InaJCC The Indonesian Journal of Cancer Control

Review Article

Lung cancer and the new paradigm: A personal journey with a chronic disease

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p-ISSN 2797-4189
e-ISSN 2797-457X
DOI : 10.52830/inajcc.v1i2.51

Received: August 28, 2021
Accepted: October 23, 2021

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Abstract

Cancer is a global health problem affecting all countries. Lung cancer is the most complicated cancer due to the involvement of various genes and intracellular processes in its carcinogenesis. It is the third most common cancer found in Indonesia after breast cancer and cervical cancer, and its impact on the patient, family, and national health burden could not be underestimated. Significant advancements have been achieved in the diagnostic procedures and treatment modalities of lung cancer. However, solving the lung cancer problem in Indonesia require a holistic solution, and good collaboration between specialists as a multidisciplinary team is crucial. The new paradigm of lung cancer views this disease as a chronic disease and offer more optimistic target of treatment to control the disease and to have good quality of life. Objective measurement of premature death can be used as a parameter to assess the achievement of lung cancer program nationally. Strict control of risk factors and early screening for high-risk groups are essential for lowering premature deaths. For the future, stem cell therapy is a promising modality in the treatment of lung cancer. Studies are currently planned for the discovery of lung cancer stem cell and the therapy that target it.

Keywords: *lung cancer, paradigm, chronic disease*

Abstrak

Kanker merupakan masalah kesehatan global yang memengaruhi semua negara. Kanker paru-paru merupakan kanker yang paling rumit karena adanya keterlibatan berbagai gen dan proses intraseluler dalam karsinogenesisnya. Kanker paru adalah kanker tersering ketiga di Indonesia setelah kanker payudara dan kanker serviks, dan dampaknya terhadap pasien, keluarga, serta beban kesehatan nasional tidak bisa diremehkan. Berbagai kemajuan telah dicapai dalam prosedur diagnostik dan modalitas terapi, namun untuk menyelesaikan masalah kanker paru-paru di Indonesia dibutuhkan solusi yang holistik. Kolaborasi yang baik antar spesialis sebagai tim multidisiplin juga penting. Paradigma baru kanker paru-paru memandang penyakit ini sebagai penyakit kronis, dan memberikan target tata laksana yang lebih optimistis untuk mengendalikan penyakit dan memiliki kualitas hidup yang baik. Pengukuran objektif kematian prematur dapat digunakan sebagai parameter dalam menilai capaian program nasional pengendalian kanker paru-paru. Pengendalian yang ketat terhadap faktor risiko serta skrining dini pada kelompok berisiko tinggi berperan penting dalam mengurangi angka kematian prematur. Untuk masa depan, terapi sel punca merupakan modalitas yang menjanjikan untuk tata laksana kanker paru-paru. Berbagai penelitian sedang direncanakan untuk menemukan sel punca kanker paru-paru dan terapi yang menargetkannya.

Kata kunci: kanker paru, paradigma, penyakit kronis

This article is translated from the author's professorial inauguration speech on March the 13th 2021 at FMUI Salemba campus, Jakarta

Background

A simple and concise title, but the word “paradigm” has quite a broad and deep meaning. Paradigm is a set of assumption, concept, values and practice which are applied in viewing the reality to understand the problem of lung cancer. Through this speech, I attempt to get us back to the basic and principles of lung cancer treatment, by altering the lung cancer stigma which has always been referred as the cancer with the worst prognosis and the most common cause of death from cancer. That stigma leads to the patients and their doctor to lose hope, while inaccurate information and miscommunication encourage most patients to seek alternative treatments and becoming the victim of irresponsible nonmedical treatments.

Cancer will always be a global health problem affecting all countries irrespective of the developed, developing, or underdeveloped country criteria. Cancer is not exclusively a problem of low-income or middle-income countries, but also high-income countries. The differences are only in the prevalence and prognosis of each cancer cell type, which are highly associated with the demographic characteristics, life style and health care system of a country. Cancer is a disease caused by the uncontrolled growth of abnormal cells inside the body which spread and damage body tissues. Cancer cell growth is affected by many factors and prolonged time is needed to finally be able to diagnose it clinically. Generally, cancer is divided into solid tumor and hematologic malignancy. Solid tumor is a cancer that originate or differentiate from the epithelial tissue of human organs. Although considered the same cancer cell type, cancer in different body organs may show diversity in genetical and molecular biology levels.

