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Review

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Single anesthetic event for lung cancer diagnosis and treatment: hype or hope for the future?

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Abstract

The concept of a single anesthetic event (SAE) for lung cancer diagnosis and treatment has recently developed with the aim to streamline care and reduce delays in treatment. SAE integrates advanced diagnostic bronchoscopy, histopathologic diagnosis, and immediate surgical resection in one single anesthetic procedure. This review explores the historical surgical treatment of lung cancer, development of SAE, and the theoretical framework and practical implementation of SAE. While offering potential advantages such as shorter treatment times and reduced hospital stays, SAE encounters logistical difficulties and limitations in use. Despite these challenges, SAE demonstrates feasibility and suggests a pathway towards improved cancer management.

Keywords: Single anesthetic event, lung cancer, robotic bronchoscopy, robotic lung resection

INTRODUCTION

Lung cancer is the third most common cancer and the number one cause of cancer-related death in the United States[1]. Despite advances in screening and treatment, lung cancer has continued to remain the leading cause of cancer-related death since the 1980s[2]. Given the high burden of mortality, there is a persistent need to develop innovations in lung cancer diagnosis and treatment[3,4].

Often a smoldering disease process, lung cancer is commonly diagnosed in its late stages. Most patients with non-small cell lung cancer (NSCLC) have progressed to Stage IV at diagnosis and present with nonspecific symptoms[5]. Due to the high mortality of late-stage lung cancer, screening computed tomography (CT) protocols have been adopted to help with earlier diagnosis[6,7]. Suspicious nodules on CT can be further be investigated with confirmatory diagnostics including advanced imaging such as Fludeoxyglucose-18 positron emission tomography (FDG-PET) and/or direct tissue sampling. The decision to pursue further testing is generally made with a multidisciplinary team which includes thoracic surgeons, radiologists, pulmonologists and oncologists.

Given the pathway outlined above, it is not surprising that there is a significant time lapse between the detection of lung cancer and treatment. To combat delay in treatment, national guidelines have recommended treatment start anywhere between one to three months[8]. Currently, average times from diagnosis to surgical treatment have been reported from 46-56 days [Figure 1][9-11]. Increasing access to timely care has been shown to decrease mortality associated with lung cancer[12].

The use of a single anesthetic event (SAE) for the diagnosis and treatment of lung cancer has recently gained much popularity. With this approach, a patient can undergo both definitive histopathologic diagnosis of lung cancer and anatomic resection in one visit, with the goal of minimizing delays in lung cancer care. In this review, we discuss the SAE for diagnosis and treatment of lung cancer and its theoretical *vs.* practical implementation.

TRADITIONAL PATHWAY TO LUNG CANCER DIAGNOSIS AND TREATMENT

When a lung nodule is deemed suspicious, there are broadly two pathways to tissue diagnosis. The first is to acquire a diagnosis of lung cancer through a minimally invasive biopsy prior to surgical resection. This includes options for percutaneous and endoscopic biopsy of a nodule. The other option is to obtain an intraoperative tissue diagnosis immediately before performing oncologic resection. Here, a surgeon will perform a wedge or excisional biopsy of a nodule with a frozen section diagnosis, with subsequent appropriate definitive resection. Overall, there is much variation in guideline recommendations. For example, the National Comprehensive Cancer Network (NCCN) recommends that patients with strong clinical suspicion of stage I or II lung cancer do not require a biopsy before surgery. Alternatively, the European Society for Medical Oncology (ESMO) does recommend pathological diagnosis prior to any curative treatment[13,14].

Despite pathway and guideline differences in preoperative pathologic confirmation of lung cancer, most patients undergo tissue diagnosis prior to surgery. In a large 10,226-patient cohort study of the Netherlands National Cancer Registry, 64% of lung cancer resections had histologic confirmation before their definitive resection[14]. The pathway of tissue biopsy first has many advantages including avoiding unnecessary procedures. Up to 20% of suspicious nodules are found to be benign at surgery[15]. Moreover, earlier diagnosis allows more time for surgical planning specific to the patient and their pathology before the operating room. Conversely, the operative frozen and subsequent resection of the lung cancer pathway allows patients to undergo just one procedure. This then reduces the risk involved with additional procedures and diagnostic costs and time. The recent development of obtaining tissue diagnosis and performing curative resection in a SAE is an approach that brings together some of the benefits of the earlier pathways.

