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Inside This Issue

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Editorial: The Role of Liquid Biopsy in the Management of Non-small Cell Carcinoma

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Lung cancer is the second most common cancer type with an estimated 228,000 new cases and 135,700 death annually representing nearly 13% of all cancer diagnoses and 22% of all cancer death in the United States[1]. Strategies to reduce lung cancer death include prevention by eliminating risk factors (i.e. reduce smoking and other toxic inhalants like radon), early detection by developing screening guidelines, and providing personalized therapy both for locoregional and metastatic disease.

Nearly 50% of all lung cancers are non-squamous non-small cell carcinomas the majority of which being adenocarcinomas. Approximately 60% of these tumors are known to have a driver genetic alteration. Personalized therapy requires accurate histologic diagnosis and staging together with identification of targetable genetic alterations (*EGFR, ALK, ROS1, BRAF etc.)* and predictive biomarkers (PD-L1). Pathologic classification requires a tissue or cytology sample and the gold standard for molecular studies is also tissue-based. Close to half (49%) of non-small cell carcinomas are diagnosed as advanced stage (IIIB or IV) disease and the diagnosis is typically is based on a biopsy of the primary tumor or a metastasis[2]. This can result in small samples containing insufficient tumor for biomarker analysis. This is particularly true for hard-to-reach small lung nodules, in the presence of marked necrosis and samples of metastatic mediastinal lymph nodes with minimal to low tumor burden. Similarly, a subset of loco-regional disease is not amenable to surgical intervention and therefore needs a biopsy to establish the diagnosis. Current NCCN guidelines require testing for targetable alterations with FDA-approved therapy (*EGFR, ALK, ROS1, BRAF, NTRK, METexon14*) all non-squamous non-small cell carcinomas, and squamous cell carcinomas of never or former light smokers. In addition, *EGFR* mutation testing should be performed in stage IB-IIIA adenocarcinomas, and PD-L1 should be assessed in all non-small cell carcinomas[3]. There is a need for an alternative testing method for patients who are not candidates for a biopsy or whose biopsy resulted in insufficient tissue for biomarkers.

Cell-free DNA (cfDNA) is a product of dying non-neoplastic cells (mostly white blood cells) that can be detected in the blood/plasma and other body fluids as can be cell-free tumor DNA (ctDNA) and exosome DNA. The amount of circulating ctDNA is determined by the number of tumor cells shedding into the bloodstream, which varies between tumor types and tumor stage. Liquid biopsy is a test that examines the presence of ctDNA, circulating tumor cells, or exosome DNA in various types of body fluids (i.e. plasma, pleural fluid, cerebrospinal fluid etc.). Liquid biopsy can be used to detect mutations, translocations, copy number alterations, and allele frequency at initial diagnosis, as well as when monitoring disease recurrence or therapeutic responses. Several different assay types are being used and they can be grouped based on the number of genes targeted, namely as single gene or multi-gene assay. Single gene assays use highly sensitive PCR-based methods (i.e. real-time PCR, digital droplet PCR), while most multi-gene assays use next-generation sequencing (NGS). Single gene assays require more tumor DNA and higher tumor content and can only detect mutations that are specifically targeted by the assay. In contrast, NGS assays

require less DNA and lower tumor content, can detect unknown mutations (hybrid capture method), and work well with fragmented DNA.

There are several FDA-approved liquid biopsy assays in advanced-stage lung cancer while there are no approved assays for early-stage (loco-regional) disease. The FDA-approved assays are the cobas® EGFR Mutation Test v2 (single-gene test, approved in June 2016)[4], as well as the Guardant360 CDx and FoundationOne Liquid CDx assays (both NGS based, approved in August and November 2020, respectively)[5,6]. Liquid biopsy testing is also performed using laboratory-developed-validated assays. These liquid biopsy assays have shown a good correlation with matched tissue-based testing results (i.e. 81.3% concordance in a study of 128 tumors)[7]. On the other hand, results in early-stage non-small cell lung cancer have shown poor correlation with tissue-based testing[8,9] even though the frequency of targetable driver mutations appears to be similar at diagnosis across all stages (i.e. a study of lung adenocarcinoma showed that the prevalence of *EGFR* mutations ranged between 22-26% in stage I-IV tumors)[10]. A recent study of 197 tumors showed concordance between matched plasma and tissue samples to be 12.4% in stage I, 58.3% in stage II, 55.6% in stage III, and 73.8% in stage IV disease[11]. The cause for this discrepancy is likely due to differences in tumor cell shedding, proliferative activity, and the extent of tumor necrosis.

Studies have also shown that liquid biopsy assays can identify circulating ctDNA in subclinical disease particularly when monitoring for disease progression or therapeutic effect. Numerous studies have also been published demonstrating that liquid biopsy can detect ctDNA in other body fluids including pleural fluids, CSF (especially in cases with leptomeningeal involvement), as well as fluid-based specimen preparations like bronchoalveolar lavage or aspirate supernatant.[12-14]

Liquid biopsy is increasingly being used in clinical practice primarily in patients with stage IV disease who have no or insufficient tumor tissue for testing. The availability and ease of collection of blood samples make plasma-based testing very attractive for oncologists, particularly in high-risk patients. The role of liquid biopsy with current approved methods in early-stage disease is in the experimental phase and the sensitivity needs to be improved before widespread adaptation can be done.

Future trends include improving sensitivity and specificity of the molecular assays, developing new methods that can detect epigenetic changes of targetable alterations, as well as tumor-specific genome-wide DNA profiles including epigenetic (methylation) patterns using cfDNA as the source[15]. This approach could help develop a blood-based screening tool for early detection of tumors, targetable alterations and potentially provide prognostic information regarding disease recurrence and therapeutic response.

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Technology Corner

Cone beam CT Applications for Bronchoscopy

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Introduction

Cone beam CT (CBCT) imaging is a relatively new modality in interventional pulmonology, but is a frequently used technology supporting interventional radiology and/or cardiovascular procedures. As such, it is often a readily available system in most centers. It is furthermore likely that these systems have considerable downtime [1] as only one or two specialties are performing specialized procedures using the CBCT which, in some institutions, offers the opportunity for the interventional pulmonologists to use it.

Background

The term cone beam CT refers to the fact that the systems allow for a 3D X-ray projection by rotating a C-arm with a cone-like diverging X-ray beam around the patient in several seconds. This is different than that of conventional CT, where it is foremostly a narrow fan-like beam of X-rays rotated in helical fashion around the patient with high speed. While this gives additional challenges from a technological perspective, it allows for unique additional features too. The fixed C-arm of the CBCT arm leaves a lot of open space as working area and is registered with the table on which the patient is positioned. Once an initial CBCT scan has given 3D information, a digital work station in the room can subsequently be used to segment certain regions of interest or pathways thereto. After segmentation, subsequent 'normal fluoroscopy' 2D imaging within the room is enhanced with the projection of the segmented volume and/or pathway. This overlay, called augmented fluoroscopy (AF), is then accurately maintained in 3D during every movement of the C-arm and table, and can be used to navigate towards the lesion.

Clinical application

When attempting to biopsy small peripheral nodules, cone beam CT guided navigation can be used to navigate towards, and subsequently biopsy the target lesion. Although multiple different modalities are available for navigation, cone beam CT systems offers additional value since it can accurately confirm target access in 3D. This confirmation is vital for optimal diagnostic sampling, deliver markers, and local therapeutic procedures.

