



A narrative review of invasive diagnostics and treatment of early lung cancer

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Abstract: The diagnosis and treatment of early-stage lung cancer remains a clinical challenge. The broadening implementation of lung cancer screening has resulted in positive findings in numerous patients that are mostly non-malignant. Many other patients have indeterminate nodules that are difficult to assess through simple observation. The critical interpretation of such screening results remains a challenge for radiologists and multidisciplinary teams involved in screening for lung cancer. The evaluation and diagnosis of each participant suspected for malignancy should be based on the basic clinical principles such as a carefully collected medical history, physical examination, and detailed analysis of all imaging tests performed. Indeed, the decision to go ahead with more invasive diagnostics requires consideration of the both the risks and benefits, with reflection upon the complete clinical and radiological picture. Although transthoracic needle aspiration biopsy remains the first-choice method of diagnosis, several newer technologies have slowly begun to emerge as potential replacements. The guiding strategy for method selection is to choose the least harmful approach that offers the most relevant potential insights. Transthoracic biopsy is an effective method that allows the collection of cytological and tissue material from small, peripheral tumors, but it carries a moderate risk of complications. Bronchofiberscopy, especially in combination with electromagnetic navigation, fluoroscopy or radial EBUS, also allows effective diagnosis of the peripheral pulmonary nodules. One of the most important diagnostic methods is the EBUS examination, which allows determining of staging in addition to diagnosis. Anatomical lung lobe resection and lymphadenectomy or sampling of the hilar and mediastinal lymph nodes is currently the treatment of choice for patients with stage I and II non-small cell lung cancer (NSCLC), but sublobar resections are recommended when a patient has limited pulmonary function or other significant comorbidities. Notably, several studies have highlighted the potential utility of more limited resections in small malignant lesions less than 2cm in diameter, with pure AIS histology, when more than 50% of the diameter of pulmonary nodule has ground-glass opacity (GGO) attenuation on CT, or long volume doubling time (VDT). Videothoracoscopy is the preferred surgical approach for resection of early-stage lung cancer. Patients who are not candidates for surgery or do not agree to surgery can be offered radical radiotherapy. Stereotactic body radiation therapy (SBRT) is a type of radical radiotherapy with proven effectiveness, a high rate of local control and an acceptable risk of the development of later complications. Future trials are expected to define the role of SBRT in the treatment of early lung cancer in healthy subjects.

Keywords: Non-small cell lung cancer (NSCLC); diagnostic techniques, surgical; minimally invasive surgical procedures; radiotherapy

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Introduction

Methods for the diagnosis and treatment of lung cancer have evolved over the past decade, mainly due to the increasing adoption of lung cancer screening (1-3), the implementation of video-assisted thoracic surgery (VATS) techniques in surgery (4,5), and the introduction of molecularly targeted therapies (6) and immunotherapy (7). The development and increasing utilization of low-dose computed tomography (LDCT) screening has made it clear that it is relatively common for patients to have a small pulmonary nodule in their lungs (8,9).

The aim of this review is to discuss key information related to the diagnosis and treatment of early lung cancer in the screening era, with an overview of current diagnostic and therapeutic procedures and particular emphasis on the comparison between lobectomy and sublobar resections. We present article in accordance with the narrative review checklist (available at <http://dx.doi.org/10.21037/tlcr-20-728>).

Methods

Literature search was based on following databases: PubMed, Ovid, Web of Science, EBSCO. Date of last search is 21st October 2020. Authors used following combinations of terms: epidemiology of NSCLC, invasive diagnostics, screening, low-dose CT, volume doubling time (VDT), transthoracic needle biopsy (TTNB), bronchoscopy, electromagnetic navigation bronchoscopy (ENB), endobronchial ultrasound, convex probe, radial probe, adenocarcinoma classification, subtypes of adenocarcinoma, ground glass opacity, micropapillary subtype, STAS, surgical treatment of NSCLC, VATS lobectomy, sublobar resections, radiotherapy of early stage NSCLC, Covid-19.

Non-invasive diagnostics

The management of a patient suspected of having early-stage lung cancer should begin with a carefully collected epidemiological and medical history, physical examination, and detailed analysis of all previous radiological tests. At this stage, according to the recommendations of the American College of Chest Physicians (ACCP), there are three important questions that should first be answered: (I) what is the extent of the disease, and is there evidence of metastases? (II) are there comorbidities that may

limit treatment options? (III) are there symptoms or paraneoplastic syndromes that must be evaluated and urgently treated (10)? Additionally, at this point, smoking cessation intervention should be initiated (11). Once the above questions are resolved, the pathological diagnosis should be promptly determined and the disease should be staged (10).

