Gamma Knife treatment of recurrent CNS metastases of pancreatic origin: a case report and review of the literature

Subha Perni¹, Tony J Wang^{1,2}, Jerry Lesser¹, Christopher Mandigo, Steven R Isaacson & David P Horowitz^{*,1,2}

Brain metastases (BM) of pancreatic origin are extremely rare. We review the literature around BM of pancreatic origin and describe a 38-year-old woman who developed BM 10 months after *pancreaticoduodenectomy* for treatment of pancreatic adenocarcinoma. She underwent resection and fractionated stereotactic radiotherapy followed by re-resection and Gamma Knife radiosurgery (GKRS) when the lesion recurred. She then developed two new BM, and was treated with GKRS. The patient is alive without progression 38 months after her most recent GKRS.

First draft submitted: 7 June 2016; Accepted for publication: 9 November 2016; Published online: 9 May 2017

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy characterized by poor prognosis, with only 7% of patients alive at 5 years [1]. Many patients have metastatic disease upon presentation, but brain metastases (BM) are rare. In one review of 1229 PDAC patients, only 4 (0.33%) developed BM [2]. Such low prevalence may be partly attributable to poor survival leading to death before development of BM, or to lack of evaluation for BM because of poor prognoses.

The literature on BM of pancreatic origin is thus limited to case reports and small series. Optimal treatment approaches have not been established, although often surgery and/or whole brain radiation are used. Gamma Knife radiosurgery (GKRS) or linear accelerator (LINAC)-based stereotactic radiosurgery (SRS) have been reported in only a few cases [3–5].

One study of 40 patients with BM from all types of gastrointestinal cancer (including 2 with pancreatic cancer), showed local control of 91% with GKRS and a median survival (MS) of 6.7 months [3]. Another study of patients with BM of gastric origin showed that patients treated with GKRS versus whole brain radiotherapy (WBRT) had an MS of 40 weeks (95% CI: 44.9–132.1 weeks) versus 9 weeks (95% CI: 8.8–21.9 weeks) [6]. These studies suggest GKRS could potentially confer prognostic benefit for patients with BM of pancreatic origin.

Here, we contribute to the literature around use of SRS and GKRS for patients with BM of pancreatic origin. We describe a 36 year-old woman who received treatments with fractionated stereotactic radiotherapy (FSRT) and GKRS for recurrent BM of pancreatic origin, and has survived for 8 years since initial diagnosis. This case report is submitted under a Columbia University Medical Center Institutional Review Board approved protocol (AAAM2358).

KEYWORDS

- brain tumor • metastasis
- radiotherapy

¹Department of Radiation Oncology, Columbia University/New York Presbyterian Hospital, New York, NY, USA

²Herbert Irving Comprehensive Cancer Center, Columbia University/New York Presbyterian Hospital, New York, NY, USA

³Department of Neurosurgery, Columbia University/New York Presbyterian Hospital, New York, NY, USA

*Author for correspondence: Tel.: +1 212 305 4982; dph2119@columbia.edu

Case presentation

We present the case of a 36 year-old woman who initially presented in April 2008 with hiccupping and epigastric pain. She had smoked one pack of cigarettes daily for 10 years. Initially, she was treated for gastroesophageal reflux disease, and her pain improved for a few months. It returned in more severe form in October 2008. She initially refused endoscopy, but sought care after developing obstructive jaundice and worsening pain a month later. She then had MRI, CT and endoscopic retrograde cholangiopancreatography/endoscopic ultrasound with stenting (ERCP/EUS), which showed a head of pancreas/uncinate mass and two liver lesions. CT-guided liver biopsy showed adenocarcinoma with mucinous characteristics.

The patient is Serbian and describes herself as of Gypsy descent. Her father developed glioblastoma at the age of 57 years. She has three paternal uncles with cancer, including liver cancer, colon cancer (diagnosed at 46 years) and an unknown cancer. A 33 year-old man in her grandfather's generation has colon cancer. Two maternal first cousins have cancer – colon (diagnosed at 30 years) and stomach (diagnosed at

33 years). There is no family history of pancreatic or ovarian cancer.

