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Review

Prognostic value of K-RAS mutations in patients with non-small cell lung cancer: A systematic review with meta-analysis

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ABSTRACT

K-RAS gene mutations have been found in 20–30% of non-small cell lung cancer and occur most commonly in adenocarcinoma, however, there was no definitive conclusion about the prognostic role of K-RAS mutations in NSCLC. Herein we performed a systematic review of the literatures with meta-analysis to assess K-RAS mutations' prognostic value in NSCLC. After a methodological assessment, survival data from published studies were aggregated. Combined hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated in terms of overall survival. 41 trials (6939 patients) were included in the analysis, the overall HR was 1.45 (95% CI: 1.29–1.62), showing that K-RAS mutations have an unfavorable impact on survival of patients with NSCLC. Then a subgroup analysis was performed about ethnicity, the combined HR was 1.97 (95% CI: 1.58–2.44) for Asians, and 1.37 (95% CI: 1.25–1.5) for non-Asians. In subgroup analysis of histology, the HR was 1.39 (95% CI: 1.24–1.55) for adenocarcinoma, suggesting that K-RAS mutations were correlated with shortened survival for adenocarcinoma. When the subgroup analysis was conducted according to disease stage, K-RAS mutations were poor prognostic factors in early stages: stage I (1.81; 95% CI: 1.36–2.39) and stage I–IIIa (1.68; 95% CI: 1.11–2.55), but not in advanced stage (IIIb–IV) (1.3; 95% CI: 0.99–1.71). At last, in subgroup analysis about test methods, all of the four methods: PCR–MSOP (1.73; 95% CI: 1.35–2.2), PCR–DGGE (1.27; 95% CI: 1.01–1.62), PCR–RFLP (1.88; 95% CI: 1.42–2.49) and PCR–seq (1.34; 95% CI: 1.14–1.58) showed statistically significant impact on survival of NSCLC patients. In conclusion, this meta-analysis suggests that K-RAS mutations are associated with a worse overall survival in patients with NSCLC, especially in patients with adenocarcinoma and early stage.

1. Introduction

Due to large improvements in diagnosis and therapy, substantial progress has been made in oncology during the past decades, but non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related death worldwide [1]. The overall 5-year survival rate for non-small cell lung cancer is about 17% [2]. Some clinical factors have already been identified for predicting survival, such as disease stage, performance status, age, sex, and weight loss [3]. During the past few years we have learned that several biological events are associated with tumor growth and progression. Some of them, like EGFR mutations [4], HER2 mutations [5], are considered as having prognostic impact on lung cancer. And they also have useful predictive value on the response to targeted therapy [6].

Ras oncogene is well known to be involved in cancer development, including H-RAS, K-RAS and N-RAS, which code for a family of 21 kDa guanosine triphosphate-binding proteins called p21. In physiologic conditions, these proteins could be activated by bounding with GTP and initiate cell proliferation through the RAS-dependent kinase cascade, then GTP are hydrolysed to GDP by their intrinsic GTPase activity and RAS proteins return to inactive state. However, in tumors, when a point mutation occurs in these genes, which would result in loss of their intrinsic GTPase activity, RAS proteins could acquire transforming potential, leading to continuous activation of RAS signaling [7]. K-RAS gene mutations occur frequently in NSCLC, mainly app:addword:especiallyin adenocarcinoma and rarely in squamous cell carcinoma [8]. Approximately 80% of K-RAS mutations in NSCLC involve codon 12, others are located in codons 13 or 61 [9]. The frequency of K-RAS mutations varies among different ethnic groups, they are observed more often among non-Asians (African Americans and white Caucasians) than Asians [10].

Although the prognostic value of K-RAS mutations in NSCLC has been researched for several years, their roles remain controversial.

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Table 1
Main characteristics and results of the eligible studies.

