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REVIEW

Clinical impacts of a micropapillary pattern in lung adenocarcinoma: a review

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Abstract: Lung adenocarcinoma with a micropapillary pattern (MPPAC) has recently drawn increased attention among researchers. Micropapillary-predominant adenocarcinoma (MPA), which is defined by micropapillary pattern (MPP), is the primary histological pattern observed semiquantitatively in 5% increments on resection specimens, and MPA was formally determined to be a new histological subtype according to the new multidisciplinary classification in 2011. According to published studies, MPPAC is most common in males and nonsmokers and is associated with lymphatic invasion, pleural invasion, and lymph node metastases. MPPAC often presents as part-solid and lobulated nodules in computed tomography scans. MPP tends to have a higher maximum standardized uptake value as determined by fluorodeoxyglucose positron emission tomography combined with computed tomography, indicating a high risk of recurrence. Molecular markers, including vimentin, napsin A, phosphorylated c-Met, cytoplasmic maspin, Notch-1, MUC1, and tumoral CD10, may have higher expression in MPPAC than other subtypes; conversely, markers such as MUC4 and surfactant apoprotein A have lower expression in MPPAC. MPPAC with *EGFR* mutations can benefit from treatment with EGFR tyrosine kinase inhibitors. Furthermore, a complete lobectomy may be more suitable than limited resection for MPPAC because of the low sensitivity of intraoperative frozen sections and the high risk of lymph node metastasis. MPA benefits more from adjuvant chemotherapy than do other histological subtypes, whereas MPA does not benefit from adjuvant radiotherapy. Of note, MPP is associated with poor prognosis in early-stage lung adenocarcinoma, but the prognostic value of MPP is controversial in advanced-stage lung adenocarcinoma.

Keywords: lung adenocarcinoma, micropapillary, clinical impacts

Introduction

Lung cancer is universally acknowledged to be a lethal disease.[1] In the USA, lung and bronchus cancer is predicted to be the second most common cancer in both men and women in 2015 as well as the leading cause of cancer death.[2] Adenocarcinoma (ADC) is the most common histological subtype of lung cancer in most countries, accounting for almost half of lung cancers.[3] Because of the remarkable heterogeneity of clinical manifestations, radiology, pathology, and molecular features among ADC, there is a desperate need to devise a more detailed classification and reach a universally accepted criterion of ADC reclassification. Therefore, the international multidisciplinary classification of lung ADC has emerged at the right moment, sponsored by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society. In the new ADC classification, some new terminologies and diagnostic criteria have been proposed. The term "predominant" is applied to describe invasive ADC, which is defined by assessment of histological patterns semiquantitatively in 5% increments on resection specimens.[4] The new classification also recommends that pathologists list every present subtype

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and the percentage of the subtype in the diagnostic reports.[4,5] Additionally, micropapillary has been added as a new histological subtype. Micropapillary-predominant adenocarcinoma (MPA) is evaluated as a high-grade subtype with a poor prognosis.[4] The micropapillary pattern (MPP) was first described in lung cancer by Silver and Askin in 1997.[6] Then, in 2002, Amin et al observed that the MPP exists in some lung ADC and is apt to metastasize.[7] In the 2004 WHO classification, lung adenocarcinoma with a micropapillary pattern (MPPAC) was identified on the basis of its aggressive biological behavior, but it was not considered to be a new histological subtype, owing to a lack of published evidence.[8] However, in recent years, MPPAC has attracted increasing attention, especially regarding its association with poor prognosis, including the tendency toward recurrence and metastasis.[9–11] In this review, we discuss the recent advances in the clinical manifestations, histopathologic characteristics and genetic mutations, prognosis and survival, and the therapeutic impacts of MPPAC.

