Lung Cancer Screening: A Comprehensive Review of the Literature with Detailed Data

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ABSTRACT

Lung cancer still has a big proportion of cancer related deaths inspite of improvements in chemotherapeutic and surgical treatment approaches. It has a strong relationship with tobacco comsumption so that it can be regard as a common health problem. The survival rates of lung cancer at earlier stages are higher than later stages, so it is worth to effort detect lung cancer at an early stages which can cause mortality reduction and survival improvement. Some screening methods were used in screening trials to achieve a satisfactory mortality reduction with increased survival rates. We discussed about the results of important big trials which have different methods and qualities. There are two important screening tools to discuss about including; chest x-ray and low dose computed thomography (CT). Although there were many randomized or non-randomized trials used these tools for screening programs, few studies have enough power and quality to interpret the results. In this review, we discuss about the latest and detailed data of screening trials including, The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, Mayo Lung Project, The National Lung Screning Trial (NLST), The NELSON trial, The International Early Lung Cancer Action Program (I-ELCAP). Among the results of the trials we discussed about, only screening with low dose CT showed a statistically significant reduction of lung cancer deaths with increased early detection in high risk patients. Of these trials, the NLST which showed 20% mortality reduction in lung cancer and 6.7% mortality reduction from any cause has enough power to achieve this target and this results have affected nearly all of guidelines and recommendations of experts. The results of studies with low dose CT, especially of the NLST, changed thoughts about lung cancer screening. According to these results, the high risk individuals are suggested to be screened with low dose CT by almost experts and societies. In contrast, there should be further evaluations to clarify costs, harm effects of screening with low dose CT programs or related consequence procedures. Smoke cessation is still the most important strategy for reducing the burden of lung cancer, despite the promising results of screening trials.

Keywords: Lung cancer, Cancer, Screening, Chest x-ray, Low dose CT, Methods

ÖZET

Akciğer Kanseri Taraması; Literatürün Güncel Veriler Eşliğinde Detaylı İncelenmesi

Akciğer kanseri kemoterapötik ve cerrahi tedavilerdeki gelişmelere rağmen hala kanserle ilişkili ölümlerin büyük bir kısmını oluşturmaktadır. Akciğer kanseri sigara tüketimi ile olan sıkı birlikteliği sebebiyle bir halk sağlığı problemi olarak görülebilir. Erken evrelerde akciğer kanserinin sağ kalım oranı ileri evrelerden daha yüksektir, bu nedenle mortalite oranını azaltabilecek ve sağ kalım oranını da arttırabilecek olan erken evrelerde akciğer kanserini teşhis etmeye dönük çabalar gerekmektedir. Mortalitede tatmin edici bir azalma ile beraber sağ kalımı artırmayı hedefleyen çalışmalarda bazı tarama metodları kullanılmıştır. Bu derlemede akciğer kanseri taramasında kullanılan tarama yöntemleri ve bu tarama yöntemlerinin etkinliğinin detaylı olarak değerlendirilmesi amaçlandı. Burada tartışılması gereken iki önemli tarama aracı; akciğer grafisi ve düşük doz bilgisayarlı tomografi (BT). Bu tarama yöntemlerini kullanan bir çok randomize ve non-randomize çalışmalar olmasına rağmen, bunlar içerisinde birkaçı, sonuçlarının değerlendirilmesini gerektirecek kadar yeterli güç ve kaliteye sahiptir. Bu derlemede, en son ve detaylı veriler ışığında The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, Mayo Lung Project, The National Lung Screning Trial (NLST), The NELSON, The International Early Lung Cancer Action Program (I-ELCAP) çalışmaları tartışılacaktır. Akciğer kanseri tarama çalışmalarının sonuçları arasında, sadece düşük doz BT ile yapılan taramalar istatiksel olarak anlamlı bir şekilde akciğer kanserine bağlı ölüm oranında azalma ya da erken tanı oranında artış göstermiştir. Bu çalışmalar içinde, akciğer kanserine bağlı ölüm oranında %20 ve herhangi bir nedene bağlı ölüm oranında %6.7 oranında düşüş yakalayan NLST çalışması bu hedefe ulaşabilecek kadar yeterli güce sahiptir ve bu çalışmanın sonuçları neredeyse tüm kılavuzların ve otoritelerin önerilerinde etkisi oldu. Düşük doz BT ile yapılan çalışmaların, özellikle de NLST çalışmasının, sonuçları akciğer kanserinde tarama ile ilgili düşünceleri değiştirdi. Bu sonuçlara göre neredeyse tüm otoriteler ve topluluklar tarafından yüksek riskli kişilere düşük doz BT ile tarama önerilmektedir. Diğer yandan, düşük doz BT ile tarama ve bununla ilişkili müteakip süreçlerin maliyet ve yan etkilerini açıklığa kavuşturmak için ileri değerlendirmeler gerekmektedir. Tarama çalışmalarının umut verici sonuçlarına rağmen sigarayı bırakma hala akciğer kanserini azaltacak en önemli stratejidir.

