Prognostic factors of patients with pathologic stage I lung adenocarcinoma

Ying-Yi Chen, Tsai-Wang Huang

Division of Thoracic Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei

Correspondence to: Tsai-Wang Huang. Division of Thoracic Surgery, Department of Surgery, Tri-Service General Hospital, 325, Section 2, Cheng-Kung Road, Taipei. Email: chi-wang@yahoo.com.tw.

Introduction

Lung cancer remains one of the most common causes of cancer-related deaths worldwide. Increasingly more research is aimed at investigating the clinicopathologic parameters or gene mutations involved in the survival of patients with lung cancer. Although the 5-year survival rate of stage I non-small cell lung cancer (NSCLC) is between 68% and 92% (stage IA1 to IB) (1), there is still much scope for progress. In our previous study (2), we reviewed the predictors of postoperative recurrence in NSCLC and postulated that those results may help optimize patient selection for specified surveillance guidelines and personalized adjuvant therapies to prevent potential occult micrometastases. In Taiwan, lung adenocarcinoma is the most common histologic subtype (12,648/21,536, 58.73%) that had become more prevalent among non-smoking women (3). Moreover, predictors of postoperative outcomes in lung adenocarcinoma have been a popular investigatory target in recent years. Therefore, we used the search engine PubMed and reviewed papers about the risk factors of postoperative outcomes in patients with stage I lung adenocarcinoma (*Table 1*).

Risk factors of postoperative outcomes in pathologic stage I lung adenocarcinoma

We utilized key words such as "predictors" or "risk factors" and "stage I lung adenocarcinoma" in PubMed. Twenty-nine papers were found published between 1994 and 2017. Among these, 21 (72.41%) papers were published in the last 5 years and the patient populations of 22 studies were Asian. Therefore, an increasing number of patients with early-stage lung adenocarcinoma have been treated in the recent decades and therapeutic outcomes are still being investigated. The studies listed in *Table 1* provide a broad overview of the geographical distribution and high prevalence of lung adenocarcinoma in Asia.

Micropapillary components were thought as predictors of poor outcomes in patients with stage I lung adenocarcinoma in 4 studies (4-7). They have been proven to reflect an aggressive subtype of lung adenocarcinomas with poor prognosis (33-36). De Oliveira Duarte Achcar *et al.* (37) concluded that *K-ras*, *EGFR*, and *BRAF* mutations occur at increased frequencies in lung adenocarcinomas showing greater than 75% micropapillary growth. There is a close relationship between histology appearances and gene mutations. Other predictors for pathologic stage I lung adenocarcinoma are clinicopathologic parameters, such as tumor size (4,16), TNM stage (4,13), aerogenous spread (5,9), tumor differentiation (4), bronchial involvement (4), lymphovascular invasion (4,18,23,26), positive thyroid transcription factor-1 (TTF-1) expression (19,28), lepidic growth pattern (16), sex (16), age (22), tumor budding (14), pleural invasion (29), carcinoembryonic antigen levels (30), and standardized uptake value (SUV) index (<1.0) (25).

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Table 1 Comparison of prognostic factors for patients with stage I lung adenocarcinoma