Clinical manifestations

Patients often have a presentation similar to that of other subtypes of ADC. Moreover, some patients initially present with metastatic symptoms, especially enlarged lymph nodes.[7] Multiple studies have shown that MPPAC is associated with the male sex[12,13] and nonsmoking status.[10,14–17] However, in some investigations, the differences were not significant with regard to sex[16,17] or smoking status.[18] Compared with other histological patterns of ADC, MPP has higher rates of lymphatic invasion,[9,19,20] visceral pleural invasion,[10,17,21,22] and lymph node metastases,[7,9,16,17,22–25] which influence the choice of the surgical method to some extent (Table 1). Zhang et al have reported a correlation of smoking (P=0.008) between MPP-positive (MPP ≥1%) and MPP-negative (MPP <1%) groups in a sample with 886 ADCs consisting of 246 MPP-positive cases. The authors also found a correlation with lymph node metastasis (P<0.001), pleural invasion (P=0.031), and lymphatic invasion (P<0.001) with frequencies of 39.6% vs 14.6%, 30.3% vs 23.6%, and 73.1% vs 13.1%, respectively, but the correlation with sex was not statistically significant (P=0.350).[16]

Table 1 Clinical features of MPPAC compared with conventional ADC without a MPP

Variables	MPPAC	Conventional ADC
Sex	Male	N[a]
Smoking status	Nonsmoker	N
Lymphatic invasion	High	Low
Visceral pleural invasion	High	Low
Lymph node metastases	High	Low
SUV_{max}	High	Low
CT findings		
Nodule appearance	Part-solid	N
Lobulation	Predominant	N
Location in tumor	Peripheral	N
Tumor size	Big	Small
Biomarkers		
Vimentin	High	Low
Napsin A	High	Low
pc-Met	High	Low
Cytoplasmic maspin	High	Low
Notch-1	High	Low
MUC1	High	Low
Tumoral CD10	High	Low
MUC4	Low	High
Surfactant apoprotein A	Low	High
EGFR mutations	High	Low
BRAF mutation	High	Low

Note: [a]N indicates that there is no apparent feature or variability.
Abbreviations: MPPAC, lung adenocarcinoma with a micropapillary pattern; ADC, adenocarcinoma; MPP, micropapillary pattern; SUV_{max}, maximum standardized uptake value; CT, computed tomography; pc-Met, phospho-c-Met.

Preoperative diagnosis

Imaging tests have an important role in preoperative diagnosis in clinical practice. Many studies have investigated the promising role of predicting histological patterns by using computed tomography (CT) scans. MPPAC is usually a solid nodule but may include slight nonsolid components.[26] Hence, Pass et al have proposed that surgeons should not choose limited resection (LR) on the basis of only the CT appearance of a solitary solid or partly solid nodule because the nodule may contain some MPP, which is a predictive factor of aggressive biological behavior.[27] Austin et al have suggested that, in clinical practice, the size of the solid component of part-solid lung ADC may be more significant than the total size including the nonsolid component, which may influence the evaluation of T status (tumor size in tumor node metastasis [TNM] classification) in the next edition of the TNM classification system.[26] Many studies have also found that using the size of the invasive component is more suitable than using the total size to evaluate T status.[4,5,20,28] However, more studies are required to clarify the impact on the evaluation of T status. Furthermore, predominantly lobulated ADC may predict the presentation of MPP.[29] The characteristics of CT such as tumor shape, sphericity, location, tumor disappearance ratio, and attenuation are not apparently different between MPPAC and other ADC, although these parameters may be related to malignant biological behaviors (Table 1).[25,29–31]

Fluorodeoxyglucose positron emission tomography combined with computed tomography (PET/CT) has gradually become routine for evaluating lung cancer staging.[32]

The maximum standardized uptake value (SUV_{max}) in fluorodeoxyglucose PET/CT, as the main value of measure, describes a semiquantitative value of glucose uptake in organic lesions. Nakamura et al have reported an SUV_{max} of 5.78±3.40 for MPA, representing the highest value among subtypes (Table 1). They have also shown that among the subgroups divided by histological classification (low, intermediate, and high grade), the higher the SUV_{max}, the greater the recurrent risk.[33] In other words, MPP has a tendency toward recurrence. Yeh et al have made a further observation predicting occult lymph node metastasis in clinically mediastinal node-negative lung ADC. They have reported an association between SUV_{max} in PET/CT and the risk of pN2 disease in univariate analysis but not in multivariate analysis. The presence of MPP was significantly related to the risk of pN2 (pathologic lymph node status in TNM classification) disease in both univariate analysis and multivariate analysis. The result is also consistent with the tendency of MPP to metastasize to lymph nodes and suggests that MPP has a higher SUV_{max} than other histological patterns.[34] This speculation has been further validated by several investigations.[35–37]

