Review Article

Prognostic impact of targetable genetic variants in resected adenocarcinoma of the lung: a narrative review and model proposal for precise evaluation

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Abstract: There has been much discussion regarding the impact targetable genetic variants on the prognosis of resected lung adenocarcinoma. With the discovery of new targetable genetic variants, genetic profiling is becoming more crucial in determining the treatment for advanced lung cancer. Targetable variants may also be important in resected cases because they can directly guide the drug indication in case of recurrence. Here, we have performed a literature review focusing on the prognostic impact of four clinically or potentially targetable major genetic variants (*EGFR/KRAS/BRAF* mutations and *ALK* fusion) in resected lung cancer. We found conflicting evidence from previous studies probably owing to the heterogeneity of the clinicopathological background. Most studies did not consider that the frequency of genetic variants depends on the pathologic stage (pStage) and the histological subtypes of adenocarcinoma, which are closely related to prognosis. The prognostic impact of genetic variants should not be discussed without considering the pStage and histological subtypes of adenocarcinoma. In addition, evaluating multiple genetic variants simultaneously is important to ensure that the impact of another variant is not overlooked. Thus, we have proposed a comparison model for precise estimation of the prognostic impact of targetable genetic variants and suggested an unfavorable comparison status. When discussing the prognostic impact of targetable genetic variants in resected lung adenocarcinoma, comprehensive genetic analysis and collection of a balanced number of cases should be conducted, and efforts to exclude the improper status should be made. In conclusion, targetable genetic variants are attractive prognostic predictors that can guide the choice of treatment after recurrence. However, their utility is limited or can be misinterpreted unless the pStage and histological subtype of adenocarcinoma are considered. Furthermore, the distribution of genetic variants vary among races, and studies set different endpoints such as overall survival, recurrence-free survival, recurrence-free interval. When discussing the prognostic impact of genetic variants in resected lung adenocarcinoma, we must consider the clinicopathological background including pStage, histological subtype, race, and evaluated endpoint.

Keywords: Genetic variant; lung adenocarcinoma; prognosis; surgery; staging

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Introduction

Targetable genetic variants have been discovered in non-small cell lung cancer (NSCLC), especially in adenocarcinoma. Newly developed drugs have more favorable results in adenocarcinoma treatment than the older ones. Targetable variants have become crucial

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for choosing treatment in advanced cases. In early-stage cases, surgery is the primary curative treatment, and the prognostic impact of targetable variants after resection remains controversial. Recently, ADAURA trial (NCT02511106), phase III, double-blind, randomized clinical trial estimating the utility of adjuvant osimertinib showed the promising results. Adjuvant osimertinib improved disease-free survival in resected stage IB, II, IIIA *EGFR*-mutant cases (1). Revealing prognostic implication of targetable variant and stratifying cases by the risk of recurrence or benefit by treatment will be more important. Herein, we review the literature concerning the prognostic impact of targetable genetic variants in resected lung cancer and propose a methodology for its precise evaluation. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/pcm-20-47).

Source and selection criteria

A review of literature through PubMed was conducted using the keywords "non-small cell lung cancer" or "lung adenocarcinoma" with a gene name with targetable variants. Literature estimating resected NSCLC was reviewed, and relevant material was explored individually through cross-references. Studies estimating non-resected or advanced lung cancer only were excluded from the review. This study focused on the gene variants that were druggable targets, such as *EGFR*/*BRAF* mutations and *ALK* fusion. The impact of *KRAS* mutation was also searched as a frequent and promising target variant.

Summary and interpretation

The manuscripts chosen for review are shown in *Table 1*. All studies included surgically treated adenocarcinoma cases. The studies already included in the meta-analysis are fundamentally excluded from *Table 1*.