How we do it

Our current navigation bronchoscopy program is based upon the therapeutic bronchoscope and catheters in combination with CBCT and rEBUS under general anesthesia. After an initial inspection bronchoscopy, commercially available steerable navigation catheters (e.g. from electromagnetic navigation systems) are inserted. After inspection, a first quick attempt is made to insert the catheter according to the pathway as memorized on pre-procedural CT. The scope is fixated above the patient. The radiation technician checks if a full collision free C-arm rotation can be made. Everyone leaves the room and an initial 3D CBCT acquisition is made in breath-hold. Both the target nodule and the route toward this nodule are segmented and overlayed as augmented fluoroscopy imaging (AF) on the dedicated workstation. For enabling navigation, small 'dots' are placed at the bifurcations along the route to highlight the route and additionally show where correct angulation is most important (Figure 1). Subsequent augmented

fluoroscopy imaging can now be performed with different C-arm angulations, having the overlayed route and lesion to confirm repositioning or progression. When the target lesion is close, radial EBUS miniprobes and 3D-image confirmation with a new CBCT acquisition are used to confirm lesion access. If needed, repositioning is performed under additional image guidance. After lesion access confirmation, tissue sampling is repeatedly performed under guidance of AF and repeated rEBUS. Sampling is performed under AF at multiple angulations and small, constant adjustments of the catheter rotation and position.

We frequently perform 2 CBCT scans (of different dose) per lesion. Depending on system settings, patient characteristics and the amount of collimation used, an initial 'high quality' CBCT acquisition will result in a patient dose of approximately 2-4 mSv. Total procedural (augmented) fluoroscopy dose is highly dependent on how specific and sparsely it is used. As an example, at the start of our program the procedural fluoroscopy patient dose was 5.2 mSv (592 seconds). In an experienced setting (i.e >100 procedures), we however reduced to a mean of 0.37 mSv per procedure (935 seconds). Knowing the staff should leave the room during CBCT acquisition and wear adequate protection and systematically put a mobile safety screen in between themselves and the c-arm, the staff dose seems to be of a lesser concern.

Accuracy

Several studies have reported on their accuracy findings when using CBCT in addition with other guidance techniques, reaching diagnostic yields of 70-84% [2]. Combining above mentioned workup with EMN in approximately half of procedures, our initial report found an overall diagnostic accuracy of 72% in 87 patients [3]. Importantly however, analysis of our program after having performed more than 150 procedures shows the changing performance over time. In a more recent series (Nov 2019 – June 2020) of 64 patients, an accurate diagnosis without changing inclusion criteria could be obtained in some 90% of patients [4]. This is a significant improvement over our own and other previously reported accuracies with commercially available technology. However, our analysis of more than 200 consecutively CBCT guided navigation bronchoscopy cases also shows that there is an important learning curve to overcome [3, 4].

Conclusion

Cone beam CT guided navigation bronchoscopy is a valuable option to navigate to, and obtain a tissue diagnosis in small, peripheral pulmonary nodules, and is likely a prerequisite to precisely deliver minimal invasive treatments. The limited data available seem to imply it has the potential of a high diagnostic accuracy, outperforming other technologies, but it is important to note there is a significant learning curve to overcome. The radiation dose needed is (relatively) low. Further research is warranted to improve the 'intuitiveness' to use this guidance tool as well as improvement of our sampling tools to reduce procedure time.

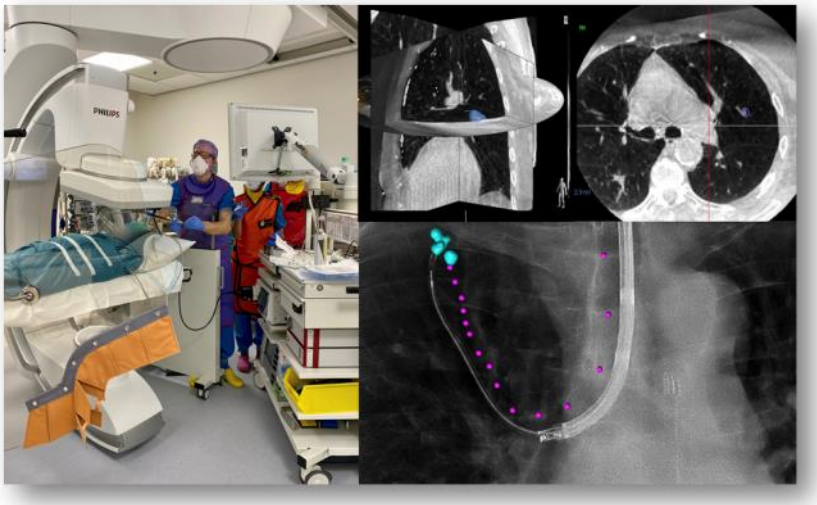

Figure 1:
On the left: CBCT-based navigation bronchoscopy in progress. On the right, top: two images of the workstation for segmentation. On the right, bottom: augmented fluoroscopy image of the extended working channel with the radial EBUS miniprobe being inserted into the target lesion (in blue-green). The red dots indicate the navigation route.

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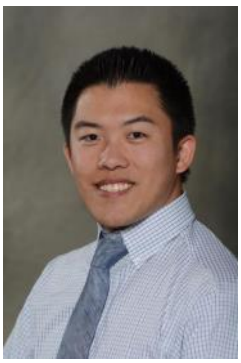
Indwelling Catheters and Pleurodesis for Managing Recurrent Malignant Pleural Effusion



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Introduction

More than 50% of patients with malignant pleural effusion (MPE) reaccumulate fluid after the initial drainage, with up to 30% of patients developing rapid re-accumulation within two weeks [1,2]. Guidelines from professional societies recommend that patients who are symptomatic with recurrent suspected or known MPE should undergo definitive pleural interventions [3-5]. These interventions include talc pleurodesis with or without thoracoscopy, and tunneled indwelling pleural catheter (TIPC) placement. These procedures result in fewer subsequent pleural procedures and complications such as pneumothorax and complex pleural space [1]. Despite the high incidence of MPE, guideline consistent care of providing definitive pleural intervention is followed in less than 25% of patients [1]. Here, we aim to provide a rationale for selecting the appropriate definitive pleural intervention for managing patients with recurrent MPE.

Indications, planning and techniques for specific pleural interventions

1. *Talc Pleurodesis with Insufflation or Slurry*

In patients with recurrent symptomatic MPE who experience relief of their dyspnea with fluid drainage and have a complete or partially expandable lung, achieving pleurodesis can minimize pleural fluid reaccumulation. This can be achieved via chemical pleurodesis by instilling a sclerosant, such as talc, into the pleural space. Talc pleurodesis can be performed by instilling talc slurry via a chest tube or by insufflation during thoracoscopy by applying a spray atomizer. This can be performed using a dedicated catheter either through the trocar adjacent to the rigid pleuroscope or a catheter inserted through the working channel of a semi-rigid pleuroscope. In both cases, talc insufflation can be applied under direct visualization, maximizing the distribution of the talc on the desired surfaces, which should include normal parietal pleura (Figures 1A,1B).