The patient underwent alcohol ablation of liver lesions and neoadjuvant chemotherapy with gemcitabine and cisplatin. In July 2009, she had a pylorus-preserving pancreaticoduodenectomy with embolization and resection of a liver metastasis. Pathology demonstrated a 2.5 cm mass in the head of the pancreas consistent with poorly differentiated adenocarcinoma. Surgical margins were uninvolved, and no disease had spread to examined lymph nodes. She did not receive adjuvant chemotherapy, and was doing well 6 months after surgery.

Management & outcome

The patient felt well with no evidence of metastatic disease for 10 months before presenting with 2 weeks of left-sided visual changes and 1 day of severe headache in May 2010. A 3.5 cm lesion in her right occipital lobe was found, as shown in **Figure 1A**. She underwent a right craniotomy with gross total resection. Pathology showed moderately differentiated metastatic adenocarcinoma consistent with pancreatic primary (CK7⁺, strongly CK20⁺, patchy strong CDX2⁺, patchy weak TTF1⁺).

After 3–4 months, she developed recurrent tumor at this location. She then underwent FSRT of unknown dose and fractionation, and FOLFIRINOX chemotherapy at an outside institution. However, she developed a recurrence at the same site after 2 months. The lesion was re-resected in February 2011, and she developed a recurrence after 3 months with invasion into the right cerebellum and occipital lobe, which is shown in **Figure 1B**. She was then treated in May 2011 with GKRS (18 Gy to 45% isodose line, **Figure 2** shows plan). After 20 months, she developed new right frontal (**Figure 1C**) and right cerebellar (**Figure 1D**) lesions and was treated again in January 2013 with GKRS (18 Gy to 50% isodose line, **Figure 3** shows plan).

The patient tolerated treatment without documented toxicities. MRI brain in March 2016 showed stable, treated metastases 38 months after GKRS treatment of right frontal and right cerebellar lesions and 56 months after first GKRS treatment to recurrent right occipital lesion. She was last seen in April 2016 with no residual neurological deficits, and has no evidence of other metastases or local recurrence on CT chest, abdomen and pelvis done in July 2015. She has survived 5 years and 10 months since

Figure 1. Initial right occipital brain metastases (A), recurrent brain metastases at same site (B) subsequently treated with Gamma Knife radiosurgery, and new right cerebellar lesion (C) and right frontal lesion (D) that were subsequently treated with Gamma Knife radiosurgery.

Figure 2. Representative images from treatment plan for Gamma Knife radiosurgery of patient's second recurrence (18 Gy to 45% isodose line).

initial development of BM, and nearly 8 years after her initial diagnosis.

Discussion

This patient had an initial BM to the right occipital lobe presenting 10 months after resection of her primary tumor. This BM recurred locally after two resections and FSRT, but was controlled after GKRS. In addition, she had two lesions that developed 3 years after her initial BM, and were treated with GKRS. These lesions likely represent additional metastases, which might occur unpredictably despite control of

the primary tumor. However, it is unusual that this patient developed these isolated metastases to the brain rather than florid metastatic disease, and the histological characteristics of the tumor that have resulted in this pattern are not clear at this time.

At our institution, 528 patients were treated with GKRS for BM between 1998 and 2013. However, this case represents the isolated instance of treatment for BM of pancreatic origin. We also performed a MEDLINE search using keywords 'pancreatic cancer' and 'brain metastasis' as well as MeSH terms 'brain

neoplasms/secondary’ and ‘pancreatic neoplasms’. We excluded non-English papers, those with only abstract available, and those focusing on non-PDAC neoplasms. One reviewer (S Perni) screened all titles and abstracts to assess relevance, and extracted data from the 22 included papers. The results are displayed in **Table 1**.