Anahtar Kelimeler: Akciğer kanseri, Kanser, Tarama,Akciğer grafisi, Düşük doz bilgisayarlı tomografi

INTRODUCTION

Lung cancer is the most common cause of cancer related death in the USA and worldwide. In 2013, it is estimated that 228.190 individuals (118.080 men and 110.110 women) will be diagnosed and 159.480 men and women will die from lung and bronchus cancer.[1] Likewise in USA, the most common cause of death from cancer was lung cancer in the worldwide, estimated to accounted for nearly one in five (18%) or 1.38 million cancer deaths in 2008.[2] The smokers undoubtedly have greater risk of this cancer compared to nonsmokers. The incidence rate of lung cancer strongly accompany with tobacco comsumption. The risk of lung cancer reduces with the length of smoking cessation.[3] On the other hand, several other risk factors have been identified, such as occupational exposures of arsenic, chromium, asbestos, nickel, cadmium, beryllium, silica, coal, smoke, soot, residental radon and previous cancer history, family history of cancer and history of lung disease.[3-5] The relationship between lung cancer and second hand smoke is not clear far now, so authors does not consider second hand smoke as an independent risk factor to enroll these individuals screening program.

Five year survival rates of lung cancer is only 15 percent for patients diagnosed with lung cancer.[3] The treatment success is related to the stage at the time of diagnosis. Unfortunately most of the patients present with symptoms and signs like cough, weight loss, dyspnea, chest pain, hemoptysis due to advanced or metastatic disease. There are some strategies for reducing burden of lung cancer such as; early detection, treatment of disease, chemoprevention and smoke cessation. The most important strategy for reducing burden of lung cancer is prevention especially promotion of smoke cessation.[6] However, early diagnoses may help to reduce burden of lung cancer as well as improve clinical outcomes. At this point screening tests may help to diagnose at earlier stage that will decrease mortality and increase survival with a proper treatment.

To achive succesful clinical outcome, screening test must be accesible, cost-effective, sensitive and specific with available effective treatment. There are some factors that can influence effectiveness of screening test like, lead time bias, length time bias, overdiagnosis. In the respect of this facts, we aimed to review lung cancer screening trials in this manuscript here.

There are some methods used as a screening test including screening with chest x-ray/sputum cytology, low dose chest computed tomography (LDCT) and other technologies; positron emission tomography (PET), immunostaining or molecular analysis of sputum for tumor markers, automated image cytometry of sputum, fluorescence bronchoscopy, genomic and proteomic analysis of bronchoscopic samples, serum protein microarrays for detecting molecular markers. Screening tests have some inherited potential benefits and harms. The most important benefits of screening tests are early detection of cancer, decreasing disease releated and overall mortality with improvement survival rates. There are few potential harms of screening tests include; false positive results such as, detection of abnormalities that require further evaluation which mostly benign nodules and anxiety related to possibility of having cancer; false negative results that cause delaying diagnosis or treatment of cancer, increased costs, radiation exposure and overdiagnosis.[7] While screening programs performed, some abnormalities detected which require further evaluations involved an invasive study with associated morbidity and mortality. Radiation from serial imaging is an another important harm of screening that may be an independent risk of developing cancer. Since screening tests performed for several rounds, cumulative dose can have more importance compared to a single test dose. There are limited data about radiation dose from reported screening studies, but data from the Italian Lung cancer Computed Tomography screening trial (ITALUNG), a randomised trial which compared LDCT examination for 4 years annually to usual care in smoker and former smokers, reported the mean collective effective dose in the 1.046 subjects between 8.75 and 9.0 mSv (Sievert).[8] In the National Lung Screning Trial (NLST), which compared screening with low dose CT (LDCT) to chest x-ray, average estimated whole-body effective radiation dose for one LDCT examination reported as 1.5 mSv.[9,10] Overdiagnosis, length time bias and lead time bias are important biases for screening tests, as in lung cancer screening. Although, overdiagnosis increases specifity and sensitivity, it does not decrease disease specific mortality which is the most reliable outcome shows efficacy of a screening test.[7] According to general opinion, lung cancers generally have a fatal and aggressive course without

