WABIP

LUNG CANCER AND INTERVENTIONAL PULMONOLOGY YEAR IN REVIEW 2019





PREFACE

Lung cancer continues to be one of the most common cancers worldwide, claiming more lives yearly than breast, colon, and prostate cancers combined. World Lung Cancer Day is a great opportunity for every health care provider and member of the community to implement initiatives that urge everyone to learn about risk factors for the disease and to encourage the increase of research efforts for improving prevention, early detection and optimal care of lung cancer all over the world.

Bronchology and Interventional Pulmonology offer many options to improve the possibilities of cure of lung cancer. Bronchoscopy is the primary procedure performed to diagnose lung cancer and interventional pulmonology are deeply involved in the research about lung cancer and the clinical care of thousands and thousands of patients around the world.

The World Association for Bronchology and Interventional Pulmonology, as a coalition of leading international research and advocacy associations of interventional pulmonology, joins the efforts of all world respiratory associations to commemorate, celebrate and support those impacted by lung cancer. WABIP as a relevant member of the lung cancer community fully aligns itself with the efforts to raise awareness about lung cancer and its global impact, mainly through education about lung cancer as well as encouraging early diagnosing and optimizing care of lung cancer around the world.

To this end, the WABIP organizes diverse initiatives to commemorate the World Lung Cancer Day. One of them is this collection of top articles published in the past year about interventional pulmonology in lung cancer, with comments by the WABIP Journal Club and a wide variety of leading experts in bronchology and interventional pulmonology.

The WABIP hopes that medicine-based evidence analysis of the selected papers and the thoughtful comments of such experts about the discussed topics will help physicians remain updated of the most relevant publications of the year.

ACKNOWLEDGMENTS

The WABIP would like to thank each and every contributor who worked tirelessly to make this collection possible.

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Expert Commentary: Dr. Lorenzo Corbetta

TITLE

Endosonographic procedures are safe and highly specific in mediastinal re-staging of lung cancer.

SOURCE CITATION

Muthu V, Sehgal IS, Dhooria S et al. Efficacy of endosonographic procedures in mediastinal re-staging of lung cancer after neoadjuvant therapy: A systematic review and diagnostic accuracy meta-analysis. Chest. 2018; 154(1):99-109. doi: 10.1016/j.chest.2018.04.014.

ABSTRACT

BACKGROUND: The optimal modality for restaging the mediastinum following neoadjuvant therapy for lung cancer remains unclear. Surgical methods are currently considered the reference standard. The present study evaluates the role of endosonographic techniques for mediastinal restaging in lung cancer.

METHODS: A systematic review of PubMed and Embase databases was performed to identify studies using endoscopic ultrasound, endobronchial ultrasound, or a combination of the two for mediastinal restaging following induction therapy for stage III lung cancer. The quality of the included studies was assessed by using the Quality Assessment of Diagnostic Accuracy Studies-2 tool. The accuracy of endosonography was analyzed by calculating the sensitivity, specificity, likelihood ratio, and diagnostic OR for each study and pooling the results by using a bivariate model. Heterogeneity and publication bias were assessed. Potential causes of heterogeneity were explored by using sensitivity analysis and meta-regression.

RESULTS: Ten studies (N = 574) were included. The pooled sensitivity, specificity, diagnostic OR, and positive and negative likelihood ratios were 67% (95% CI, 56-77), 99% (95% CI, 89-100), 157, 52.0, and 0.33, respectively. No complications were reported. Significant heterogeneity was observed for the outcome of sensitivity. Sensitivity analysis identified several factors accounting for heterogeneity, including study design and risk of bias. The sensitivity of the endosonographic procedure was also linked to the prevalence of N2 disease on meta-regression. Funnel plot showed publication bias, but this finding was not evident on statistical tests.

CONCLUSIONS: Endosonographic procedures are safe and highly specific in mediastinal restaging of lung cancer.

JOURNAL CLUB COMMENTS

For any well-formulated research question, systematic reviews and meta-analyses can identify all the available relevant evidence (systematic search), critically appraise the risk of bias of the identified evidence, combine the results to increase statistical power (meta-analysis when appropriate), identify sources of variation across studies (subgroup analyses) and rate the overall quality of the evidence (certainty in the results).

Question: In patients with neoadjuvant therapy for lung cancer restaging with endosonographic procedures are safe and have an important role in the follow-up?

Design: Meta analysis

Main results: Not significant heterogeneity was observed for the specificity, with a LR+ 52. These result shows a very large change in the pretest results when the endosonographic procedure is positive. On the other hand, when the procedure is negative, the pretest probability does not vary enough for a confirmatory decision.

COMMENTS by Dr. Lorenzo Corbetta

The limits of effectiveness of surgery in the group of patients with stage IIIa, N2 metastatic mediastinal nodes is a challenging issue. Although, multimodality treatment, with or without subsequent surgical intervention, is usually considered the best treatment option, the role of surgery as part of multimodality therapy in patients with stage IIIA disease is still not clearly defined. The results of the Albain study in US (Lancet 2009) and the European Organisation for Research and Treatment of Cancer-Lung Cancer Group (van Meerbeeck et al, J Natl Cancer Inst. 2007) did demonstrate some benefit of including surgical management to the neoadjuvant regimen, therefore it seems there exists a subset of patients that may benefit from surgical resection after chemotherapy with or without radiotherapy. Nevertheless, identifying this subset is extremely challenging.

Some authors have recommended surgery intervention in patients who have stage IIIA disease, yet with the involvement of only one mediastinal lymph node station involved wherein the node is smaller than 3 cm in diameter. Although, a survey conducted among institution members of the NCCN showed that 90% of the responders would consider surgery as part of the therapy in this same clinical scenario, the strongest evidence available from the EORTC study and by others, maintains that surgery is unlikely to be beneficial if the mediastinum is persistently involved even after induction treatment. At present, the pathological status of postoperative mediastinal nodes seems to be the crucial decision-maker dictating further treatment; thereby arises the need of a repeated staging (restaging) procedure in patients who have received neoadjuvant treatment and are being considered for subsequent radical surgery.

Non-invasive techniques traditionally have a rather low sensitivity and specificity with regards to restaging and the false-negative rate of minimally invasive techniques remains high. On the other hand, while repeated mediastinoscopy provides larger tissue

biopsies, it is not only more technically challenging but also has a lower accuracy than the first mediastinoscopy. Moreover, experience with VATS for restaging is still limited and therefore the best available method for restaging after induction therapy remains a highly debated issue. The introduction of transcervical extended mediastinal lymphadenectomy (TEMLA) is a new surgical staging procedure for initial mediastinal evaluation that provides a thorough and extensive mediastinal lymph node dissection, leaving almost no lymphatic tissue behind. The sensitivity and accuracy of the same for primary staging of the mediastinum have been reported to be 90% and 96% respectively. Unfortunately, TEMLA was associated with a mortality of 0.3% and morbidity (such as recurrent laryngeal nerve palsy, pneumothorax and requirement of mechanical ventilation) of 6.4% and thus, for various reasons, TEMLA is not routinely available in most of the centers.

The results of efficacy of endosonography for restaging in stage IIIA-N2 NSCLC after induction therapy are quite variable. Herth et al. reported, in 2008, a diagnostic sensitivity of 76% for EBUS-TBNA used for restaging after induction chemotherapy. Other studies showed a sensitivity of 50% and a negative predictive value of 88% for EBUS. Combined EBUS-TBNA and EUS-B-FNA after induction therapy, showed a sensitivity of 67%, a negative predictive value of 73% and accuracy of 81 per cent. In spite of the initial enthusiasm about EBUS, the consensus amongst most of the experts is that the diagnostic sensitivity of EBUS-TBNA for restaging after induction therapy in patients with stage IIIA-N2 NSCLC is lower than that of initial staging and therefore, it is reasonable to perform EBUS-TBNA first for initial mediastinal staging and reserve mediastinoscopy for restaging after induction therapy.

One of the difficulties in analyzing the published research is the inability to consider the many technical aspects influencing the results and mainly, how these results may be extrapolated to real life scenarios. The level of expertise of the team is crucial; it is known, there is significant variability in the learning curve of the fellows in training and that almost 33% of them could not master the technique during their training program. Currently, the length of the learning curve for EBUS-TBNA proficiency is unclear and is probably different for each operator; no diagnostic yield cut-off has yet been established to define the standard capability of performing EBUS-TBNA. Additionally, in many countries, formal training to perform EBUS is either not required or not offered.

The performance indices of EBUS-TNBA mediastinal staging may be influenced by numerous factors EBUS-TBNA specimen acquisition and processing many be obtained by cytology slides, cell-block, core-tissue, combination of cytology slides and core-tissue, combination of cytology slides and cell-block. There is no consensus on the optimal method of specimen preparation. Prevalence of N2 nodes, technique used for sedation, the use of ROSE and mainly the extension of the procedure may result in different outcomes. Although, current guidelines recommend testing at least three lymph node stations-typically 4R, 4L and 7, in real life, the EBUS-TBNA practice is generally characterized by <3 sampled mediastinal nodal stations per patient for different reasons. How the procedure is implemented in each institution, must be carefully taken into account before assuming that the same results published by highly experienced institutions will be reproduced.

In this article, Muthu V et al performed a systematic review and meta-analysis to evaluate the diagnostic performance of endosonography in mediastinal re-staging of lung cancer. They included 10 eligible articles (574 patients, 7 retrospective studies). They found that the sensitivity of endosonographic procedures in mediastinal re-staging ranged from 40-89% with a pooled sensitivity of 67% and the specificity ranged from 91-99% with a pooled specificity of 99 per cent. As expected, there was clinical heterogeneity amongst the included studies in terms of study design, patient selection, the reference standard used and the technical aspects of the endosonographic procedure. Heterogeneity was observed in terms of pooled sensitivity but not for the specificity.

This meta-analysis confirms that the sensitivity of endosonography for mediastinal restaging is significantly lower than that of endosonography for initial mediastinal staging (88%). Possible reasons include the technical difficulty in accessing certain lymph node stations, smaller size of nodes and the occurrence of fibrosis or necrosis following neoadjuvant therapy. Even when these figures support the current recommendations (EBUS for initial evaluation, mediastinoscopy for restaging) they must be interpreted cautiously. Most of the included studies were small, single center studies from specialized endoscopy or thoracic surgery units. Obviously, the sensitivity of the examined procedure (EBUS) cannot be compared to the gold standard i.e. mediastinoscopy. The heterogeneity for sensitivity surely reflects the heterogeneity of procedural techniques. It emphasizes the need of future multicentric studies in which the data should be gathered prospectively and all the potential influencing factors be stratified. It is also important the use of a standardized database for prospective collection of relevant EBUS-TBNA data. Additionally, it is important to take into account that the results of EBUS and EUS reported by the most experienced endoscopists may not necessarily be achieved by the novice. It is imperative that every practitioner involved in diagnosis and treatment of NSCLC collect their own data as the real value of this technique will be shown in hands of an average endoscopist, with his or her available training, equipment, techniques and conditions of practice.

WHAT THIS ARTICLE ADDS

- The diagnostic sensitivities of endosonography and re-mediastinoscopy for restaging were lower than those of initial staging in previous studies
- These results support the recommendation to perform EBUS-TBNA first for initial mediastinal staging and reserve mediastinoscopy for restaging after induction therapy.

