Quest Journals
Journal of Medical and Dental Science Research
Volume 8~ Issue 6 (2021) pp: 33-45
ISSN(Online) : 2394-076X ISSN (Print):2394-0751
www.questjournals.org

Research Paper

Myths and facts behind invasive mucinous adenocarcinoma: A narrative review

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ABSTRACT: *Invasive mucinous adenocarcinoma (IMA) is a sub-type and rare variant of lung adenocarcinoma. It usually occurs in 60+ aged patients presenting with vague respiratory symptoms. The extra-thoracic and lymph node metastasis are very rare here. However, the inter-lobar and lung to lung metastases are quite common. IMA differs immunohistochemically from Invasive non-mucinous adenocarcinoma (INMA) and other lung cancers. KRAS (Kirsten rat sarcoma viral oncogene homolog) mutation occurs frequently in IMAs while EGFR (Epidermal growth factor receptor) mutation being rare. It has a more predilection for the lower lung lobe unilaterally or bilaterally. The CT findings of lung IMAs can be fluctuating and unclear. Hence, the diagnosis of IMAs is difficult and often delayed. Due to its low incidence and multiple studies in a small cohort, the appropriate treatment approach and survival data available for the IMA is less and often contradictory. Surgical resection is the conventional treatment option for IMAs but still, several contradictions are there about it. In our review, the diagnosis of IMA is solely based on IASLC/ERS/ATS 2011 published report. The present study is aimed to provide a detailed fact about IMAs including their clinicopathological, radiological, genomic factor, definitive diagnosis at an early stage, treatment protocol, and their prognostic outcome.*

KEYWORDS: *Lung Cancer, Invasive Mucinous Adenocarcinoma, Mucinous Bronchoalveolar Carcinoma, Epidemiology, CT Features, Treatment Strategy, Prognostic Outcomes*

Received 03 June, 2021; Revised: 15 June, 2021; Accepted 17 June, 2021 © The author(s) 2021. Published with open access at www.questjournals.org

I. INTRODUCTION

Lung cancer is the most common cause of cancer-related deaths worldwide after prostate cancer in males and breast cancer in females [1]. More than 80% of all lung cancers include non-small cell lung cancer, among which adenocarcinoma being its most common histologic type [2]. In 2011, A new classification for lung adenocarcinoma was proposed by an international multidisciplinary expert panel 0f The International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society and stated invasive mucinous adenocarcinomas (IMAs) as distinct variants of invasive ADCs [2-4] and placed it into a separate category. Later on, in 2015 World Health Organization also accepted the 2011 statement given by various organizations. IMAs were formerly known as mucinous bronchoalveolar carcinoma and accounts for 2-5% of lung invasive adenocarcinomas (ADCs) cases [2]. Although IMAs have a relatively low incidence rate, several past studies have demonstrated the unique characteristics of IMAs that can show significant differences from other lung ADCs in terms of clinical, radiologic, pathologic, genomic, treatment, and prognostic aspects [5-11].

Histopathologically, IMAs show tumor cells having goblet or columnar cell structures with basally located nuclei and abundant intracytoplasmic mucin [4]. Based on the percentage of mucin present, IMAs can be divided into the pure mucinous pattern (>90% pure mucinous pattern/ lipidic pattern) and mixed mucinous / non-mucinous pattern (≥10% of a non-mucinous invasive component) [2]. Apart from this, multiple other growth patterns are also seen in IMAs such as acinar, papillary, micropapillary, lipidic, and solitary. The Lipidic pattern being the most commonly observed one. H. Ichinokawa et al. reported that aerogenous spread and satellite tumors surrounding the main lesion frequently occur in a patient with IMAs [12].

IMAs are rare compared with other lung cancers but also knowledge about their radiological findings is extremely important because of poor survival and high mortality rate. Computed Tomography (CT) has always been the first line of investigation for diagnosis and routine follow-up for IMAs although the 100% confirm diagnosis could not be assured without histopathology or biopsy (invasive procedures). However for screening purpose, early detection of tumor and treatment guidance, CT might play a major role which can't be refused.

IMAs have a distinct genetic profile compared with other non-mucinous adenocarcinomas [2, 6, 7, 13-15] which might be becoming a burden for thoracic surgeons to go with conventional treatment protocols that they have adopted for other lungs ADCs. While going through various past research papers, we have come up to know that the combined effect of clinicopathological, radiological, genomic, and treatment strategy influence the prognostic outcome of a patient with IMAs and we had tried to sort out all these problems.

Here, we report our review to clarify the correlation between clinicopathological, radiological, and genomic factors to establish a definitive diagnosis, guide the treatment protocol, and assess the prognostic outcomes of IMAs.

II. EPIDEMIOLOGICAL AND CLINICAL CHARACTERISTICS OF IMAS

IMAs have been placed in a separate category since 2011 but still, limited information is available about them, it might be due to their rarity, past studies in a small cohort (so unreliable result), and its features mimicking with other lung diseases. Because of all these problems, its diagnosis is always delayed and overall survival is poor.

Nowadays, Researchers are more interested in IMA as its incidence is known to be rising [15]. The patients with IMAs are usually old-aged females presenting with vague signs and symptoms like progressive cough with expectoration, dyspnoea, anorexia, chest pain, etc.