treatment, recent studies showed a longest overall survival even without treatment in some types of non-small cell lung cancer (NSCLC) (ie, Bronchioloalveolar carcinoma- BAC). According to results of some studies, lung adenocarcinomas was categorized to some histopathological subtypes with low-intermediate-high grade classification. After adequate surgical resection of these subtypes, both low grade comprised of adenocarcinoma in situ and minimally invasive adenocarcinoma (MIA) had 100% disease-free survival at 5 years.[11,12] On these grounds, individuals with these subtypes of adenocarcinomas will not benefit from screening.

SCREENING WITH CHEST X-RAY/SPUTUM CYTOLOGY

There is still no reported randomized lung cancer screening trial that show significant mortality reduction with chest x-ray or chest x-ray plus sputum cytology. A meta-analysis which included nine studies (eight randomized studies and one controlled trial) did not find statistically significant reduction in mortality of lung cancer with chest x-ray screening plus sputum cytology compared to chest x-ray screening alone or chest x-ray screening compared to usual care.[13]

The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial

PLCO is one of the largest randomized trial evaluating the effect of screening for several cancers including lung cancer.[14] In this randomized controlled trial, 154.901 participants aged from 55 to 74 years were included. In this study, 77.445 participants were randomized to screening arm with chest x-ray annually for 4 years and 77.456 patients were randomized to control arm with usual care. This trial aimed to have 90% power to detect 10% or greater reduction in lung cancer mortality at intervention group compared with usual care. There were no significance demographic differences between intervention and control group. In both groups, aprroximately half of group were women (50.5% women), 45% never smoker, 42% former smoker and 10% current smoker. Participants followed up for 13 years, adherence rate was 86.6% at baseline with decreasing to 79% on following three years.[15] After initial screening round, 5.991 radiographs were found abnormal, 126 of them were diagnosed as lung cancer with biopsy. Current and former smokers were the major portion of the participants diagnosed with lung cancer.[16] After 13 years follow up, cumulative lung cancer incidence rate was 20.1 per 10.000 person-years in the intervention group and 19.2 per 10.000 person-years in the usual care group (RR: 1.05; 95% CI: 0.98-1.12). After total 13 years follow up period, 1.213 participants died from lung cancer in the intervention group and 1.230 in the usual care group. Cumulative lung cancer mortality rates were 14.0 and 14.2 for intervention and usual care groups per 10.000 person years (95% CI: 0.87-1.22), respectively. After completion of this study, a subgroup of participants had been described who would have been eligible for NLST, which showed 20% reduction in lung cancer mortality compared LDCT screening with chest x-ray. This subset consist of 15.183 participants in the intervention group and 15.138 in the usual care group. Mortality rates (per 10.000 person years) releated to lung cancer, through 6 years follow up, were 36.1 in intervention group and 38.3 in usual care group, respectively (RR: 0.94; 95% CI: 0.81-1.10). It seems there would be same reduction in mortality rates if this group had been enrolled in the NLST. As a result, screening with chest x-ray annually has no benefit on lung cancer mortality compared with usual care.[15]