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Expert Commentary: Dr.Eric Edell

TITLE

Peripheral pulmonary lesions with CT bronchus sign are more likely to be diagnosed with guided bronchoscopy

SOURCE CITATION

Ali MS, Sethi J, Taneja A, Musani A, Maldonado F. et al. Computed Tomography Bronchus Sign and the Diagnostic Yield of Guided Bronchoscopy for Peripheral Pulmonary Lesions. A Systematic Review and Meta-Analysis. Ann Am Thorac Soc. 2018;15(8):978-987. doi: 10.1513/AnnalsATS.201711-856OC. <u>Pubmed</u>

ABSTRACT

<u>Rationale</u>

Indeterminate peripheral pulmonary lesions often require tissue diagnosis. If nonsurgical

biopsy techniques are considered, deciding between bronchoscopic transbronchial vs.

CT guided transthoracic biopsy can be difficult. The former has a low diagnostic yield with a low complication risk, while the latter has a better diagnostic yield but a higher complication rate.

Investigators have looked at various lesion characteristics that can predict the diagnostic yield of guided bronchoscopic biopsies. While consensus exists that larger size and proximity to the hilum increase the diagnostic yield, there is ongoing debate about the

association between CT bronchus sign (air-filled bronchus in close proximity of the lesion as seen on CT) and the diagnostic yield of guided bronchoscopic modalities.

Objectives

To perform a meta-analysis and systematic review, determining the association between CT bronchus sign and the diagnostic yield of guided bronchoscopy for peripheral pulmonary lesions.

<u>Methods</u>

MEDLINE, Embase, Scopus and Google Scholar were searched in January 2018 for guided bronchoscopy studies that had assessed the impact of CT bronchus sign on the diagnostic yield. The quality of included studies was assessed using Quality Assessment, Data Abstraction and Synthesis-2 tool. Meta-analysis was performed using MedCalc (version 18). Odds ratios were used to compare yield of lesions with and without bronchus sign. Random effects model was used when significant heterogeneity was observed (I2>40%).

<u>Results</u>

For 2199 lesions with CT bronchus sign, the overall weighted diagnostic yield was 74.1% (95% CI: 68.3-79.5%). For 971 lesions without CT bronchus sign, the overall weighted diagnostic yield was 49.6% (95% CI: 39.6-59.5%). The odds ratio for successfully diagnosing a lesion with CT bronchus was 3.4 (95% CI: 2.4-5.0). Possible sources of heterogeneity in the meta-analysis included differences in study designs, guidance modalities and cancer prevalence. The odds ratio for successfully diagnosing a lesion with CT bronchus ratio for successfully diagnosing a lesion with CT bronchus ratio for successfully diagnosing a lesion with CT bronchus ratio for successfully diagnosing a lesion with CT bronchus sign was relatively lower for prospective studies.

Conclusions

Peripheral pulmonary lesions with CT bronchus sign are more likely to be diagnosed with guided bronchoscopy as compared to the lesions without CT bronchus sign. Clinicians should consider this along with the lesion size and distance from hilum, when contemplating guided bronchoscopy for peripheral pulmonary lesions.

JOURNAL CLUB COMMENTS

I² provides an estimate of the percentage of variability in results across studies that is likely due to true differences in treatment effect, as opposed to chance. When I2 is 0%, chance provides a satisfactory explanation for the variability we have observed, and we are more likely to be comfortable with a single pooled estimate of treatment effect. one rule of thumb characterizes I2 of less than 0.25 as low heterogeneity, 0.25 to 0.5 as moderate heterogeneity and over 0.5 as high heterogeneity

Question Are there any association between the CT-BS and the diagnostic yield.?

Design: meta analysis. Data source MEDLINE, Embase, Scopus and Google Scholar in January 2018 using terms bronchus sign, bronchoscopy, lung nodule, lung lesion, pulmonary nodule, pulmonary lesion, endobronchial ultrasound, endobronchial ultrasonography, radial probe, electromagnetic navigation bronchoscopy, virtual bronchoscopy and CT guided bronchoscopy

Study selection: Quality assessment were doing with QUADAS-2 tool application . QUADAS 2 In 2003, the QUADAS tool was developed to assess the quality of the diagnostic test studies included in the a systematic review, . From the feedback provided by your users emerged areas for improvement, which consists of four domains: 1) patient selection, 2) index test, 3) reference test, 4) flow and times. Each domain is evaluated in terms of its risk of biases and the first three domains are also evaluated for their applicability.

Main results: For 2199 PPLs with positive CT-BS, the pooled diagnostic yield was 74.1% (95% CI: 68.3-79.5%).I² index was 88% (95% CI: 83.2-91.4%). For 971 PPLs without CT BS, the pooled diagnostic yield was 49.6% (95% CI: 39.6-59.5%). I² index was 87.8 (95%CI: 83.0-91.3%). The odds ratio (OR) for successfully diagnosing a PPL with CT-BS vs. a PPL without CT-BS was 3.4 (95% CI: 2.4-5.0). I² index was 62.1 (95% CI: 39.9-76.0%) but there was significant heterogeneity between studies, which is likely attributable to differences in study designs techniques used and the differences in patient populations studied The utility of CT-BS for predicting diagnostic yield of guided bronchoscopies for PPLs. CT-BS appears to be associated with a higher diagnostic yield.

COMMENTS by Dr. Eric Edell

The detection of peripheral pulmonary nodules continues to increase with the use of CT screening in patients at high risk for lung cancer. Current management strategies for these patients include close observation, surgical resection or attempts to obtain diagnostic sampling. Diagnostic sampling, prior to resection, can be accomplished via CT guided biopsy or bronchoscopy. CT guided biopsy has the best diagnostic accuracy but is associated with a risk of pneumothorax. Bronchoscopy has a much lower rate of pneumothorax, than CT guided biopsy, but the diagnostic accuracy is lower. Attempts to increase the accuracy of bronchoscopy has included the introduction of navigational tools and radial EBUS, referred to as guided bronchoscopy. Several studies have reviewed clinical parameters that predict the accuracy of guided bronchoscopy. These include nodule size, location, and the presence or absence of the bronchus sign. The bronchus sign would intuitively suggest that guided bronchoscopy would have a better chance of obtaining diagnostic sampling than cases without a bronchus sign and several studies confirm this. There are a few studies that have not identified the bronchus sign as a predictor of diagnostic accuracy. The authors of this study have completed a metaanalysis and systematic review of several published studies on this topic and have determined that the bronchus sign does predict diagnostic accuracy.

WHAT THIS ARTICLE ADDS

This paper does confirm the presence of a bronchus sign improves the diagnostic yield of guided bronchoscopy. However, new technologies are being that may allow sampling of nodules without a bronchus sign with the same or better accuracy. More studies will be needed to determine whether nodule size, location and presence of bronchus sign predicts accuracy in the future.

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Expert Commentary: Dr. Dave Fielding

TITLE

Conventional TBNA can play a role for identifying EGFR mutations in lung adenocarcinoma.

SOURCE CITATION

Hsu LH, Ko JS, Liu CC, Feng AC, Chu NM, et al. Conventional transbronchial needle aspiration is promising for identifying EGFR mutations in lung adenocarcinoma. Thorac Cancer. 2019;10(4):856-863. doi: 10.1111/1759-7714.13014. Epub 2019 Feb 27. <u>PUBMED</u>

ABSTRACT

BACKGROUND: Conventional transbronchial needle aspiration (TBNA) is advantageous for the one-step diagnosis and staging of lung adenocarcinoma under topical anesthesia and conscious sedation. We examined its efficacy for identifying EGFR mutations.

METHODS: Forty-seven patients with proven or suspected lung adenocarcinoma indicated for hilar-mediastinal lymph node (LN) staging between June 2011 and December 2017 were enrolled. The cellblock was prepared using the plasma-thrombin method. TaqMan PCR was used to detect mutations. Considering cost effectiveness, only the sample with the highest tumor cell fraction in the same patient was chosen for analysis.

RESULTS: TBNA provided positive results of malignancy in 27 patients. Seventeen patients (63.0%) had cellblocks eligible for mutation testing. Bronchial biopsy (n = 6), neck LN fine needle aspiration (n = 1), and brushing (n = 1), provided higher tumor cell fractions for analysis in eight patients. TBNA was the exclusive method used in nine patients (19.1%). For patients with an inadequate TBNA cellblock, bronchial biopsy (n = 5), neck LN fine needle aspiration (n = 3), computed tomography-guided transthoracic needle biopsy (n = 1), and brushing (n = 1) were used for analysis. Modification to specimen processing to prevent exhaustion by cytology after June 2016 improved the adequacy of cellblock samples (9/10, 90% vs. 8/17, 47.1%; P = 0.042).

CONCLUSIONS: These findings suggest the promising role of conventional TBNA and highlight the challenges of doing more with less in an era of precision medicine

JOURNAL CLUB COMMENTS

A study of series of clinical cases is an epidemiological, descriptive study, which is limited to the simple identification and description of a set of clinical cases that have appeared in a time interval. In the case of new diseases, drugs or diagnostic methods, the series of cases contribute to the characterization of the profile and delimitation of new nosological entities or the implementation of new diagnostics techniques. Case series do not, in themselves, involve <u>hypothesis testing</u> to look for evidence, are especially vulnerable to <u>selection bias</u>, <u>Internal validity</u> is usually very low, due to the lack of a comparator group exposed to the same array of intervening variables

Question: Is TBNA useful for the identification of EGFR in lung carcinoma?

Design Case series

Main results: The promising role of conventional TBNA for identifying EGFR mutations

COMMENTS by Dr. David Fielding

This paper is an example of the way bronchoscopists can use all the biopsy tools at their disposal to provide all important genetic information on lung adenocarcinomas. This is particularly true in high prevalence areas for EGFR mutations such as China (where this paper comes from) but is relevant to all bronchoscopists.

These authors used the increasingly common liquid biopsy media (here it is "Thin Prep" (Methanol) which provided good quality specimens. Developing communications with the pathologist is important for all bronchoscopists to maximise the potential of cell blocks for this purpose.

The paper shows the benefits of adding as many specimens as possible, such that brushes, and biopsies of peripheral masses can be added to the nodal samples and the best sample chosen for mutation testing. Here, by including conventional TBNA, fully 19% of the total samples used for EGFR testing were solely from TBNA specimens. So,

one fifth of patients were saved a second procedure by this addition. The use of conventional TBNA means one bronchoscope can be used for all specimens, and this in itself provides flexibility for bronchoscopists.

WHAT THIS ARTICLE ADDS

- It confirms the importance of creating a good cell block and maximising the cellularity in that specimen.
- It confirms that conventional TBNA still has a central role in bronchoscopic diagnosis; there is nothing particular about an EBUS TBNA sample, other than that EBUS assists the proceduralist to localise the node.
- Adding as many specimens as possible, such that brushes, and biopsies of peripheral masses to the nodal samples allow to choose the best sample for mutation testing

Expert Commentary: Dr. Rosa Cordovilla

TITLE

Guided bronchoscopy could increase the diagnostic yield of peripheral pulmonary lesions.

SOURCE CITATION

Bo L, Li C, Pan L et al. Diagnosing a solitary pulmonary nodule using multiple bronchoscopic guided technologies: A prospective randomized study. Lung Cancer. 2019; 129:48-54. doi: 10.1016/j.lungcan.2019.01.006. Epub 2019 Jan 16. <u>PUBMED</u>

ABSTRACT

BACKGROUND: The rate of detection of pulmonary nodules on computed radiography (CR) is approximately 0.09-0.2%, so rapid identification of the nature of solitary pulmonary nodules (SPNs) with a likelihood of malignancy is a critical challenge in the early diagnosis of lung cancer.

OBJECTIVE: We conducted this study to compare the diagnostic yield and safety of endobronchial ultrasonography with a guide sheath (EBUS-GS), and the combination of EBUS-GS and virtual bronchoscopic navigation (VBN).

