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Brain Metastases (BM) in Pancreatic Ductal Adenocarcinoma (PDAC): Assessment of molecular genotype-phenotype features. An Entity with an Increasing Incidence?

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Abstract

Brain metastases (BM) from pancreatic ductal adenocarcinoma (PDAC) are an infrequent event. We identified n=25 pts from MSKCC with BM and PDAC; median age 58years. Median time to the development of BM was 17 months (range 0 to 79). Median overall survival from the time of BM development was 1.5 months (1 to 31). Six patients had germline testing; with BRCA1 (n=1) or BRCA2 (n=2) alterations detected. Seven patients had molecular profiling with *KRAS*, *TP53* and *MYC* amplification most frequent.

Background: The purpose of this study was to assess clinical characteristics of patients with metastatic pancreas ductal adenocarcinoma (PDAC) and brain metastases (BM) as well as the somatic and germline molecular profiles where performed.

Patients and Methods: Patients with PDAC and BM between January 1990 and January 2016 were identified. Molecular characteristics of somatic and germline testing where performed in the

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subset of patients that had provided informed consent. Somatic alterations were assessed by either MSK-IMPACT testing (>340 key cancer genes) or Sequenom testing (8 gene panel). Overall survival (OS) was calculated from date of diagnosis to either date of last follow up or death. Survival post brain metastasis was calculated from date of diagnosis of brain metastases by radiology or pathology to either date of last follow up or death.

Results: From a total of 5,824 patients with PDAC identified from January 2000 to January 2016, twenty-five (0.4%) patients had brain metastases. Median age of PDAC diagnosis was 58 years. Median time to the development of BM from initial PDAC diagnosis was 17 months (0 to 79). Median OS following BM diagnosis was 1.5 months (range 1 to 31). OS for patients that had craniotomy (n=4) was 11 months (1 to 31 months) with two long term survivors; 21 and 31 months respectively. Four patients had leptomeningeal disease. 6/25 pts had germline testing, 3 had *BRCA* mutations; *BRCA1* (n=2) and *BRCA2* (n=1). Somatic profiling identified *KRAS* mutations in 100%; G12D (n=4), G12V (n=2) and Q61K (n=1).

Conclusion: BM from PDAC is a rare event. We identified a speculative association of germline *BRCA1/2* alterations with BM in PDAC, which requires corroboration. Survival post BM development is poor with prolonged survival in selected patients via a multidisciplinary approach.

Introduction:

Pancreatic ductal adenocarcinoma (PDAC) is the fourth most common cause of cancer related death with an estimated 53,070 cases occurring in the United States in 2016. [1] PDAC is a challenging disease with the majority of patients presenting with either locally advanced or metastatic disease at time of diagnosis. Metastatic disease from PDAC is more commonly evident at sites such as the liver, lymph nodes, peritoneum and lung. In contrast, brain metastases from pancreatic ductal adenocarcinoma are rare with a reported incidence of <0.6%. [2, 3] Given PDAC is underscored by an aggressive tumor biology with an adverse prognostic outlook, a possible hypothesis for the rarity of brain metastases in PDAC is that patients do not survive sufficiently long enough for brain metastases to develop or become clinically apparent. At post mortem, brain metastases from PDAC have been described both in a case report [4] and in a larger series with a rate of 7.9%, [5] suggesting that the actual rate of <0.6% may be potentially underrepresented. Furthermore, since 2011 modest clinical therapeutic progress has been made in PDAC with cytotoxic chemotherapy triplet regimens such as FOLFIRINOX [6] and the doublet regimen of gemcitabine plus nab-paclitaxel [7] improving survival in patients with metastatic disease compared to single agent gemcitabine therapy. We hypothesize that the ability to achieve longer systemic disease control through sequencing of active agents may result in a more frequent incidence of clinically evident brain metastases. We reviewed records of patients with PDAC evaluated at MSKCC over a 16-year period to identify patients with brain metastases to determine associated clinical, pathologic and molecular features and describe the natural history.