Early lung cancer frequently develops asymptotically. A small tumor in the lung is often detected incidentally, e.g., from chest radiography or a low-dose CT scan performed as part of a screening test. However, symptoms often accompany the more advanced stages of lung cancers. The detection of an indeterminate pulmonary lesion in the lung as a result of LDCT lung cancer screening opens the door to further diagnostic procedures in 2–3% of screened population (8,9).

Although LDCT is becoming more widely used, chest X-ray remains the primary method used for detecting lung diseases in the everyday practice despite its ineffectiveness in lung cancer screening (12). Chest radiography examination allows the detection of solid lesions in the lungs, as well as identification of the presence of atelectasis, inflammation, and pleural effusions (13). The sensitivity of this test declines as the diameter of the focal lesion decreases. Nearly a quarter of x-rays requested by primary care physicians for patients diagnosed with early lung cancer may be negative (14).

A thin-section chest CT scan with intravenous contrast-enhancement is the gold standard in the diagnosis of pulmonary lesions (15). The test is characterized by high sensitivity in detecting lung nodules. It enables assessment of tumor growth, size, location, margin, attenuation, and evaluation of the presence of fat, calcifications, or cavitations. For patients with suspected lung cancer, it is recommended to do a contrast enhancement chest CT scan with an assessment of the liver, adrenals, and neck before any invasive procedure (16). The growth of the lesion, which can be assessed by comparing two CT scans, can be reported as the VDT. VDT in the range of 20–400 days, indicates a malignant lesion. VDT shorter than 20 days, indicating very fast growth, usually reflects inflammatory lesions. In contrast, VDT over 400 days, suggesting slow growth, is most often observed for benign lesions (15).

The increasing availability of the PET/CT, as its clinical and economic effectiveness, has made it a standard in the diagnosis and staging of lung cancer (17). Where possible, it is recommended to offer PET/CT to all patients who could receive potentially curative lung cancer treatment (16). There are scarce data on the clinical relevance of PET/

CT in the majority of the early lung cancers detected from screening. Indeed, if the tumor diameter is less than 10 mm the clinical usefulness of PET/CT is limited (18,19), and is also less useful for non-solid lesions (20). However, Chun *et al.* reported that if ground-glass opacity (GGO) nodule has SUV >1.2 there is a high probability of cancer in that lesion (21).

Invasive diagnostics

The sequence of diagnostic investigation should be customized for each patient according to their clinical and radiological evaluation. The chosen test should be aimed to provide the most information about diagnosis and stage with minimal risk to the patient (16). A single-step diagnostic and staging procedure is preferred. Such a method should provide an appropriate amount of material to perform pathological diagnosis, as well as any required immunohistochemistry and molecular tests.

The consideration of diagnostics in the context of early lung cancer detected by LDCT screening has significantly evolved over the last decade, primarily due to the progress in molecular targeted therapy and immunotherapy. Historically, there was a difference in the diagnostic strategy used for local disease *vs.* advanced lung cancer wherein the evaluation of advanced cancers was mainly focused on detailed histopathological diagnosis with molecular profiling. Currently, there is no standardized recommendation for molecular testing (mainly EGFR, ALK, ROS1, BRAF, RET, PD-L1) in early-stage lung cancer (22,23), in pre-resection or resection specimens outside of clinical trials. However, pre-operative testing may be required to fulfill the inclusion criteria of ongoing trials. Patients are stratified into study groups depending on PD-1/PD-L1 status in some protocols, but not in others. Commonly, patients with driver mutations detected in pre-operative specimens are excluded from immunotherapy studies due to distinct biological characteristics of the disease.

Molecular testing of operative specimens of patients with early lung cancer is not supported by current guidelines. To date, studies have failed to prove a survival benefit from molecularly driven adjuvant therapies in early lung cancer (24). However, subgroup analyses are ongoing in further studies of molecularly targeted therapies in patients with specific mutations. Molecular analyses are also conducted for patients in some adjuvant trials. The ALCHEMIST trial is assessing the effect of adjuvant treatment in patients

with ALK- and EGFR-mutant tumors (25). Pending those results, this strategy may prove to be a standard in the future.