Prognostic impact of EGFR mutation

Three systematic meta-analyses concluded with conflicting results. Two analyses concluded that the *EGFR* mutation has no significant impact on the prognosis of adenocarcinoma (2,5), while the other suggested that the *EGFR* mutation is related to better prognosis (18). Systematic meta-analyses reviewed the literature thoroughly, and therefore inevitably included limitations. Several studies analyzed early and advanced stage cases as well as the non-adenocarcinoma cases while some considered adenocarcinoma to be of a single histological phenotype. The controversy about the impact of *EGFR* mutations has continued even after these meta-analyses. Two studies with large sample sizes suggested that the *EGFR* mutation is related to a worse prognosis (3,7). Another study that included non-adenocarcinoma cases indicated that the impact of *EGFR* mutation is limited in stage IB, with no impact on stage 0–IA (24). As a strong influencing factor on prognosis, the tumor-node-metastasis (TNM) staging system and pathological classification have been revised. The subtypes of adenocarcinoma were proposed in 2011 (25), therefore literature published before 2011 could not distinguish the histological subtypes of adenocarcinoma. Recently, our group and another group demonstrated *EGFR* mutation status as a poor prognostic factor in resected lung cancer while taking into consideration the pStage, histological subtype, and/or radiological features (4,6,8). *EGFR* mutations are more frequently harbored in cases involving lepidic lesions (4,6-8,20,26), which are histological features related to better prognosis. Therefore, it is rational that the studies that did not account for the recurrence risk by histological subtypes of adenocarcinoma concluded that *EGFR* mutation is a favorable prognostic factor. The majority of the *EGFR*-mutated cases in these studies could have been harbored in cases completely or almost free from relapse, such as adenocarcinoma *in situ* (AIS), minimally invasive adenocarcinoma (MIA), or lepidic predominant cases. Although quantitative estimation of histological components is highly recommended in resected cases (25), most studies only evaluated the pStage and not the histological subtypes of adenocarcinoma. Currently, there is no evidence regarding whether pStage or histological subtype is more important in invasive lung adenocarcinoma cases. More studies considering the pStage and the recurrence risk based on the histological subtypes of adenocarcinoma are warranted for precise estimation of the prognostic impact of genetic variants.

Prognostic impact of KRAS mutation

A systematic meta-analysis concluded that *KRAS* mutations are associated with worse overall survival (OS), especially in adenocarcinoma and early-stage cases (9). Another meta-analysis concluded similar results (18). Most studies published later also reported *KRAS* mutation status to be related to worse prognosis even when evaluated with

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Table 1 Summary of reviewed articles about the prognostic impact of targetable genetic variants

Analyzed gene	Author [year]	Number of analyzed cases (% of variant cases)	pStage (TNM edition)	Prognostic impact of genetic variant	Reference
EGFR	Zhang [2014]†	3,337 (12.2–52.5)	I–IIIA (–)	No significance on OS and DFS	(2)
	Takamochi [2017]	741 (47.2)	I (IASLC, 7th)	longer OS	(3)
	Ito [2018]	279 (47.0)	pN0, IA1–IIA (IASLC, 8th)	Shorter RFI	(4)
	He [2019]†	4,872 (42.8)	I–IIIA (–)	No significance on DFS	(5)
	Ito [2020]	664 (48.9)	≤5 cm, pN0–1, IA1–IIIA (IASLC, 8th)	Shorter RFS	(6)
	Suda [2020]	5,780 (41.7)	I–IV (–)	Better RFS and OS	(7)
	Deng [2020]	1,249 (62.4)	I–III (unknown, 8th)	Worse RFS in radiological solid, Pap/Aci/IMA, or stage II–III	(8)
KRAS	Meng [2013]‡	6,939 (4.5–36.4)	I–V (–)	Poorer prognostic status in adenocarcinoma, stage I, or stage I–IIIA	(9)
	Ma [2020]	1,181 (9.3)	I–III (unknown, 8th)	Poorer RFS and OS in part-solid or stage I	(10)
ALK	Fukui [2012]	720 (3.9)	IA–IV (unknown)	No significance in DFS and OS	(11)
	Blackhall [2014]	1,281 (2.2–6.2)	I–III (unknown)	Significantly better OS, no significance about RFS	(12)
	Gao [2017]	534 (7.9)	I–III (unknown)	Shorter DFS, TSS, OS	(13)
	Shin [2018]	309 (7.4)	IA (AJCC, 7th)	Lower DFS	(14)
	Liu [2019]	81 (3.9)	I–IIIA (unknown, 8th)	No significance in DFS and OS, but higher risk of liver recurrence	(15)
EGFR/*KRAS*	Ohba [2014]	354 (41.1/6.4)	I (unknown)	Shorter DFS and OS in KRAS (+)	(16)
	Izar [2014]	312 (19.6/40.7)	I (AJCC, 7th)	Worse DFS and OS in KRAS (+)	(17)
	Zhang [2018]§	10,869 (33.6/15.5)	I–V (–)	Prolonged DFS and OS in EGFR (+), worse DFS and OS in KRAS (+)	(18)
EGFR/*KRAS*/*BRAF*	Marchetti [2011]	739 (11.6/27.5/4.9)	I–IV (unknown)	Shorter median DFS and OS in BRAF V600E (+)	(19)
	Kadota [2016]	482 (17.8/26.8/1.7)	I–II (AJCC, 7th)	Worse OS in KRAS (+), tendency of better OS in EGFR (+)	(20)
	Kneuertz [2020]	324 (17.9/38.1/5.9)	IA–IIIB (AJCC, 8th)	Worse DFS and OS in KRAS (+) or BRAF (+)	(21)
EGFR/*KRAS*/*ALK*/*BRAF*	Ohba [2016]	256 (46.8/5.5/2.3/0.8)	I (unknown)	Worse DFS and OS in KRAS (+)	(22)
EGFR/*KRAS*/*ALK*	Chaft [2018]§	764 (33.4/62.8/3.8)	I–III (AJCC, 7th)	Worse RFS in ALK (+) than in EGFR (+)	(23)