Science has developed rapidly including the knowledge about malignancy and cancer, especially after the Polymerase Chain Reaction (PCR) technique was founded by Kary Banks Mullis. Since its first application approximately 37 years ago, PCR technology has revolutionized several molecular biology aspects in the world. Due to that phenomenal invention in 1993, the inventor of PCR was awarded the Nobel prize in Chemistry. That method has slowly unraveled the mystery of carcinogenesis, including the problem of cancer cell’s unresponsiveness towards anti cancer therapy. Genetic and molecular diversities will affect the different treatment and prognosis of each cancer type. For example, breast cancer adeno-carcinoma, servical cancer adenocarcinoma or lung adenocarcinoma have different method of determining the progress of the disease when it is found, called staging system. These types and molecular differences also enable the therapeutic modality choice that is expected to be the best for the patients. These are what drive the development of targeted therapy and changes the method of cancer treatment using individual approach or personal medicine for each cancer patient.

The Problem of Lung Cancer

Lung cancer is the most complicated cancer due to the involvement of various genes (multi-genes) and intracellular processes (multi-processes) in its carcino-genesis. This is understandable as the respiratory tract and lung are connected and exposed directly to the atmosphere, and we normally bring the air with all its contents into the respiratory tract and lung for respiration by inhaling and exhaling 16-20 times every minute. The anatomical position of the respiratory system makes lung cancer very difficult to detect during its early stage.

I remember that in 2004 my mentor, Prof. dr. Anwar Jusuf, SpP(K), expressed his many hopes for the development of lung cancer treatment in his professorial inauguration speech. It has been 16 years since then, and part of that challenge has been answered along with the development of knowledge regarding cancer. Nowadays, the new generation of cancer therapies used in therapy guidelines or chemotherapy regimens offers more options, with easier administration, less side effect, and better therapeutical response.

However, the progress of knowledge that influence clinical implication makes me realize that the knowledge about cancer, especially lung cancer, is like a never-ending story. The more we discover abnormalities, the more we are forced to seek the answer on what affect it. Therefore, I was relieved when Prof. Anwar, as the Head of the Department of Pulmonology and Respiratory Medicine FMUI back then, once asked me, a staff in the Oncology Division since 2000, to also explore other lung diseases. I declined because I was going to focus in thoracic malignancies. (Prof. Anwar maybe forgot, but I declined because we discussed it on the way to an event at Dharmais Cancer Hospital for a Lung Cancer study group activity every Wednesday morning in my tiny red Ceria car).

The year 2018 was an exceptional year for us who were involved in cancer problem in Indonesia. When Prof. Dr. dr. Nila Djuwita Anfasa Moeloek, SpM(K), an oncologist, was appointed as the Minister of Health, cancer problem was given special attention by the formation of the National Cancer Control Committee (NCCC) / *Komite Penanggulangan Kanker Nasional (KPKN)*, which was first chaired by Prof. Dr. dr. Soehartati A. Gondhowiardjo, Sp.Rad(K),Onk.Rad. We certainly agreed and realized that to effectively unravel the problem and determine the priority scale for cancer control, good and accurate data were needed. We, the members of NCCC, together with the Ministry of Health and Dharmais Cancer Hospital, developed and renewed the national cancer registry system, which encompasses many regions according the the international standard. This task was led by dr. Evlina Suzanna, SpPA. This effort has paid off, as we now have an estimation of cancer data profile in Indonesia which can be accessed as it was listed in the global registry written and published by the World Health Organization (WHO) in Globocan 2018, and is updated every year.[1]

Cancer problem in Indonesia is pictured (Figure 1) in this 2020 statistical data published in early 2021.[2] Lung cancer is the third most common cancer found in Indonesia after breast cancer and cervical cancer. According to gender, lung cancer is the most common cancer in males, followed by colorectal cancer and liver cancer. In females, lung cancer is not included in the five most common cancer. This is in contrast with the global data of 19.3 million new cases, the top three cancer types are female breast cancer (11.7%), lung cancer (11.4%) and liver cancer (11.0%). Similar to Indonesia, lung cancer is the most common cancer found in males globally, followed by prostate cancer and colorectal cancer. Another difference is that lung cancer in females is the second most common cancer globally following breast cancer.[3,4]

