Stereotactic Radiosurgery Plays a Critical Role in Enhancing Long-term Survival in a Patient with Pancreatic Cancer Metastatic to the Brain

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Abstract. *Background: Pancreatic cancer is an aggressive disease which metastasizes readily. The presence of brain metastases from pancreatic cancer is rare and it carries a poor prognosis. Our approach to treating these lesions stresses extensive use of stereotactic radiosurgery (SRS), whereas other reports focus on surgical resection. Case Report: Information regarding the patient's clinical history was extracted from a retrospective review of the medical records and imaging studies. The patient survived seven years after his primary diagnosis of pancreatic cancer, and 36 months after diagnosis of metastatic disease to the brain. In addition to surgical resection and the use of multiple chemotherapeutic agents, the patient received six separate radiosurgery treatments. Conclusion: We present a case of brain metastasis from pancreatic cancer that is remarkable for an unusually long survivorship and discuss the utility of SRS along with a multimodality treatment approach for dealing with these cases.*

Pancreatic cancer is an extremely aggressive and ultimately fatal disease. Patients diagnosed with pancreatic cancer experience 5-year survival rates of 3-5% (1). In 2010, deaths from pancreatic cancer were estimated at 19,000 (2). While the long-term prognosis is bleak, new advances, primarily effective systemic chemo-radiotherapies, have improved overall survival for these patients. As a result, there is more time for metastases to arise in previously rare sites.

Sixty-five to 70% of patients with pancreatic cancer will eventually have nodal or distant metastases to the lung, liver, or bone at the time of primary diagnosis (3). In contrast, brain metastases from pancreatic cancer are rare, reported at 0.33% of pancreatic adenocarcinoma cases (2). One possible explanation for this low rate of brain metastases may be the short life expectancy, which limits the time for neurological symptoms to arise (3, 4).

The presence of brain metastases from pancreatic cancer carries a dismal prognosis. In this report we highlight the role of stereotactic radiosurgery (SRS) as a complement to surgical resection to achieve extended survival rates.

Case Report

A 67-year-old Caucasian male presented with abdominal pain and was subsequently diagnosed with adenocarcinoma of the pancreatic tail with concurrent liver metastasis. He was placed on a multi-agent systemic chemotherapy regimen consisting of gemzaar, 5-fluorouracil, oxaliplatin, and taxotere. Four years after primary diagnosis, full-body positron-emission topographic (PET) scan revealed a new hypermetabolic area in the brain. Further magnetic resonance imaging (MRI) confirmed a large right occipital, ring-enhancing cystic mass (5.1×2.8×3.0) (Figure 1a and b). The patient then underwent a craniotomy with gross total tumor resection (Figure 2a and b). The histological diagnosis was consistent with metastatic adenocarcinoma. Immunohistochemical stains were strongly positive for cytokeratin-7 (CK7), cytokeratin-9 (CK19), cancer

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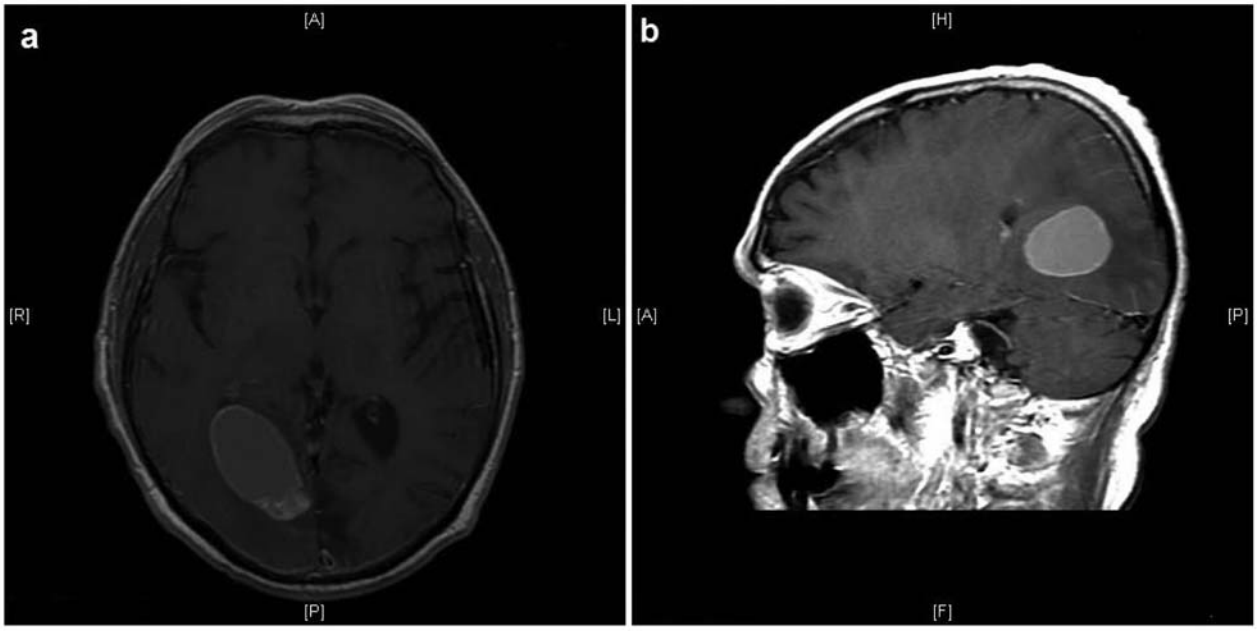

