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Case Report

Gamma knife therapy combined with S-1 and Nituzumab in the treatment of localized unresectable pancreatic cancer in the elderly: a case report

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Abstract: The age of incidence of pancreatic cancer (PC) is generally greater than 60 years old. It is most common in men. Palliative chemotherapy is still the first choice for patients with advanced disease. Local disease control remains a major problem in patients with locally advanced unresectable pancreatic cancer (LAPC). However, there are few reports of patients with LAPC receiving stereotactic radiotherapy multiple times and receiving S-1 again after stopping drug therapy. This report describes a case where an 83-year-old man was diagnosed with LAPC. He received Gamma knife radiotherapy-based chemotherapy and Targeted therapy for more than 62 months. No obvious adverse reaction occurred and the metastatic disease was well controlled. The long term survival case indicated that Gamma knife combined with S-1 and Nituzumab seems to be a good choice for the treatment of LAPC in the elderly.

Keywords: Elderly, gamma knife, S-1, nituzumab, LAPC

Introduction

Pancreatic cancer (PC) is one of the most common malignant tumors of the digestive system. It is most common in elderly patients with a median age of diagnosis of 70 years [1]. Approximately 50% of newly diagnosed PC patients have local and regional disease [2]. At the time of diagnosis, only 10% to 20% of patients can undergo pancreatectomy, and the surgical mortality rate is relatively high.

In addition, for a large proportion of unresectable pancreatic cancers, it's definition is very important. The definition of locally advanced unresectable pancreatic cancer (LAPC) implies that there is no evidence of metastatic disease. Although the definition of unresectability may vary somewhat, it is generally accepted that unresectability is determined by the presence and extent of local vascular involvement. Unlike potentially curable (resectable) pancreatic cancer, in which preoperative treatments can potentially improve margin negative resectability, patients with LAPC rarely undergo resection with curative intent. Furthermore, patients with LAPC are more likely to have significant symptom burdens relating to their primary malignancy, including pain, pancreatic insufficiency, biliary obstruction, and early satiety/gastric outlet obstruction. Although most people with unresectable LAPC are unlikely to be cured, the natural history and treatment approaches toward LAPC differ from that of metastatic disease because patients lack systemic dissemination. This has been reported in the past. For relevant evidence, see reference [3].

The efficacy and reliability of Gamma Knife therapy in the treatment of brain metastases have been confirmed [4]. It has also become a new choice for local control of pancreatic cancer. Clinical practice has confirmed the efficacy and safety of S-1 monotherapy in elderly patients with LAPC [5]. Currently, in elderly patients, there is little experience in the efficacy and safety of re-radiotherapy, single-agent chemotherapy and Targeted drug combination therapy. Here, we report about a rare case with an 83-year-old patient with LAPC. The

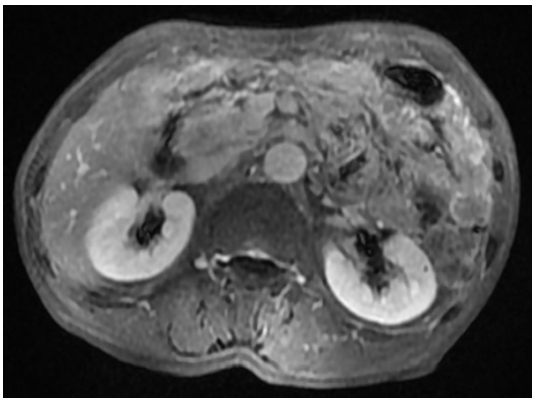

Figure 1. (2015-8-11) Pancreatic MRI suggested that the head of the pancreas occupied space, consistent with malignant tumors.

patient received multiple Gamma Knife and S-1 treatments. Next, so far, he had received S-1 combined with Nituzumab treatment. He achieved a total survival period of 62 months. This case had a good clinical treatment efficacy and the patient was tolerable to the above treatments.