Materials and Methods:

Samples:

A retrospective review of patients evaluated at MSKCC with brain metastases from PDAC from January 2000 to January 2016 was undertaken from several prospectively maintained

databases following IRB review. Charts were reviewed to determine clinicopathological characteristics including age at diagnosis, stage at presentation, treatment of primary tumor, use of chemotherapy (neoadjuvant, adjuvant or metastatic settings), management of brain metastases (surgery or radiotherapy). In addition, molecular characteristics determined via somatic and germline testing were performed in the subset of patient that had provided informed consent. Somatic alterations were assessed by either MSK-IMPACT testing (>340 key cancer genes) or Sequenom testing (8 gene panel).

Statistics:

Overall survival was calculated from date of diagnosis to either date of last follow up or death. Survival post brain metastasis was calculated from date of diagnosis of brain metastases by radiology or pathology to either date of last follow up or death.

Target capture and sequencing:

Molecular profiling was performed by the MSK-IMPACT assay which detects mutations and copy number alterations using DNA derived from frozen and formalin-fixed, paraffin-embedded (FFPE) tissue [8]. The assay has been designed to sequence all coding exons of >340 cancer-associated genes and provide 98% power to detect mutations with a true variant allele frequency of 10%, novel mutations down to a threshold of 5% variant allele frequency and mutations at recurrent hotspots down to a threshold of 2% variant allele frequency. Prior to the introduction of MSK-IMPACT testing in 2014, a Sequenom mass spectrometry panel which included 8 genes assessing for hotspot mutations in; AKT1, BRAF, EGFR, ERBB2, KRAS, MAP2K1, NRAS and PIK3CA genes was utilized.

Results

Clinical characteristics.

From a total of 5,824 patients with PDAC identified from January 2000 to January 2016, twenty-five (0.4%) patients had brain metastases. Seventeen patients (68%) had locally advanced or metastatic disease at initial diagnosis. Clinical characteristics are outlined in Table 2. Males were more frequently affected (60%) with a median age of pancreas adenocarcinoma diagnosis of 58 years (range 44 to 79 years). The median time to the development of brain metastases from initial diagnosis of pancreas adenocarcinoma was 17 months (range 0 to 79). All patients had evidence of brain metastases by CT or MRI imaging (See Figure 1, Figure 2A and Figure 2B for selected cases). The most common indication for CNS imaging was headache (36%, 9/25). Other neurological symptoms that prompted imaging included; facial/limb weakness (16%), visual disturbance (12%), ataxia (8%) and seizure (8%). One patient had imaging for persistent nausea. Another patient had a diagnosis of brain metastases incidentally discovered as part of work up of a concurrent diagnosis of diffuse large B cell lymphoma and stage IV pancreas adenocarcinoma. Biopsy of the brain lesion confirmed the CNS lesion was of pancreatic origin.

Brain metastases were evident at time of initial diagnosis of metastatic disease in three patients. All patients developed extracranial disease at some point during their disease trajectory. One patient developed a solitary brain metastases seventeen months post initial

diagnosis of stage III pancreas adenocarcinoma but developed peritoneal disease twelve months post craniotomy. The majority (68%, n=17) had evidence of liver metastases at time of metastatic presentation followed by lung metastases (52%, n=13) and peritoneal disease (20%, n=5).

Treatment.

First line systemic chemotherapy regimens are listed in Table 3. Mean number of systemic treatments was 2 (range 0 to 8). Six patients received prior adjuvant therapy, four received single agent gemcitabine and one patient each received adjuvant GTX and FOLFIRINOX. The treatment modalities employed in 24 patients with available follow up of their brain metastases are outlined in Table 3. Four (16.6%) patients underwent craniotomy and fifteen (62.5%) patients receiving radiotherapy. Eight (33.3%) patients received best supportive care alone. Of the patients who received radiotherapy, the majority (n=13) received whole brain radiotherapy (WBRT), with two patients receiving stereotactic radiosurgery (SRS). Median overall survival for all patients following diagnosis of brain metastases was 1.5 months (range 1 to 31 months). Median overall survival patients (n=4) post craniotomy was 11 months (1 to 31 months). Location of brain metastases varied with >50% having evidence of frontal lobe involvement. Four patients had evidence of leptomeningeal disease and five (21%) had cerebellar metastases, Table 3.

Molecular Testing.