Figure 1. *a: Axial preoperative MRI imaging with contrast. b: Sagittal preoperative MRI imaging with contrast.*

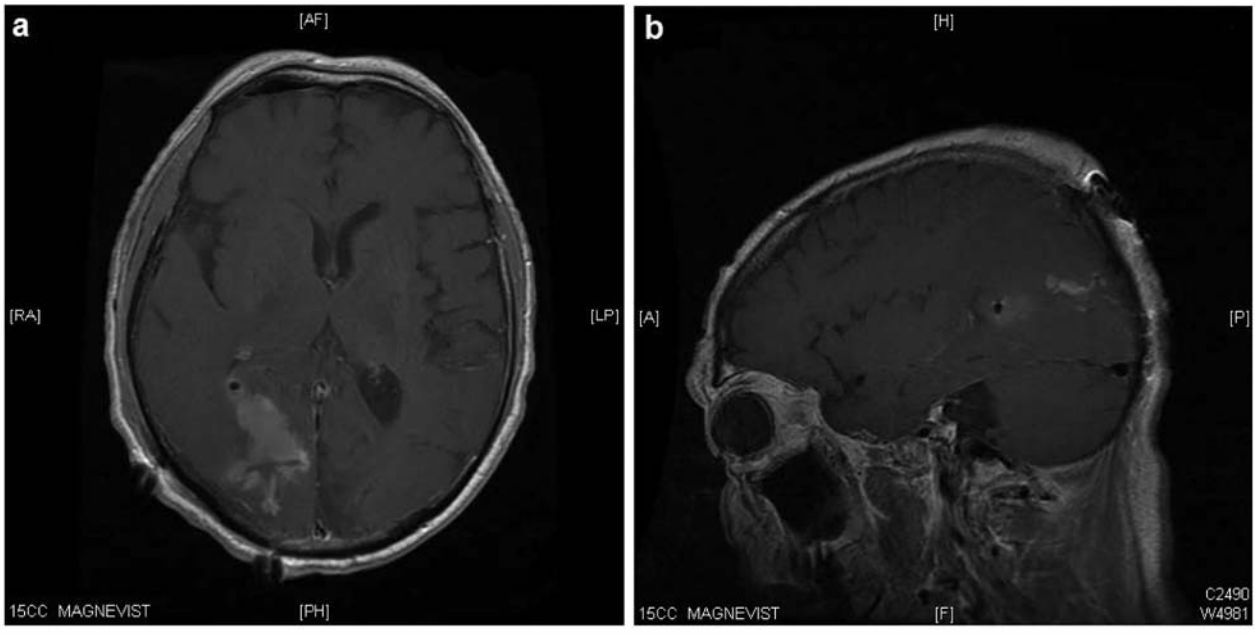

Figure 2. a: Axial postoperative MRI imaging with contrast. b: Sagittal postoperative MRI imaging with contrast (b).

antigen 19-9 (CA19-9) and weakly positive for caudal type homeobox-2 (CDX2), and negative for thyroid transcription factor-1 (TTF-1) and prostate cancer antigen (PSA), consistent with pancreatic adenocarcinoma (Figure 3).