Case report

An 83-year-old man was admitted to the hospital in August 2015. He complained of repeated abdominal distension and abdominal pain, accompanied by radiating pain in the shoulder, with darkened urine color for 8 months. He was healthy prior to the onset of current symptoms. KPS score: 80 points. Physical examination showed a surgical scar after cholecystectomy in the right middle and lower abdomen, which healed well, and there were no obvious abnormalities in the rest of the system. Serum tumor markers suggested that: CA19-9 serum concentration >2019.0 U/ml (normal limit: 0-25 U/ml), CEA serum concentration increased to 43.3 ng/ml (normal limit: 0-5 ng/ml), the serum concentration of CA12-5 increased to 272.1 U/ml (normal limit: 0-35 U/ml). Pancreatic MRI suggested that the head of the pancreas occupied space, consistent with malignant tumors (**Figure 1**). PET-CT suggested increased glucose metabolism in the head of the pancreas with significant expansion of the pancreatic duct, indicating a malignant tumor (**Figure 2**). In addition, pathologic examination of the ultrasound-guided biopsy revealed pancreatic cancer (**Figure 3**). Therefore, the patient was diagnosed with PC. On August 20, 2015, a Gamma knife was used to locally control the pancreatic lesions. It was delivered at 3.3 Gy per fraction every day, with a total dose of 33 Gy. During the same period, a single-agent S-1 regimen was used for chemotherapy, taken orally twice a day, and the dose was calculated based on the body surface area (< 1.25 m^2, 40 mg/d; ≥ 1.25 to < 1.5 m^2, 50 mg/d; ≥ 1.5 m^2, 60 mg/d). He received 40 mg/day on days 1 through 14 of the 21-day cycle. Treatment progressed smoothly, and the patient subsequently received maintenance therapy with a single-agent S-1 regimen. Follow-up was good. During the follow-up period, there was no recurrence in imaging or serum tumor markers. On September 19, 2016, the patient took Chinese medicine after stopping chemotherapy. In March 2017, due to "aggravated abdominal pain for half a month", the patient's pancreas MRI reexamination indicated that the lesion was larger than before. The patient still received oral Chinese medicine treatment. On July 20, 2017, serum tumor markers were reexamined: The level of CA19-9 increased to 1436.3 U/ml, CEA level increased to 6.8 ng/ml. PET-CT showed that there was an enlarged lesion of the head of the pancreas compared with August 14, 2015 (**Figure 4**), and Enhanced MRI of the pancreas showed that the lesions of the head of the pancreas were larger than before (**Figure 5**). Therefore, post-treatment progress was confirmed. The lesion was locally controlled by Gamma knife treatment on August 25, 2017. It was delivered at 3 Gy per fraction every day, with a total dose of 33 Gy. In the same period, S-1 combined with Nituzumab regimen was given for treatment, specifically: "S-1 40 mg, per oral, d1-14, q21d" combined with "Nituzumab 100 mg, intravenous drip, d1 qw". The patient received S-1 combined with Nituzumab for maintenance treatment after that. On December 26, 2017, the serum concentration of CA19-9 decreased to 31.9 U/ml. Follow-up enhanced MRI of the pancreas showed that the lesion was smaller than before (**Figure 6**). The patient showed partial remission (PR) according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Since then, he was in a stable condition during the subsequent MRI follow-up. He achieved an overall survival of 62 months with a very good performance status (Karnofsky 90%). The treatment process of the patient was shown in **Table 1**.

