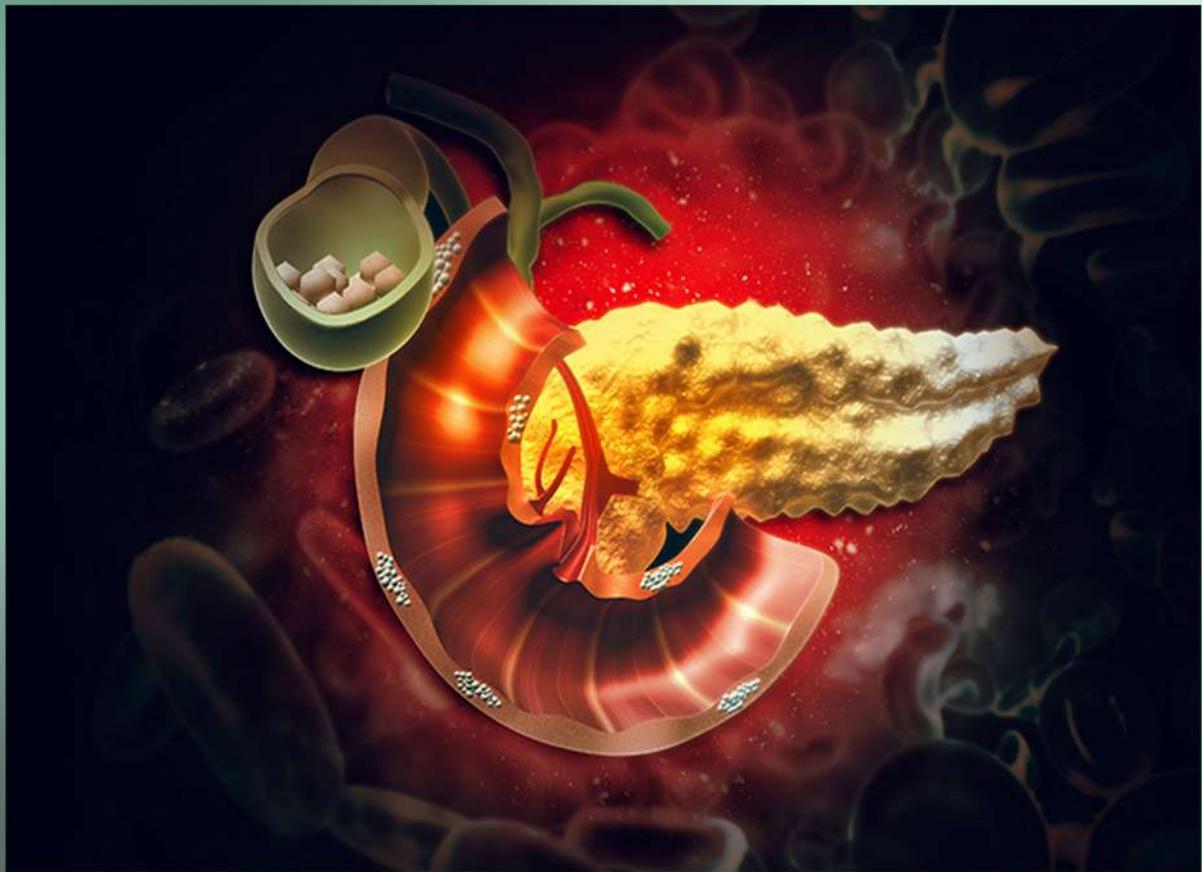


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Editorial

Outstanding Outcome of Pancreatic Cancer: What Lessons Do We Learn

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The American Cancer Society's estimates that 57,600 people (30,400 men and 27,200 women) will be diagnosed with pancreatic cancer in the United States for 2020 and approximately 47,050 people (24,640 men and 22,410 women) will die of pancreatic cancer in 2020.¹ Despite advances in first-line therapy such as gemcitabine/nab-paclitaxel and fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFIRINOX) in advanced pancreatic cancer (aPC), median overall survival remains less than 12-months.²