One month after resection, the patient underwent linear accelerator (LINAC) SRS to the tumor bed at 15 Gy [82% isodose line with 2 mm planning target volume (PTV)]. Four months later, MRI revealed a recurrent tumor adjacent to the resection cavity in the right occipital lobe and a new metastasis in the inferior right cerebellum. Whole-body positron emission tomography–computed tomography (PET/CT) scan also confirmed new lung metastases for which the patient was

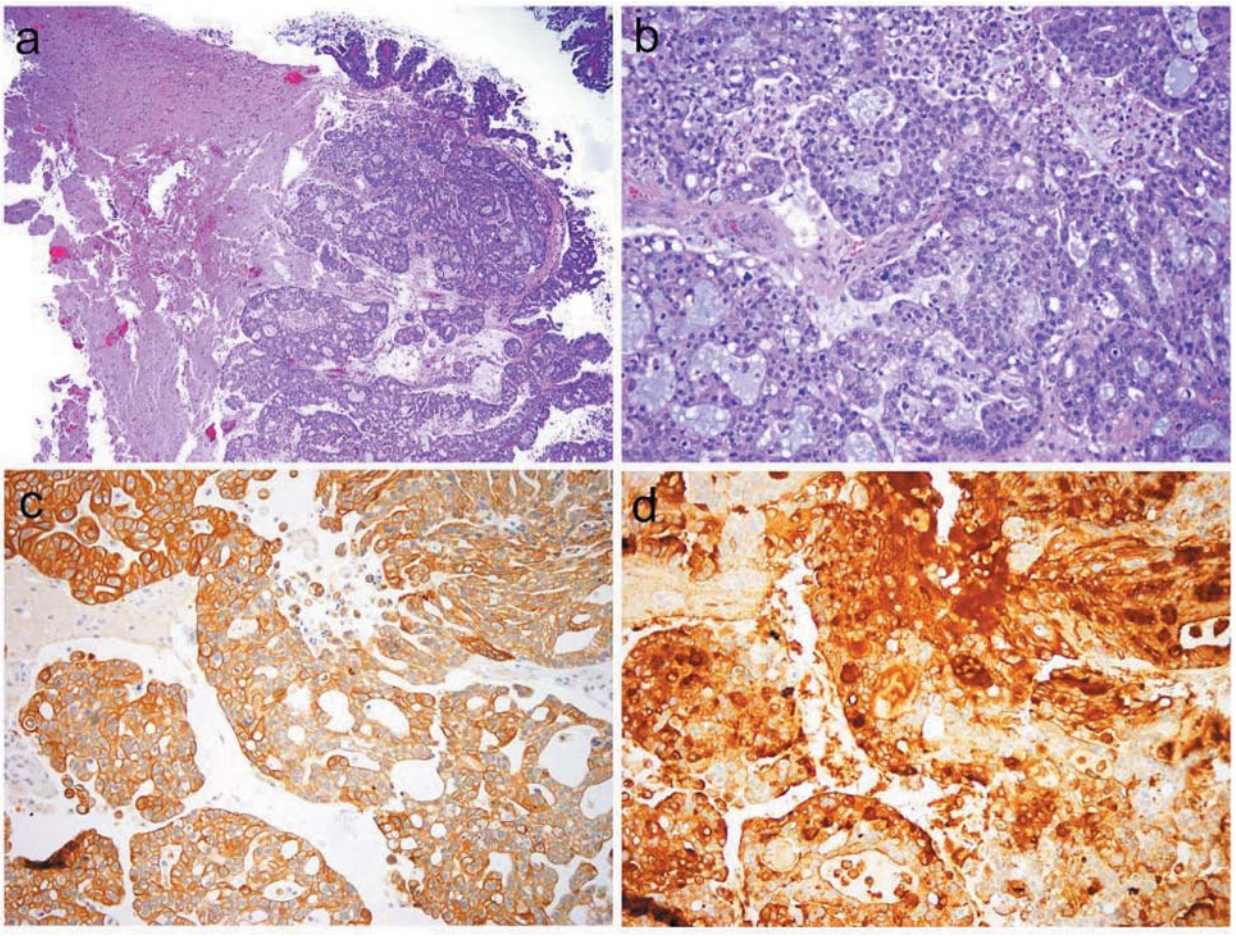

Figure 3. Histological examination of the resected brain tumor. At ×40, the tumor displays cribriform, acinar and papillary architectural patterns infiltrating the brain parenchyma (a). At ×200, the tumor cells display nuclear hyperchromasia and pleomorphism (b). Mucin production is present. Mitoses are frequently identified. Immunohistochemical stains show that the tumor cells are positive for cytokeratin-19 (CK19) (c) and cancer antigen 19-9 (CA19.9) at ×200 (d). The tumor cells stained positively for CK7 and were negative for thyroid transcription factor-1 (TTF-1) and prostate specific antigen (PSA) (not shown). These histological features and immunohistochemical profile are consistent with metastatic carcinoma of pancreatic origin.

