의학석사 학위논문

FOLFIRINOX 치료를 받는 췌장암 환자에서 주요 돌연변이 유전자들의 임상적 의의

Clinical significance of main driver mutation genes in pancreatic cancer patients undergoing FOLFIRINOX

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Clinical significance of main driver mutation genes in pancreatic cancer patients undergoing FOLFIRINOX

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KRAS, *TP53, CDKN2A*, and *SMAD4* have been reported in pancreatic cancer as main driver mutations. Studies on clinical significance and treatment response to FOLFIRINOX(5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) regarding presence of these mutations remain inconclusive.

This study included patients diagnosed with pancreatic ductal adenocarcinoma(PDAC) and analyzed by targeted next-generation sequencing platform at Seoul National University Hospital and Seoul National University Bundang Hospital from January 2016 to March 2022. Patient who underwent FOLFIRINOX as initial treatment were retrospectively investigated.

102 patients were included in analysis. *KRAS* mutation was identified in 94 patients(92.2%), followed by *TP53* (65, 63.7%), *CDKN2A*(18, 17.6%), and *SMAD4*(17, 16.7%). *TP53* wildtype group exhibited longer overall survival(OS) compared to the group with mutated

TP53 (median OS 29 months vs. 19 months, p=0.03), and also served as prognostic factor for survival (hazard ratio=1.76, 95% confidence interval 1.02−3.04, p=0.041). Difference in OS according to *TP53* mutation was intensified in localized PDAC (37 months vs. 19 months, p=0.01). *TP53* wildtype group exhibited longer OS than *TP53* wildtype group had higher objective response rate to FOLFIRINOX than the *TP53* mutation group in localized PDAC. (50.0% vs. 16.7%, p=0.024)

In conclusion, PDAC with wildtype *TP53* had longer overall survival compared to patients with *TP53* mutation, and this trend was intensified in patients with localized disease. This result is possibly due to improved response to FOLFIRINOX. Further research is warranted with larger number of patients and in−depth analysis of mutation profiles.

Keyword : pancreatic ductal adenocarcinoma, *TP53*, FOLFIRINOX, overall survival, objective response rate

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Introduction

Pancreatic ductal adenocarcinoma(PDAC) is the fourth leading cause of death from cancer in United States and around 62,000 patients are diagnosed annually.(1) Only 10−20% of PDAC is resectable at the time of diagnosis, which explains the poor prognosis of PDAC.(2) However, gradual improvement in treatment of PDAC is being reported within past decade with the introduction of FOLFIRINOX(5−fluorouracil(5−FU), leucovorin, irinotecan, and oxaliplatin) regimen. With an objective response rate of 32%, FOLFIRINOX has exhibited notable efficacy in the treatment of metastatic PDAC.(3) Currently, it stands as a preferred treatment option for patients with a tolerable performance status in both neoadjuvant and palliative settings.

With the introduction of next generation sequencing(NGS), identification of molecular mutation profile has spread and is commercially available at numerous centers around the world. Studies attempting to link mutation profiles of PDAC with treatment options have yielded limited results. While some options have been suggested to be effective against specific mutations, their applicability is limited to a small subset of PDAC patients.(4) Mutations found with high frequency include oncogene *KRAS* and tumor suppressor genes *TP53*, *CDKN2A*, and *SMAD4*.(5, 6) Many studies have been conducted on these main driver mutation genes and their clinical relevance. Still, their relevance and clinical implication remains inconclusive. In addition, there are no studies

focusing on response to FOLFIRINOX as an outcome of interest. Our study aims to compare the survival outcome and response to FOLFIRINOX based on the presence of four driver mutation genes in PDAC patients.

Methods

Patient and study design

Patients diagnosed with PDAC at two medical centers, Seoul National University Hospital(SNUH) and Seoul National University Bundang Hospital(SNUBH) were investigated. Patients whose tumor specimen went through NGS test from January 2016 to March 2022 were investigated. Among them, patients who were treated with FOLFIRNOX as initial treatment were included in this study. Patients 1) who went through upfront resection, and 2) whose initial chemotherapy regimen was not FOLFIRINOX were excluded from our analysis. Data of the study patients were retrospectively collected from electronic medical records. Demographics. Eastern Cooperative Oncology Group(ECOG) performance status, location and size of tumor, pathologic reports, follow up data including survival and progression were collected. Subgroup analysis was conducted on localized and metastatic PDAC. Localized disease was defined as resectable, borderline resectable(BR), and locally advanced(LA) PDAC. The study protocol was approved by the institutional review board of Seoul National University Hospital (IRB no.2207-121-1342) and Seoul National University Bundang Hospital (IRB no. B-2305-827-402).