There is mixed data regarding the optimal method for talc delivery. Several randomized trials, systematic reviews, and meta-analysis suggest no overall difference between thoracoscopic talc insufflation and bedside talc slurry via chest tube in regard to pleurodesis success, complications, clinical outcome, or recurrence of pleural effusion [6-10]. That being said, pleurodesis success rate using thoracoscopic talc insufflation for MPE has been reported as high as 77-98% [11-16]. One systematic review suggested that talc insufflation was associated with less risk of recurrence than talc slurry via chest tube [17]. In addition, in a post-hoc analysis, Dresler *et al.* showed that patients with primary lung or breast cancer were noted to have higher rate of pleurodesis with talc insufflation compared to talc slurry via chest tube (82% vs 67%) [8]. Terra *et al.* noted that immediate partial lung expansion was more frequently seen in patients who received thoracoscopy with talc insufflation as opposed to talc slurry via chest tube (60% vs 30%) [9]. Whether this translates to improved clinical outcomes is unclear.

The decision to proceed with either talc insufflation or talc slurry depends on the local resources, operator experience, patient risk factors, and patient values. In our institution, patients with relatively good performance status (ECOG 0-2) and sometime ECOG 3, are offered both

thoracoscopic talc insufflation and TIPC. Patients with poor performance status (ECOG 3-4) at high risk for anesthesia, are usually managed with TIPC. We do not routinely place a chest tube for talc slurry in these patients, but if patients already have an indwelling chest tube, then talc slurry via the existing chest tube is performed.

2. ***Tunneled Indwelling Pleural Catheter Placement***

While partial or complete re-expandable lung is needed for chemical pleurodesis, TIPC placement is the treatment of choice for patients with non-expandable lung, or those who failed chemical pleurodesis. This is relevant, especially since some data suggest that approximately 30% of patients with MPE have non-expandable lung [8]. The major disadvantages are the need for frequent drainage (sometime considered by patients an intervention per se), the need for clinic appointments to troubleshoot catheter occlusion and management of catheter-related skin infection, as well as lifestyle modifications that have to account for time to drain the catheter on a regular basis (every day per some protocols) and avoiding soaking the catheter in water (e.g. pool, bathtub). Regardless of lung expandability, several guidelines suggest that TIPC placement is just as effective as talc pleurodesis in relieving symptoms of dyspnea and improving quality of life in patients with recurrent MPE [2-4]. Two landmark studies (TIME2 and AMPLE) showed no difference in the relief of dyspnea between TIPC placement and talc pleurodesis, however showed reduced length of hospital stay and need for subsequent pleural procedures in patients who received TIPC placement [18,19].

TIPC can be placed either under local anesthesia at the bedside (or procedure suite) with ultrasound guidance or via thoracoscopy under direct visualization (Figures 1C,1D). In both cases, the indwelling catheter should be guided towards the diaphragmatic recess to facilitate complete evacuation of the pleural fluid. Although pleurodesis is not necessarily the goal for TIPC placement, spontaneous pleurodesis has been reported in 30-58% of patients who undergo TIPC placement [19-23]. This may be the result of keeping the pleural space dry with daily drainage allowing for approximation of the pleural surfaces, and the inflammatory response caused by the presence of the indwelling catheter in the pleural space. We have also noted spontaneous pleurodesis in some patients with non-expandable lung on initial evaluation. This may be due to shifting of thoracic structures within the chest cavity (ipsilateral mediastinal shift, elevation of the hemidiaphragm) as a result of daily drainage of pleural fluid resulting in the approximation of pleural surfaces, lack of drainage, and subsequent catheter removal.

In our opinion, a meaningful dialogue with patients and their caregivers is in order prior to inserting a TIPC that may be needed for months (median time to TIPC removal: 44-90 days), if not for the rest of the patient's life [20,24]. Correct expectations should be set in regard to frequency of drainage, chance of catheter removal, possibility of fluid recurrence after catheter removal (4-14%) [24], and potential TIPC-related complications and their management (including occlusion and infection).

3. ***Thoracoscopy: Stand Alone, with TIPC Placement, Talc Insufflation or a Multimodal Approach***

Thoracoscopy can be performed either under moderate sedation or general anesthesia. In our practice, thoracoscopy is performed in the operating room with the patient under general anesthesia. Double lumen intubation is used to permit single lung ventilation during the procedure. This allows for deflation and isolation of the target pleural space, giving the operator maximal pleural cavity to work with during the procedure. We routinely use ultrasound guidance not only to confirm that the lung has been properly isolated (US reveals pneumothorax pattern at the desired point of entry), but also to define the complexity of the pleural space, which may predict the need for a more complex intervention, rather than a single port thoracoscopy. Once the trocar is inserted, either rigid or semi-rigid pleuroscope is used for drainage, exploration of the pleural cavity, and to obtain pleural biopsies, if needed for tissue diagnosis or ancillary studies (molecular testing, PD-L1 testing, etc.).

Even though thoracoscopy is often used in conjunction with either TIPC placement or talc pleurodesis, the ability to induce pleurodesis may also be intrinsic to thoracoscopy. Suzuki *et al.* noted that spontaneous pleurodesis occurred in 53% of patients who underwent thoracoscopic placement of TIPC as compared with 28% of patients who underwent TIPC placement via standard technique [25]. Another study demonstrated spontaneous pleurodesis rate of 58% in patients with trapped lung undergoing TIPC placement via thoracoscopy [26]. This may be the result of completely drying out the pleural space under direct visualization, mechanical irritation of the pleural space from thoracoscopy incision and pleural biopsies leading to an inflammatory response, and the ability to perform adhesiolysis in patients with loculated effusions.

There is increasing interest in combining the use of TIPC placement with talc insufflation in patients undergoing thoracoscopy during the same procedure in order to improve the likelihood of pleurodesis and reduce the time to catheter removal. We routinely apply this approach. We believe that in addition to the intrinsic ability of thoracoscopy to induce pleurodesis, direct visualization under thoracoscopy allows for directed application of talc insufflation across the pleural surfaces and guidance of the TIPC placement towards the diaphragmatic recess. The data supporting this practice is limited, but emerging. In a pilot study, the combination of thoracoscopy with talc insufflation and TIPC place-

ment in the same procedure resulted in high pleurodesis success of 92% and early TIPC removal, with median duration of TIPC of 7.54 days post-intervention, and median length of hospital stay of 1.79 days [27]. Similarly, in a prospective observational study, the combination of thoracoscopy with talc pleurodesis and TIPC placement also resulted in high pleurodesis success of 92% at 1 month, 96% at 6 months, and early TIPC removal, with median duration of TIPC of 6 days post-intervention, and median length of hospital stay of 3 days [28]. Therefore, we believe that when discussing with patients the options for more definitive pleural interventions for their recurrent and symptomatic MPE, it is important to assess their values and evaluate whether the benefits of early TIPC removal seen with thoracoscopic TIPC placement, outweighs the risks of thoracoscopy and the costs of post-procedural hospitalization. In addition, hospitalization is not always necessary; in fact, some operators apply a rapid pleurodesis protocol, which involves discharging patients 24-hours after combined thoracoscopy with TIPC placement and talc pleurodesis, with continued home TIPC drainage [27]. In patients with concurrent need for pleural biopsies, complex pleural effusions, or unwillingness to have a long-term TIPC, a multimodal approach should be considered given the possibility for early TIPC removal.