Notably, Menendez *et al.* also describe the case of a patient with PDAC treated with GKRS. A 65 year-old man had four tumors treated with GKRS to a dose of 20 Gy. He only survived 35 days post GKRS, but had no progression

of his brain disease [5]. In contrast, our patient had unusually long survivorship, which may be related to the control of her primary and systemic disease, which has been shown to be predictive of 10-year survival in patients with BM [20].

A few other case reports also describe long survivorship. Rajappa *et al.* describe a 67 year-old man with PDAC who developed a large right occipital mass 4 years after his primary diagnosis and underwent resection followed by LINAC SRS to the tumor bed at 15 Gy (82% isodose line). He had multiple local recurrences

Figure 3. Representative images from treatment plan for Gamma Knife radiosurgery of patient's new frontal lesion (18 Gy to 50% isodose line).

Table 1. Cases of brain metastases of pancreatic origin, with exceptionally long survivorship highlighted.

Study	Age/sex	Time to BM	Lesions	Treatment of BM	Survival	Ref.
<i>Surgical resection without radiation for treatment of BM</i>						
Matsumoto <i>et al.</i>	68/male	Diagnosed at same time as PDAC	Right temporoparietal	Resection	3 months after diagnosis of PDAC/BM	[7]
Kumar <i>et al.</i>	Unknown (Series median: 61.5; range: 49–70 years)	13 months after Whipple	Right parietal	Resection	9 years after diagnosis of PDAC/BM, then lost to follow-up	[8]
Kuratsu <i>et al.</i>	58/male	5 months	Vermis	Resection	2 weeks after surgery	[9]
<i>WBI for treatment of BM</i>						
Kumar <i>et al.</i>	Unknown (Series median: 61.5; range: 49–70 years)	22 months after Whipple 2 months after initial diagnosis 53 months after Whipple	Recurrent left parieto-occipital Cerebellar lesions and numerous intra-axial brain lesions CN XII	Three resections, WBI WBI WBI, gemcitabine-based chemotherapy	Unknown	[8]
Lemke <i>et al.</i>	48/female	5 years 4 months	Right cerebellum	Resection, WBI	17 years since resection of primary	[10]
	66/male	11 months	Postcentral cerebrum	Resection, WBI	7 years since resection of primary	
Park <i>et al.</i>	48/male	Unknown (series mean: 4.5 ± 0.7 months)	Small, multiple areas	WBI	Unknown (series median survival: 2.9 ± 1.0 months; range: 1.5–3.8 months)	[2]
	52/male		Left parietal	WBI		
Yamada <i>et al.</i>	62/male	Diagnosed at same time as PDAC	Multiple tumors	Chemotherapy, WBI	2 months after diagnosis	[11]
Rao <i>et al.</i>	57/male	Diagnosed at same time as PDAC	Multiple tumors	WBI, palliative chemotherapy with FOLFIRINOX	Transitioned to hospice after 2 cycles chemotherapy	[12]
Yoo <i>et al.</i>	80/male	Diagnosed at same time as PDAC	Leptomeningeal carcinomatosis	WBI, intrathecal chemotherapy	Transferred after 4 rounds of radiation, lost to follow-up	[13]
<i>LINAC SRS or GKRS for treatment of BM</i>						
Menendez <i>et al.</i>	65/male	Unknown	4 tumors	GKRS, adjuvant chemotherapy	35 days post radiation	[5]
Rajappa <i>et al.</i>	67/male	4 years	Recurrent right occipital, right cerebellum, left thalamic and right insular lesions	Resection, LINAC SRS $\times 5$	7 years after PDAC diagnosis, 3 year after BM diagnosis	[4]
Kuratsu <i>et al.</i>	56/male	1 year 3 months	Left thalamus	Ommaya reservoir, cyst aspiration, 'local radiation'	9 months after surgery	[9]
<i>No treatment of BM (patient choice/poor prognosis)</i>						
Park <i>et al.</i>	51/male	Unknown (series mean: 4.5 ± 0.7 months)	Left frontal	No treatment	Unknown (series median survival: 2.9 ± 1.0 months; range: 1.5–3.8 months)	[6]
	62/male		Left frontal, left basal ganglia	No treatment		
Hong <i>et al.</i>	72/male	7 months	Leptomeningeal carcinomatosis	No treatment	3 weeks after resection	[14]

Table 1. Cases of brain metastases of pancreatic origin, with exceptionally long survivorship highlighted (cont.).

