Clinical Case Report

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Brain metastasis in pancreatic cancer

Two case reports

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Abstract

Rationale: Brain metastases are extremely rare for patients with pancreatic adenocarcinoma due to the poor prognoses. In the present study, we reported 2 cases of pancreatic adenocarcinoma with brain metastases.

Patient concerns: The 1st patient was diagnosed asymptomatic brain metastasis by a follow-up brain magnetic resonance imaging (MRI) due to a medical history of subarachnoid hemorrhage. The 2nd patient experienced dizziness, neck pain, and seizure. Computed tomography (CT) was used for the diagnosis of brain metastasis because he was inserted a pacemaker.

Diagnosis: In case 1, brain MRI revealed that a solitary brain metastasis 14-mm in size was identified at the cortico-medullary junction in the left frontal lobe. In case 2, brain enhanced CT revealed multiple brain metastases with calcification at the cerebral cortex. Times to develop central nervous system metastasis were 19 months and 33 months, respectively.

Interventions: The 1st patient was treated with 45.2 Gy γ-knife irradiation for the solitary brain metastasis, and the 2nd patient was treated with supportive care due to the poor general condition.

Outcomes: The prognoses of these 2 patients were 13 months, and 32 days from the diagnosis of brain metastasis. The 1st patient did not experience complication of a γ-knife irradiation and brain metastasis was controlled until death.

Lessons: The incidence of brain metastases from pancreatic adenocarcinoma is expected to increase due to prolonged survival from improved treatment. Therefore, increased awareness of brain involvement is necessary when neurological disorder is suspected in patients with advanced pancreatic cancer.

Abbreviations: ALK = anaplastic lymphoma kinase, BRAF = v-raf murine sarcoma viral oncogene homolog B1, CNS = central nervous system, EGFR = epidermal growth factor receptor, HER2 = human epidermal growth factor receptor 2, NSCLC = non-small cell lung cancer, TKI = tyrosine kinase inhibitor.

Keywords: brain metastasis, pancreatic cancer, prognosis, treatment

1. Introduction

The prognosis of pancreatic adenocarcinoma remains dismal. Unfortunately, fewer than 20% of patients are candidates for surgical resection.[1] Even for patients with resected tumors, the 5-year overall survival rate is only 30%.[2] Many pancreatic cancer patients are diagnosed with distant metastasis. Median overall survival for metastatic pancreatic adenocarcinoma is less than 1 year, with most patients dying within 2 years.[1] Pancreatic adenocarcinoma usually metastasizes to the liver (76%), followed by lung (19.9%), distant lymph nodes (9.4%) and bone (6.8%).[3] Brain metastases are extremely rare (0.6%).[3] Here, we report 2 cases of brain metastases from pancreatic adenocarcinoma.

2. Case reports

2.1. Case 1

A 72-year-old woman was diagnosed with pancreatic adenocarcinoma and multiple liver metastases. She received gemcitabine and nab-paclitaxel combination therapy. Partial response was achieved and was maintained for 18 months. Due to the appearance of mesenteric lymph nodes metastases, S-1 monotherapy was introduced as a 2nd-line chemotherapy. Because the patient had a medical history of subarachnoid hemorrhage, a follow-up brain magnetic resonance imaging (MRI) was performed. A solitary brain metastasis 14-mm in size was identified at the cortico-medullary junction in the left frontal lobe (Fig. 1). The patient was 73 years old at diagnosis of the brain metastasis, and it was 19 months after diagnosis of the pancreatic cancer. Although she was asymptomatic, patient received 45.2 Gy γ-knife irradiation for the brain metastasis. S-1 monotherapy