Quality Control: Post-procedural Management

Hospitalization

TIPC placement with local anesthesia can be performed on an outpatient basis and does not require hospitalization. However, with thoracoscopic TIPC placement and talc pleurodesis, there is a subsequent increased inflammatory response in the pleural space usually leading to pain and increased pleural drainage. In our practice, in addition to the TIPC, a 24-28Fr chest tube is placed during thoracoscopy in order to allow for continuous drainage to keep the pleural space as dry as possible to optimize the effects of talc pleurodesis. We typically keep patients hospitalized for 1-3 days until the pleural fluid drainage is minimal (<100-150 cc) and to allow for optimizing pain control and continuous pleural drainage [29]. An alternative approach, using rapid pleurodesis concept, involves discharging patients 24-hours after combined thoracoscopy with TIPC placement and talc pleurodesis, with continued home TIPC drainage (three times daily on post-op day 1, two times daily on post-op day 2-3, and then daily) [27]. Randomized trials have not been performed comparing the two approaches in regard to pleurodesis success, symptomatic improvement and need for repeat interventions.

Drainage Protocol

The ASAP and AMPLE2 trials evaluated daily TIPC drainage as compared with alternate day drainage and symptom-based drainage, respectively, and demonstrated higher rates of spontaneous pleurodesis in patients who drained daily [20,21]. Although, there was no significant difference in dyspnea control between the two groups, the higher rates of spontaneous pleurodesis in patients who drained daily may translate to early TIPC removal. In our practice, we recommend daily drainage until drainage is less than 150 cc daily on three occasions, which is then extended to every other day drainage. Once drainage is less than 150 cc on three occasions, drainage is extended to every three days. If drainage is still less than 150 cc on three occasions, we evaluate patients at that time for TIPC removal.

Follow-Up

Post-procedural care is often institutional and resource dependent. At our institution, we evaluate patients in clinic two weeks after the procedure or sooner if needed with repeat chest imaging and suture removal on the day of clinic visit. There is emerging evidence that TIPC removal is sometime performed at the time of disease control, not because of pleurodesis. In fact, we routinely perform thoracic US at the time of TIPC removal with the intent to predict which patients are more likely to recur after catheter removal based on sonographic findings of lung sliding or to document possible pleurodesis by visualizing the lack of lung sliding [24].

Conclusion

Pleural interventions for palliating symptoms due to MPE are recommended for patients with recurrent symptomatic MPE who experience relief of their dyspnea with fluid drainage. Decision to select the appropriate intervention should be individualized based on local resources, operator experience, patient's comorbidities, functional status, and values. A multimodal approach including thoracoscopy with talc pleurodesis and TIPC placement as a more definitive pleural management may fasten the time to pleurodesis, allowing for early TIPC removal.

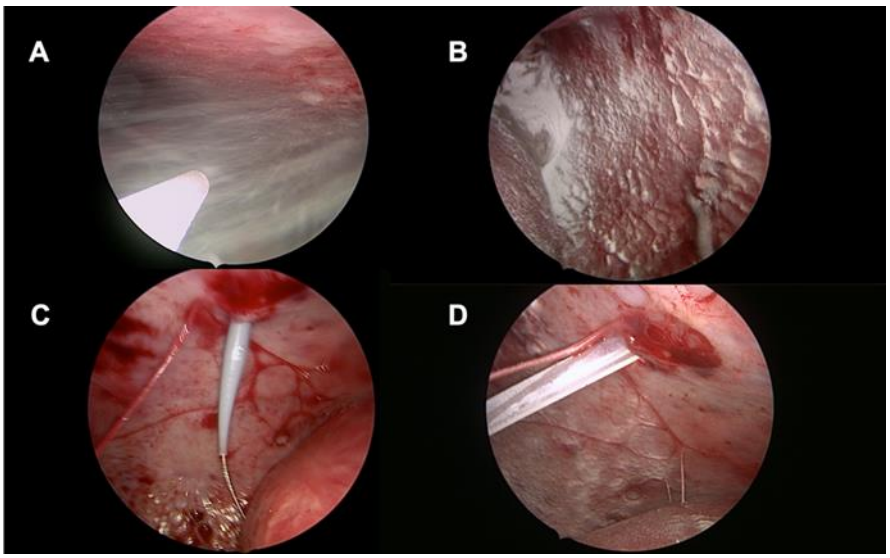

Figure 1: (A) Talc insufflation applied with thoracoscopic guidance. (B) Talc powder is distributed homogenously over the parietal pleura. (C) Dilator and guidewire are oriented towards the diaphragmatic recess during TIPC placement under direct visualization. (D) Successful TIPC placement with thoracoscopic guidance.

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Ethical Issues of Immunity Passports

Since the beginning of the pandemic, strict lockdown measures have been imposed in most of the countries in order to reduce the spread of the coronavirus. Social distancing, home working, only virtual activities for school, university and academic conventions were implemented in different times and with different length as well as mask wearing and home quarantining. Some of these measures had very significant social and economic costs, mainly by preventing many people from working. The main reason that has obliged to lockdown measures (increasingly unpopular because of their economic impact) is the potential for asymptomatic infection and spreading of COVID-19. People who do not experience symptoms when infected with COVID-19 is estimated to be around 40% and there is evidence that support the hypothesis that a large proportion of the transmission of the virus occurs before the onset of symptoms, making necessary to have ways of preventing of spreading of the disease from asymptomatic persons.

Most of governments do not consider mandatory vaccination as an acceptable strategy. But more recently, taking into account the new waves, new variants, increasing pressures to return to free circulation of people, many governments are considering some sort of immunity passports. Those certificates would allow people with proof of immunity (because of having suffered the disease and/or having received full vaccination) to have more freedom of circulation. But those proposals raise many logistical and ethical concerns as people without that certification will be excluded from everyday life.

The main purpose of vaccine passports is to allow people to travel, attend large gatherings, access public venues, and return to work without compromising personal safety and public health. The UK government recently announced that it is being analysed whether Britons will need a vaccination test or a negative Covid-19 test to visit bars, return to the office, or attend theaters and sporting events. Different countries are considering different activities that would be permitted for holders of those immunity passports but not to other people.

In Israel, a vaccine passport allows those vaccinated to go to hotels and gyms while Iceland is distributing vaccine passports to facilitate travel abroad for the vaccinated. In the US government, some agencies are evaluating the feasibility of creating digital Covid-19 vaccination certificates. New York's "Excelsior Pass" permits attendance at theaters, arenas, event venues, and large weddings and European Union plans a "Digital Green Certificate" that would allow free travel within the EU

Beyond different government intentions, it is pretty certain that proof of vaccination against COVID-19 may soon be a requirement for airline or cruise ship passengers. Some companies—like Qantas Airlines and the American Queen Steamboat Company—have announced that they will soon require "immunity passports," to use their services and some employers may soon mandate vaccinations as well.

Many tech companies, are working around the clock to provide the technology required for digital immunity passports, predicting that they will be widely used in the near future and many countries see they will need to develop those passport if they are requested by other countries in order to be able to ensure alignment with global standards.

But in spite of this rapid progress to the acceptability of the idea of the implementation of those certificates, there are still many scientific challenges and the discussion about if they are lawful and ethical Is not closed yet.