†, meta-analysis; ‡, meta-analysis including non-resected cases; §, including non-adenocarcinoma cases. Aci, acinar predominant adenocarcinoma; AJCC, American Joint Committee on Cancer; DFS, disease-free survival; IASLC, International Association for the Study of Lung Cancer; IMA, invasive mucinous adenocarcinoma; OS, overall survival; Pap, papillary predominant adenocarcinoma; RFI, recurrence-free interval; RFS, recurrence-free survival.

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other variants (16-18,20-22). *KRAS* mutation is likely to be harbored in cases involving a solid component (10,26,27). Solid predominant subtypes are high malignant phenotype (28,29), and the presence of solid component is also an unfavorable feature in prognosis even when it is not predominant (30,31). Therefore, poorer prognosis in *KRAS* mutant cases might reflect high malignant behavior stemming from the solid component. The high frequency of *KRAS* mutations in cases involving solid components might be akin to the tendency of wild-type *KRAS* in cases without solid components, such as AIS/MIA/lepidic predominant subtypes. To precisely determine whether the prognostic value of *KRAS* mutant cases comes from the mutation itself or the solid component, the histological subtypes should also be distinguished.

Prognostic impact of ALK fusion or BRAF mutation

ALK fusion is likely to be harbored in younger and/or more advanced cases (11-14,23) and histologically related to solid predominant or invasive mucinous adenocarcinoma (12,13). *BRAF* mutations are associated with adenocarcinoma with micropapillary components (19,32). The problem concerning *ALK* fusion or *BRAF* mutation is the low prevalence in general. Most studies estimating the impact of *ALK* fusion or *BRAF* mutation alone or with other variations reported worse prognostic tendency in *ALK* or *BRAF* variant cases (13,14,19,23). However, due to the low frequency of the *ALK* fusion or *BRAF* mutation, more validation studies with larger sample sizes are warranted. Although the analysis using propensity score matching (PSM) might be a useful methodology, especially in rare variants, two studies that used PSM did not indicate significant results in disease-free survival (DFS) or recurrence-free survival (RFS) for *ALK* fusion (12,15).

Estimation of several genetic variants

Most studies evaluated a single gene and discussed the prognostic impact (*Table 1*). In general, studies evaluating several genetic variants simultaneously are more reliable than those that study single genes. A comparison of *EGFR*-mutant and *EGFR* wild type in mono-gene analysis is insufficient to estimate the impact of *EGFR* mutation. The 'wild type' may include *KRAS*-mutant, *BRAF*-mutant, *ALK*-rearrangement, and other targetable variants. Labeling cases not involving *EGFR* mutation as 'Wild type' is risky, as the effects of another variant may be overlooked.

