SPECIAL ARTICLE

A Proposed System Toward Standardizing Surgical-Based Treatments for Malignant Pleural Mesothelioma, From the Joint National Cancer Institute–International Association for the Study of Lung Cancer–Mesothelioma Applied Research Foundation Taskforce

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ABSTRACT

This article is a joint effort arising from a task force formed at a National Cancer Institute-International Association for the Study of Lung Cancer-Mesothelioma Applied Research Foundation Mesothelioma Clinical Trials Planning Meeting, held at the NIH in March 2017. Malignant pleural mesothelioma remains one of the most virulent and recalcitrant malignancies, still considered incurable, and in desperate need of clinical trials in order to make progress for our patients. Although not standard of care, there is compelling evidence that a select subgroup of mesothelioma patients benefit from a surgery-based *multimodal* approach. As it is not possible to achieve a microscopically complete resection with mesothelioma, there appears to be no role for surgery alone. Thus, it is anticipated that significant strides in the surgery-based treatment of this cancer will require trials that determine which complementary treatments best augment the cytoreductive efficacy of surgery. Although

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lung-sacrificing surgery for mesothelioma is fairly standardized, approaches to lung-sparing surgery are highly variable and lung sparing surgery is emerging internationally as the dominant extirpative procedure for this cancer. It is not currently possible to rigorously assess the contribution of the adjuvant treatments combined with surgery because of the variability in procedures used to debulk this cancer, the extreme variability of the cancer itself, the variability in patient selection, the variability in treatment of the inevitable recurrence, and even the variability in follow up schedules. This article is an effort to address these problems by suggesting a more uniform approach to the surgical procedure and also proposing a series of data collection forms that could be adopted immediately, with any eye toward collecting the information that will be necessary to facilitate patient selection and determine which aspects of mesothelioma surgery can and should be standardized – with the goal being extension of life while maintaining quality of life as an equal priority. Furthermore, a completely original contribution in this manuscript is the proposal of a grading system that takes the information from the surgical procedure data forms and generates a completeness of resection score. This is the initial effort to establish a common denominator for mesothelioma surgery that will allow for more accurate comparison between surgical series and better assessment of the impact of the treatments combined with surgery.

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Introduction

Malignant pleural mesothelioma (MPM) remains one of the most lethal cancers and is still considered nearly incurable and with a median survival typically cited in the 1- to 2-year range for patients who undergo any therapy. The current standard-of-care treatment is generally accepted as platinum-pemetrexed–based systemic therapy alone.[1] There is, however, logical and intuitive appeal to including surgery as part of a multimodal treatment plan for MPM, as surgery is currently the only modality that can predictably and reliably render a patient with no evidence of disease for this cancer that commonly exceeds 1 liter in volume. Because it is almost certainly not possible to achieve a microscopically complete, R0, resection for a pleural cancers such as MPM, it is not possible to cure someone with surgery alone. Even as part of a surgery-based multimodal treatment plan, there is currently no level I evidence supporting the use of surgery as a treatment for this cancer. Still, there is compelling evidence that there are some patients who do appear to benefit from a surgery-based multimodal approach significantly beyond what is reported, and would be expected, with the current standard-of-care treatment — chemotherapy alone. Despite this compelling evidence, we do not know with certainty that these same patients, treated medically, would not have done as well. However, consistently selecting patients who will benefit from surgery, establishing the optimal operation they should have, and determining the additional treatments to combine with surgery has not yet been established.

There are many reasons for this, but it is largely due to the extreme variability of the cancer itself combined with the variability of the surgical techniques being used and the variability of treatments being combined with surgery. In addition, even if there was complete consistency in surgery-based treatments, MPM is an orphan disease for which only a minority of patients even undergo surgery, so it will always be challenging to accrue enough patients to achieve statistical rigor when assessing results. It has, therefore, been extremely challenging to make significant progress in surgery-based treatments for MPM and, for the foreseeable future, it seems reasonable the first step toward making substantial progress in surgery-based treatments for MPM would be to establish some degrees of standardization that would attempt to counter the extreme variability associated with this cancer.

This article is a joint effort arising from discussions held at the National Cancer Institute (NCI) – International Association for the Study of Lung Cancer (IASLC) – Mesothelioma Applied Research Foundation (MARF) Clinical Trials Planning Meeting in March 2017 to propose a suggested approach to the essential elements of surgery for MPM, as well as a standardized system for data collection. While attempting to initiate a more uniform surgical approach to MPM, especially for lung-sparing surgery, which is currently highly variable, the data collection system is designed to gather the information that will eventually allow for evidence-based recommendations for standardization of MPM surgery. The ultimate goal is to allow the surgical portion of multimodal trials to serve as a stable platform to rigorously evaluate the contribution of the other treatments being combined with surgery. This, the authors believe, will be a necessary step in definitively establishing the role of surgery for MPM and determining what, when, and how to combine other treatments with surgery to maximally contribute to overall survival (OS) of MPM patients while still maintaining quality of life.