Mayo Lung Project

Mayo Lung Project trial aimed to show effect of intense regimen screening with chest x-ray and sputum cytology compared to usual care on lung cancer mortality.[17] The trial started at 1971 and finished at 1983, because of some comments suggested follow up time had been too short, it extended through 1996. In this randomized controlled trial, 9.211 male smoker participants enrolled in the study. At the beginning of the study, chest x-ray and sputum cytology was performed to all participants then 9.211 men were randomly assigned to two arm of study as intervention and usual care groups. In the intervention arm, participants (n= 4.618) were offered chest x-ray and sputum cytology every 4 months for 6 years. In the usual care arm (n= 4.593) participants were advised to have an annual chest x-ray and sputum cytology. After 6 years follow up, lung cancer death rates were similar, 3.2 per 1000 person years in the intervention arm and 3.0 per 1000 person years in the usual care arm. However,

throughout this period, in the intervention arm 206 participants and in the usual care arm 160 participants had been diagnosed with lung cancer. After extended follow up, as of 1996, lung cancer deaths were 337 in the intervention arm, 303 in the usual care arm; death rates were 4.4 versus 3.9 per 1000 patients years. These two difference death rates were not statistically significant. After adjustment for four lung cancer risk factors (age, smoking as pack-years smoked, exposure to non-tobacco lung carcinogens, and history of pulmonary illness) lung cancer mortality rates did not change for two arms. The other hand, a better survival had been showed in the intervention arm especially prior to 1983 with no reduction mortality rates and these findings would be related to length bias or overdiagnosis.[17] This trial had some issues could effect the results, length bias, overdiagnosis, contamination and low rates of compliance. This trial showed no mortality reduction related lung cancer with intense regimen screening with chest x-ray and sputum cytology to usual care.[17]

Although these randomized trials which mentioned above and used chest x-ray as a screening tool showed no efficacy on mortality rates; some non-randomized trials that conducted in Japan showed a mortality reduction with a rate of about 40%. The results of these trials need to furthermore evaluations likely because of some biases. A case control study performed in Italy, showed an increase in survival time but there is no sufficient evidence that indicate a reduction in mortality rate.[18]

SCREENING WITH LOW DOSE CHEST CT

After findings that could not achieved reduction in lung cancer mortality rates with chest x-ray, low dose CT became center of interest as a screening tool. So, some studies with low dose CT have started and some of them showed benefit in lung cancer mortality rates.[19] In these studies, the NLST which concluded 20% mortality reduction in lung cancer was the largest and the highest quality randomized trial in resulted randomized trials.[20] Some of the other trials with low dose CT screening are ongoing.

The National Lung Screning Trial (NLST)

The NLST is a randomized trial conducted at 33 centers in United States from 2002 to 2004 and compared annual screening with low dose CT to chest radiography for 3 years.[19] In this randomized controlled trial, a total of 53.439 participants aged between 55 to 74 with smoking history at least 30 pack-years either current smoker or had been smoker within the previous 15 years enrolled study and were randomly assigned to a study group. In this study 26.715 participants were randomized to low dose CT group and 26.724 to chest radiography group.[19] The demographic features and smoking history of participants were similar between two groups.[9,10] In this study, participants underwent screening for 3 years annually with low dose CT or with posteroanterior view chest X-ray. All non-calcified nodules with long-axis diameters of 4 mm or greater in the axial plane were considered to be positive for low dose CT and all non-calcified nodules and masses were considered to be potentially positive for chest radiography. After the initial screening rounds, in the low dose CT group 7.191 of 26.309 participants (27.3%) had positive result and 2.387 of 26.035 (9.2%) participants had positive result in chest radiography group. After baseline screening round, 292 of 26.309 (1.1%) participants were diagnosed with lung cancer in the low dose CT group and 190 of 26.305 (0.7%) paticipants in the chest radiography screening group. True positive results were found in 270 patients (92.5%) in the low dose CT group and in 136 patients (71.6%) in the chest radiography group. The positive predictive values at the initial screening from overall positive results were 3.8% and 5.8% respectively, in the low dose CT and chest radiography group. These values correlatively increased in the nodules which had greater diameter. There were also significant differences in the stage and histologic features at the time of diagnoses of detected lung cancers, as in the total number of detected lung cancers. In low dose CT group, 158 participants diagnosed with stage 1 lung cancer whereas 70 participants diagnosed with stage 1 lung cancer in the chest radiography group. Also in low dose CT group, there were more diagnosed patients with bronchioloalveolar carcinoma and adenocarcinoma compared to chest radiography group, 38 vs 8, and 123 vs 71, respectively. The differences mainly occured in the stage of cancers which stage 1 higher in low dose CT group and histologic subtypes that bronchioloalveolar carcinomas and adenocarcinomas higher in the low dose CT group. There were no significant differences in the diagnoses of late