Apart from imaging diagnosis before surgery, pathologic diagnosis on the basis of small biopsies and cytology is of great importance, especially for advanced-stage lung ADC. However, pathologic diagnosis cannot adequately identify MPP from other ADCs. Rudomina et al have performed a retrospective analysis of 46 MPPACs with cytologic specimens (45 fine-needle aspirations of the lung and one of a pleural mass) and 33 ADCs without MPP for comparison. They found no significant difference between the two groups regarding the distribution of micropapillary tufts in the cytological materials and no relation with the percentage of MPP and the presence of micropapillary tufts.[38] The discordance between resection samples and cytological specimens has also been reported by other studies.[31,39]

Histopathologic characteristics

MPP is often discovered in the peripheral area of a nodule or mass.[40,41] Histologically, MPP has been characterized by papillary tufts with no fibrovascular cores (Figure 1A and B), which is distinct from general tumors in which the vascularity is integral and important for the access to nourishment.[4,7] To date, the mechanism of nourishment of MPP is uncertain, and these tumor cells may acquire nourishment from surrounding fluids in the alveolar spaces.[42] Amin et al have classified MPP into two types: the classical type, in which micropapillary tufts float in the alveolar spaces or cluster in connective tissue spaces, and the variant type, in which micropapillary tufts float within cystic spaces lined by tumor cells.[7]

The cells of MPP are generally small and cuboidal with minimal nuclear atypia, detaching and/or connecting to alveolar walls.[4,8] Because of the positive staining of E-cadherin and β-catenin, the negative staining of laminin, and the loss of the basement membrane, tight adhesion is validated to be present in MPP cells, whereas cell–matrix contact and cell polarity are absent.[42] Kamiya et al have suggested that the disordered structure may contribute to the characteristics of metastasis.[42]

In primary tumors, almost all ADCs are a mixture of several histological subtypes, and the percentage of MPP varies.[7,9,16,20,24,38,41,43–45] MPP is mainly observed at the periphery rather than in the center of the primary tumor,[7,8] and the presentation of MPP in metastases is remarkably higher than in the primary tumors.[4,7,8] Moreover, the concordance of histological subtype is 100% between the primary ADC and the metastatic tumor.[46,47]

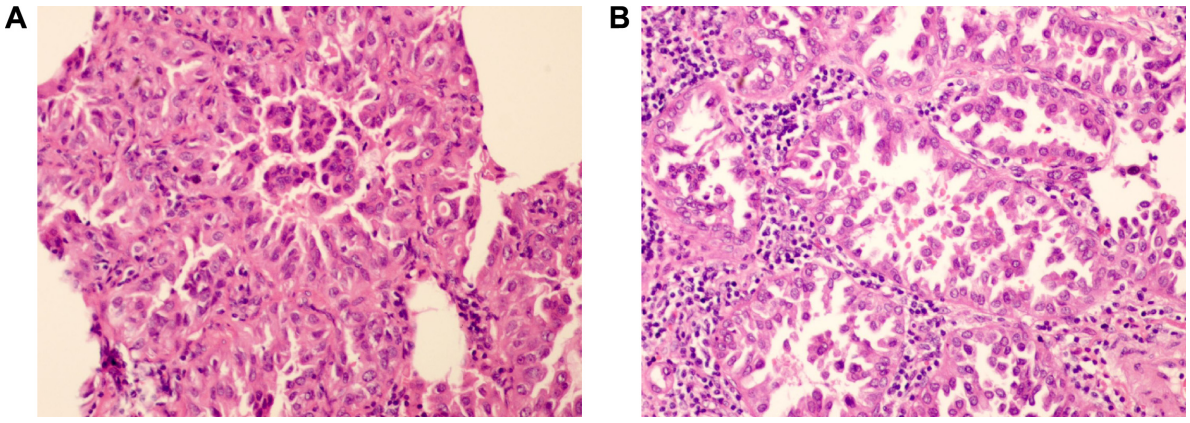

Figure 1 Pathological images show the morphology of a micropapillary pattern.
Notes: (**A** and **B**) Images showing hematoxylin–eosin staining at magnification ×200. (**A**) Micropapillary tufts float in the alveolar space. (**B**) Lung adenocarcinoma cells cluster like micropapillary pattern and bulge into alveolar space.