Pathological and molecular diagnoses can actually be made from the biopsy specimen taken from fine needle and small lung lesions, but this requires a highly organized diagnostic team. It is challenging and time-consuming to obtain enough tumor material from a biopsy specimen to perform multiple molecular studies or to apply next-generation sequencing (NGS). This requires the work of a multidisciplinary team, preferably enabling rapid onsite specimen evaluation (ROSE). The interventionist performing the biopsy should acquire sufficient tissue material with several passes of the needle, and, most importantly, should work with an experienced, dedicated pathologist. This approach, while difficult, significantly improves the likelihood of collection of adequate material with sufficient cellularity to perform the necessary examinations (26,27).

TTNB

CT-guided TTNB is recommended for patients with peripheral pulmonary lesions in circumstances when a treatment can be planned based on the results (16). In some cases, ultrasound is used for biopsy of pleural lesions or tumors adhering to the pleural surface (28). TTNB provides excellent diagnostic efficiency, in experienced hands, with sensitivity exceeding 90% in detecting malignancy (29-32). Understandably, several studies have reported lesion size as a predictor of diagnostic failure (30,31,33). Similarly, sub-solid character or GGO attenuation have been proposed as a negative prognostic factor affecting the diagnostic accuracy (34,35). However, a recent pooled analysis failed to find a significant relationship between of tumor size or sub-solid character and diagnostic accuracy (32). Despite the excellent results and low cost, some authors question the justification for performing a transthoracic biopsy, mainly due to the significant risk of complications (29-31,36). According to the pooled analysis of Di Bardino *et al.*, the most common complication is pneumothorax, occurring in about 20 % of patients, along with chest tube drainage (7.3%), hemorrhage (3%) and air-embolism (<0.1%) (32).

According to the National Comprehensive Cancer Network (NCCN) guidelines, patients with significant suspicion of lung cancer do not require a biopsy before surgery, because biopsy adds time, cost, risk, and will not affect treatment decisions (37). NCCN recommends biopsy

if a non-lung cancer diagnosis is suspected or intraoperative diagnosis appears to be difficult or risky (37). However, guidelines are changing constantly due to the recent progress in the field of targeted therapies. Of note, there are many ongoing trials of adjuvant or neoadjuvant treatment for early-stage lung cancer, consisting mainly of targeted therapy, immunotherapy, and surgery or stereotactic body radiation therapy (SBRT). Such a treatments will require a pre-treatment specimen of tissue material with sufficient cellularity (38).

Bronchofiberoscopy

Bronchofiberoscopic evaluation is recommended for patients with centrally located tumors on the CT scan if nodal staging with EBUS/EUS or mediastinoscopy is not required (16).

The main indication for diagnostic bronchoscopy is the presence of a tumor that obstructs the bronchi or the presence of hemoptysis. The examination is also recommended for patients before surgery, especially for planned sleeve lobectomy (37). Peripheral pulmonary lesions, not available in conventional bronchofiberoscopy, may be subjected to image-guided bronchoscopic evaluation under the control of an additional tool—radial probe endobronchial ultrasound (RP-EBUS), ENB and other techniques, including virtual bronchoscopy navigation, CT-guided bronchoscopy, or robotic bronchoscopy.

ENB

The ENB technique combines computed tomography with conventional bronchoscopy. It enables the location of the probe introduced by the bronchoscope, which is detected in the electromagnetic field generated by a board placed under the patient. The clinical efficiency of ENB has been investigated in numerous retrospective observational trials (39,40), one randomized control trial (41), one prospective multi-center study (42,43), and several meta-analyses (44-47). In a meta-analysis conducted by Wang *et al.* that included 17 observational studies, the sensitivity and specificity of ENB were 82 and 100%, respectively. In the large, prospective multicenter study (NAVIGATE), among 1,157 enrolled patients, 94% had completed ENB and obtained tissue. The sensitivity and specificity for malignancy were 69% and 100%, respectively. The study showed a low procedural complication rate with 2.9% experiencing pneumothorax, 1.5% bronchopulmonary

hemorrhage, and 0.7% pulmonary failure (42,43). Although the cost of the test is high and its results depend on the experience of the bronchoscopist, the low risk associated with ENB and the potential future use of the test for micro-wave ablation procedures gives it an advantage over transthoracic biopsy.