Study	Age/sex	Time to BM	Lesions	Treatment of BM	Survival	Ref.
No treatment of BM (patient choice/poor prognosis) (cont.)						
El Kamar <i>et al.</i>	56/male	6 months	Multiple cerebral nodules	No treatment	17 days after onset of BM symptoms	[15]
Naugler <i>et al.</i>	68/female	Post-mortem diagnosis	Pineal gland	No treatment	2 weeks after hospital admission for symptoms	[16]
Zaanan <i>et al.</i>	57/male	4 years 6 months	Multiple tumors	No treatment	3 days after BM diagnosis	[17]
Blows <i>et al.</i>	72/male	Post-mortem diagnosis	Leptomeningeal carcinomatosis	No treatment	3 weeks after hospital admission for symptoms	[18]
Other or unknown treatment of BM						
Kumar <i>et al.</i>	Unknown (series median: 61.5; range: 49–70 years)	2 months after Whipple 43 months after Whipple 36 months after diagnosis 57 months after initial diagnosis	Clivus, pituitary stalk, CN VI Anterior vermis Choroid Multiple cystic metastasis to cortical/sub-cortical interface	Unknown	Unknown	[8]
Ferreira Filho <i>et al.</i>	49/male	6 months	Carcinomatous meningitis	Intrathecal chemotherapy	8.5 months after diagnosis	[19]

as well as other lesions in the cerebellum and a superficial scalp metastasis, and ultimately underwent treatments of CyberKnife SRS and LINAC SRS. He then developed thalamic and insular lesions which were treated with LINAC SRS, died 2 months later, which was 7 years after his initial PDAC diagnosis and 36 months after diagnosis of BM [4].

Lemke *et al.* describe the case of a 48 year-old woman who developed a right cerebellar metastasis 6 years after her initial diagnosis of PDAC. She was treated with resection and WBRT to 46 Gy, and continued to survive at the time of publication of her report, more than 10 years after development of BM. The second patient they describe, a 66-year-old man with resected pancreatic cancer, developed a cerebral tumor after 11 months that was resected and underwent WBRT to 30 Gy. He was alive 5 years later [10]. Kumar *et al.* also include in their report the case of a patient of unknown age and gender with a right parietal BM of pancreatic origin that was surgically resected, who was alive without local recurrence for 9 years before being lost to follow up [8].

However, these cases appear to be exceptions rather than rules. In other reports, survival after development of BM appears to be extremely poor. In a review of 13 case reports

of patients with BM of pancreatic origin, Esmailzadeh *et al.* found MS after diagnosis of BM was 4 months [21]. Matsumoto and Yoshida reviewed 20 case reports, and found that MS was generally less than a year [7].

Our patient has an unusual presentation of pancreatic cancer for multiple reasons, including her age and her family history as well as the longstanding control of her primary tumor and metastatic disease isolated to the brain. This lack of systemic disease or primary recurrence has not only likely contributed significantly to her survival, but has also demonstrated the long-term potential for durable local control of BM of pancreatic origin for patients with use of GKRS.

This patient developed recurrence of her right occipital metastasis following two resections and one treatment with FSRT, each within a matter of a few months. The margin status of her resections and the dose and fractionation of her FSRT is not available, so these treatments may have been suboptimal. However, it is notable that despite these recurrences, she had long-term local control of 56 months after she had GKRS to the same lesion. She also had long-term control of 38 months after treatment of her other two BM.