stages cancer (stage 2B to stage 4); 120 vs 112 participants diagnosed in the low dose CT and chest radioghraphy group, respectively.[19] After overall three rounds of screening, there were 247 lung cancer deaths per 100.000 person-years in the low dose CT and 309 deaths per 100.000 person-years in the chest radiography group, yielding a relative mortality reduction of 20% in lung cancer releated mortality rates. Deaths occured from any cause also reduced by 6.7% in the low dose CT group compared to chest radiography group. The median follow-up was 6.5 years with a maximum 7.4 years for two groups. The number of participants diagnosed with lung cancer were 645 per 100.000 person-years (1.060 cancers) in the low-dose CT group and 572 per 100.000 person-years (941 cancers) in the chest radiography group. Overall three screening rounds, the rates of positive screening tests were 24.2% and 6.9% respectively in the low dose CT and chest radiography groups. The rate of positive tests were 27.3% vs. 9.2% at first round, 27.9% vs. 6.2% at second round, and 16.8% vs. 5.0% at third round in the low dose CT and chest radiography groups, respectively. The positive rates decreased noticeably at T2 for both groups, because abnormalities suscipious for cancer which were stable across three screening rounds were categorized as negative with minor abnormalities. The number of diagnosed lung cancer at stage 1 was 620 vs 289 respectively, in the low dose CT and chest x-ray groups. In addition, the number of bronchioloalveolar carcinomas were 110 vs 35 and adenocarcinomas were 380 vs 328 in the low dose CT and chest x-ray groups, respectively. The amount of stage 1 lung cancers, bronchioloalveolar carcinomas and adenocarcinomas were significantly higher in low dose CT group than the chest x-ray group. The rates of false positive were similar but high in both groups with the rate of 96.4% vs 94.5% in the low dose CT and chest x-ray groups, respectively. After three rounds of screening, sensitivity and specifity for low dose CT were 93.8% and 73.4% and for chest x-ray were 73.5% and 91.3%. The positive predictive value for low dose CT is higher at T2 than T1 and T0 (5.2, 2.4 and 3.8) respectively.[19,21] Because some abnormalities which did not changed through screening periods but defined as positive in the first round were categorized negative.

The NLST achieved a satisifying mortality reduction in lung cancer and overall mortality.[9] Despite this trial highly effect opinions and recommendetions of experts especially in definitons of high risk individuals, it has several deficiencies. Firstly, high rates of false positive results which can lead to a further diagnostic evaluation mostly additional imaging, sometimes surgical interventions which may cause complications and increase costs. After 3 years screenings, of the positive results 713 participants in low dose CT group and 239 participants in the chest x-ray group had surgical procedure. Complications occured from invasive diagnostic procedures were not common. Of the participants diagnosed with lung cancer, 184 participants (28.4%) in the low dose CT group and 65 participants (23.3%) in the chest x-ray had at least one complications. The rate of adherence was high in the both groups, 95% and 93% in low dose CT and chest x-ray group respectively, due to educational status of participants or younger age. Of course, this rate increased the power of trial but may effect the success in the community, because of possibility of decreased adherence rate. Overdiagnosis, as in the other screening methods, is an important bias that falsely increases the mortality reduction rates, but magnitute of overdiagnosis seems not large and needs to be additional follow up and further analyses.[9] The cost effectiveness of low dose CT likely to be high, because it includes not only screening examination itself but also additional diagnostic procedures or follow up and treatment. The further analyses of NLST and datas on cost effectiveness, quality of life and potential harmful effect of radiation exposure in long time will be avaliable in the future.