Background

The Problem and the Goal

One of the goals for any surgical procedure, particularly one of the magnitude and relatively unpredictable outcomes of surgery for MPM, is to have a reliable system to select the patients who will benefit from the operation. Furthermore, for this cancer in which surgery is not curative and a multimodal approach is essential, selecting the appropriate pre-, intra- and/or postoperative treatments is also critical. Lastly, given that the operation is almost certainly going to be palliative and that the patients are most commonly older, the entire treatment plan must be developed and/or modified within the context that maintaining quality of life is a top priority, near or on par with OS.

Some of the many factors hobbling the rigorous study of surgery for MPM include: (1) There are multiple significant prognosticators for MPM that are not captured by the current staging system, such as histologic subtype, tumor volume, sex, and laboratory studies such as platelet count.[2-9] Thus, unlike many cancers, the staging system does not provide a common denominator for comparing results, thereby precluding the ability to establish the impact of different surgical approaches and/or adjuvant therapies. That is, even taking stage into account, trying to compare the results between two surgical series is commonly similar to comparing apples and oranges. (2) The number of patients undergoing surgery for MPM is relatively small making it challenging to reach statistical significance with single-institution studies, and the inherent variability of the cancer and inconsistent treatments makes rigorous and meaningful comparisons between studies, let alone meta-analyses, challenging. (3) It is extremely difficult to conduct a randomized trial of surgical versus nonsurgical treatments for many cancers, and this has proven particularly difficult for MPM.[10-12] (4) The time zero to report calculated survival rates (i.e., from diagnosis or initiation of treatment or time of surgery) is not standardized and this can skew results, especially for this cancer where OS is typically measured in months. (5) Lung-sacrificing and lung-sparing surgeries for MPM have significantly different physiologic and potentially oncologic implications that can obfuscate the impact of the treatments combined with the surgery. (6) Although lung-sacrificing surgery is fairly well standardized, lung-sparing surgery is highly variable with respect to selection criteria, surgical technique, and even nomenclature — all of which hinder attempts at comparison. (7) There is no standardization of the treatments that are combined with surgery — pre-, post-, or intraoperatively. Even when the same treatment combinations are used, they may be given in different orders.[12] Lastly, (8) there is no standardization in the treatment approach for the inevitable postoperative recurrence of this cancer. Little to no data exist on how the different treatments for recurrence are selected, whether a particular surgical approach influences treatment selections, or the impact the different treatments have on survival or quality of life.[13]

This article proposes a data collection system for MPM surgery that could readily and immediately be adopted by all investigators. There are four data collection worksheets. Only two worksheets must be completed by the surgeon immediately after surgery. These two surgical forms document the operation and extent of disease and are designed to take no more than 5 to 10 minutes to complete. The worksheets offer a series of consensus suggestions for different aspects of MPM surgery that surgeons could adopt in an attempt to standardize, as much as possible, the actual surgical approach. Understanding that it is unreasonable to expect surgeons to immediately change their approach to an operation, particularly one this complex, it is hoped that the proposed data collection system will ultimately allow analysis of all the different approaches being used and provide a means to supply the MPM surgical community with a set of evidence-based recommendations for how best to perform this operation. The goal of this effort is to yield a surgical approach that is standardized and can serve as a stable platform to both establish the role of surgery for MPM as well as allow for rigorous and meaningful trials to determine the most effective therapies to combine with surgery to extend life while maintaining quality of life.

Surgery for MPM

Surgery as a Treatment

There remains controversy within the surgical community regarding the optimal surgical approach for MPM, but it is generally agreed that the goal should be to achieve a macroscopic complete resection (MCR), commonly defined as no residual visible or palpable cancer (an R1 resection). This is, realistically, the best one can hope to surgically accomplish with MPM, or other pleural malignancies, in that there is almost certainly going to be residual microscopic disease remaining after even the most aggressive attempt at surgical extirpation. This is a consequence of the fact that the cancer coats/invades all surfaces in the affected hemithorax achieving microscopically negative margins by including a boundary of normal tissue surrounding all of the resected cancer. The principle of an R0 resection is simply not possible in the majority of the cases.

