

Major points

[Introduction] 1) I reconsidered the main text, specifying the trend of deaths and incident cases by gender and using the recommended article (GBD 2017 Pancreatic Cancer Collaborators. *Lancet Gastroenterol Hepatol.* 2019 Dec;4(12):934-947. doi: 10.1016/S2468-1253(19)30347-4.).

[Hereditary risks factors and screening] 1) I created, as suggested, an independent paragraph for surgical resection for IPMNs and other cystic lesions. 2) I reported in table 1 the frequency of mutated genes as requested, taking advantage of the recommended article (Holter et al. *J Clin Oncol.* 2015 Oct 1;33(28):3124-9. doi: 10.1200/JCO.2014.59.7401) and Yurgelun MB, Chittenden AB, Morales-Oyarvide V, et al. Germline cancer susceptibility gene variants, somatic second hits, and survival outcomes in patients with resected pancreatic cancer. *Genet Med.* 2019;21(1):213-223. doi:10.1038/s41436-018-0009-5.

[Biomarkers and early detection] 1) I mentioned the use of Span-1 and DUPAN 2, as well as their respective sensitivity and specificity 2) I described the usefulness of pancreatic juice, pancreatic cyst fluid and other liquid materials, such as urine and saliva.

[DIAGNOSIS] 1) I described the pros and cons of ERCP considering the suggested article (Ishii et al. *Diagnostics (Basel).* 2021 Feb 4;11(2):238. doi: 10.3390/diagnostics11020238.) 2) In the “Biopsy” section, I reported the risk of needle-tract seeding when performing EUS-FNA, although it doesn’t affect to the patient’s overall survival (Yane et al. *Dig Endosc.* 2020 Jul;32(5):801-811. doi: 10.1111/den.13615).

[Surgery] 1) I replaced the term “Whipple’s operation” with the term “pancreatoduodenectomy”. 2) I have added a detailed description of the complications of the pancreatoduodenectomy and the surgical techniques to reduce the risk of these complications, with particular emphasis on pancreatic fistula and the Blumgart anastomosis (Ricci et al. *World J Surg.* 2021 Jun;45(6):1929-1939. doi: 10.1007/s00268-021-06039-x.

[Chemotherapy for resectable PDAC and BR-PDAC borderline resectable PDAC]

[Immunotherapy] 1) I have added a table to show evidence level and clinical trial phase of each trial of these paragraphs.

[Neoadjuvant chemotherapy (NACT)] 1) I described the Gemcitabine+S-1 regimen and I mentioned the result of the PREP-02/JSPS-05 study (Motoi et al. *Jpn J Clin Oncol.* 2019 Feb 1;49(2):190-194. doi: 10.1093/jjco/hyy190.)

Minor points [Immunotherapy; Immune checkpoint blockade] 1) I replaced the term immune checkpoint blockade with immune checkpoint inhibitors