Prestigious Supreme Court judge announced that she is a four-time survivor of cancer. She was diagnosed with colorectal cancer in 1999 for which she underwent surgery followed by chemotherapy and radiation therapy.^{3,4} During the course, she did not miss a day on the bench, despite being physically beaten by the cancer treatment. She overcame this weakness by working with a personal trainer, named Bryant Johnson, a former Army reservist attached to the Special Forces, who has trained Ginsburg twice weekly in the justices-only gym at the Supreme Court. A decade later on February 05, 2009 she was diagnosed with pancreatic adenocarcinoma, often deadly but in her case detected early. She underwent surgery and was released from the hospital on February 13.^{5,6} Though not known, but it was reported that spleen was removed indicating the tumor could be in the tail part of the pancreas. She went back into session on February 23, 2009. On November 8, 2018, she fractured three ribs following a fall in her office and returned to work after a day of observation.⁷ A computerized tomography (CT) scan at that time revealed suspicious lesions in her lungs for which she underwent surgical removal of these nodules on December 21, 2018.⁸ It was in August 24, 2019 when it was reported that Ginsburg had completed three weeks of focused radiation treatment to ablate a tumor found in her pancreas. Finally, on January 7, 2020, Ginsburg reported that she is again cancer free.

Pancreatic cancer remains a devastating disease but in resecting lung metastases resulting from pancreatic cancer has been reported in medical literature as well as in our experience in selected cases.² Only a few cases of long-term survival after such a procedure have been reported. Certain factors are very valuable in predicting this survival including the relatively long interval between the initial resection to treat the pancreatic cancer and lung metastasis, as well as whether the metastatic lung tumor is solitary and stable over time.⁹ We consider performing lung resection in such a patient if the following conditions are met:

1. The patient is fit for surgery;
2. The primary lesion is controlled;
3. No additional metastases are found outside in other parts of the body in addition to the lung;
4. Multiple lung metastases can be removed.

Medical literature has also shown that patients in whom lung is the first site of recurrence of pancreatic cancer had better survival rates than those who developed pulmonary metastases as a second or synchronous site of recurrence. It is important to notice here that distinction between lung metastases from pancreatic cancer from primary lung cancer or a lung metastasis from a different/new cancer is prudent, especially these two tumors share few risk factors, such as smoking.¹⁰

Though, surgery remains the standard of care and the sole hope for cure in operable pancreatic cancer but radiation therapy can also offer local control in some patients. Particularly, in patients with local recurrence or positive margins, radiation therapy has shown considerable promise for local control. Moreover, with the improvement in radiation technology such as stereotactic body radiation therapy (SBRT), we are now able to deliver extremely precise, very intense doses of radiation to cancer cells while mini-

mizing damage to healthy tissue in comparison to conventional radiotherapy.¹¹

There are two extremely important points to be made here about her amazing outcome and they relate to her will and commitment. It is now a well-known fact that patients who exercises like Ginsburg does, tend to do better than folks who are very much affected by the tumor.¹² In addition, family support and a will and desire to fight the cancer are additive factors. Many patients give up the fight due to depression or other factors.¹³

Another comment worth-mentioning here is the occurrence of both colorectal cancer and pancreatic cancer in an individual or in an individual with a first-degree relative deserves the testing for an identifiable genetic syndrome underlying their cancer risk, such as Lynch Syndrome.¹⁴ With the availability of novel diagnostic tools and risk-reducing plus therapeutic strategies, it is prudent that physicians must be vigilant about evaluating patients for hereditary cancer syndromes.