The NELSON Trial

The NELSON trial conducted in Netherlands and Belgium and designed as randomized controlled trial to power a 25% decrease in high risk individuals with low dose CT screening compared to no screening.[22] In this study, 15.428 participants aged from 50 to 74 men and women, current smoker or former smokers with 10 years or less of cessation who had smoking history >15 cigarettes/day during >25 years or >10 cigarettes/day during >30 years were enrolled to this study. Another important feature of the participants was having of a diagnosis with lung

Table 1. Selected published trials about lung cancer screening

Name of Study	Method	Number of participant	Age of participant	Screening period	Results or Mortality rates	Total or median follow up time
The PLCO	Chest x-ray vs. Usual care	77.445 in screening arm Vs. 77.456 in control arm	55 to 74 years	Annually for 4 years	14.0 per 10.000 person years in screening arm Vs. 14.2 per 10.000 person years in control arm	13 years
Mayo Lung Project	Chest x-ray with sputum cytology Vs. Usual care	4.618 in screening arm Vs. 4.593 in control arm	No information	Every 4 months for 6 years	3.2 per 1.000 person years in intervention arm Vs. 3.0 per 1.000 person years in usual care arm	12 years than expanded to 25 years
The NLST	Low dose CT Vs. Chest x-ray	26.175 in low dose CT group Vs. 26.724 in chest x-ray gorup	55 to 74 years	Annually for 3 years	247 per 100.000 person years in low dose CT group Vs. 309 per 100.000 person years in chest x-ray group	6.5 years
The NELSON	Low dose CT Vs. No screening	Totally 15.428	55 to 74 years	For years 1,2,4 and 6.	Not reported yet	Not reported
The I-ELCAP	Non-randomized	31.567 participants baseline; than 27.456 screened annually	No information	Baseline than annually after 7 to 18 months previous screening	No significant differences in survival rate between just baseline or annually screening	Not reported

Abbreviations: I-ELCAP= International Early Lung Cancer Action Program; NELSON= The Dutch-Belgian Randomized Lung Cancer Screening Trial; NLST= National Lung Screning Trial; PLCO= Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

cancer before and survive for 5 years. Participants were randomly assigned to low dose CT or usual care group. In the intervention group, participants underwent screening with LDCT for years 1, 2, 4 and 6. In the usual care group, participants only had usual care. In this trial, nodul management which aimed to achieve less false positive rates based on volumetry.[23] The volume and some features (shape,surface) of nodules were noted and followed up subsequent CT scannings. The NELSON protocols defined growth nodule as change in volume of at least 25% between scans. The doubling time of growing nodules measured and these nodules classified into three growth categories according to volume-doubling time.[22,24] In 2009, results from first and second screening rounds were published.[24] According to these results, the sensitivity of first round was 94.6% with a negative predictive value of 99.7%. At the second round, the sensitivity was 96.4% and negative predictive value of 99.9%.[24] The mortality results of this study will be available within 2 years. The management of nodules based on volumetric evaluation will likely decrease the rate of false positivity and increase specifity unlike the NLST trial.

The International Early Lung Cancer Action Program (I-ELCAP)

Beside these randomized trials, there is an important non-randomized trial named The International Early Lung Cancer Action Program (I-ELCAP) which also attempt to evaulate the effect of screening with low dose CT in lung cancer.[25] In this trial 31.567 individuals screened at baseline and 27.456 annually after 7 to 18 months the previous screening. The numbers of diagnosed lung cancer after the baseline and annual screening rounds were 405 and 74, respectively. There were no significant diffirence in survival rates between individuals who screened just baseline or annually. The estimated 10 years survival rate of 484 participants with lung cancer was 80% (95% CI, 74 to 85). The number of participants who had stage 1 lung cancer was 412. Of the participants with lung cancer stage 1.375 participants underwent surgical resection with a number of 302 had within 1 months after diagnosis. The estimated 10 year survival rate of participants diagnosed with lung cancer stage 1 was 88% (95% CI, 84 to 91) and 92% in patients who had surgical resection after the first month of diagnosis (95% CI, 88to 95). Although, this trial showed higher detection rate of lung cancer at stage 1 in the baseline screening, it has a fair quality to interprete as important result due to the non-randomization planning of trial.[25] Selected published trials of lung cancer screening were summarized in Table1.