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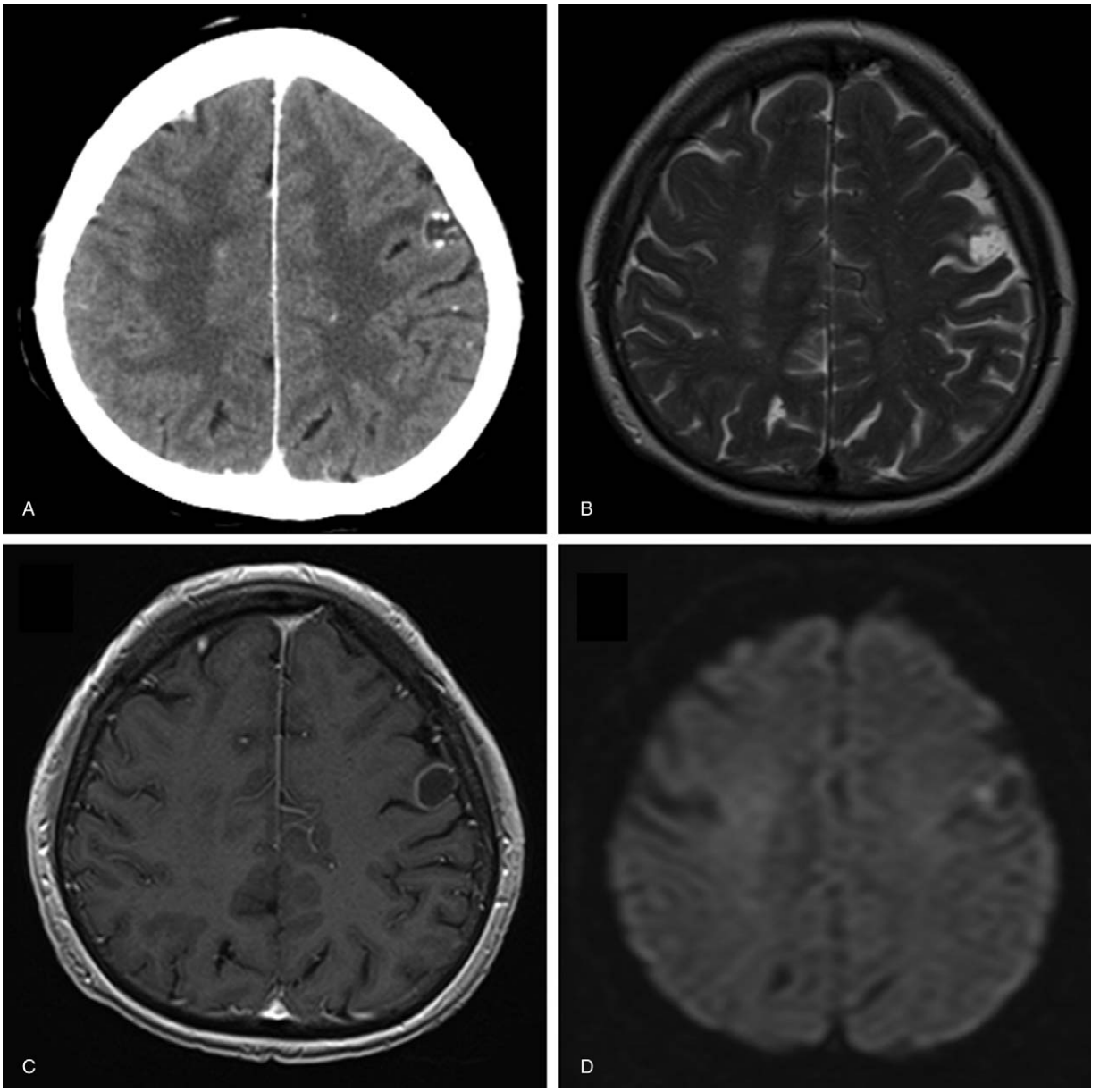

Figure 1. Solitary brain metastasis 14-mm in size identified at the cortico-medullary junction of the left frontal lobe. (A) Contrast enhanced brain computed tomography (CT). (B) T2-weighted magnetic resonance imaging (MRI). (C) Gadolinium-enhanced T1-weighted MRI. (D) Diffusion weighted image.

was continued for 1 year afterwards, and she ultimately transitioned to supportive care. She died 13 months after diagnosis of the brain metastasis without central nervous system (CNS) progression.

2.2. Case 2

A 78-year-old man was diagnosed with borderline resectable pancreatic cancer. He was treated with neoadjuvant chemoradiotherapy (S-1+cisplatin+radiation) followed by S-1 monotherapy. The patient underwent distal pancreatectomy after 4 months of neoadjuvant therapy. Pathological results showed a moderately differentiated tubular adenocarcinoma, and R0 resection was achieved. However, lung metastases were confirmed by computed tomography (CT) 5 months after starting adjuvant S-1 monotherapy. Gemcitabine and nab-paclitaxel combination therapy was introduced to treat recurrent tumor, and this chemotherapy elicited a partial response for 21 months. At the time that tumor progression with multiple lung metastases was confirmed, patient began to experience dizziness and neck pain. He was admitted to our hospital for detailed examination, and he experienced complicated seizure during that stay. Although a pacemaker had been inserted due to atrioventricular block, no abnormality was detected in the pacemaker. Brain enhanced CT revealed multiple brain metastases with calcification at the cerebral cortex (Fig. 2). He was 81 years old at diagnosis of the brain metastasis, and 33 months had passed from diagnosis of the pancreatic cancer. Whole brain irradiation was considered but was not performed due to patient's poor general condition. He died 32 days after diagnosis of the multiple brain metastases due to the deterioration of CNS metastases.