Endobronchial ultrasound (EBUS)

There are two types of EBUS: radial probe (RP-EBUS), and convex probe (CP-EBUS). RP-EBUS is performed using a thin ultrasound probe that is introduced through the working channel of the bronchoscope. This test allows the assessment of lung tissue in a 360-degree view around the bronchus in which the probe is located. Radial EBUS is usually used to locate the peripheral pulmonary lesion or to confirm the position of a probe during navigational techniques such as ENB. In a recently published meta-analysis of 51 studies with a total of 7,601 patients, the pooled sensitivity of RP-EBUS was 72%, and area under the ROC curve was 96%. The complication rate was very low, with a pooled pneumothorax rate of 0.7% (48).

Convex probe endobronchial ultrasound (CP-EBUS) is widely used for mediastinal and hilar non-small cell lung cancer (NSCLC) staging in CT/PET-suspected N1 or N2 disease in candidates for radical treatment (16). According to the guidelines of the European Gastrointestinal Endoscopy (ESGE), the European Respiratory Society (ERS), and the European Society of Thoracic Surgeons (ESTS) (49), endosonography is recommended over surgical staging as an initial procedure for patients with abnormal mediastinal and/or hilar lymph nodes on CT-scan or PET/CT. The combination of two tests, endobronchial ultrasound with transbronchial needle biopsy (EBUS-TBNA) with endo-esophageal ultrasound biopsy (EUS-FNA) or esophageal inspection with EBUS (EUS-B-FNA) is recommended (49). Mediastinal and hilar staging with EBUS-TBNA and/or EUS-B-FNA is also recommended for staging patients with suspected or proven NSCLC without mediastinal involvement on CT or PET/CT when at least one of the following conditions occur: (I) when the ipsilateral hilar lymph node is positive on CT or PET/CT, (II) when the primary tumor is not metabolically active on PET/CT, or (III) tumor size is ≥ 3 cm (49). When the pathological results of mediastinal and hilar sonography do not show metastases, mediastinoscopy is recommended, especially when the station N1 station is suspected.

The clinical effectiveness and accuracy of EBUS-TBNA

and EUS-FNA staging of hilar and mediastinal lymph nodes has been evaluated in several studies. In a meta-analysis by Gu *et al.* in which 11 studies and 1,299 patients were assessed, the pooled sensitivity of EBUS-TBNA in NSCLC staging was 93% (50). According to a systematic review by Varela-Lema *et al.* in which 20 observational studies were evaluated, the sensitivity of EBUS-TBNA ranged from 85 to 100% for the staging of NSCLC (51).

EBUS-TBNA and EUS-FNA are both safe procedures and reported complication rates are rare. In the systematic review of von Bartheld *et al.*, which included a set of 90 studies with more than 16,000 patients, serious adverse events and adverse events were only reported in 0.14% and 0.22% patients, respectively. No procedure-related mortality was observed. Infectious complications occurring after EUS-FNA were the most common, predominantly after biopsy of cystic lesions or sarcoidosis (52).

Treatment of early stage lung cancer

Surgical treatment

The treatment of choice in early lung cancer is surgery. The major issue in the lung cancer screening era is to define which patients can receive sublobar resection, and, among those, which patients should receive wedge resection with or without lymphadenectomy. The latter attempt should be very precisely defined according to the current ESTS guidelines for resection (53). Moreover, different measures should probably be applied for invasive (solid) and indolent (non-solid) adenocarcinomas.

Anatomical lung lobe resection and lymphadenectomy or sampling of the hilar and mediastinal lymph nodes is the treatment of choice for patients with stage I and II NSCLC (16,37). The only randomized study on this topic was reported by Ginsberg *et al.*, on behalf of the Lung Cancer Study Group. That study compared overall survival (OS) in stage I NSCLC patients who received lobectomy versus wedge resection or segmentectomy. Their findings clearly showed significantly reduced survival and 50% greater risk of local recurrences in the wedge resection and segmentectomy groups compared to lobectomy (54). However, this study was conducted in 1995 and was biased by several factors. Importantly, when that study was conducted 25 years ago, patients were not properly staged compared to the current state of the art. Moreover, not all of the patients in that study had CT, and were accepted for inclusion in the trial with only a traditional chest X-ray (54).