NGS data

We used the NGS report of SNUH pan-cancer panel(version 3.3) and SNUBH-Macrogen panel(version 2.0). These panel analyzed 185 genes and 544 genes, respectively. Single nucleotide variants (SNVs), small insertion/deletions(INDELs), microsatellite instability(MSI), and tumor mutational burden(TMB) were included in the NGS report. NGS reports of included patients were retrospectively reviewed. We focused on the presence of four driver mutations (*KRAS, TP53, CDKN2A, SMAD4*) for each patient.

Assessment and definition

Overall survival(OS) was defined from the date of diagnosis to the date of death or last follow-up. Progression was defined by progressive disease(PD) according to the RECIST 1.1 criteria(7) or recurrence of tumor, if already resected. Progression free survival(PFS) was defined from the date of start of FOLFIRINOX to the date of progression or last follow-up, if not progressed. Patient's response to FOLFIRINOX was evaluated according to the RECIST 1.1 criteria.(7) Best response was investigated, which was defined as the most favorable outcome observed throughout the treatment period of FOLFIRINOX. Resectability of PDAC was defined following the National Comprehensive Cancer Network criteria.(8) Objective response rate(ORR) was defined as the percentage of people who had partial response(PR) or complete response(CR).

Statistical analysis

Continuous variables were provided as median values with an interquartile range(IQR), and categorical variables were provided as numbers and proportions(%). $\chi 2$ test or Fisher's exact test was used to compare categorial variables between two groups, and Kruskal–Wallis test was used for comparison between three groups. Student's t–test was used to compare continuous variables between groups. Kaplan–Meier survival analysis and log–rank test were used to compare OS and PFS between groups. To evaluate prognostic factors related to survival, Cox proportional hazards analysis was conducted. In the multivariable Cox analysis, we included variables that were effective in the univariable Cox analysis($p<0.05$) or clinically meaningful. A p–value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were conducted using R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria)

Results

Study population and baseline characteristics

Our study included 102 patients diagnosed with PDAC, underwent NGS panel-based test, and received FOLFIRINOX as their initial treatment. Of these patients, 63 were from SNUH and 39 were from SNUBH. Table 1 summarizes the baseline characteristics of included patients. There were 54 males (52.9%), and median age was 62 years(IQR 57-67). All patients had good ECOG performance status of 0 or 1. PDAC consisted of resectable(1.9%), BR(16.7%), LA (34.3%), and metastatic(47.1%) PDAC. *KRAS* mutation was identified in 94 patients(92.2%). G12D mutation(48 out of 94, 51.1%) was mostly identified in *KRAS* mutation, followed by G12V mutation(31 out of 94, 33.0%). *TP53* mutation accounted for 63.7% of total cohort, followed by *CDKN2A*(17.6%), and *SMAD4*(16.7%). Best response to FOLFIRINOX by RECIST 1.1 criteria was as follows: PR(32, 31.4%), stable disease(SD)(50, 49.0%), and PD(20, 19.6%). CR was not reported. Median PFS and OS of entire cohort was 10 and 23 months, respectively. The median value of FOLFIRINOX cycle at best response was 7 cycles(IQR 4-10).

Table 1. Baseline characteristics of patients

Variables		Numbers (proportions) or median value (IQR)		
		Total	SNUH	SNUBH
Number		102	63	39
Sex	Man	54 (52.9)	32 (50.8)	22 (56.4)
	Woman	48 (47.1)	31 (49.2)	17 (43.6)
Age (years)		62 (57–67)	62 (56–66)	63 (59–68)
ECOG-PS	0	59 (57.8)	58 (92.1)	1 (2.6)
	1	43 (42.2)	5 (7.9)	38 (97.4)
Location of Tumor	Head	53 (52.0)	38 (60.3)	15 (38.5)
	body/tail	49 (48.0)	25 (39.7)	24 (61.5)
Resectability of Tumor	Resectable	2 (1.9)	2 (3.2)	0 (0.0)
	Borderline resectable	17 (16.7)	13 (20.6)	4 (10.3)
	Locally advanced	35 (34.3)	26 (41.3)	9 (23.1)
	Metastatic	48 (47.1)	22 (34.9)	26 (66.7)
Resection of tumor	No	76 (74.5)	41 (65.1)	35 (89.7)
	Yes	26 (25.5)	22 (34.9)	4 (10.3)
Mutations	*KRAS*	94 (92.2)	57 (90.5)	37 (94.9)
	TP53	65 (63.7)	40 (63.5)	25 (64.1)
	CDKN2A	18 (17.6)	12 (19.0)	6 (15.4)
	SMAD4	17 (16.7)	11 (17.5)	6 (15.4)
FOLFIRINOX cycle at best response		7 (4–10)	8 (4–12)	4 (3–8)
Best response to FOLFIRINOX	PR	32 (31.4)	17 (27.0)	15 (38.5)
	SD	50 (49.0)	32 (50.8)	18 (46.2)
	PD	20 (19.6)	14 (22.2)	6 (15.4)

Abbreviations; ECOG-PS: Eastern Cooperative Oncology Group performance status, PR: partial response, SD: stable disease, PD: progressive disease, CI: confidence interval, IQR: interquartile range

