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EDITORIAL – THORACIC ONCOLOGY

Surgical Management of Incidentally Detected Pleural Disease in Lung Cancer Patients: A Complex Decision

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One of the classic dilemmas encountered by cancer surgeons throughout their careers is the decision of whether to resect. This decision is typically guided by existing evidence, protocols, and tumor board discussions as part of the surgical planning process. In thoracic oncology, surgeons sometimes face this decision when dealing with patients who present with incidentally discovered metastatic pleural disease (MPD) or malignant pleural effusion (MPE) during surgery. The presence of MPD or MPE in non-small cell lung cancer (NSCLC) is a strong indication of advanced cancer and has historically been associated with a poor prognosis, with an estimated survival of only 4–12 months.[1] In the eighth edition of the International Association for the Study of Lung Cancer (IASLC) classification, these conditions were classified as M1a disease, recognizing their aggressive potential.[2]

Thoracic surgeons typically encounter MPD or MPE in two scenarios. Some cases are clinically negative (cM0) but incidentally reveal metastatic pleural disease (M1a) during surgery; others are already clinically diagnosed as cM1a. Although some authors argue that surgery should not be excluded as an option in the multimodal management of clinical M1a disease, most guidelines do not recommend surgical resection as the first option. Neoadjuvant therapy to downstage the cancer before definitive surgical management or systemic therapy are two preferred treatment approaches. The controversy arises when pleural disease is incidentally detected during surgery. Surgeons are split about resecting the primary lesion versus leaving it alone. Many make a snap judgement based on extent of pleural disease, node positivity, type of surgery, and the fitness of the patient.

To address this clinical dilemma, researchers from Japan explored prognostic factors in patients with MPD or MPE.[3] This retrospective study titled "EGFR mutation is a prognostic factor in lung cancer patients with pleural dissemination detected during or after surgery," utilized the OUTSSG multicenter database from 2005 to 2015 to examine the outcomes of 114 patients initially misclassified but later upstaged to IVA due to incidental detection of pleural disease during surgery. Fifty-seven percent of these patients underwent primary tumor resection and 43% underwent exploratory thoracotomy only. The almost 50-50 split highlights the difficulty of the clinical decision-making process in incidentally detected pleural disease. The study revealed that adenocarcinoma, absence of clinical lymph node involvement, presence of EGFR mutation, and adjuvant therapy were significant positive factors for survival on univariate analysis. In the multivariable analysis, adenocarcinoma, absence of clinical lymph node involvement, and EGFR mutation remained significant. The 5-year OS difference between the primary lung tumor resected ($n=65$) and exploratory thoracotomy groups ($n=49$) trended to but was not significantly different (resection vs. exploration; 41% vs. 28%, $p=0.247$). Subgroup analysis revealed a significantly better 5-year OS for patients with EGFR mutation who underwent primary lung tumor resection ($n=20$) compared with those who had exploratory thoracotomy ($n=21$) (86.4 vs. 44.8%, $p<0.001$). It is important to exercise caution when interpreting the subgroup analysis, considering the small sample size involved. In such cases, even minor variations in patient characteristics can lead to significantly different populations. Notably, the patient population who underwent resection in the EGFR mutant group exhibited distinct characteristics compared with those who underwent exploratory thoracotomy. The resection group had a higher proportion of patients receiving distilled water therapy and

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EGFR tyrosine kinase inhibitor therapy. The exploratory thoracotomy group had nine clinical Stage 4 patients and 20 patients with more than five disseminated pleural nodules, whereas the resection group had 0 and 9, respectively. These dissimilarities can introduce bias into the analysis and potentially account for the observed effect of primary resection in the EGFR mutant population. Conducting a propensity score-matched subgroup analysis may be appropriate to address these issues.

The existing evidence on optimal management strategies for patients with incidentally detected M1a disease is limited and often conflicting. All studies are retrospective in nature, because conducting prospective studies to identify misclassified Stage IVA patients is impractical. A meta-analysis by Xu et al., including five articles with survival data, found that primary tumor resection, female gender, and lower N stage were associated with improved survival in patients with pleural disease detected during surgery.[4] Another meta-analysis by Deng et al. in 2020, which included the previous meta-analysis and ten additional retrospective cohorts, also supported surgical excision for overall survival.[5] The above two are the strongest evidence advocating for the surgeon to continue with primary resection on incidentally detecting MPE or MPD. The role of EGFR mutation status in guiding the decision for resection remains unclear, and it is not standard practice to assess EGFR status before surgery if resection is planned. Furthermore, in contrast to the findings of this paper, studies by Li et al. and Hu et al. have indicated that EGFR mutation-positivity negatively affects survival when resection is undertaken.[6,7] Further research on the response of EGFR positive tumors to resection and targeted therapy is necessary. For now, it is prudent to base surgical decisions on established principles and not let the EGFR status impact patient management. Several limitations exist in the current body of literature, including small study sizes, conflicting outcomes, and lack of crucial details, such as the type and extent of resection. The diverse range of disease states in M1a patients with lung cancer also poses a significant challenge. These variations include limited versus extensive MPD, presence or absence of MPE, clinical lymph node status, the size and extent of tumor, and preoperative stage of the disease. A final confounding factor was that most existing literature had long recruitment periods. The treatment landscape in the past decade has changed dramatically with the introduction of immunotherapy and targeted therapy. Although postoperative therapy has been associated with improved survival,[8,9] results from both meta-analyses and this study were not statistically significant. Nevertheless, this study demonstrated that EGFR status positively influenced survival on a multivariable analysis, likely due to the availability of targeted therapy options. These findings, although novel and important, need to be validated by larger datasets.

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