METHODS: This was a prospective, multicenter, multi-arm, randomized controlled trial involving a total of 1010 subjects. All the patients recruited underwent a chest CT scan which found SPNs that needed to be diagnosed. The subjects were randomly divided

into one of three groups: a traditional, non-guided, bronchoscopy biopsy group (NGB group), an EBUS-GS guided bronchoscopy biopsy group (EBUS group), and a guided bronchoscopy biopsy group that combined EBUS-GS with VBN (combined group). The primary endpoint was to investigate the differences between the diagnostic yields of the three groups.

RESULTS: There was no significant difference in the diagnostic yield between the EBUS group (72.3%) and the combined group (74.3%), but the diagnostic yield for the NGB group was 41.2%. The time required to reach biopsy position was significantly less in the combined group (7.96 ± 1.18 min in the combined group versus 11.92 ± 5.37 min in the EBUS group, p < 0.05). However, the bronchoscope operation time was the same in the EBUS-GS and combined groups. The diagnostic yield for peripheral pulmonary lesions (PPLs) >20 mm in diameter was significantly higher than for those <20 mm in diameter.

CONCLUSION: The results of our study suggest that guided bronchoscopy could increase the diagnostic yield in the context of peripheral lesions. There was no significant difference in the diagnostic yield between the EBUS and combined groups, but use of EBUS-GS with VBN could significantly shorten the bronchoscope arrival time.

JOURNAL CLUB COMMENTS

Question: In patients with a solitary pulmonary nodule, how accurate are bronchoscopic guided technologies for diagnosing cancer?

Design: Prospective Randomized trial. ClinicalTrials.gov (NCT02268162)

Allocation: Not Concealed.

Blinding: Unblinded.

Follow-up period: 2 years.

Setting: 8 hospitals in China a total of 1095 patients met the inclusion criteria and were recruited into this trial between January 2014 and December 2016;

Patients: (\geq 18 years of age \leq 75 years) who had SPNs with a high likelihood of malignancy being non-calcified lung nodules with pleural retraction, lobular sign, spiculation, or other indications that need biopsy as recommended by the guidelines, the diameter of the nodule=30mm and=8 mm and SPNs without an endobronchial component observed using a traditional bronchoscope

Intervention: The three groups comprised the traditional non-guided bronchoscopy biopsy group (NGB group), the EBUS-GS-guided bronchoscopy biopsy group (EBUS-GS group), and the guided bronchoscopy biopsy group that combined EBUS-GS with VBN (combined group).

Main results: The EBUS-GS and combined groups had a significantly higher diagnostic yield (72.3% and 74.3%) than the NGB group (41.2%, p < 0.01).

COMMENTS by Dr. Rosa Cordovilla

With the improvement of availability of imaging examinations, solitary pulmonary nodules (SPN) are increasingly detected. In heavy or long-term smoker aged 50 years or older a prevalence of SPN as high as 8% to 51% has been reported. In some screening programs, in patients who received a thoracotomy or VATS to exclude malignancy in a lung nodule, 34.1% received a noncancer final diagnosis. Determining whether nodules are malignant or benign is a difficult problem in clinical practice, especially if the SPN is peripheral. Samples of small SPN can usually be acquired via percutaneous or transbronchial route. The most accurate available method is CT-guided transthoracic needle biopsy (CT-TNB), with a diagnostic sensitivity of 82% to 99%. However, the rate of complications, such as bleeding or pneumothorax, is higher using the transthoracic route than using the bronchoscopic approach.

The advent of radial EBUS (rEBUS), which acquires tumor images by advancing a probe to the target lesion has improved the yield of bronchoscopy. Radial probe EBUS employs a flexible catheter housing a rotating ultrasound transducer which produces a 360° ("radial") ultrasound image. In addition, using a guide sheath (GS) with rEBUS enhances diagnostic yield and shortens the procedure time. A metanalysis published in 2011 on 13 articles showed that sensitivity for detection of malignancy with a GS-assisted approach in individual studies ranged from 49% to 88%. The pooled positive likelihood ratio was 26.8 and the negative likelihood ratio 0.28, but significant heterogeneity between sensitivity of individual studies was observed. Several factors that surely have a great influence on the sensitivity could not be analysed as they were not studied in the source papers. These include bronchoscopist experience, number of biopsies taken, proximity to central airways, SPN of solid versus ground-glass opacity and lobar location of SPN.

On the other hand, virtual bronchoscopy navigation (VBN), a new method of image reconstruction using multidetector CT data, allows visualization of the path to the peripheral target SPN during bronchoscopy. In some studies, it has been suggested that VBN combined with rEBUS-GS further improved the diagnostic yield to over 90% for lesions between 2 cm and 3 cm in diameter, turning the diagnostic yield of bronchoscopic methods comparable to the CT guided percutaneous needle aspiration. A meta-analysis published by Ham et al. in 2018 showed that the pooled diagnostic yield was 75% using the bronchoscopic approach (combined methods) while using the percutaneous approach it was 93%. For peripheral SPN \leq 2 cm, the percutaneous approach was clearly superior to the bronchoscopic approach (92 vs 66%) but if SPN was > 2 cm (but \leq 3 cm), the diagnostic yield of bronchoscopy approach was improved to 81%. It means that for SPN > 2cm bronchoscopy may be considered taking into account its acceptable diagnostic yield and the low risk of procedure-related complications. The decisive point is which bronchoscopy technologies do really make a difference to justify their routine use in the diagnosis of peripheral SPN.

In the present study, Bo et al report the results in 1010 eligible cases, 631 cases of which were diagnosed using the histological results from the tissue collected by transbronchial

biopsy under bronchoscopic guidance. Patients were divided into one of three groups: 1) a traditional, non-guided, bronchoscopy biopsy group (NGB group), 2) an EBUS-GS guided bronchoscopy biopsy group (EBUS group), and 3) a guided bronchoscopy biopsy group that combined EBUS-GS with VBN (combined group). They showed that the EBUS-GS and combined (VBN + EBUS-GS) groups had a significantly higher diagnostic yield (72.3% and 74.3%) than the NGB group (41.2%, p < 0.01), independently of the lobar distribution, final diagnosis or nodule size. But the addition of virtual bronchoscopic navigation did not increase the diagnostic yield, as the combined (EBUS-GS + VBN) group was not significantly different from that of the EBUS-only group.

VBN is a very attractive method because EBUS enables direct visualization of the target lesion before biopsy but does not have a navigation system and requires the operator to maneuver the bronchoscope blindly towards the lesion. VBN requires no specific training, has a low overall complication rate of 1.0%. In the VBN system, the scan data from multidetector chest CT acquired from patients before bronchoscopy, are transferred to a workstation on which VBN software automatically creates virtual bronchoscopic images. The 3-dimensional reconstruction gives artificial pseudo-color and simulate endobronchial condition, obtaining the consecutive images as a bronchoscope in a monitor positioned beside the video-bronchoscopic screen. At present, virtual navigation technology can reach to the bronchus of grade 0 to 6.

However, in spite of this potential, the results of this large prospective randomized trial, show that that the application of VBN may not improve the diagnostic accuracy for SPNs when EBUS-GS is already being used. These results are in agreement with the published by Chunhua Xu et al this same year.

In the context of escalating costs there is an increasing a demand to identify clinically beneficial and cost-effective new technologies. As health care economists estimate that 40–50% of annual cost increases can be traced to new technologies or the intensified use of old ones, providing the strongest evidence for the use of each new technology is a central point of the healthcare agenda. Further studies will be needed to define the exact role of VBN in the diagnosis of peripheral small lesions when EBUS is available, also knowing that the evolution of technology requires permanent research. Medical history reveals a number of technologies that were determined to be ineffective for a time but that eventually showed to be really effective with the progress of the devices.

WHAT THIS ARTICLE ADDS

- 1. There is no difference of complication rate with the addition VBN, concluding that VBN is a safe technology.
- 2. When EBUS-GS guided bronchoscopy biopsy is available, using VBN does not increase the diagnostic yield
- 3. The use of EBUS-GS with VBN could significantly shorten the bronchoscope arrival time.

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Expert Commentary: Dr. Fabien Maldonado

TITLE

Needle-based confocal laser endomicroscopy for real-time lung cancer detection can be feasible and safe.

SOURCE CITATION

Wijmans L, Yared J, de Bruin DM et al. Needle-based confocal laser endomicroscopy (nCLE³⁰⁹³

ABSTRACT

OBJECTIVES: Diagnosing lung cancer in the absence of endobronchial abnormalities is challenging. Needle-based confocal laser endomicroscopy (nCLE) enables real-time microscopic imaging of cells. We assessed the feasibility and safety of using nCLE for real time identification of lung cancer

METHODS: In patients with suspected or proven lung cancer scheduled for endoscopic ultrasound (EUS), lung tumors and mediastinal lymph nodes were imaged with nCLE before fine needle aspiration (FNA) was performed. nCLE lung cancer characteristics were identified by comparison with pathology. Multiple blinded raters validated CLE videos of lung tumors and mediastinal nodes twice.

RESULTS: EUS-nCLE-FNA was performed in 22 patients with suspected or proven lung cancer in whom 27 lesions (6 tumours, 21 mediastinal nodes) were evaluated without complications. Three nCLE-lung cancer criteria (enlarged pleomorphic cells, dark clumps,

directional streaming) were identified. Accuracy of nCLE imaging for detecting malignancy in tumours and metastatic lymph nodes was 90% and 89% respectively. Both interobserver (mean IOA (k=0.68 (95% CI: 0.66-0.70)) and intra-observer agreement (mean IOR (k=0.70±0.15)), were substantial.

CONCLUSION: Real-time lung cancer detection by endosonography-guided nCLE was feasible and safe. Lung cancer characteristics were accurately recognised.

JOURNAL CLUB COMMENTS

Question: In lung cancer patients the nCLE-technique could allow real-time visualization of malignant cellular structures in pulmonary tumors and metastatic lymph nodes?

Design: case series

Main results: using the 3 identified nCLE criteria of lung cancer, the sensitivity to detect lung cancer o metastatic lymph node was almost 90 % (LHR – 0.12), and specificity 89% (LHR + 8.2). With substantial interobserver and intra-observer agreement.

COMMENTS by Dr. Fabien Maldonado

With an exponential increase in the number of chest computed tomography (CT) scans performed worldwide, and the upcoming implementation of lung cancer screening with low-dose chest CT, the identification of incidentally and screen-detected lung nodules and mediastinal or hilar lymphadenopathy is expected to increase. Among the many technical limitations of currently available bronchoscopic techniques, two major questions remain unanswered: (1) how can we be confident, once the bronchoscopic examination has supposedly reached its target abnormality (e.g. lung nodule), that the biopsies will indeed sample the area of interest and (2) in the case of heterogeneous lymph nodes, what is the best area to biopsy? While radial ultrasound offers some guidance for lung nodules, it is limited by its inability to discriminate tumor from atelectasis, pleura or non-tumoral alveolar filling processes (e.g. blood) and biopsies of unrepresentative or non-diagnostic areas increase risk, time an healthcare costs. This very interesting feasibility study proposes to explore the value of a confocal microscopy miniprobe to obtain real-time non-invasive "optical biopsies" before invasive sampling, to address these issues. This miniprobe can be advanced through and endoscopic ultrasound (not yet endobronchial ultrasound scopes) 19 gauge needle and provide realtime images from which features suggestive of malignancy can be analyzed: enlarged pleiomorphic cells, "dark clumps" and so-called "directional streaming". With these features selected as indicative of malignancy, the investigators analyzed data from 22 patients and 27 lesions (6 tumors and 21 mediastinal lymph nodes), and found that needle-based confocal microscopy had 90% sensitivity and 89% specificity. Importantly, in this feasibility study, inter and intra-observer agreement were substantial, across a variety of tumor cell type. Clearly his technique, which needs further refinement and validation, will not replace pathology in our era of personalized medicine, targeted and immunotherapy, but could prove invaluable in (1) addressing the limitation of radial EBUS for accurate confirmation of successful navigation for lug nodules and (2) identifying regions of interest suitable for invasive sampling in heterogeneous lymphadenopathy.