EGFR mutations are one of the most frequent targetable variants. *KRAS* mutations have not been clinically targetable yet. However, *KRAS* mutation includes a promising druggable variant (33), and most studies concluded that *KRAS* mutation leads to worse prognostic status. Therefore, it might be better to evaluate the prognostic impact of genetic variants in multi-gene analysis, including at least *EGFR* and *KRAS* mutations.

Discussion

As a prognostic reflector, the TNM staging system is the gold standard. It covers all phases of tumorigenesis, from *in situ* to multiple distant metastases. Histological classification is another standard for predicting prognosis, especially in resected cases. As staging and pathological features can vary according to the timing of diagnosis, they can reflect prognosis in detail. On the other hand, the prognostic impact of genetic variants remains controversial. Compared to the TNM staging or pathological classification, evaluating genetic status is more challenging due to various factors, such as cost, wide variety of variants, different sensitivity of methodologies, the necessity for a larger sample volume. In individual cases, the genetic status is fundamentally unchanged by the timing of diagnosis and is labeled simply as positive or negative. It is the strength and weakness of genetic variants as prognostic factors; genetic status is objective and quantitative, but too simple to reflect the change in the malignant phase. Nevertheless, genetic variants have the advantage of being useful in the choice of treatment for adenocarcinoma in case of recurrence. It must be noted that the distribution of genetic variants can differ according to the stage and pathological features. Because staging and pathological diagnosis are rigid standards and reflect the disease prognosis more sensitively, the impact of genetic variants should be considered after estimating staging and pathological features. Even for the *KRAS* mutation, which is the most promising prognostic marker in genetic variants, one of the latest studies suggested that considering stage and clinicopathological features is crucial for its use as a prognostic predictor (10).

We propose a distribution model of *EGFR* and *KRAS* mutations according to the stage and pathological status (*Figure 1*). Based on this, we propose an ideal methodology for estimating the prognostic impact of genetic variants by considering histological variants. Briefly, the stage and histological subtype should be matched, and several variants should be estimated (*Figure 2A*). However, it is not easy

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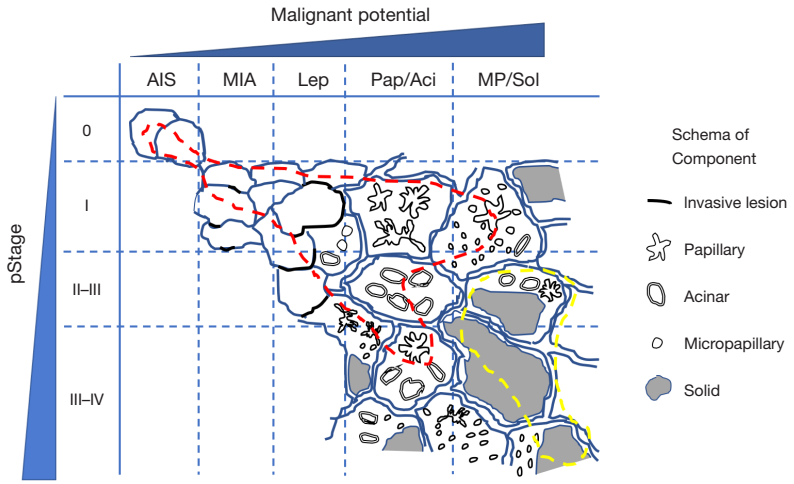

Figure 1 Schema of the distribution of *EGFR/KRAS* mutations and histological change in adenocarcinoma components according to pStage and malignant potential. According to the advancement in pStage, the proportion of AIS/MIA/lepidic predominant subtype decreases and the ratio of components of intermediate or high malignant subtypes increases. *EGFR* mutations are likely to be harbored in cases involving lepidic lesions or earlier pStage. Whereas *KRAS* mutation is more harbored in cases with a solid component or advanced pStage. The red and yellow circles with dashed lines indicate the high frequency distribution of *EGFR* and *KRAS* mutations, respectively.

