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CLINICAL PRACTICE GUIDELINE

The Society of Thoracic Surgeons (STS) Clinical Practice Guideline on Surgical Management of Oligometastatic Non-small Cell Lung Cancer

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ABSTRACT

BACKGROUND The use of local consolidative therapy (LCT) in patients with oligometastatic non-small cell lung cancer (NSCLC) is rapidly evolving, with a preponderance of data supporting the benefits of such therapeutic approaches incorporating pulmonary resection for appropriately selected candidates. However, practices vary widely institutionally and regionally, and evidence-based guidelines are lacking.

METHODS The Society of Thoracic Surgeons assembled a panel of thoracic surgical oncologists to evaluate and synthesize the available evidence regarding the role of pulmonary resection as LCT. Clinical and research questions of interest were identified, and a complete literature review was conducted. Best practice guidelines were developed accordingly.

RESULTS The panel identified 7 areas of controversy, and data were assimilated to support the best recommended practices related to these clinical issues. Ultimately, a number of issues in this realm were found to have a high level of evidence to support the role for surgical therapy in patients with stage IV lung cancer. However, the nuances of how these operations are conducted remain in equipoise, without ample evidence to support the extent of resection or nodal dissection.

CONCLUSIONS Clear data exist to support the use of surgical resection of the primary lung tumor as LCT in stage IV lung cancer. Evidence-based recommendations have been provided to guide multidisciplinary teams on the implementation of treatment plans as well as to guide researchers on areas of ongoing need for further investigation.

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Abbreviations and Acronyms

EGFR = epidermal growth factor receptor
HR = hazard ratio
LCT = local consolidative therapy
MT/O = maintenance therapy/observation
MVA = multivariable analysis
NSCLC = non-small cell lung cancer
OR = odds ratio
OS = overall survival
PFS = progression-free survival
PICO = Patient/problem/population, Intervention, Comparison/control/comparator, Outcome
QoL = quality of life
RATS = robotic-assisted thoracoscopic surgery
RCT = randomized controlled trial
STS = The Society of Thoracic Surgeons
SEER = Surveillance, Epidemiology, and End Results
TKI = tyrosine-kinase inhibitor
VATS = video-assisted thoracoscopic surgery
WG = writing group

EXECUTIVE SUMMARY

The use of local consolidative therapy (LCT) to improve survival outcomes in patients with oligometastatic non-small cell lung cancer (NSCLC) is a rapidly evolving management paradigm. The Society of Thoracic Surgeons (STS) assembled a panel of thoracic surgical oncologists to evaluate and synthesize the available evidence regarding the role of pulmonary resection as a local therapeutic modality in this context.

MAJOR FINDINGS. Class I (strong) recommendations support consideration of pulmonary resection as a local therapeutic modality in oligometastatic NSCLC. All patients with oligometastatic NSCLC should undergo a multidisciplinary evaluation, including consultation with an appropriately experienced thoracic surgeon. Additional recommendations (moderate) include performing pulmonary resection for appropriately selected patients with >3 sites of disease as well as for select cohorts with oligoprogressive disease. Insufficient evidence exists to support recommendations regarding the benefit of formal systematic mediastinal lymphadenectomy, the optimal extent of pulmonary resection (ie, lobectomy or anatomic resection vs parenchymal-sparing techniques), and surgical approach (thoracotomy vs minimally invasive approaches such as video-assisted or robotic-assisted thoracoscopy).

LIMITATIONS. Although randomized trials demonstrated an improvement in progression-free survival (PFS) and/or overall survival (OS) in oligometastatic patients who were treated with comprehensive LCT, completed trials to date allowed for treatment of primary lesions with radiotherapy or surgical therapy. Prevailing retrospective data are compelling for surgery while notably susceptible to potential selection bias. Consequently, further investigation is warranted based on existing data in the pursuit of stronger evidence-based recommendations regarding several of the prioritized study questions. Given that most randomized trials in this space include radiotherapy, with or without surgery, evidence for surgery has been slower to accumulate. Nonetheless, the body of evidence for surgery continues to grow, and there exist clear potential advantages of surgical resection in the opportunity for pathologic assessment and patient-reported outcomes that render pulmonary resection an important consideration in patient care and ongoing trials.

Historically, metastatic NSCLC has been considered incurable, with therapeutic goals emphasizing disease control, life prolongation, and symptom management, with emphasis on quality of life (QoL). Resection for the purposes of complete local disease clearance has not been a frequent consideration, with the concept of tumor debulking considered somewhat unconventional, with past connotations of oncologic heresy. However, advances in systemic options, including the introduction of immune checkpoint inhibitors and targeted therapies for patients with actionable mutations, have resulted in substantial improvements in disease control and overall survival.[1-5] Systemic therapy remains the cornerstone of treatment in stage IV NSCLC, yet recent data have clearly shown that appropriately selected patients may achieve significant improvement in outcomes with LCT, which may be comprised of surgical resection and/or radiotherapy to the primary tumor and metastatic sites of spread.[6-9]