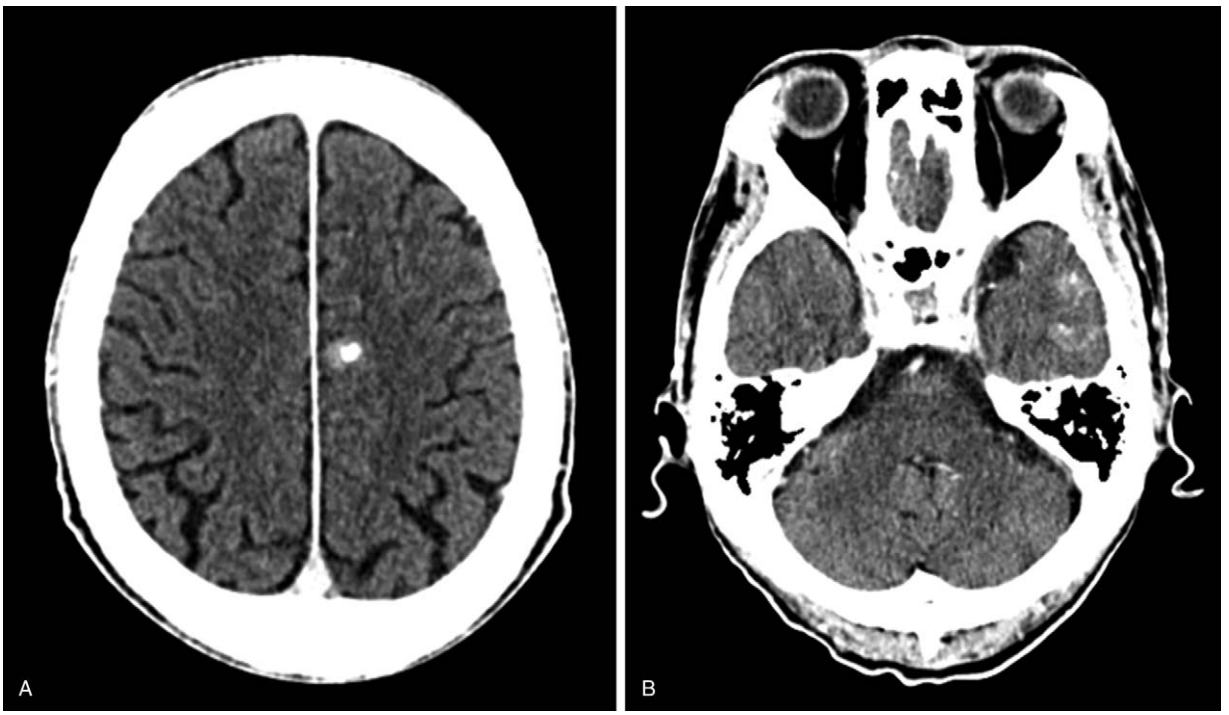

Figure 2. Multi-focal calcification was identified in the cerebral cortex. Enhancement was observed around brain metastasis. (A, B) Contrast enhanced brain computed tomography (CT).

The authors took great care to maintain these patients' anonymities. Informed written consent was obtained from the patient for publication of this case report and accompanying images. Approval from the hospital's institutional review board was not mandated due to the retrospective nature of this small case reports.

3. Discussion

The exact incidence of brain metastases is unknown because brain imaging studies are not routinely performed on neurologically asymptomatic cancer patients. The global prevalence of brain metastases in patients with cancer is probably approximately 8.5–9.6%.[4,5] The most common primary tumors of brain metastases are lung cancer, breast cancer, melanoma, renal cancer, and colorectal cancer.[5] In Japan, the major origins of brain metastases are lung cancer (46.1%), breast cancer (14.5%), colon cancer (6.0%), and renal cancer (4.2%).[6] Brain metastases from gastrointestinal cancer are rare, except in colon cancer: stomach (3.3%), rectum (3.0%), esophagus (2.6%), and liver (1.8%). Brain metastases from pancreatic cancer are considered extremely rare (0.2%).