Molecular features

Recently, biomarker studies have become increasingly heated. With the development of biotechnology, molecular testing has gradually been put into clinical practice to identify the origin, histological type, and proper treatment strategies, especially for advanced lung cancer, which is diagnosed on the basis of small biopsies and cytology. Here, we introduce some special markers for MPP (Table 1).

Vimentin

Vimentin is a type-III intermediate filament. Vimentin intermediate filaments play an important role in the initiation and progression of lung cancer.[48,49] In recent studies, vimentin has been found to have higher expression in MPPAC, and it is correlated with higher risks of vascular invasion and lymph node metastasis.[50,51] In a sample of 101 MPPACs and 119 conventional ADCs of stages I–III, vimentin expression was detected by semiquantitative immunohistochemistry. Of the 101 MPPACs, vimentin expression scores of MPP and background non-MPP were 4.0±2.1 and 2.3±1.9, respectively, with a *P*-value of <0.0001. Compared with 119 conventional ADCs, the vimentin expression score of MPP was significantly higher than that of well- and moderately differentiated conventional ADC (0.6±1.2 and 1.9±1.7, respectively), instead of that of poorly differentiated conventional ADC with the score of 3.8±2.7. Moreover, vimentin expression scores in 101 MPPACs with vascular invasion and lymph node metastasis were 4.2±2.1 and 4.4±1.9, respectively, and were statistically higher than those without vascular invasion or node metastasis (2.8±2.0 and 3.3±2.3, respectively), with *P*=0.0196 and *P*=0.0122, respectively. High vimentin expression in MPP was an independent adverse prognostic factor for both overall survival (OS) and disease-free survival (DFS) (hazards ratio [HR] =1.71, 95% confidence interval [CI] =1.00–2.99, *P*=0.047).[51]

Napsin A

Napsin A is an aspartic proteinase and a marker for identifying primary lung ADC, which is more sensitive and specific than TTF-1.[52] Warth et al have demonstrated that MPA has the highest frequency of napsin A expression compared with that in other predominant histological subtypes (*P*<0.001).[53]

Phosphorylated c-Met

The mesenchymal–epidermal transition (c-Met) protein and its ligand, hepatocyte growth factor, make a great influence on the prognosis and targeted therapy in non-small-cell lung cancer (NSCLC).[54] Koga et al have investigated a cohort of pT1-size lung ADC and have found that c-Met immunoreactivity was irrelevant to the presence of MPP but phospho-c-Met (pc-Met) was significantly more highly expressed in the MPP-positive (the percentage of MPP ≥10%) group compared with the MPP-negative (<10%) group, with a frequency of 0.293 and 0.100, respectively (*P*=0.01). Highly expressed pc-Met in the MPP-positive group was statistically related to lymphatic involvement (*P*=0.0001), 82% vs 18%, respectively. Only in p-stage IA ADC, highly expressed pc-Met was statistically adversely associated with 5-year survival compared with weakly expressed pc-Met, with a percentage of 51.3% and 79.4% (*P*=0.0313).[55] Lee et al have declared a similar conclusion.[36] Therefore, the phosphorylation of c-Met is related to MPP and probably contributes to the aggressive biological behavior of MPP. Therefore, crizotinib, as a c-Met inhibitor, may provide another option for MPPAC treatment.

MUC1, MUC4, and surfactant apoprotein A

Previous studies have indicated that high expression of MUC1[56–58] and low expression of MUC4[59,60] and surfactant apoprotein A[61] are related to an adverse prognosis in lung cancer. Tsutsumida et al have found higher expression of MUC1 and lower expression of MUC4 in the MPP-positive group (MPP ≥1%) than the MPP-negative group. Additionally, a reduced expression of surfactant apoprotein A has been reported to be an unfavorable prognostic factor in MPPAC in small-sized ADC.[62] Ohe et al confirmed the unfavorable prognostic value of surfactant apoprotein A in MPPAC again.[63]

Apart from the aforementioned reports, there are other biomarkers associated with MPP that have been reported, such as higher expression of cytoplasmic maspin,[64] Notch-1,[65] and tumoral CD10.[66] However, there is a lack of additional literature to validate the correlations between these biomarkers and the presence of MPP, so we will not clarify them in detail here. MPPAC also has molecular markers specifically related to ADC, for example, TTF-1.