There are two approaches to attempt MCR, sacrificing the lung or sparing the lung, each with relative

advantages and disadvantages. Lung-sacrificing surgery, extrapleural pneumonectomy, has the advantages of being a highly standardized procedure, simplifying the use of adjuvant radiation by avoiding pulmonary radiotoxicity, and almost certainly leaving behind a smaller burden of residual microscopic disease than lung-sparing surgery.[14] The disadvantages are primarily the safety and quality-of-life issues related to the loss of a lung and also the complications related to the necessary prosthetic reconstruction of the diaphragm and pericardium.

The primary advantages of lung-sparing surgery are the safety and quality-of-life issues related to preserving both lungs, including decreased or eliminated need for prosthetic reconstructions.[15] There is conjecture that the remaining lung may play a role in processing the residual microscopic disease and generating an immunologic response to the cancer, at least in combination with certain intraoperative adjuvants.[16] There is also conjecture that having two lungs generally leads to more physiologic reserve than having one lung and, consequently, greater ability to tolerate more aggressive treatments for the inevitable recurrence. This could potentially translate into greater OS than one could expect with less aggressive recurrence treatments. The disadvantages compared to extrapleural pneumonectomy include: typically taking longer to perform the operation, almost certainly leaving behind a higher burden of microscopic disease by virtue of leaving the additional surface area of the lung, the inherent variability associated with qualitative assessment of completeness of resection, the issue of managing postoperative air leaks, challenges to using adjuvant radiation, persistent confusion in nomenclature, and no standardization in technique.

There has been an attempt to standardize the nomenclature surrounding lung-sparing surgery, with extended pleurectomy decortication defining the most extensive and, ostensibly, microscopically complete lung-sparing operation.[17] Even this definition, however, is somewhat confusing as "decortication" implies preservation of the visceral pleura and some of the better results for this operation have been achieved by surgeons who routinely attempt to remove the entire visceral pleura. In short, from technique to nomenclature, the variability surrounding lung-sparing surgery for MPM currently prevents any attempt to rigorously compare results by precluding the ability to assume that the operations being compared were the same. Extrapleural pneumonectomy is far more standardized, in every regard.

Proposed Goals and Definitions for the Two Surgical Approaches for MPM

Ideally, surgery for MPM could become as standardized as it is for other malignancies, such as NSCLC. That is, although different surgeons may use different surgical approaches for NSCLC, at the conclusion of a lobectomy, for instance, it can be safely assumed that the same cancer operation has been performed regardless of whether it was performed minimally invasively, the order in which the hilar structures were divided, or how the bronchus or vessels were divided.

As a first step toward reaching an analogous status for MPM surgery, there should be agreement regarding the goals and definitions of the surgical procedure. The situation is more complex for MPM than NSCLC, however, in that there are two radically different operations — lung-sacrificing and lung-sparing, with lung-sacrificing surgery already being much more standardized than lung-sparing surgery. The subsequent discourse reflects this difference, with much more attention focused on lung-sparing surgery. What follows are the generally agreed upon definitions, goals, and brief recommendations of techniques for lung-sacrificing surgery and the first attempt at a similar degree of recommended standardization for the key elements of lung-sparing surgery.

Lung-Sacrificing Surgery. The accepted term for this operation is an extrapleural pneumonectomy.

Goal. The accepted goal for this operation is MCR, achieved by en bloc removal of the parietal pleural envelope, containing the lung and including the ipsilateral diaphragm and pericardium, and subsequent prosthetic reconstruction of the pericardium and diaphragm. Detailed descriptions of this procedure can be found elsewhere.[14]

Briefly, the following steps are performed: (1) The extrapleural plane is developed along the chest wall, superior mediastinum and posterior mediastinum; (2) The diaphragm is then resected, attempting to preserve the peritoneum; (3) The pericardium is then resected, dividing the pulmonary vessels intrapericardially that were not divided extrapericardially; (4) The bronchus is then divided, completing the extrapleural pneumonectomy; (5) A lymphadenectomy is then performed; (6) Any intraoperative adjuvant is then performed; (7) The bronchus should be buttressed; (8) The pericardium should be reconstructed to prevent cardiac herniation. If a nonporous patch such as Gore-Tex is used, then it should be fenestrated to avoid tamponade; (9) If the peritoneum was preserved, then a porous or nonporous mesh can be used for diaphragm reconstruction. If the peritoneum was sacrificed then a nonporous mesh, such as Gore-Tex, should be used.

Lung-Sparing Surgery. There has been an attempt to standardize the nomenclature by extent of resection[17]: Extended pleurectomy/decortication indicates parietal

and visceral pleurectomy to remove all gross tumor with resection of the diaphragm and/or pericardium. Pleurectomy/decortication indicates parietal and visceral pleurectomy to remove all gross tumor without diaphragm or pericardial resection. Partial pleurectomy indicates partial removal of parietal and/or visceral pleura for diagnostic or palliative purposes but leaving gross tumor behind.