In a study of 68 IMA patients including 41(60.3%) females and 27(39.7%) males with a median age of 61years, Nie et al. found that none of the patients in his study showed any specific symptoms. 18 of 68 patients had coughed out white sputum, 6 patients have symptoms of pneumonia while the rest are asymptomatic [16]. Similarly, J.W. Beom and J.H. Lee et al. also reported a case of a 64year old female with IMA misdiagnosing as a case of chronic eosinophilic pneumonia [17] due to vague complaints mimicking with other lung diseases. Nie et al. also found that only 29.4% of patients with IMA in their study was a smoker. The above study was also supported by Watanabe et al., H. Ichinokawa et al., Lee et al., Cha et al, and Shim et al. [9,12,18,19,31] literature. Therefore, we conclude that IMAs usually occur in 60+ age people with female predominant and the correlation between smoking and IMA remains insignificant. Table.1 explains the above scenarios in detail.

Meanwhile, Boland et al. [20] conducted a study and reported that the overall survival (OS) and progression-free survival (PFS) were worst among smokers than do non-smokers with IMAs. Hence after going through his study, the correlation between smoking and IMA needs to be further investigated using a large sample size.

Table 1: A comparative study about clinical characteristics of IMAs by different researchers-

Study by	**Nie et al.**	**Watanabe et al.**	**H.Ichinokawa Et al.**	**Lee et al.**	**Cha et al.**	**Shim et al.**
Total no. of patients	68	40	45	81	35(excluding INMAs)	83(excluding non-mucinous)
Age	61(median, years)	68(mean)	<65years=19(42%) ≥65years=26(58%)	58.4±11.6(mean±$S.d$)	57.7±9.4($mean \pm s.d$)	62.2(mean,years)
Gender						
Male	27(39.7%)	11(27.5%)	19(42%)	36(44%)	13(37%)	36(43.4%)
Female	41(60.9%)	29(72.5%)	26(58%)	45(56%)	22(63%)	47(56.6%)
Smoking history						
Positive	20(29.4%)	11(27.5%)	S.I. <200=28(62%)	24(30%)	10(29%)	44(53%)
Negative	48(70.6%)	29(72.5%)	≥200=17(38%)	57(70%)	25(71%)	39(47%)
Symptoms						
Positive	24(35.3%)	9(22.5%)	-	-	-	-
Negative	44(64.7%)	31(77.5%)	-	-Type equation here.	-	-

Note- S.I.=Smoking Index

S.d.= Standard deviation

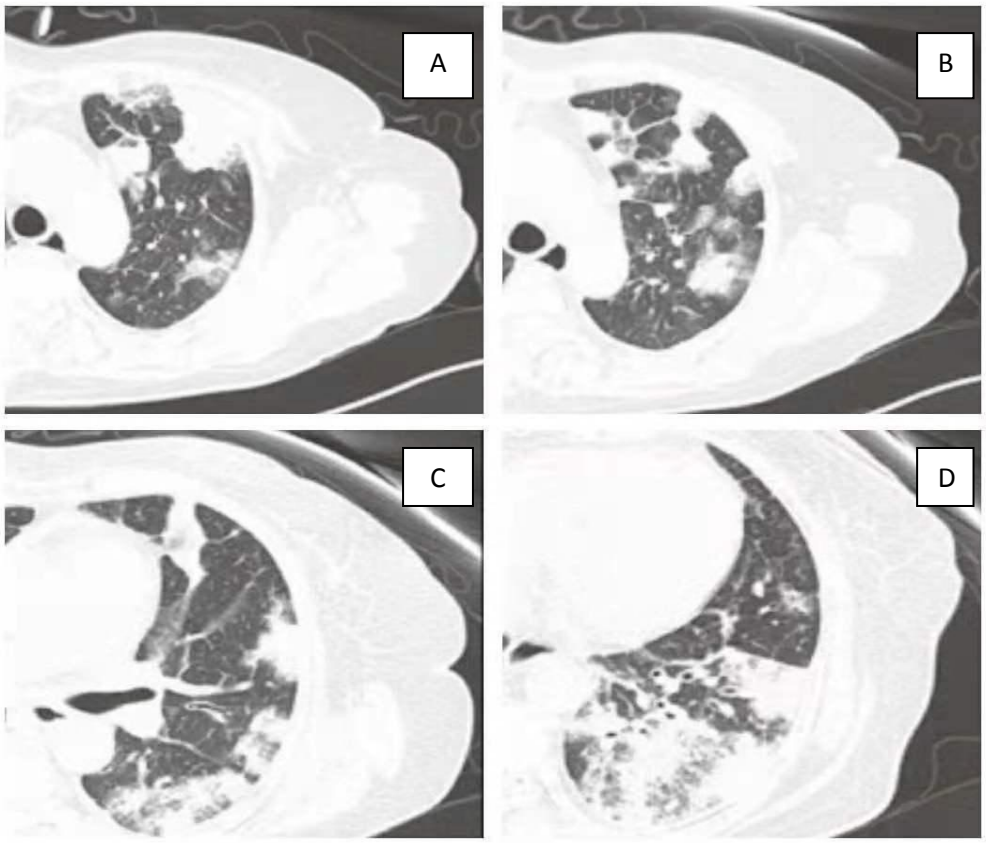

Figure 1: Axial chest CT scan of a 68-year-old female admitted to our hospital with vague signs and symptoms and misdiagnosed as a case of chronic eosinophilic pneumonia. Later on, a biopsy confirmed it as a case of IMA. CT Chest of the same patient demonstrates lobular consolidation and ground-glass attenuation with a crazy-paving pattern in both lung fields (A-D). (D) Dense consolidation in the left lower lobe.

