INFLUENCE OF OPIOID ANALGESIA, OPIOID AND CANNABINOID RECEPTORS EXPRESSION IN TUMOR TISSUE ON SURVIVAL OF PATIENTS WITH PANCREATIC CANCER

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INTRODUCTION

Pancreatic cancer (PDAC) is one of the most common causes of cancer-related death in the world. PDAC patients are often treated with opioid analgesia after surgery. These drugs act through opioid and cannabinoid receptors, which pathways are involved in tumor progression and metastases and can negatively affect the survival of patients. In a previous study, we determined the effect of morphine analgesia and gene expression of cannabinoid receptor 2, opioid growth factor receptor and cannabinoid receptor delta on survival of pancreatic cancer patients. In this study, we associate our gene expression results with protein expression in selected patients.

PATIENTS

A total of 137 patients (70 women and 66 men, mean age 63 years) with clinical stage I-III and radicality R0 and R1 were examined. Of the 71 patients analyzed, 48 (67.6%) received morphine analgesia and 23 (32.4%) received piritramide analgesia in the postoperative period. The gene expression of opioid receptor mu (OPRM), kappa (OPRK), delta (OPRD), nociceptin receptor (OPRL), opioid growth factor receptor (OGFR) and cannabinoid receptor 1 (CB1) and 2 (CB2) in tumor tissue of patients with pancreatic cancer (PDAC) was analyzed by Real-time PCR.

		All patients (n=137)	OGFR gene		OPRM gene		OPRD gene		OPRK gene		OPRL gene		CB1 gene		CB2 gene	
		n (%)	Pos./Total (%)	p-value	Pos./Total (%)	p-value	Pos./Total (%)	p-value	Pos./Total (%)	p-value	Pos./Total (%)	p-value	Pos./Total (%)	p-value	Pos./Total (%)	p-value
Sex	F	70 (51,5%)	6/66 (9,1%)	1,000	5/66 (7,6%)	0,096	32/66 (48,5%)	0,918	3/66 (4,5%)	0,2	58/66 (87,9%)	0,849	25/66 (37,9%)	0,448	33/66 (50%)	0,649
	M	66 (48,5%)	6/63 (9,5%)		12/63 (19%)		29/63 (46%)		7/63 (11,1%)		57/63 (90,5%)		29/63 (46%)		35/63 (55,6%)	
Stage	I	14 (10,2%)	1/12 (8,3%)		1/12 (8,3%)		9/12 (75%)		1/12 (8,3%)		12/12 (100%)		**7/12 (58,3%)**		**11/12 (91,7%)**	
	II	109 (79,6%)	11/104 (10,6%)	0,635	15/104 (14,4%)	1,000	46/104 (44,2%)	0,128	10/104 (9,6%)	0,715	93/104 (89,4%)	0,268	**47/104 (45,2%)**	**0,013**	**54/104 (51,9%)**	**0,002**
	III	14 (10,2%)	0/14 (0%)		2/14 (14,3%)		7/14 (50%)		0/14 (0%)		11/14 (78,6%)		**1/14 (7,1%)**		**3/14 (21,4%)**	
Grading	1	6 (4,4%)	0/5 (0%)		1/5 (20%)		2/5 (40%)		0/5 (0%)		5/5 (100%)		4/5 (80%)		3/5 (60%)	
	2	78 (56,9)	7/75 (9,3%)	1,000	12/75 (16%)	0,452	37/75 (49,3%)	0,952	7/75 (9,3%)	1	68/75 (90,7%)	0,756	33/75 (44%)	0,184	43/75 (57,3%)	0,294
	3	53 (38,7%)	5/50 (10%)		5/50 (10%)		23/50 (46%)		4/50 (8%)		43/50 (86%)		18/50 (36%)		22/50 (44%)	
Resection R0		80 (58,4%)	6/73 (8.2%)	0,884	12/73 (16.4%)	0,476	36/73 (49.3%)	0,809	4/73 (5.5%)	0,21	**70/73 (95.9%)**	**0,013**	**42/73 (57.5%)**	**0,0001**	**48/73 (65.8%)**	**0,001**
R1		57 (41,6%)	6/57 (10.5%)		6/57 (10.5%)		26/57 (45.6%)		7/57 (12.3%)		**46/57 (80.7%)**		**13/57 (22.8%)**		**20/57 (35.1%)**	

Thirty patients (12 women and 18 men, mean age 64 years) with clinical stage I-III and radicality R0 and R1 were examined. In this group of patients, the expression of opioid receptor mu (OPRM), opioid receptor delta (OPRD), nociceptin receptor (OPRL) and cannabinoid receptor 2 (CB2) genes was analyzed in formalin-fixed paraffin-embedded (FFPE) tumor tissue samples from patients with pancreatic cancer (PDAC) using immunohistochemistry.