Although this agreed-upon terminology is a step in the right direction, there is some ambiguity in the definitions, such as what extent of resection qualifies as "extended" for extended pleurectomy/decortication. For example, would resecting a 10-mm portion of pericardium qualify as an extended resection? Furthermore, the implied gradation of the definitions does not necessarily correlate with the completeness of resection, as it is sometimes possible to achieve a macroscopic complete resection by resecting the parietal pleura from both the diaphragm and pericardium, without resecting either of these structures. This speaks to the need for a system that captures completeness of resection and incorporates a method for accurately deciphering how that resection was accomplished. This is likely important as functional outcomes after lung-sparing surgery are potentially proportional to the amount of normal anatomy that is preserved. This, in turn, may correlate with OS, perhaps by establishing a more robust state of health in anticipation of the inevitable recurrence and almost certainly correlates with postoperative quality of life.

With respect to defining MCR, it might be prudent to include "no viable" tumor along with "no visible or palpable" tumor in that description as there are times in lung-sparing surgery when ablation by cautery or freezing of thin surface tumor may well be a reasonable, or even preferable, treatment to surgical removal.

Goals. As opposed to extrapleural pneumonectomy, where the operation is well defined and the goals are clear for every step of the operation, there are certain aspects of lung-sparing surgery that are nuanced and for which completeness of resection may be open for interpretation and for which multiple options exist. Bearing in mind that lung-sparing surgery typically takes longer than an extrapleural pneumonectomy, almost certainly leaves behind a greater burden of microscopic disease regardless of technique, and typically entails the postoperative challenges associated with large and persistent air leaks, then it is logical to assume that this operation is generally selected for its safety profile and likely superior quality-of-life results. However, there is some evidence suggesting greater OS may be associated with lung-sparing surgery in certain patients but, as with essentially all data regarding MPM surgery, this is not level I evidence. Furthermore, there are some recent results with lung-sacrificing surgery that have yielded encouraging results for highly selected patients that are rarely matched in lung-sparing series.[16,18-24]

Thus, as opposed to lung-sacrificing surgery, lung-sparing surgery commonly presents the surgeon with intraoperative judgment situations in which a more radical and likely more microscopically complete resection will potentially increase complications and/or decrease residual function. This situation is most often encountered with how the visceral pleura are handled. Surgeons who perform lung-sparing procedures will be confronted with situations where several options may exist and, given the aforementioned motivations, the option most likely to retain function and limit complications will need to be balanced against the desire to execute a radical resection. These situations can be encountered on the debridement of the pericardium, phrenic nerve, and diaphragm but most commonly occur with the handling of the visceral pleura, especially when it appears healthy. Handling of normal-appearing visceral pleura may range from leaving it alone, to performing a frozen section and only acting if cancer is identified, to cauterizing the normal appearing pleura, to summarily resecting the entire visceral pleura regardless of appearance. There are proponents for each of these approaches and, furthermore, surgeons may vary the approach from patient to patient based upon a multitude of factors, such as how well the patient would tolerate a persistent air leak or how easily the normal-appearing pleura separates from the lung parenchyma. None of these approaches has been proven right or wrong, and it is the hope that this proposal will ultimately help identify the optimal techniques to use in different situations.

What follows in the lung-sparing technique section is a description for each region of the chest encountered in lung-sparing surgery and a suggested algorithm for treating different situations that may be encountered in each of these regions. Areas where similar decision-making might be used with extrapleural pneumonectomy will be noted. In both cases, the critical element for this stage of the standardization project is to capture the information on what was performed, such that future evidence-based recommendations may be derived.

Suggested Standardized Technique for Lung-Sparing Surgery. The overarching strategy is to leave the patient with no visible, palpable or viable tumor. In the case of a thick tumor rind, one approach is to mobilize the tumor off all parietal pleural surfaces, such that the cancer is tethered solely to the lung, and then remove it

en bloc with the visceral pleura. This final dissection, separating the visceral pleura from the underlying lung parenchyma, is often facilitated by using a double lumen endotracheal tube and maintaining the operative lung on constant positive pressure while the nonoperative lung is ventilated normally. In cases of lower tumor burden, where the patient has a pleural effusion, the same approach can be applied with the exception that the visceral and parietal pleural surfaces may not be fused and will need to be removed separately. Suggestions for addressing the different regions of the chest in a proposed standardized approach to lung-sparing surgery are detailed below.