III. HISTOPATHOLOGY AND IMMUNOHISTOCHEMICAL FEATURES OF IMAS

According to the 2011 classification system, IMAs are histopathologically characterized by goblet and/or columnar tumor cells with abundant intracytoplasmic mucin and small basally situated nuclei [4] (figure 2). IMAs usually show inconspicuous or absent cytologic atypia, hence the confirmatory diagnosis of malignancy is frequently challenging via biopsy. IMAs tend to present with multi-centric, multi-lobar, and bilateral lung involvement [4] which maybe because of the frequent a erogenous spread of tumor cells. It has more predilection for peripheral lower lung lobe involvement [21] and is often observed with segmental or lobular consolidation along with solid or sub-solid nodules or masses, and bronchial aeration [2].

Cystic presentation of IMA is rare. However, Masuzawa et al. [22] reported a case of a 75-year- old male who underwent a bronchoscopy biopsy and was pathologically diagnosed as a case of IMA, with radiologically demonstrating irregular large cystic lesions. IMAs during early stages are easily misdiagnosed as other lung diseases and confirmatory diagnosis of malignancy via any biopsies is often challenging. This is because of mainly two reasons- one is its location (peripheral lower lobe situation) and the other is the alveolar cavity surrounding the tumor is usually filled with mucin. However, CT-guided lung biopsies may be somewhat helpful for reaching a diagnosis but the best being the histological evaluation of surgically resected gross specimens.

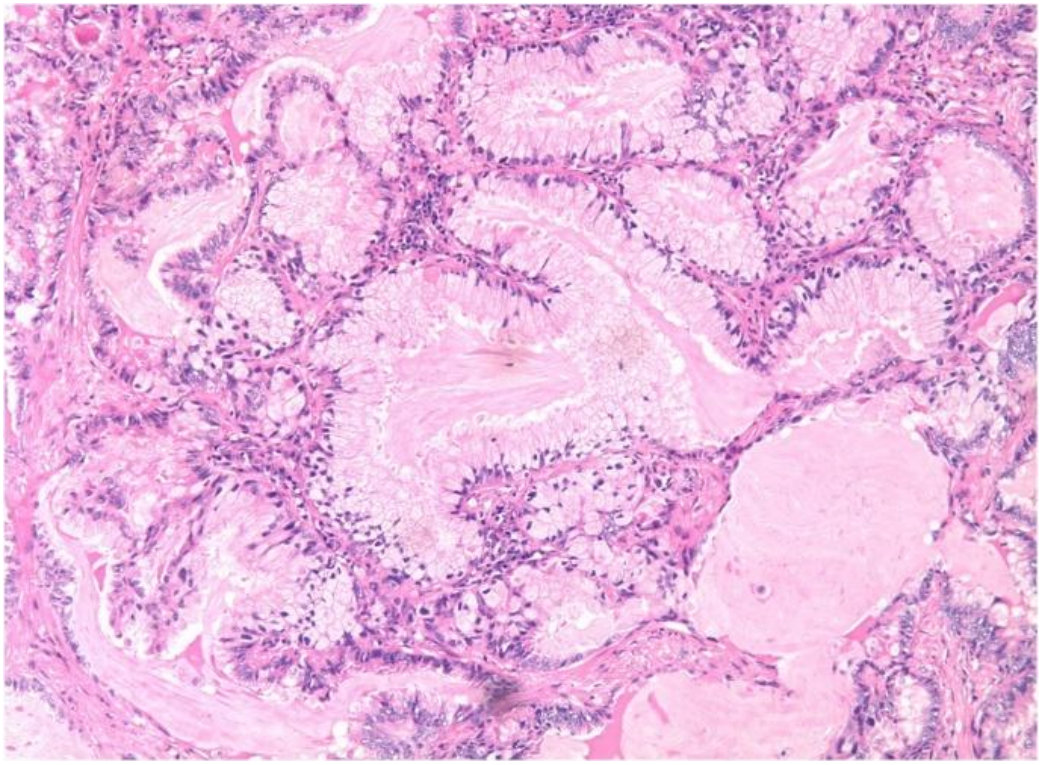

Figure 2: A microscopic specimen of invasive mucinous adenocarcinoma (IMA) demonstrating goblet or columnar cell morphology with abundant intracytoplasmic mucin and basally situated nuclei, a characteristic feature of IMA. (Hematoxylin and eosin stain, magnification ×100).

Lung IMA expresses different immunohistochemical expression than do INMA. IMAs typically express Cytokeratin7 (CK7) and cytokeratin20 (CK20) expression [23-26]. The expression levels of thyroid transcription factor-1 (TTF-1) and novel aspartic proteinase of the pepsin family A (Napsin A) are lower in IMA compared to INMA, this is due to their different cellular lineages. TTF-1 is expressed in about 75-80% of lung adenocarcinomas, especially in terminal respiratory unit (TRU) morphology [26, 27] which comprises peripheral airway cells and small-sized bronchioles. Kunii et al. conducted a study and reported that most TTF- 1- negative pulmonary adenocarcinomas i.e. IMAs are mucinous lesions with the predominant expression of hepatocyte nuclear factor- 4α (HNF4α) and Mucin5AC (MUC5AC) [28, 29]. Such gene expression separates the IMAs from other lung adenocarcinomas. Hence, His study illustrates inverse correlation was confirmed between the expression of TTF- 1 and that of HNF4α and MUC5AC.