Among the many drawbacks, the combined analysis of wedge resection and segmentectomy as a sublobar group seems to be the most significant, considering the majority of the later retrospective reports. Wedge excision accounted for almost one third (40 out of 122) of patients in the sublobar group, so the inferior results of this type of surgery had an impact on the results of the whole sub-lobar group. Today, there are two RCTs comparing lobectomies with sublobar resections underway, a North American trial (CALGB 140503) (55), and a Japanese trial (JCOG0802/WJOG4607L) (56). These studies will provide the basis to establish new standards but should not preclude further analysis of high-quality retrospective or prospective cohorts. There are several limitations of RCTs including the logistics, statistics, external applicability, and ethical issues. Further, there is a risk for positive selection bias. Randomized, controlled studies are important but, when we consider the relatively small number of patients, long periods of recruitment and number of study locations, the results are not always guaranteed to be fully correct. Indeed, there may not be a significant difference between the clinical utility of insights gained from small RCTs over a retrospective study on a large population coming from high-quality national databases. In our opinion, if appropriately planned, single-arm studies (both retrospective and prospective) are valuable complementary studies.

A recent literature review discussed a range of observational studies with (57-60) or without (61-63) propensity score matching, several systematic reviews (5,64,65), and several meta-analyses (5,66-68) comparing different types of pulmonary resections. A meta-analysis by Winckelmans *et al.*, compared lobectomy to segmentectomy in NSCLC patients with stages I and IA as well as patients with tumors <2 cm. In stage I NSCLC patients, lobectomy was superior to segmentectomy in terms of OS, cancer-specific survival (CSS), and recurrence-free survival (RFS). For tumors <2 cm, there was no difference between segmentectomies and lobectomies for OS, CSS, and RFS (66).

A meta-analysis by Zhang *et al.* also compared outcomes of patients treated with lobectomies, wedge resections, and segmentectomies, and found that, for stage I NSCLC, the OS of patients who received segmentectomies was significantly worse compared to lobectomies. On the other hand, the outcomes of patients treated with segmentectomies were not inferior to lobectomies treated with a minimally invasive approach (68).

In the retrospective, multicenter propensity-score matched study, we evaluated nearly 7,000 patients,

and observed no differences in overall nor propensity score-matched analyses of long-term survival in the segmentectomy and lobectomy groups of patients treated for stage I NSCLC (57). However, we observed significantly inferior long-term survival in the wedge resection group compared to those who received lobectomies and segmentectomies (57).

Kent *et al.* evaluated high-risk operable patients with stage I NSCLC who had limited pulmonary function. Those patients were randomized to receive sublobar resection with or without brachytherapy. In that RCT, wedge resection compared to segmentectomy, was associated with a smaller parenchymal margin and lower diagnostic yield of lymphadenectomy (69).

Lung adenocarcinoma describes a heterogeneous group of neoplasms. Apart from the stage according to the TNM classification, the histopathological diagnosis is one of the most important prognostic factors. In a 2015 publication describing classifications of adenocarcinoma (70) clinically significant subtypes of adenocarcinoma were described such as adenocarcinoma in-situ (AIS), a pre-invasive neoplasm with a purely lepidic growth type. Minimally invasive adenocarcinoma (MIA), a lepidic tumor with an invasive component up to 5 mm in diameter, has also been defined (71). A publication by Yoshizawa *et al.* analyzed the impact of stage I adenocarcinoma subtype on disease-free survival (DFS) rates. Among the analyzed subtypes of adenocarcinoma, AIS and MIA have the best prognoses, as high as 100% 5-year DFS. Non-mucinous lepidic predominant, acinar predominant, and papillary predominant subtypes of adenocarcinoma have a slightly worse prognosis, with 5-year DFS of 90%, 84% and 83%, respectively. The worst prognoses are observed among patients with invasive mucinous adenocarcinoma, solid predominant and micropapillary predominant adenocarcinomas, with 5-year DFS of 75%, 70% and 67%, respectively (72). Numerous studies have shown that a micropapillary subtype is a particularly poor prognostic factor (73-75). A study by Lee *et al.* found that the presence of >1% of the micropapillary component influences the appearance of metastases and worsens the prognosis (74). According to Nitadori *et al.*, the presence of more than 5% of micropapillary component is associated with increased risk of tumor recurrence after sublobar resection, but not after lobectomy. Micropapillary subtype is also associated with a higher risk of local recurrence or metastasis to the lymph nodes (75). Nevertheless, the adequate assessment of subtypes of adenocarcinoma is rarely available

preoperatively. A sufficient tissue sample is rarely required in clinical stage I NSCLC in a patient who is a prompt surgical candidate. It is difficult to unequivocally assess the subtype of adenocarcinoma based on the radiological analysis of CT images. However, due to the progress in the field of radiomic evaluation, this tool may become helpful in the preoperative prediction of adenocarcinoma subtypes (76-79).