The 1st antemortem diagnosis of brain metastasis in a patient with pancreatic adenocarcinoma was reported in 1977.[7] From a Korean report, only 4 patients (0.3%) were diagnosed with brain metastases among 1229 patients with pancreatic adenocarcinoma between 1980 and 2000.[8] According to the SEER database (2010–2013) of 13,233 patients with stage IV pancreatic cancers, the incidences of brain metastases were 0.6% (90 patients).[3] On the other hand, autopsy studies showed a higher incidence of brain metastases in those who had died of pancreatic cancer (7.9%).[9] This discrepancy may be due to the aggressive nature of pancreatic adenocarcinoma and the fact that most patients do not survive long enough to experience clinical manifestations of brain metastasis. It is also possible that many patients may not be evaluated for a CNS lesion during treatment of pancreatic adenocarcinoma. A previous report showed that there are some cases in which the primary origin of brain metastases was clarified as pancreas only by autopsy.[10]

There are several case reports concerning brain metastases from rare types of pancreatic tumors.[11–13] There are also several case reports about other types of metastases to the CNS, such as leptomeningeal carcinomatosis and ocular metastases.[14,15] The largest case series of brain metastases from pancreatic adenocarcinoma include eight patients from Johns Hopkins Hospital between 2004 and 2012 from a database of over 800 pancreatic cancer patients.[16] The median age was 61.5 years (49–70 years), and the median time to develop CNS metastasis was 29 months (2–57 months). Three patients presented with extremity weakness, 2 patients with imbalance, 2 patients with blurry vision, 1 patient with tongue weakness, and 1 patient with headaches, diplopia, and CN VI palsy. Three patients had lung metastasis (37.5%). From the Brain Tumor Registry of Japan database (2005–2008), the median age of 7 patients with pancreatic cancer was 62 years.[6] Two patients underwent surgery, and 5 patients received stereotactic radiosurgery during treatment. Two patients (29%) experienced complicated lung metastases. The prognoses of these 7 patients were only 5 months (0–7 months). Risk factors for brain metastases are not clarified for patients with pancreatic cancer. For colorectal cancer, development of brain metastases is associated with young age, lung metastases, primary rectal tumors, and KRAS mutation.[17] From previous reports, the incidence of pancreatic cancer patients with brain metastasis with complicated lung metastases was higher than that of overall pancreatic cancer patients (29–37.5% vs 19.9%).[3,6,16] Therefore, lung metastases might be one of the risk factor for development of brain metastasis in patients with pancreatic cancer.