Goldstein NS and Thomas [23] MA conducted a study to compare the expression levels of TTF, CK7, CK20, and villin and concluded that the mucinous BACs are usually TTF and villin non-reactive and CK20 reactive. His study also stated that all the mucinous and nonmucinous BACs had strong CK7 reactivity in more than 50% of the neoplastic cells. However, the evaluation of TTF-1 and CK20 expression may have little diagnostic value in the context of identifying mucinous BACs and extrapulmonary mucinous tumor metastasis in the lungs [24].

IV. RADIOLOGICAL FEATURES OF IMAS

The CT appearance of lung IMA varies widely from ground-glass opacities and consolidation to solid and sub-solid nodules and masses [30]. Both unifocal and multifocal forms of the disease show a peripherally distributed lower lobe predominance of varying size lesions. Based on CT attenuation, Shimizu et al. [31-33]divided IMAs into 3 sub-groups-1) Solitary type, in which shadows represented solitary nodules or masses; 2)Bubbling type, in which shadows represented bubble like a shadow; and 3)Pneumonic type, in which shadows represented consolidation with or without air bronchograms. (figure 3). Because of these subtypes, it becomes somewhat difficult to distinguish IMAs from other lung diseases such as interstitial pneumonia, tuberculosis, and metastatic lung cancer. Of these three sub-types, the pneumonic type was associated with a high proportion of signs and symptoms and a higher pathological stage because of its large tumor size, and bubbling type was associated with a lower maximal standardized uptake value (SUV max) on fluorodeoxyglucose-positron emission tomography [31-33]. He also reported a high rate of recurrence and intrathoracic metastases with

pneumonic type IMAs, it might be due to aerogenous spread. No extrathoracic metastases of IMAs were reported in his study. Compared with solid and bubbling type, the pneumonic type IMAs had a significantly poor 5- year recurrence-free survival (RFS) (P=0.018).

In 2016, Lee et al. [9] also conducted a study on 81 IMA patients and found that the tumors in consolidative type IMAs (mean diameter 62mm) were large as compared to nodular type (mean diameter 28mm). The SUV max of tumors with a consolidative type was significantly higher than the nodular type tumors (P=0.033). He also reported that the nodular type IMAs have relatively better 5-year disease-free survival (DFS) and overall survival (OS) as compared to consolidative type, it might be due to small tumor size. Hence, we conclude that his study findings support the study done by Shimizu et al.

Miyamoto et al. [34] illustrated the CT findings of IMAs in his study as vaguely outlined or lobular-bounded tumor margins with CT attenuation of mixed ground-glass opacity and consolidation associated with or without air bronchogram bubble-like low attenuation. These findings were significantly more common in patients with pneumonic type IMAs than any other ADCs. He also found an enlarged cystic lesion within the tumor pre-surgery though it's rare (figure 4). Therefore, we conclude without a biopsy, confirmatory diagnosis can't be reached as the CT attenuation of the tumor varies too much and mimics are also common here.

Few past studies revealed that solitary type IMAs are more common than pneumonic type [35]. However, despite a large number of the solitary pulmonary nodule (SPN)-type IMA cases but still, very little information is available in past literature. In a study by Chang et al. [36], IMAs showed significantly low SUVs compared to other lung carcinomas. Cha et al. [19] also conducted a study and proposed a new diagnostic idea suggesting that the identification of the absence of Morphologic-Metabolic (M-M) dissociation sign is an accurate indication to exclude IMA from other SPN-type lungs ADCs. The specificity of this sign in discriminating SPN-type IMA from invasive non-mucinous ADCs was 89.7% which was better than that of CT (53.8%) or PET/CT (51.7%) alone.

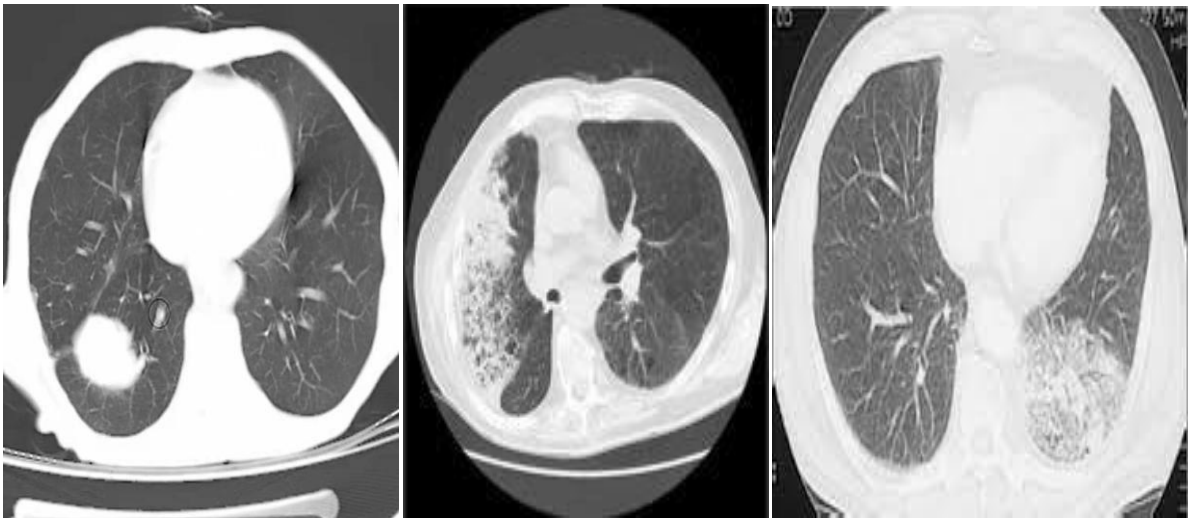

Figure 3: Axial chest CT findings of lung invasive mucinous adenocarcinoma demonstrating
A. Solitary/Solid type
B. Bubbling type and
C. Pneumonic type