WHAT THIS ARTICLE ADDS

Real-time imaging techniques remain a major obstacle to significant improvement in diagnostic yield in bronchoscopy. Radial ultrasound is useful but limited by difficulties in distinguishing tumor from other alveolar filling processes, and advanced techniques such as cone-beam CT are unlikely to become available to most bronchoscopists. Needle-based confocal laser endomicroscopy offers an alternative approach, allowing non-invasive "optical biopsies" that can direct biopsies more effectively and potentially decrease complications, save time and reduce costs. This feasibility study is an exciting first step in evaluating this new technology which if validated, is poised to transform our approach to nodule and lymph node sampling.

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Expert Commentary: Dr. Marioara Simon

TITLE

Hospital Volume Its Inversely Associated with Mortality Following Diagnostic Bronchoscopy in Lung Cancer Patients

SOURCE CITATION

Hiraishi Y, Jo T, Michihata N, et al.Hospital Volume and Mortality following Diagnostic Bronchoscopy in Lung Cancer Patients: Data from a National Inpatient Database in Japan. Respiration. 2019;97(3):264-272. doi: 10.1159/000493859. <u>PUBMED</u>

ABSTRACT

BACKGROUND: Recent advances in bronchoscopy utilizing endobronchial ultrasound (EBUS) as well as lung cancer therapy may have driven physicians to perform diagnostic bronchoscopy (DB) for high-risk patients.

OBJECTIVES: The aim of this study was to clarify the relationship between hospital volume (HV) and outcomes of DB.

METHODS: We collected data on inpatients with lung cancer who underwent DB from July 2010 to March 31, 2014. The annual HV of DB was classified as "very low" (≤50 cases/year), "low" (51-100 cases/year), "high" (101-300 cases/year), or "very high" (> 300 cases/year). The primary outcome was all-cause 7-day mortality after DB. Multivariable logistic regression fitted with a generalized estimation equation was performed to evaluate the association between HV and all-cause 7-day mortality after DB, adjusted for patient background factors.

RESULTS: We identified a total of 77,755 eligible patients in 954 hospitals. All-cause 7day mortality was 0.5%. Compared with the low-volume group, 7-day mortality was significantly lower in the high-volume group (odds ratio [OR] = 0.69, 95% confidence interval [CI]: 0.52-0.92, p = 0.010), and a similar trend was shown in the very-highvolume group (OR = 0.67; 95% CI: 0.43-1.05, p = 0.080). Radial EBUS with the guide sheath method and EBUS-guided transbronchial needle aspiration showed a significantly lower 7-day mortality.

CONCLUSIONS: All-cause 7-day mortality was inversely associated with HV. The risk of DB in patients with lung cancer should be recognized, and the exploitation of EBUS may help reduce mortality after DB.

JOURNAL CLUB COMMENTS

Selection bias would have occurred if the cohort selected from the Japan national discharge register was not representative, because hospitals with low and very low cases /year has sicker and older patients

Question: Is there a relationship between the volume of hospital studies and the mortality in diagnosed bronchoscopy?

Design: retrospective cohort study.

Setting: They used the Diagnosis Procedure Combination Database, which is a nationwide administrative claims and discharge data base in Japan

Patients: 77755 in 954 hospitals.

Interventions: According to HV in DB patients with lung cancer were categorized into "very low" (50 cases/year), "low" (51–100 cases/year), "high" (101–300 cases/ year),

and "very high" (> 300 cases/year) volume groups. Adjusted for demographics data, comorbidities and staging.

Main results: the volume of hospital studies can be a risk factor for deaths associated with endoscopic procedures in patients with lung cancer.

COMMENTS by Dr. Marioara Simon

Worldwide, lung cancer (LC) is the most common malignancy and the most common cause of cancer mortality.

The authors report the results of an original study about a relation between hospital volume (HV) and mortality in LC patients following diagnostic bronchoscopy (DB). They have shown for the first time that a higher HV is associated with a lower 7-day mortality rate after DB.

The higher mortality after DB than other studies that reported only mortality related to DB has three explanations. First, the primary outcome of the study was "all-cause" mortality and secondly, the patients with LC are at a higher risk of undergoing DB. Moreover, the authors evaluated only hospitalized patients who may have a higher risk and higher activities of daily living (ADL) score than outpatient DB.

Recent improvements in LC due to treatments with molecular-targeted drugs and immune checkpoint-targeted drugs increased the number of high-risk patients that undergo DB and also increase the number of minimal invasive procedures such as EBUS-TBNA and rEBUS-GS.

The study reveals an association between the use of EBUS-TBNA and rEBUS-GS in high HV and the reduced rate of mortality. The explanation can be also because of the role of EBUS-TBNA in the staging of LC and the possibility to diagnose more operable cases, with better prognostic and survival.

Because of the higher complications, higher mortality and the underuse of EBUS-TBNA in low HV the authors propose an original solution for reducing hospital mortality after DB: to refer the LC patients with well-preserved ADL to higher-volume hospitals with experienced bronchoscopists and advanced equipment, instead of lower-volume ones. One option for patients with low ADL may be to have experienced doctors from high-volume centers visit low-volume hospitals and perform DB, without patient transfer.

The conclusions of the study were that the risk of DB in patient with LC should be recognized and that the careful management before and after bronchoscopy of the patients is very important. Recent advances in bronchoscopy utilizing endobronchial ultrasound (EBUS) as well as lung cancer therapy may have driven physicians to perform diagnostic bronchoscopy (DB) for high-risk patients

WHAT THIS ARTICLE ADDS

The originality features of this article are: the analysis of all-cause mortality after DB only in hospitalized patients, the classification of HV of DB centers in four groups ("very low", "low", "high", "very high"), the contribution of EBUS-TBNA and rEBUS-GS to the decrease of mortality in high HV centers and the solution of the decrease of the mortality by proper selection and orientation of high-risk patients toward high HV centers.

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- 3. EBUS: Faster, cheaper and most effective in lung cancer staging, Fotios Sampsonas et al. Clinical Practice, 2018

Expert Commentary: Dr. Mohammed Munavvar

TITLE

Spectrum analysis of EBUS radiofrequency can be used as non-invasive predictor of malignancy of peripheral pulmonary lesions.

SOURCE CITATION

Ishiwata T, Terada J, Nakajima T, et al. Transbronchial evaluation of peripheral pulmonary lesions using ultrasonic spectrum analysis in lung cancer patients. Respirology. 2019 Mar 25. doi: 10.1111/resp.13534. <u>PUBMED</u>

ABSTRACT

BACKGROUND AND OBJECTIVE: Analysis of the endobronchial ultrasound (EBUS) radiofrequency spectrum has been used for convex-probe EBUS technology. Quantitative imaging analysis is also warranted for guided bronchoscopy using radial-probe EBUS (RP-EBUS) targeting peripheral pulmonary lesions (PPL). This study aimed to determine the feasibility of radiofrequency spectrum analysis for distinguishing malignant and benign PPL during diagnostic bronchoscopy.

METHODS: Raw RP-EBUS images with radiofrequency data, including backscatter signals, were prospectively recorded. The ultrasonic spectral parameters, such as intercept, midband-fit and slope within the region of interest, were retrospectively computed by linear regression analysis and compared with the final diagnosis.

RESULTS: A total of 71 PPL, including 45 malignant and 26 benign lesions, were analyzed. Malignant PPL showed a significantly lower intercept (P < 0.0001), lower midband-fit (P < 0.0001) and higher slope (P = 0.014) than benign PPL. Analyses of the area under the curve of receiver operating characteristic plots demonstrated that the intercept showed the best diagnostic performance among three parameters (0.87, 0.77 and 0.69 for intercept, midband-fit and slope, respectively). The sensitivity, specificity, accuracy, positive likelihood and negative likelihood were 75.6%, 96.2%, 83.1%, 19.6 and 0.25 for the intercept; 88.9%, 57.7%, 77.5%, 2.1 and 0.19 for the midband-fit; and 68.9%, 73.1%, 70.4%, 2.6 and 0.43 for the slope.

CONCLUSION: Spectrum analysis of EBUS radiofrequency can be used as a novel noninvasive predictor of malignant or benign PPL. Analysis of the 'intercept' of the targeted lesion may provide useful supporting data for real-time sampling from PPL during diagnostic bronchoscopy.

JOURNAL CLUB COMMENTS

Some elements of the proper clinical evaluation of a diagnostic test are very important to consider 1) The comparison between the new study and the gold standard must be blind and independent. 2)The gold standard must be performed in all patients regardless of the result of the test we are analyzing. 3) The patient sample include an appropriate spectrum of disease.

Question: In patients with peripheral pulmonary nodules, the EBUS with radiofrequency (as a non-invasive measure of analysis of PPL), can distinguish between benign or malignant lesions through three spectral parameters (lower intercept, lower midband fit and slope)

Design: case series

Main results: changes in the likelihood ratio affects post-test probability of disease, Values greater than 2 *increase* the probability of disease (+LR) 15%, greater than 5 (30%) and greater than 10 (45%). In the article of Ishiwata et al , one of the radiofrequency spectrum parameters (intercept) has a (+ LR) of 19.6 . Conversely values lower than 0.5 decreased the probability of disease (-LR) 15%, lower than 02 (30%) and lower than 0.1 (45%). In the article of Ishiwata the spectrum parameter midband fit has (-LR) of 0.19. More studies with an adequate spectrum of patients and with blind people from those who perform the procedure, are necessary to consider these findings as valid, however the results are promising.

COMMENTS by Dr. Mohammed Munavvar

Accurate diagnosis of peripheral pulmonary lesions remains a massive challenge in clinical practice, despite the utilization of a variety of novel technologies, the most common and extensively evaluated of which is Radial miniprobe EBUS. The overall diagnostic yield of this technique, though, has been disappointingly low.

Ishiwata et al have adopted an innovative approach in this study to carry out a quantitative ultrasonic spectrum analysis using the three parameters of intercept, midband-fit and slope. Despite being retrospective work in a single center with only 71 peripheral lesions, the results are indeed promising, and could potentially open the door for more detailed prospective multicenter work, with much needed real time guidance and thus enhance the diagnostic yield of PPLs in clinical practice.

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Expert Commentary: Dr. Venerino Poletti

TITLE

Cryobiopsy can be useful and safe for diagnosis of peripheral pulmonary lesions with guided bronchoscopy.

SOURCE CITATION

Imabayashi T, Uchino J, Yoshimura A, et al. Safety and Usefulness of Cryobiopsy and Stamp Cytology for the Diagnosis of Peripheral Pulmonary Lesions. Cancers (Basel). 2019 Mar 22;11(3). pii: E410. doi

ABSTRACT

Background

Reports on the use of cryobiopsy (CB) for lung cancer diagnosis are limited.

Objective

The aims of the present study were to evaluate the safety and usefulness of CB using radial endobronchial ultrasonography, without a guide sheath, for the diagnosis of peripheral pulmonary lesions and determine the utility of stamp cytology, an on-site diagnostic technique for determining tumor inclusion in CB samples.

Methods

Retrospective analysis of data for 35 patients (36 lesions) with suspected peripheral lung cancer who underwent CB between August 2017 and February 2019 at our medical facility. The diagnostic yield, incidence of complications, and the utility of stamp cytology for diagnosis were investigated.

Results

The diagnostic yield of CB was 86.1% (31/36) with histological diagnosis, and 80.5% (29/36) with diagnosis using stamp cytology; the overall yield was 91.6% (33/36). Pneumothorax requiring thoracic drainage occurred in two patients, both of whom had lesions contacting the pleura. Grade 2 and grade 1 bleeding occurred in one and 25 patients, respectively.