Result of survival and progression outcomes

The OS according to the presence of *KRAS, TP53, CDKN2A,* and *SMAD4* mutations was analyzed and compared.(**Figure 1**) *TP53* wildtype exhibited a longer median OS compared to mutated *TP53* group (29 months vs. 19 months, p=0.03, **Figure 1b**). Subgroup analysis was performed on patients with localized and metastatic disease. Difference in OS according to *TP53* mutation was intensified in localized PDAC (37 months vs. 19 months, p=0.01, **Figure 2b**). However, there was no significant difference in metastatic PDAC according to presence of *TP53* mutation.(25 months vs. 19 months, p=0.7, **Figure 2f**) No differences in OS were observed for other mutations, both in the entire cohort and subgroup analysis. (**Figure 1**, **Figure 2**)

The analysis and comparison of PFS were conducted based on the presence of *KRAS, TP53, CDKN2A*, and *SMAD4* mutations. In the entire cohort, no difference was observed in relation to the presence of these mutations.(**Figure 3**) Subgroup analysis of localized / metastatic disease did not show significant results, as well.(**Figure 4**)

Figure 1. Kaplan–Meier curve of overall survival according to presence of mutated a.*KRAS* b.*TP53* c.*CDKN2A* and d.*SMAD4*

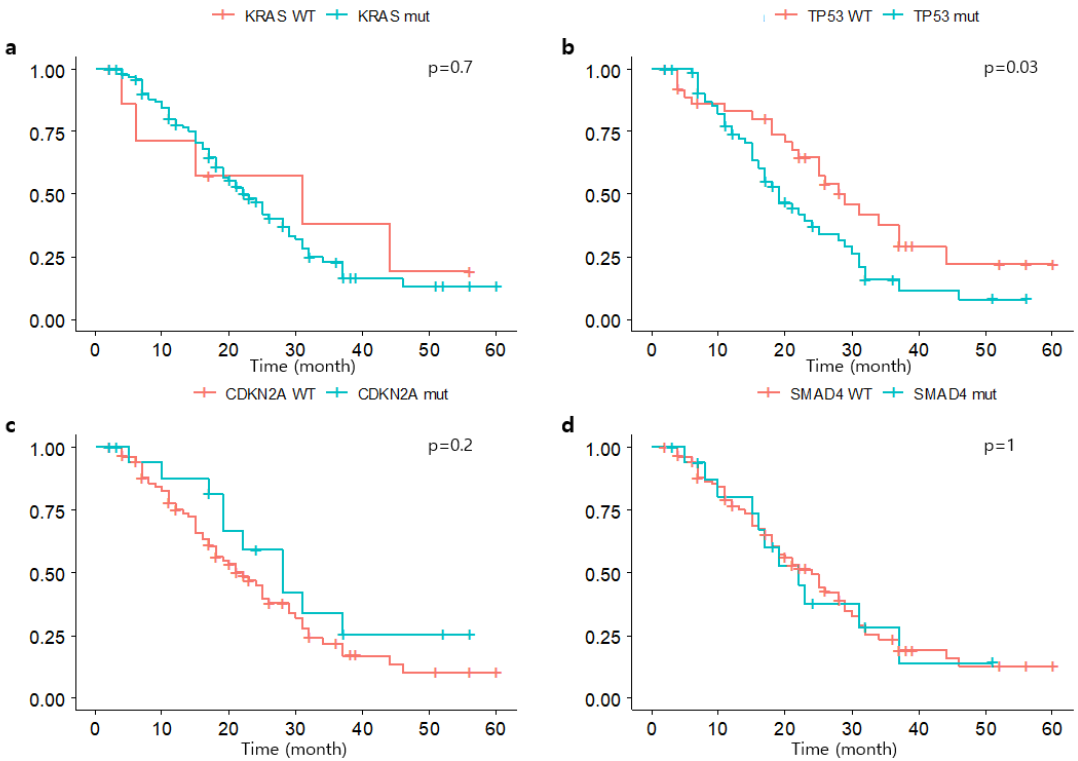


Figure 2. Kaplan–Meier curve of overall survival according to presence of mutated genes in localized(a–d) and metastatic(e–f) disease