Genetic mutations

Recently, gene detection has gradually become conventional for advanced lung cancer,[28] and targeted drugs may be more efficient than traditional chemotherapy. *EGFR* mutations are one of the most frequent mutations detected and have been confirmed as predictors of response to tyrosine kinase inhibitors (TKIs), which are the first-line therapy

in advanced-stage lung ADC with mutated *EGFR*.[4] MPA has a higher frequency of *EGFR* mutations compared with other histological subtypes (Table 1).[53,67–69] Warth et al have investigated 416 ADCs, and have found that, of 25 MPAs, 32% had *EGFR* mutations, which was higher than the 23.3% of lepidic-predominant ADC, 18.8% of acinar-predominant ADC, 9.4% of solid-predominant ADC, and 14.3% of papillary-predominant ADC. Therefore, it is crucial to detect the *EGFR* genetic status for MPA because it impacts initial therapy. However, because of ethnic differences and other factors, some controversial correlations between *EGFR* mutations and predominant histological subtypes have also been demonstrated.[28,45,69–72] The frequency of *EGFR* mutations varies from 25% to 84.6% in MPPAC in variable cohorts and has been found to be higher in an Asian cohort.[40,46,53,67,69,70,73–75] It is noteworthy that there is a controversy as to whether the frequency of *EGFR* mutations is associated with the percentage of MPP in the entire tumor.[43,76] Regarding survival analysis, patients with MPP harboring *EGFR* mutations have been reported to have better survival when they received a TKI treatment compared with those with either no treatment[76] or conventional platinum-based chemotherapy.[13] Therefore, the application of *EGFR* TKIs to *EGFR*-mutated patients with MPPAC may benefit in controlling the disease.

BRAF is a downstream molecule in the *EGFR* signaling pathway, and its mutations play a role in resisting the function of *EGFR* TKIs. Some studies have shown that *BRAF* mutations are more frequent in MPA than in other subtypes (Table 1).[53,77] Warth et al have reported that *BRAF* mutations were mainly present in MPA with a frequency of 8%, higher than 0% of lepidic-predominant ADC, 4% of acinar-predominant ADC, 5.4% of solid-predominant ADC, and 0% of papillary-predominant ADC. To our knowledge, there is not a difference between MPA and other predominant histological subtypes with regard to *KRAS* mutations or *ALK* rearrangement.[45,53,71,78]

Prognosis and survival

An MPP has been reported in various cancers, such as breast,[79] thyroid,[80] bladder,[81] ovarian,[82] renal,[83] salivary,[84] colorectal,[85,86] and lung cancers. For some of these tumors, the presentation of MPP has prognostic significance. The prognostic significance of MPP in lung ADC has also gradually become apparent.[22,24,73,87] Warth et al have performed a study in 487 ADCs with surgery (stages I–IV) and have found that the predominant histological pattern has a statistically significant effect on survival. MPA had the poorest outcome compared with the other histological patterns with OS of 44.9±6.3 months, disease-specific survival (DSS) of 50.4±6.7 months, and DFS of 33.8±6.1 months.[20] Although the novel classification of ADC has defined MPA in 5% increments, some studies indicated that even a minimal amount of MPP (<5% increments) was associated with poor prognosis.[16,62,75] Lee et al have classified 525 ADCs into three groups based on the percentage of MPP: 1) ≥5% of MPP (n=114), 2) <5% (but ≥1%) of MPP (n=115), and 3) absent (<1%) MPP (n=296). They found that OS was significantly better in the group with absent MPP compared with the other two groups, whereas the difference in OS was not significant between the ≥5% group and <5% group.[43] Until now, in terms of the influence of MPP on the prognosis of lung ADC, there has not been a well-defined criterion of the percentage of MPP or a consensus on whether MPP is predominant in the total tumor matters in prognosis. Zhang et al have demonstrated that MPA (≥5% of MPP) had a statistically worse recurrence-free survival compared with nonmicropapillary-predominant ADC with ≥5% MPP in stage I patients, whereas a similar correlation was not present in stage II–III patients.[76] Moreover, there has been a fierce controversy about whether the percentage of MPP is proportionate to the poor prognosis. Kamiya et al have divided 383 cases into four groups according to the proportion of MPP: none (0% of the tumor), focal (<10%), moderate (<50%), and extensive (≥50%). They observed from the survival curves that the prognosis was worse with the increase in proportion of MPP in tumors, and both DFS and OS for each of the latter three groups were worse than those for the group with no MPP. Comparisons among the latter three groups were absent, so whether statistical significance existed is uncertain.[42] Zhang et al have divided 886 cases into four groups according to the extent of MPP in lung ADC, namely <1%, 1–5%, 5–50%, and ≥50%. They have reported a conclusion similar to that made by Kamiya et al.[16] In contrast, Sumiyoshi et al have revealed that the mean percentages of MPP in the recurrence and nonrecurrence groups were 20.4% and 18.3%, respectively, with no significance (P=0.996).[13] These studies further indicate the importance of both the identification of MPP and the determination of the percentage in pathological reports. More investigations are needed to resolve the former two problems in the future.