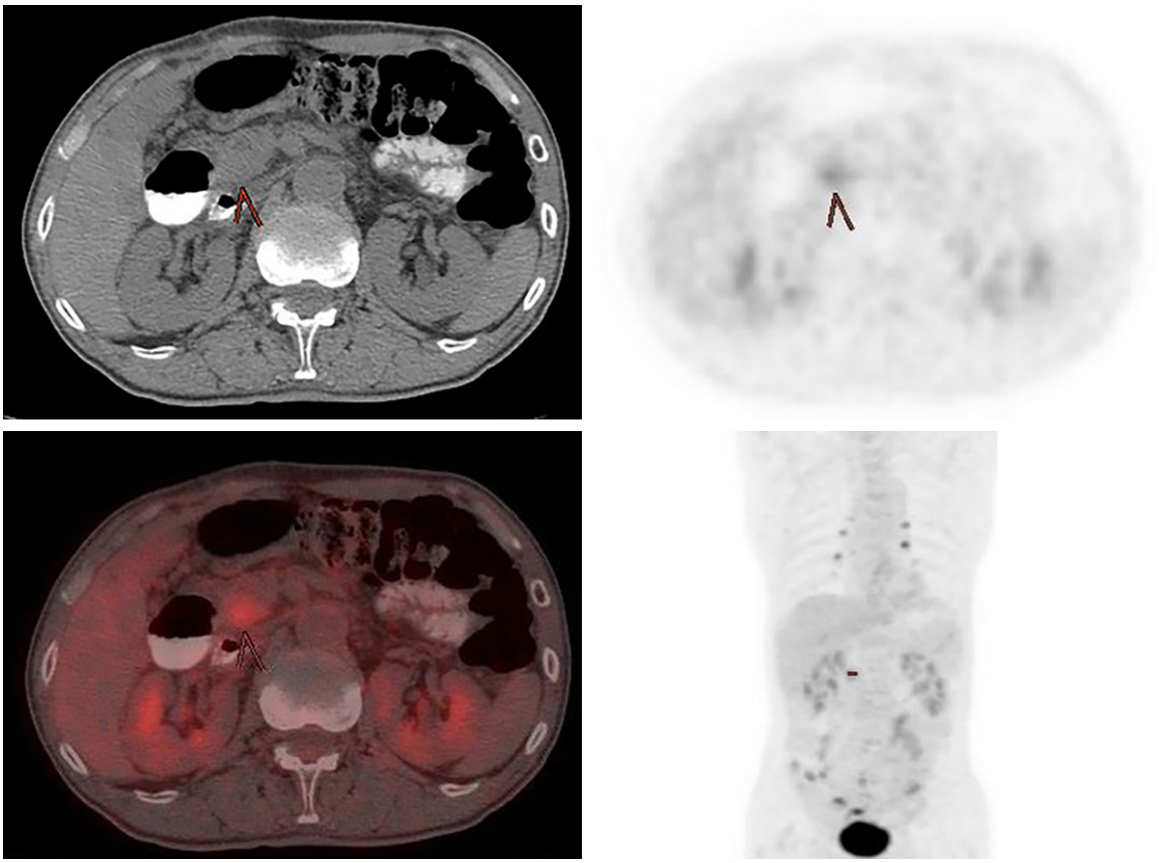

Figure 2. (2015-8-14) PET-CT suggested increased glucose metabolism in the head of the pancreas with significant expansion of the pancreatic duct, indicating a malignant tumor.

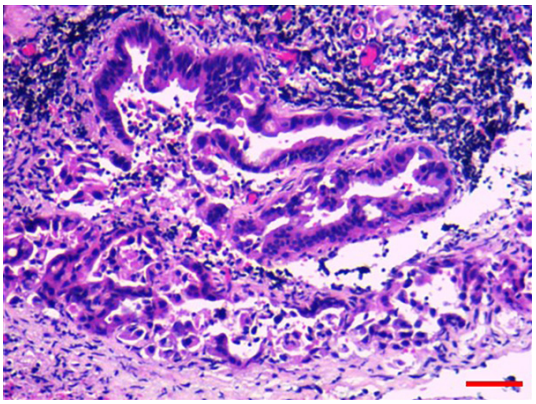

Figure 3. (2015-8-16) H&E staining and immunohistopathology of pancreatic cancer. Bar = 100 μm.

Discussion

Early diagnosis of PC is not common. Furthermore, the curative rate of PC is very low. Pancreatic adenocarcinoma usually progresses rapidly and has a limited response to chemotherapy, leading to a poor prognosis. As a result, the median survival time of patients with metastatic diseases is only 3 to 6 months [6]. Despite advances in multiple treatments, the incidence of PC is still close to its mortality rate [7], and the 5-year survival rate is less than 5% [8]. The incidence of PC increases with age, with 70% occurring over 65 years of age [9]. The general condition, comorbidity, senile syndrome and tolerance to treatment should be taken into account when selecting treatment for patients in this age group. Currently, there is no consensus on clinical guidelines for the treatment of advanced PC in the elderly. Some studies have shown that for resectable PC in the elderly, they are suitable for safe surgical resection in a specialized center, but more intensive postoperative rehabilitation may be required [10]. Most PC patients can only tolerate a single treatment caused by various medical conditions. Multiple drug combination chemotherapy, including FOLFIRINOX, gemcitabine plus nab-paclitaxel, nanoliposomal irinotecan