There are several treatment options for brain metastases: surgical resection, radiation therapy (including whole-brain radiation therapy and stereotactic radiosurgery), and systemic therapy.[18] The choice of management in patients with newly diagnosed brain metastases depends on the estimated prognosis and the aims of treatment (survival, local control, distant brain control, neurocognitive preservation). The European Association of Neuro-Oncology (EANO) reported guidelines for the treatment of brain metastases from solid tumors.[19] In general, surgical resection should be considered in patients with a limited number (1 to 3) of newly diagnosed brain metastases, especially in case of lesion of $\geq$ 3 cm in diameter, lesions with necrotic or cystic appearance and edema/mass effect, lesions located in the posterior fossa with associated hydrocephalus, and lesions located in symptomatic eloquent areas. Surgical resection can be an option when the systemic disease is active but effective systemic treatment options are available or when the primary tumor is relatively radioresistant (i.e. melanoma, renal carcinoma, colon carcinoma). Stereotactic radiosurgery should be considered in patients with metastases of a diameter of $\leq$ 3–3.5 cm. When both surgical resection and stereotactic radiosurgery are feasible, the choice should be made on a case-by-case basis with consideration given to tumor size, site, type of neurological symptoms, need for steroids, patient preference, and/or physician expertise. In cases of multiple brain metastases, whole-brain radiation therapy is considered; however, this treatment modality has the complication of cognitive impairment and is not fully recommended for patients likely to live longer than 6 months. There is increasing evidence that systemic therapy with targeted therapy, or immunotherapy, is effective against brain metastases and may be an early choice, especially in patients with sensitive primary tumors such as lung cancer, breast cancer, and melanoma.[20] Therefore, stereotactic radiosurgery is sometimes chosen instead of whole-brain irradiation during the treatment course of systemic therapy, even in cases of multiple brain metastases.[21] In cases of epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC), which often complicate brain metastases, EGFR tyrosine kinase inhibitors (TKIs) (gefitinib, erlotinib, afatinib, osimertinib) have shown high efficacy for local control of brain metastases and overall survival. For patients with anaplastic lymphoma kinase (ALK) rearrangement NSCLC, a 2nd-generation ALK TKI (alectinib) showed high tumor efficacy for NSCLC with brain metastases.[22] Similar findings are evident with use of anti-human epidermal growth factor receptor 2- (HER2-) targeted therapies (lapatinib) combined with capecitabine for brain metastases from HER2-overexpressing breast cancer.[23] In the case of melanoma, v-raf murine sarcoma viral oncogene homolog B1 (BRAF) inhibitors appear active in patients with BRAF-mutant melanoma.[24] Immune checkpoint inhibitors also show efficacy against brain metastases caused by NSCLC and melanoma. These emerging novel targeted therapies that successfully target brain metastasis from NSCLC, breast cancer, and melanoma represent a paradigm shift in the management of brain metastases. However, there is no evidence for brain metastasis from pancreatic cancer. It is not clear that gemcitabine and erlotinib combination therapy, which is efficacious for metastatic pancreatic cancer, is also effective for brain metastasis, even though erlotinib can cross the blood brain barrier.[25] In the present circumstances, radiation therapy might be the treatment option of choice for brain metastasis with pancreatic cancer with neurological symptoms or for a patient who is asymptomatic with a controlled extracranial lesion. Although the long-term prognosis of brain metastasis from pancreatic cancer is unclear and whether whole-brain irradiation should be avoided is also unresolved, stereotactic radiosurgery might be preferred because there are some patients who survive longer than 6 months, as with our patients. Moreover, it is not known whether local treatment for asymptomatic brain metastasis affects the prognosis of pancreatic cancer. It is necessary to accumulate evidence for treatment outcomes of brain metastases from pancreatic cancer to definitively make these conclusions.

There are several points to discuss from our 2 cases. In case 1, it is not known whether local treatment for asymptomatic brain metastasis affected the prognosis of pancreatic cancer or whether local treatment preserved quality of life for the patient. In case 2, it is not clarified that lung metastasis is indeed a risk factor for the development of brain metastases such as colon cancer, and we also need to verify brain imaging in cases of lung metastasis.

Claims of increasing incidence of brain metastasis are controversial. In a comparison of patients with brain metastases treated from 1983 to 1989 versus (vs) 2005 to 2009, the incidence of lung cancers was reduced (52% vs 40%), and the frequency of melanomas (5% vs 9%), colorectal cancers (5% vs 13%) and renal cancers (3% vs 11%) were increased, whereas breast cancer cases remained stable (17% vs 17%).[26] Incidence of brain metastases will decrease if the cancer itself is diagnosed at early stages owing to surveillance and treated with curative intent. However, incidence of brain metastasis will increase if the incidence of cancer itself increases and the prognoses of cancer are improved. Increases in brain metastases from colorectal cancer are affected because of these 2 factors.[27] It is not clear whether the incidence of brain metastases from pancreatic cancer is increasing. Early diagnosis of pancreatic cancer remains a challenge, and there is no efficient surveillance until recently. Meanwhile, the incidence of pancreatic cancer is increasing, and it will become the second leading cause of cancer-related death in United States by 2030.[28] Improvements in chemotherapy have been achieved by the emergence of new combination chemotherapies (FOLFIRINOX and gemcitabine and nab-paclitaxel combination therapy).[29,30] The prognoses of pancreatic adenocarcinoma will be prolonged, and it is anticipated that the chances of encountering brain metastases from pancreatic adenocarcinoma will increase gradually, as in colorectal cancer.

4. Conclusion

We reported 2 cases of brain metastases from pancreatic adenocarcinoma. The incidence of brain metastases from pancreatic adenocarcinoma is expected to increase due to prolonged survival from improved treatments. Therefore, increased awareness of brain involvement is necessary when neurological disorder is suspected in patients with advanced pancreatic cancer.