ADVANCES IN ENDOSCOPIC DIAGNOSIS OF LUNG CANCER

To understand SAE, we must review advances in endoscopy and lung cancer diagnosis. While percutaneous

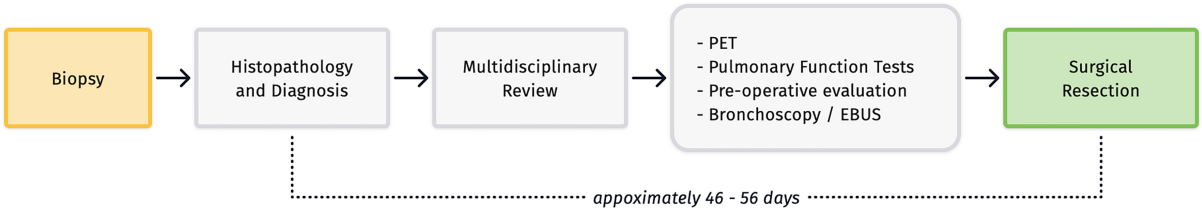

Figure 1. General pathway from lung cancer diagnosis to surgical treatment. PET: Positron emission tomography scan; EBUS: endobronchial ultrasound.

methods remain an option for lung nodule sampling, advances in endoscopic techniques have expanded diagnostic capabilities, particularly for patients with challenging lesion locations. Flexible bronchoscopy paired with electromagnetic navigation bronchoscopy (ENB) and endobronchial ultrasound (EBUS) are just a few techniques that have broadened the diagnostics of lung cancer[16].

Introduced in the 1990s, EBUS allowed for enhanced visualization of mediastinal structures, lymph nodes, tumors, and vasculature far above the capability of traditional bronchoscopy[17]. However, EBUS did not allow for sampling until the 2000s. The advent of transbronchial needle aspiration to EBUS enabled real-time diagnosis and staging of lung cancer, making it particularly useful for patients with mediastinal or hilar lymphadenopathy[18]. ENB is another technology that has enhanced traditional bronchoscopy. Here, a CT scan is linked to real-time electromagnetic field generators to create a virtual environment to assist in sampling of peripheral lung lesions. A recent meta-analysis of over 40 studies found ENB to be a safe and effective method for diagnosing malignancy with a pooled sensitivity of 77% and specificity of 100%[19].

The most recent addition to bronchoscopy has been robotic technology. In 2018, the Food and Drug Administration (FDA) approved the first robotic-assisted bronchoscopy platform and since then, many centers have adopted its use for staging of lung cancer[20]. The PRECISION-1 study found that in cadaver models, robotic-assisted bronchoscopy significantly increased the localization and sampling yield compared to other endoscopic biopsy techniques[21]. The multicenter prospective BENEFIT trial confirmed the utility of robotic-assisted bronchoscopy with a 96.2% rate of lesion localization and 74.1% diagnostic yield of peripheral pulmonary lesions[22]. Subsequent studies have continued to validate robotic-assisted bronchoscopy as a safe and effective modality for diagnosis[23-25]. Due to the increased diagnostic yield, an opportunity for rapid and accurate analysis of difficult-to-sample lung lesions has risen and with it, an additional opportunity for same-day lung cancer resection. Robotic-assisted bronchoscopy systems are now widely available and used throughout the United States.

RISE OF ROBOTIC THORACIC SURGERY

Robotic surgical techniques for lung cancer resection have also gained popularity with the rise of minimally invasive techniques for biopsy. Before the 2000s, lung cancer was primarily resected through an open approach but video-assisted thoracoscopic surgery (VATS) and robotic surgery have now become more common than their open counterpart. Just from 2009 to 2013, the US Agency for Healthcare Research and Quality found rates of robotic lobectomies increased from 1% to 11%[26]. A review of 6,216 lobectomies in the United States from 21 institutions performing lobectomies for stage IA-IIIA lung cancer found 41% of cases were performed robotically *vs.* 37% VATS and 21% open[27]. Given the rise in minimally invasive techniques, the addition of robotic surgery in combination with robotic-assisted/navigational bronchoscopy is seemingly a natural progression in the advancement of cancer care.