MPP has been validated as an unfavorable prognostic marker in early-stage lung ADC regardless of cohorts.[13,47,88–94] However, the role of MPP, with regard to prognosis, is uncertain in advanced-stage lung ADC. Zhang et al have reported that MPA (≥5% of MPP) had statistically worse recurrence-free survival compared with nonmicropapillary-predominant

ADC with ≥5% of MPP in stage I patients, whereas they did not find a similar correlation in stage II–III patients.[76] Campos-Parra et al have claimed that high-grade ADC (micropapillary-, papillary-, and solid-predominant) is associated with better survival compared with intermediate-grade ADC (lepidic- and acinar-predominant) in advanced ADC (stages IIIB and IV), and the median progression-free survival (PFS) and OS were 6.4 vs 5.5 months (P=0.009) and 25 vs 16.8 months (P=0.023), respectively. For this result, they considered that a better response to chemotherapy probably contributed to this phenomenon.[95] Subsequently, Clay et al have also shown that MPP is not a predictor of unfavorable survival in stages III–IV.[74] In contrast, Cakir et al have indicated that the presentation of MPP is a predictor of unfavorable outcome in not only early-stage ADC but also late-stage ADC.[18]

Therapeutic impacts

Influences on surgical treatment

As described earlier, MPPAC usually presents as a solitary nodule or mass. The current gold standard operation of early-stage lung cancer is lobectomy (LO) with hilar and mediastinal lymph node dissection.[96,97] With the development of imaging technology and the widespread use of CT screening, there has been a marked increase in the detection rate of small early-stage ADC. Herein, LR is used in place of LO in peripheral early-stage ADC because of its comparably curative effect and decreased damage to lung function.[98,99] However, the prognostic utility of LR is uncertain. Hung et al have indicated that the micropapillary-/solid-predominant pattern is a marker of adverse prognosis (P=0.003) in patients after complete resection of lung ADC.[11] Therefore, considering the tendency toward recurrence and metastasis of MPP, a deliberate choice must be made in peripheral early-stage MPPAC. Nitadori et al have reported that, in 734 patients undergoing LR or LO for small (≤2 cm) lung ADCs, in the LR group, ≥5% MPP had a higher risk of recurrence than patients with <5% MPP (P<0.001). The 5-year cumulative incidences of recurrence were 34.2% and 12.4%, respectively, and most recurrences were local recurrence; in the LR group, when the surgical margin was <1 cm, there was a similar outcome in terms of local recurrence (P=0.007), but neither the LO group nor patients with a surgical margin of ≥1 cm showed statistically significant recurrence.[100] In patients with LR, ≥5% MPP is an independent predictor of recurrence. Subsequently, Bao et al have revealed that MPA is significantly more likely to present with pathological lymph node metastases in patients with clinical T1aN0 NSCLC.[23] Kadota et al have also demonstrated the adverse predictive value of tumors that have spread through air spaces regarding recurrence after LR for small stage I ADC.[101] Because of the tendency to recur, Ye et al have suggested that the intraoperative diagnosis of histological subtype should be made to determine whether systematic lymph nodes need dissection in clinical stage IA ADCs.[19] Therefore, considering the underestimated lymph node status before surgery, a complete LO may be more suitable for MPPAC rather than an LR, and surgeons need to examine lymph nodes carefully during surgery.

