Editorial Commentary

Oncologic validity of minimally invasive lobectomy for early stage lung cancer

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Introduction

Minimally invasive pulmonary lobectomy was first performed decades ago and was adopted quite slowly compared to other common major laparoscopic or thoracoscopic procedures. The reasons behind slow adoption were complex, multifactorial and beyond the scope of this article, but concerns about oncologic validity have been cited as concerns by traditional open surgeons. A recent article by Yang and colleagues adds to a growing body of works serving to dispel these concerns (1). In this commentary, we will discuss this paper as well as supplement our previously published arguments regarding the oncologic validity of minimally invasive lobectomy (MIL) with more recent research (2).

Randomized comparisons are desirable but extremely hard to attract volunteers to agree to be allotted to more invasive procedures. It took a very high-volume consortium in China to achieve recruitment (compared to axillary thoracotomy) and long-term results are pending (3). Long term survival data are pending but the short-term results replicate the preponderance of evidence showing fewer complications and faster recovery (3). A number of meta-analyses including a recent systematic review on the optimal approach to thoracoscopic lobectomy demonstrate equivalent or favorable outcomes with MIL (4). In the past several years, there has been more written about longer term outcomes with MIL. *Table 1* summarizes other work since our last review on long-term survival (2).

Pros and cons of large database reviews

The article by Yang and colleagues uses results from the National Cancer Database (NCDB) to help us understand long-term survival (1). These resources are powerful because of the large sample sizes that allow detection of small effects and ability to match many cases to control for bias. In addition, as these databases collate data not just from quaternary care centers, but from other treating hospitals on the frontline of healthcare delivery, it is useful to understand the impact of new surgical approaches as they are adopted more broadly. However, there are many limitations as well because selection bias was inherent with the introduction of MIL initially accepted only for small peripheral tumors (13). Central tumors in lymph node rich basins requiring complex resection techniques were approached more by open surgery but a variable easily defining centrality does not exist in most current data sets. One European center was able to control for this centrality bias in its prospective database (14). In addition, important dependent variables are not captured by databases such as the NCDB. Also, in the discussion of long-term oncologic outcome, the relevant outcome is recurrence free survival or disease-specific survival, both of which are absent in the NCDB. Hospital selection bias is likely and when every hospital is captured in a state such as the New York Statewide Planning and Research Cooperative System covariates that trend with MIL become more evident like female sex, lower comorbidity index, insurance, older age,

Table 1 Select recent comparative trials of lung cancer minimally invasive lobectomy with long-term outcomes grouped by methodology

Author, year	Design, N[a]	Primary endpoint[b]	Comment
Early stage, randomized, ongoing			
Long, 2018 (3)	Multicenter early stage VATS *vs.* axillary thoracotomy, N=215	Accrual completed. Survival data pending	VATS times shorter with less blood loss (each P<0.01). Similar morbidity, mortality positive margin rates and nodes retrieved
Early stage high volume single center retrospective			
Allakhverdiev, 2018 (5)	T1N0, compared to 189 thoracotomy patients, N=317	94% *vs.* 78%, P=0.045	Blokhin Cancer Research Center, Moscow. 0% *vs.* 2.6% operative mortality
Dziedzic, 2018 (6)	Propensity-matched, N=225	78% *vs.* 61%, P=0.008	Medical University of Gdansk, Gdansk, Poland. Also fewer complications for MIL
Lutz, 2019 (7)	Stage-specific historical comparison, N=621	75% 5-year survival for stage I	Institut Mutualiste Montsouris, Paris, France. Only port access approach
Early stage meta-analyses			
Ng, 2019 (4)	138 non-randomized and 7 randomized, N=16,200	72 *vs.* 67%, P<0.001	Included robotic, uniportal, multiport MIL. Similar outcomes between minimal approaches except possibly less pain for uniportal
Early stage large administrative and quality database studies			
Onaitis, 2018 (8)	STS database linked to Medicare Database, Cox risk adjusted, N=14,182	57% *vs.* 50%, HR =0.86, P<0.001	Patients over 65 yrs of age. VATS in 47% of resections
Boffa, 2018 (9); Ezer, 2018 (10)	STS Database linked to Medicare Database, Cox risk adjusted, N=6,149	69% *vs.* 65%, P=0.003	Patients over 65 yrs of age. Fewer cardiovascular complications, infections and operative mortalities for VATS after controlling for patient and tumor characteristics
Advanced stage high volume single center retrospective			
Fang, 2018 (11)	Concurrent cohort with open, N=14	80 *vs.* 80% overall 3-year survival	Hangzhou, China. Stage 3A&B cases except for one T3 stage 2B case
Veronesi, 2018 (12)	Stage-specific historical comparison, N=210	61% 3-year survival	7 high volume robotic centers operating on patient with occult or known N2 disease
Yang, 2019 (1)	National Cancer Database [2010–2012], propensity matched, N=334	49% *vs.* 49% overall 5-year survival	Stage 2 cases. Outcomes also similar in larger non-matched groups but open cases done more frequently (3:1)