STAS—another factor that may influence the choice between the sublobar resection and lobectomy is the occurrence of tumor spread through air spaces (STAS). STAS is defined as neoplastic cells—including micropapillary structures, solid nests, or single neoplastic cells—spreading within air spaces in the lung parenchyma beyond the edge of the main tumor (80). Kadota *et al.* observed the presence of STAS in 38% of operated patients who were diagnosed with adenocarcinoma with a tumor diameter of up to 2 cm. It was shown that the risk of recurrence was significantly higher in STAS-positive patients after sublobar resection compared to STAS-negative patients, 40.6% *vs.* 10.9%. The presence of STAS significantly influences the risk of both local and distant recurrence. In contrast, there was no increased risk of recurrence in STAS-positive patients who underwent lobectomy. The presence of STAS may justify a lobectomy, but not a sublobar resection (80). Similar results were observed by Eguchi *et al.*, who analyzed T1N0M0 patients diagnosed with adenocarcinoma who underwent sublobar resection or lobectomy. That study confirmed the value of intraoperative examinations for detecting the presence of STAS. It has been shown that lobectomy is associated with better long-term results compared to sublobar resection in T1N0M0 STAS-positive lung adenocarcinoma patients (81). It is even more difficult to predict whether the tumor is STAS-positive comparing to preoperative assessment of adenocarcinoma subtype. Even histopathological sampling does not provide information about eventual STAS status. Radiological image of the solid tumor may be suggestive (82). However, similarly to adenocarcinoma subtypes, we do not have enough data to independently recommend changing of the surgical strategy basing on the premises concerning histopathological subtype or STAS status on the basis of radiomic assessment of solid tumors.

Typically, GGO lesions represent lepidic growth of adenocarcinoma and have significantly better prognosis than solid cancers. For such lesions, limited surgical resection (that preserves lung parenchyma) is an attractive option. There have been many reports on rates of RFS after the limited resection of a GGO lesion. Ye *et al.* reported RFS

and OS of nearly 1,000 patients who received operation for pure-GGO, mixed-GGO, and solid nodules in a Chinese hospital. The prognosis for patients with pure-GGO and mixed-GGO lung cancers were substantially better than for those with solid cancers. However, they observed a slight survival difference between pure and mixed-GGO both in terms of recurrence-free and OS (83).

Several reports on both pure and mixed-GGO have shown 100% 5-year survival in patients who received sublobar resection for GGO NSCLC (84,85). In contrast, Nakao *et al.* reported local relapses in the resection margin in the period beyond 5 years (86). Considering this finding, the observation period for NSCLC patients treated for GGO lesions must be longer than 5 years to definitively decide if sublobar resection is the most appropriate treatment option.

Finally, a recent important issue concerning subsolid lesions is their intraoperative identification both during either open or VATS surgery. Several types of marking techniques have been proposed but none of them are sufficiently standardized to be recommended as favorable. Further, all of them are time-consuming and require considerable organizational efforts (87,88).

In summary, sublobar resections such as anatomical segmentectomy are recommended when the patient has limited performance on pulmonary function tests or has other significant comorbidities (16,37). Sublobar resection should also be considered for patients with nodule diameter ≤ 2 cm, with pure AIS histology, when more than 50% of the diameter of the pulmonary nodule has GGO attenuation on CT, or when there is a slow VDT (longer than 400 days, indicating low aggressiveness) (37). Sublobar resections should provide an adequate, at least 2 cm margin of resection within the lung parenchyma or the margin that extends tumor diameter in larger lesions (37). In addition, lymphadenectomy or sampling of the hilar and mediastinal lymph nodes is indicated in sublobar resection (37). Qualification for sublobar resection of solid adenocarcinoma up to 2 cm should be cautious. Even small tumors may contain aggressive components such as a micropapillary component or the presence of STAS, while both features are unavailable preoperatively. Further work is needed to assess the influence of the adenocarcinoma subtype and the type of the surgery performed on the risk of local recurrence or long-term survival.