Stage IV cancer encompasses a wide distribution of disease patterns, with recognition that a subset of patients exist with limited disease burden. These patients harbor a small number of metastatic deposits and may experience distinctly different prognoses while potentially able to benefit from treatment options beyond systemic therapy alone.[10,11] There is a lack of general consensus on a uniform definition of the oligometastatic NSCLC state, with a key landmark prospective trial defining oligometastatic disease as that with ≤3 metastases, exclusive of the primary tumor, with subsequent studies following suit.[6,12-15] Regardless of the exact definition of sites,

multidisciplinary management of this disease has rapidly evolved, with clear demonstration that patients with oligometastatic NSCLC can achieve long-term survival benefits with aggressive treatment of local sites of disease sites.[16]

Through such studies, it has become clear that aggressive local therapy can provide promise to a subset of patients who had been previously provided particularly poor prognoses. LCT in stage IV NSCLC, consisting of various forms of local therapy, has been supported through a number of investigations that have elucidated the feasibility, previous success, and potential future opportunities to drastically alter the course of disease for many patients.[17-19] Compelling evidence supporting LCT has been provided within the last decade through randomized trials that have typically included heterogeneous treatment modalities.[6,20] Importantly, recent work has shown the long-term benefits of surgery specifically as a treatment strategy.[21,22]

Despite the recent surge in studies in this area, guidelines in this realm have been lacking. In 2023, the European Society for Medical Oncology provided clinical practice guidelines for metastatic lung cancer, specifically recommending surgery or radiotherapy for disease that is oligometastatic at diagnosis as well as that which is oligoprogressive.[23] In the same year, the European Society for Radiotherapy and Oncology and the American Society for Radiation Oncology published a joint statement providing recommendations for the use of radiotherapy in the setting of stage IV lung cancer.

However, recommendations pertaining to the specific use of surgery, particularly the application of pulmonary resection, in this patient population have not been clarified despite the growing body of supporting evidence. As such, this document seeks to establish clinical practice guidelines based on supportive evidence and best practices for the inclusion of surgery within the multidisciplinary management of metastatic lung cancer.

METHODS

The STS Workforce on Evidence Based Surgery assembled a writing group (WG) in 2023, including thoracic surgeons who are experts in the field with relevant methodologic scientific background and strong clinical experience. WG members were required to declare any industry collaborations or support, as well as any other conflict of interest pertaining to the topic, before beginning the project.

The WG reviewed the existing literature published on LCT for patients with oligometastatic NSCLC and identified 7 clinically impactful questions in the Patient/problem/population, Intervention, Comparison/control/comparator, Outcome (PICO) framework, focusing on the key components of population, intervention, comparison, and outcomes.[24]

A qualified medical librarian developed a comprehensive search strategy for the MEDLINE and Embase databases. The full search strategy is detailed in Supplemental Appendix A. Formal search results were limited to articles in English pertaining to human participants published between January 1, 2000, and October 18, 2023. The literature search targeted study designs including randomized controlled trials (RCTs), meta-analyses, systematic reviews, observational studies, and case studies. The document was structured based on the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) framework.[25]

A total of 525 articles were retrieved, among which 451 were found through database searches and 74 through expert identification. After duplicates were excluded, 493 remained as potentially relevant. A 2-step screening process was implemented using Covidence, a web-based collaboration software platform that streamlines the production of systematic and other literature reviews.[26] The first step required screening of titles and abstracts for in-depth evaluation. The second step encompassed reviewing full texts for final inclusion. All conflicts were resolved through discussion by WG members.

Included in the review were 72 articles. The full PRISMA flow chart can be found in the Figure. The relevant data using standardized extraction forms were extracted, and a quality assessment of the articles was done to assess their risk of bias (Supplemental Appendix B). The Newcastle-Ottawa Scale was used for observational studies, Cochrane Risk of Bias Version 1 was used for RCTs, and A MeaSurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) was used to assess systematic reviews and meta-analyses.[27-29] Only studies with a direct comparator were assessed for their risk of bias due to the inherent design of the selected quality assessment tools requiring a comparator.

Recommendations were formulated and reviewed by all WG members in keeping with Institute of Medicine standards. The recommendations were graded according to the American

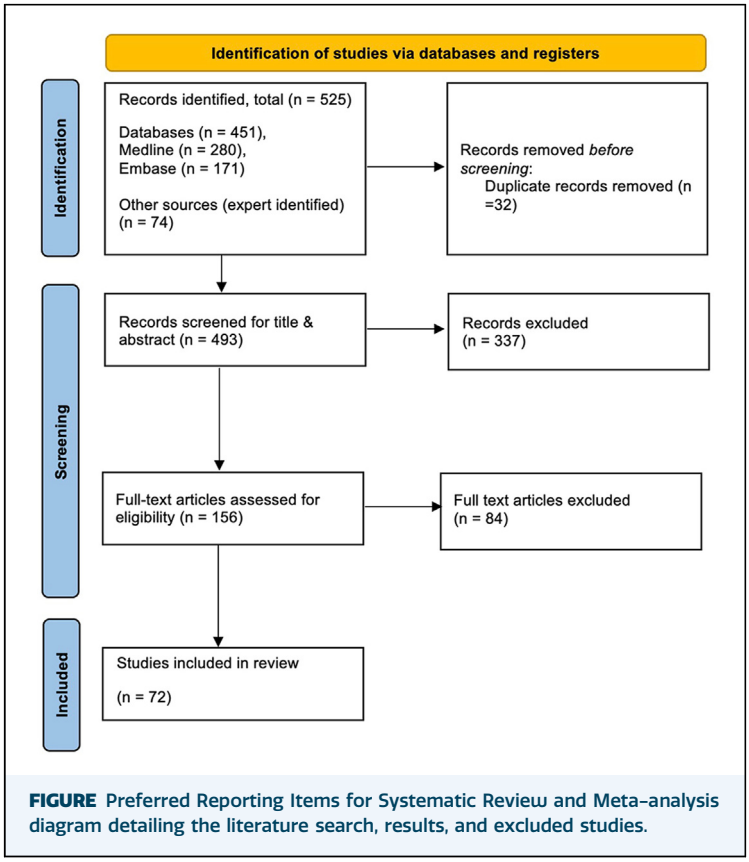

FIGURE Preferred Reporting Items for Systematic Review and Meta-analysis diagram detailing the literature search, results, and excluded studies.