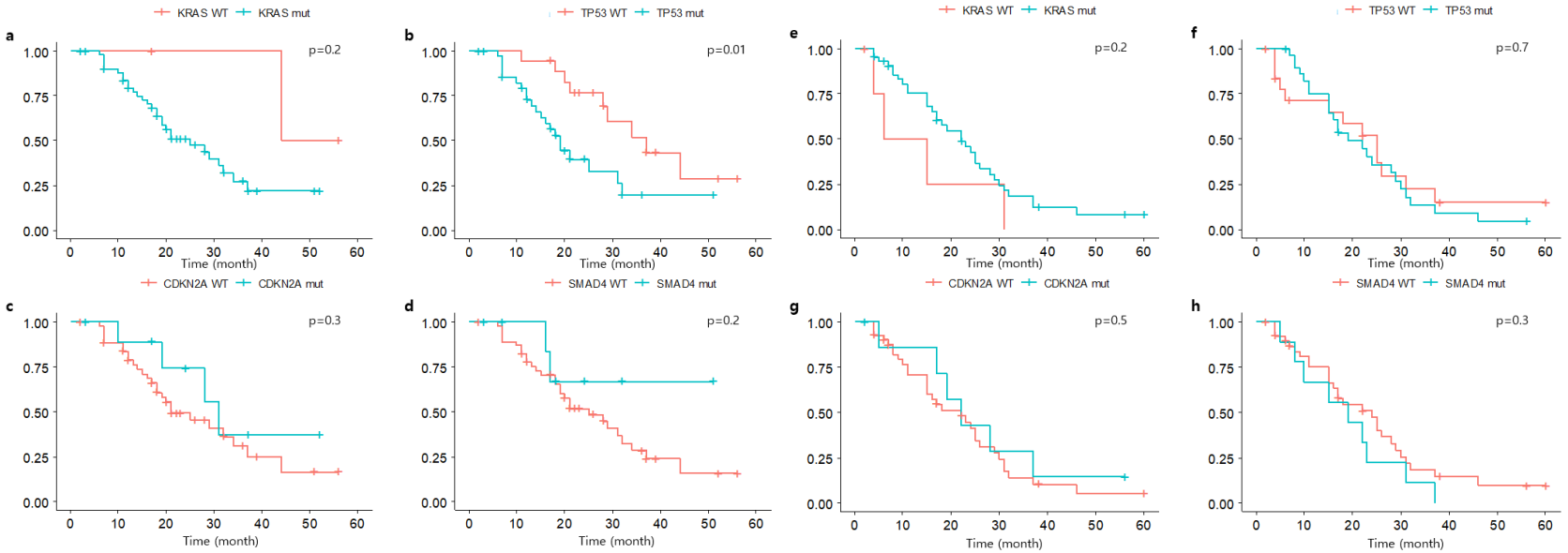


Figure 3. Kaplan–Meier curve of progression free survival according to presence of mutated a.*KRAS* b.*TP53* c.*CDKN2A* and d.*SMAD4*