continued on 5-fluorouracil, gemzaar, oxaliplatin (plus leucovorin), dacarbazine, along with oral thalidomide and rapamune. Next the patient underwent CyberKnife SRS for the local recurrence, as well as for the new lesion in the inferior right cerebellum, at 18Gy to each focus (79% isodose line). Follow-up MRI demonstrated early resolution of the cerebellar metastasis and reduction in size of the right occipital recurrence, with durable response for 15 months post-SRS.

Upon serial surveillance MRI, a new enhancing lesion in the right parieto-occipital lobe less than 2 mm in size and a painful metastasis of the right scapula were detected. The scapular lesion was treated with external-beam radiation and hyperthermia treatment, and the brain lesion was treated with another session of SRS at 18 Gy (82% isodose line). At this point, the patient was maintained on a systemic chemotherapy regimen that consisted of 5-fluorouracil, gemzaar, oxaliplatin, leucovorin, and dacarbazine. Fourteen months later, a new enhancing, 6-mm dural-based lesion was identified at the lateral margin of the right occipital craniotomy site. Further brain PET scan revealed the presence of four small lesions in the cerebellum based in the right lateral, far lateral, and left medial (posterior left vermis) zones. The patient underwent a five-fraction 25-Gy treatment of LINAC SRS to treat these lesions, as well as a superficial scalp metastasis.

At this point in his disease course, 22 months after the initial diagnosis of brain metastasis and nearly six years after diagnosis with pancreatic adenocarcinoma, the patient was still exhibiting an excellent Karnofsky performance status [(KPS) of 90)]. Five months after this treatment, new 4-mm left thalamic and 4-mm right insular lesions were identified on MRI. His motor and sensory function was grossly intact at this point, however, he appeared frail, chronically ill, and weak, and his KPS score had decreased to 60. The chemotherapeutic regimen at this point consisted of

methotrexate, dacarbazine, irinotican, and leucovorin. The thalamic and insular lesions were treated with single-fraction LINAC SRS on separate occasions (18 Gy to each location, both with an 86% isodose line). The patient tolerated the treatments well; however, he died two months later. Ultimately, the patient survived seven years after the primary diagnosis of pancreatic cancer, and 36 months after the diagnosis of metastatic disease to the brain.

Discussion

Brain metastases from pancreatic cancer are an extremely rare pathological entity. A recent literature review yielded only 12 published reports of metastatic pancreatic cancer to the brain (14). Overwhelmingly, outcomes were extremely poor, with the majority of patients dying within a year, most of them within weeks or months (14). Only recently have reports surfaced of long-term survival with this disease (5, 15). Three patients from these reports are described as living without tumor recurrence 20 months, six years, and 10 years after the diagnosis of brain metastases (5, 15). Our case is yet another exception to the rule that pancreatic cancer with brain metastases carries an extremely limited prognosis; however, our treatment approach differs in that we stress the extensive use of multiple treatments with SRS, while the cases mentioned above focus on surgical resection. Furthermore, our patient's brain metastases manifested as multiple small lesions rather than a solitary tumor.

Advances in medical oncology have created a sense of optimism that exceptions from the dismal prognosis with pancreatic cancer are indeed possible. However, a growing rate of cases with brain metastases is expected to result from the increased survival of these patients (2). Therefore, signs of suspicious neurological symptoms should lead to an early imaging study and prompt treatment of brain metastases. Closer and more vigilant patient surveillance may afford the chance of detecting these lesions at earlier stages, with obvious benefit to these patients. At the current time, serial MRI imaging every three months is generally accepted as adequate brain imaging follow-up (6).