College of Cardiology/American Heart Association Recommendation System.[30-32] The final recommendations were approved through a modified Delphi process using anonymous electronic voting. All WG members were required to vote, and a 75% agreement on recommendation statements, the class of recommendation, and the level of evidence was necessary to finalize the recommendations. If the consensus was not reached, multiple rounds of voting were conducted until a 75% consensus was achieved.[33] In this document, 75% consensus on all statements was achieved in the first round of voting. Anonymous voting results for each recommendation are detailed in Supplemental Appendix C.

The document was reviewed and approved by the STS Workforce on Evidence Based Surgery, the Council on Quality and Research, and the STS Executive Committee, along with a 2-week period for public comment.

RESULTS

Results are presented in the Table.

PICO 1. Among patients with oligometastatic NSCLC, does pulmonary resection offer a therapeutic benefit in terms of OS and PFS compared with best supportive care or maintenance systemic therapy?

RECOMMENDATION. Among patients with oligometastatic NSCLC, pulmonary resection used as LCT offers a therapeutic benefit, as demonstrated by prolonged OS and PFS compared with best supportive care or maintenance systemic therapy. As such, pulmonary resection should be considered as a local consolidative therapeutic modality in patients with oligometastatic NSCLC.

CLASS OF RECOMMENDATION. Class I.

LEVEL OF EVIDENCE. Level B-R

SUMMARY OF THE EVIDENCE. Support for the use of surgery as a local consolidative therapeutic modality in the context of oligometastatic NSCLC is derived from several phase 2 trials that demonstrated improvement in PFS and/or OS among patients treated with LCT compared with systemic therapy alone. The first of these reports was a multicenter, randomized trial that enrolled patients with oligometastatic NSCLC who did not progress after first-line systemic therapy to receipt of comprehensive LCT (radiotherapy and/or surgery to all sites of disease) or maintenance systemic therapy/observation (MT/O).[6,12] This trial was closed to accrual early after 49 patients were randomized and an interim analysis demonstrated substantial therapeutic benefit in the LCT arm. The investigators observed an improvement in PFS (LCT median PFS time, 11.9 months vs MT/O, 3.9 months; hazard ratio [HR], 0.35; $P = .005$), as well as a prolonged time to the development of new metastases, among those patients who underwent LCT. A subsequent report of longer-term follow-up from this study at a median follow-up time of 38.8 months corroborated the previous findings of PFS benefit and additionally demonstrated an improvement in OS (LCT median survival time, 41.2 months vs MT/O, 17.0 months; $P = .017$).

Several other trials evaluating radiotherapy alone as a local consolidative therapeutic modality have observed similar improvements in survival outcomes. A phase 2 trial randomized 29 patients with oligometastatic NSCLC who did not progress after systemic therapy to maintenance systemic therapy alone vs maintenance systemic therapy with stereotactic radiotherapy.[20] Similar to the study by Gomez and colleagues,[6,12] this investigation also closed early due to an improvement in the primary outcome of PFS (median PFS time, 9.7 months vs 3.5 months;

TABLE The Society of Thoracic Surgeons Clinical Practice Guideline on Surgical Management of Oligometastatic Non-small Cell Lung Cancer

Recommendation	COR	LOE
Among patients with oligometastatic NSCLC, pulmonary resection used as local consolidative therapy offers a therapeutic benefit as demonstrated by prolonged OS and PFS compared with best supportive care or maintenance systemic therapy. As such, pulmonary resection should be considered as a local consolidative therapeutic modality in patients with oligometastatic NSCLC.	I	B-R
There is currently insufficient evidence to support routine systematic lymphadenectomy at the time of pulmonary resection for oligometastatic lung cancer; however, there may be prognostic utility and individual benefits must be weighed with risks.	IIb	B-NR
Currently, there is insufficient evidence to recommend lobectomy over parenchymal-sparing sublobar resection for oligometastatic lung cancer.	IIb	B-NR
The benefit of local consolidative therapy likely extends beyond 3 metastases, and surgery should be considered in appropriately selected patients.	IIa	B-R
Among patients with oligoprogressive disease, surgery may be considered provided that all sites of disease are either addressable with local consolidative therapy or responsive to systemic therapy.	IIb	B-R
There is insufficient evidence to support any surgical approach over another for pulmonary resection as local consolidative therapy in oligometastatic lung cancer.	IIb	C-LD
Patients with oligometastatic NSCLC and disease stability should receive multidisciplinary evaluation including surgical consultation.	I	B-NR

COR, class of recommendation; LOE, level of evidence; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

HR, 0.304; $P = .01$). More recently, the Stereotactic Body Radiation Therapy (SBRT) in Newly Diagnosed Advanced Staged Lung Adenocarcinoma (SINDAS) trial randomized 133 patients with epidermal growth factor receptor (*EGFR*)-mutant oligometastatic NSCLC to receipt of stereotactic radiotherapy in addition to a first-generation tyrosine kinase inhibitor (TKI) vs systemic therapy with a TKI alone.[34] LCT improved the primary outcome of PFS (median PFS time, 20.2 months vs 12.5 months; $P < .001$) and the secondary outcome of OS (median survival time, 25.5 months vs 17.4 months; $P < .001$).