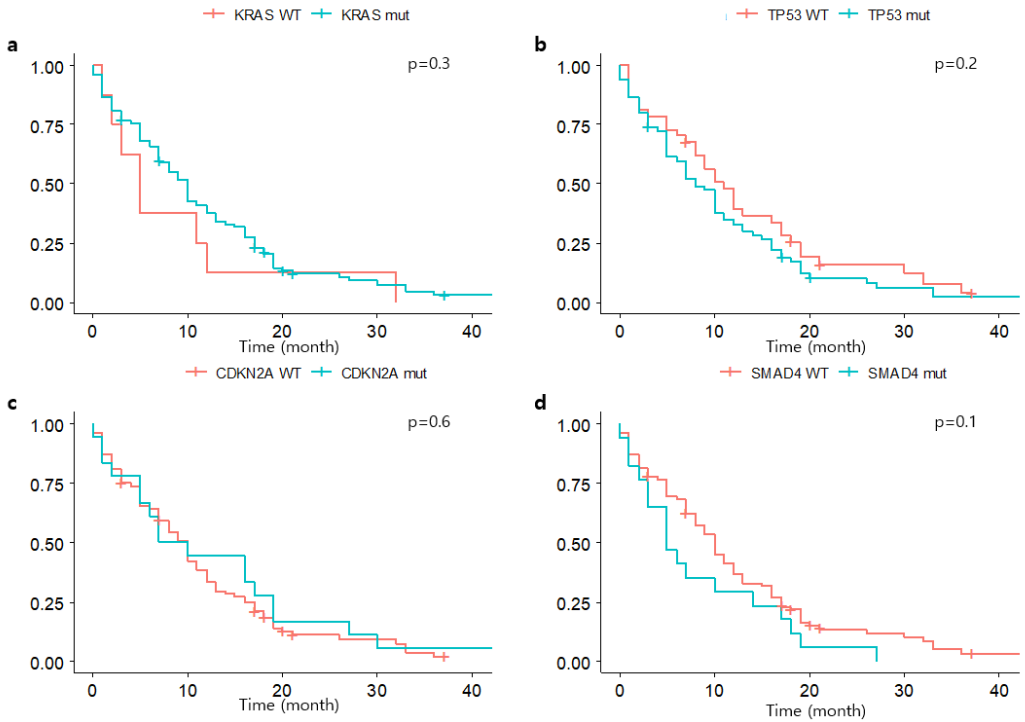
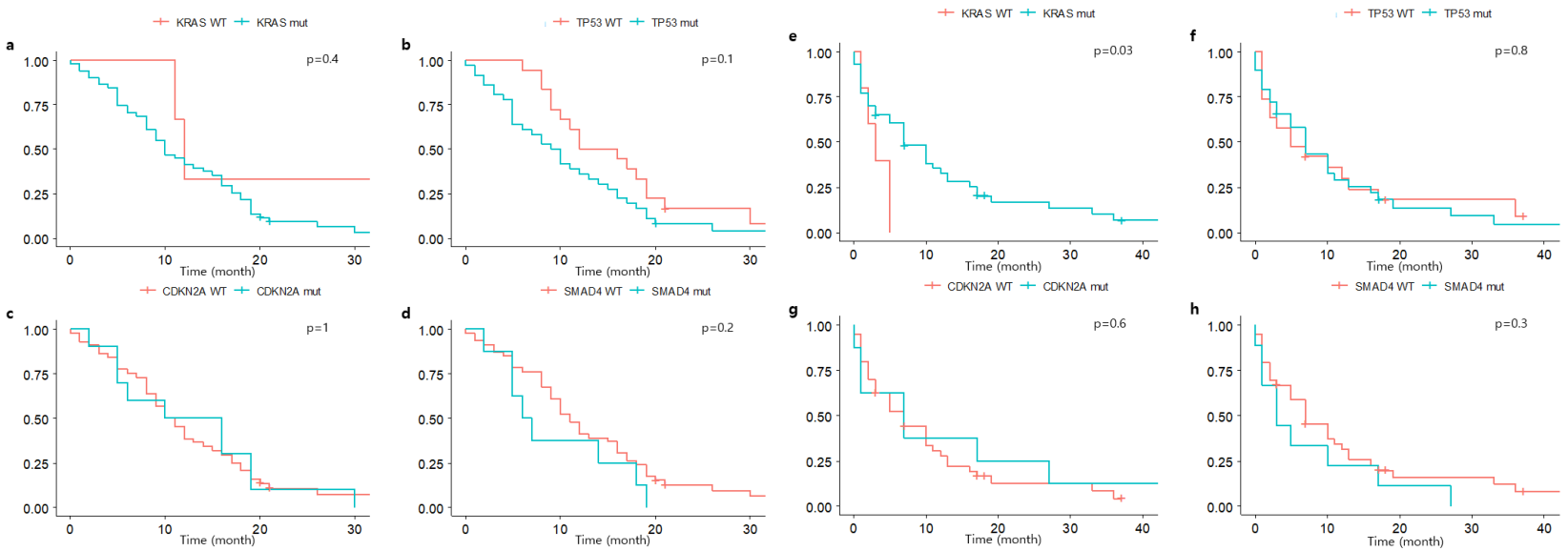


Figure 4. Kaplan-Meier curve of progression free survival according to presence of mutated genes in localized(a-d) and metastatic(e-f) disease



Prognostic factors associated with survival.

Cox proportional hazards analysis was conducted on various prognostic factors including presence of each mutation, to investigate their prognostic impact on survival outcomes. Multivariable analysis indicated that ECOG performance status (hazard ratio(HR) = 2.39, 95% CI 0.58−9.75, p=0.002) was a significant prognostic factor, and the presence of *TP53* mutation (HR=1.76, 95% CI 1.02−3.04, p=0.041) also exhibited a substantial impact (Table 2). Subgroup analysis of patients with localized disease identified *TP53* mutation as a significant prognostic factor for OS (HR 4.49, 95% CI 1.74−11.53; p=0.002). In localized disease, SNUBH center was a negative prognostic factor for survival than SNUH center in multivariable analysis as well (HR 4.50, 95% CI 1.92−10.57; p=0.001 , Table 3).

Table 2. Prognostic factors for survival of total cohort

Variables		Univariable analysis		Multivariable analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Sex	Man	1.00			
	Woman	0.98 (0.61-1.59)	0.944		
Age	< 65yrs	1.00		1.00	
	≥65yrs	1.01 (0.61-1.67)	0.971	0.96 (0.56-1.65)	0.891
ECOG-PS	0	1.00		1.00	
	1	2.42 (1.46-3.98)	0.001	2.39 (0.58-9.75)	0.002
Center	SNUH	1.00		1.00	
	SNUBH	2.40 (1.46-3.93)	0.001	0.95 (0.24-3.75)	0.947
Location of tumor	head	1.00			
	body/tail	0.94 (0.58-1.53)	0.808		
KRAS	Wildtype	1.00			
	mutation	1.18 (0.47-2.96)	0.727		
TP53	wildtype	1.00		1.00	
	mutation	1.78 (1.06-3.00)	0.029	1.76 (1.02-3.04)	0.041
CDKN2A	wildtype	1.00			
	mutation	0.65 (0.33-1.27)	0.210		
SMAD4	wildtype	1.00			
	mutation	1.02 (0.53-1.95)	0.954		
Resectability	R+BR	1.00		1.00	
	LA+M	2.27 (1.08-4.76)	0.030	1.66 (0.77-3.61)	0.193
Resectability	R+BR+LA	1.00			
	M	1.55 (0.96-2.51)	0.076		