Summary statistic 2020

	Males	Females	Both sexes
Population	137 717 861	135 805 760	273 523 621
Number of new cancer cases	183 368	213 546	396 914
Age-standardized incidence rate (World)	138.9	145.4	141.1
Risk of developing cancer before the age of 75 years (%)	15.0	14.9	14.9
Number of cancer deaths	124 698	109 813	234 511
Age-standardized mortality rate (World)	96.3	75.9	85.1
Risk of dying from cancer before the age of 75 years (%)	10.5	8.3	9.4
5-year prevalent cases	389 640	556 448	946 088
Top 5 most frequent cancers excluding non-melanoma skin cancer (ranked by cases)	Lung Colorectum Liver Nasopharynx Prostate	Breast Cervix uteri Ovary Colorectum Thyroid	Breast Cervix uteri Lung Colorectum Liver

Figure 1. Cancer statistics in Indonesia 2020.[2]

Those statistical data are not merely numbers. Based on those estimated figures, we can learn so much regarding the factors that affect those differences. Those data will provide us academics, with our responsibility as researchers, and the government as regulators with the necessary tools to establish priority scale which enables more effective lung cancer control program and well-targeted health service.

Are the data published by the WHO represent the real practical condition? The Oncology Division, Department of Pulmonology and Respiratory Medicine FMUI, located

at Persahabatan National Respiratory Referral Hospital (RSUP Persahabatan), has the annual report. The lung cancer characteristics data in 2017-2019 (Table 1) represents the national characteristic, considering the abundance of referral cases from all regions of Indonesia.[5] Lung cancer is more often found in males, in reproductive age (40-65 years old) and the majority of cases were discovered on its late stage.[5]

Table 1. Characteristics of lung cancer patients at RSUP Persahabatan, Jakarta, year 2017-2019

Characteristic	Total	(%)
Gender		
• Male	1,513	66.89
• Female	749	33.11
Age		
• Median	60	
• Rate	21-98	
Cancer cell type		
• Adenocarcinoma	1,455	64.32
• Squamous cell carcinoma	596	26.35
• Others	211	9.33
Stages of disease		
• Early stages (stage 1 and 2)	31	4.64
• Late stages (stage 3 and 4)	2,157	95.36

However, several issues were not revealed by these statistics. Lung cancer is not a communicable disease, but causes disruption or social impacts that could not be underestimated. The fact that the morbidity and mortality rates of lung cancer are still high surely creates problems not only for the family and social environment. It must be understood that cancer treatments are generally expensive, thus causing financial problem for the family and contributing to the national health burden. The National Social Security on Health or Badan Penyelenggara Jaminan Sosial (BPJS) Kesehatan currently cover at least eight catastrophic diseases, such as heart disease, cancer, stroke, kidney failure, thalassaemia, haemophilia, cirrhosis hepatitis and leukaemia. The three most costly diseases for BPJS Kesehatan amongst those eight are heart disease, cancer and stroke.[6]

We should be grateful that Indonesia is one of the countries, maybe the only one, that have a National Health Insurance / Jaminan Kesehatan Nasional (JKN) with its BPJS Kesehatan program which insure the cost of lung cancer management, starting from diagnosis to treatment. The BPJS system supports many lung cancer patients, however this service platform is not yet perfect as it oftenly causes late payments due to the convoluted nature of the system. Therefore, BPJS needs to listen to suggestions from us clinicians and patients as their consumers, so that lung cancer treatment will be more effective and efficient with the aim of providing the optimal management.

Until today, we at RSUP Persahabatan and other academic hospitals in Indonesia that have similar department can say that molecular-level diagnostic procedure is a challenge for us to provide individual therapy. The loss of the country's foreign exchange to other countries associated with health service in Indonesia is a concern for us. This problem is not as simple as blaming the clinicians, because clinicians only play a small part in our whole health service system. Therefore, once again we appeal to the new BPJS board of directors to listen to our suggestions for a better system. Let us leave the old expression that "using BPJS is exhausting, complicated, and annoying" as a past hoax, and let us help lung cancer patients that could not afford to pay more at private hospital only for convenience. The government, in this case BPJS, must change because all the Indonesian people are constitutionally obligated to participate in this health insurance system.