Minimally-invasive approach to resection

VATS or a robotic approach should be considered if there

are no surgical contraindications (37). It has been shown in many observational studies that videothoroscopic procedures have at least the same long-term outcome benefits in the treatment of lung cancer as operations performed by traditional thoracotomy. In many reports, the early postoperative period is more favorable after a videothoroscopic procedure (89,90). Minimally invasive access is associated with a shorter hospital stay, lower risk of perioperative complications, and significantly less postoperative pain (89-94). The results of numerous observational studies, as well as meta-analyses, also confirm favorable long-term survival after surgical treatment performed with the VATS technique. In the recently published meta-analyses by Chen *et al.*, 20 studies were evaluated, comparing the videothoroscopic approach with thoracotomy. That report found advantages of the VATS technique, including decreased blood loss, chest tube drainage removal, length of hospital stay, and lower incidence of complications (95). There was greater improvement in the 5-year survival rate of the VATS group compared to the thoracotomy group. ACCP recommends choosing a minimally invasive technique in resections of early lung cancer stages at experienced centers (96). A VATS approach should be chosen as the surgical approach for resection of the early-stage lung cancer as often as possible (37).

Non-surgical treatment approaches to early stage NSCLC

To date, there are no data comparing the results of surgical and non-surgical treatment for patients with stage I NSCLC. Several attempts at RCTs comparing long term results of stage I NSCLC treatment of surgery and SBRT have been conducted. However, each of those studies had to be terminated due to poor recruitment, there are several ongoing trials studying neo and adjuvant treatments combining SBRT with immunotherapy or targeted therapies (38). Together with systemic treatment radical radiotherapy is the basis for the treatment of patients with TNM stage III. Currently, stage I and II patients are considered to be eligible for radical radiotherapy when they are not candidates for surgery or do not agree to surgery (37).

SBRT is a type of radiotherapy with a proven, high rate of local control and low toxicity in the treatment of early lung cancer. According to a systematic review by Senthil *et al.* the median survival of patients treated with SBRT is 40.7 months, and the rates of local, regional and distant recurrence are 4.9%, 7.8% and 14.7% over 2 years and 10.5, 12.7% and 19.9% over 5 years, respectively (97). The

most common complication after SBRT is pneumonitis, which often appears within 4–5 months of therapy. Other complications include a rib fracture, occurring in approximately 3% of patients, dermatitis in 2%, myositis in 1% (98). In the 2 years following treatment, some patients have a worsening of lung function, and FEV1 and DLCO are reduced by 3.6 and 6.8% on average (99).

In today's screening era there is a great need for RCTs comparing all types of local treatments to determine the most effective and less harmful local and systemic adjuvant treatments for a newly created group of patients with a variety of different lung cancers. Optimally, such a study should be three-arm study comparing surgery, radiotherapy, and other ablative therapies (i.e., radiofrequency ablative therapy) that were suggested by Tramontano *et al.* in their simulation (100).

Treatment of early lung cancer patients in COVID-19 pandemic

The COVID-19 pandemic, caused by the virus SARS-CoV-2, has had a broad array of significant epidemiology, economic and sociologic effects. Importantly, there is a risk that patients may skip regularly scheduled cancer screenings out of an abundance of caution of spreading or contracting SARS-CoV-2. Indeed, the rescheduling of oncological care in regions suffering from the pandemic is a delicate issue. Providers must balance the necessity to appropriately treat patients with malignancy and also to take measures to prevent the spread of the epidemic. The difficulties in controlling the epidemic are a direct result of the biology of the virus. The incubation period of 2–7 days (median 4 days) leads to the uncontrolled spread of the disease during the asymptomatic period (101). The presence of comorbidities (including malignancies), male sex, and older age are associated with worse outcomes for patients with COVID-19 (101–103). In a multifactorial analysis, COPD (HR 2.68, 95% CI: 1.42–5.05) and malignancies (HR 3.50, 95% CI: 1.60–2.77) were found to be independent risk factors for composed risk of respiratory insufficiency and death (103).

Sixteen percent of patients diagnosed with COVID-19 suffer from a severe course of the disease leading to profound respiratory insufficiency (101). The symptoms of COVID-19 may be similar to those of lung cancer and may be mistaken, especially at the patient's initial presentation. Fever, dry cough, fatigue, anorexia myalgia, dyspnea, and sputum production are almost uniformly shared symptoms

for lung cancer and COVID-19 (101,104,105). This pattern of similar symptoms leads to the distress in some patients. Mental status is impacted not only through suffering from lung cancer but also by the uncertain threat of viral infection.

Patients with early lung cancer often present with significantly heterogeneous symptoms. Indeed, most patients need to visit the healthcare facilities many times to adequately diagnose, stage, treat, and then observe lung cancer (106). They commonly require assistance from members of their family. The lung cancer population is typically old, with comorbidities, not well-educated, and potentially at risk of worse adherence to recommended COVID-19 prevention guidelines. Any pneumonia, including COVID-19 complicates lung cancer in patients with marginal lung function, can be an obvious life-threatening event (106).