Abbreviations; ECOG-PS: Eastern Cooperative Oncology Group performance status, R: resectable, BR: borderline resectable, LA: locally advanced, M: metastatic, HR: hazard ratio, CI: confidence interval

Table 3. Prognostic factors for survival in patients with localized disease

Variables		Univariable analysis		Multivariable analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Sex	Man	1.00			
	Woman	1.18 (0.58-2.42)	0.650		
Age	< 65yrs	1.00		1.00	
	≥65yrs	0.64 (0.29-1.40)	0.262	0.79 (0.34-1.85)	0.589
ECOG-PS	0	1.00			
	1	2.08 (0.99-4.38)	0.053		
Center	SNUH	1.00		1.00	
	SNUBH	2.50 (1.19-5.25)	0.015	4.50 (1.92-10.57)	0.001
Location of tumor	head	1.00			
	body/tail	0.96 (0.46-2.01)	0.921		
KRAS	Wildtype	1.00			
	mutation	3.95 (0.52-30.23)	0.185		
TP53	wildtype	1.00		1.00	
	mutation	2.71 (1.20-6.12)	0.016	4.49 (1.74-11.53)	0.002
CDKN2A	wildtype	1.00			
	mutation	0.58 (0.20-1.66)	0.308		
SMAD4	wildtype	1.00			
	mutation	0.43 (0.10-1.79)	0.245		
Resectability	R+BR	1.00		1.67	
	LA	2.04 (0.90-4.61)	0.086	1.67 (0.72-3.89)	0.232

Abbreviations; ECOG-PS: Eastern Cooperative Oncology Group performance status, R: resectable, BR: borderline resectable, LA: locally advanced, HR: hazard ratio, CI: confidence interval

Treatment response to FOLFIRINOX

Response to FOLFIRINOX according to the presence of mutations was analyzed and compared. There was no significant difference observed in the distribution of PR, SD, and PD (Table 4). The same analysis was conducted on subgroup of patients with localized disease. The presence of mutations in *KRAS* and *TP53* was found to affect the treatment outcome of FOLFIRINOX significantly (Table 5). In post-hoc analysis, ORR (proportion of CR and PR) was different according to presence of *TP53*. ORR was higher in *TP53* wildtype than mutated *TP53* group (50.0% vs. 16.7%, p=0.024, Table 5)

Table 4. Comparison of treatment response to FOLFIRINOX according to the presence of main driver mutations.

mutation		PR (number,%)	SD (number,%)	PD (number,%)	total number	p-value
KRAS	wildtype	3 (37.5)	3 (37.5)	2 (25.0)	8	0.792
	mutation	29 (30.9)	47 (50.0)	18 (19.1)	94	
TP53	wildtype	15 (40.5)	15 (40.5)	7 (18.9)	37	0.298
	mutation	17 (26.2)	35 (53.8)	13 (20.0)	65	
CDKN2A	wildtype	28 (33.3)	39 (46.4)	17 (20.2)	84	0.514
	mutation	4 (22.2)	11 (61.1)	3 (16.7)	18	
SMAD4	wildtype	29 (34.1)	39 (45.9)	17 (20.0)	85	0.318
	mutation	3 (17.6)	11 (64.7)	3 (17.6)	17	

Abbreviations; PR: partial response, SD: stable disease, PD: progressive disease,

Table 5. Comparison of treatment response to FOLFIRINOX according to the presence of main driver mutations in patients with localized disease

mutation		PR (number,%)	SD (number,%)	PD (number,%)	total number	p-value
KRAS	wildtype	3 (100.0)	0 (0.0)	0 (0.0)	3	0.016
	mutation	12 (23.5)	34 (66.7)	5 (9.8)	51	
TP53	wildtype	9 (50.0)	9 (50.0)	0 (0.0)	18	0.018
	mutation	6 (16.7)	25 (69.4)	5 (13.9)	36	
CDKN2A	wildtype	13 (29.5)	26 (59.1)	5 (11.4)	44	0.374
	mutation	2 (20.0)	8 (80.0)	0 (0.0)	10	
SMAD4	wildtype	14 (30.4)	27 (58.7)	5 (10.9)	46	0.278
	mutation	1 (12.5)	7 (87.5)	0	8	
Post-hoc analysis for *TP53*						
mutation		PR (number,%)	SD+PD (number,%)		total number	p-value
TP53	wildtype	9 (50.0)	9 (50.0)		18	0.024
	mutation	6 (16.7)	34 (83.3)		36	
		PR+SD (number,%)	PD (number,%)			
TP53	wildtype	18 (100.0)	0		18	0.245
	mutation	31 (86.1)	5 (13.9)		36	

Abbreviations; PR: partial response, SD: stable disease, PD: progressive disease

Discussion

This study focused on investigating the four most frequent mutations (*KRAS*, *TP53, CDKN2A,* and *SMAD4*) in PDAC and analyzing their association with survival and response to FOLFIRINOX, which is one of the largely used treatment option in PDAC. Patients who had wildtype *TP53* exhibited longer OS compared with mutated *TP53* group, and the trend was more prominent in PDAC with localized disease in subgroup analysis. In addition, higher ORR to FOLFIRNOX was observed in *TP53* wildtype group in patients with localized disease.