Conclusions

CB enables the collection of very large, nearly intact tissue samples, thus resulting in an improvement in the true diagnosis rate and facilitating the measurement of multiple biomarkers as well as rapid histological diagnosis.

JOURNAL CLUB COMMENTS

Case series are characterized by collection of multiple noteworthy clinical occurrences. In this case, Tatsuya et al. have developed a novel minimally invasive technique (CB with EBUS) for the diagnosis of PPL. They have performed this technique on 36 cases and now report the outcomes from their procedure on these cases, A lack of hypothesis or a comparison group is the biggest weakness of a case series. As a result, most case series help to generate hypotheses, not answer clinical questions of efficacy or effectiveness.

Question: Is CB with radial EBUS and stamp cytology a useful and safety technique for diagnosis of PPL

Design: Tatsuya Imabayashi performed a retrospective study of a series of cases.

Main results: High diagnostic yield of 91.6% of the cases with a low complication rate in the procedure.

COMMENTS by Dr. Venerino Poletti

Implementation of screening programs for lung cancer and also an increased frequency of incidentally found peripheral pulmonary lesions, have increased the need of the evaluation of those lesions in order to avoid as many futile surgeries as possible.

Unfortunately, conventional forceps transbronchial biopsy (TBB) shows a low diagnostic yield (30–60%). The development of new modalities such as radial endobronchial ultrasound (R-EBUS), virtual bronchoscopy (VB), electromagnetic navigation bronchoscopy (ENB) and ultrathin bronchoscopes offers the possibility of a better diagnostic accuracy. A recent metanalysis has shown that diagnostic yield of R-EBUS was 70.6% being higher than the reported for conventional bronchoscopy. Most interestingly that yield is comparable to endobronchial navigation bronchoscopy (74%) and virtual bronchoscopy (VB) (67.1%). In most of the studies, the diagnostic yield is higher in larger lesions (>2 cm or 3cm in size), malignant lesions and those showing a bronchus sign on computerized tomography (CT) scan. To improve those results, in the last years investigators have been exploring diagnostic yields with a multimodality approach, for instance by combining R-EBUS, ultrathin bronchoscopy and VB.

In 2014, the Heidelberg group evaluated the safety and feasibility of the cryoprobe in combination with EBUS for the diagnosis of peripheral lung lesion. In a randomized study of 39 patients they showed an increase of the overall diagnostic yield from 60.5% with CB without US to 74.2% in the lesions reached by EBUS. Some later studies have shown similar results although (as in most of the literature about cryobiopsy) diagnostic yields and complication rates are quite variable. Brar et al in Canada did not find any significant difference by adding CB to EBUS location of the lesion, but with an unusually high diagnostic yield for the conventional TBB (52%) and an unusually low yield for CB (56%). As in any indication of cryobiopsy (mainly studied in interstitial lung diseases -ILD-), this divergence of results emphasizes the need of definition of standards for equipment, personnel, indications, contraindications, risks, and training requirements for TBCB to uniform the practice. Also, given the wide reported variability in diagnostic yield (50–100% in ILD) and complications (rate of pneumothorax from 0% up to about 30%), there is a need for standardization of TBCB procedures

The present study by Imabayashi et al of 35 patients, even being retrospective offers a very detailed description of the technical issues and explore the alternative of using radial endobronchial ultrasonography, without a guide sheath. They found a lower rate of pneumothorax requiring thoracic drainage than previously published (only 5.5%) and, as previously suggested, the incidence of bleeding for longer freezing times was higher (35.7% for 2s vs 80.0% for 5s). The authors showed a diagnostic yield of CB of 86.1% which increased to 91.6% with adding the use of stamp cytology.

Imabayashi et al have shown that the use of CB guided by ultrasound is safe and increases the diagnostic yield of conventional methods. This is particularly important in

areas with a high prevalence of granulomatous diseases (TB and histoplasmosis, mainly) in which the proportion of benign nodules is significantly higher and the indication of surgery without previously confirming malignancy may result in a high rate of futile surgeries. Further large-scale, randomized, prospective, comparative trials are necessary to confirm these findings. Following the standardized approaches suggested by expert consensus documents to maximize the accuracy and increase patient safety is strongly recommended.

WHAT THIS ARTICLE ADDS

- Criobiopsy guided for ultrasound (US) for diagnosis of peripheral nodules is a safe method with a good diagnostic yield.
- The use US without guided sheet improves the access to certain lesions, mainly in the upper lobes
- As the size of the sample is not as critical as in the diagnosis of interstitial lung diseases, in the diagnosis of nodules a 2s freezing time should be recommended to decrease the rate of bleeding
- the use of stamp cytology with CB not only facilitates the on-site confirmation of tumor inclusion but also improves diagnostic yield

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Expert Commentary: Dr. Spasoje Popevic

TITLE

Re-biopsy can change the treatment management of patients with NSCLC and resistance to EGFR-TKIs.

SOURCE CITATION

Zhou J, Zhao C, Zhao J, et al.Re-biopsy and liquid biopsy for patients with non-small cell lung cancer after EGFR-tyrosine kinase inhibitor failure. Thorac Cancer. 2019 Apr;10(4):957-965. doi: 10.1111/1759-7714.13035. <u>PUBMED</u>

ABSTRACT

BACKGROUND: Re-biopsy is important for exploring resistance mechanisms, especially for non-small cell lung cancer (NSCLC) patients who develop resistance to EGFR-tyrosine kinase inhibitors (TKIs). Liquid biopsy using circulating tumor DNA has come into use for this purpose. This retrospective study investigated the status of re-biopsy and liquid biopsy in NSCLC patients with EGFR mutations and evaluated their effect on clinical strategies and prognosis.

METHODS: Five hundred fifty-five NSCLC patients with resistance to EGFR-TKIs were included and divided into three groups: re-biopsy, liquid biopsy, and no re-biopsy. Amplification refractory mutation system (ARMS) PCR or super ARMS PCR was used to detect EGFR mutations.

RESULTS: Three hundred eight (55.5%) patients underwent re-biopsy; 45.5% (140/308) were positive for T790M. The most common re-biopsy procedure was computed tomography-guided percutaneous core needle biopsy (60.1%), followed by effusion drainage (29.5%) and superficial lymph node biopsy (6.5%). One hundred eighteen (21.3%) patients underwent liquid biopsy; the T790M detection rate was 41.5% (49/118.) Of the 308 patients who underwent re-biopsy, 69 were examined for EGFR mutations with plasma. The concordance rate of T790M detection between tissue and plasma was 66.7%. A statistical difference in further treatment after EGFR-TKI failure was observed among all groups (P = 0.014). Patients in the biopsy groups were more likely to receive third-generation EGFR-TKIs. Multivariate analysis showed that re-biopsy had a significant impact on overall survival (P < 0.001).

CONCLUSION: Re-biopsy plays a pivotal role in the management of patients with NSCLC and resistance to EGFR-TKIs. Liquid biopsy may be an alternative if difficulties performing re-biopsy exist.

JOURNAL CLUB COMMENTS

In this study, diagnostic and prognostic factors are mixed in a group of patients with resistant NSCLC. As the biopsy was not done across the spectrum of patients the risk of selection bias exists in this group of patients.

On the results of the study two important concepts are introduced in this article Hazard ratio and survival curves. Hazard Ratio is a measure of how often a particular event happens in one group compare to how often it happens in another group over time.

(example re biopsy /no re biopsy). Survival curves The Kaplan Meiers curves that starts at 100% of the study population and shows the percentage of the population still surviving or free of disease at successive time.

Question: What is the implication of the diagnostic test of the re-biopsy (liquid or tissue / cytology) in patients with NSCLC with EGFR resistant mutations in terms of prognosis and management strategy –

Design: Retrospective cohort performed in a single center

Main results: Re biopsy (including liquid biopsy) play a pivotal role in the management of resistant NSCLC and could improves the clinical outcomes to some extent.

COMMENTS by Dr. Spasoje Popevic

Despite the notable efficacy achieved with EGFR TKIs, a majority of patients develop resistance after a median progression-free survival (PFS) of approximately one year.

Current guidelines state that performing a re-biopsy of progressive lesions after EGFR TKI therapy is a reasonable course of action, whenever it's possible, to determine the mechanism of acquired resistance (especially in detecting EGFR Exon 20 T790M mutation), to obtain material for molecular testing in order to apply targeted therapy.

On the other hand, liquid biopsy presents a valid alternative and, in cases where detection of EGFR T790M mutation in plasma is achieved, it's justified to start 3rd generation EGFR TKI's without tissue confirmation. If a liquid biopsy, as a non-invasive approach, fails to detect T790M mutations, tissue re-biopsy, if possible, should be offered to the patient, because of significant false negative rate of liquid biopsy, which is one of the known limitations of the method. Explanation can be tumor heterogeneity (differences between different ctDNA samples taken from circulation and/or between a ctDNA sample and a sample from a biopsy of the primary tumor).

Complementary role of both methods is well shown in European Society for Medical Oncology (ESMO)¹ and National Comprehensive Cancer Network (NCCN)² clinical practice guidelines for diagnosis and treatment of NSCLC.

WHAT THIS ARTICLE ADDS

This retrospective study clearly depicts the importance of re-biopsy on overall survival (OS) in a large group of patients with progressive NSCLC resistant to first and second generation TKI's. Re-biopsy led to treatment change after progression (osimertinib and/or chemotherapy/radiotherapy) and thus to prolonged OS. Liquid biopsy and re-biopsy had T790M detection concordance of 66.3%, which is satisfactory, but with surprisingly low sensitivity of liquid biopsy of only 33.3%, which may be explained by method used in majority of patients (ARMS-PCR). Similar T790M mutation detection rate between tissue and plasma, show that liquid biopsy can also provide guidance for

further treatment strategies. Adequate molecular diagnostics (whether from tissue or plasma) is a key determining factor for treatment.

The retrospective nature, in my opinion, limitation of this study.

What is the real impact of re-biopsy and how can it improve clinical outcomes in lung cancer patients is yet to be determined in larger prospective studies.

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- 2. NCCN guidelines version 5.2017. Non-small Cell Lung Cancer

Expert Commentary: Dr. Silvia Quadrelli

TITLE

Detection of T790M in rebiopsy specimen can predict response to osimertinib better than liquid biopsy results.

SOURCE CITATION

Hong MH, Kim HR, Ahn BC, et al.Real-World Analysis of the Efficacy of Rebiopsy and EGFR Mutation Test of Tissue and Plasma Samples in Drug-Resistant Non-Small Cell Lung Cancer. Yonsei Med J. 2019 Jun;60(6):525-534. doi: 10.3349/ymj.2019.60.6.525.

ABSTRACT

Purpose: Standard treatment for cases of non-small cell lung cancer (NSCLC) exhibiting acquired drug resistance includes tumor rebiopsy, epidermal growth factor receptor (EGFR) mutation testing (e.g., for T790M mutations), and the subsequent administration of third-generation EGFR-tyrosine kinase inhibitors (EGFR-TKIs). However, rebiopsies are typically invasive, costly, and occasionally not feasible. Therefore, the present study aimed to assess rebiopsy procedures by analyzing real-world data collected by the ASTRIS study of patients with resistant NSCLC.

Materials and Methods: The present study used statistical models to evaluate data collected by the ASTRIS trial (NCT02474355) conducted at Yonsei Cancer Center, including the rebiopsy success rate, incidence of T790M mutations in collected tissue and plasma samples, and association of administered osimertinib treatment efficacy.