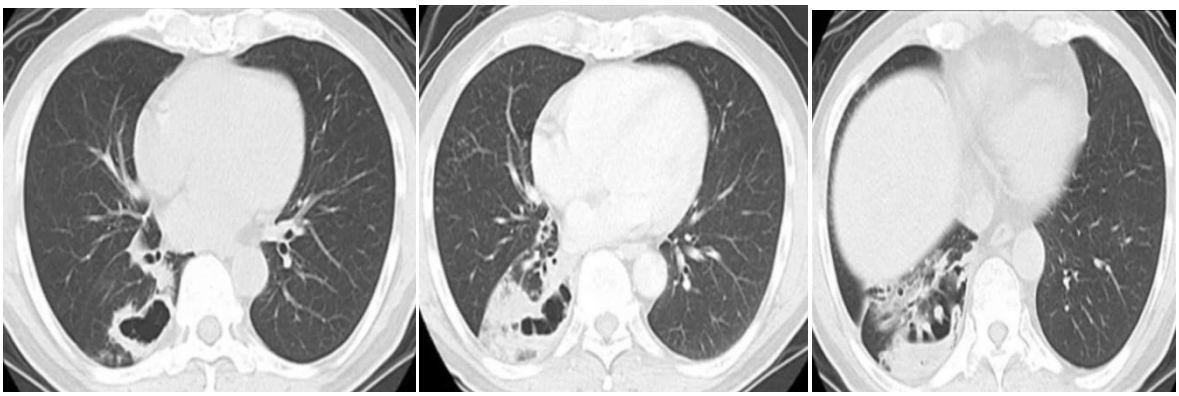

Figure 4: Axial chest CT of a 75-year-old man with IMA presenting as a large, irregularly shaped cystic lesion in the right lower lung lobe admixed with GGO.

V. GENOMICS OF IMAS

Multiple genetic abnormalities in IMA have recently been discovered including mutations in Kirsten Rat Sarcoma (KRAS), v-RAF, murine sarcoma viral oncogene homolog B1(BRAF), v-erb-b2 erythroblastic leukemia viral oncogene homolog 2(ERBB2), phosphatidylinositol-3 kinase catalytic alpha (PIK3CA), Neuregulin 1(NRG1), neurotrophic tyrosine kinase receptor type 1(NTRK1), Anaplastic lymphoma kinase(ALK), rearranged during transfection(RET), v-erb-a erythroblastic leukemia viral oncogene homolog4(ERBB4) rearrangements, and tumor protein 53(TP53)(18,37). Among all, KRAS is the most common oncogenic driver mutation occurring in IMAs while NRG1, NTRK1, ALK, RET, ERBB4, and TP53 were rare [18, 37]. The KRAS mutation found in IMAs differs from INMAs. G12D and G12V are the common types of KRAS mutation found in lung IMAs which are also commonly seen in colorectal and pancreaticobiliary carcinomas, suggesting that lung IMA may be biologically more similar to pancreaticobiliary and intestinal tract cancers while INMAs possess G12C(18).

Tsuta et al. [38] investigated 904 post-operative lung adenocarcinoma patients retrospectively and demonstrated that KRAS mutation was the most common mutation seen in IMA patients as compared to other subtypes of lung adenocarcinoma. Similarly, a retrospective study by Kadota et al. [7] also illustrated that the incidence of KRAS mutation in patients with simple IMA was considerably higher than the mixed IMA. KRAS point mutations (G-A) are more frequently seen in IMA patients compared to G-T or G-C substitutions. Meng et al[39], investigated the correlation between KRAS mutations and overall survival (OS) in 6,939 NSCLC patients and found that OS in patients with early and mid-stage lung adenocarcinoma with KRAS mutation were significantly lower. Hence, KRAS mutations may be linked to a bad outcome in IMA patients.

Several past studies have shown that Non-mucinous ADC has a higher EGFR mutation rate though they are rare in IMA [6, 18, 37, 40]. EGFR mutations are detected in 20% to 50% of lung adenocarcinomas while KRAS mutations are detected in only 10% to 40% [41-45]. The presence of EGFR mutations influences the decision-making regarding the use/not-use of EGFR tyrosine kinase inhibitors (TKIs) in the treatment protocol. Such mutations are most frequently observed in Asian non-smoker female patients suffering from adenocarcinomas[46-50]. Few past reports had indicated that EGFR mutation is associated with lipidic-pattern lung adenocarcinoma(i.e.BAC) and this has led to the hypothesis that tumors with lepidic (formerly BAC) patterns may be associated with EGFR mutation and that lepidic pattern may predict responses to TKIs [51-53]. Kadota et al. [7] evaluated associations between mutations and histologic patterns of mucin in lung adenocarcinoma of 864 patients of which 127 tumors (15%) had EGFR mutations, and 228 (26%) had KRAS mutations and found that none of the mucinous subtype tumors have EGFR mutations. Hence, Invasive mucinous subtype lung cancers were found to have a stronger link to KRAS mutation than EGFR mutation. Among invasive mucinous adenocarcinomas, pure mucinous tumors were significantly more likely to have KRAS mutations, compared with mixed mucinous/ nonmucinous tumors. As said before, Kadota et al. also found that tumors in the lepidic predominant group were more likely to have EGFR mutations, compared to tumors with the other predominant subtypes.