Without putting unnecessary burden to the government, we have implemented quality and equality improvement in synergical cooperation or collaboration with our peers in other specialties involved in lung cancer management. In 1992, I started my residency and witnessed my teachers, Prof. dr Anwar Jusuf, Sp.P(K), Prof. dr. Ismid D. Busro, Sp.BTKV(K), Prof. dr. Nirwan Arief, Sp.P(K), dr. Sutjahjo Endardjo, Sp.PA(K) and dr. Suginem Mujiantoro, Sp.Rad.Onk, as the multidisciplinary team (MDT) routinely held discussion in the lung cancer conference at RSUP Persahabatan every Thursday noon. Then in 2004, the seniors instructed me, Dr. dr Ahmad Hudoyo, Sp.P(K), dr Agung Wibawanto, Sp.BTKV(K), Dr. dr Aziza G. Icksan, Sp.Rad(K), dr Juniarti Sp.Rad.Onk, dr. Heriawaty Hidajat, Sp.PA and many other next generation clinicians to form a study group (Indonesian Association for the Study on Lung Cancer or InSCLC) that specifically discuss about the Indonesian version of lung cancer management. In 2005, this study group published a recommendation and it became the first national lung cancer management guideline, which is updated every 5 years. The InSCLC has developed significantly with the active involvement of Pumonary and Respiratory Medicine specialists, Anatomical Pathology specialists, Radiotherapy specialists, Radiology specialists and other specialists, not only at RSUP Persahabatan, but also in the national scope

by actively working with those who are involved in lung cancer management in Pulmonology and Respiratory Medicine academic centre hospitals. Good collaboration between specialists as a multidisciplinary team (MDT) is crucial for lung cancer management. We have also widened our focus to other thoracic malignancies such as mediastinal tumor, lung metastases, chest wall tumor and mesothelioma. In 2019, InSCLC changed its name to Indonesian Association for the Study of Thoracic Oncology (IASTO) to answer and provide solutions according to the development of knowledge and experience in the field.

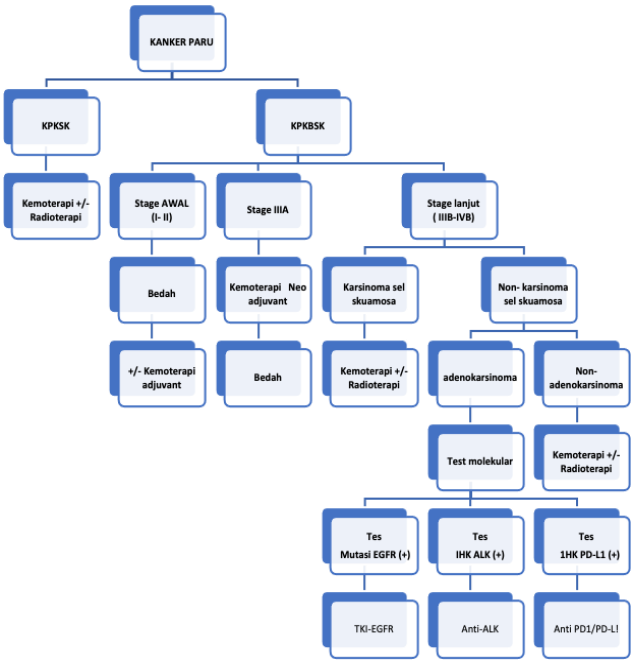

Figure 2. Diagram of lung cancer management according to cell type and molecular examination.[12]

With the advancement of our ability in diagnostic procedural techniques, as well as undergoing numerous researches and participating in clinical trials on new drugs for lung cancer, we are now entering the targeted therapy era. Studies in gene mutation (EGFR) and gene products (ALK, PD-L1) needed for targeted therapy have been done, albeit with limited research fund.[7-9] Our contribution on clinical trials of new drugs can serve as proofs that the management that we provide to our patients is on the same level with other countries.[10-12] Unfortunately, the opportunity to be involved in clinical trials on new cancer drugs are now slimmer due to the government regulation of material transfer agreement (MTA). It is not an exaggeration to hope for a joint decree involving three ministries (Health, Education and Research) to open up more opportunities to be involved in multicenter clinical trials, not only to provide solution for health problems, but also to produce more reputable international publications representing our beloved Universitas Indonesia. Multicenter studies may also provide opportunities for patients to get access to drugs currently in trials. We are quite envious with the perks obtained by overseas researchers and patients due to the easiness of procedure for clinical trial.

