenomatous tumors, 1 aspergilloma, 1 fibrotic lesion, 1 coelomic cyst, 1 benign rib tumor, 1 paraganglioma). The LC/benign lesions resection rate observed in the program (21/36 — 58% benign lesions) seems to be relatively low, but nevertheless it is much higher than for the whole population treated by thoracic surgery in Poland (3245/ /20 390 — 15% of LC resections in 2007) [4]. Statistical analysis of this initial period of the program indicates that 1 case of LC was detected every 173 CT performed. It means that the cost of one LC detection was appr. 51 900 PLN (300 PLN per CT). It was significantly lower than in other screening programs [15, 16]. We should note that the number LC cases may increase because more than 900 patients are currently observed or diagnosed in accordance with approved algorithm. One can speculate that at least some of them, sooner or later, will be diagnosed with LC. It should diminish the costs of one LC detection. However, all other potential and relevant procedural expenses (hospitalizations, invasive diagnostics or treatment) may increase the final cost.

In the year 2005, there were only 6 cases staged IA treated surgically in the age-matched population from all over the region. Currently,

15 cases staged IA from were detected and successfully resected in the period of 8 months in Szczecin (150% increase while the total number of LC resections in 2005 and 2008 in our center remains similar).

It seems too early to assess specificity and sensitivity of the program because many of the detected lesions are being evaluated. This assessment will be performed at the end of the program.

Discussion

The program of early LC detection, initiated in Szczecin in May 2008, resulted in the detection of 21 primary LC after 8 months of its activity. 70% of the lesions were stage I and 11/21 of them were smaller than 15mm. One should note the unexpected female/male ratio of detected LC (17 females/4 males). It may be explained by higher accrual of females, however, the accrual female/male ratio (59% females, 41% males) does not justify such difference, particularly in comparison with the incidence rate of LC in Western Pomerania (33.5/100 000 for females and 100.9/100 000 for males). This phenomenon requires further studies and analysis. The same pattern of higher predominance of the right side lobectomies in females (12/4) can be detected during an early phase of the program. All LC patients treated surgically were asymptomatic, and we could speculate that they would probably be detected in much later, symptomatic stage without the CT performed due to the program of early LC detection. The LC detection rate in this program is higher than in the comparable published trials (Table 2) [15, 17, 18]. Although the detection rate may decrease in the later phase of the program, it will remain higher than in other mass population studies due to the higher incidence of LC versus other malignancies.

One can speculate that the increased number of early detected and resected LC will result in overall increase of 5-years survival rate [6]. We would be able to conclude in this regard not earlier than in 2012–2013.

There were lots of doubts regarding influence of LC screening programs on the overall survival rate up to 2004 [3]. Despite good results of the Japanese trial by Nijgata [8], radiography remains controversial due to its lower than CT diagnostic value. The situation started to change in 2006 after publications presenting results of the NLST (National Lung Screening Trial), led by I-ELCAP, which accrued more than 30 000 persons [19]. 93% of the patients detected and resected in the stage I of LC survived more than 5 years, while 8 persons, who refused surgery, all died within the 5 years period. There are a few screenings being conducted in USA, Japan, Denmark, Holland and Italy including more than 50 000 persons [7–13]. It is expected to draw more precise conclusions regarding cost effectiveness and survival benefits on a basis of such large group. However, there are no signs of influence of screening programs on lower LC mortality up to date. Some authors explain it by high incidence of LC compared with relatively low numbered cases accrued to the screening programs (usually much less than 1% of all LC cases diagnosed in the country). It significantly weakens the statistical power of screening and makes the conclusions regarding lowered LC mortality difficult, if not impossible to prove. We can only speculate that the rule based on better prognosis for LC diagnosed and treated in earlier stages is universal and applicable for mass screening programs [6]. There are preliminary reports based on Bayesian analysis indicating that there is a possibility to lower population mortality more than 15–23% by regular, repeated large scale screening conducted for at least several years [12]. On the other side, there are no doubts about the ability of LC screening to detect early stages of the disease [1, 7, 8, 19]. Some experts indicate the potential bias of increased risk of malignancy development due to repeated exposure to CT, but this seems not justified. Modern CT devices and low-dose protocols of screening examinations, theoretically, might incre-

Table 2. Results of other lung cancer screening programs based on low dose computed tomography

Author	n	Lung cancer detection rate per 1000 examinations	Resected nodules (%)	Average diameter [mm]	Lesions visible on conventional radiograms (%)	Stage I lung cancer (%)
Ohmatsu	9452	3.7	–	15	26	82
Sone	5483	4.8	86	17	21	84
Yasuda	2201	3.6	–	20	38	100
Kaneko	1369	4.3	95	16	27	93
Henschke	1000	2.8	96	10	25	85
Szczecin	3647	5.7	–	12	20	70

ase the risk of malignancy for 0.65%, while tobacco smoking alone increases it for 17% [20]. Also, there are reports indicating quitting smoking as the beneficial psychosocial side effect of screening programs — this positive factor balances more than adequately potential small negative effect of radiation dose received during CT scanning [21, 22].

Massive LC screening programs result in the detection of many small lesions, usually of low clinical importance, which require pulmonary diagnostics and generate additional costs. The differentiation between benign and malignant lesions is not easy despite algorithms suggesting the nature of the tumor based on their size, density, margins, volume doubling time etc. [18, 23]. One should be aware that some benign lesions are also clinically significant such as: tuberculosis, aspergillosis, fibrotic lesions including asbestosis, lymph nodes enlargements including lymphomas or aortic aneurysms. Further follow up of small lesions detected by initial CT will probably reveal malignant nature of at least some of them [10, 24].

Cost effectiveness of screening programs performed abroad is not precisely assessed due to differences in methodology of calculation ranging from CT examination costs only to wide inclusion of all related costs [15, 16]. There have been no such calculations made in Poland so far. It definitely requires further explanation preferably done by the Polish specialists in medicine economics.

Preliminary results of our pioneer program of early lung cancer detection by low dose CT allow us to indicate first positive effects: very good reception of the program by Szczecin community resulting in accrual higher than expected (more than 400 people per month). There are more early LC detected in stage I in comparison to the previous comparable periods and examined population. All LC patients detected by the program were treated by lobectomy with mediastinal lymphadenectomy. This type of treatment is considered the "gold standard" for LC. Early postoperative mortality was 0%. Due to the early stage of the disease there has been no need to perform pneumonectomy, which affects respiration and circulation significantly [8].

A few other Polish cities have planned to initiate similar programs pretty soon. Polish Group of Lung Cancer plans to cover larger population by implementing the national early LC detection project.

Conclusions

The initiation and conduction of the early LC detection program is feasible despite limited financial resources. It requires close cooperation of many specialists engaged in the early detection of LC initiative. Our program increased the number of stage I LC patient referrals for radical surgical treatment. The influence of the program on overall LC mortality and long term survival rate might be assessed after much longer observation, in the future. The program detects many small lesions potentially not important clinically, but their differential diagnostics engage more resources of pulmonology, radiology, thoracic surgery and family doctors, than it is currently available.

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