References	Year	Prognostic factors for survival	Patients' distribution
Yang et al. (4)	2017	Tumor size, TNM stage, tumor differentiation, bronchial involvement, lymphovascular invasion, and micropapillary pattern	Asia (China)
Yi et al. (5)	2017	Aerogenous spread, micropapillary pattern	Asia (Korea)
Leeman et al. (6)	2017	Micropapillary and solid patterns	USA
Dai et al. (7)	2017	Lymph node micrometastasis with micropapillary component	Asia (China)
Sun et al. (8)	2016	BRCA1 and ERBB3	Asia (China)
Shiono et al. (9)	2016	Spread through air spaces	Asia (Japan)
Kadota et al. (10)	2016	KRAS mutation	USA
Enokida et al. (11)	2016	MDM2 protein	Asia (Japan)
Xu et al. (12)	2015	Increased nuclear CCND1	Asia (China)
Xu et al. (13)	2015	The new IASLC/ATS/ERS classification	Asia (China)
Kadota et al. (14)	2015	Tumor budding	USA
Kadota et al. (15)	2015	Tumoral CD10	USA
Yang et al. (16)	2014	Lepidic growth pattern, female sex, and tumor size ≤2 cm	Asia (China)
Noro et al. (17)	2013	Amplification of the ACTN4 gene	Asia (Japan)
Kaseda et al. (18)	2013	Histological vascular invasion	Asia (Japan)
Kadota et al. (19)	2013	Positive TTF-1 expression	USA
Akagi et al. (20)	2013	Combination of the four-gene (BRCA1, HIF1A, DLC1, XPO1) classifier with miRNA miR-21 expression	Asia (Japan)
Yamachi et al. (21)	2012	EGFR	Asia (Japan)
Ryu et al. (22)	2012	Age	Asia (Korea)
Kato et al. (23)	2012	Angiolymphatic invasion	Asia (Japan)
Ito et al. (24)	2012	Podoplanin-positive CAFs	Asia (Japan)
Shiono et al. (25)	2011	SUV index (<1.0), which was calculated as the ratio of tumor SUV(max) to liver SUV(mean)	Asia (Japan)
Funai et al. (26)	2011	Lymphatic vessel invasion	Asia (Japan)
Seki et al. (27)	2010	eIF4E and 4E-BP1	Asia (Japan)
Anagnostou et al. (28)	2009	TTF-1	USA
Mizino et al. (29)	2008	Pleural invasion	Asia (Japan)
Sakao et al. (30)	2004	Increased serum CEA	Asia (Japan)
Pelosi et al. (31)	2004	CD117 (c-kit)	Europe (Italy)
Isobe et al. (32)	1994	p53 and ras genes	Asia (Japan)

TNM, tumor–node–metastasis; BRCA, breast cancer susceptibility gene; ERBB, erythroblastic leukemia viral oncogene homolog; KRAS, kirsten-ras gene; MDM2, mouse double minute 2 homolog; CCND1, cyclin D1; ACTN4, actinin alpha 4; TTF-1, thyroid transcription factor-1; HIF1A, hypoxia inducible factor 1 alpha subunit; DLC1, deleted in liver cancer 1; XPO1, exportin 1; EGFR, epidermal growth factor receptor; CAF, cancer-associated fibroblast; SUV, standardized uptake value; eIF4E and 4E-BP1, eukaryotic initiation factor 4E and 4E binding protein 1; CEA, carcinoembryonic antigen; c-kit, stem cell growth factor receptor (proto-oncogene); p53, CG33336 gene product from transcript CG33336-RB.

Epigenetic factors or gene mutations involved with surgical outcomes of patients with stage I lung adenocarcinoma include *BRCAl* (8,20) and *ERBB3* (8), *K-ras* mutation (10,32), *HIF1A* (20), *DLC1* (20), *XPO1* (20), MDM2 protein (11), increased nuclear CCND1 (12), tumoral CD10 (15), *ACTN4* (17), *EGFR* (21), Podoplanin-positive CAFs (24), eukaryotic initiation factor 4E and 4E binding protein 1 (eIF4E and 4E-BP1) (27), CD117 (c-kit) (31), and *p53* expression (32).

Conclusions

The studies identified in this review concluded many different factors affecting surgical outcomes of patients with stage I lung adenocarcinoma. It is difficult to clarify why these predictors showed different results in various studies. Although there are too many confounding factors, such as patient selection criteria, surgical techniques, or other comorbidities, these pathways could be novel therapeutic strategies for lung adenocarcinoma and these predictors could help in selecting high-risk patients with stage I lung adenocarcinoma for adjuvant therapy, such as target therapy, chemotherapy, radiotherapy, or immunotherapy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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