Recently, a second long-term survivor of pancreatic cancer with metastatic disease to the brain cancer came to our attention. While the very recent diagnosis of this patient's metastatic disease excludes the possibility of our commenting on the treatment of this lesion, her clinical history is important in that it underlines the importance of vigilant patient surveillance. This 61-year-old white female with a history of breast cancer was diagnosed with pancreatic cancer in 2006. She underwent a Whipple procedure and was placed on a long-term chemotherapeutic regiment and was stable with pancreatic cancer for six years. She then presented with frontal headaches, a loss of peripheral vision, and blurred vision. An MRI of the brain did not show any abnormalities. However, persistent symptoms prompted a second MRI less than a month later, which revealed a small frontal metastasis and diffuse enhancement, consistent with leptomeningeal disease. In light of the extremely rare nature of these metastases, it is likely that important clinical clues are missed and these lesions are discovered too late. On this occasion, suspicious neurological symptoms were investigated adequately, affording the patient an earlier and potentially more effective treatment of her metastatic disease.

These brain metastases pose a special challenge compared to other systemic metastases since systemic chemotherapeutic regimens must overcome the blood-brain barrier (BBB). Therefore, the sole use of chemotherapy for brain metastases is not adequate and additional treatment modalities are commonly employed. The current trend in the treatment of a resectable brain metastasis in a patient with stable systemic disease is to consider surgical resection followed by whole-brain radiation therapy (WBRT) (Category 1 recommendation) or surgical resection followed by SRS (Category 2A recommendation) (6). Although both options are appropriate, the category 1 recommendation is based on high-level evidence compared to a lower level of evidence for category 2A. The treatment of recurrences includes SRS, or surgery, or WBRT, which are all category 2A options (6). The option of choosing SRS instead of WBRT in the first place has the advantage of a potential reduced rate of cognitive deficits that may be incurred with WBRT (8, 9, 12, 13). This remains a controversial issue as SRS also carries the risk of neurological complications (11). The brain's exposure to radiation is also less with SRS when compared to WBRT. Furthermore, should any recurrences emerge, the reduced radiation exposure allows for the use of multiple, subsequent SRS therapies for rapid succession treatment. An initial WBRT followed by subsequent SRSs would probably result in a higher risk of complications due to increased radiation levels within the brain.

The SRS approach instead of a WBRT regimen has the disadvantage that it lacks the prophylactic effect of WBRT in the development of recurrences. This is certainly an important consideration, but it is felt that newer, molecularly-targeted chemotherapeutic drugs that achieve a better penetration of the BBB may potentially substitute for the prophylactic effect of WBRT. Moreover, the increased relapse rate with the SRS approach compared to the combined use of WBRT does not negatively affect the survival or functional independence of the patient (7, 10).

A major advantage of utilizing SRS in the treatment of recurrences rests not only in its less invasive nature compared to surgery, but also in its ability to effectively and safely control any metastases in inaccessible or eloquent brain areas. To that end, SRS offers the patient a non-invasive procedure with minimal risk and considerably lower morbidity. Moreover, this facet of the treatment modality allows for the option of re-treatment if a recurrence is found and can be carried out within a short time frame if required.

Although our approach is generally considered appropriate, it is still not supported by a cohort-based evidence group. Further evidence from prospective studies is required in order to evaluate this approach for treating brain metastases in general. However, with the growing reported incidence of patients with pancreatic cancer with brain metastases, this treatment modality may be offered with a view to studying a regimen geared towards reaching a highly efficacious standard while minimizing morbidity for patients.

While the number of cases with brain metastases of pancreatic cancer continues to rise, there is a paucity of studies addressing the genetic composition of these distant metastases along with a lack of any targeted therapies for these specific metastases. To date, these tumors have not been characterized with a view to identifying potential molecular targets for therapy or to understanding why some pancreatic adenocarcinomas metastasize to the brain in the first place. Additionally, the molecular profiling of brain metastases from pancreatic cancer in patients with an unexpectedly long survival may contribute to the identification of more accurate markers of prognostication. The early identification of patients with a relatively favorable prognosis may lead to utilization of less invasive therapies that may augment surgical resection as was implemented in our case. Genomic profiling of cases of long-term survivors may also serve as a platform for the development of tailored therapies that target these tumors on the molecular level.

Conclusion

Brain metastases from pancreatic cancer are rare and there are no specific treatment approaches. The prognosis is generally poor but exceptions do occur. In contemplating the treatment options, SRS is a viable option and might be beneficial in terms of reduced morbidity. The rate of these metastases is expected to rise and this should be taken into consideration during the follow-up of patients with pancreatic cancer.