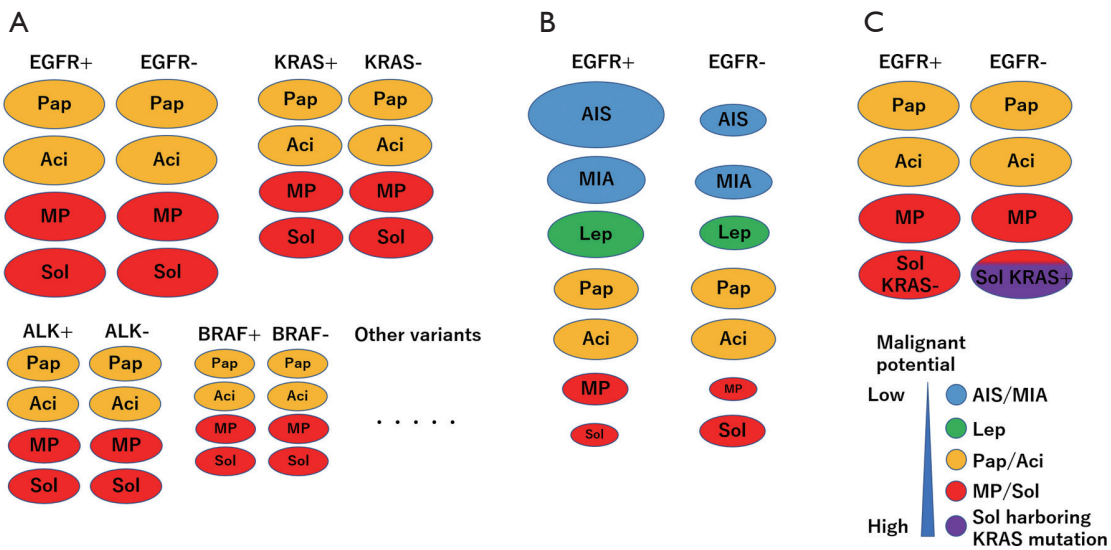

Figure 2 Proposal of the ideal comparison model (A) and examples of improper models for estimating the prognostic impact of *EGFR* mutations in mono-gene estimation (B,C). (A) Ideal comparison model. The subtypes with the risk of recurrence were compared in the multigene model, and pStage and the numbers of each subtype are balanced between the variant-positive and -negative cohorts. (B) An example of the unfavorable comparison model. The subtypes with no or little risk of recurrence were included, and/or the numbers of each subtype are not balanced between the cohorts. The size of the ellipse reflects the number of cases. (C) Another example of the unfavorable comparison model including the risk of false results by mono-gene comparison. The numbers of each subtype are balanced between cohorts, but the EFGR mutation-negative cohort can include more *KRAS* mutant cases if only the *EGFR* mutation was estimated. The high risk of recurrence by the *KRAS* mutation can be misinterpreted as a risk stemming from the *EFGR* wild-type status.

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to perform comprehensive genetic analysis and collect a balanced number of cases. In case a mono-gene comparison is performed, we must exclude the improper setting (*Figure 2B,C*) as much as possible.

Apart from the abovementioned problem, attention must be paid to several other issues. To this end, the frequency of genetic variants differs among races or regions. It must be noted that even major variants, such as *EGFR* or *KRAS* mutations can be low frequent variants, such as *BRAF* mutation or *ALK* rearrangement and the prognostic impact can be underestimated in different races or regions.

OS is prolonged by target therapy after recurrence (34,35). To estimate the prognostic impact of genetic variants in a natural course, OS is not always a proper endpoint. We also have to consider race and treatment course in estimating the genetic prognostic value.

