SUBSEQUENT MALIGNANT NEOPLASMS AMONG PANCREATIC CANCER LONG-TERM SURVIVORS; NEW POTENTIAL HEREDITARY GENETIC ALTERATIONS.

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Objectives

Pancreatic ductal adenocarcinoma (PDAC) is a malignant disease with extremely poor prognosis. There is only a very small number of potential candidates who may develop another extrapancreatic subsequent malignant neoplasm (SMN) among PDAC long-term survivors. Only very few reports and information about SMN developed among PDAC surviving patients can be found.
Aim of this study was to identify and describe SMNs of PDAC long-term survivors with regards to the potential genetic background of the disease.

Methods

The retrospective study involved 118 PDAC patients who underwent a curative-intent surgery between the years 2006 and 2011.
Inclusion criteria for study enrollment included 1/ curative-intent surgical treatment, 2/ PDAC diagnosis histopathologically independently confirmed by two experienced pathologists, 3/ at least 5-year survival after surgery, 4/ post-resection surveillance consisted of biochemical tumor marker monitoring (CA 19-9, CEA, CA 125) every 3 months, cross section (CT or PET/CT) scans performed every 6-12 months or in cases of CA 19-9 elevation.
The clinical data, age, sex, date of diagnosis, pTNM stage, the histopathological type and grade of the tumor, lymphovascular-, perineural invasion and angioinvasion, the therapy administered and follow-up, were obtained from medical records.
Criteria for subsequent secondary malignancy were used: 1/ histological proof of the secondary malignancy, 2/ spatial separation of both tumors (in cases of synchronous tumors) and metastasis or recurrence were excluded; 3/ second tumor diagnosed later than 6 months after diagnosis of first tumor.

Results

Six patients (5%) from all radically resected PDAC patients developed SMN. Its rate among long-term survivors is 27%. The median time to diagnosis of SMNs was 52.5 months (ranged 8.8 to 87.1 months). The SMNs included prostate cancer (N= 1), rectal cancer (N= 2), malignant melanoma (N= 1), breast cancer (N= 1) and urinary bladder cancer (N=1). None of these patients died because of the malignant disease progression. Using the next-generation sequencing, we revealed missense germline variants in four of five analyzed patients. In two patients, variants with in silico predicted deleterious effect included rare variant in RECQL5 in a patient with prostate cancer and a PTCH1 variant in a patient with malignant melanoma.

Table 1: Basic patient's clinical data SMN group

Sex	Age	pT	pN	G	pP	pA	pL	Adjuvant treatment	FH PDAC	DFS	SMN	TTS	Treatment of SMN	TTTh	OS	Status
Male	68	3	0	3	Yes	No	No	GEM	No	64	rectal cancer	60	Surgery	60	64	Died
Male	69	2	1	3	No	No	No	GEM	No	105	urin blader cancer	17	Surgery	63	105	Alive
Male	67	3	1	3	No	No	No	GEM	Yes	14	Malignant melanoma	45	Surgery	45	104	Alive
Male	51	3	0	2	Yes	No	Yes	GEM	No	92	Prostate cancer	87	Hormonal therapy	87	92	Alive
Male	75	2	0	1	No	No	No	R/5FU	No	62	rectal cancer	61	None		62	Died
Female	70	3	0	2	No	No	Yes	GEM	No	73	breast cancer	9	Surgery	9	73	Alive

pT- tumor size, **pN**- lymph node metastasis, **G**- histological grading, **pP**- perineural invasion, **pA**- angioinvasion, **pL**- lymphovascular invasion, **FH PDAC**- family history of pancreatic ductal adenocarcinoma, **DFS**- disease-free survival (months), **SMN**- subsequent secondary malignant neoplasm, **TTS**- time to diagnosis of SMN (months), **TTTh** - time to therapy of SMN (months), **OS**- overall survival (months), **GEM**- 6 cycles of gemcitabine, **R/5 FU**- concomitant chemoradiotherapy

Table 2: Missense variants identified in patients with SSMs after PDAC.

SMN	TTS (months)	Gene	Variation according to HGVS	Functional consequence (LR/SVM)#
Urinary bladder	17.0	None	-	
Malignant melanoma	45.4	PTCH1	NM_000264.3:c.2597G>A	deleterious/deleterious
		ATM	NM_000051.3:c.3208G>A	tolerated/tolerated
Prostate cancer	87.1	PLA2G2A	NM_000300.3:c.185G>A	tolerated/tolerated
		RECQL5	NM_004259.6:c.1801G>A	deleterious/deleterious
Breast cancer	8.8	PREX2	NM_024870.3:c.1672C>G	tolerated/tolerated

TTS – time to secondary malignancy diagnosis, TCHTSM - time from chemotherapy to subsequent malignancy diagnosis (type of chemotherapy) #Functional consequence according to ANNOVAR using metaanalysis with MetaLR (logistic regression) and MetaSVM (support vector machines) prediction method

Conclusions

SMNs following radical surgery for PDAC are very rare. This retrospective analysis shows that subsequent secondary tumors in PDAC survivors became reality and seem to be more frequent than it used to be acknowledged before. Careful surveillance can identify these secondary tumors early, at a curable stage. If the performance status of these patients allows surgical therapy and a second primary tumor has favorable prognosis, subsequent surgery should be performed.
In the presented cohort there are 27% of patients with SMNs among 5-years pancreatic cancer survivors. SMNs risk factors are longer survival, higher age in time of diagnosis of PDAC and no metastatic pattern in five years following primary surgery. In two patients, variants with in silico predicted deleterious effect included rare variant in RECQL5 in a patient with prostate cancer and a PTCH1 variant in a patient with malignant melanoma.