Immunity passports would a way to go back to a more normal social and economic life, but their potential benefits will be unequally distributed, giving rise to doubt about how ethical their implementation will be.

On the one hand, immunity passports offer an opportunity for employees to go back to work and families to reunite. On the other hand, they will not be available to everyone, and they will exacerbate existing inequalities.

An initial distinction should be established between "immunity passports" (those given to those who have suffered the disease and have proof of circulating antibodies) and the "vaccination passports" (applied only to those who have received a full vaccination).

As the COVID-19 pandemic progresses, many people worldwide will contract the virus and recover. Many of these will be asymptomatic or experience mild symptoms only. Whether all illness results in sufficient levels of neutralising antibodies to prevent against reinfection is still under investigation. Although experience with diseases like severe acute respiratory syn-

drome (SARS) and Middle East respiratory syndrome (MERS) suggests that antibody responses are likely to persist for at least a year it is not fully established yet what level of immunity is conferred by infection. It is reasonable (although not proved) to believe that people who have been infected and subsequently recovered are likely to be at least temporarily at lower risk of reinfection or severe disease and less likely to spread the virus to other people. But the extent and duration of immunity infection from COVID-19 is uncertain and the WHO has repeatedly stated that there is no evidence of lasting immunity in those recovered from COVID-19. In fact that evidence would be to wait very long after infection and test the immunity in recovered patients to confirm the prevalence of antibodies at 1, 5, 10 or more years.

If antibody responses to COVID as in SARS and MERS are waned after 2–3 years, immune passports should be time limited. A significant limitation on the introduction of immunity passports is the need for a sufficiently reliable rapid test for COVID-19 antibodies. Antibody, or serology, tests identify whether someone has developed antibodies to COVID-19. Assuming that antibodies do indicate solid immunity, the challenge lies in correctly identifying those antibodies in a way that permits testing to be scaled up significantly, without exceeding a tolerable level of false positives/negatives.

Different tests vary in their accuracy and the quality of the evidence we have about their accuracy. The sensitivity of tests in the first week or two after infection may be low. An additional problem is that the numbers of false positive and false negative tests (and so the impact those errors have) will depend on the baseline rates of infection. If the rates of seropositivity are low, many of those identified as being immune will be false positives. On the other hand, antibodies might not be identifiable in blood tests until days or weeks after illness has resolved, resulting in a delay between an individual being infected with COVID-19 and being tested seropositive.

Widespread antibody testing could facilitate a faster return to a more normal way of life for at least some of the population. But it could also create new pressures to intrude on people's privacy and free choice. Employers may want all their employees to undergo testing creating pressure on people into testing in this manner.

The feasibility of being tested (and consequently have the possibility of having proof of immunity) requires the consideration of who should be prioritized for testing, not only taking into account the cost and logistic burden of over testing but also the need to avoid harmful misdiagnoses. It is likely that testing will be prioritized to healthcare staff and other key workers as care home staff, police, supermarket staff, transport workers and some others that need to keep on working to permit social functioning. It means that those populations would receive the privilege of having access to tests and consequently proof of immunity. It would not necessarily be unfair. The public good that those workers mean if they are allowed to move around more freely, justifies their position of privilege for antibody testing and immunity passports. But if immunity passports were to be introduced, it is unclear how other groups should be prioritized relative to one another to not create an unfair inequality of access to restricted activities as it is likely that possessing an immunity passport would be a significant benefit, advantaging holders relative to non-holders.

As fairness requires all people to be treated the same in a strict sense, this would indeed be the case. But it is also true that such a simplistic model of fairness is not appropriate in the current extraordinary conditions and that privileging fairness above other values (such as benefits to individual well-being and economic recovery) is not necessarily a moral imperative.

The more people that are able to return to some of their normal functioning, the better for society as a whole. On the other hand, there is a risk of resentment from those unable to work or socialize due to their continued susceptibility. This could result in a reduction in social cohesion and a loss of support of restriction measures, which could have a negative impact in the longer term management of the pandemic. There might also be some concerns that those most likely to acquire immunity (and thus, immunity passports) are those who have been least responsible in following government guidelines while those who strictly respected social distancing are the least likely to acquire immunity and immunity passports. It would mean that immunity passports could reward the least responsible or even incentivize incautious behavior (as intentional exposure to the virus), in order to acquire an immunity passport 'legitimately' . It would undermine the efforts of containing spread of the virus.

Successfully avoid getting COVID-19 should be enough advantage for those who behave conscientiously, but it would still be unfair. To avoid that, governments should withhold immunity passports from those who acquire immunity through reckless behaviour. It would require public education campaigns that make people aware that if they are caught violating the rules, they will be ineligible for immunity passports. But, it will be difficult to determine retrospectively whether an individual with immunity acquired it through incautious behavior or not.

Humanitarian News

In order to prevent the creation of fraudulent immunity passports, systems of verification will be needed. A higher investment in technology would be necessary for the passports be harder to forge and punishments should be applied for those involved in the black market of passports. All that machinery would largely decrease the economic benefits of immunity passports.

Taking into account all the challenging issues, especially the many ethical questions but mainly the enormous scientific uncertainty to support the use of immunity certification for those having suffered the disease and showing proof of having antibodies, have not been widely accepted.

But with the availability of vaccination the idea of using certification of immunity, but restricted to immunity conferred by vaccines, has re-emerged with force, as there is more scientific evidence for immunity from vaccines than from natural immunity.

However, even when the scientific foundations are stronger and some logistic issues are easier to resolve, vaccination passports still have their own ethical challenges. It could discriminate against minority communities, against people less eligible or less likely to accept the vaccines, against those less likely to be given priority to receive them. And of course, globally against people residing in countries with less access to vaccines. There are also big questions about the ethics of granting businesses access to peoples' health records. In the current world of media technology corporations the risk of big companies having access to private information and commercialize it or merge it with other information and then use it for their advantage, is a concrete and real threat.

The project turns vaccination, if not mandatory, into almost compulsory in order to access to highly desirable activities. For instance, while vaccination in Israel is not mandated, parliament passed a law that would allow the Ministry of Health to identify unvaccinated people and notify them to the authorities.

Because of the discrimination that the certificates potentially impose, some opinions question if those passports are even lawful.

Proof of immunization is far from being a new idea; during campaigns for the smallpox vaccine, the vaccine scar often served as this proof and gave access to activities as train travel. Many countries require proof of immunization for school entry and in most of the countries health care workers are required to present proof of vaccination against hepatitis B. The Equal Employment Opportunity Commission in the US allows employers to require SARS-CoV-2 vaccination to return to the workplace, thus ensuring employees do "not pose a direct threat to health or safety. If employees are not required to provide any medical additional information as part of the proof, employers could require vaccination passports as proof their staff have received a COVID-19 vaccination.

In fact, vaccine passports are not only permissible under international health regulations, but also they already exist. The World Health Organization endorses certificates confirming vaccination against yellow fever for entry into countries where the disease is endemic. Governments have power to validate and monitor vaccination status while requiring proof of vaccination for access to certain privileges. International law poses few restrictions on vaccination certifications. The International Health Regulations, signed by 196 countries, grant wide discretion to exercise evidence-based public health powers. It is the Article 31 of these regulations which specifically allows governments to require "proof of vaccination or other prophylaxis," while Annex 7 authorizes yellow fever vaccination certificates for international travel.