In terms of intraoperative diagnosis, there is a lack of effective methods for diagnosing the presence of MPP during an operation. Intraoperative frozen sections are the primary method of diagnosis, which has been reported to have poor sensitivity for MPP. Yeh et al have assessed frozen sections from 361 ADCs in stage I with a tumor size ≤3 cm, including 24 MPAs, and compared their concordance with permanent sections. The sensitivities of the frozen sections for acinar, lepidic, papillary, solid, and MPPs were 90%, 75%, 70%, 69%, and 37%, respectively.[102] Trejo et al have also reported a lower consistency between intraoperative frozen sections and permanent sections in MPA compared with other histological patterns in stage I lung ADC.[103] Therefore, at present, permanent sections, as a postoperative diagnosis, are the only reliable method to identify the presence of MPP, rather than preoperative imaging, small biopsies, and cytology or frozen sections during an operation.[31,104]

Influences on medical treatment

Tumor recurrence after resection is still the primary reason leading to therapeutic failure. Chemotherapy, aside from surgery, is an indispensable part of the treatment of lung cancer, especially adjuvant chemotherapy for stage II–IIIA NSCLC,[105] but to date, the role of adjuvant chemotherapy in stage IB NSCLC has been controversial.[106] Xu et al have studied prognostic factors in patients with completely resected lung ADC in stage IB. They found that histologic subtypes had a prognostic value in this cohort, but MPP was only a prognostic factor for PFS in univariate analysis rather than multivariate analysis.[107] Tsao et al have designed a study on the predictive value of predominant histological patterns in lung ADC in stages I–III regarding survival benefitting from adjuvant chemotherapy. They reclassified micropapillary- and solid-predominant ADC as one group and found that this group benefitted from chemotherapy in both DFS (HR=0.60, 95% CI=0.44–0.82, P=0.001) and OS (HR=0.71, 95% CI=0.51–0.99, P=0.04) compared with other predominant histological patterns in multivariable

analyses. Additionally, they investigated the predictive value of histological subtypes for chemotherapy response among different stages but found no statistical significance, although micropapillary- and solid-predominant ADCs in stages II and III rather than stage I had a tendency to respond better to chemotherapy than did the other subtypes presented.[108] This study may indicate that MPP is sensitive to chemotherapy. As with adjuvant radiotherapy, Hung et al have shown that MPA could not improve the prognosis of adjuvant radiotherapy for stages I–III.[9] In terms of the selection of chemotherapy regimens, Campos-Parra et al have demonstrated that MPA responded better than intermediate-grade ADC including lepidic- and acinar-predominant ADC, as demonstrated by the response rate (36.9% vs 25.4%, P=0.034, respectively) and PFS (6.4 vs 5.5 months, P=0.009, respectively) after platinum-based chemotherapy in stages IIIB–IV; however, they lacked comparisons among different chemotherapy regimens in the cohort of MPA.[95]

Conclusion and future prospects

In conclusion, according to published studies, MPP in lung ADC has presented special clinical impacts, in particular, its influence on survival. However, numerous problems remain unaddressed. First, the diagnosis of MPP, whether preoperation, intraoperation, or postoperation, encounter challenges, especially in advanced-stage ADC, accounting for a lack of resection samples. More studies of molecular biomarkers and radiological findings are needed to identify MPP from other subtypes to stratify the prognosis of MPPAC. Experienced pathologists as well as specific and sensitive detection methods are required. The prognostic value of MPP needs to be elucidated clearly, including the associations between prognosis and the percentage of MPP and the status of MPP in the entire tumor (predominant or not) and tumor node metastasis stage. The mechanism of its aggressive biological behavior requires further elucidation, and the therapeutic response of MPP poses a problem because it influences the choice of operation and the postoperative management. There is a lack of reliable evidence to clarify the necessity of adjuvant chemotherapy for early-stage MPPAC, especially stage IB MPPAC. Last, given that recent studies have mostly been conducted in small populations, large-sample studies are needed that can comprehensively reveal the clinical features of MPP so that decisions about clinical management can be made.

Disclosure

The authors report no conflicts of interest in this work.

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