Prior Incision Sites. It is common to operate on a patient who has had a diagnostic/palliative thoracoscopy or thoracotomy or attempted resection performed by another surgeon. In this setting, the incision(s) may be remote and the surgeon is confronted by what to do with those incision sites given the proclivity of mesothelioma to seed incisions. For prior incision sites the following is proposed: (1) If the prior incision(s) can be incorporated into the current thoracotomy, and there is no overt tumor growth in the incision, then the skin is excised and checked with frozen section pathology. If tumor is detected, then all the soft tissue along the prior surgical site, chest wall musculature, and intercostal muscle is excised down into the chest and the margins are marked with surgical clips to guide adjuvant radiation, if deemed appropriate. It is recommended that an attempt be made to achieve gross clear margins. It is common for there to be a palpable cord that demarcates the course of the prior incision and can guide the surgeon from the subcutaneous tissue down to the parietal pleura. (2) If no cancer is detected in the skin portion of the prior incision that was sent to pathology, then the additional soft tissue resection can be avoided, thereby making subsequent chest closure less complicated. (3) If the prior incisions are remote from the current thoracotomy, then they can be left unperturbed unless there is visual or tactile suggestion of tumor infiltration. This includes not only the status of this region, as assessed from the skin, but also the appearance and feel of the prior incision site from within the chest. Sometimes the cancer will be found to infiltrate the interspace from within and should be excised. In this situation the surgeon should judge whether the skin must be excised. The same internal assessment should be performed even when the skin incision was excised, as the prior surgeon may have used multiple interspaces through the same skin incision. In either case, it is prudent to place surgical clips for radiographic identification in the event that adjuvant radiation is indicated.

Chest Wall. This portion of the operation is identical to extrapleural pneumonectomy and simply involves separation of the parietal pleura from the entire bony hemithorax. One situation that may be encountered with both lung-sparing and lung-sacrificing surgery is transgression of a portion of the tumor through the ribs and into the chest wall soft tissues. This is most commonly in the setting of a previous surgical or percutaneous biopsy, but it may occur de novo. In either case the surgeon must decide how to address this finding in an effort to achieve MCR. (1) In the absence of rib invasion a "bird cage" procedure is proposed, resecting all soft tissue infiltrated by tumor and using the electrocautery to skeletonize the ribs running through the tumor. The margins of this dissection should then be marked with surgical clips in the event that adjuvant radiation is indicated. (2) If the ribs are invaded, then the surgeon will have no option but to perform a chest wall resection. Standard criteria apply to the conduct of chest wall reconstruction, but the surgeon must weigh this decision and the selection of prosthetic material within the context that significant postoperative air leaks are anticipated and the risk of infecting the prosthetic is likely increased. At a minimum, the surgeon should consider extending antibiotic coverage until chest tubes are removed and, again, surgical clips should be placed for radiographic identification of dissection margins in the event that adjuvant radiation is used.

Posterior and Superior Mediastinum. These portions of the operation are, again, identical to the techniques used for extrapleural pneumonectomy. It is recommended that cream with methylene blue be administered through the nasogastric tube once placement in the stomach is confirmed as this can both help identify the thoracic duct and, in particular, can allow the surgeon to intervene intraoperatively to avoid a postoperative chyle leak. Presumptive ligation of the thoracic duct may have unclear consequences and is not recommended if this duct-identification technique is used and no leak is identified.

Pericardium/Phrenic Nerve. For this portion of the operation, every effort is made to achieve MCR while preserving as much normal anatomy as possible. A suggested standardized escalating approach for addressing the anterior mediastinum is as follows. (1) Anteriorly, the pericardial fat typically extends to the pericardiosternal recess and can be swept dorsally, off the pericardium, until the parietal pleura of the pericardium is visible. The parietal pleura are then separated from the fibrous pericardium, with the pericardial fat dissection often helping to identify the correct plane. The phrenic nerve is skeletonized and elevated, including its arborization into the diaphragm, allowing the dissection to be extended

dorsally to the pulmonary hilum. If the phrenic nerve is actually invaded, which is relatively uncommon, then it is resected. It is unclear if preserving the phrenic nerve is beneficial for this operation, but adoption of this practice, along with the proposed record keeping system, should provide data to answer this question. (2) If the tumor has invaded into the fibrous pericardium, then an attempt should be made to split the serous and fibrous layers of the pericardium, harvesting the fibrous pericardium en bloc with the parietal pleura and the cancer. (3) If the above techniques fail, then the pericardium can be resected full thickness. As opposed to extrapleural pneumonectomy where it is typically advised to reconstruct the pericardium, some surgeons advocate not reconstructing the pericardium with lung-sparing surgery, assuming the lung will expand to fill the pleural space and prevent torsion. If a reconstruction is deemed necessary, then the prosthetic should be selected within the context that a large air leak, and potential contamination, is possible. That is, it may be prudent to use an absorbable prosthetic rather than a permanent foreign body. At a minimum, consideration should be given to continuing antibiotics until air leaks are resolved and chest tubes are removed. (4) Sometimes the pleura and/or fibrous pericardium can be removed from the majority of the pericardium, except for several small isolated tumor deposits. In these cases, these small areas can be excised full thickness, leaving the remainder of the pericardium. (5) Sometimes there are areas that appear to have cleaved in the appropriate plane, but still appear concerning for residual cancer. In these cases, if the pericardium has been opened, and some type of insulator such as a plastic suction can be placed between the pericardium and the heart, then it is acceptable to cauterize the pericardial surface. The Aquamantys bipolar cautery *(*Aquamantys System, Medtronic, Parsippany, New Jersey) appears safe and effective for this purpose. (6) If an intraoperative adjuvant has been used, or if there was a significant amount of mechanical abrasion to the pericardium, then consideration should be given to fenestrating the pericardium at the conclusion of the operation to avoid the possibility of pericardial tamponade from a reactive effusion.