Opposite to immunity passports, which has the risk of incentivizing infection, vaccine passports incentivize vaccination, which is a positive benefit and contributes to the whole population immunity.

It is also in accordance with the public health principle of least infringement that dictates that policy makers should implement the option that least impairs individual liberties in order to achieve a common good. Lockdowns may be required in order to decrease the number of cases and deaths, even when it is one of the major restriction of the civil liberties. Vaccine passports could provide more freedom of movements for those with minimal risk of getting and spreading the disease and help prevent other health and socioeconomic harms caused by lockdowns.

Ethical concerns about these passports are not resolved at all. The Nuffield Council on Bioethics states that such passports could enable coercive and stigmatizing workplaces. Vaccine passports should be available and accessible to all countries and to all populations in each country. Otherwise they risk to increase the already existing societal inequalities and worsening

the health inequality. But that is not and easily achievable goal. Vaccines are scarce and access remains deeply unequal, both globally and within countries. People facing vaccination access problems will be unable to obtain vaccine passports.

Even with a more fair access to vaccines, some groups are excluded from vaccination for medical reasons, cultural beliefs or religious convictions.Covid-19 vaccines are contraindicated in some people with serious health conditions and allergies and pregnant women do not have evidence (as clinical trials did not include pregnant women) about the safety of vaccination and may choose not to take that risk. In some countries, ethnic minorities are also more likely to be vaccine hesitant, political inclinations may determine higher distrust in the vaccines and younger people, not being a prioritized group, will take much longer to be vaccinated as well as believing less vulnerable to severe disease, may be less inclined to get the vaccines.

But the most obscene inequality is that most vaccine doses are being delivered in high income countries, WHO warned that the world is facing a catastrophic moral failure represented by the insufficient efforts to support globally coordinated access to covid-19 vaccines. It is estimated that nearly 25% of the world's population will not have access to any COVID vaccine until 2022, resulting in thousands of preventable deaths in less developed countries. Far from the initial dream that this global crisis would improve the understanding of the urgent need of decreasing the unacceptable inequity between poor and rich countries and poor and rich individuals, in most of the countries the pandemic is widening those differences. Requiring proof of vaccination mainly to be able to travel, will deepen the inequality and exclusion of the low income countries compared to the high income countries.

Only when everyone can gain access to vaccines, there would be a strong ethical justification for vaccine passports in order to create safer environments to work, shop, socialize, and travel, that could be preferable as a less restrictive alternative to lockdown measures. It means that if wanting to enjoy the potential benefits of vaccine passports without paying an unacceptable moral price of unfairness and discrimination, every country should contribute to the global effort in order to increase access to vaccination, both globally and within countries. By definition, a pandemic is a global problem and must be faced globally. Beyond any ethical concern, a world with less than half of the world's population vaccinated will not be safe for anyone.

If vaccines are fully and equally available to all members of society, including the most disadvantaged people, and in that way, not taking the vaccine is a personal choice, it would be possible to argue that unvaccinated individuals have no right to impose risks on others, thus impeding a return to normal activities. Requiring people who decline vaccination to bear some consequence for their refusal seems only fair, especially if, collectively, such hesitancy puts herd immunity out of reach. In that scenario, individuals who cannot be vaccinated for medical reasons should not be excluded from passport privileges and granting exemptions for genuine religious or conscientious objections should be considered.

In the same way that the previously planned immunity passports, technical challenges are not resolved. Mechanisms for reliable and accurate certification are important. The development of such mechanisms is a technical issue that sooner than later some leading technology companies should be able to answer successfully. As vaccine passports would probably be digital and require access to private medical records, there are important questions around internet access, costs of acquiring and maintaining the passports, privacy, and data protection that must be carefully studied. In some countries a large proportion of the population do not have smartphones or stable internet connections and their exclusion would breach their rights to equality. Allowing workplaces, airlines, and entertainment and leisure venues to access to vaccination data remains controversial as it may permit patient sensitive data be used for other purposes than the vaccine passports. It could also allow immunization information to be used by private companies like airlines, workplaces or amusement parks to deny entry with the excuse of keeping people safe and limiting the spread of this deadly virus. That would create an additional form of elitism and a deeper societal gap.

A key component of any internationally valid passport should be that those certifications need to be internationally standardised and must have verifiable credentials that prevent problems such as forgery and loss of privacy. Software, implemented in a standardized fashion, will be required to verify vaccination status and to determine whether immunization passports meet current requirements for entry or access. Mechanisms must also exist to revoke passports if, for example, data emerge that new variants of SARS-CoV-2 are resistant to vaccines. Technological development should occur in concert with legal and ethical review to ensure that the solution is the least restrictive means of reopening society, without adversely affecting populations that are already marginalized. WHO has initiated a Smart Vaccination Certificate Working Group to establish key specifications and standards for effective and interoperable digital solutions for covid-19 vaccination. Some institutions have developed potential criteria for such passports, for instance, the Royal Society which suggests passports should accommo-

date differences between vaccines in their efficacy, register changes in vaccine efficacy against emerging variants, be internationally standardized and have verifiable credential. They should also be based on a platform of interoperable technologies, be secure for personal data, be portable and be affordable to individuals and governments

Taking into account all these considerations, while the merits of vaccine passports may be undeniable, implementation will require ethical justifications and practical solutions that do not discriminate against the poor, the less technically literate, and people from low and middle income countries. The policies to implement those passports will require a flexible adaptation as we have learnt that pandemic policies that are sensible when launched may need to be rethought a month later. Without mitigation strategies for inequality of access and alternative solutions, the hardships experienced by marginalised and vulnerable groups will be intensified through the perpetuation of discrimination.

The most formidable challenge of this time is to decrease the morally and practically inadmissible levels of inequity all over the world. That situation represents not only a scandalous moral defeat but also a danger for democracy as we have known it until now. If not carefully, thoughtfully and ethically planned, the negative impacts of a certification system are likely to fall disproportionately on those who are already socially marginalised and disadvantaged. Societies globally must strive to ensure that passports are available to all in the most fair manner and with the highest respect for fundamental human rights.

**The views expressed in this article are those of the author (Silvia Quadrelli) and do not necessarily reflect the official positions of the Executive Board or International Board of Regents of the WABIP.*

