Detection and treatment of lung adenocarcinoma at pre-/minimally invasive stage: is it lead-time bias?

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Abstract

Objectives This study investigates whether lead-time bias contributes to the excellent survival of AIS and MIA.

Methods We enrolled patients with resected adenocarcinoma from 2008 to 2012. Age, sex, smoke history, surgical approach, radiological features, invasive stage and postoperative follow-up data were documented. 1:1 PSM was performed to balance the influence of sex and smoking status on survival. After matching, the average age of the two groups was compared to calculate the lead time of diagnosis. The gain in life years for adenocarcinoma diagnosed at pre-/minimally invasive stage was estimated by subtracting the “lead time” and “median survival year of IAC” from “the life expectancy of AIS/MIA patients” referring to the Centre for Health and Information.

Results There were 124 AIS/MIA patients and 1148 IAC patients. The frequency of female and never-smoking patients in AIS/MIA group was much higher than that in IAC group. PSM analysis identified 124 patient pairs. No cancer-related death and recurrence were observed among AIS/MIA patients 5 years after surgery. For IAC patients, the 5-year disease-specific survival rate was 73.5% and the median survival is 13.5 years. The average age of AIS/MIA group and IAC group are 53.6 years and 58.2 years, respectively. The lead time between diagnosis of AIS/MIA and IAC is 4.6 years. Referring to the Centre for Health and Information, the life expectancy of patients with AIS/MIA diagnosed at 53.6 years old is 28.9 years. With adjustment for the lead time, the gain in life years for adenocarcinoma diagnosed at pre-/minimally invasive stage is 10.8 years.

Conclusions With adjustment for the lead time between diagnosis of AIS/MIA and IAC, resecting lung adenocarcinoma at pre-/minimally invasive stage can improve life expectancy. The excellent survival of AIS/MIA is not lead-time bias.

Keywords Lung cancer screening · Lead-time bias · Adenocarcinoma in situ · Minimally invasive adenocarcinoma

Abbreviations

CT Computed tomography
AIS Adenocarcinoma in situ
MIA Minimally invasive adenocarcinoma
IAC Invasive adenocarcinoma
IASLC International Association for the Study of Lung Cancer
ATS American thoracic society
ERS European respiratory society
GGO Ground-glass opacity
PSM Propensity score matching

Introduction

Lung cancer by far remains the leading cause of cancer death worldwide, representing an estimated 18% of all cancer deaths (Sung et al. 2020). In recent years, several
independent, international, randomized controlled clinical trials have demonstrated that low-dose computed tomography (CT) screening reduces lung cancer mortality (Aberle et al. 2011a; Koning et al. 2020a; National Lung Screening Trial Research T 2019; Pastorino et al. 2019). The earlier detection of lung cancer made by low-dose CT screening can explain the reduction of mortality as the diagnosis at an early-stage can lead to earlier surgical intervention. However, the concerns about lead-time bias in low-dose CT screening have been raised (Gill et al. 2013; Yang et al. 2017a).

Detection of the disease at an earlier time point by screening causes a false prolonged survival time. This is called lead-time bias (Zojwalla et al. 2004; Rollison et al. 2007; Tzung and Julien 2010). In low-dose CT screening trials, lung adenocarcinoma was the most often detected subtype of lung cancer (Pastorino et al. 2019; Aberle et al. 2011b; Koning et al. 2020b). In 2011, adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) were newly defined as two special subtypes of lung adenocarcinoma (Travis et al. 2011). 5 or 10-year recurrence-free survival of AIS/MIA has been reported 100% (Yotsukura et al. 2021). In this study, we aim to find out whether the lead-time bias contributes to the excellent survival of AIS/MIA.

Methods

We enrolled patients with resected adenocarcinoma from 2008 to 2012. Patients with previous cancer history were excluded. Age, sex, smoke history, surgical approach, radiological features and postoperative follow-up data were documented. Patients were followed with routinely chest CT every 4 months for the first 3 years after the operation, every 6 months for the next 2 years, and every 12 months thereafter. Telephone follow-up was also used as a compliment. Disease-specific survival rate is defined as the percentage of patients who have not died from cancer recurrence or metastasis.

All the identified patients underwent a complete surgical resection and signed informed consent to allow their biological samples to be pathologically analyzed. AIS/MIA and invasive adenocarcinoma (IAC) were confirmed by paraffin section and based on the classification of lung adenocarcinoma released by International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) (Travis et al. 2015). Stage IV lung adenocarcinoma was excluded. Each histologic sample was reviewed by two pathologists.