		All patients (n=30)	OPRM protein		OPRD protein		OPRL protein		CB2 protein	
		n (%)	Pos./Total (%)	p-value	Pos./Total (%)	p-value	Pos./Total (%)	p-value	Pos./Total (%)	p-value
Sex	F	12 (40%)	1/16 (6,2%)	0,560	1/14 (7,1 %)	1	3/17 (17,6 %)	0,653	12/17 (70,6 %)	1
	M	18 (60%)	2/12 (16,7)		0/10 (0 %)		3/11 (27,3 %)		9/12 (75 %)	
Stage	I	12 (40%)	1/12 (8,3 %)		1/10 (10 %)		2/12 (16,7 %)		9/12 (75 %)	
	II	14 (46,7%)	2/13 (15,4 %)	1	0/12 (0 %)	0,5	2/12 (16,7 %)	0,390	9/13 (69,2 %)	1
	III	4 (13,3%)	0/3 (0 %)		0/2 (0 %)		2/4 (50 %)		3/4 (75 %)	
Grading	1	8 (27,6%)	1/7 (14,3 %)		0/4 (0 %)		3/6 (50 %)		7/7 (100 %)	
	2	13 (44,8%)	1/12 (8,3 %)	1	0/11 (0 %)	0,522	2/13 (15,4 %)	0,285	8/13 (61,5 %)	0,149
	3	8 (27,6%)	1/8 (12,5 %)		1/8 (12,5 %)		1/8 (12,5 %)		5/8 (62,5 %)	
Resection R0		23 (76,7%)	3/22 (13,6 %)	1	1/19 (5,3 %)	1	5/21 (23,8 %)	1	17/22 (77,3 %)	0,357
R1		7 (23,3%)	0/6 (0 %)		0/5 (0 %)		1/7 (14,3 %)		4/7 (57,1 %)	

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CONTACT

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PUBLICATION AVAILABLE

RESULTS

INFLUENCE OF MORPHINE/PIRITRAMIDE ANALGESIA TREATMENT ON PATIENTS´ SURVIVAL

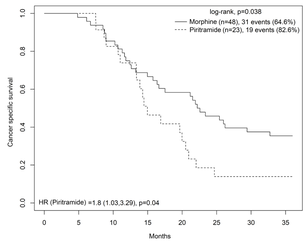

Fig. 1: Kaplan-Meier curve showing CSS survival for PDAC patients treated with morphine or piritramide during the perioperative period. Abbreviations: HR = hazard ratio.

RNA EXPRESSION OF OPIOID AND CANNABINOID RECEPTORS IN PDAC PATIENTS´ TUMOR TISSUE

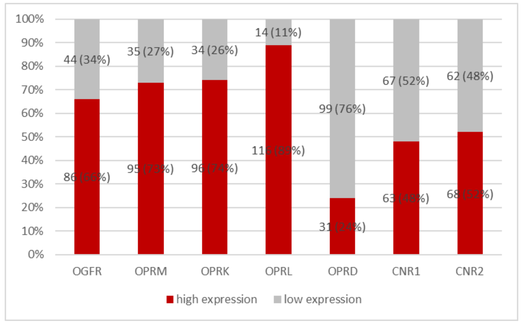

Fig. 2: Opioid and cannabinoid receptor RNA expression in PDAC patients´ tissue.

INFLUENCE OF THE EXPRESSION OF OPIOID AND CANNABINOID RECEPTORS IN TUMOR TISSUE ON SURVIVAL OF PDAC PATIENTS

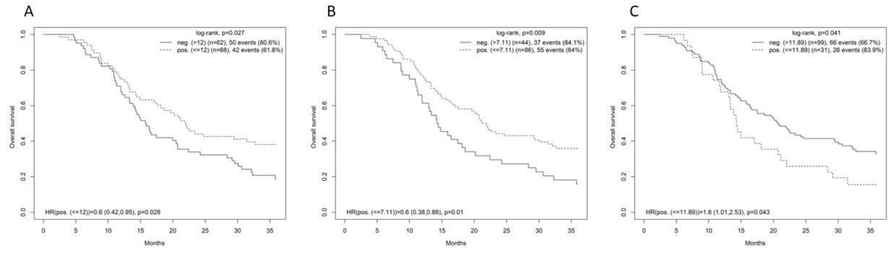

Fig. 3: Kaplan-Meier curve showing OS survival for PDAC based on (A) cannabinoid receptor 2 (CB2), (B) opioid growth factor receptor (OGFR), (C) delta opioid receptor (OPRD) gene expression survival. Abbreviations: HR = hazard ratio.