In addition to these randomized trials confirming the survival benefit of comprehensive LCT (using surgery and/or radiotherapy) in the context of oligometastatic NSCLC, a preponderance of prospective and retrospective data have suggested improved survival outcomes (compared with nonsurgical local consolidation, to systemic therapy alone, or to historical controls) when pulmonary resection was used as component of comprehensive LCT.[7,21,22,35-56] A multi-institutional, nonrandomized Japanese trial enrolled patients with synchronous (cT1-2 N0-1 M1) or metachronous (pT1-2 N0-1) oligometastatic (single-organ metastasis) NSCLC to undergo surgical resection of all sites of disease.[35] Of 20 enrolled patients, the observed 5-year OS was 44.7%. Although the available retrospective data are susceptible to selection biases,[7,21,22,36-50] meta-analyses have shown a consistent demonstration of the association between pulmonary resection and improved OS and/or PFS in oligometastatic NSCLC.[51-53] Finally, consistent with the results of the SINDAS trial, the association between surgical LCT and improved survival outcomes appears to persist and to be particularly promising in the context of targeted systemic therapies for *EGFR*-mutated oligometastatic adenocarcinoma.[54-56]

PICO 2. Among patients with oligometastatic NSCLC undergoing pulmonary resection, does the addition of mediastinal lymphadenectomy offer therapeutic benefit (OS, PFS) greater than the risk compared with parenchymal resection without lymphadenectomy?

RECOMMENDATION. There is currently insufficient evidence to support routine systematic lymphadenectomy at the time of pulmonary resection for oligometastatic lung cancer; however, there may

be prognostic utility, and individual benefits must be weighed with risks.

CLASS OF RECOMMENDATION. Class IIb

LEVEL OF EVIDENCE. Level B-NR

SUMMARY OF THE EVIDENCE. Results are variable, and evidence is generally lacking in support of lymphadenectomy during pulmonary resection for oligometastatic NSCLC. In contrast, several studies found that positive nodal disease is a significant, negative prognostic factor for *earlier-staged disease*. Complete mediastinal dissection or sampling was used in most of the 17 studies on retrospectively analyzed series or meta-analyses of surgical LCT.[7,21,36,37,46,47,50,57-65] Two of these reports predominantly focused on patients extracted from the Surveillance, Epidemiology, and End Results (SEER) database.[50,58] Definitions of oligometastatic disease in these studies were, unfortunately, variable, including between 1 and 5 involved synchronous sites.[7,21,36,37,46,47,50,57-65] Outcomes were assessed after median follow-up times ranging between 15 months and 5 years.[7,21,36,37,46,47,50,57-65] The in-hospital and 30-day mortality rates ranged between 0% and 6.2%, whereas the highest reported morbidity rates reached 33%.[7,21,36,37,46,47,50,57-65]

Nodal vs no nodal dissection. The median OS of patients with oligometastatic disease who underwent nodal dissection vs no nodal dissection was 21 vs 15 months, respectively.[57] Albeit associated with lower median OS figures (18 vs 6 months) compared with the previous study, Zhu and colleagues[37] demonstrated that lymphadenectomy resulted in an OS HR of 0.767. Similarly, the median PFS of patients with oligometastatic disease undergoing nodal dissection was 23 months compared with 16 months for those receiving no nodal dissection.[57] Once again, in the study by Zhu and colleagues,[37] lymphadenectomy was associated with a lower median PFS (20 vs 7 months), but the HR for PFS was 0.649, favoring lymphadenectomy.

pN0 vs pN+. Investigators in a study from Turkey[58] found no significant difference in the 5-year OS of patients with pN0 vs pN+ disease (P = .30). These findings were subsequently corroborated by Shyr and colleagues[50] (57% pN0 vs 22% pN1/pN2, P = .729). Sample size limitations must be considered in review of these data, with underpowering a potential possibility. Of note, in the study by Spaggiari and colleagues,[46] the difference in OS between pN0 and pN1/pN2 was significant (P = .0013) to the point that pathologic N2 emerged as an OS predictor from Cox regression multivariable analysis (MVA) (HR, 1.27; P = .027). When pN0 was compared with the pN1/N2 status, the difference in 5-year OS was more obvious (36% vs 14%).[46] The presence of pN2 was a negative predictor of both OS (HR, 2.00) and PFS (HR, 1.80).[46] Similar findings were described by Tönnies and colleagues,[59] who reported pN2/pN3 as a significant, negative OS predictor on the Cox regression MVA (HR, 2.00; P = .015). Congedo and colleagues[60] assessed the association of pN0 vs pN1/pN2 with long-term survival as well as disease-free local and distant survival. On MVA, advanced nodal status was correlated only with local disease-free survival (HR, 0.21; P = .008).