The stepwise progression of lung adenocarcinoma proposed by Noguchi revealed that AIS/MIA would develop into IAC (Noguchi 2010). 1:1 propensity score matching (PSM) was performed to control the influence of sex and smoking status on survival, with a caliper value set at 0.01. We compared the average age of AIS/MIA patients and IAC patients to calculate the lead time of diagnosis, following the method in the work of Yang et al. (2017). The gain in life years for adenocarcinoma diagnosed at pre-/minimally invasive stage was estimated by subtracting the “lead time” and “median survival year of IAC” from “the life expectancy of AIS/MIA patients” referring to the Centre for Health and Information (Yue et al. 2016) (Fig. 1). SPSS (version 22.0; IBM Corp, Armonk, NY) was used to analyze the baseline data of AIS/MIA and IAC patients with Pearson’s chi-squared test.

Results

Totally 124 AIS/MIA patients and 1148 IAC patients were reviewed. There were 68.5% female patients and 87.1% never-smoking patients in AIS/MIA group, while 55.4% were female patients and 64.0% were never-smoking patients in the IAC group. 63.7% AIS/MIA patients underwent wedge resection and 88.4% IAC patients underwent lobectomy (Table 1).

As the frequency of female and never-smoking patients in the AIS/MIA group was much higher than that in IAC group, we performed 1:1 PSM to the influence of sex and smoking status on survival. PSM analysis identified 124 patient pairs from two patient groups. No cancer-related death and recurrence were observed among AIS/MIA patients in 5 years after surgery. For IAC patients, the 5-year disease-specific survival rate was 73.5% and the median survival of IAC patients is 13.5 years (Table 2).
The average age of AIS/MIA group and IAC group are 53.6 years and 58.2 years, respectively (Table 2). The lead time between diagnosis of AIS/MIA and IAC is 4.6 years. Referring to the estimation of Chinese life expectancy from the Centre for Health and Information, the life expectancy of people aging 50–54 years old are 28.9 years (Yue et al. 2016). Life expectancy of AIS/MIA patients was regarded as the life expectancy of the normal population for excellent survival and no recurrence. If the patient with adenocarcinoma is diagnosed at pre-/minimally invasive stage, the survival benefit seems to be 15.4 years (28.9 years minus 13.5 years). With adjustment for the lead time, the gain of life years is 10.8 years (15.4 years minus 4.6 years) (Fig. 2).

Discussion

In the National Lung Screening Trial research, there were 58.8% detected lung adenocarcinomas were stage I in low dose CT group and 38.4% detected lung adenocarcinomas were stage I in the radiography group (National Lung Screening Trial Research T 2019). In the Multicentric Italian Lung Detection trial, a significantly larger proportion of stage I lung adenocarcinoma was detected in the screening arm (50%) compared with the control arm (21.7%) (Pastorino et al. 2019). In Nelson trials, screening-detected 58.6% lung cancers were diagnosed in stage I, while only 14.2% of non–screening-detected lung cancers were diagnosed in stage I (Koning et al. 2020b). Thus, the shift to early-stage lung cancer at detection by low-dose CT screening may cause a lead time of diagnosis.

In radiology, AIS majorly featured as pure ground-glass opacity (GGO) nodule and MIA mostly contained ground-glass component (Ishida et al. 2019; Zhang et al. 2020a). Along with the widely using of low-dose CT screening, a rising number of GGO nodules are detected (Zhang et al. 2020b). It can be concluded that low-dose CT screening allows lung adenocarcinoma to be earlier diagnosed at pre- and minimally invasive stage. Similarly, low-dose CT screening made a shift to early-invasive-stage lung cancer at the time of diagnosis. That is the reason why this study focused on the role of lead-time bias in earlier detection of AIS/MIA.

In this investigation, the 5-year disease-specific survival rate of AIS/MIA was 100% and no recurrence was observed.