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Letter to the Editor

Pancreas and Coronavirus Disease-2019

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Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) virus affects many other organs than lung and upper airways. Gastrointestinal system appears to be affected both in the upper and in the lower portions. Moreover, hepatic, myocardial, and renal involvements are reported. Furthermore, pancreas can be affected in coronavirus disease-2019 (COVID-19) and the presence of SARS-COV-2 in the pancreatic tissue has been confirmed during autopsy.¹

This is related to the presence of angiotensin-converting enzyme type 2 (ACE-2) receptor localized both in the exocrine and endocrine parts of pancreas. Thus, Yang et al² and colleagues reported frequent hyperglycemia in SARS-COV infections that can be related to damage of pancreatic islets (through ACE-2 binding).

Following, I presented a brief review of the few papers described the potential relationship between COVID-19 and pancreas.³⁻⁸

Liu et al³ and colleagues confirmed that the possible pancreatic damage of SARS-COV-2 infection may be related to ACE-2 expression and assessed that expression of this receptor is higher in the pancreas than in the lung according to ribonucleic acid (RNA) analysis. One hundred twenty-one (121) COVID-19 positive patients of their case series reported high-levels of amylase and lipase according to the severity of the disease; but pancreatic necrosis was not seen at imaging in the study. Moreover, the authors pointed drug-induced pancreatic damage due to non-steroidal anti-inflammatory drugs (NSAIDs) and/or glucocorticoids as possible confounding factor. It was also underlined that the prolonged effect on pancreas could cause a worsening of systemic inflammation and acute respiratory distress syndrome (ARDS) and could evolve in chronic pancreatitis. I agree with the authors that, on one hand, pancreatic damage can contribute to the “cytokines’ storm” during COVID-19 from activation of complement system (as in acute pancreatitis) and subsequent worsening of ARDS; on the other hand, chronic pancreatic damage can follow the same

mechanisms of fibrosis observed for the lung

Wang et al⁴ and colleagues discovered that 17% of 52 COVID-19 patients had a pancreatic injury (defined as increased blood level of amylases and lipases): for me, this is a controversial finding.

Commenting on this finding, De-Madaria et al⁵ explained that increased amylases and lipases in COVID-19 patients can be associated to acidosis, renal failure and gastroenteritis, especially if imaging is negative for pancreatic injury. And, I completely agree that hyperamylasemia and hyperlipasemia do not mean pancreatitis in absence of symptoms and imaging correlation.

Mukherjee et al⁶ concluded that, considering the available data, COVID-19-associated pancreatic dysfunction may exist and can be responsible of atypical “pancreatitis-like” clinical presentation of the disease. However, the authors did not report any personal cases and based their conclusions on the previous findings that I reported above.

Hadi et al⁷ described two out of three family members diagnosed with acute pancreatitis associated with COVID-19 excluding many other potential confounding factors.

Patel et al⁸ reported that gastrointestinal symptoms, included abdominal pain in 2.2% of patients, occurred later than respiratory symptoms without a clear physiopathological mechanism. I think that late onset is at the base of the doubts of COVID-19 related pancreatitis.

The American National Pancreas Foundation, on its website, assessed that, on one hand, acute pancreatitis can worsen the immune response to COVID-19 and that, on the other hand, chronic pancreatitis-associated diabetes represents a bad prognostic factor in COVID-19 patients.

Recently (during April 2020), we reported four cases of hyperamylasemia associated to hyperlipasemia in COVID-19 patients in Niguarda Hospital, Milan, Italy. Three cases resolved spontaneously in a mean of 15-days and no abdominal imaging was performed; one evolved in walled-off pancreatic necrosis (WOPN) treated by endoscopic ultrasound-guided transgastric drainage.

We can conclude that the expression of ACE-2 in pancreatic tissue make the pancreas a target organ for SARS-COV-2 and the virus can damage both exocrine and endocrine function of the gland. Increase of amylases and lipases can be caused by many confounding factors in COVID-19 patients; so, imaging and symptoms are important to evaluate the true involvement. Considering that abdominal pain is one of the known symptoms associated with SARS-COV-2 infection we must consider acute pancreatitis as a main cause especially in case of diffuse or upper abdominal pain.

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