Conclusions

The staging system and pathological classification sensitively reflect the prognosis. The distribution of genetic status varies by stage, histological features, and race, especially in adenocarcinoma. Although genetic variants are promising prognostic predictors, their use is currently limited and can be misinterpreted unless they are considered along with stage and histology. Further discussion should be conducted by considering stage and histological features with multi-gene analysis studies.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

1. Herbst RS, Tsuboi M, John T, et al. Osimertinib as adjuvant therapy in patients (pts) with stage IB–IIIA EGFR mutation positive (EGFRm) NSCLC after complete tumor resection: ADAURA. J Clin Oncol 2020;38:LBA5.
2. Zhang Z, Wang T, Zhang J, et al. Prognostic value of epidermal growth factor receptor mutations in resected non-small cell lung cancer: a systematic review with meta-analysis. PLoS One 2014;9:e106053.
3. Takamochi K, Oh S, Matsunaga T, et al. Prognostic impacts of EGFR mutation status and subtype in patients with surgically resected lung adenocarcinoma. J Thorac Cardiovasc Surg 2017;154:1768-74.e1.
4. Ito M, Miyata Y, Kushitani K, et al. Increased risk of recurrence in resected EGFR-positive pN0M0 invasive lung adenocarcinoma. Thorac Cancer 2018;9:1594-602.
5. He Q, Xin P, Zhang M, et al. The impact of epidermal growth factor receptor mutations on the prognosis of resected non-small cell lung cancer: A meta-analysis of literatures. Transl Lung Cancer Res 2019;8:124-34.
6. Ito M, Miyata Y, Tsutani Y, et al. Positive EGFR mutation status is a risk of recurrence in pN0-1 lung adenocarcinoma when combined with pathological stage and histological subtype: A retrospective multi-center analysis. Lung Cancer 2020;141:107-13.
7. Suda K, Mitsudomi T, Shintani Y, et al. Clinical impacts of EGFR mutation status: analysis of 5,780 surgically resected lung cancer cases. Ann Thorac Surg 2020. [Epub ahead of print].
8. Deng C, Zhang Y, Ma Z, et al. Prognostic value of epidermal growth factor receptor gene mutation in