![Fig. 2](image-url) The gain of life years for lung adenocarcinoma diagnosed at pre-/minimally invasive stage
Furthermore, our previous study found no lymph node metastasis was revealed in AIS/MIA (Zhang et al. 2013). Many studies found the same consequences. Notably, the latest research of Yotsukura reported no recurrence was observed in AIS/MIA patient cohort during long-term follow-up and 10-year postoperative disease-specific survival rate was 100% (Yotsukura et al. 2021). As the long-term postoperative survival of AIS/MIA is extremely excellent, we regard the life expectancy of patients with AIS/MIA to be equal to the life expectancy of the normal Chinese population at the same age. Comparably, five-year overall survival of invasive stage I adenocarcinoma is approximately 78.4% and five-year disease-free survival of stage IA and stage IB adenocarcinoma are nearly 95.4% and 64.8% (Zhang et al. 2020a; Kadota et al. 2014; Murakami et al. 2015; Takahashi et al. 2014). In 2019, Okami et al. (2019) found the 5-year overall survival and disease-free survival of stage IA1, IA2, IA3, IB were 91.6%, 81.4%, 74.8%, 71.5% and 88.2%, 73.6%, 64.5%, 60.1%, respectively. These results reveal that even compared with stage IA1 invasive adenocarcinoma, AIS/MIA shows a much better survival.

As the diagnosis time point is in advance, the surgical intervention followed by earlier detection can seem to falsely increase survival even though death point time is not delayed. Since the biologically progression pattern of lung cancer from pre- and minimal invasive stage to invasive stage is still unaddressed, we try to estimate if survival is truly prolonged by surgical treatment for AIS/MIA from the view of clinical statistics. Our estimation model regards that lung cancer will develop from pre- and minimal invasive stage into the invasive stage without resection based on several reasons: (a) The stepwise progression of lung adenocarcinoma proposed by Noguchi revealed that AIS/MIA would develop into IAC (Noguchi 2010). (b) We follow the lead time estimating method in the work of Yang, which regards lung cancer will develop from stage I to stage IV (Yang et al. 2017).

In our study, after being adjusted for the lead time, the gain in life years for adenocarcinoma diagnosed at pre-/minimally invasive stage is remarkable. In addition, once AIS/MIA progress to IAC, the 5-year disease-specific survival rate will significantly reduce from 100 to 73.5%. On one hand, surgical treatment performed at pre-/minimal invasive stage indeed provides excellent survival. On the other hand, AIS/MIA can develop into an invasive stage without surgical intervention (Travis et al. 2013). Resection of AIS/MIA can be regarded as a cure at pre- and minimally invasive stage for improving life expectancy. It is convincing that the excellent survival of AIS/MIA is not lead-time bias.

A recent study found that the surgery approach made no influence on the survival of AIS/MIA. and the overall surgical complication rate was significantly lower for patients receiving wedge resection (Zhang et al. 2020a). These results indicated that sublobar resection without lymph node dissection might be the generally suitable surgical procedure for AIS/MIA. The exact diagnosis of AIS/MIA cannot be confirmed by radiology but requires the tumor being completely sampled by histology (Travis et al. 2013), a previous study demonstrated that the concordance rate between intraoperative frozen section diagnosis and final pathology for AIS/MIA was 95.9% (Liu et al. 2016). A followed study focused on the errors of frozen section and discovered that patients undergoing limited resection of invasive adenocarcinoma underestimated as AIS/MIA still had excellent prognoses (Zhang et al. 2021). Thus, limited resection following intraoperative frozen section is enough to cure high-like AIS/MIA on image and guarantees the excellent survival benefit.

There are some limitations of our study. First, some AIS/MIA remains indolent and will not progress to invasive stage. According to the newest histological classification and linear progression proposed by Noguchi (Travis et al. 2015; Noguchi 2010), we acknowledge that invasive lung adenocarcinomas are all developed from AIS/MIA. There will be a lead time of diagnosis if a lung adenocarcinoma was detected at pre-/minimal invasive stage. Second, we admit that the progression speed of AIS/MIA are different. In the clinic, solid components and size growth were related to high probability of invasiveness (Yanagawa et al. 2017; Saji et al. 2015; Lee et al. 2014). We also have observed stable pure GGOs grew after follow-up over 5 years and 10 years (Fig. 3), which indicated that AIS/MIA could grow slowly and develop into an invasive stage after a long time. We cannot predict the speed of cancer progression and describe a specific model of cancer development for each AIS/MIA.

In conclusion, with adjustment for the lead time between diagnosis of AIS/MIA and IAC, resecting lung adenocarcinoma at pre-/minimally invasive stage can improve life

![Fig. 3 Stable pure GGOs grow after a long-term follow-up](image-url)
expectancy. Thus, the excellent survival of AIS/MIA is not lead-time bias.

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**Declarations**

**Conflict of interest** The authors declare no relevant conflicts of interest.

**Ethical statement** The investigation was conducted based on the Declaration of Helsinki and approved by the Institutional Review Board of the Fudan University Shanghai Cancer Center (No. 090977-1). Each patient signed informed consent to allow biological samples to be pathologically examined.

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