First author	Year	Source of Pts	No. of Pts	Histology	Stage	Test method	Mutation point (codon)	Positive (%)	HR estimation	HR (95% CI)
Slebos [50]	1990	Netherlands	69	AC	I–IIIa	PCR–MSOP	12	27.5	Log rank	2.43(1.14–5.15)
Sugio [51]	1992	Japan	115	AC	I–IV	PCR–dotblot	12,13	15.7	Sur curve	1.64(0.84–3.23)
Kern [52]	1994	USA	44	AC	I–IV	PCR–MSOP	12	36.4	HR + CI	2.10(1.00–4.40)
Silini	1994	Italy	109	AC	I–IV	PCR–DGGE	12,13	30.3	Sur curve	1.61(0.97–2.66)
[53]			81		I(subgroup)			28.4	Sur curve	2.40(1.22–4.71)
Rosell [54]	1995	Spain	192	NSCLC	I–IV	PCR–MSOP	12,61	26.6	Sur curve	1.78(1.28–2.47)
Keohavong	1996	USA	126	NSCLC	I–IV	PCR–DGGE	12,13, 61	31.0	Log rank	1.02(0.56–1.84)
[55]			63		I(subgroup)			31.7	Sur curve	2.53(0.86–7.43)
Fukuyama [57]	1997	Japan	159	NSCLC	I–IV	PCR–RFLP	12	6.9	HR + CI	5.60(2.17–14.2)
Cho [56]	1997	Korea	58	NSCLC	I–III	PCR–SSCP	12	24.1	Sur curve	3.60(1.69–7.67)
Rodenhuis [58]	1997	Netherlands	62	AC	III–IV	EPCR	12,61	26.0	Log rank	1.37(0.77–2.44)
Siegfried	1997	USA	181	AC	I–IV	PCR–DGGE	12,13	31.5	Sur curve	1.24(0.91–1.67)
[59]			96		I(subgroup)			29.2	Sur curve	1.61(0.95–2.72)
Graziano [60]	1999	USA	213	NSCLC	I–II	PCR–MSOP	12	16.4	Sur curve	1.28(0.78–2.08)
Nelson	1999	USA	195	AC	I–IV	PCR–RFLP	12	22.1	HR + CI	1.80(1.10–3.10)
[61]			117		I(subgroup)			17.9	HR + CI	3.70(1.60–8.60)
Schiller [62]	2001	USA	184	NSCLC	II–IIIa	PCR–RFLP	12	23.9	HR + CI	1.56(0.97–2.52)
Tomizawa [63]	2002	Japan	84	AC	I	PCR–seq	12,13, 61	11.8	Log rank	2.25(0.69–7.41)
Kim [65]	2003	Korea	125	AC	I–IV	PCR–seq	12,13, 61	28.0	HR + CI	2.31(1.62–5.97)
Grossi [64]	2003	Italy	249	NSCLC	I–IIIa	PCR–seq	12,13, 61	18.9	HR + CI	1.66(0.94–2.93)
Ramirez [66]	2003	Spain	50	NSCLC	I–IV	PCR–seq	12	18.0	Sur curve	0.91(0.22–3.81)
Lu [67]	2004	USA	94	NSCLC	I	others	12	34.0	HR + CI	1.18(0.71–1.95)
Endoh [68]	2006	Japan	78	NSCLC	I–IV	PCR–seq	12	9.0	HR + CI	2.54(1.05–6.17)
Schneider [70]	2008	Germany	113	NSCLC	IIIb–IV	PCR–seq	12,13, 61	15.0	HR + CI	1.64(0.97–2.80)
Ruiz [69]	2009	Netherlands	136	NSCLC	I–III	PCR–seq	12,13, 61	18.4	HR + CI	0.39(0.18–0.84)
Kosaka [72]	2009	Japan	212	AC	I–IV	PCR–seq	12,13, 61	13.2	HR + CI	1.09(0.44–2.69)
Jackman [71]	2009	multinational	124	NSCLC	IIIb–IV	PCR–seq	NA	33.1	Sur curve	1.41(0.97–2.05)
Pesek [73]	2009	Czech	71	NSCLC	I–IV	others	12,13	32.4	Sur curve	1.07(0.55–2.08)
Kalikaki [76]	2010	Greece	133	NSCLC	IIIb–IV	PCR–seq	12,13	24.8	Sur curve	1.38(0.86–2.21)
Onitsuka [78]	2010	Japan	183	AC	I–III	PCR–RFLP	12	9.3	HR + CI	1.74(1.00–3.00)
Liu [77]	2010	Taiwan	156	NSCLC	I–IIIa	PCR–seq	12	4.5	HR + CI	0.88(0.31–2.45)
Bonanno [75]	2010	Italy	62	AC	IIIb–IV	PCR–seq	12,13	19.4	HR + CI	3.52(1.39–8.90)
Ready [79]	2010	USA	45	NSCLC	IIIa IIIb	others	NA	15.6	Log rank	1.05(0.44–2.49)
Amann [74]	2010	USA	41	NSCLC	IIIb–IV	PCR–seq	12,13	22.0	HR + CI	1.02(0.47–2.24)
Kakegawa [81]	2011	Japan	182	AC	I–IV	PCR–seq	12	16.5	Sur curve	1.55(0.94–2.56)
Sasaki [85]	2011	Japan	172	NSCLC	I–IV	RT–PCR	12,13	20.9	Log rank	2.12(1.09–4.11)
Brugger [80]	2011	multinational	239	NSCLC	IIIb–IV	PCR–seq	12,13, 61	17.2	HR + CI	0.76(0.53–1.11)
Byrne [84]	2011	multinational	196	NSCLC	IIIb–IV	others	12,13	18.9	HR + CI	1.02(0.68–1.54)
Ludovini [82]	2011	Italy	162	NSCLC	III–IV	PCR–seq	12,61	6.8	HR + CI	1.30(0.63–2.66)
Mazzoni [83]	2011	Italy	50	NSCLC	IV	others	12,13	26.0	Sur curve	1.00(0.46–2.18)
Metro [89]	2012	Italy	67	NSCLC	IIIb–IV	PCR–seq	12,13	26.9	Log rank	1.83(0.93–3.58)
Cadranel [86]	2012	France	263	NSCLC	I–IV	PCR–seq	NA	16.0	Sur curve	1.65(1.17–2.31)
Hallqvist [88]	2012	Sweden	66	NSCLC	III	others	NA	28.8	HR + CI	2.32(1.27–4.26)
Johnson [90]	2012	USA	761	AC	IV	PCR–seq	12,13	31.7	HR + CI	1.21(1.01–1.46)
Angelo [87]	2012	USA	1118	AC	I–III	PCR–seq	NA	24.8	HR + CI	1.17(0.87–1.57)