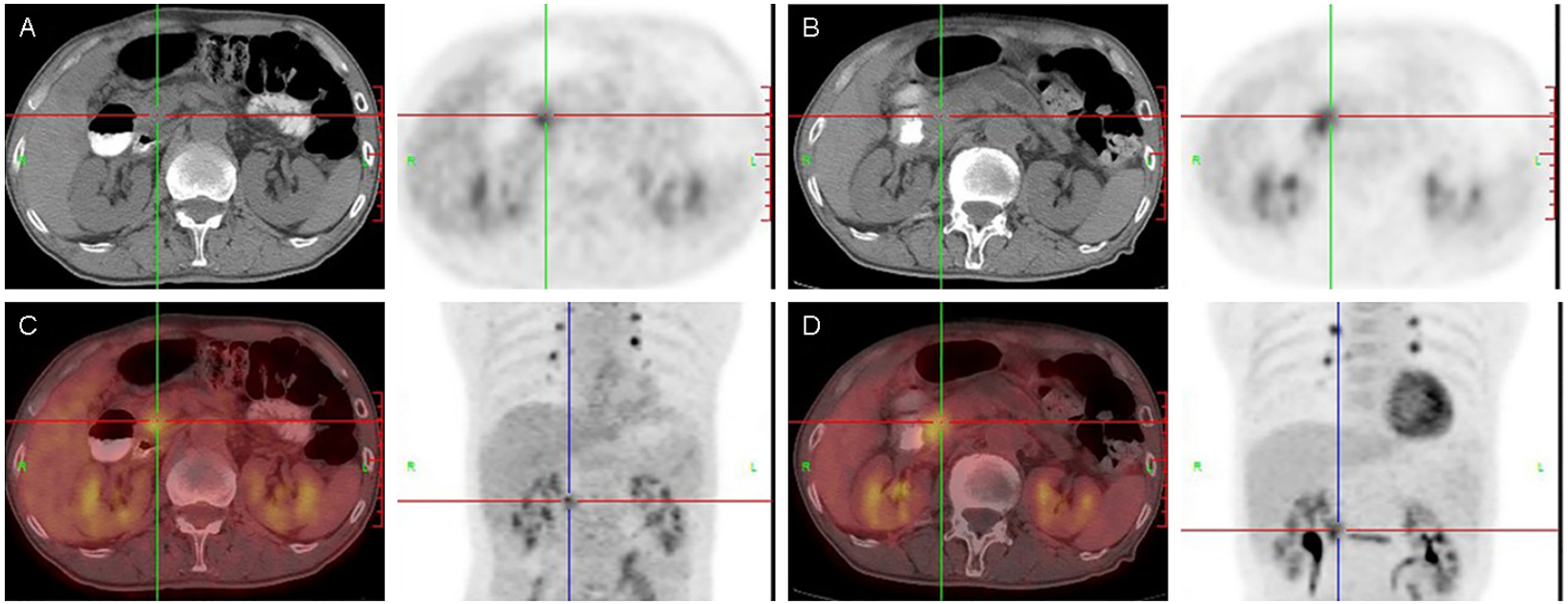

Figure 4. PET-CT (A and C, 2017-6-26) showed that an enlarged lesion of the head of the pancreas compared with PET-CT (B and D, 2015-8-14).

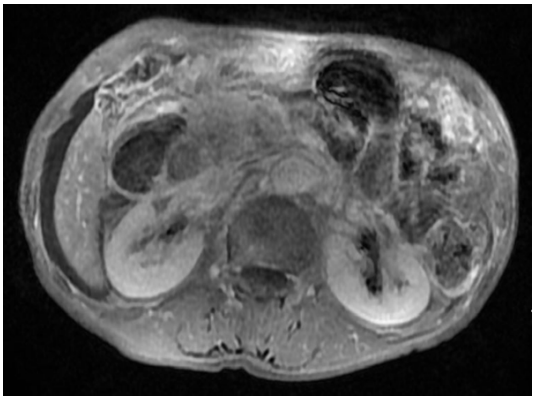

Figure 5. (2017-7-20) Enhanced MRI of the pancreas showed that the lesions of the head of the pancreas were larger than before.

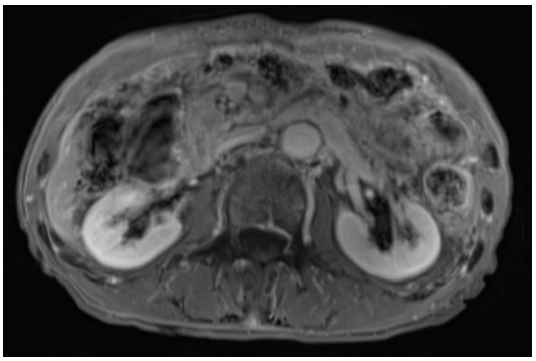

Figure 6. (2017-12-26) Enhanced MRI of pancreas showed that the lesion was smaller than before.

plus 5-fluorouracil and leucovorin, and gemcitabine plus capecitabine [1], can easily lead to severe liver and kidney damage, bone marrow suppression, and vital organ failure, refractory infection, bleeding and even death and other serious complications.