Compared to tumors without extracellular mucin, tumors with extra-cellular mucin were more likely to have KRAS mutations. More interestingly, KRAS mutations were significantly more frequently detected in pure invasive mucinous adenocarcinomas (85%) than in mixed mucinous/ nonmucinous tumors (31%). This finding supports the practical value of sub-classifying invasive mucinous adenocarcinoma as either pure mucinous or mixed mucinous/ nonmucinous.

In IMA patients, ALK rearrangements have also been reported. It is more prevalent in micropapillary–predominant adenocarcinomas (MPAs) and 2.2% of IMAs. Promising results have been obtained among NSCLC patients harboring ALK rearrangements treated with PF02341066, an oral ALK inhibitor, indicating that ALK represents a new therapeutic target in this molecularly defined subset of NSCLC (54).

Recently, aside from KRAS and ALK rearrangements, several recurrent NRG1 fusions have been identified in lung adenocarcinomas and they are considered as novel driver mutations, where the 3'-gene NRG1 gets fused to various 5'-partners, especially CD74. Its association with mucinous had also been noted in various studies. Hence, NRG1 fusions are considered novel and promising molecular targets for IMA [55-57]. In past literature, The estimated frequencies of these fusions are approximately 7–27% [55-57]. Several NRG1 gene fusions observed in IMA patients include CD74 (the most common), SLC3A2, VAMP2, RBPMS, and SDC4. NRG1 fusions are most mutually exclusive with KRAS mutations. NRG1 is a glycoprotein in the neuregulin family that acts on the EGFR family of receptors and with the NEU/ERBB2 receptor tyrosine kinase to increase its phosphorylation on tyrosine residues. NRG1 fusion leads to continual activation of the human epidermal growth factor receptor-2 (HER2) and human epidermal growth factor receptor-4 (HER4) signaling pathways which lead to uncontrolled cell proliferation and tumorigenesis [58].

In research, Fernandez-Cuesta et al. [59] sequenced the transcriptomes of 25 nonsmokers with KRAS and EGFR gene-negative lung adenocarcinomas. Among them Fifteen of the individuals were diagnosed with IMA and were also found to be negative for the following gene mutations; KRAS, EGFR, ALK, ROS1, RET, BRAF, and Her2. RT-PCR revealed that CD74- NRG1 fusions were present in only four of those 15patients (27%) and Interestingly, those four patients were Asian. This suggests that CD74-NRG1 fusions appear to be mutually exclusive to known oncogenic mutations, including EGFR/KRAS/BRAF/ERBB2/ALK/ ROS1. The author also demonstrated that CD74-NRG1 signaled through ERBB2-ERBB3 heterodimers to activate the PI3K/ AKT pathway to induce oncogenic growth. Hence, CD74- NRG1 fusions may be a treatment option for IMA.This is based on several available drugs that target ERBB2, ERBB3, and their downstream pathways. Shin et al. [60] reported that in 59 patients with IMA, NRG1 fusions were observed only in 16 patients, with NRG1-SLC3A2 fusions accounting for 81.25% (13 patients), and CD74- NRG1 accounting for 18.75% (3 patients). Besides, 10 NRG1 fusions with KRAS mutations(62.5%) and 2 NRG1 fusions with NRAS Q61L mutations, EML4-ALK fusions were also observed. Survival analysis indicated that OS for IMA patients with NRG1-fusions was significantly worse compared to patients without NRG1 gene fusions.

VI. TREATMENT STRATEGY

Lots of research on IMAs had done to date and is continuing, but the treatment of IMAs is still contradictory. As a rare variant of lung adenocarcinoma, IMA is treated in the same way as other lung adenocarcinomas. So, while considering its appropriate treatment, the following key points should be kept in mind-

1. The size of the tumor
2. The location of tumor-multilobar/unilobar
3. Staging of the tumor at diagnosis/pre-operative
4. The mutations it contains
5. The metastasis -present/absent, intrathoracic/extrathoracic
6. The type of tumor present- solitary/pneumonic (consolidative)/GGO
7. The patient pulmonary function- good or poor physiologic respiratory reserve.

Surgery is the conventional treatment option for IMA except for patients with stage IIIB, IV[61], and large size advanced stage tumor detection with poor physiologic respiratory reserve at initial diagnosis (see table 2). So, in such cases, pharmacological agents need to be prescribed. The pharmacological agents are based on mutations that the tumor harbor.

EGFR-TKIs is considered as the first-line therapy for EGFR mutated advance stage lung adenocarcinomas [62-66] and has also demonstrated a significant survival benefit over platinum-based chemotherapy. It is mainly used for the treatment of INMAs as IMAs rarely contain EGFR mutation. Hence, the data for the efficacy of EGFR-TKIs (gefitinib, erlotinib, Afatinib) in patients with IMA is limited. IMA is strongly correlated with KRAS mutation and almost entirely lacks EGFR mutations. Hence, several past literatures has mentioned that mutant KRAS can be targeted for therapeutic intervention.