Seven patients had somatic mutational profiling, four had MSK-IMPACT and three had Sequenom testing (8 gene panel), Figure 3. *KRAS* mutations were detected in all seven cases. Six of seven *KRAS* mutations were located at codon 12, four of which were *KRAS* G12D and two were *KRAS* G12V mutations. One patient had a *KRAS* Q61K mutation. Sample origins for molecular testing for MSK-IMPACT included; skin (n=1), lung (n=1), pancreas (n=1) and brain (n=1). For patients that had the limited eight-gene panel, one sample each was from brain, pleura and pancreas.

Two patients with brain metastases from PDAC were known *BRCA1* and *BRCA2* carriers. Four other patients had germline BRCA testing of which one had a *BRCA2* V2111 germline alteration. The germline mutation status of the other 19 patients was unknown.

Discussion.

This is the largest reported series to date of brain metastases in patients with PDAC. Previously reported cases include case reports, and a single institution experience [9], are summarized in Table 1. Consistent with prior data reported, males were more frequently affected in our dataset and represented 60% of patients. Median age at time of pancreas adenocarcinoma diagnosis within our patient cohort was 58 years (range 44 to 79 years) similar to a median age of 61.5 years reported previously [9]. The median time to development of brain metastases was 17 months for the 24 patients within our dataset, one year shorter than the 29 months reported previously [9]. Notably, our series included a higher number of patients with locally advanced or de novo metastatic disease at

presentation; 71% (17/24pts) compared to 11% (1/9) [9] and no patients had ampullary carcinoma.

We sought to identify somatic genetic alterations in PDAC which may predispose to the development of brain metastases. In a prior series, *TP53* mutations were detected in three patients with brain metastases and all were *SMAD4* wild-type by immunohistochemistry. [9] In a cohort of ten patients with *ERBB2* amplified PDAC cases, one of eight patients with metastatic disease developed brain metastases [10]. In our dataset, we identified *KRAS* mutations in all patients, predominantly located at codon 12 in 86% (n=6) cases. *TP53* was altered in two of four patients that had broader profiling by MSK-IMPACT in our dataset. We did not identify any *ERBB2* mutations in either the eight-gene panel or *ERBB2* amplifications/mutations by broader MSK-IMPACT testing. Two patients in this dataset had molecular testing performed on their brain metastases, Figure 1. Both harbored codon 12 *KRAS* mutations. Concurrent *TP53* and *RB1* loss in one patient sample coexisting with *KRAS* by MSK-IMPACT which would indicate a possible small cell phenotype [11]. Additionally, the presence of a *GNAS*R201 mutation concurrent with a *KRAS*G12V mutation in one patient infers the likelihood of this tumor arising from a precursor intraductal pancreatic neoplasm (IPMN) [12]. This patient developed brain metastases seventy months post diagnosis of a stage IIA tumor and 54 months from diagnosis with metastatic disease consistent with a more favorable biological profile [13]. Similarly, a case report of oncocytic carcinoma derived from an IPMN and metachronous brain metastases harbored a *KRAS*G12V mutation with the presence of *GNAS* not commented. [14] *MYC* amplification was noted in two of four samples by MSK-IMPACT (Figure 3) and has been reported as an inducer for metastases in *in-vivo* models of lung cancer [15].

A novel aspect to our cohort was the finding of germline *BRCA1* or *BRCA2* in three of six patients that had germline testing. Germline *BRCA1* alterations have been associated with an increased propensity for brain metastases in breast cancer [16] and ovarian cancer [17]. Germline *BRCA1* or *BRCA2* mutations have not been associated with brain metastases in PDAC to date. We anticipate that ongoing prospective studies in patients with *BRCA1/2* associated PDAC will contribute more information in this regard. Very specifically, data from our group and others have demonstrated the potential value of platinum based therapies and Poly ADP ribose polymerase (PARP) inhibitors in patients with germline *BRCA* mutations[18–20]. As these patients may live longer compared to patients without germline *BRCA* mutations, speculatively they may be at higher risk of developing rarer sites of metastases, including brain metastases.

