EDITORIAL

Treating lung cancer: defining surgical curative time window

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Lung cancer remains the leading cause of cancer-related deaths worldwide. Despite the great strides made by emerging treatment regimens, such as targeted therapy and immunotherapy, surgery remains the sole effective method of cure for early-stage non-small cell lung cancer (NSCLC). As the disease progresses from early to advanced stages, the 5-year survival rate decreases drastically. Even for stage I NSCLC, the 5-year recurrence-free survival (RFS) barely reaches 80% after surgical resection with curative intent,[1] indicating that ~20% of patients experience disease recurrence within 5 years and are not definitively "cured". Currently, there is no definite way to predict lung cancer recurrence individually. With the clinical application of low-dose computed tomography (LDCT) in lung cancer screening, some patients meeting certain requirements achieve 100% 5-year RFS after surgical resection, suggesting that they are definitely cured. However, there still remains a lack of clarity regarding the characteristics of this particular group. We propose that defining the curative time window, during which patients attain definite cure without overdiagnosis and overtreatment, would better guide clinical management of lung cancer.

Most of lung adenocarcinomas follow a gradual or rapid progressive trajectory from atypical adenomatous hyperplasia to adenocarcinoma in situ (AIS), then minimally invasive adenocarcinoma (MIA), and ultimately invasive adenocarcinoma (from stages I to IV). Radiologically, some lung adenocarcinomas manifested as pure ground glass opacity (GGO) in the beginning, then as part-solid nodules, and eventually as solid nodules, accompanied with increasing tumor size. GGO-featured lung adenocarcinoma represents a special stage of the natural evolution of lung cancer and a unique clinical subtype with distinctive characteristics and prognosis. The surgical curative time window for lung adenocarcinoma is defined as the clinical or pathological disease stages during which the 5-year RFS or disease-free survival (DFS) reaches 100% after complete resection. This time window includes AIS and MIA stages in pathology,[2,3] as well as pure GGOs in radiology with size < 3 cm.[1,4] As a result, patients who undergo surgical resection within this curative time window can be considered cured.

The pace of lung adenocarcinoma progression through each stage is not even, and there is no validated method to predict progression for individuals. For some tumors, this natural development course is swift, such as those with *ALK* fusion or *SMAD4* deficiency. These tumors generally present as solid nodules with or without a short stage of GGO, and the time window of definitive cure might be too short to catch in clinical setting. For other patients, the natural evolution may last years or even decades, offering a window of definitive cure. Traditional biomarkers, such as DNA mutation status (e.g., *EGFR* mutation) and proteins detected by immunohistochemistry in primary tumors (e.g., Ki-67), have been commonly used as prognostic factors. Liquid biopsy, an emerging noninvasive method for biomarker assessment, offers potential alternatives through the detection of circulating tumor DNA, DNA methylation, and circulating tumor cells. However, as of now, no specific subgroups have been identified by these biomarkers that can be definitively classified as cured. Further research is warranted to utilize biomarkers in defining the curative time window.

There is a growing concern that performing surgical resection on pre-invasive or GGO-featured tumors could lead to over-diagnosis and overtreatment at a population level. Overdiagnosis is defined as the detection of lung cancer which would have never affected the lifetime if screening had not occurred. Any treatments to overdiagnosed cases can result in overtreatment. In the era of using chest X-ray as the primary screening tool for lung cancer, there was little possibility of overdiagnosis due to its low sensitivity. After the lung cancer screening tool switched from chest X-ray to LDCT, the increased sensitivity may lead to overdiagnosis. Some screening-detected lung cancers have indolent behavior and long volume doubling time, and will not cause any consequences within the lifetime if left untreated. Nevertheless, as people live longer and more lung cancers are detected in younger patients, how to manage these cancers without overdiagnosis and overtreatment is a big challenge.

It is crucial to compare the natural course of GGO-featured lung adenocarcinoma with the patient's life expectancy to prevent overdiagnosis and overtreatment. Although the natural course of GGOs and life expectancy of patients cannot be precisely calculated, they can be generally estimated on an individual basis. For screening-detected GGOs, a follow-up CT should be performed to confirm the persistency, and > 90% of persistent and slowly growing GGO are reported to be malignant.[5] Nevertheless, in some cases, persistent GGOs may be indolent and remain stable for a long time; thus surgical resection is not recommended for these cases. Only if there is an increase in size or the appearance of a solid component, should further evaluation be considered. The rates of progression within five years for pure GGO and mixed GGO with size < 10 mm were 11% and 30%, while the rates for those with size > 10 mm climbed to 54% and 87%, respectively.[6] Another study found that the exponential model was the best fitted model for GGO growth.[7] These findings indicate a high possibility of progression for GGO with size exceeding 10 mm or the presence of solid components. For young patients with long life expectancy, the possibility of progression could be even higher. Taken together, the above studies help estimate the natural course of GGOs. Once pure GGOs develop into part-solid nodules, a 100% 5-year RFS cannot be guaranteed. Early surgical intervention within the curative time window can block the process of tumor progression and cure patients.