ONGOING TRIALS

There are some randomized trials that are ongoing or recently finished especially in Europe. These include the Dutch-Belgian Randomized Lung Cancer Screening Trial (Dutch acronym: NELSON study) trial, the Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays (DANTE) trial, the Danish Lung Cancer Screening Trial (DLCST), the Multi-centric Italian Lung Detection Trial (MILD), the Italian Lung cancer Computed Tomography screening trial (ITALUNG), the German Lung Cancer Screening Intervention Study (LUSI) and the United Kingdom Lung Cancer Screening trial (UKLS). These trials differ in features, numbers of participants and screening methods or number of rounds. Of these studies, the only trial large enough to power reduction in lung cancer mortality is the NELSON trial. However, detailed datas estimated to be available in the future.[8,22,25-29]

RECOMMENDATIONS FOR SCREENING BY EXPERTS GROUPS

Lung cancer screening is a controversial and complex topic which still need to further studies. Because of risks and benefits of screening especially with low dose CT, it is important to choose appropriate individuals. High risk individuals are eligible for screening. The NLST trial definition of high risk indivuals have effected nearly all of the experts group and societies.

The National Comprehensive Cancer Network (NCCN) recommends screening with low dose CT in high risk individuals with a multidisciplinary approach. The NCCN guideline defines high risk individuals as aged 55 to 74 years with 30 or more pack year history of smoking or if former smoker have quit within 15 years or those have additional risk factors (cancer history, lung disease history, family lung cancer history, radon exposure and occupational exposure) aged 50 years or older with history of smoking 20 or more pack years. The NCCN do not define a time limit but suggest annual screening at least 2 years with low dose CT and also at selected high risk individuals older than 74 years who are eligible for curative treatment. The NCCN recommends considering annual low dose CT regardless of age, until patients are not appropriate for definitive treatment.[30]

American College of Chest Physicians (ACCP) and the American Society of Clinical Oncology (ASCO) recommend screening with low dose CT in high risk individuals who meet certain criteria of the NLST. ACCP and ASCO do not suggest screening with low dose CT except that individuals meet the criteria and also do not limit a time of duration.[31]

The American Cancer Society (ACS) also suggest screening with low dose CT annually in high risk individuals who meet criteria of the NLST until aged 74. Additionally, ACS recommends decide together with individuals after a satisfactory information about harms and benefits of screening tests. The individuals who do not intent to enter a screening program because of harm effects of screening or risks of further diagnostic tests also understand and accept the risk of dying from lung cancer should not

be screened. The screening must be obtained in a skilled center with multidisciplinary team otherwise must not be performed.[32]

The U.S. Preventive Services Task Force (USPSTF) was concluded a guideline in 2004 that evidences were insufficient to recommend any screening methods include chest x-ray, sputum cytology, low dose CT or combination of these tests.[33] But after conclusion of the NLST results, the USPSTF reviewed lung cancer screening and revised the screening guideline in 2013. According to this last review, the USPSTF suggest screening with low dose CT annually for individuals aged 55 to 80; with a 30 pack-year or more smoking history and if former smoker, quitted within the last 15 years. Additionally, the USPSTF does not suggest screening under a condition that limit life expentacy or prevent a curative lung surgery.[34] All groups and experts also recommends to counsel patients to quit smoking and screening should not be an alternative of smoke cessation.

CONCLUSION

The lung cancer still has a big proportion of cancer related deaths inspite of improvements in chemotherapeutics and surgical treatment. It has a strong relationship with tobacco comsumption so that it can be regard as a common health problem. The survival rates of lung cancer at earlier stages are higher than later stages, so it is worth to effort detect lung cancer at an early stages which can cause a mortality reduction and improvements in survival rates. Some methods have been used in screening trials to achieve a satisfactory mortality reduction with increased survival rates. We discussed about the results of important big trials that have different methods that have enough quality. There are two important tools to discuss about screening including, chest x-ray and low dose computed tomography. Among the results of the trials we discussed about, only screening with low dose CT showed statistically significant reduction of lung cancer deaths with increase of early detection. Of these trials, the NLST has enough power to achieve this target and effects nearly all of the guidelines and recommendations of experts. There should be further evaluations to clarify costs, harm effects of screening programs or releated consequence procedures. Smoke cessation is still the most important strategy for reducing the burden of lung cancer despite the promising results of screening trials.

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