[a], N= total accrual for randomized studies or number of VATS cases for other comparative designs. [b], VATS compared to open, 5-year survival, and not different statistically unless noted. HR, hazard ratio; MIL, minimally invasive lobectomy; VATS, video-assisted thoracic surgery.

surgery in recent year, nonteaching hospital, and higher annual lung surgery volume (15).

Technician versus the technology

An important point not been emphasized much in the debate about MIL is that significant upgrades in optics and instruments have been made during the time these databases aggregated patients and continue to evolve (16,17). Early on, many excellent surgeons were frustrated with the ability to see the anatomy and manipulate it compared with open approaches. A mechanism of inferior technology impairing surgeon intentions and thereby outcomes was very plausible. Now that high definition cameras and better articulated tools including robotic platforms are very accessible, surgeons can replicate and sometimes exceed what they were trained (or inclined) to do before MIL. This is exemplified by research showing that oncologic concerns of upstaging and quality of lymphatic dissection are associated more with the experience of the program than the technology or the approach, *per se* (18). Current technological trends such as enhanced optics (including augmented reality, near infrared imaging, and very high pixel density) and new robotic or robotic emulating hand-held instruments will approach or even surpass open technical capabilities (19).

Other issues limit surgeon interest in approach effect on early stage disease. For one, our surgical investigator predecessors tended to be interested more in effects resulting from operative anatomic changes than the exposure used to achieve them. Visual inspection that a new technology or exposure approach achieved a result comparable to previous methods was enough to justify a modest non-randomized series and consider substitution or adoption if there were no medium or long-term variations from expected classic outcomes. If an update to imaging software or therapeutic radiation medicine equipment generates ostensible improvement to anatomic clarity or ablative precision, subjecting large numbers of patients to comparisons with inferior technology beyond limited safety trials becomes ethically problematic. Similarly, expensive phase III drug research generally is warranted only by non-randomized phase 2 signaling a therapeutic benefit.

Special populations are particularly well suited to less invasive approaches. Frail patients such as the elderly gain better access to aggressive surgical procedures if thoracotomy can be avoided and represented the vanguard at some centers (20). Arguably, comorbid medical problems might obscure higher local recurrence rates; however, research indicates that avoidance of non-oncologic mortality from various complications is one of the strongest arguments for MIL even for aggressive diseases like lung cancer (21).

Surgeons are not the only professionals tasked with introducing new technologies designed to improve safety and results. Architects and engineers do this by using stress testing and computer models on new materials. Likewise, some thoracic surgeons are "stress testing" our minimally invasive approaches on patients with higher stage lung cancer. We have not seen reports of accelerated local recurrences that would be expected intuitively if MIL was fundamentally an inferior oncologic operation. *Table 1* adds to the advanced resection studies listed in our previous review that compare similarly or favorably to open studies. The lack of a "failure" signal for patients with aggressive extensive stage tumors reduces enthusiasm for pursuing research for recurrence in stage 1 populations.