Results: In a total of 188 screened patients, 112 underwent rebiopsy. An adequate tumor specimen was obtained in 95 of these patients, the greatest majority of whom (43.8%) were subjected to bronchoscopy. T790M mutations were detected in 53.3% of successfully EGFR-tested rebiopsy samples. A total of 88 patients received osimertinib treatment, and the objective response rate and median progression-free survival time was 44.3% and 32.7 weeks, respectively, among the treated patients overall, but 57.8% and 45.0 weeks, and 35.2% and 20.4 weeks among patients who exhibited T790M-positive tissue (n=45) and plasma (n=54) samples, respectively.

Conclusion: Approximately 60% of patients in the analyzed real-world cohort were eligible for tissue rebiopsy upon NSCLC progression. Osimertinib activity was higher in patients in whom T790M mutations were detected in tissues rather than in plasma samples.

JOURNAL CLUB COMMENTS

Real world medicine is an elusive concept that refers to information on health care that is derived from multiple sources outside typical clinical research settings. The usefulness of real-world evidence is an appreciation of its potential for complementing the knowledge gained from traditional clinical trials whose well known weakness is the difficult to generalize findings to a large populations patients, providers and health care systems . Real-world evidence can be viewed as a means of incorporating diverse types of evidence into information on health care. In order to avoid misuse, it is essential to clarify adequately the setting where the data was developed and the methodology to be used to analyze it.

Question: In Patients with resistance NSCLC who were rebiopsied, the incidence of T790M in collected tissue and plasma samples were associated with better response to Osimetrtinib

Design: historic cohort study

Main results: Progresion Free Survival time in patients who received osimertinib was significantly longer (45.0 weeks) in patients that exhibited T790M- positive tumor tissue samples

COMMENTS by Dr. Silvia Quadrelli

Despite high tumor response rates with first-line EGFR-TKIs (epidermal growth factor receptor, tyrosine kinase inhibitors) among patients with advanced NSCLC, a disease progression occurs frequently after 9 to 13 months. Genotyping post-progression tumor samples for EGFR T790M is recommended for guiding therapy in current guidelines. However, rebiopsy of histological samples includes several disadvantages regarding invasiveness, convenience, and feasibility. Today, a "liquid biopsy" of cell-free DNA (cfDNA) shed from the tumor and collected from serum is increasingly being used to

direct treatment of NSCLC, both as an adjunct to biopsy of tumor tissue after drug resistance and, increasingly, instead of tissue biopsy.

T790M mutation is currently used as an indicator of treatment efficacy in patients treated with EGFR TKI. It is known that the genomic composition of individual tumor changes over time, leading to resistance. This has led to the development of an increasing number of third fourth-generation TKIs for NSCLC. Monitoring T790M may indicate when the cancer is developing resistance to first- and second-generation TKIs and provides a basis for changing treatment toward new TKIs such as osimertinib or chemotherapy.

In spite of the increasing interest in liquid biopsy reliable data about its value to predict response to third-generation TKIs is incomplete. For instance, a review of 247 articles published between 2015 and 2018 showed that majority (32%) of the articles were review papers and when only clinical trials were included, only eight articles remained, and only three articles were about the T790M mutation and treatment with osimertinib.

Currently ESMO guidelines about metastatic NSCLC (2016) accepts that liquid biopsy represents a surrogate source of DNA at the time of progression for EGFR-mutated patients. The recommendation is that if a T790M mutation in peripheral blood is observed, treatment with third-generation EGFR TKIs is justified but if a T790M-negative liquid biopsy is found, a tissue rebiopsy should be performed if feasible and if accepted by the patient. Similar recommendations were sustained by the IASLC stament in 2018.

In the current article Min Hee Hong et al analised the feasibility, sensitivity and prediction value for response to osimertinib in the real-world clinical settings, by analising the success rate of tissue rebiopsies and the incidence of T790M mutations in tissue and plasma samples that were collected upon NSCLC progression from patients enrolled in the ASTRIS study (an open-label, single-arm, multinational, real-world treatment study that investigated the safety and efficacy of using osimertinib to treat patients with T790M-positive advanced NSCLC).

Of the 112 patients who underwent rebiopsy, 49 (43.8%) were subjected to bronchoscopy, including endobronchial biopsy, fluoroscopy-guided transbronchial lung biopsy (TBLB), or endobronchial ultrasound (EBUS)-transbronchial needle aspiration (TBNA). The different bronchoscopy biopsies were successful in 75-84% of the procedures. The authors showed that rebiopsy was performed in almost 60% of patients, with 85% of biopsies getting pathological diagnosis and in 95% of them EGFR analysis was possible. Of the 188 patients in the ASTRIS cohort, 75 provided matched tumor tissue and plasma samples. A comparison of these matched samples revealed the positive predictive value of plasma T790M mutation screening to be 45.8%, and the false-positive rate among screened plasma samples to be 54.2%. Most interestingly, the median PFS time in patients who received osimertinib was significantly longer (45.0 weeks) in 45 patients that exhibited T790M- positive tumor tissue samples than in 13 patients who exhibited T790M-negative tissue and T790M- positive plasma samples (9.4 weeks). Torricelli E et al had shown recently in a small series of 18 patients that only in 14% plasma T790 status was negative while the pulmonary re-biopsy was positive. In a

previous study by Takahama T et al patients with paired samples showed a concordance of 65.9% for T790M

Those results about the outcome of osimertinib were different from the obtained by Oxnard, et al who reported a very similar median PFS time for tissue T790M- positive and plasma T790M-positive patients. The inferior efficacy of osimertinib in plasma T790M-positive patients in the present study is likely reflective of the high false-positive rate (54.2%). Patients with discordant tissue T790M-positivity (tissue positivity, plasma negativity) experienced better outcomes. It may mean that the absence of circulating T790M clones, the presence of T790M-positive tumors may indicate a more indolent form of NSCLC.

Further studies are needed, but these results may mean that in selected patients, rebiopsy may be considered in spite of the results of a previous T790M positivity in the liquid biopsies.

WHAT THIS ARTICLE ADDS

- 1. Liquid biopsies for T790M mutation detection show a non-neglectable rate of false positive (54%) in real life samples
- 2. Rebiopsy results of T790M shows a better prediction of response to osimertinib than liquid biopsy results
- 3. Patients with discordant tissue T790M-positivity (tissue positivity, plasma negativity) experienced better outcomes for treatment with osimertinib.

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Expert Commentary: Dr. Antoni Rosell

TITLE

Malignancy Risk Prediction Model for Pulmonary Nodules May Help to Guide Clinicians' Decision-Making.

SOURCE CITATION

Reid M, Choi HK, Han X, et al. Development of a Risk Prediction Model to Estimate the Probability of Malignancy in Pulmonary Nodules Being Considered for Biopsy. Chest. 2019 Mar 30. pii: S0012-3692(19)30689-0. doi: 10.1016/j.chest.2019.01.038. <u>PUBMED</u>

ABSTRACT

BACKGROUND: Malignancy probability models for pulmonary nodules (PN) are most accurate when used within populations similar to those in which they were developed. Our goal was to develop a malignancy probability model that estimates the probability of malignancy for PNs considered high enough risk to recommend biopsy.

METHODS: This retrospective analysis included training and validation datasets of patients with PNs who had a histopathologic diagnosis of malignant or benign. Radiographic and clinical characteristics associated with lung cancer were collected. Univariate logistic regression was used to identify potential predictors. Stepdown selection and multivariate logistic regression were used to build several models, each differing according to available data.

RESULTS: Two hundred malignant nodules and 101 benign nodules were used to generate and internally validate eight models. Predictors of lung cancer used in the final models included age, smoking history, upper lobe location, solid and irregular/spiculated nodule edges, emphysema, fluorodeoxyglucose-PET avidity, and history of cancer other than lung. The concordance index (C-index) of the models ranged from 0.75 to 0.81. They were more accurate than the Mayo Clinic model (P < .05 for four of the models), and each had fair to excellent calibration. In an independent sample used for validation, the C-index for our model was 0.67 compared with 0.63 for the Mayo Clinic model. The ratio of malignant to benign nodules within each probability decile showed a greater potential to influence clinical decisions than the Mayo Clinic model.

CONCLUSIONS: We developed eight models to help characterize PNs considered high enough risk by a clinician to recommend biopsy. These models may help to guide clinicians' decision-making and be used as a resource for patient communication.

JOURNAL CLUB COMMENTS

Michal Reid et al. developed a diagnostic model to determine the probability of malignancy of pulmonary nodules. Although it is challenging in one respect they are easier to construct than models designated to identify prognostic factors. In diagnostic settings causality is unimportant. The steps for the construction of the model were adequate ,(perform the bivariate analysis , methods for variable selection , an assessment of the fit of the model and finally the dataset was validated .¹

Question: In patients with PNs the development of malignancy probability model could be consider a useful tool to recommend biopsy

Design: Observational study

Main results: The concordance index (C-index) of the models ranged from 0.75 to 0.81. The C index is a measure of the concordance between predicted and observed outcomes. The higher the value the greater the ability of your model to predict outcome.

COMMENTS by Dr. Antoni Rosell

The solitary pulmonary nodule (SPN) is frequently encountered on chest imaging and poses an important diagnostic challenge to clinicians. SPN are seen in 0.09% to 0.2% of chest radiographs and can be the initial presentation of lung cancer in 20% to 30% of patients. But most SPNs are benign; only 30% to 50% are malignant. The detection of a SPN may be the first and only chance of cure in the patient with lung cancer. But it is also very important to identify benign lesions correctly in order to prevent the morbidity and mortality associated with a futile surgical intervention.

In order to accurately differentiate benign from malignant lesions, morphologic analysis based on the assessment of size, shape, and internal characteristics using CT has been the mainstay in evaluating pulmonary nodules. Some signs like the presence of intranodular fat are a reliable indicator of a hamartoma, size is important as the smaller the nodule, the more likely it is to be benign, especially nodules less than 5 mm in diameter. Calcification and lack of growth for at least 2 years are generally accepted as reliable signs of a benign nodule. Importantly the evaluation of tumor vascularity using contrast-enhanced CT has proven helpful, as the absence of significant lung nodule enhancement on CT is strongly predictive of benignancy.

As none of those variables gives complete certainty by itself, as early as in the 80s, different algorithms were developed in order to increase the accuracy of prediction. More recently, several prediction models using clinical and radiological values have been developed. Some of the most widely used prediction models are the Mayo Clinic, the Veterans Association and the Brock University (based only on clinical values and CT characteristics) and the Herder et al. model that also includes the 18F-fluorodeoxyglucose (FDG) uptake value in positron emission tomography (PET/CT). Most of available models include similar variables as they strongly predict malignancy.

The Mayo model (1997) includes older age, smoking history, cancer history, nodule diameter, location of nodule (especially the upper lobe), and spiculation. The VA model (2007) is based on patient age, smoking history, and nodule diameter. The Brock model (2013) includes age, family history of lung cancer, sex, nodule size, emphysema, nodule count, location of the nodule in the upper lobe, spiculation and part-solid nodule. The Herder model (2005) seems to have a higher accuracy of prediction by including the results of 18FDG-PET. The British Thoracic Guidelines for Pulmonary Nodules include the use of a calculator for the Brock model and other for the Herder model. It allows to calculate the probability of malignancy following CT (Brock Model) and the probability of malignancy following retroct (Herder Model) and both are downloadable as apps on iPhone or Android phones. The inclusion of the two options is important as PET is an expensive technology, not universally available that in some occasions may also be not considered cost-effective and worthy to be used.

Statistical models are often used to predict the probability that an individual with a given set of risk factors will experience an "event." Risk models are developed using several risk factors typically based on patient characteristics associated with the health event of interest. Including data about patient characteristics, the risk model can calculate the probability of a patient having the event. However, before a risk model is used in clinical practice, the predictive ability of the model should be evaluated. The model validation must include "calibration" (the agreement between the observed outcomes and predictions) and "discrimination" (the ability to discriminate between low and high risk patients).

