Letter

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PIK3CA mutations in cutaneous squamous cell carcinoma

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SUMMARY Oncogenic *PIK3CA* mutation activates phosphoinositide 3-kinase (PI3K) enzyme, and PI3K-AKT signaling activation induces several growth-regulatory transcription factors. *PIK3CA* mutations have attracted attention as biomarker in clinical trials of various inhibitors including PI3K inhibitors. About 80% of *PIK3CA* mutations in human cancers are observed in 'hot spot' regions: exon 9 (E542K and E545K) and exon 20 (H1047R). There were few reports about clinical significance of *PIK3CA* mutations in cutaneous cell carcinoma (cSCC). Thus, we investigate the prevalence of three *PIK3CA* hot spot mutations in 143 cases with cSCC and evaluate the correlation between the presence of these mutations and clinical characteristics by using ddPCR. The frequency of each E542K, E545K and H1047R PIK3CA mutations was 1.4% (2/143), 2.8% (4/143), and 0.7% (1/143) respectively. No significant correlation was found between *PIK3CA* mutations and clinical characteristics. Although additional basic researches and clinical trials are necessary, various inhibitors may be effective therapeutics for *PIK3CA* mutation-positive cSCC. Our study revealed the prevalence of *PIK3CA* mutations in cSCC.

Keywords cutaneous squamous cell carcinoma, *PIK3CA* mutations, Droplet digital polymerase chain reaction (ddPCR), metastasis

PI3K (Phosphoinositide 3-kinase)-Akt pathway can be activated by *PIK3CA* mutations and contributes to cancer progression. *PIK3CA* mutations have been found in various cancers, such as breast and colon cancer, and approximately 80% of them are in "hot spot" regions such as exon 9 (E542K and E545K) and exon 20 (H1047R) (*1*). To our knowledge, there are only two reports of *PIK3CA* mutations in cutaneous squamous cell carcinoma (cSCC). None of the *PIK3CA* hot spot mutations were observed in 30 patients with cSCC (*2*). In addition, 40% (4/10) of cases with cSSC had *PIK3CA* mutations in regions outside of hot spots, and no *PIK3CA* hot spot mutations were identified in 10 patients with cSCC (*3*). However, there have been no reports of the *PIK3CA* mutations in a large number of SCC cases. Therefore, we investigated the prevalence and clinical significance of three *PIK3CA* hot spot mutations (E542K, E545K, and H1047R) in 143 cases with cSCC.

All experimental protocols were approved by the Institutional Review Board and were carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients. Tissue samples were obtained from 143 patients diagnosed at Kumamoto University Hospital between July 2015 and August 2020. DNA was isolated from formalin-fixed paraffin-embedded FFPE tissues using the QIAmp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany). ddPCR was performed using a QX200 droplet digital PCR system (Bio-Rad, Berkeley, CA, USA) as previously described4 using ddPCR probes for three PIK3CA mutations (E542K, E545K, and H1047R), which were also purchased from Bio-Rad. The variant allele frequency (VAF) cutoff was 1% as in our previous study (*4*).

The overall frequency of the *PIK3CA* hot spot mutations in cSCC was 4.9% (7/143), and the frequencies of E542K, E545K, and H1047R were 1.4% (2/143), 2.8% (4/143), and 0.7% (1/143), respectively. No case with multiple *PIK3CA* hot spot mutations was observed. No significant correlations between the *PIK3CA* mutations (total, E542K, E545K, and H1047R) and clinical characteristics were found (Table 1).

Our study revealed that the overall prevalence of *PIK3CA* hot spot mutations in cSCC was approximately 5%, which differed from past reports (*2,3*). This discrepancy may be attributable to differences in research method and patient cohorts. Recently, *PIK3CA*

Table 1. Correlations between PIK3CA mutations and clinical characteristics in cutaneous squamous cell carcinomas

Clinical characteristics	E542K			E545K			H1047R			Total		
	+ (n = 2)	- (n = 141)	P	+ (n = 4)	- (n = 139)	P	+ (n = 1)	- (n = 142)	P	+ (n = 7)	- (n = 136)	P
Age (yares : mean ± SD)	80.3 ± 10.4	83.0 ± 5.0	0.875	80.3 ± 10.5	82.3 ± 6.4	0.212	80.4 ± 10.4	69.0 ± 0	NA	80.3 ± 10.5	80.6 ± 7.3	0.785
Sex (male : female)	2:0	91:50	0.542	2:2	91:48	0.612	1:0	92:50	> 0.999	5:2	88:48	> 0.999
Lymph node metastasis (– : +)	2:0	130:11	> 0.999	4:0	128:11	> 0.999	0:1	132:10	0.077	6:1	126:10	0.436
Distant organ metastasis (– : +)	2:0	140:1	> 0.999	4:0	138:1	> 0.999	1:0	141:1	> 0.999	7:0	135:1	> 0.999

NA: not assessed, SD: standard deviation.

mutations have attracted attention as biomarker in clinical trials of various inhibitors including PI3K inhibitor (5). Taken together, various inhibitors may be effective therapeutics for *PIK3CA* mutation-positive cSCC, although additional basic researches and clinical trials are necessary to confirm this.

This study has several limitations. First, *PIK3CA* mutations other than hot spot mutations were not investigated, and second, the number of cases with lymph node metastasis and distant organ metastasis was low.

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