Survival is poor for the majority of patients upon development of brain metastases with rare exceptions in select patients who undergo resection; with long term survival reported in three patients who had oligo-metastatic disease.[9, 21] Median survival post brain metastasis was 1.5 months in our dataset. For the selected patients who had resection within our described cohort a longer median survival time post diagnosis of brain metastases was noted at 11 months (range 1 to 31 months). Two patients survived >1-year post brain metastases development for 21 and 31 months respectively. Both had surgical resection and received subsequent systemic chemotherapy. One patient had a solitary brain metastasis resected followed by GTX chemotherapy and two subsequent lines of therapy upon systemic

progression. The other longterm survivor had resection of a dominant mass followed by WBRT followed by two lines of chemotherapy. Both patients died of extracranial disease. Less common sites of CNS related disease from PDAC reported in the literature include the presence leptomeningeal disease and cerebellar metastases. Leptomeningeal disease from PDAC has been described at initial presentation of PDAC [22–24], both in the presence [25] and absence [26] of parenchymal brain metastases. Four patients had evidence of leptomeningeal disease all occurred late in the disease trajectory with parenchymal brain metastases. Additionally, cerebellar metastases has also been reported [9, 27], and was evident in five patients in our dataset.

Conclusion

This is the largest reported clinical dataset of brain metastases in pancreas ductal adenocarcinoma. Brain metastases from pancreas ductal adenocarcinoma are rare and not exclusively seen in patients with prolonged survival. Indeed, the minority (32%, n=8) of patients within our dataset had evidence of brain metastases after 2011 which is following the introduction of both FOLFIRINOX and gemcitabine plus nab-paclitaxel for metastatic PDAC, suggesting no definitive increase in incidence since these regimens have been introduced. We provide insights into the somatic and germline alterations identified in patients that had molecular testing. Acknowledging small numbers that had germline testing in this dataset, a putative association of brain metastases with germline *BRCA1/2* alterations was noted. Survival is poor upon metastatic brain disease development, however in select patients long term survival can be achieved utilizing a multidisciplinary approach to treatment, highlighted by two long term survivors. With advances in germline and somatic profiling our findings of a possible association of germline *BRCA1/2* alterations with as well as other molecular patterns may be uncovered to provide insight into the molecular features of this uncommon clinical entity.

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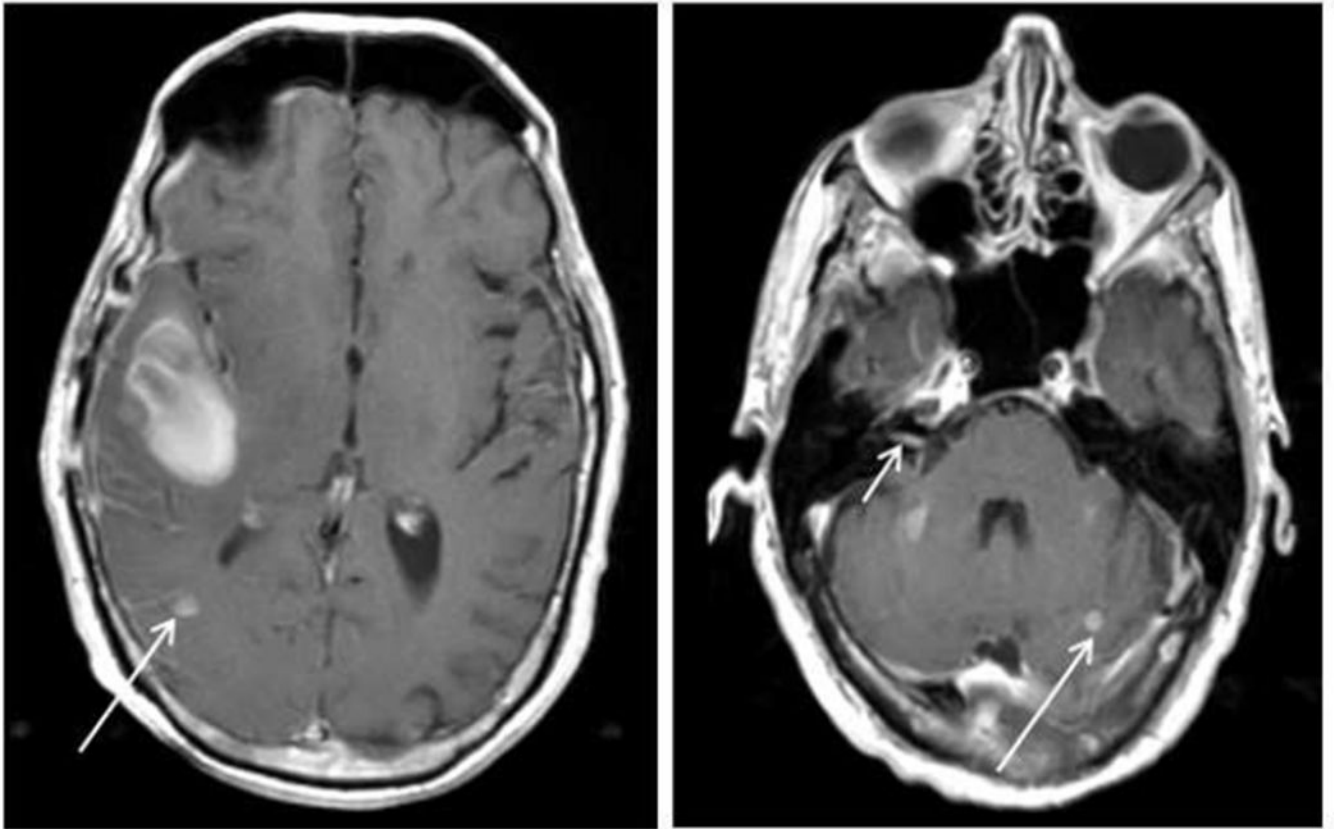
Clinical Practice Points