PROTEIN EXPRESSION OF OPIOID AND CANNABINOID RECEPTORS IN PDAC PATIENTS´ TUMOR TISSUE

The expression levels of the monitored proteins were assessed by a pathologist using the H score method, which incorporates both the percentage of positively stained cells and the staining intensity (0 – negative, 1+ – weak, 2+ – moderate, 3+ – strong). Based on the staining intensity, samples were categorized into two groups: low expression (0 and 1+) and high expression (2+ and 3+). The degree of positivity was determined by evaluating the intensity of brown staining in the positive tissue samples (as shown in Fig. 5B, 5D, 5F, and 5H) under the specified conditions. In contrast, the negative tissue samples (Fig. 5A, 5C, 5E, and 5G) exhibited no staining.

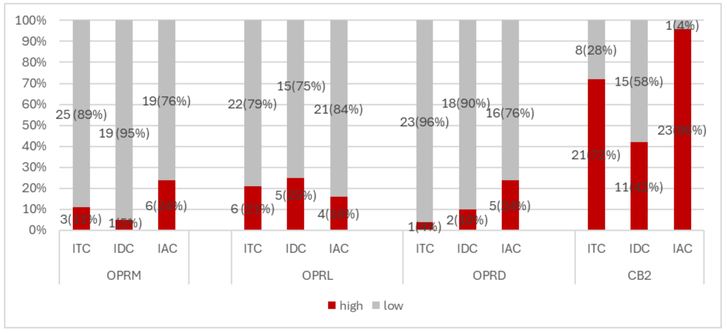

Fig. 4: Opioid and cannabinoid receptor protein expression in PDAC patients´ tissue in 3 different pancreatic compartments: tumor cells, acinar cells, and ductal cells. Abbreviations: ITC = intensity of tumor cells cytoplasm; IDC = intensity of ductal cells cytoplasm; IAC = intensity of acinar cells cytoplasm.

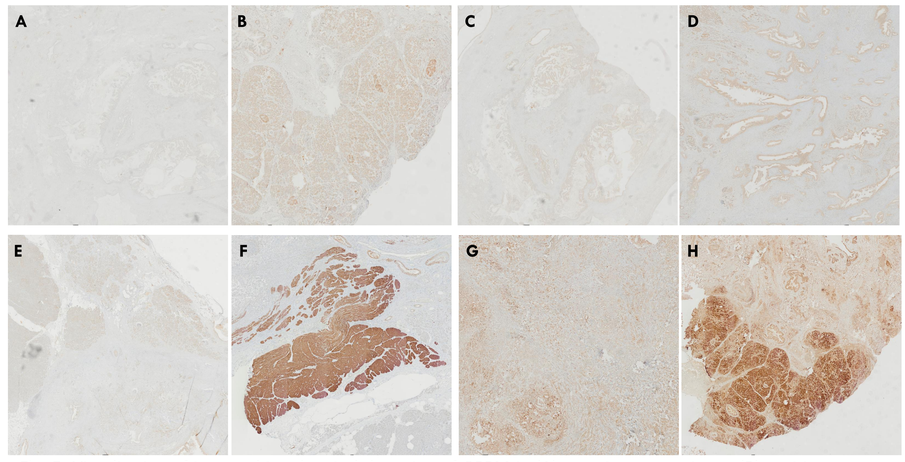

Fig. 5: Vizualization of immunohistochemical detection of OPRM in (A) negative tumor tissue, (B) positive tumor tissue; OPRL in (C) negative tumor tissue, (D) positive tumor tissue; OPRD in (E) negative tumor tissue, (F) positive tumor tissue, and CB2 in (G) negative tumor tissue, (H) positive tumor tissue.

CONCLUSION

Morphine analgesia improves CSS compared to piritramide analgesia after radical pancreatic cancer surgery. Cannabinoid receptor 2 and opioid growth factor receptor are highly expressed in pancreatic cancer tissue and their high expression improves OS, whereas high delta opioid receptor expression reduces OS. More studies are needed to elucidate the effects of opioid treatment and the expression of opioid and cannabinoid receptors on the treatment of pancreatic cancer and to determine their prognostic value.