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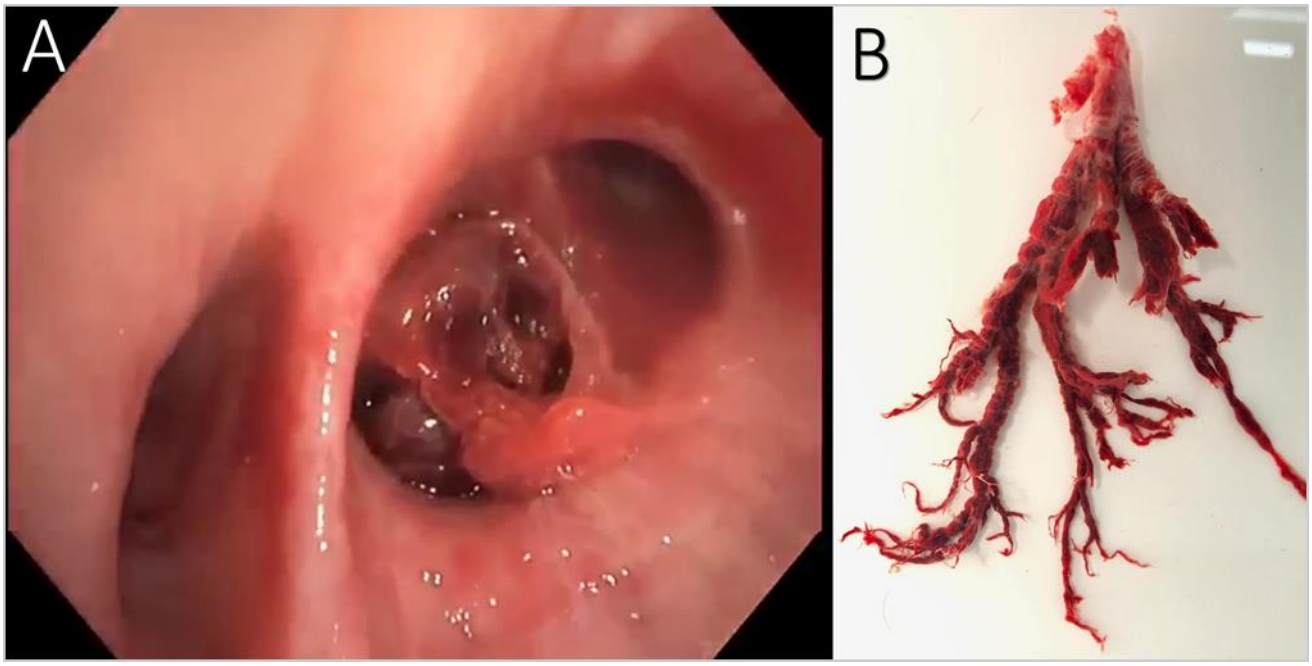
Best Image Contest

Best Image Contest 2021 (2 of 3)



Description:

(A) Organized blood clot in the RLL

(B) Cryo-extraction of the clot

Submitter:

Dr. Syeda Samia Rasheed M.D

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WABIP News

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- Pre analytic variables
- Cellularity evaluation
- Specimen enrichment

WATCH LECTURE

Upcoming Events

- 8th Indonesian Pediatric Respiratory Meeting in conjunction with The 3rd Asian Pediatric Interventional Pulmonology Association Meeting
  When: June 4-6, 2021
  Where: Virtual / Indonesia
  Program Director: Prof. Mohammad Ashkan Moslehi, Prof. Wahyuni Indawati
  Program Type: Educational seminar (postgraduate may include physicians in practice and trainees), Conference (didactic lectures)
  Website: https://iprm2021.id/

- SCOPE 2021: Breaking Barriers in Lung Cancer (Philippines/Virtual)
  When: June 23-25, 2021
  Where: Virtual / Philippines
  Program Director: Ronald A. Fajardo, MD
  Program Type: Educational seminar (postgraduate may include physicians in practice and trainees), Hands-on workshop, Conference (didactic lectures)
  Website: http://www.scope2021.net/

- Introduction to Bronchoscopy and Pulmonary Procedures Course (USA)
  When: June 27 and 30, 2021
  Where: Beth Israel Deaconess Medical Center, Boston, MA, USA
  Program Director: Mihir Parikh, MD
  Program Type: Educational seminar (for trainees only), Hands-on workshop, Conference (didactic lectures)

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Research

"When in Doubt-Cut it Out" May Not Be the Best Strategy Anymore

With the implementation of lung cancer screening, albeit fragmented, the numbers of pulmonary nodules discovered have increased exponentially in the United States and the rest of the world. However, our capability to predict malignant from benign nodules remains unreliable and limited. Performing biopsies or surgically removing all "high-risk nodules" is neither feasible nor scientifically sound, as shown by numerous clinical trials including, the National Lung cancer Screening Trial (NLST). NLST showed that more than 95% of surgeries in "high-risk patients" revealed non-malignant nodules. Even with ever-evolving technologies such as navigation and robotic bronchoscopies, sampling of nodules remains particularly questionable when it's negative.

Genetic classifiers are being developed and implemented to enhance pre and post-test probability of malignancy in pulmonary nodules to help navigate invasive workup, particularly, surgical procedures.

A study (1) of a genomic classifier (Percepta) based on the "field of injury" assessed cancer-associated gene expression in cytologically normal-appearing bronchial epithelial cells in the mainstem bronchus in patients undergoing bronchoscopies and is able to distinguish malignant pulmonary nodules from benign lesions. The study looked at two different cohorts. Two independent prospective cohorts revealed that the gene-expression classifier had high sensitivity across different lesion sizes, locations, stages, and cell types of lung cancer. The combination of the classifier plus bronchoscopy had a sensitivity of 96% and 98% in the both (AEGIS-1 and AEGIS-2) validation cohorts. Consequently, Percepta successfully down-classified nodules with an intermediate pretest probability of malignancy (10%-60%) to a low-risk probability of malignancy (< 10%) with a 91% negative predictive value.

Another recent study published in CHEST 2021 (2) set out to evaluate the impact of Percepta on clinical decision-making in a "real-world" setting. This study is a multicenter patient registry to observe a physician management of patients with pulmonary nodules who have had a nondiagnostic bronchoscopy. Within that registry, the authors studied physician behavior and outcomes of decisions in patients with Percepta results. This subset, the "decision impact study," included documented physician risk assessment and decision-making results (planned and actual), in concert with Percepta results to evaluate the impact on decision making of the test result.

In patients who were slated for invasive procedures (biopsy/resection), the Percepta genomic classifier downgraded one-third of (approximately 34%) of patients to lower risk of malignancy, precluding invasive procedures in approximately 79% of these downgraded patients for up to one year. This study also showed that performing a genetic classifier tests did not delay in diagnosis of lung cancer.

Given this rapidly evolving data and the breadth of evidence, showing gene-expression classifier improved the diagnostic performance of bronchoscopy to detect lung cancer. Notably, in intermediate-risk patients with a nondiagnostic bronchoscopic examination, a negative classifier score supports for a more conservative diagnostic approach.

I hope that our ability to predict the malignant potential of a nodule improves substantially. Ultimately, we want to minimize unnecessary procedures/resection for non-malignant lesions and capture malignant lesions in time. Hence, when in doubt, consider genetic classifiers might be a better approach than "cut it out."