The Diaphragm. The diaphragm is often one of the most challenging parts of this operation and the part that least lends itself to a standardized approach, at least if the goal is to preserve as much functional muscle as possible. Again, it is unclear how much function is retained by a diaphragm, devoid of parietal pleura and, most likely, with a damaged or traumatized phrenic nerve. Still, with an eye toward maximizing the benefit from preserving a lung, it seems reasonable to make diaphragmatic preservation the goal of a standardized approach and capture the information resulting from this approach to determine if this is worthwhile or if the diaphragm should simply be resected and reconstructed, as with an extrapleural pneumonectomy. If the surgeon wishes to preserve as much diaphragm as possible: (1) The first attempt is to separate the parietal pleura from the underlying musculature and tendon. Typically, it is easiest to start the plane in the anterior sulcus. Working on a broad plane, the pleura will sometimes peel away from the underlying muscle using a sponge stick or fingers (sometimes easier if wrapping coarse gauze around the fingers), using slow gentle retraction. (2) If the muscle is only partially invaded, either for the entire diaphragm or more commonly in portions, then the next step is to attempt partial thickness resection of the underlying muscle in those areas. This is often most easily accomplished using broad tipped scissors, "feeling" the interface between the hard tumor and soft underlying muscle. (3) For areas where the diaphragm is invaded through the muscle, those regions should be resected down to the peritoneum, using essentially the same technique as in the diaphragm resection in an extrapleural pneumonectomy. (4) Sometimes, most often over the bare area of the liver, the diaphragm is breached full thickness. In this situation care is taken to avoid spillage of blood and other material into the abdominal cavity and the peritoneum is closed primarily. All patients are different, but a significant amount of diaphragm can usually be resected and still closed primarily without undue tension, thereby avoiding the placement of a prosthetic into a chest with an air leak and potential risk of infection. (5) The phrenic nerve is retracted and its arborization into the diaphragm is identified and preserved. Often there is a lymph node at the phrenic insertion site that should be harvested. (6) At this time, with the exception of complete diaphragm resection, it is unclear if reconstruction is necessary or beneficial. While rendering the diaphragm taught will decrease paradoxical motion, unless phrenic innervation is regained and the diaphragm can function with its new configuration, the greater volume of the pleural space could potentially complicate management of the postoperative air leaks. Again, prosthetic selection for reconstruction should be made within the context of a significant air leak and consideration should be given to continuing antibiotics. (7) Whether reconstruction and/or reinforcement with prosthetic is beneficial, whether it is beneficial to preserve the phrenic, and whether the diaphragm functions effectively without pleura and, if so, how much diaphragm must be preserved, are all unknowns. Standardizing the approach to the diaphragm with this algorithm will allow for the collection of the

data, which ultimately will allow these questions to be answered.

The Lung. The goals of the lung portion of this operation include leaving the patient with no detectable viable tumor, expansion of the lung if it was entrapped, and limiting postoperative air leaks — in that order. As previously mentioned, one technique that can facilitate resection of the visceral pleura from the underlying parenchyma is to place the operative lung on constant positive pressure, often starting out at 20 cm of water pressure and increasing or decreasing as needed. However, one word of caution: dissection of the pleura off of the pulmonary artery in the fissure is usually best accomplished with the lung deflated to promote better visualization. 23 A proposed standardized approach to the lung portion of the operation is as follows:

(1) The technique that would likely leave the least amount of residual microscopic disease is to remove the entire visceral pleura from the lung. Whether this is necessary, beneficial, or harmful is unknown and determining this is one of the goals of the proposed data collection system. Paradoxically, it is often easier to remove the visceral pleura in patients with thicker rinds of tumor completely encasing the lung than in patients with minimal visceral pleural disease. In these cases, use of a broad-tipped Cobb dissector with gentle traction on the lung parenchyma while it is under positive pressure is one technique that often works well. It is critical that the tumor be followed into all fissures of the lung, often resulting in skeletonization of the pulmonary arterial branches in the major fissure. This is also necessary to expose any pathologic interlobar lymph nodes that must be resected as part of achieving MCR. Counter intuitively, the fissure is commonly the part of the lung where the subpleural plane is most easily developed, at least using the described technique.
(2) If the tumor is highly invasive and recalcitrant to the blunt dissection technique to remove the visceral pleura, then for those portions of the lung electrocautery is used to find and develop the plane, sparing as much lung parenchyma as possible. It is very unusual for MPM to be rooted in the lung parenchyma for more than several millimeters.
(3) Sometimes the tumor is very thin, or the visceral pleura may even appear normal, most commonly in patients with minimal disease and significant pleural effusions. In these cases, the visceral pleura may not separate from the lung parenchyma with sharp or blunt techniques and is too thin to give purchase for retraction and electrocautery dissection. There are several options, each with their own proponents: (a) If the lung expands to normal volume and the visceral pleura looks completely normal, then a portion of the pleura can be excised and sent for frozen section pathologic analysis. If it is reported as showing no cancer, then the surgeon may opt to leave the pleura alone. Again, however, it is important that all fissures are opened to their full extent to avoid missing a rind of tumor within the fissure and not visible from the surface. (b) Some surgeons advocate, especially if an intraoperative adjuvant is being used, to leave completely normal appearing pleural unperturbed. It does seem likely that this could result in a higher burden of residual microscopic disease if the normal appearance is not confirmed on frozen section pathology but, again, this is an unknown. The argument of proponents for this approach is that a high degree of expertise is required for a pathologist to render an accurate assessment on frozen section and also that not violating the visceral pleura will eliminate air leaks and, almost certainly, hasten recovery. However, it is very rare to encounter a patient in whom the entire visceral pleural surface appears normal. (c) If the visceral pleura appears normal, but frozen section reveals microscopic disease, or the surgeon is uncomfortable with leaving any surface untreated, than the visceral pleura can be treated. If the surgeon cannot or does not want to resect the visceral pleura, then one technique that works well for this purpose is to treat the surface with the Aquamantys bipolar cautery. Other cautery techniques, application of the argon laser, or even cryotherapy, might be applicable. (d) Sometimes the visceral pleura appears normal, but with the exception of multiple papular lesions. In this situation, a visceral pleurectomy is indicated, but if that is not possible, then a surface cautery or cryotherapy treatment can be performed, dwelling on the papular lesions to assure no viable tumor remains.
(4) The impact of this proposed standardized approach on survival, pulmonary function, and postoperative air leaks will ultimately be able to be evaluated using information from the proposed data collection system and may permit firm recommendations on how to treat any encountered scenario of tumor-lung interaction.[24]

Lymph Node Dissection. Lymph nodes should be harvested from all of the standard NSCLC stations. In addition, phrenic lymph nodes and internal mammary lymph nodes should also be harvested. Lastly, posterior intercostal lymph nodes should also be harvested. These nodes are accessed by incising the endothoracic fascia at the level of the rib head and exploring the underlying

interspace. These should be dissected for at least five interspaces, typically the entered interspace and two above and two below.[9]

Proposed System for Universal Data Collection

The previous sections have detailed a suggested standardized approach to surgery for MPM as well as summarizing some of the issues that have hindered attempts to make significant progress in surgery-based treatment for MPM. As there is not even level I evidence to support the benefit of surgery for this cancer, let alone an established best approach, it is not realistic to expect that investigators would immediately adopt a standard set of selection criteria, surgical approach, or combination of adjuvant therapies. It is, however, reasonable to expect that data and documentation for surgery-based treatments could be standardized and immediately adopted. Establishing a body of standard information regarding MPM surgery is the first step toward allowing rigorous comparison between surgical series, determining what is promising and what is not, and, ultimately, performing meaningful surgery-based collaborative clinical trials to establish the role for surgery in this cancer. Four data collection worksheets are proposed for this purpose (see Supplementary Appendix).

Patient Selection and Staging Worksheet

This worksheet incorporates clinical and pathologic staging information and non–staging system prognosticators. Included are some follow-up measurements of preoperative parameters in an effort to help decipher the effect of different surgical approaches. It is hoped this will provide information that will ultimately assist in refining patient selection (see Supplementary Appendix).

Details of Lung-Sparing Operation Worksheet

This worksheet incorporates a detailed account of how each section of the chest cavity is handled during surgery. It is hoped that this will ultimately lead to standardization of lung-sparing surgical techniques, similar to lung-sacrificing surgery, and will also provide a basis for defining the circumstances under which lung-sparing or lung-sacrificing surgery is more appropriate (see Supplementary Appendix).