I am grateful to be a part of this revolution in lung cancer knowledge which influence lung cancer management rapidly. The year 1992-1994 are my early years in studying, understanding and performing therapies. We were quite proficient in performing diagnostic procedures during our second semester. Due to the presence of Prof. dr. Nirwan Arief, Sp.P(K) and Prof. dr. Menaldi Rasmin, Sp.P(K), and also the dynamic collaboration with our peers in Radiology and Thoracic Surgery, the time limit of 2 weeks for diagnosis was usually achieved. Chemotherapy administration is a required competency for Pulmonology residents, not simply deciding the regimen type, but also preparing the drug and evaluating the result. However, there were only few cancer patients undergoing therapy, due to financial problem and the lack of health insurance system for lung cancer patients, as well as the bad stigma of lung cancer.

In the year 1994-1999, I started a new journey in cancer field, one which was made possible by Prof. dr. Faisal Yunus, PhD, Sp.P(K) and Prof. Michio Yamakido, MD, PhD. Armed with scholarship from Monbusho, Japan, I enlisted in a postdoctorate program in the Second Department of Internal Medicine, School of Medicine Hiroshima University, Japan. All praise to God, I was at “the right time, the right person and the right place”. As a researcher, it was a great experience because I did not need to consider the fund limit for materials and facilities. The number of lung cancer patients also kept increasing which provided me with sufficient specimens for research materials. The year 2000 is the year when I started to work at RSUP Persahabatan, as well as the increase of lung cancer patients visiting the hospital and the implementation of ASKES insurance system for government employees, resulting in more lung cancer cases receiving better treatment. The incorporation of new generation anti-cancer therapies in the guidelines or chemotherapy regimens for lung cancer enabled us to choose the best regimen for a cancer patient. The protocol for chemotherapy administration, the overall mild side effects and the

better survival rate of lung cancer patients receiving treatments all showed promising results.

Around the middle of the year 2005, lung cancer management has entered the era of targeted therapy. We were involved in a multi center clinical trial for an orally-administered lung cancer therapy. Since returning from Japan, we adjusted with the available facilities and fund, and we kept doing molecular epidemiology studies to assess the characteristics of lung cancer patients in Indonesia. By the end of 2020, the types of cancer therapy have increased with more specific indications. If in the end of the nineties we dwelled on whether a new lung cancer patient may survive for one year, nowadays we can easily discuss the variety of therapeutic modalities for lung cancer patients, especially in the last five years when BPJS Kesehatan enabled the access to several types of targeted therapy.

The New Paradigm of Lung Cancer

If the beginning of my speech was more of a reflection and complaint, then for the next part I would like to propose an idea for thought on what should be done. In my opinion, solving the lung cancer problem in Indonesia require a holistic solution. Hence, I remember an old phrase which in its native language reads “baraja ka nan manang, baguru ka nan pandai”. It means, we do not need to be reluctant to learn from others who are successful. Therefore, we can adopt the good things and adjust the bad ones for a better result suitable with our condition.

We do not need to use the gloomy vibe of whether lung cancer can be cured or not anymore. With the new paradigm, we can offer more enlightening options, and the target of our treatment is to control the lung cancer. Palliative approach in lung cancer patient management will provide optimistic targets, for example, for elderly patients who wish to have grandchildren, which God willing can be achieved by helping their children to get married. Some patients may want to witness their children graduating as specialists, or having the opportunity to perform the Hajj pilgrimage, or any other optimistic targets. We should certainly avoid giving false promise or unrealistic target, such as completely eliminating the cancer without any surgery. The target for terminal stage lung cancer patients is to control the disease and to have good quality of life.