Ali I. Musani MD

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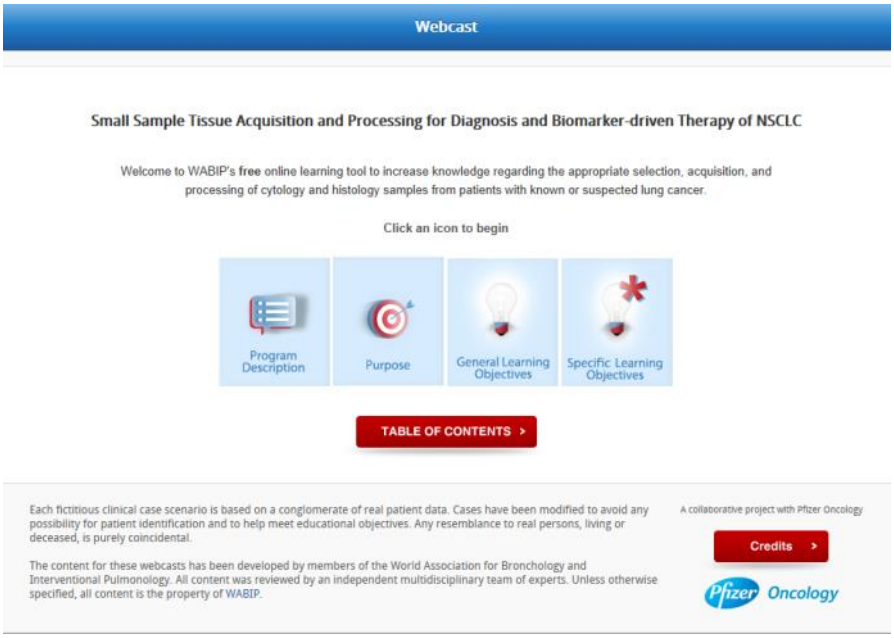
WABIP ACADEMY- WEBCASTS

The WABIP has started a new education project recently: *THE WABIP ACADEMY.* The WABIP Academy will provide free online webcasts with new and hot topics that will interest pulmonologists and interventionalists.

Current webcast topic: **Tissue acquisition for biomarker directed therapy of NSCLC**



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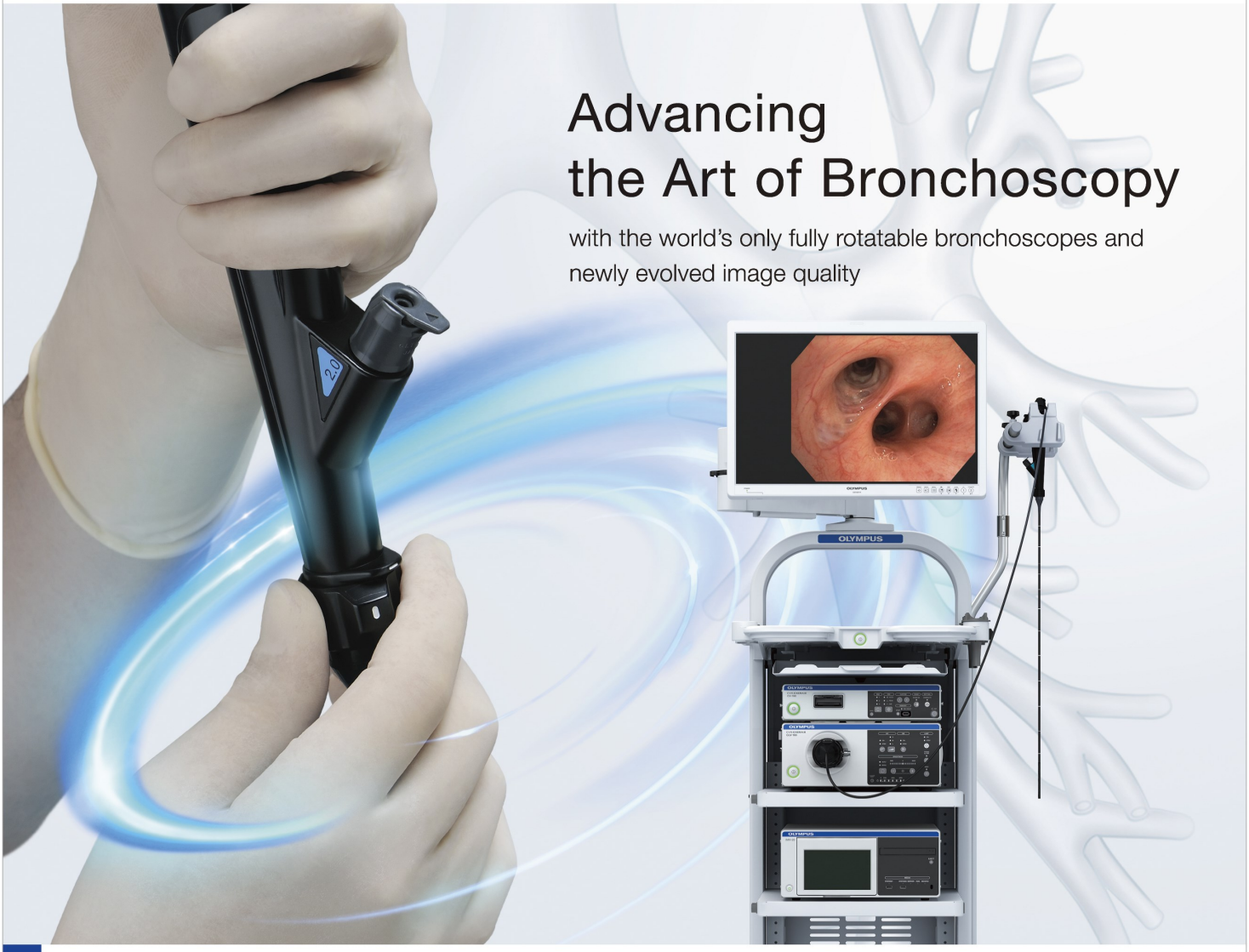

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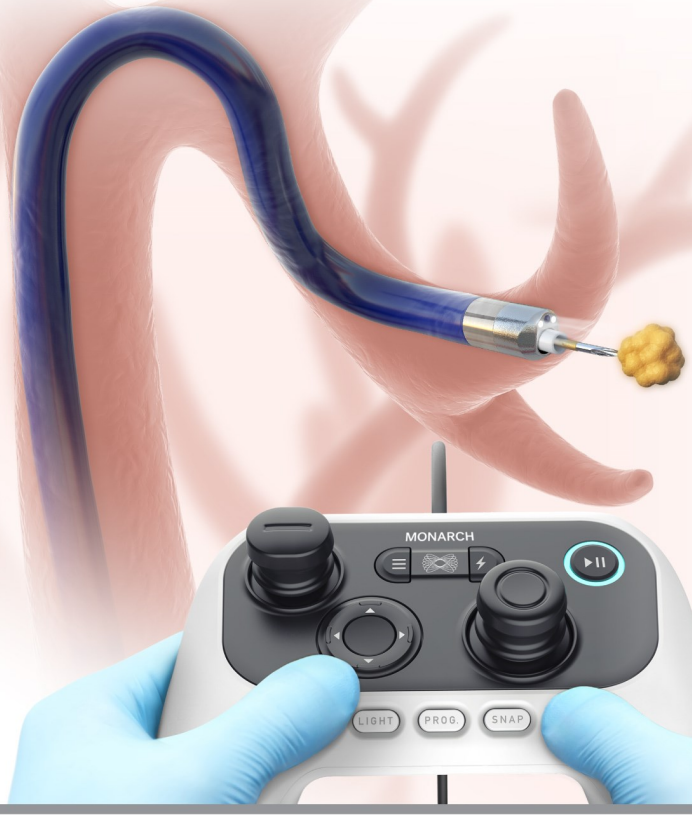

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1. Chen AC, Pastis NJ, Silvestri GA, et al. Robotic Bronchoscopy for Peripheral Pulmonary Lesions: A Multicenter Pilot and Feasibility Study (BENEFIT) Chest 3525, 19 August 2020,