Previous studies have investigated the relationship between frequent driver mutations and clinical significance including the prognosis of pancreatic cancer. In general, pancreatic cancer patients with mutations in the main driver gene tend to have a poor prognosis. Based on data obtained from 283 resected pancreatic cancer patients, alterations in the *KRAS* and *TP53* genes were each associated with poor OS.(9) Other studies reported that among the four driver mutation genes (*KRAS*, *TP53*, *CDKN2A*, and *SMAD4*), patients with fewer mutated genes exhibited better survival outcomes.(10, 11) Furthermore, a meta-analysis of 17 studies found that overexpression of *TP53* mutation was associated with poorer OS, along with other driver mutations as well.(6) Overall, it is reported that presence of main driver mutations is associated with a poorer prognosis compared to wildtype. However, to our knowledge, no

other studies have identified these driver mutations to their response to cytotoxic chemotherapy.

Tumor heterogeneity is apparent in pancreatic cancer. Intratumor heterogeneity, including heterogeneity between primary lesion and its metastatic part plays a key role in tumor progression and drug resistance.(12) While there is a lack of direct studies comparing the main mutation profiles of matched primary and metastatic lesions in pancreatic cancer, two large studies involving 1080 and 718 patients have shown a higher frequency of *TP53* mutations in the metastatic sites compared to the primary sites.(13, 14) Our results have shown that the negative predictive role of mutated *TP53* is more evident when excluding patients with distant metastasis. Intratumor heterogeneity observed in pancreatic cancer, in addition to higher frequency of *TP53* mutations in metastatic lesions can be considered to explain this view.

Over the past decade, the spread of NGS and advancements in bioinformatics have led to the emergence of novel treatment strategies that target specific subgroups of PDAC based on their genomic profile. Golan et al. demonstrated the effectiveness of using olaparib, a poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitor, as maintenance therapy in metastatic pancreatic cancer patients who have germline *BRCA* mutation.(15) Sotorasib proved anti-cancer effect against *KRAS* G12C patients in phase 1 and 2 trial.(16) In KEYNOTE 158 study, immune checkpoint inhibitor

pembrolizumab was effective in mismatch repair deficiency / MSI-high and TMB-high pancreatic cancer.(17, 18) Still, despite the introduction of these innovative treatments, the incidence of PDAC that are indicated for these options is exceedingly low. Currently, there is no specific option recommended for the patients with main driver mutations. Still, FOLFIRINOX remains the treatment of choice for most PDAC patients with adequate performance status.

TP53 is a tumor suppressor gene that encodes the genetic information for the p53 protein. It is also one of the most mutated genes in cancer. Wildtype p53 is known for its pro-apoptotic effects. It detects DNA damage, activate cell-cycle checkpoints, and subsequently induce cell death.(19, 20) During a study aimed at colon cancer cell lines, it was observed that oxaliplatin was effective in inhibiting the growth of all p53 wildtype cell lines, while most of the p53 mutated cell lines demonstrated innate resistance to the treatment.(21) The relationship between 5-FU and p53 protein is more evident. 5-FU, a DNA-damaging reagent, effectively induces cell cycle arrest, preventing cancer cells from proliferating and triggering apoptosis.(22) The role of *TP53* in regulating the cell cycle is crucial, therefore efficacy of 5-FU as a therapeutic agent is partially contingent on the *TP53* status of cancer cells. One study revealed that the Ca^{2+}-calmodulin-p53 axis plays an important role in the extrinsic apoptosis induced by 5-FU. Inhibiting this pathway eliminated the ability of 5-FU to induce caspase activity, indicating

the role of p53 in 5-FU induced cell death. Moreover, the apoptotic response to 5-FU was more than 50% reduced in cells expressing mutant p53 compared to cells expressing exogenous wildtype p53.(23, 24) It is believed that p53 may be involved in downstream signaling pathways in response to 5-FU.(25) Overall, *TP53* mutations could potentially contribute to the development of resistance to FOLFIRINOX, although conclusive clinical evidence to confirm remains to be established.