Although, we have focused here on GKRS, it is also possible that she may have received the

same benefit from LINAC-based SRS. Single-dose SRS, as compared with FSRT, may be more effective for BM because of an increased tumor cell destruction from a higher dose of radiation as well as increased immune system stimulation and vascular effects [22]. Since we do not know the dose of her previous FSRT, it is also possible that she did not receive a high enough biologically effective dose to control her tumor.

An optimal management strategy for treatment of BM of pancreatic origin has not yet been developed. Patients with BM of pancreatic origin have had historically poor survival due to local progression of their primary tumor or death from systemic metastases. However, we report a patient that has had long survivorship, likely due in large part to a lack of local recurrence and metastases outside of the brain. Given that improvements in systemic agents may lead to more patients with controlled disease outside of the CNS, treatment of BM of pancreatic origin will increase in importance.

Although, this patient has local recurrence after resection, our review shows that the other four patients with exceptionally long survivorship all had surgical resection [4,8,10]. In addition, Matsumoto and Yoshida also found that survival after surgical resection of BM of pancreatic origin was significantly longer (mean: 883.7 days) than in cases where surgical resection was not performed (mean: 75 days; $p = 0.03$). The 5-year survival rate after surgical resection for BM was 22% [7]. While patients who can tolerate resection are more likely to be those who otherwise have better prognoses, we would still recommend surgical resection as a treatment modality for BM of pancreatic origin.

Two of the patients with long survivorship had resection followed by WBRT, while one had resection followed by LINAC SRS [4,10]. We also report this case of long survivorship following GKRS after surgical resection. We would thus recommend adjuvant radiation if resection is possible.

If resection is not possible, WBRT is the preferred modality for patients who have many BM. However, in the case of a few BM, as

improvements in systemic agents lead to longer survival, diminishing toxicity by using more targeted treatments such as SRS rather than WBRT will be of more importance. Our report provides a description of durable local control (38 months) of two lesions treated with GKRS only, which suggests that GKRS alone may also be efficacious for local control of BM.

Conclusion

We report the rare case of a patient with multiple recurrent BM of pancreatic origin. This case is remarkable for a long survivorship of 8 years since initial diagnosis with pancreatic adenocarcinoma. She has had excellent local control of 38 months after GKRS treatment of her multiple BM, even after developing recurrences after treatment with LINAC FSRT as well as surgical resection. Although further studies are required, this report suggests that GKRS might be considered as a treatment for BM of pancreatic origin, even in the setting of recurrence.

Disclosure

Identifying information has been removed in order to protect the anonymity of the patient. Portions of this work were presented in poster form at the 17th Leksell Gamma Knife Society Meeting in Amsterdam, The Netherlands, 15–19 May 2016.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Informed consent disclosure

This case report is submitted under a Columbia University Medical Center Institutional Review Board-approved protocol (AAAM2358). The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

References

- 1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J. Clin.* 65(1), 5–29 (2015).
- 2 Park KS, Kim M, Park SH, Lee KW. Nervous system involvement by pancreatic cancer. *J. Neurooncol.* 63(3), 313–316 (2003).
- 3 Da Silva AN, Nagayama K, Schlesinger DJ, Sheehan JP. Gamma knife surgery for brain metastases from gastrointestinal cancer. *J. Neurosurg.* 111(3), 423–430 (2009).