Shi and colleagues[61] conducted a meta-analysis of 6 studies to identify survival predictors of patients with oligometastatic disease. A sensitivity analysis was used to assess outcome stability.[61] In the evaluation of sex, stage, nodal status, smoking status, age, and histology, only nodal status was significantly correlated with the overall survival rate of NSCLC oligometastatic patients (HR, 1.69; P = .001).[61]

More recently, the results from 2 high-volume academic centers were reported.[36,47] In the study from Zurich,[47] the 5-year OS for patients with pN0 was 61%; together with age <60 years, pN0 was positively correlated with OS (HR, 0.41) on Cox regression MVA. In the study from Memorial Sloan Kettering Cancer Center,[36] along with primary tumor size, receipt of induction therapy, and visceral pleural invasion, pN1/pN2 was associated on MVA with worse OS (HR, 1.83; P = .033). However, nodal status was associated with event-free survival only in univariable analysis. A study from MD Anderson demonstrated that along with absence of bone metastases and the presence of only 1 metastatic site, pN0 was a favorable predictor for local consolidative therapeutic effect.[7] Contrary to other studies, no significant difference between pN0 and pN+ in impact on OS was reported.[7]

Despite such data suggesting nodal status impact on survival outcomes, these findings do not necessarily mean that surgical removal of those nodes would have a downstream effect on the outcomes of interest. Moreover, given the limited relevance of node positivity on the potential benefit of LCT, we do not have evidence to support routine use of invasive mediastinal staging in these circumstances. Ultimately, it is imperative for us to recognize that although data do not support systemic lymphadenectomy in stage IV NSCLC resections, there may be prognostic benefit, and further studies in metastatic

disease are clearly needed rather than extrapolating from dogma and data based on studies in early-stage resectable disease.

PICO 3. Among patients with oligometastatic NSCLC undergoing pulmonary resection, does anatomic resection (lobectomy) offer therapeutic benefit for OS and PFS compared with sublobar resection?

RECOMMENDATION. Currently, there is insufficient evidence to recommend lobectomy over parenchymal-sparing sublobar resection for oligometastatic lung cancer.

CLASS OF RECOMMENDATION. Class IIb

LEVEL OF EVIDENCE. Level B-NR

SUMMARY OF THE EVIDENCE. Resection of the primary tumor as a component of a comprehensive LCT management strategy is a feasible option associated with long-term OS in appropriately selected subsets of patients with NSCLC presenting with synchronous oligometastatic disease.[21,39] However, the extent of surgical resection providing optimal treatment in these patients remains an unresolved question, the answer to which cannot and should not be extrapolated from data in earlier-stage disease.

Evidence comparing the extent of pulmonary resection for surgical LCT in oligometastatic lung cancer patients remains sparse, because most studies on this subject did not conduct subgroup analyses based on types of surgical procedures. However, of those studies that differentiated between lobectomy and sublobar resection, there are conflicting reports on the optimal surgical intervention. Hao and colleagues[66] used the SEER database to conduct a propensity-matched analysis of metastatic NSCLC patients (2004-2016) who underwent primary tumor resection. They observed that lobectomy resulted in longer OS compared with sublobar resection, with a median OS of 25 and 16 months, respectively (HR, 0.73; 95% CI, 0.65-0.83; $P < .001$).[66] A similar result was reported by Wang and colleagues[42] in an analysis of SEER data from 2010-2015, noting that lobectomy, compared with sublobar resection, demonstrated improved lung cancer-specific survival for NSCLC patients with single-organ metastasis but not for multiple metastases ($P < .001$). Yang and colleagues[38] investigated the treatment effect of surgery for metastatic NSCLC among patients reported in the National Cancer Database and observed on subgroup analysis that segmentectomy (HR, 1.36; 95% CI, 1.08-1.71; $P = .009$) and wedge resection (HR, 1.70; 95% CI, 1.55-1.88; $P < .001$) were associated with worse survival outcomes compared with lobectomy in stage IV NSCLC patients.

In contrast, a multi-institution retrospective analysis of selected synchronous oligometastatic NSCLC patients reported that the type of resection (lobectomy vs sublobar resection) had no effect on survival, whereas other factors, such as single metastasis (HR, 0.71; 95% CI, 0.45-1.13; $P = .15$), the presence of contralateral lung metastases (HR, 0.30; 95% CI, 0.15-0.62; $P = .001$), and N2 node involvement (HR, 2.00; 95% CI, 1.21-3.32; $P = .0065$) affected OS; however, the type of resection (lobectomy vs sublobar resection) had no effect on survival.[46] A similar finding was noted in other single-institutional studies that did not observe any significant outcome differences based on the type of surgical resection performed.[46] These studies, however, reported on particularly limited-sized cohorts, impeding any meaningful comparison.

Finally, a small single-institution study by Kaba and colleagues[67] showed that sublobar resection resulted in improved median OS compared with lobectomy, at 39 and 15 months, respectively. The authors hypothesized that oligometastatic patients who received parenchymal-sparing lung resections might have been left with greater physiological reserve to better tolerate systemic therapies, thus improving survival.[67]

On the basis of these reports, existing data to recommend lobectomy over parenchymal-sparing or sublobar resections for oligometastatic lung cancer are insufficient. The published literature lacks the consistency and high-quality evidence to make informed decisions on this subject. For example, the evidence drawn from national registry databases (SEER and National Cancer Database) lacks granular elements, such as preoperative comorbidities or detailed information about metastatic disease or adjuvant treatments, to avoid potential patient selection bias. Moreover, smaller institutional studies are not adequately powered for meaningful analysis. Thus, extent of resection at this time should be determined by using a personalized approach, tailoring to the tumor location, its size, safety of anatomic resection, and the patient's overall medical status.