In this paper, Reid et al from the Cleveland Clinic, developed a new model based on the retrospective analysis of 301 patients with SPNs, 66.5% of them resulting in malignant SPNs. They selected the potential predictive factors identifying them first by univariate logistic regression, and then by a stepdown selection and several multivariate logistic regression models. In that way, they built a first model (M1) that included age, CT scan, pack years, presence of emphysema on initial CT scan, upper-lobe location, nodule density/border (ie, part-solid, GGN, solid/smooth, solid/irregular, solid/spiculated, solid/lobulated), and history of cancer other than lung). That model M1 resulted in a median C-index of 0.79 compared with 0.69 for the Mayo Clinic model. They subsequently develop models that included FDG-PET avidity (M2), SPN change in size (M3), and both FDG-PET avidity and change in size (M4). Those models produced similar results with a median C-index of 0.79, 0.77, and 0.77, respectively.

All models generated using data on only solid nodules had a higher median C-index for their respective population than the Mayo Clinic model. Interestingly, the authors built multiple models to fit the clinical data available for a given patient (ie, FDG-PET, follow-up CT scan). The models were validated using an independent sample and selecting the most appropriate model for the given clinical scenario. They include an online tool in the publication that allows the user to enter the data available, and then the tool will select the model that is most appropriate for that data

https://statml.shinyapps.io/pulmonary-nodule-risk-prediction/.)

Initially, this model seems to be quite attractive and with a better accuracy of prediction than the Mayo Clinic model. However, some cautions are needed when analyzing a new model. As the different models are built using different methods, any new model

presented need external validation. Additionally, the influence of the population in which the model was developed is crucial and it may work differently in other populations when applied in clinical practice. For instance, when compared in an Asian population, even when the Brock, VA and Mayo models did not have significant differences, the Brock model showed significantly higher accuracy for predicting malignancy than the Herder model, which included the 18FDG uptake value. It shows that in an area with a high prevalence of granulomatous diseases and a different epidemiological pattern of lung prevalence (for instance, higher prevalence in young women), the utility of PET/CT for predicting malignancy is very limited.

A key factor is that models for patients with incidentally or screening-detected nodules may behave differently in screened patients (a population of increasing interest). This new model in particular was only compared to the Mayo model. The Mayo and VA models were developed for patients with incidentally detected nodules while the Brock model was developed for patients with nodules detected by screening. When a secondary analysis of data from the National Lung Screening Trial (NLST) was used to compare the accuracy and calibration of the Brock model with the Mayo and VA, Nair V et al, found that among patients with a nodule size 8 mm or larger or nodule size 4 mm or larger on baseline screen in the NLST, the Brock model was most accurate for identifying cancerous nodules, and that the Brock model was reasonably well while the Mayo and VA models overestimated the probability of cancer.

This new model is a promising tool which still requires external validation. But most importantly, before adopting a prediction model, individual physicians (and mainly guideline writers) should consider the effects of regional differences, mainly prevalence of granulomatous disease and local epidemiology of lung cancer.

WHAT THIS ARTICLE ADDS

• A new risk prediction model for pulmonary nodules is offered

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Expert Commentary: Dr. Grigoris Stratakos

TITLE

Evaluation of Patients with NSCLC Through Thoracic Oncology Multidisciplinary Clinic Can Reduce the Cost of Health Care.

SOURCE CITATION

Voong KR1, Liang OS2, Dugan P, et al. Thoracic Oncology Multidisciplinary Clinic Reduces Unnecessary Health Care Expenditure Used in the Workup of Patients with Non small-cell Lung Cancer. Clin Lung Cancer. 2019 Mar 12. pii: S1525-7304(19)30060-9. doi: 10.1016/j.cllc.2019.02.010. <u>PUBMED</u>

ABSTRACT

National costs of lung cancer care exceed \$12 billion. We investigate the resourcesavings benefit of a single-day thoracic oncology multidisciplinary clinic (MDC) in the diagnostic period prior to non-small-cell lung cancer (NSCLC) treatment.

MATERIALS AND METHODS: From July 2007 to January 2015, patients with NSCLC treated with multimodality therapy at a tertiary hospital-based cancer center in Maryland were identified. Patient and treatment details were collected. Health care resources utilized in the 90 days prior to receipt of first oncologic treatment were identified using billed activity codes. Associated total charges, including professional fees and hospital-based technical fees, were identified and inflated to 2014 dollars using the Consumer Price Index. Codes were categorized into provider visits, procedures, pathology/laboratory, radiology, and other tests. χ 2, Student t, and Wilcoxon rank-sum tests compared charges of patients seen in and out of the MDC.

RESULTS: Two-hundred ninety-seven (non-MDC = 161, 54%; MDC = 136, 46%) of 308 patients identified had total charges available. Patients seen through MDC had on average a 23% decrease in total charges per patient incurred (\$5839 savings; range, \$5213-\$6464) compared with patients seen through non-MDC settings. Evaluation through MDC reduced the average number of provider visits per patient (non-MDC, 6.8 vs. MDC, 4.8; P < .01) prior to treatment start, which led to a 50% (average \$3092; range, \$2451-\$3732) reduction in provider charges per patient (p < .01).

CONCLUSIONS: Evaluation of patients with NSCLC through a coordinated single-day MDC reduced hospital charges per patient by 23% during the diagnostic period prior to treatment when compared with evaluation through traditional referral-based thoracic oncology clinics.

JOURNAL CLUB COMMENTS

Health economics evaluation (HEE), as context-specific tools, are not easily generalizable from setting to setting. Existing studies regarding generalizability and transferability of HEEs have primarily been conducted in different countries. Therefore, a legitimate question for policy makers is to what extent HEEs conducted in different context could be applicable to everyone. While we found relatively good standards of reporting the study's question, population, interventions, comparators and conclusions, the overall reporting did not report incremental analysis, of discounting long-term costs and effects affecting the external validity Improving these aspects in is paramount to maximizing their potential benefits such as increasing the generalizability/transferability of their results

Question: A simplified study strategy for patients with lung cancer can reduce study costs

Design: cost effectiveness study

Main results: single center study reduced hospital charge per patient by 23% during the diagnostic period evaluation

COMMENTS by Dr. Grigoris Stratakos

Although this retrospective study aimed to evaluate the cost of medical management before the start of treatment in lung ca patients, its results may prove of far wider importance.

The reduction of cost in the MDC setting by 23% is of course essential but is mainly related to reduced number of independent visits to medical specialists which in other countries may not be charged within the public sector. The reduction of "other" (additional) exams in the same cohort marks a tendency towards a simpler and more rationalized approach with economy of resources and respect to patients' safety.

Unfortunately, no query was predicted for patients' preference and comfort. We can rightly hypothesize that the multidisciplinary one-day clinic means quick, simple and tightly organized overall management adding to patients comfort and wellbeing. More studies are warranted to change the paradigm of clinical management in lung cancer patients towards this direction leading -among others - to medical costs reduction.

Expert Commentary: Dr.Guangfa Wang & Iris Boyeras

TITLE

EGFR mutation can predict the efficacy of PD-1/PD-L1 inhibitors in patients with pulmonary adenocarcinoma.

SOURCE CITATION

Cho JH, Jung HA, Lee SH et al. Impact of EGFR mutation on the clinical efficacy of PD-1 inhibitors in patients with pulmonary adenocarcinoma. J Cancer Res Clin Oncol. 2019 May;145(5):1341-1349. doi: 10.1007/s00432-019-02889-0. Epub 2019 Mar 21.

ABSTRACT

PURPOSE: To evaluate the predictive role of EGFR mutation on the efficacy of PD-1/PD-L1 inhibitor therapy in patients with advanced pulmonary adenocarcinoma while considering clinical factors such as PD-L1 expression, gender, and smoking status.

METHODS: Patients were required to have available data for EGFR mutation, PD-L1 expression, and efficacy of PD-1/PD-L1 inhibitors.

RESULTS: Among 178 patients with EGFR-mutant (n = 38) or wild-type (WT) (n = 140) tumors, the EGFR mutation group had a lower objective response rate (ORR) (15.8% vs. 32.9%, p = 0.04) than the EGFR WT group, similar to the pattern observed for other factors: weak/negative PD-L1 expression vs. strong PD-L1 expression (17.3% vs. 39.2%, p = 0.001); never smokers vs. smokers (19.4% vs. 35.1%, p = 0.03); and females vs. males (21.0% vs. 33.6%, p = 0.08). EGFR mutation and weak/negative PD-L1 expression were associated with a significantly shorter median PFS than EGFR WT (1.9 vs. 3.0 months, p = 0.04) and strong PD-L1 expression (1.6 vs. 3.9 months, p = 0.007), respectively. In multivariate analysis, EGFR mutation predicted worse ORR [hazard ratio (HR) 3.15; 95% confidence interval (CI) 1.15-8.63] and PFS (HR 1.75, 95% CI 1.11-2.75), as did weak/negative PD-L1 expression (ORR, HR 3.46, 95% CI 1.62-7.37; and PFS, HR 1.72, 95% CI 1.17-2.53).

CONCLUSIONS: Together with PD-L1 expression, EGFR mutation status is an important factor to predict the efficacy of PD-1/PD-L1 inhibitors in patients with pulmonary adenocarcinoma.

JOURNAL CLUB COMMENTS

This article with characteristics of retrospective and a single center meets the risk of selection bias. The authors used to find the determinants of the predictive role of EGFR

mutation on the efficacy of PD-1 / PD-L1 inhibitor therapy multivariate analysis. It is a statistical tool that tries to determine the unique contribution of several factors to a single event or outcome. The type of multivariable used is proportional hazard regression used frequently when the outcome is the length of time to reach a discrete event (such as time from the initiation of therapy with pembrolizumab or nivolumab to death).

Question: In patients with advanced pulmonary adenocarcinoma, which is the predictive role of EGFR mutation on the efficacy of PD-1/PD-L1 inhibitor therapy? Design: single center retrospective cohort study

Main results: EGFR mutation and weak or negative PDL1 expression were associated with worse prognosis in patients with advanced adenocarcinoma

COMMENTS by Dr. Guangfa Wang & Iris Boyeras

Non-Small Cell Lung Cancer (NSCLC) is a heterogeneous disease, both in its genotype and in its phenotype; this diversity its particularly noteworthy regarding the response patterns to treatment.

Currently, immunotherapy, with the use of inhibitors of the immune check point, has improved the management of metastatic disease, most markedly in cases with high expression of the programmed death ligand-1 (PD-L1). But only a part of the patients responds, and more effective predictive factors are lacking. In turn, the presence of EGFR mutations predicts better response to tyrosine kinase inhibitors (TKIs), but eventually the disease may progress after TKIs treatment, and here an opportunity for the use of immunotherapy could be opened.

Therefore, the scientific community continues to invest its efforts in the search for predictive characteristics of the clinical outcome of the different therapeutic tools available, which allow us to better choose which patients will benefit from what treatment.

Others biomarkers for response to immuno-oncologic agents beyond PD-L1 expression levels are presently being investigated, due to the intricacy of the immune system, and also because, although the response to the PD-1/PDL1 immune-checkpoint—inhibitor antibodies its superior in patients with NSCLC with increasing PD-L1 expression, benefits have been reported regardless of the PD-L1 expression level and vice versa.

We now know that the main genetic alterations influence the immunological profile of the NSCLC lesions. Studies of animal models of NSCLC report that EGFR mutant tumors show a strong myeloid recruitment, but defective CD8+T cells. Also, NSCLC oncogenic drivers as EGFR can set in motion the AKT-mTOR pathway to promote PD-L1 expression in cancer cells.⁶

Human studies report ALK-positive tumors showed a more common PD-L1 positivity rivalled to EGFR-mutated or Wild Type cancers. This information signpost that the oncogene profile can influence PD-L1 expression in some NSCLC scene.