SAE FOR DIAGNOSIS AND TREATMENT

SAE for diagnosis and treatment of lung cancer is an appealing concept that has gained popularity as the diagnostic yield and accuracy of robotic-assisted bronchoscopy has been validated. This technique allows for the appropriate staging, diagnosis, and treatment of a patient with a malignant-appearing lung nodule, all within a single procedure and under one administration of anesthesia. First, a patient is seen by a multidisciplinary team. Preoperative testing will typically include a PET scan, a preoperative evaluation and pulmonary function tests. Currently, there are no major guidelines for selection for SAE. In published literature, Patel *et al.* reported selecting for patients with clinical Stage I to II NSCLC, and Wolf *et al.* reported only selecting for Stage I NSCLC determined by PET[28,29]. Patients were also selected based on pulmonary function tests and acceptable risk for general anesthesia. The patient then arrives on the day of their procedure and undergoes robotic-assisted/navigational bronchoscopy with a biopsy of their lung lesion [Figure 2]. Biopsies are read by pathologists and if malignant the patient can undergo appropriate oncologic mediastinal staging. If both the nodule is malignant and there is no nodal stage II (N2) disease, the patient can then undergo immediate surgical resection. Sometimes, a nodule or ground glass opacity that is not amenable to navigational bronchoscopic biopsy can be dye-marked to assist with resection for diagnosis and/or treatment.

Currently, there are few published experiences with single anesthetic robotic bronchoscopy and lung resection. In 2021, a small series of ten patients underwent a feasibility study of robotic bronchoscopy and subsequent same anesthetic resection without any noted compilation[30]. A follow-up series by Ross *et al.* of 52 patients undergoing this accelerated pathway found similarly, no major complications or mortality[31]. Wolf *et al.* compared their experience with 22 patients undergoing a single anesthetic pathway *vs.* historical controls in patients with stage I non-small cell carcinoma and found robotic-assisted bronchoscopy with subsequent robotic-assisted lobectomy had a shorter rate from identification of pulmonary nodule to surgical intervention (65 days *vs.* 116 days), lower rates of complications (0% *vs.* 5%) and shorter hospitalizations (3.6 days *vs.* 6.2 days)[29]. Brownlee *et al.* additionally published a retrospective analysis of 41 cases of robotic bronchoscopy to robotic resection and found no mortality and only three complications of prolonged air leaks (> 5 days). Interestingly, there was a 16% benign resection rate which was proposed to be attributable to the initial propensity of the authors to confirm benign pathology with a surgical resection[32].

ADVANTAGES OF SAE

The main advantage of the SAE bronchoscopy to surgical resection pathway is that it decreases the time from diagnosis to definitive treatment for patients with lung cancer. A study of 2,861 patients with stage I/II lung cancer found time to resection from imaging or histologic diagnosis of greater than four weeks was associated with a greater risk of death (HR 1.18) and cancer recurrence (HR 1.33)[11]. Similarly, a retrospective cohort study of 9904 patients with clinic stage I NSCLC noted that surgical resection delayed for more than 12 weeks from the date of radiographic diagnosis was associated with increased risk of recurrence (HR 0.4% per year) and worse mortality (HR 1.132)[33]. SAE has been shown to decrease time from biopsy to intervention by an average of 36 days[29]. As such, SAE has potential to reduce rates of recurrence and mortality by streamlining cancer care and decreasing time to definitive resection.

Another benefit to SAE is its cost efficiency. In this model, a health system can reduce the length of hospital stay as SAE cuts down the need for additional procedural days and anesthetic events. In their case-control series, Wolf *et al.* did find SAE was associated with shorter hospitalizations compared to resection alone (3.6 days *vs.* 6.2 days)[29]. There is some evidence to suggest that single anesthetic surgical biopsy to resection is more cost-effective than its percutaneous needle biopsy to resection counterpart. Na *et al.* found that lung cancer operations following surgical biopsy were associated with less cost (USD 12,669 *vs.* USD 14,403) than

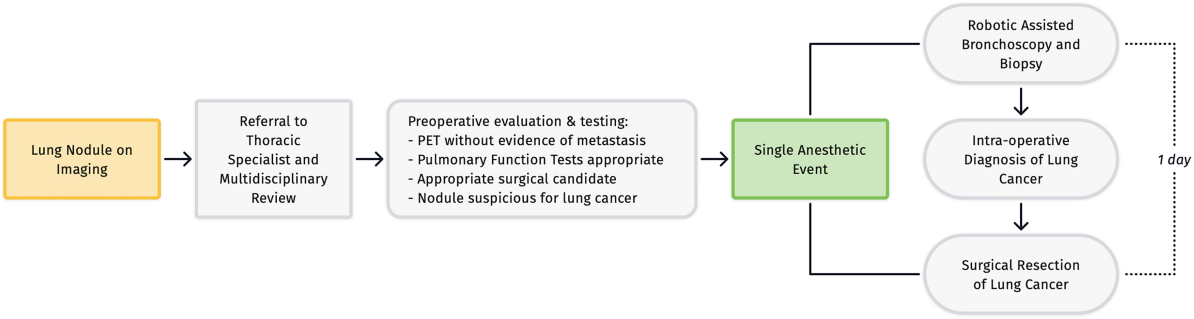

Figure 2. Pathway to single anesthetic event for treatment of lung cancer. PET: Positron emission tomography scan.