PICO 4. Among patients with stage IV NSCLC undergoing pulmonary resection, does the benefit remain for patients with >3 metastases (polymetastatic disease) compared with those with ≤3 sites (oligometastatic disease)?

RECOMMENDATION. The benefit of local consolidative therapy observed in oligometastatic disease likely extends to patients with >3 metastases, and surgery should be considered in appropriately selected cases of polymetastatic disease (>3 sites).

CLASS OF RECOMMENDATION. Class IIa

LEVEL OF EVIDENCE. Level B-R

SUMMARY OF THE EVIDENCE. The survival benefit derived from LCT for patients with >3 metastatic deposits stems largely from retrospective analyses. These studies were often conducted with the alternative definition of oligometastasis as having ≤5 lesions. Few studies have substratified the treatment groups by number of metastases, although there are ongoing trials that explicitly stratify by oligometastatic vs polymetastatic disease.[14,15] For those studies that included subgroup analyses, no consensus on a cutoff value and the inflection point was determined retrospectively from an appropriate statistical analysis. The benefit of LCT for oligometastatic NSCLC was most pronounced in the multicenter RCT by Gomez and colleagues[6,12] and the single-institution phase II RCT by Iyengar and colleagues.[20] Although the former only enrolled those with ≤3 metastases, Iyengar and colleagues included patients with up to 6 metastases. Interim analyses in both trials revealed longer PFS in the local consolidative arm (Gomez: HR, 0.35 [95% CI, 0.18-0.66], P = .0054; Iyengar: HR, 0.30 [95% CI, 0.113,0.815], P = .01).[6,12,20] The interim analysis led to early termination of accrual in both trials. However, importantly, subgroup analysis by Iyengar and colleagues[20] noted no statistically significant differences in PFS or OS between patients with <2 metastases vs those with >2. Importantly, these data were obtained from prospective studies that reported a clear benefit for LCT, recognizing that most of the patients in these trials underwent radiotherapy rather than surgery.

Furthermore, Wang and colleagues[34] randomized 133 patients with ≤5 sites of EGFR-mutated NSCLC in receiving TKI alone vs TKI therapy plus LCT.[34] The results were similarly in favor of LCT, with median PFS of 20.2 vs 12.5 months (P < .001) and median OS of 25.5 vs 17.4 months (P < .001). MVA noted that those with 3 to 5 lesions had a higher HR for both PFS (HR, 1.96; 95% CI, 1.30-4.70; P = .004) and OS (HR, 1.93; 95% CI, 1.21-3.07; P = .004). A retrospective study by Chen and colleagues[43] evaluated 231 patients and found that 1 to 3 metastatic deposits were associated with improved PFS (HR, 0.23; 95% CI, 0.45-0.9; P = .02) and OS (HR, 0.17; 95% CI, 0.35-0.74; P = .006). Similarly, Shimada and colleagues[68] evaluated 272 patients with metachronous metastases and noted a HR of 1.743 (95% CI, 1.178-2.581; P = .003) for those with >5 tumor deposits (polymetastatic). Several other retrospective cohort analyses did not detect any significant differences in survival between oligometastatic and polymetastatic disease.

Between 2017 and 2023, 4 meta-analyses assessed the role of LCT in oligometastatic disease.[51-53,69] Of these, only Rim and colleagues[53] reported the odds ratio (OR) for both OS and PFS in patients with ≤3 metastatic deposits. They included 20 studies involving 1750 patients. Subgroup analyses found that those with lower metastatic burden (≤3) had higher OR in PFS (OR, 5.129l [95% CI, 3.186-8.256] vs OR, 3.259 [95% CI, 2.010-5.283]; P < .001) but not OS (OR, 3.243 [95% CI, 1.748-6.017] vs OR, 3.532 [95% CI, 2.523-4.946]; P < .001). Other meta-analyses did not address the specific number of metastatic sites.

The discrepancies among these studies likely stem from heterogeneity in patient selection, mixed tumor histologies, location and quantity of metastases, as well as treatment modalities (both locoregional and systemic). The study by Iyengar and colleagues[20] was a RCT but was inadequately powered (n = 29) to detect survival differences between the subgroups, partially due to early closure of accrual. In contrast, enrollment in the trial by Wang and colleagues[34] had very specific histologic requirements, which may render the results of that trial to be less generalizable.

Of 22 assessed retrospective analyses, only 7 analyzed outcomes between low and high metastatic burden, and only 2 identified significant differences in survival.[8,36,37,43,46,47,56,64,68,70-82] Most of the prior studies included patients with varying numbers and locations of metastatic deposits and timing of metastatic presentation. Very few studies excluded patients whose metastases were not amenable to local consolidation. In addition, the location of metastatic burden carries prognostic value. Again, most studies report these details, but few have parsed out their impact within the analyses and thus result in data and statistical heterogeneity. In addition, a number of studies used a combination of surgery and radiotherapy as the LCT modality. Those studies using

surgery as the sole LCT arm did not assess survival benefits between 3 and >3 metastases.