References

1 Iovanna J, Mallmann MC, Goncalves A, Turrini O and Dagorn JC: Current knowledge on pancreatic cancer. FrontOncol *2*: 6, 2012

2 Go PH, Klaassen Z, Meadows MC and Chamberlain RS: Gastrointestinal cancer and brain metastasis: A rare and ominous sign. Cancer *117*: 3630-3640, 2011.

3 Park KS, Kim M, Park SH and Lee KW: Nervous system involvement by pancreatic cancer. J Neuro-Oncol *63*: 313-316, 2013.

4 Caricato M, Borzomati D, Ausania F, Garberini A, Rabitti C, Tonini G and Coppola R: Cerebellar metastasis from pancreatic adenocarcinoma - A case report. Pancreatology *6*: 306-308, 2006.

5 Lemke J, Barth TF, Juchems M, Kapapa T, Henne-Bruns D and Kornmann M: Long-term survival following resection of brain metastases from pancreatic cancer. Anticancer Res *31*: 4599-4603, 2011.

6 Brem SS, Bierman PJ, Black P, Blumenthal DT, Brem H, Chamberlain MC, Chiocca EA, DeAngelis LM, Fenstermaker RA, Fine HA, Friedman A, Glass J, Grossman SA, Heimberger AB, Junck L, Levin V, Loeffler JJ, Maor MH, Narayana A, Newton HB, Olivi A, Portnow J, Prados M, Raizer JJ, Rosenfeld SS, Shrieve DC, Sills AK Jr., Spence AM, Vrionis FD, National Comprehensive Cancer Network: Central nervous system cancers: Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw: *3*: 644-690, 2005.

7 Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, Kenjyo M, Oya N, Hirota S, Shioura H, Kunieda E, Inomata T, Hayakawa K, Katoh N and Kobashi G: Stereotactic radiosurgery plus whole-brain radiation therapy *vs*. stereotactic radiosurgery alone for treatment of brain metastases: A randomized controlled trial. JAMA *295*: 2483-2491: 2006.

8 Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, Arbuckle RB, Swint JM, Shiu AS, Maor MH and Meyers CA: Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: A randomised controlled trial. Lancet Oncol *10*: 1037-1044, 2009.

9 DeAngelis LM, Delattre JY and Posner JB: Radiation-induced dementia in patients cured of brain metastases. Neurology *39*: 789-796, 1989.

10 Kocher M, Soffietti R, Abacioglu U, Villa S, Fauchon F, Baumert BG, Fariselli L, Tzuk-Shina T, Kortmann RD, Carrie C, Ben Hassel M, Kouri M, Valeinis E, van den Berge D, Collette S, Collette L and Mueller RP: Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: Results of the EORTC 22952-26001 study. J Clin Oncol *29*: 134-141, 2011.

11 Minniti G, Clarke E, Lanzetta G, Osti MF, Trasimeni G, Bozzao A, Romano A and Enrici RM: Stereotactic radiosurgery for brain metastases: Analysis of outcome and risk of brain radionecrosis. Radiation oncology *6*: 48, 2011.

12 Warrington JP, Csiszar A, Mitschelen M, Lee YW and Sonntag WE: Whole-brain radiation-induced impairments in learning and memory are time-sensitive and reversible by systemic hypoxia. PloS One *7*: e30444, 2012.

13 Karlovits BJ, Quigley MR, Karlovits SM, Miller L, Johnson M, Gayou O and Fuhrer R: Stereotactic radiosurgery boost to the resection bed for oligometastatic brain disease: Challenging the tradition of adjuvant whole-brain radiotherapy. Neurosurg Focus *27*: E7, 2009.

14 Lemke J, Scheele J, Kapapa T, Wirtz CR, Henne-Bruns D and Kornmann M: Brain metastasis in pancreatic cancer. Int J Mol Sci *14*: 4163-4173, 2013.

15 Chiang KC, Yu CC, Chen JR, Huang YT, Huang CC, Yeh CN, Tsai CS, Chen LW, Chen HC, Hsu JT, Wang CH and Chen HY: Oncocytic-type intraductal papillary mucinous neoplasm (IPMN)-derived invasive oncocytic pancreatic carcinoma with brain metastasis - a case report. W J Surg Oncol *10*: 138, 2012.

16 Menendez JY, Bauer DF, Shannon CN, Fiveash J and Markert JM: Stereotactic radiosurgical treatment of brain metastasis of primary tumors that rarely metastasize to the central nervous system. J Neurooncol *109*: 513-519, 2012.

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