Research priorities

Because of plausible hypotheses that impaired exposures would adversely affect oncologic outcomes and extra resources needed to establish MIL at busy high-performing open surgery centers, it was reasonable to study surgical approach. Before MIL, innovations in open oncologic surgical approaches typically gained acceptance with similar or less controversy. The adequacy of anatomic dissection (like nodal sampling versus radical lymphadenectomy) or sublobar resection remain questions of interest. Now that we have results of Yang and so many other trials without negative signals, it seems time to move past the simple question of approach as the research focus. It can be revisited if concerns with long-term oncologic outcomes emerge unexpectantly in different research efforts or in the study of special populations where approach is more likely to generate a measurable effect (like advanced stage patients). Once such a signal is detected, then it will be necessary not only to design a study to analyze an outcome problem but also test a hypothesis that will explain the adverse outcomes. Minimally invasive operations may have longer operative times and perhaps tumor manipulations that could be suboptimal with small instruments. Apart from these, it is difficult to conceive of mechanisms by which more traumatic incisions and the bleeding and pain associated with them will benefit patients.

Without easier accessibility to randomized research, our databases need to evolve to answer scientific questions

of future relevance. For this to happen, there needs to be much more flexible, dynamic, granular data and formatting that allows for testing hypotheses not predicted by the traditional database organizing committees. This will require a great expansion of optional data fields with participating programs empowered to enter structured data if they have the resources to do so. Surgical specialty societies might promote a uniform description rubric for operative reports to allow for attachment of deidentified text files that could be searched by artificial intelligence engines. Then, for example, important questions requiring large sample sizes like whether general anesthetic duration or order of vascular division during lobectomy affects survivals could be then tested with big databases.

It is reasonable to expect that data integration that is currently underway to deal with the problem of duplicate storage and lack of uniform accessibility to radiology images could be leveraged to make patient participation in an outcomes database more dynamic. That is, centralized administrative databases like NCDB could have metadata links back to healthcare records and even images that allow accessing data points that become meaningful over time. As mentioned, one of the major limitations of the Yang article and any large database study is that there is natural selection bias against central tumors because the associated difficulty with dissection made this a relative contraindication for MIL. Unfortunately, centrality is difficult to define just as it often challenging to determine preoperatively whether anatomic structures are invaded or simply effaced. The ability to link imaging back to the record would be useful to quantify centrality for propensity matching, for database quality control, and ultimately allow merging of radiomic, genomic, and clinical data points.

Currently databases like NCDB are highly controlled, constrained by financial resources and centralized bureaucracies, and change slowly unlike the human beings that they study. While controlling for variability is essential to scientists in general (and surgeons in particular), it may not be a practical solution for our future as surgical investigators. It is also inconsistent with the expectations, practices and on-line social interconnectivity of our patients. It seems inevitable that a hybrid approach to studying clinical outcomes will emerge. Current infrastructures for database abstraction at the institution level will be necessary to accurately and consistently document events that occur perioperatively. After a patient leaves that environment, better data might be obtained by other health care providers who interact directly with the patient or even the participant themselves.

Authors have attempted to validate hypotheses generated by much smaller cohorts at their own institutions by using larger datasets. If databases like the NCDB could authorize optional collection of expanded data forms that could reside centrally or at the local institutional level, then it could become a powerful engine of investigator collaboration. At relatively low cost, consortiums could emerge quickly around their existing core infrastructures by backloading data to test new hypotheses or validate or refute the publications of others.

This will require a disruptive change to the governance of database and human research protections organizations. Yet this change seems inevitable because of electronic medical record integration across all healthcare environments necessary to eliminate handoff errors and duplication of services. It is reasonable to expect that patients (as they do now) will trade privacy of their personal content to achieve convenience of an integrated health care service that will probably be offered to them free of charge and perhaps with rewards for validating data. Researchers will be able to access the record of the patient for a fee to an organization (akin to Facebook) that has provided that service. All in all, that fee will probably be less than the salary of a research assistant to make phone calls.

This opportunity is under development indirectly or directly by companies like Amazon, Google, Apple, and Microsoft that have multi-billion-dollar partnerships to enhance services in the medical space that ultimately will require research mechanisms to prove their worth.

In summary, it is high time for thoracic surgeons to move past testing things like surgical approach given paucity of evidence suggesting that open surgery benefits patient longevity or human desire for less body invasion or lifestyle disruption. Instead, physician investigators need to lead or partner with industry in the effort to enhance cooperative database design. In this way, collaborative group science will improve and the surgeon's role in designing meaningful, mechanistic-based randomized trials for the diseases we treat will be enhanced.

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Footnote

Conflicts of Interest: TL Demmy: Medtronic. S Yendamuri has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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