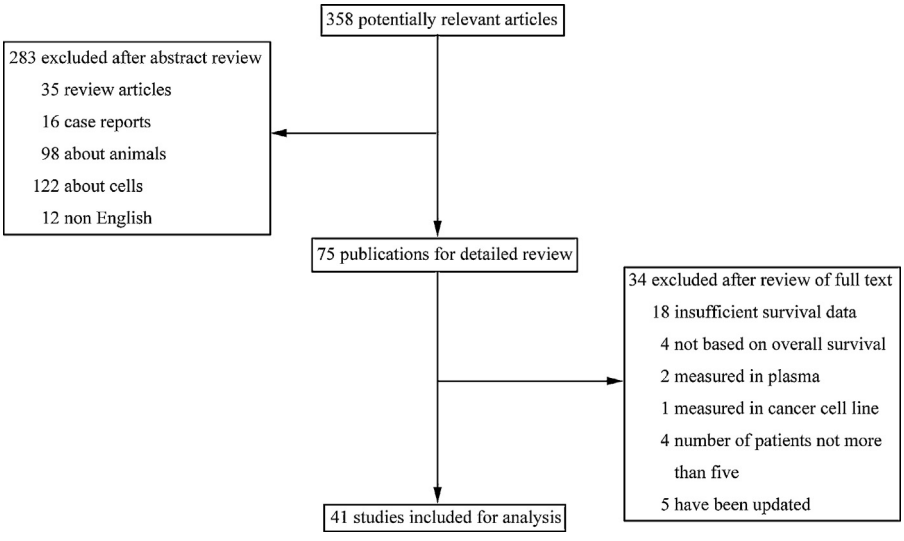

Fig. 1. The flow diagram of search strategy.