Nonetheless, considering the current data, the survival benefit favoring LCT in addition to systemic therapy appears to exist for well-selected patients with >3 metastases. Treatments should be administered in patient populations in whom LCT can achieve control at all sites of metastases. Benefits in some studies of polymetastatic disease appear to diminish beyond 5 metastatic foci, although the current studies are not adequately designed to address the burden beyond 5, and ongoing trials[15] and their analyses will prove highly beneficial in addressing these challenges.

PICO 5. Among patients with oligoprogressive NSCLC, does salvage pulmonary resection offer a therapeutic benefit of OS and/or PFS compared with best supportive care or maintenance systemic therapy?

RECOMMENDATION. Among patients with oligoprogressive disease, surgery may be considered, provided that all sites of disease are either addressable with local consolidative therapy or responsive to systemic therapy.

CLASS OF RECOMMENDATION. Class IIb

LEVEL OF EVIDENCE. Level B-R

SUMMARY OF THE EVIDENCE. Although pulmonary resection for local consolidation of oligometastatic disease is supported by a number of the studies highlighted thus far, there remains less definitive evidence with regard to resection in oligoprogressive disease. For the purpose of these guidelines, *oligoprogressive* is defined as disease progression in which only a small number of lesions (≤3) develop or grow after or during systemic therapy, with relative control of the primary as well as other sites of metastasis.[83] Nuanced considerations acknowledge whether such disease originally presented as oligometastatic at baseline vs presenting as nonmetastatic or even polymetastatic, with only a small number of sites progressing. The concept of oligoprogressive disease centers around the notion that heterogeneity in the foci of disease may render progressive lesions resistant to previous or current systemic therapy and that if one can remove those resistant cells and prevent their downstream growth, the remainder of disease may be adequately treated with systemic therapy. This concept gains further appeal in an era of continuous drug development, with impressive efficacy of newer agents on the horizon.

It should be acknowledged that surgical resection in the setting of progressive disease tends to counter many of the tenets of oncologic surgery, which have traditionally emphasized surgery in the setting controlled or controllable primary malignancy.[84] In fact, nonprogresssion has been used as a criterion for randomization in recent clinical trials evaluating local consolidative therapy in oligometastatic disease (clinicaltrials.gov NCT04782752 and NCT03391869).

There are limited studies evaluating the role of surgery for oligoprogression, based on the on the premise that there may be a window of opportunity before polymetastatic disease, a window before development of resistance, and that it may be the only option for those who are no longer responding to or able to tolerate systemic treatment and are not candidates for radiotherapy due to size of treatment field or other contraindications. That there may be a specific role for local therapy even in progression in subgroups has been suggested, such as those harboring *EGFR* mutations, because these patients clearly have better outcomes with LCT, have more frequent development of resistance, experience disease with a predilection for brain metastases, and are often healthier, younger patients.[85]

Two retrospective series specifically evaluated lung resection in oligoprogressive disease. Yu and colleagues[86] conducted a retrospective, single-institution review of 184 patients with oligoprogressive *EGFR*-mutated NSCLC. Among these patients, 18 (10%) underwent LCT, with 11 patients treated with pulmonary resection. In their study, local therapy added to TKI therapy was associated with prolonged PFS and OS, with a median OS after LCT of 41 months. A more recent study by Joosten and colleagues[87] evaluated surgery specifically as LCT in oligoprogressive NSCLC, reporting no major morbidities or perioperative deaths, with 1- and 2-year OS of 48% and 21%, respectively, at a median follow-up of 44 months, demonstrating feasibility, safety, and potential impact on survival outcomes.

Offering the highest level of evidence in the setting of oligoprogressive disease, results of a randomized trial in this space were recently reported.[87] The Consolidative Use of Radiotherapy to Block (CURB) Oligoprogression trial[88] was an open-label, phase II, randomized study evaluating LCT in the form of stereotactic radiation to patients with breast and lung cancer. Importantly, this study showed that oligoprogression in NSCLC treated with LCT led to a >4-fold increase in PFS compared with standard of care only.

These data supporting LCT in in oligoprogression, taken alongside work from other authors demonstrating feasibility and safety of pulmonary resection as the form of LCT, highlight the role of surgery in this patient population. The specific operation to be performed should be determined based on clinicopathologic details of the patient and tumor.

PICO 6. Among patients with oligometastatic NSCLC, do minimally invasive approaches (video-assisted thoracoscopic surgery[VATS]/robot-assisted thoracoscopic surgery [RATS]) offer a therapeutic benefit with regard to perioperative morbidity and survival outcomes that outweigh risks compared with thoracotomy?

RECOMMENDATION. There is insufficient evidence to support any surgical approach over another for pulmonary resection as LCT in oligometastatic lung cancer.