It is time for us to apply other parameters to assess the achievement of lung cancer program nationally. One of which is to use premature death on lung cancer that can be measured objectively. Lung cancer premature death is death that occurred before the average death rate of a certain population. Developed countries set the age limit of 75 years as the threshold to measure premature death and estimating the risk of lung cancer patient before 75 years. Indonesia can use the age limit of 65 or 70 years, considering the data by Statistics Indonesia (Badan Pusat Statistik / BPS) in 2020 that the life expectancy at birth of Indonesian people is 71.47 years. In Australia, lung cancer was the second most common cause of premature death in 2012, with three of five (59%) premature deaths caused by lung cancer occurred in males. However, these figures showed significant drop of 45% in the last three decades from 1982-2012.[13]

Figure 3. Premature deaths due to lung cancer in Austrialia, according to gender and age group in 2012.[13]

Learning from other countries that have succeeded in decreasing the lung cancer premature deaths, lung cancer management in Indonesia really needs improvement. Upstream, we have to recognize and control the risk factors. The main risk factor for lung cancer is cigarette smoke exposure.[5] Without serious control of risk factors, the number of cancer patients will never decrease. We have not been controlling the main risk factor seriously. Indonesia is still one of the countries that has not yeen ratified the tobacco control treaty due to economic considerations while also positioning the tobacco industry as an important foreign exchange contributor. Nevertheless, we should appreciate some attempts that have been made in the regulation of non-smoking area in public

spaces and raising the customs and price of cigarette. What is lacking is a firm and strict regulation to limit the increasing numbers of beginner and teenager smokers. Setting the age limit of smoking will raise the age of being diagnosed with lung cancer. Right now, the majority of lung cancer patients were diagnosed at the age of 40-65 years (66.18%), > 65 years (29.18%) dan < 40 years (4.47%), as the consequences of starting to smoke at a very young age. Downstream, we need to urge high-risk groups for lung cancer to get screening. Table 2 shows the percentage of lung cancer risk factors.[13]

Table 2. Risk factors for lung cancer at RSUP Persahabatan, Jakarta, year 2017-2019

Risk Factors	Total	(%)
Cigarette smoke exposure		
• **Yes**		**91.4**
(Active or former smoker)	1,435	(63.44)
(Passive smoker)	633	(27.98)
• Non-smoker	108	4.77
• N/A	86	3.83
Tuberculosis		
• **Yes**	675	**29.84**
• No	1,508	66.72
• N/A	79	3.44
Family history of cancer		
• **Yes**	204	**9.02**
• No	2,013	88.99
• N/A	45	1.99
Environment (workplace, home, etc.)		
• **Yes**	345	**15.26**
• No exposure	1,512	66.84
• N/A	405	17.90

The biggest risk for lung cancer is cigarette smoke exposure, however there are other factors that need attention. History of lung tuberculosis as a risk factor needs further studies, as presently lung cancer diagnosis is more of a factor that delay the diagnosis (underdiagnosis), but a study has found correlation between them.[14] The risk of lung cancer according to family history has not yet been proven, but may become a factor that increases one's susceptibility.[15] Similar statement can be concluded with carcinogen exposure at workplace.[16]

The high-risk groups for lung cancer include people over 45 years old and smokers, or ex-smokers for less than 10 years that do not exhibit any symptoms. The suggested screening tests are low-dose thoracal CT scan. Those who are high risk and have symptoms, should actively perform early detection. The discovery of lung cancer in early stage and undergoing surgery will give long survival rate, or even complete cure. With the correct therapeutic modality, we hope to be able to increase the five-year survival rate percentage. It is promising that by choosing the right regimen and anticancer drugs in late stage lung cancer, the efficacy rate is better.

Conclusion

In my opinion, advocating prevention by risk factor control will not succeed if it is only rhetorical. Therefore, we need to provide scientific evidences to encourage the public and the government as regulators regarding the risk factor control. Currently, the outcome of risk factor control was not satisfying, as it is incredibly difficult to educate people regarding the danger of smoking. Studies showed that several genes were involved in the early process of lung cancer formation. Inhibition in the molecular level needs to be considered to prevent lung cancer in smokers (chemoprevention), while keeping in mind that cigeratte smoke is like a double-edged knife, not only because of the carcinogens contained inside but also by causing continuous irritation on the respiratory tract epithelium that may become precursor of lung cancer.

Even though recent treatments for lung cancer showed better result, there is still one dream that we are trying to achieve. Together with our colleagues in the Human Cancer Research Center cluster at IMERI, we are planning to conduct studies to discover lung cancer stem cells. Stem cell therapies have been applied for other diseases successfully at FMUI, but not yet in lung cancer. Lung cancer stem cell is the factory that produce lung cancer cells, and it provides answer to the suboptimal results of current treatment modalities. The cure to lung cancer can be realized if one day we can discover the location of the factory (stem cell) and destroy it completely. So please help us realize that dream.

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