- Brain metastases from PDAC are a rare event, 0.4% frequency in our series. Brain metastases confer a poor prognostic implication with a median survival following diagnosis of BM of 1.5 months (range 1 to 31).
- In select patients long term survival can be achieved when incorporating a multidisciplinary approach, for example the median survival for the four patients that were able to undergo craniotomy post BM development was 11 months (range 1 to 31), with two patients surviving >1-year; at 21 and 31 months respectively.
- The molecular profile of patients who develop brain metastases from PDAC is poorly understood, our results a speculative association of BM in PDAC with germline BRCA1/2 alterations which occurred in three of six patients that had germline testing.
- Somatic profiling of six patients identified KRAS mutations in all patients; G12D (n=4), G12V (n=2), Q61K (1) with *TP53* mutations and *MYC* amplification most commonly in two of four patients that had broader profiling by MSK-IMPACT.
- Median time to development of BM was 17 months (0 to 79) with three patients harboring de novo BM involvement, which indicate that development of BM is not confined to patients with PDAC that achieve long term systemic disease control.

A.



B.

**Figure 1.**

A. MRI Brain (Patient 3 in Table 3 - KRAS mutant pancreas cancer)

Hemorrhagic 3.1cm mass in R frontal lobe with surrounding edema and mild L midline shift.

B. MRI brain one month post craniotomy with evidence of two new subcentimeter brain metastases (arrow) and leptomenigeal enhancement (arrow). Cytology positive from lumbar puncture.