CLASS OF RECOMMENDATION. Class IIb

LEVEL OF EVIDENCE. Level C-LD

SUMMARY OF THE EVIDENCE. Over the last decade, the benefits of minimally invasive surgery (VATS/RATS) as a treatment option for patients with early-stage lung cancer have been widely reported. Several observational studies and a randomized study have demonstrated improved QoL—specifically in immediate postoperative physical functioning and bodily pain domains—for patients undergoing minimally invasive approaches. However, data on this topic related to the treatment of oligometastatic lung cancer are limited. Moreover, the impact of LCT on QoL for patients with stage IV disease is both highly understudied and carries the potential to be substantially different from that of patients with earlier-staged disease. Published investigations for LCT in metastatic disease, as highlighted previously, have hitherto predominantly focused on survival outcomes, with inadequate investigations to date on patient-reported outcomes and QoL metrics.

Despite such limitations, we identified 5 prior studies providing best available data (Supplemental Appendix B). One study excluded surgical approach (VATS vs open) from its analysis due to potential confounding biases from other variables. The use of minimally invasive approaches in this patient population ranges from 20% to 60% in the reported literature. More recent studies suggest higher rates of application of VATS and RATS, which may reflect overall evolution of surgical approaches in the field or perhaps greater comfort and familiarity with the complexities of such operations.

Patients with oligometastatic disease present a unique challenge: long-standing systemic therapy, including chemotherapy historically as well as current regimens inclusive of immunotherapy and TKIs, can lead to extensive local tissue fibrosis.[89,90] Unexpected changes in the surgical plan occur in 7% to 15% of patients. Examples include larger-than-planned parenchymal resections, bronchial or vascular reconstructions, and the need for intrapericardial vascular control. Such nuances highlight the importance of evaluation by a dedicated thoracic surgeon with expertise in such operations. Surgeons must anticipate specific maneuvers due to significant transformations of surgical planes/tissue, dictating the extent of resection.

There is insufficient evidence to favor one surgical approach over another for patients with oligometastatic NSCLC. The decision should weigh the risks and benefits of the planned surgery, the duration and type of systemic therapy administered, resources available, the ability to implement local Enhanced Recovery After Surgery protocols, and impact on the patient's current and anticipated QoL. In general, patient safety should be of utmost priority in these cases, with a clear understanding of the complexity of the operations and resources required to provide a safe operation and postoperative recovery.

PICO 7. Among patients with oligometastatic NSCLC and disease stability, should patients receive multidisciplinary evaluation including surgical consultation?

RECOMMENDATION. Patients with oligometastatic NSCLC and disease stability should receive multidisciplinary evaluation including surgical consultation.

CLASS OF RECOMMENDATION. Class I

LEVEL OF EVIDENCE. Level B-NR

SUMMARY OF THE EVIDENCE. Oligometastatic NSCLC presents a unique clinical challenge, characterized by limited metastatic spread and opportunity for potentially curative treatment approaches. In the pursuit of the highest standard of care, we endorse the use of a formal multidisciplinary tumor board to guide decision-making in the care of these patients. The process draws upon the insights, expert opinions, collaboration, and collective expertise of medical oncologists, radiation oncologists, pathologists, pulmonologists, and thoracic

surgeons, permitting a comprehensive evaluation and individualized treatment plan for each patient. By harnessing the diverse perspectives and experiences of these specialists, multidisciplinary tumor boards facilitate informed discussions and evidence-based decision-making that most accurately define patient risk stratification, eligibility for neoadjuvant and adjuvant therapy, alongside clinical trials that incorporate the latest advancements in medical and radiation oncology, pulmonary medicine, and surgical techniques to ensure delivery of personalized care. Additionally, they foster ongoing communication and coordination among health care providers, resulting in seamless transitions between treatment modalities and better continuity of care. Derived from evidence from single and multicenter trials, this should be considered a Class I (strong) recommendation.

LIMITATIONS. The dominant limitations in existing data sets for this disease process center around the heterogeneous nature of the treatment paradigms as well as the widely ranging states of disease of patients included. As noted, although randomized trials demonstrated an improvement in PFS and/or OS in oligometastatic patients who were treated with comprehensive LCT, completed trials to date allowed for treatment of primary lesions with either radiotherapy or surgical therapy. Moreover, retrospective data are compelling for surgery, although noted to have a risk for selection bias. This review is limited by the constraints of the systemic review, acknowledging that data published in languages other than English were not included.

For this review, we considered the full existing prior body of evidence, which may carry inherent limitations to future applicability of dogma, given the changes in our evolving paradigms of systemic therapy. Although small retrospective series in historical cohorts receiving cytotoxic chemotherapy have identified the relevance of N2 disease, bony metastases, and other clinical features, these previous findings may have much less relevance in an era of targeted therapies for driver mutations, and further studies are clearly in need. We also acknowledge that a number of clinical nuances have not yet been adequately explored in prior investigations, and, as such, cannot yet be considered for guidelines statements, such as the impact of the site of metastases or the histology of the primary tumor.

Finally, the expert opinion of members of the WG represents the knowledge and views of academic clinicians working at centers with extensive experience in managing complex lung cancer; as such, expert opinions may not be extrapolatable and require cautious assessment of available expertise and resources before implementation at new facilities or institutions.

CONCLUSION. This Consensus Practice Guidelines document defines several recommendations regarding the use of pulmonary resection as a local therapeutic modality in oligometastatic NSCLC. Importantly, all patients with oligometastatic NSCLC should undergo a multidisciplinary evaluation, including consultation with an experienced thoracic surgeon. Moreover, lung resection should be offered to appropriately selected patients regardless of the number of sites of disease. More data are needed to determine the potential impact of lymphadenectomy, surgical approach, and extent of resection.

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