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resected lung adenocarcinoma. J Thorac Cardiovasc Surg 2020. [Epub ahead of print].
9. Meng D, Yuan M, Li X, et al. Prognostic value of K-RAS mutations in patients with non-small cell lung cancer: A systematic review with meta-analysis. Lung Cancer 2013;81:1-10.
10. Ma Z, Zhang Y, Deng C, et al. The prognostic value of Kirsten rat sarcoma viral oncogene homolog mutations in resected lung adenocarcinoma differs according to clinical features. J Thorac Cardiovasc Surg 2020. [Epub ahead of print].
11. Fukui T, Yatabe Y, Kobayashi Y, et al. Clinicoradiologic characteristics of patients with lung adenocarcinoma harboring EML4-ALK fusion oncogene. Lung Cancer 2012;77:319-25.
12. Blackhall FH, Peters S, Bubendorf L, et al. Prevalence and clinical outcomes for patients with ALK-positive resected stage I to III adenocarcinoma: results from the European Thoracic Oncology Platform Lungscape Project. J Clin Oncol 2014;32:2780-7.
13. Gao Q, Li P, Jiang X, et al. Worse disease-free, tumor-specific, and overall survival in surgically-resected lung adenocarcinoma patients with ALK rearrangement. Oncotarget 2017;8:86066-81.
14. Shin SH, Lee H, Jeong BH, et al. Anaplastic lymphoma kinase rearrangement in surgically resected stage IA lung adenocarcinoma. J Thorac Dis 2018;10:3460-7.
15. Liu Y, Ye X, Yu Y, et al. Prognostic significance of anaplastic lymphoma kinase rearrangement in patients with completely resected lung adenocarcinoma. J Thorac Dis 2019;11:4258-70.
16. Ohba T, Toyokawa G, Kometani T, et al. Mutations of the EGFR and K-ras genes in resected stage I lung adenocarcinoma and their clinical significance. Surg Today 2014;44:478-86.
17. Izar B, Zhou H, Heist RS, et al. The prognostic impact of KRAS, its codon and amino acid specific mutations, on survival in resected stage I lung adenocarcinoma. J Thorac Oncol 2014;9:1363-9.
18. Zhang SM, Zhu QG, Ding XX, et al. Prognostic value of EGFR and KRAS in resected non-small cell lung cancer: a systematic review and meta-analysis. Cancer Manag Res 2018;10:3393-404.
19. Marchetti A, Felicioni L, Malatesta S, et al. Clinical features and outcome of patients with non-small-cell lung cancer harboring BRAF mutations. J Clin Oncol 2011;29:3574-9.
20. Kadota K, Sima CS, Arcila ME, et al. KRAS mutation is a significant prognostic factor in early-stage lung adenocarcinoma. Am J Surg Pathol 2016;40:1579-90.
21. Kneuertz PJ, Carbone DP, D'Souza DM, et al. Prognostic value and therapeutic implications of expanded molecular testing for resected early stage lung adenocarcinoma. Lung Cancer 2020;143:60-6.
22. Ohba T, Toyokawa G, Osoegawa A, et al. Mutations of the EGFR, K-ras, EML4-ALK, and BRAF genes in resected pathological stage I lung adenocarcinoma. Surg Today 2016;46:1091-8.
23. Chaft JE, Dagogo-Jack I, Santini FC, et al. Clinical outcomes of patients with resected, early-stage ALK-positive lung cancer. Lung Cancer 2018;122:67-71.
24. Isaka T, Ito H, Nakayama H, et al. Effect of epidermal growth factor receptor mutation on early-stage non-small cell lung cancer according to the 8th TNM classification. Lung Cancer 2020;145:111-8.
25. Travis WD, Brambilla E, Noguchi M, et al. International association for the study of lung cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6:244-85.
26. Yoshizawa A, Sumiyoshi S, Sonobe M, et al. Validation of the IASLC/ATS/ERS lung adenocarcinoma classification for prognosis and association with EGFR and KRAS gene mutations: Analysis of 440 Japanese patients. J Thorac Oncol 2013;8:52-61.
27. Rekhtman N, Ang DC, Riely GJ, et al. KRAS mutations are associated with solid growth pattern and tumor-infiltrating leukocytes in lung adenocarcinoma. Mod Pathol 2013;26:1307-19.
28. Yoshizawa A, Motoi N, Riely GJ, et al. Impact of proposed IASLC/ATS/ERS classification of lung adenocarcinoma: prognostic subgroups and implications for further revision of staging based on analysis of 514 stage I cases. Mod Pathol 2011;24:653-64.
29. Ujiie H, Kadota K, Chaft JE, et al. Solid predominant histologic subtype in resected stage I lung adenocarcinoma is an independent predictor of early, extrathoracic, multisite recurrence and of poor postrecurrence survival. J Clin Oncol 2015;33:2877-84.
30. Yanagawa N, Shiono S, Abiko M, et al. The clinical impact of solid and micropapillary patterns in resected lung adenocarcinoma. J Thorac Oncol 2016;11:1976-83.
31. Wang Y, Zheng D, Zheng J, et al. Predictors of recurrence and survival of pathological T1N0M0 invasive

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adenocarcinoma following lobectomy. J Cancer Res Clin Oncol 2018;144:1015-23.
32. Warth A, Penzel R, Lindenmaier H, et al. EGFR, KRAS, BRAF and ALK gene alterations in lung adenocarcinomas: Patient outcome, interplay with morphology and immunophenotype. Eur Respir J 2014;43:872-83.
33. AMG 510 first to inhibit "Undruggable" KRAS. Cancer Discov 2019;9:988-9. Available online: https://doi.org/10.1158/2159-8290.cd-nb2019-073
34. Takenaka T, Takenoyama M, Yamaguchi M, et al. Impact of the epidermal growth factor receptor mutation status on the post-recurrence survival of patients with surgically resected non-small-cell lung cancer. Eur J Cardiothorac Surg 2015;47:550-5.
35. Ito M, Miyata Y, Hirano S, et al. Synchronicity of genetic variants between primary sites and metastatic lymph nodes, and prognostic impact in nodal metastatic lung adenocarcinoma. J Cancer Res Clin Oncol 2019;145:2325-33.

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