Despite this data showing that there are associations between PD-L1 expression and EGFR signaling in NSCLC, is not well established whether this could affect response to immunotherapy, and information from clinical studies suggest that the subset of patient with EGFR mutant have poorer response to immunotherapy agents.⁸ To the present, the only prospective study design to address this question, a phase II trial to evaluate the response to Pembrolizumab, in patients with advanced NSCLC, *EGFR* mutant, PD-L1 positive (≥1%), and without previous TKI treatment; was stopped after results showed an objective response (ORR) of 0% to pembrolizumab, for the ten patients who met inclusion criteria.

Another interesting observation it's how other factors, such as smoking status, or gender affected response rates to PD-1/PD-L1 inhibitors, independently of EGFR status, highlighting the usefulness of the clinical aspect as a predictor of response.

WHAT THIS ARTICLE ADDS

This data support previously published evidence indicating the scarcity of benefit from PD-1/PD-L1 inhibitors in *EGFR* mutant NSCLC. Earlier information on this topic, came mostly from secondary analyzes of trials that were not designed in the first instance to address this question; and several possible confounding factors such as smoking status, gender, performance status, and number of previous chemotherapy treatments were not previously considered.

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Expert Commentary: Dr. David Lazo

TITLE

Therapeutic bronchoscopy improves health-related quality of life in patient with malignant central airway obstruction.

SOURCE CITATION

Ong P, Grosu HB, Debiane L, et al.Long-term quality-adjusted survival following therapeutic bronchoscopy for malignant central airway obstruction. Thorax. 2019 Feb;74(2):141-156. doi: 10.1136/thoraxjnl-2018-211521. Epub 2018 Sep 25. <u>PUBMED</u>

ABSTRACT

BACKGROUND: While therapeutic bronchoscopy has been used to treat malignant central (CAO) airway obstruction for >25 years, there are no studies quantifying the impact of therapeutic bronchoscopy on long-term quality-adjusted survival.

METHODS: A prospective observational study of consecutive patients undergoing therapeutic bronchoscopy for CAO. Patients had follow-up at 1 week and monthly thereafter until death. Outcomes included technical success (ie, relief of anatomic obstruction), dyspnoea, health-related quality of life (HRQOL) and quality-adjusted survival.

RESULTS: Therapeutic bronchoscopy was performed on 102 patients with malignant CAO. Partial or complete technical success was achieved in 90% of patients. At 7 days postbronchoscopy, dyspnoea improved (mean Δ Borg-day-7=-1.8, 95% CI -2.2 to -1.3, p<0.0001) and HRQOL improved (median prebronchoscopy 0.618 utiles, 25%-75% IQR 0.569 to 0.699, mean Δ utility-day-7+0.047 utiles, 95% CI +0.023 to 0.071, p=0.0002). Improvements in dyspnoea and HRQOL were maintained long-term. Compared with the prebronchoscopy baseline, HRQOL per day of life postbronchoscopy improved (mean Δ utility-long-term+0.036 utiles, 95% CI +0.014 to 0.057, p=0.002). Median quality-adjusted survival was 109 quality-adjusted life-days (QALDs) (95% CI 74 to 201 QALDs). Factors associated with longer quality-adjusted survival included better functional status, treatment-naïve tumour, endobronchial disease, less dyspnoea, shorter time from diagnosis to bronchoscopy, absence of cardiac disease, bronchoscopic dilation and receiving chemotherapy.

CONCLUSIONS: Therapeutic bronchoscopy improves HRQOL as compared with baseline, resulting in approximately a 5.8% improvement in HRQOL per day of life. The risk-benefit profile in these carefully selected patients was very favourable.

JOURNAL CLUB COMMENTS

When doctors treat patients, try to achieve one or more of three main objectives: prolong survival, reduce complications and contribute to the patients feel better. It is infrequent to measure a final point related to the third objective, not because it is not important but its measurement is comparatively more complex In these case HRQOL was measure with SF6D, it is a reliable and valid instrument, sensitive to changes. The magnitude of the effect has been important and will definitely help the care of patients. The main attributable weakness to SF6D is the evidence for floor effects that in these case is the inability to classification system seems to adequately describe relatively serious health condition.

The authors looked for variables associated with better survival, using multivariable analysis. In deciding which variables include in a model, they distinguish between explanatory models and predictive models. Regards to the first one (explanatory) the goal is to correctly characterize the relationship of each predictor to the outcome variable. That is the reason why each category is critical. In the opposite predictive models aim to calculate a probability that an event occurs, the accuracy of the inputs is more important than the details of its inputs

Question: Does therapeutic bronchoscopy for malignant CAO improves long-term quality-adjusted survival? In patients with CAO which are the factors associated with better quality-adjusted survival?

Design Single: center prospective observational study

Folow up period: Patients had systematic follow-up at 1 week, 1 month and monthly thereafter and were followed until death.

Patients 102: adults \geq 18 years of age , undergoing therapeutic flexible or rigid bronchoscopy for malignant CAO were included between 1 september 2011 to 17 june 2014.

Main results: Dyspnea was measured using the Borg score, HRQOL was measured using the SF-6D.

Outcomes: Primary outcome was HRQOL measured [SF6D]. Secondary outcomes included factors associated with better quality of life. 99 patients provided 90% power to detect a 0.033 utilities with alpha 0.05.

Main results: Compared with the prebronchoscopy baseline, HRQOL per day of life post bronchoscopy improved (mean .utility-long-term+0.036 utiles (5.8%), 95% CI +0.014 to 0.057, p=0.002)In multivariate predictive or explanatory analysis, higher baseline Borg score, not having COPD and having no prior therapeutic bronchoscopies were associated with higher .utility-day-7 In a multivariate predictive analysis, only having fewer lung segments occluded (p=0.05) was associated with having a clinically significant improvement in dyspnea In an explanatory multivariate analysis, older age (p=0.03),

greater improvements in dyspnea (p=0.01) and not having COPD (p=0.03) were associated with having a clinically significant improvement in dyspnea.

COMMENTS by Dr. David Lazo

This is a single center great effort to try to help us, all the bronchoscopists who treat the malignant CAO, to justify our interventions (most of the time more than one) in a setting of palliative care. The AQuIRE Bronchoscopy group 2015 study, started to show us about the utility of the actions that permits the reopening of the airways compromised by tumors, not only by the technical results, but also for the relief of dyspnea and the improvement in quality of life. The main problem was the short term of its outcomes, 30 days, and was clearly suggested by the authors in they discussions. What happened after the first week, 30 days, and monthly until the death of the intervened patients, was evaluated by MD Anderson's interventional bronchoscopists in this prospective observational study. It is very important to mention that the authors were part of the leaders of the AQuRE initiative, and they took the witness to answer this question adding the not less important factor of cost-effectiveness.

After this paper, they make us clear that our rigid corings, lasers, cryocannalizations, stents, and all our efforts to reopen the airway, seems to really have an important and long-term benefit in patients with the following factors: better functional status, treatment naïve tumour, endobronchial disease, less dyspnea, shorter time from diagnosis to bronchoscopy, absence of cardiac disease, bronchoscopic dilation and receiving chemotherapy. Benefits not only in survival, but also in dyspnea and HRQOL. I hope that this remarkable effort will continue in a multicentric manner and including decision analysis techniques as they suggest.

WHAT THIS ARTICLE ADDS

The confidence for the interventional bronchoscopist community, that we are in the right way, treating advanced cancer patients. This paper not only confirm the previous published results in long-term, but also quantifies the quality of life and identifies factors that alter them.

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Expert Commentary: Dr. Patricia Vujacich

TITLE

Change in definitions of central tumor can be useful to predict occult N2 disease in patients with NSCLC.

SOURCE CITATION

Shin SH, Jeong DY, Lee KS, et al. Which definition of a central tumor is more predictive of occult mediastinal metastasis in non-small cell lung cancer patients with radiological NO disease? Eur Respir J. 2019 Mar 18;53(3). pii: 1801508. doi: 10.1183/13993003.01508-2018. <u>PUBMED</u>

ABSTRACT

BACKGROUND: Guidelines recommend invasive mediastinal staging for centrally located tumors, even in radiological N0 non small cell lung cancer (NSCLC). However, there is no uniform definition of a central tumor that is more predictive of occult mediastinal metastasis.

METHODS: A total of 1337 consecutive patients with radiological N0 disease underwent invasive mediastinal staging. Tumors were categorized into central and peripheral by seven different definitions.

RESULTS: About 7% (93 out of 1337) of patients had occult N2 disease, and they had significantly larger tumor size and more solid tumors on computed tomography. After adjustment for patient- and tumor-related characteristics, only the central tumor definition of the inner one-third of the hemithorax adopted by drawing concentric lines arising from the midline significantly predicted occult N2 disease (adjusted OR 2.13, 95% CI 1.17-3.87; p=0.013). This association was maintained after excluding patients with pure ground-glass nodules (adjusted OR 2.54, 95% CI 1.37-4.71; p=0.003) or only including those with solid tumors (adjusted OR 2.30, 95% CI 1.08-4.88; p=0.030).

CONCLUSIONS: We suggest that a central tumor should be defined using the inner onethird of the hemithorax adopted by drawing concentric lines from the midline. This is particularly useful for predicting occult N2 disease in patients with NSCLC.

JOURNAL CLUB COMMENTS

As the authors clarified, it is a retrospective study conducted in a single center. Because of these characteristics, the risk of selection bias is one of the most important issues, also the external validity of the studies in a single center are always data to consider.

Question: Which definition of a central tumour is more predictive of occult mediastinal metastasis in nonsmall cell lung cancer patients with radiological NO disease?

Design: restrospective cohort study

Main results: The main result is the decrease of false negatives when staging the mediastinum by an adequate definition of central tumor

COMMENTS by Dr. Patricia Vujacich

The N2 occult disease has been always a matter of concern. Should we stadify the CT or PET-CT normal mediastinum, either by EBUS-TBNA or mediastinoscopy, to avoid final N2 pathological upstaging?

According to the NCCN Guidelines central tumors are one of the main conditions associated with N2 occult disease. The original approach of Shin SH et al. stresses the value of the best "centric" definition providing data from mediastinal lymph nodes (LN) dissection and EBUS-TBNA. It has been confusing to use different definitions particularly on tumors located on apical regions and para-diaphragmatic tumors as the authors pointed out.

Mediastinal mapping may become a standard of care in preoperative staging of NSCLC. EBUS-TBNA is undoubtedly the best method avoiding unnecessary mediastinoscopy. However, in this study, EBUS-TBNA was positive in only 10 of 159 patients (6.2%). Many years ago, Herth et al had found up to 13% of positive LN in the radiologically normal mediastinum, however no data is available on tumor size or peripheral/central location. In a recent meta-analysis of 13 studies on preoperative EBUS in cN0-N1 lung cancer, the mean prevalence of N2/N3 disease was 15% (6% to 24%) with EBUS-TBNA pooled sensitivity of 49% and a mean negative predictive value of 91%.

Rapid on-site examination (ROSE) was not available in the present cohort; this may be a reason for lower results although not statistically proven. The retrospective design could have influenced it too. Despite this, prevalence of N2 occult disease was 7% in this study (combining results from EBUS-TBNA and LN mediastinal dissection), which is still less than reported.

WHAT THIS ARTICLE ADDS

The originality of this article relies on comparing different definitions of central tumors to predict occult N2 disease: only concentric lines arising from midline regardless of tumor size or attenuation were significantly associated to N2 occult metastasis, with the mediastinal LN dissection as a gold standard.

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