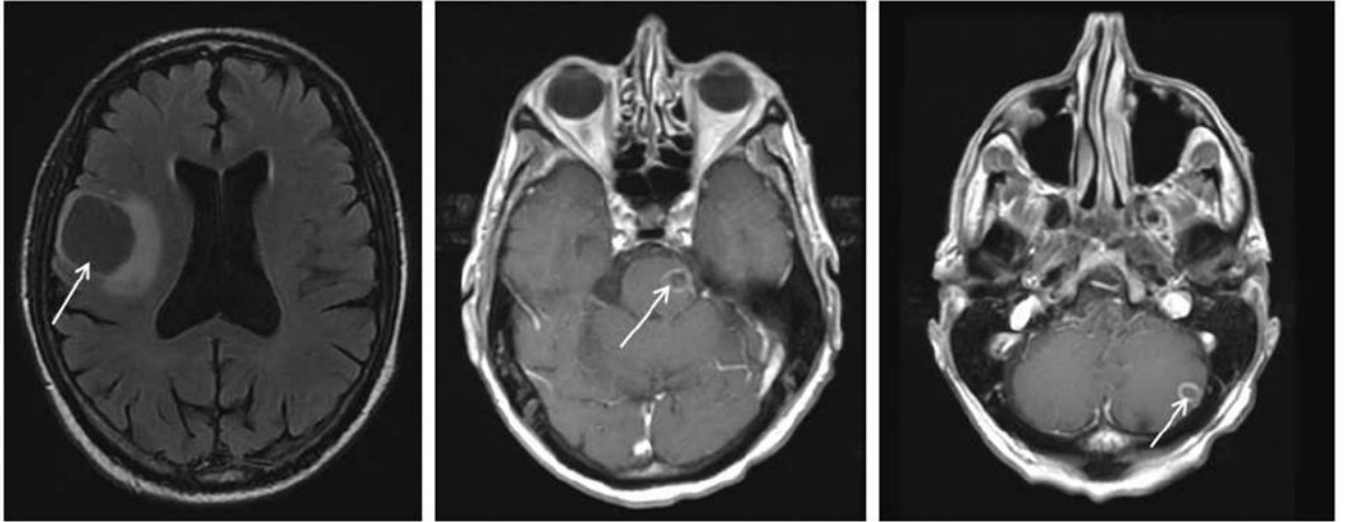


Figure 2.
Metastatic KRAS mutant pancreas cancer. (Patient 1 in table 3)
MRI brain with evidence of right frontal lobe, midbrain and cerebellar metastases (arrows).

Site	Pancreas	Pleura	Brain	Brain	Lung	Pancreas	Skin		
KRAS	G12D*	G12D*	G12V*	G12D	G12V	G12D	Q61K		
TP53				R273H	I251F				
ARID1A									DEL
ARID1A									FUSION
RB1						A17Pfs*3			
GNAS							R201H		
SMAD4							S150I		
CTNNB1							D83N		
POLE								Q345*	
PALB2								FUSION	
RNF43								FUSION	
MYC							AMP		AMP
CCNE1							AMP		
AKT2							AMP		
FGFR1									AMP



* 8 gene panel

Figure 3:
Molecular profiling of seven patients with brain metastases from PDAC

Table 1.

Clinical characteristics, treatment and outcomes of patients with brain metastases from pancreas cancer previously reported in the literature

Author Year	BM at diagnosis	Pt.	Primary	Location BM	Treatment BM	OS from BM
Kuratsu [21]	N N	56yo M 58yo M	Head Not reported (NR)	Thalamus Cerebellum	Ommaya + RT Resection	9 months 2 weeks
Chiang [17]	N	54yo M	Uncinate process (KRAS G12V)	Left Frontal	Resection + RT	20 months (ongoing)
Caricato [22]	N	67yo M	Head	Cerebellum	Resection	12 months (ongoing)
Park [2]	N Y N Y	48yo, M 51yo, M 52yo, M 62yo, M	NR NR NR NR	Multiple Left frontal Left parietal Left frontal, L basal ganglia	RT Supportive care Radiation Supportive care	Median Survival 2.9 months (1.5-3.8)
El Kamar [23]	N	56yo, M	NR	Multiple cerebral and pons	Supportive care	3 days
Lemke [20]	N	48yo, F 66yo, M	Tail Tail	Cerebellum Right cerebrum	Resection + RT Resection + RT	>10yrs >6 yrs
Matsumura [24]	N	64yo M	Tail	Cerebrum	Resection + RT	>10 months
Marepaily [25]	N	36yo, F	Tail	Cerebellum (adenosquamous)	Resection	<1 month
Matsumoto [26]	Y	68yo, M	Head	Right Cerebrum	Resection	3 months
Rajappa [27]	N	67 yo, M	Tail	Right Occipital	Resection + SRS	36 months
Zaanan [28]	N	57yo, M	Head	Multiple cerebrum	Supportive care	3 days
Rao [29]	Y	57yo, M	Mass neck, body, tail	Multiple cerebral and cerebellar	Radiation	<3 months
Kumar [9]	N	Median 61.5 yrs (N=8)	Head n=6 Ampullary n=1 Tail n=1	Cerebral Cerebellar n=1 Vermis n=1 Choroid n=1	Reported (n=4) Resection + RT (n=1) Resection (n=1) RT (n=2)	One pt >9 yrs post resection

*NR= not reported

RT= radiotherapy

SRS= stereotactic radiosurgery

Table 2.