percutaneous needle biopsy first[34]. This could potentially imply that SAE resections would have similar cost-effectiveness by reducing hospital stays.

Additionally, SAE has the theoretical advantage of lowering patient anxiety and exacerbation of depression by providing a "direct to treatment" pathway. As many as 34% of lung cancer patients are reported to have anxiety and up to 58% have depression[35]. Anxiety and depression have also been shown to be associated with poor cancer-related outcomes. In a screening of 684 patients with stage III lung cancer, anxiety was an independent risk factor for lung cancer-specific (HR 1.04) and all-cause mortality (HR 1.04)[36]. Likewise, a prospective study of patients with stage IIIB-IV NSCLC found depression to also be an independent risk factor for decreased survival (median survival 6.8 months *vs.* 14 months)[37]. In general, delays in cancer treatment have been associated with increased patient-reported anxiety and exacerbation of mental health issues[38]. By reducing time significantly from diagnosis to treatment, SAE provides an opportunity to reduce anxiety and exacerbation of mental health and improve overall mortality.

LIMITATIONS OF SAE

Despite several advantages to SAE, its practical implementation remains in question. One significant limiting factor is the availability and coordination of providers and operating rooms. In the single anesthetic model, a surgeon is available if a nodule returns as malignant or non-diagnostic but is not needed with a non-malignant nodule. While this has individual benefits for the on-table patient, the need for a surgeon on standby may negatively affect operating room availability from other patients who have confirmed lung malignancy. This could also affect the declared cost benefit that the approach offers. Additionally, pulmonologists must be available simultaneously to perform advanced robotic bronchoscopy. The ability to coordinate multiple providers and operative space may be logistically prohibitive to most centers providing lung cancer treatment.

Another limitation of SAE is the potential poor resource utilization in the event of changing diagnosis or re-staging. Staging of a patient depends on pathology, metastasis and so forth. Patients with metastatic nonprimary lung cancer will receive a different workup than those with primary lung cancer. In the SAE pathway, patients are selected with suspicion of primary resectable lung cancer without metastasis to be efficient. Patients then must undergo comprehensive imaging [such as PET and brain magnetic resonance imaging (MRI)] and a full diagnostic workup before biopsy to ensure complete staging. Current reported SAE pathways do not include brain MRI but do include PET. In a biopsy first model, if pathology is benign then additional workup is often not indicated and resources such as PET and bronchoscopy/EBUS are spared. Additionally, SAE may result in upstaging as EBUS may find metastasis over a preoperative PET and is standard despite a negative PET in certain guidelines[39]. However, none of the three limited series on

SAE reported upstaging. Only one series reported specifics on preoperative workup of patients which limited their selected cases to solitary pulmonary nodules with no evidence of metastasis on PET[29]. In the largest study cohort of 52 patients undergoing SAE, seven (13%) patients were found to have non-lung cancer primary metastasis[31]. These patients potentially could have benefited from neoadjuvant treatments for their metastasis without morbidity associated with pulmonary resection. In general, SAE also does not allow for time between biopsy and resection for neoadjuvant therapies if warranted - of course, the resection could be deferred with evidence of primary metastasis. Of the available literature, only one study reported one (2%) case of metastatic lung adenocarcinoma out of 41 cases of SAE[32]. Despite highly selective criteria for SAE, changing diagnosis and stage of malignancy can limit its effective use and may lead to risk of inferior oncologic treatment.

An additional provider-based barrier is the capacity of onsite pathologists to confirm malignancy on initial biopsy. Traditionally, biopsy from bronchoscopy has a processing time of multiple days which includes time for preparation and immunologic staining needed for diagnosis. SAE relies on quick and definitive pathologic diagnosis. Reviews have shown that agreement between pathologists between subtypes for NSCLC may range from 67%-89%[40]. Additionally, even with advances in sampling technique and performance, non-diagnostic biopsies for robotic and endoscopic bronchoscopies range widely from 14%-40% with diagnostic yield ranging from 67%-84%[41-45]. Ultimately, SAE's success is limited by variability in provider diagnosis, wide range of non-diagnostic biopsies, and need for real-time diagnosis by onsite pathology.