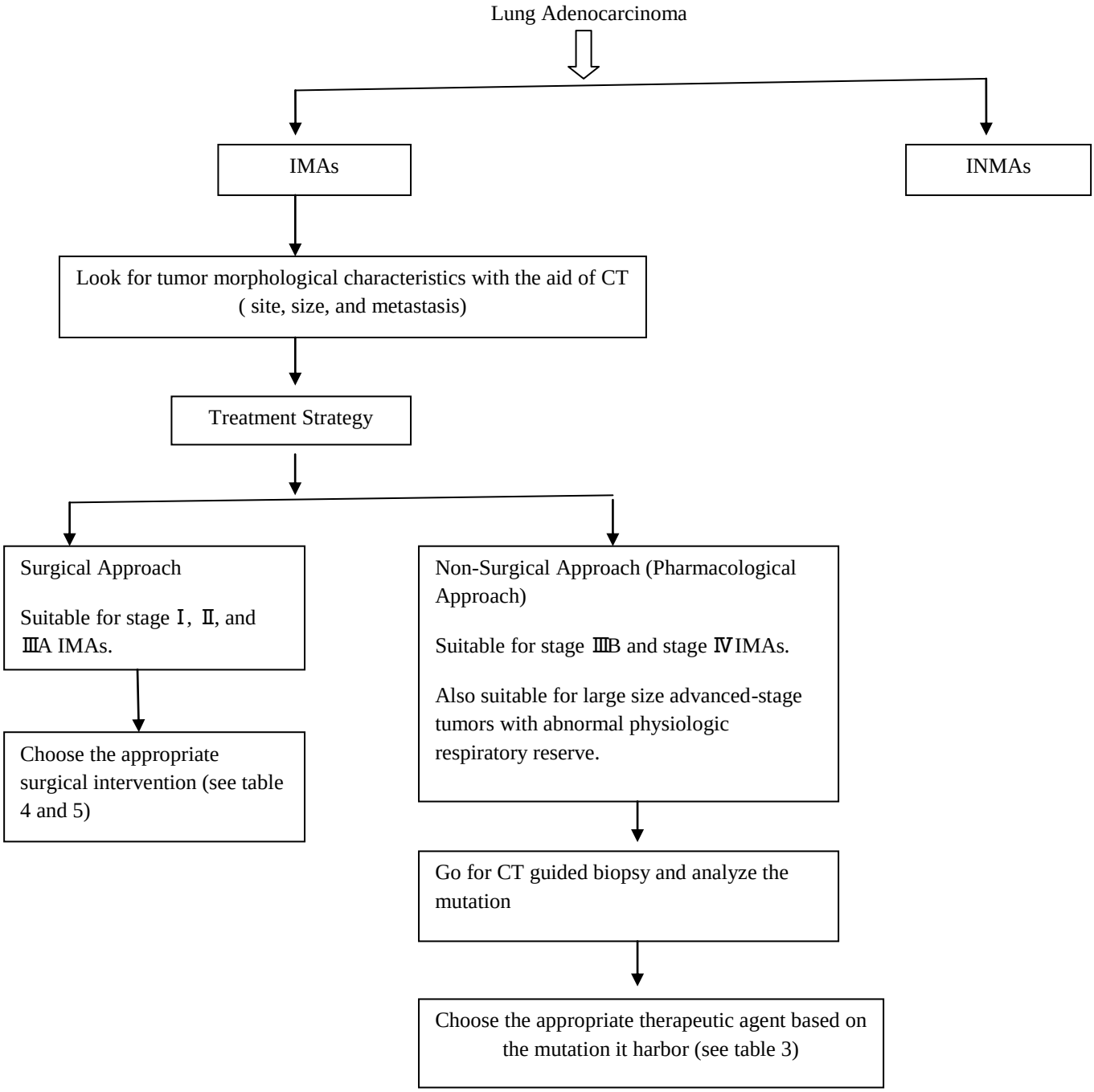

Table 2: Roadmap for treatment of IMAs.

Ku et al. [63] reported that sterminib (AZD6244) combined with BYL719 could improve the treatment efficacy for KRAS mutant NSCLC. However, it has not been used in clinical practice to date.

Lung adenocarcinoma harboring ALK rearrangements have been demonstrated to be benefitted from ALK inhibitors, hence its efficacy for IMA patients harboring ALK rearrangements is worth being investigated.

Shimizu et al. [67] carried a study including 605(including 29 patients with IMAs) primary lung cancer patients who underwent surgical resection and reported that IMAs might be susceptible to cisplatin or pemetrexed, but not to gemcitabine or taxane. In 2015, Nivolumab, a new immunotherapy drug was approved by FDA for the treatment of lung cancers [68, 69]. Nivolumab was found to be associated with greater efficacy depending on the expression level of PD-L1 but IMAs specimen had low PD-L1. Hence, IMAs were found to be not susceptible to nivolumab [68, 69].

In a study of 72 IMA patients, Shim et al. [70] reported that with KRAS negative cases, several targetable gene fusions and mutations occur including CD74-NRGI, VAMP2-NRGI, TRIM4-BRAF, TPM3-NTRK1, and EML4-ALK gene fusions and ERBB2, BRAF, PIK3CA, and TP53 mutations. His study revealed that 63% of the total cases had KRAS mutations, which as thought were the most frequent variant observed while NRG1 fusions were the second most common and also stated that IMA patients with CD74-NRG1 may be treated by blocking ligand-receptor interactions or by inhibition of ERBB receptors which acts by ERBB2 and ERBB3 dimerization through activation of ERBB3 and PI3K-AKT signaling pathway by the CD74-NRG1 fusion protein. RAF or MEK inhibitors can also be used for cancer patients harboring BRAF fusion [71, 72], and for patients with *NTRK1* fusions, NTRK1 inhibitors [73] can be a therapeutic target. Table.3 explains the above scenarios in detail.