Clinical characteristics of 24 patients with brain metastases from PDAC.

Characteristics	N=25 (%)
Gender	
Male	15 (60)
Female	10 (40)
Race/Ethnicity	
White	20 (80)
Asian	3 (12)
Black	2 (8)
Smoking status	
Never	12 (48)
Prior/current smoking history	13 (52)
Location of primary pancreas tumor	
Head	10 (40)
Body	8 (32)
Tail	7 (28)
Stage at diagnosis	
I	0 (0)
IIA	4 (16)
IIB	4 (16)
III	1 (4)
IV	16 (64)

Table 3

Location, treatment, survival and molecular characteristics of 24 patients with brain metastases from PDAC

Pt	Molecular	Site of BM	Surgery Y/N	RT	LMD	BM Survival (days)	1 ST Line chemo.	OS advanced disease (months)
1	<i>KRAS</i> G12D	Cerebellum, Right frontal	N	WBRT	N	2	Cisplatin + gemcitabine	82
2	<i>KRAS</i> Q61K, <i>MYC</i> Amp, <i>FGFR1</i> Amp	Right occipital, Right frontal	N	WBRT	N	77	FOLFIRINOX	3
3	<i>KRAS</i> G12D, <i>TP53</i> R273H	Right frontal	Y	WBRT	Y	52	Gemcitabine plus nab-paclitaxel	10
4	<i>KRAS</i> G12V <i>BRCA2</i> Germline	Right parietal, Right temporooccipital	N	WBRT	Y	233	GemOX	24
5	No testing	Left frontal	Y	N	N	975	GTX	31
6	No testing	Multiple cerebral hemisphere, cerebellum	N	N	N	28	Supportive care	<1
7	No testing	Multiple cerebral	N	N	N	12	Supportive care	<1
8	No testing	Right frontal then parietal, cerebellum	N	SRS then WBRT (new lesions)	N	165	Gemcitabine	30
9	No testing	Right frontal, Left parietal, Left frontal	N	N	N	20	Gemcitabine plus irinotecan	7
10	<i>KRAS</i> G12D	Precentral gyrus, cerebellum	N	WBRT	N	50	Gemcitabine	9
11	No testing	Left frontal, right temporal, left occipital	N	N	N	11	GemOX	12
12	No testing	Multiple cerebral hemisphere	N	N	N	21	Gemcitabine plus erlotinib	22
13	No testing	Left occipital	N	SRS	N	56	GemOX	18
14	No testing	Left frontal, Left temporal	N	WBRT	N	27	Supportive care	<1
15	No testing	Left frontal, left parietal, cerebellum	N	WBRT	N	193	Unknown	6
16	No testing	Left frontal, Right occipital	Y	WBRT	N	656	Cisplatin plus gemcitabine	39
17	No testing	Left frontal	N	SRS	N	184	GemOX	16
18	No testing	Left parietal	N	N	N	41	FOLFIRINOX	43
19	No testing	Multiple cerebral hemisphere	N	WBRT	Y	23	GemOX	18
20	No testing	Right frontal, superior vermis	Y	WBRT	N	26	GTX	29
21	No testing	Left hemisphere, cerebellum	N	N	N	7	FOLFIRINOX	10
22	<i>BRCA1</i> Germline	Left frontal, right occipital	N	N	N	23	Cisplatin plus gemcitabine +/-PARP inhibitor	22
23	<i>KRAS</i> G12V, <i>TP53</i> 1251F	Left Frontal, left precentral gyrus	N	WBRT	N	76	FOLFIRINOX	57

Pt	Molecular	Site of BM	Surgery Y/N	RT	LMD	BM Survival (days)	1 ST Line chemo.	OS advanced disease (months)
24	BRCA1 Germline	Right Temporal lobe, Cerebellum	N	WBRT	Y	118	Cisplatin plus gemcitabine +/- PARP inhibitor	14

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