For the other mutated genes included in our study, the evidence associated with resistance to FOLFIRINOX is not as extensive. Nonetheless, one study demonstrated improved survival outcomes in pancreatic cancer patients with wildtype *KRAS* compared to those with mutated *KRAS*. Interestingly, this survival advantage was more prominent in the subgroup that received treatment with 5-FU and oxaliplatin.(26)

From the perspective of NGS data analysis, TMB and MSI were not included in our analysis. However, we confirmed that none of patients included were classified TMB-high or MSI-high. SNUH-pan-cancer panel and SNUBH-Macrogen panel used DNA based targeted panel, although targeted sequencing analysis is sufficient to analyze presence of main driver mutations. Whole genome sequencing and whole exome sequencing are frequently employed in contemporary studies examining the mutational landscape of pancreatic cancer.(27-30) Due to our study's use of targeted sequencing

analysis for categorizing mutations in pancreatic cancer, there is a constraint in generalizing the findings of these other studies in our analysis. However, identifying the predominant driver mutations which are commonly occurring and easily identifiable in pancreatic cancer, can still be accomplished using cost-effective targeted sequencing analysis. Moreover, these key driver mutations serve as potential targets for treating pancreatic cancer.(4) Targeted gene panel was based on the understanding that out of the vast pool of over 20,000 human genes, only around 500 are true driver genes in cancer.(31) Utilizing NGS-based cancer gene panels, the molecular traits of tumor tissues can be analyzed simultaneously, providing comprehensive coverage and allowing for the detection of minor allele frequencies in a cost-effective manner.(32)

Along with the aspect of the NGS data analysis, our research also has several limitations that should be taken into consideration. First, the number of included patients in group selected for FOLFIRINOX was limited, resulting in a relatively small sample size that may have impacted the study's overall outcomes. Second, collection of specimens for NGS test were not well organized. In certain patients, specimens were gathered after initiation of FOLFIRINOX, while in other patients, specimens from non-primary lesions were used. Finally, conducting a transcriptomic analysis is essential to gain a better understanding of the precise role played by p53 in resistance to FOLFIRINOX, which was not performed in our analysis.

To conclude, our study investigated the relation between the most frequently found driver mutation genes of PDAC and their clinical significance, including survival, progression, and response to FOLFIRINOX. *TP53* wildtype group exhibited better survival outcomes compared to the group with *TP53* mutation, possibly due to improved response to FOLFIRINOX. Additionally, our findings suggest that *TP53* could serve as a predictive marker for survival. Still, further in-depth analysis of NGS panel data is required to obtain a more comprehensive understanding on this subject.

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초 록

FOLFIRINOX 치료를 받는 췌장암 환자에서 주요 돌연변이 유전자들의 임상적 의의

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KRAS, *TP53*, *CDKN2A*, *SMAD4* 돌연변이는 췌장암에서 가장 높은 빈도로 보고되는 주요 돌연변이들이다. 췌장암 환자에서 이들 돌연변이의 여부에 따른 임상적 의의와 FOLFIRINOX 에 대한 치료 반응에 대한 기존의 연구는 아직 부족하다.

이 연구는 2016 년 1 월부터 2022 년 3 월의 사이 서울대학교병원과 분당서울대학교병원에서 췌장선암 (pancreatic ductal adenocarcinoma)로 진단받고 next generation sequencing 검사를 받은 환자를 대상으로 하였다. 이들 중 췌장암에 대해 FOLFIRINOX 를 최초 치료로 받은 환자군의 정보를 후향적으로 분석하였다.

102 명의 환자들이 분석에 포함되었다. *KRAS* 돌연변이가 94 명(92.2%)으로 가장 많았고, *TP53*(65 명, 63.7%), *CDKN2A*(18 명, 17.6%), 그리고 *SMAD4*(17 명, 16.7%)의 순으로 빈도를 보였다. 정상 *TP53* 환자군의 전체 생존기간은 중위 값 29 개월로 19 개월의 중위 값을 보인 돌연변이 *TP53* 환자군보다 더 길었고,(p=0.03) *TP53* 돌연변이는 사망의 위험성을 높여주는 예후인자로 연관되었다(Hazard

ratio=1.76 95% 신뢰구간 1.04-2.98, p=0.036). *TP53* 돌연변이 여부에 따른 생존기간의 차이는 원격 전이가 없는 췌장암 환자의 하위 분석에서 더 큰 차이를 보였다(37 개월 vs. 19 개월, p=0.01). 추가적으로, 정상 *TP53* 군의 FOLFIRINOX 에 대한 치료 반응률은 50.0% 로 *TP53* 돌연변이 군의 16.7% 보다 높았다(p=0.024).

정상 *TP53* 유전자를 가진 췌장암 환자들은 *TP53* 돌연변이 유전자를 가진 환자들에 비해 전체 생존기간이 길었고, 이는 원격 전이를 동반하지 않은 환자에서 더 두드러졌다. 이 결과는 FOLFIRINOX 에 대한 더 좋은 치료 반응으로 인한 것일 수 있다. 더 많은 수의 환자군과 돌연변이에 대한 심층적 분석을 포함하는 추가적 연구가 필요하다.

주요어 : 췌장선암, *TP53*, FOLFIRINOX, 전체 생존기간, 치료 반응률

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