Completeness of Resection Score Worksheet

This chart generates a score taken from the sections of the Details of Lung-Sparing Operation Worksheet that is intended to reflect the degree to which MCR was achieved. It is hoped this system will be another step toward more rigorous stratification and groupings of patients undergoing lung-sparing surgery-based treatment for MPM and, consequently, more valid attribution of results to therapeutic variables combined with surgery. It is also hoped that the information available in the Details of Lung-Sparing Operation Worksheet, from which the score is derived, will allow for more granular analyses to determine which techniques used to achieve macroscopic complete resections are to be recommended (see Supplementary Appendix).

Tumor Recurrence Worksheet

Beyond the pattern and timing of recurrence, this worksheet aims to capture information that eludes essentially all current surgical series reports and almost certainly has significant impact on both quality of life and OS — documenting the treatments used for recurrence after surgery. In addition to serving as the first step toward grasping how recurrences are treated, it should provide data, along with the other worksheets, to help devise more standardized situation-specific approaches to recurrent MPM (see Supplementary Appendix).

Quality of Life

As of this writing, surgery for MPM has not been established as standard of care. Although performed with curative intent, the realistic goal for patients undergoing surgery-based treatment for MPM is to extend their life beyond what would be anticipated without surgery. Consequently, surgery for MPM should be considered a palliative procedure, arguably the largest known palliative operation. In addition, because of the latency period between asbestos exposure and the development of the cancer, the majority of the patients are in the geriatric population. Hence it is critical that quality of life be placed as a top priority in evaluating the efficacy of surgery-based treatments. A separate NCI-IASLC-MARF task force is working on a mesothelioma-specific quality-of-life instrument. It is recommended that this instrument be adopted and reported as the fifth standard data collection worksheet for all patients undergoing surgery-based treatment for MPM.

Follow-Up After Surgery for MPM

At this time there is no standard for follow-up of MPM patients after surgery. Due to the virulence of the cancer, its relatively unpredictable behavior, and the near certainty of a recurrence, it is important that patients be followed indefinitely and, at least initially, closely. The suggested follow-up for patients undergoing surgery for MPM is a history and physical exam and computed tomographic scan every 3 months for the first 2 years, every 4 months for the third year, and every 6

months thereafter. The use of positron-emission tomographic scan and/or serologic markers is discretional at this time, but should be recorded in the recurrence follow-up worksheet. Quality-of-life measurements and interval assessment of pulmonary function tests are also data that should be gathered to move this field forward.

Summary and Conclusion

In conclusion, progress in surgery-based treatment of MPM has been stymied by variability: variability in the type of operations that are used, variability in the reporting of these operations, variability in the treatments combined with surgery, variability in the treatment of the inevitable recurrence, and the extreme inherent variability of the cancer itself. Although there is a new and improved staging system for MPM, the results of surgery-based treatments for this cancer continue to be heavily influenced by other prognosticators, such as histologic subtype, that are not captured by the current staging system. Hence, there is currently no way to establish a common denominator that allows rigorous comparison between surgical series and definitive establishment of which operative approach and which adjuvants are beneficial, if at all, and in which circumstances/sequences they should be combined/used. Together, these issues have conspired to prevent the type of progress for surgery-based MPM treatments that the specialists would like to see and the patients deserve.[25]

A significant limitation is represented by the authors being exclusively from North America, which might incompletely align with the opinions of mesothelioma surgeons in European or worldwide. This joint NCI-IASLC-MARF task force work is a proposal to establish a suggested standardized approach for surgery and a standard set of data to collect for patients undergoing surgery-based treatment for MPM. This is the first step toward a system that will allow for valid comparison of results between surgical series, attribution of cause and effect for the different surgical procedures and adjuvant therapies, and, ultimately, easier and more effective collaborative trials. Proposed are four data collection worksheets that capture critical information from the preoperative, intraoperative, and postoperative periods, as well as a system for scoring the completeness of resection/residual disease burden. Lastly, a separate task force is developing a quality-of-life instrument designed specifically for patients undergoing surgery for MPM. This should be considered the fifth data sheet that should be used for all patients undergoing surgery for MPM since, as of this writing, surgery-based treatments for MPM are performed with curative intent but are, in almost all cases, palliative.

It is hoped that adoption of the data collection and surgical/practice guidelines offered in this article, combined with collection of the forthcoming quality-of-life measurements, will allow for international collaboration and accelerated progress toward the goals of what MPM patients want — significant extension of life with a good quality of life.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.04.029.

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