Mutations	Drug	Therapeutic effect
EGFR mutated advance stage Lung adenocarcinoma (mainly use for INMAs, rarely for IMAs)	EGFR-TKI inhibitors	Effective, need more clinical trial
KRAS mutated NSCLC (IMAs)	Sterminib(AZD6244)+BYL719	Effective in vivo
EGFR, HER2, and HER3 mutated NSCLC	Afatinib (EGFR-TKI)	Effective
Lung adenocarcinoma with NRG1 fusion	Afatinib	Case reports show effective
Lung adenocarcinoma harboring ALK rearrangements	ALK inhibitors	Effective, need more clinical trial
Lung caecinoma with high expression level of PD-L1	Nivolumab	FDA approved drug in 2015
IMA with CD74-NRG1	ERBB receptor inhibitors	Effective, need more clinical trial
Lung carcinoma with BRAF fusion	RAF or MEK Inhibitors	Effective
Lung cancer with ALK or ROS1 or NTRK1 fusions	NTRK1 inhibitors	Effective, need more clinical trial

Table 3: Treatment protocol for IMAs based on mutation

Surgery is the conventional treatment option for IMA patients practiced everywhere though several controversies are there regarding it. However, while planning curative surgery, it is very important to choose the appropriate type of surgery based on the type of tumor and the chest CT findings. Based on CT findings, IMA can appear as GGO, solitary or solid type, and pneumonic or consolidative type. As there are no specific guidelines on GGO, surgical interventions are often based on personal experience. Many surgeons believe that a GGO should be removed only when its size is increasing so follow-up is needed for this. Suzuki et al. [74] suggested that minimal invasive resection VATS should be considered for peripheral lung nodules with a large GGO which is not disappearing on follow-up and having a propensity to be carcinoma at the initial stage. Lobectomy is another treatment option for lung cancer but many surgeons prefer to perform minimally invasive surgery such as segmentectomy or wedge resection for GGO and solitary lung nodule or mass (see table 4).

Recently, The Fleischner Society[75], British Thoracic Society [76], and the Japan Clinical Oncology Group (JCOG)[77] have published some guidelines for the treatment of lung cancers. According to the JCOG strategy for lung cancer(solitary or solid type) with GGO, lobectomy should be considered for GGO greater than 3 cm, segmentectomy for GGO between 2 and 3 cm, and wedge resection for GGO smaller than 2 cm (see table 5). Surgery is appropriate for stage Ⅰ to stage ⅢA patients with IMA but not for stage ⅢB and stage Ⅳ patients [61]. Patients with pneumonic type IMAs should undergo lobectomy with lymph node dissection as the chances of aerogenous spread and recurrence are very high.

In a study of 29patients with IMAs, 10 of 29patients with pneumonic type underwent standard lobectomy, 5patients with solid or bubbling type underwent wedge resection due to poor respiratory function, and 9 patients underwent adjuvant chemotherapy who were pathologically diagnosed with large tumor size(>4cm) or lymph node metastasis. Shimizu et al. [33] reported 7 out of 10 patients with pneumonic type developed cancer recurrence after resection. Hence, A significant association between pneumonic-type IMA and a high rate of recurrence (60.0% v/s 10.0% for solid type and 0% for bubbling type) was seen in his study.

CT appearance of IMA	Surgical Intervention preferred
GGO	Lobectomy/ Segmentectomy/ Wedge resection based on site, size, and follow-up)
Solitary or Solid type	Lobectomy/ Segmentectomy/ Wedge resection (based on site and size)
Pneumonic or Consolidative type	Lobectomy with lymph node dissection

Table 4: Surgical interventions based on CT findings for IMAs

GGO	Type of surgery
>3cm	Lobectomy
Between 2-3cm	Segmentectomy
<2cm	Wedge resection

Table 5: JCOG strategy for lung cancer (solitary or solid type) with GGO

VII. PROGNOSIS OF IMA

Being a rare variant of mucinous adenocarcinoma, the available survival data for IMA is limited and often contradictory. In a study of post-operative 79 patients diagnosed with IMA and 269 patients diagnosed with INMA, Shim et al. [18] performed survival analysis and found that there was no significant difference noted in overall survival combining all the stages among patients of IMA and INMA. The overall 5-year survival rates for IMA and INMA were 71.7% and 67.2% respectively. Here, we conclude that 5-year survival rates for IMA were better than INMA. The study also reported that patients with mucinous tumors possess better recurrence-free survival as compared to non-mucinous ones. Meanwhile, Russell et al. [78] conducted a study and found that IMA was a subtype of lung adenocarcinoma with a poor prognosis which is contradictory to Shim's study.

Watanabe et al. [31] also conducted a study including 40 IMA patients who underwent surgical resection, among them 13 patients developed recurrences which include 3 patients with solitary type IMA and 10 with pneumonic type. All the recurrences were noted in the ipsilateral/contralateral lung. No lymph nodes and distant metastasis were noted in the study. Here, we found that the recurrences were more common in pneumonic type IMAs. The overall and relapse-free survival rates at 5-years were 83.3% and 88.8% respectively in patients with solitary-type tumors while 20% and 0% respectively in patients with pneumonic-type tumors. Hence, we concluded that the survival rate was significantly poorer in patients with pneumonic type tumors than in those with solitary type tumors. In another study comparing the survival rate between patients with solitary-type and those with pneumonic-type tumors, Nie et al. [17] found that the 5-year DFS rate for solitary type and pneumonic type was 67.4% and 0% respectively. Therefore, this study also showed that compared with solitary-type, pneumonic-type tumors had significantly poor DFS.

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