In a large study by Liang *et al.* lung cancer patients were the most common among cancer patients infected with SARS-CoV-2. Patients with malignancies were older, smoked more, and had faster respiratory rates. All of these factors resulted in an increased risk of respiratory insufficiency (requiring ventilation) and death (39% *vs.* 8% $P < 0.001$). The general condition of patients with malignancies deteriorated more rapidly (HR 3.56, 95% CI: 1.65–7.69). However, presumably, due to a small number of cases, patients with lung cancer were not significantly different from other patients with malignancies (107).

Li *et al.* presented preliminary recommendations for lung cancer surgery in the epidemic period (108). These recommendations were developed in an early period of the pandemic and published electronically in late February. The organizational remarks indicate that lung cancer diagnosis and staging should continue to be conducted in community hospitals. Patients and their families should avoid unnecessary journeys to high volume centers. Another recommendation suggests postponing the assessment of benign and doubtful lesions until the post-pandemic period. A similar approach should be followed for pure, mixed, or multiple GGO lesions. Every symptomatic patient should be tested for SARS-CoV-2 infection before transfer to the thoracic surgery department. However, the most important indications from that paper refer to the treatment of confirmed lung cancer. The lesions confirmed by cytology or that are highly suspected on PET/CT, and smaller than 3 cm should be closely observed (not less than 3 months) and operated as soon as tolerable with the respect to the local viral outbreak. The control chest CT

should be performed monthly. If, during the observation, the tumor diameter increases more than 20% or exceeds 3 cm, the patient should be scheduled for surgery. In locally advanced, resectable tumors, Li *et al.* recommends the use of neoadjuvant therapy to postpone the extensive surgical resection. The salvage surgery may be recommended if postponing is not an option due to the occurrence of life-threatening symptoms such as severe hemoptysis (108).

The authors underline the importance of not performing lung cancer surgery in patients with SARS-CoV-2 infection. Testing should be performed in symptomatic patients and should be followed by 14-day-long quarantine. On the day before surgery, blood tests (CRP) and chest CT should be repeated, if possible (108).

Intensified measures should be undertaken to prevent cross infections. In urgent cases, when there is no sufficient time to undertake optimal precautions patients should be tested and the protective procedures should be implemented right away. Patients with confirmed SARS-CoV-2 infection should be isolated and transferred to the designated hospital. Negative patients should continue their treatment in the regular ward.

The paper by Li *et al.* also presents a local protocol for postoperative care. The authors recommend blood tests on a postoperative day one and then every 3 days thereafter. Postoperative chest CT should be performed routinely. In the case of increased body temperature ($>37.3^{\circ}\text{C}$), the treatment should be performed after the exclusion of SARS-CoV-2 infection. If the fever persists for more than 48 hours and other reasons like surgical wound infection or empyema are excluded, the tests for SARS-CoV-2 should be repeated. The postoperative in-hospital stay period should be short to reduce the risk of cross-infection. These patients require a multi-specialist approach which may not be possible due to shortages of specialist staff. In one sense, this shortage key resources due to the epidemic may support delaying the implementation of intensive therapy, then reasonable. There is no doubt that SARS-CoV-2 is changing oncological practice. Realistically, it is not possible to suggest a single policy to be adopted across the world. However, there is a place for local consensus—national or regional which take into consideration the local incidence, and mortality, and are in line with local resources.

Summary

In summary, transthoracic needle aspiration biopsy remains the first-choice method of diagnosis of early

stage lung cancer. Bronchofiberscopy, especially in combination with ENB, fluoroscopy or radial EBUS, also allows effective diagnosis of the peripheral pulmonary nodules. One of the most important diagnostic methods is the EBUS examination, which allows determining of staging in addition to diagnosis. An anatomical lung lobe resection and lymphadenectomy or sampling of the hilar and mediastinal lymph nodes is the treatment of choice for patients with stage I and II NSCLC. Sublobar resections are recommended when the patient has limited performance on pulmonary function tests or has other significant comorbidities. Sublobar resection should also be considered for patients with nodule diameter ≤ 2 cm, with pure AIS histology, when more than 50% of the diameter of the pulmonary nodule has GGO attenuation on CT, or when there is a VDT >400 days. A minimally invasive technique, VATS approach should be chosen as the surgical approach for resection of the early-stage lung cancer as often as possible. Patients who are not candidates for surgery can be offered SBRT.

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