S-1 is a third-generation fluorouracil derivative, mainly used for the treatment of unresectable locally advanced tumors. It is composed of tegafur/gimeracil/Oteracil with a ratio of 1:0.4:1 [11]. Tegafur is a precursor of 5-fluorouracil, which is decomposed into 5-fluorouracil and has a good anti-cancer effect on the body. Gemeracil can inhibit the key enzymes that catalyze this process during the decomposition of 5-fluorouracil, increase the concentration of 5-fluorouracil, and enhance its efficacy. Otirazide potassium has a higher concentration in the gastrointestinal tract, which can reduce the occurrence of gastrointestinal reactions. S-1 is an oral fluoropyrimidine derivative; it is economical in price, convenient and safe to take, clinically effective and well tolerated. Therefore, elderly patients easily accept this treatment. S-1 first-line treatment may be a reasonable treatment option for elderly patients with pancreatic cancer.

Because autopsy studies show that 30% of patients die from local diseases, local control remains a major problem for LAPC [12]. A number of single-agency studies have examined the role of SBRT in LAPC settings. SBRT is a new treatment option for LAPC, because it may provide a good quality of life and potential therapeutic benefits for patients in a short period of time compared to conventional RT for 5-6 weeks [7]. The advent of the Gamma knife therapy increased the radiation dose given to the tumor. It also protects the surrounding tissues. The Gamma knife is well tolerated. It has been successfully used to repair brain metastases in patients who have failed whole brain radiotherapy. The application of Gamma knife treatment in PC has attracted more and more clinical researchers.

Nituzumab is a humanized IgG1 monoclonal antibody against the extracellular domain of EGFR. It mediates anti-tumor effects because of its capacity of inhibiting proliferation, survival and angiogenesis [8]. The expression of EGFR is increased in 30% to 70% of primary and metastatic PC tissues. The binding properties of Nituzumab strongly depend on the level of EGFR expression in cancer cells. Nituzumab is less toxic compared with other EGFR inhibitors. It can significantly increase the one-year OS and PFS rates in patients with advanced or metastatic PC. Especially in patients with wild-type KRAS, it seems to benefit [8]. Moreover, due to the enhancement of cell cycle arrest and cell apoptosis, Nituzumab can enhance the anti-cancer effects of radiation in PC cells [13].

In this case, the combination of Gamma knife treatment and S-1 with Nituzumab was the best option, because our patient was 83 years old and could not tolerate aggressive surgery and chemotherapy. The patient got worse when he stopped taking S-1. We again chose Gamma knife therapy for local control and continued to administer S-1. The therapy was proven to be effective. The patient well tolerated this treatment in combination with Nituzumab. This

Table 1. Process of therapy for the patient

Time	Treatment	Response
2015/8	Gamma Knife+S-1	PR
2015/8-2016/9	S-1	SD
2016/10-2017/7	Chinese herbal medicine	PD
2017/8	Gamma Knife+S-1+Nituzumab	PR
2017/9-So far	S-1+Nituzumab	SD

option is recommended by the guidelines: (1) S-1 was chosen because the patient was an 83-year-old elderly patient with pancreatic cancer. Various clinical data indicated that S-1 has a very high efficiency for pancreatic cancer patients [14, 15]. (2) Studies have shown that Nituzumab could enhance the anticancer effect of radiation and S-1-based chemoradiation in PC cancer cells because of the enhancement of cell cycle arrest and apoptosis. In addition, Nituzumab is safe and very well tolerated [16, 17]. The means of 'combined with S-1 and Nituzumab' was: "S-1 40 mg, per oral, d1-14, q21d" combined with "Nituzumab 100 mg, intravenous drip, d1 qw". The patient achieved a total survival period of 62 months, with excellent performance. With careful selection, a combination of Gamma knife, S-1, and Nimozumab therapy may be a suitable treatment strategy.

In conclusion, due to the fact that there are few studies on the treatment of PC in the elderly, especially in patients over 80 years of age. Also due to the side effects of radiotherapy, there are particularly few studies on re-radiotherapy of PC in the elderly. The reapplication of the original chemotherapy regimen is uncertain. Our case shows that this strategy may be beneficial for some patients. Gamma knife therapy combined with S-1 and Nituzumab may have synergistic effects. For elderly patients with locally unresectable recurrence of pancreatic cancer, this combination therapy may help patients achieve long-term survival.

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Disclosure of conflict of interest

None.

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