SAE is also limited by operating room and hospital resources. To perform the proposed single anesthetic procedure, there is a minimum need of multiple machines including a robotic-assisted bronchoscopy platform, fluoroscopy capability, and EBUS. Should the surgeon's standard be robotic lobectomy rather than VATS then there is a need for further equipment including a robotic platform and console. The proposed pathway must have staff employed who are familiar with each system and the resources for each system. Operating rooms may also not have logistical capability to hold many technical pieces in one room. It is overall unclear how many centers have the resources needed to offer both robotic bronchoscopy and robotic resection.

Lastly, evidence for SAE is limited to few literature reports and small cohort studies in the United States. The largest cohort study to date is an abstract that lacks details on patient demographics and comorbidities[31]. While their reported 80% malignancy resection rate is promising, the findings cannot be generalized without further information on patient characteristics and study methodology. Similarly, Wolf *et al.* do not provide a comprehensive overview of patient comorbidities, although they do report metrics such as body mass index (BMI), tobacco use (pack-years), and underlying lung disease[29]. Another limitation of small studies is potential for selection bias. Currently, identification of patients who undergo SAE is made by a multidisciplinary team with undefined criteria. Brownlee *et al.* selected 41 patients for SAE, but the mean FEV1 among these patients was 101.8%, substantially higher than the normal value of 80%, suggesting a bias toward healthier individuals[32]. Furthermore, these studies were only performed in the United States. A comparison of the Society of Thoracic Surgeons (STS) database and the European Society of Thoracic Surgeons (ESTS) registry found that the rate of N2 disease at the time of lobectomy was 8% in the United States *vs.* 14% in Europe, suggesting underlying differences in preoperative management including the increased use of EBUS in the United States to detect N2 disease prior to surgery. The difference in geographic preoperative management and patients may limit the adoption of SAE[46]. Given these limitations, the findings of these studies should be interpreted cautiously when applied to the general population. Additional research is needed to assess the generalizability of SAE.

CURRENT UTILIZATION AND FUTURE DIRECTIONS

Currently, there is a limited amount of literature describing SAE and its outcomes. The number of centers adopting SAE is unclear in the United States and internationally. However, private and university hospitals have advertised adoption of SAE across the United States from Hawaii to New York[47-50]. Despite the seemingly increasing adoption, there are also no current guidelines for the implementation or use of SAE. The literature available has limited the utility of this approach to patients with clinical stage I-II lung cancer.

SAE is a viable pathway for the treatment of early-stage lung cancer despite its limitations. With its early adoption, patients selected should have a high suspicion of primary lung malignancy without evidence of metastasis to lower cases of benign diagnosis, failure to proceed with surgical resection, and incomplete staging. Additionally, patients selected should have a low American Society of Anesthesiologists (ASA) physical status class so as to undergo prolonged periods of anesthesia. It is also important to complete the workup and staging prior to SAE such as PET or brain MRI if the suspicion is high for advanced disease.

Looking ahead, SAE can potentially enhance lung cancer diagnosis and treatment at centers with adequate capacity and resources. Success will require collaboration and commitment from multidisciplinary teams along the whole pathway to lung cancer care. Primary care physicians must be aware of SAE and hospital administration must be convinced of its efficacy. Thoracic surgeons and pulmonologists must work together with their pathologists to provide accurate biopsy, diagnosis, and subsequent treatment. We will have to carefully weigh this technical advancement against the current exponential growth of neoadjuvant treatments for lung cancer to evaluate its true value. Programs with successful SAE must share their experiences for implementation and pitfalls along the way. Ultimately, SAE is likely to become common in high-resource areas such as the United States; however, its access to other developing countries remains in question.

CONCLUSION

SAE for lung cancer care is a new, promising pathway in its early stages of development. Though there are many theoretical benefits, its practicality may limit its utilization. It will be important for centers advancing lung cancer care to share protocols and long-term outcomes for successful implementation.

DECLARATIONS

Authors' contributions

Data collection, review analysis, and manuscript writing: Nguyen SH
Study concept, design, and manuscript review: Rao M

Availability of data materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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