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References

[1] Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med 2014;371:1039–49.
[2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30.
[3] Oweira H, Petrausch U, Helbling D, et al. Prognostic value of site-specific metastases in pancreatic adenocarcinoma: a surveillance epidemiology and end results database analysis. World J Gastroenterol 2017;23:1872–80.
[4] Schouten LJ, Rutten J, Huveneers HA, et al. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. Cancer 2002;94:2698–705.
[5] Barnholtz-Sloan JS, Sloan AE, Davis FG, et al. Incidence proportions of brain metastases in patients with diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. J Clin Oncol 2004;22:2865–72.
[6] Brain Tumor Registry of Japan (2005–2008). Neurol Med Chir (Tokyo). 2017; 57 (Supplement-1): 9-102.
[7] Demchuk AI. Clinical picture and diagnosis of metastatic brain cancer with its primary source in the pancreas. Vrach Delo 1977;38–41.
[8] Park KS, Kim M, Park SH, et al. Nervous system involvement by pancreatic cancer. J Neurooncol 2003;63:313–6.
[9] Lee YT, Tatter D. Carcinoma of pancreas and periampullary structures pattern of metastasis at autopsy. Arch Pathol Lab Med 1984;108:584–7.
[10] Yamada K, Miura M, Miyayama H, et al. Brain metastases from asymptomatic adenocarcinoma of the pancreas: an autopsy case report. Surg Neurol 2002;58:332–6.
[11] Szerlip NJ, Fox E, Manosca F, et al. Pancreatoblastoma metastases to the brain. Case illustration. J Neurosurg 2007;106:169.
[12] Chiang KC, Yu CC, Chen JR, et al. Oncocytic-type intraductal papillary mucinous neoplasm (IPMN)-derived invasive oncocytic pancreatic carcinoma with brain metastasis—a case report. World J Surg Oncol 2012;10:138.
[13] Ruess DA, Kayser C, Neubauer J, et al. Carcinosarcoma of the pancreas: case report with comprehensive literature review. Pancreas 2017;46:1225–33.
[14] Yoo IK, Lee HS, Kim CD, et al. Rare cases of pancreatic cancer with leptomeningeal carcinomatosis. World J Gastroenterol 2015;21:1020–3.
[15] Lin CJ, Yang CM, Chen MS. Intraocular metastasis of pancreatic cancer: report of two cases. Retina 2001;21:666–9.
[16] Kumar A, Dagar M, Herman J, et al. CNS involvement in pancreatic adenocarcinoma: a report of eight cases from the Johns Hopkins Hospital and review of literature. J Gastrointest Cancer 2015;46:5–8.
[17] Troels Dreier Christensen, Karen-Lise Garm Spindler, Jesper Andreas Palshof, Dorte Lisbet Nielsen. Systematic review: brain metastases from colorectal cancer—incidence and patient characteristics. BMC Cancer. 2016; 16: 260.
[18] Caffo M, Barresi V, Caruso G, et al. Innovative therapeutic strategies in the treatment of brain metastases. Int J Mol Sci 2013;14:2135–74.
[19] Soffietti R, Abacioglu U, Baumert B, et al. Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO). Neuro Oncol 2017;19:162–74.
[20] Chamberlain MC, Baik CS, Gadi VK, et al. Systemic therapy of brain metastases: non-small cell lung cancer, breast cancer, and melanoma. Neuro Oncol 2017;19:i1–24.
[21] Li J, Brown PD. The diminishing role of whole-brain radiation therapy in the treatment of brain metastases. JAMA Oncol 2017;3:1023–4.
[22] Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med 2017;377:829–38.
[23] Ramakrishna N, Temin S, Chandarlapaty S, et al. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast canceer and brain metastases: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2014;32:2100–8.
[24] Kircher DA, Silvis MR, Cho JH, et al. Melanoma brain metastasis: mechanisms, model, and medicine. Int J Mol Sci 2016;17:1468.
[25] Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2017;25:1960–6.
[26] Nieder C, Spanne O, Mehta MP, et al. Presentation, patterns of care, and survival in patients with brain metastases: what has changed in the last 20 years? Cancer 2011;117:2505–12.
[27] Atreya CE, Yaeger R, Chu E. Systemic therapy for metastatic colorectal cancer: from current standards to future molecular targeted approaches. Am Soc Clin Oncol Educ Book 2017;37:246–56.
[28] Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74:2913–21.
[29] Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817–25.
[30] Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691–703.