Life expectancy can be estimated by the patient's age, general health condition, and the regional average lifespan. If patients are likely to outlive the time interval to lung cancer-specific death, surgical intervention within the curative time window should be promptly considered. Under this circumstance, patients can be cured with no concerns of overdiagnosis and overtreatment. Conversely, if a patient's life expectancy is limited due to

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advanced age or severe comorbidities, surgery may not be recommended, as the time it takes for GGOs to progress to a lethal state may exceed the patient's remaining lifespan.

If decision is made to surgically resect GGOs, the surgical timing should be restricted within the curative time window, instead of waiting for solid component to appear. The exact timing is flexible within this time window and should be determined by the following principles. First, the surgery for GGOs within curative time window should be treated as elective surgery, rather than urgent surgery. The decision to proceed with surgery should be made after thoughtful discussions between doctors and patients to avoid jeopardizing their life and career. Short-term postponement in surgery may help avoid "disease penalty" from lung cancer, e.g., by allowing patients to attend important life events or seize opportunities in career advancement. Patients with GGOs should not feel anxious and depressed since the indolent nature of GGO provides ample time for surgery, and it is not an urgent medical condition requiring immediate intervention. Second, progression rate should be discerned as an indication for the actual timing of surgical intervention. In cases of rapidly progressing lung adenocarcinoma, immediate intervention is necessary. For slowly growing GGOs, surgical resection within the curative time window should be encouraged. If slowly growing GGOs are within the curative time window, surveillance until progression occurs is generally a safe approach. Third, the location of nodules also should be taken into considerations. In cases of peripheral GGOs, the increase in size should be restricted within the upper limit for sublobar resection to avoid the unnecessary loss of lung parenchyma. Otherwise, if the size of nodules exceeds the upper limit for sublobar resection, lobectomy may be necessary for radical resection. For centrally located GGOs requiring lobectomy, the timing of surgical resection could be postponed until the latest limitation within the curative time window.

Finally, the principles of minimally invasive surgery (reducing incisional injury, extent of resection, and systemic damage) should be applied to lung cancer treatment.[8] Although lobectomy and systematic lymph node dissection have traditionally been considered standard surgical procedures for lung cancer, recent studies have confirmed that sublobar resection without mediastinal lymph node dissection was curative for GGOs within the curative time window,[2–4] while preserving more lung parenchyma and functional lymph nodes. Therefore, lobectomy and systematic lymph node dissection are overly extensive and an "overtreating" method for these GGOs, and sublobar resection without mediastinal lymph node dissection should be encouraged to avoid overtreatment. Nevertheless, in clinical scenarios where both wedge resection and segmentectomy are viable options, wedge resection is preferred when the location of the lesion permits, because it keeps the lung hilum intact. Therefore, the least extent of radical resection is recommended, and the first choice should be wedge resection, then segmentectomy, finally lobectomy. The proper treatment strategy is the key to minimizing or even eliminating overdiagnosis and overtreatment.

In conclusion, surgery within the curative time window is feasible and offers definitive cure without overdiagnosis and overtreatment for some patients with lung adenocarcinoma. As our knowledge of lung cancer deepens, the definition of the curative time window and optimal timing of surgical intervention for lung adenocarcinoma may evolve. Prognostic analysis can help identify more subgroups with 100% RFS or DFS that can be included in the surgical curative time window. Further investigations are warranted to explore the molecular mechanisms driving the progression of GGO and to discover trigger points associated with invasiveness and prognosis of lung adenocarcinoma. We call for focused research on the evolution of lung adenocarcinoma, including the development of molecular biomarkers that can help predict the progression of GGO. Artificial intelligence on CT images and liquid biopsy of blood are promising approaches to acquire potentially effective variables for predicting disease progression. The definition of curative time window updates our current knowledge on the surgical timing for lung adenocarcinoma and should help determine the optimal timing of intervention in the era of lung cancer screening using LDCT.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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