- 4 Rajappa P, Margetis K, Wernicke G *et al.* Stereotactic radiosurgery plays a critical role in enhancing long-term survival in a patient with pancreatic cancer metastatic to the brain. *Anticancer Res.* 33(9), 3899–3903 (2013).
- 5 Menendez JY, Bauer DF, Shannon CN, Fiveash J, Markert JM. Stereotactic radiosurgical treatment of brain metastasis of primary tumors that rarely metastasize to the central nervous system. *J. Neurooncol.* 109(3), 513–519 (2012).
- 6 Park YS, Chang JH, Chang JW, Park YG. The efficacy of gamma knife radiosurgery for advanced gastric cancer with brain metastases. *J. Neurooncol.* 103(3), 513–521 (2011).
- 7 Matsumoto H, Yoshida Y. Brain metastasis from pancreatic cancer: a case report and literature review. *Asian J. Neurosurg.* 10(1), 35–39 (2015).
- 8 Kumar A, Dagar M, Herman J, Iacobuzio-Donahue C, Laheru D. CNS involvement in pancreatic adenocarcinoma: a report of eight cases from the Johns Hopkins Hospital and review of literature. *J. Gastrointest. Cancer* 46(1), 5–8 (2015).
- 9 Kuratsu J, Murakami M, Uemura S, Ushio Y. Brain and skull metastases of hepatic or pancreatic cancer – report of six cases. *Neurol. Med. Chir. (Tokyo)* 30(7), 476–482 (1990).
- 10 Lemke J, Barth TF, Juchems M, Kapapa T, Henne-Bruns D, Kornmann M. Long-term survival following resection of brain metastases from pancreatic cancer. *Anticancer Res.* 31(12), 4599–4603 (2011).
- 11 Yamada K, Miura M, Miyayama H, Sakashita N, Kochi M, Ushio Y. Brain metastases from asymptomatic adenocarcinoma of the pancreas: an autopsy case report. *Surg. Neurol.* 58(5), 332–336; discussion 336–337 (2002).
- 12 Rao R, Sadashiv SK, Goday S, Monga D. An extremely rare case of pancreatic cancer presenting with leptomeningeal carcinomatosis and synchronous intraparenchymal brain metastasis. *Gastrointest. Cancer Res.* 6(3), 90–92 (2013).
- 13 Yoo IK, Lee HS, Kim CD *et al.* Rare case of pancreatic cancer with leptomeningeal carcinomatosis. *World J. Gastroenterol.* 21(3), 1020–1023 (2015).
- 14 Hong CS, Kurt H, Elder JB. Asynchronous leptomeningeal carcinomatosis from pancreatic cancer: a case report and review of the literature. *Clin. J. Gastroenterol.* 7(5), 434–440 (2014).
- 15 El Kamar FG, Jindal K, Grossbard ML, Mizrahi HH, Kozuch PS. Pancreatic carcinoma with brain metastases: case report and literature review. *Dig. Liver Dis.* 36(5), 355–360 (2004).
- 16 Naugler C, Xu Z. Pancreatic adenocarcinoma metastatic to the pineal gland. *J. Clin. Neurosci.* 15(11), 1284–1286 (2008).
- 17 Zaanen A, Lequoy M, Landi B, Lievre A, Franco D, Taieb J. Brain metastases from pancreatic adenocarcinoma. *BMJ Case Rep.* pii:bcr08.0620 (2009) (Epub ahead of print).
- 18 Blows SJ, Morgan R, Dhariwal U, Petts G, Roncaroli F. Pancreatic adenocarcinoma presenting with sudden onset bilateral deafness secondary to metastatic leptomeningeal infiltration. *Age Ageing* 41(6), 818–819 (2012).
- 19 Ferreira Filho AF, Cardoso F, Di Leo A *et al.* Carcinomatous meningitis as a clinical manifestation of pancreatic carcinoma. *Ann. Oncol.* 12(12), 1757–1759 (2001).
- 20 Kotecha R, Vogel S, Suh JH *et al.* A cure is possible: a study of 10-year survivors of brain metastases. *J. Neurooncol.* 129(3), 545–555 (2016).
- 21 Esmailzadeh M, Majlesara A, Faridar A *et al.* Brain metastasis from gastrointestinal cancers: a systematic review. *Int. J. Clin. Pract.* 68(7), 890–899 (2014).
- 22 Szeifert GT, Atteberry DS, Kondziolka D, Levivier M, Lunsford LD. Cerebral metastases pathology after radiosurgery: a multicenter study. *Cancer* 106(12), 2672–2681 (2006).