Cancer Surgery

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# Wharton's jelly-derived mesenchymal stem cell: Conditioned media induces apoptosis of pancreatic cancer

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According to the NCCN criteria, resectability of Pancreatic Carcinoma (PC) is commonly assessed by MDCT and depends on tumor's relation to neighboring blood vessels, such as Celiac Trunk (CT), Hepatic Artery (HA), Superior Mesenteric Artery (SMA), Portal Vein (PV) and Superior Mesenteric Vein (SMV). The aim of this study was to investigate methodology of the assessment of local vascular invasion of pancreatic carcinoma by MDCT using the angle measuring too. 50 consecutive 64-MDCT scans of patients with the PC were retrospectively analyzed. Maximal angle of blood vessel's circumference that was in direct contact with the tumor was measured using the angle measuring tool on axial section and length of direct contact on MPR-reconstructed section. Accordingly, resectability was estimated using the NCCN criteria. Frequencies and correlations were statistically analyzed using Spearman's (rS) and Pearson's correlation coefficient (r). Average size of tumor was 36±13 mm (10-68 mm). Majority of PCs were in advanced stage (60% T3 and 36% T4), located in the head of the pancreas (62%). 22% tumors were estimated as resectable, 48% borderline resectable and 30% unresectable. SMV and PV were invaded most frequently (50% and 46%) and surrounding arteries in lower percent (SMA in 26%, HA in 22% and CT in 16%). Location, size and T-stage correlated with the frequency of local vascular invasion (rS>0.450). Maximal angle correlated with the length of the vascular infiltration (r>0.450). Precise estimation of vascular invasion in PC by MDCT is possible using the angle measuring tool.Pancreatic cancer begins in the tissues of your pancreas — an organ in your abdomen that lies behind the lower part of your stomach. Your pancreas releases enzymes that aid digestion and produces hormones that help manage your blood sugar.Several types of growths can occur in the pancreas, including cancerous and noncancerous tumors. The most common type of cancer that forms in the pancreas begins in the cells that line the ducts that carry digestive enzymes out of the pancreas (pancreatic ductal adenocarcinoma).Pancreatic cancer is seldom detected at its early stages when it's most curable. This is because it often doesn't cause symptoms until after it has spread to other organs. Pancreatic cancer treatment options are chosen based on the extent of the cancer. Options may include surgery, chemotherapy, radiation therapy or a combination of these. Signs and symptoms of pancreatic cancer often don't occur until the disease is advanced. They may include: Abdominal pain that radiates to your back, Loss of appetite or unintended weight loss, Yellowing of your skin and the whites of your eyes (jaundice), Light-colored stools, Dark-colored urine, Itchy skin, New diagnosis of diabetes or existing diabetes that's becoming more difficult to control. Blood clots & Fatigue pancreas is about 6 inches (15 centimeters) long and looks something like a pear lying on its side. It releases (secretes) hormones, including insulin, to help your body process sugar in the foods . Pancreatic cancer occurs when cells in your pancreas develop changes (mutations) in their DNA. A cell's DNA contains the instructions that tell a cell what to do. These mutations tell the cells to grow uncontrollably and to continue living after normal cells would die. These accumulating cells can form a tumor. When left untreated, the pancreatic cancer cells can spread to nearby organs and blood vessels and to distant parts of the body.Most pancreatic cancer begins in the cells that line the ducts of the pancreas. This type of cancer is called pancreatic adenocarcinoma or pancreatic exocrine cancer. Less frequently, cancer can form in the hormone-producing cells or the neuroendocrine cells of the pancreas. These types of cancer are called pancreatic neuroendocrine tumors, islet cell tumors or pancreatic endocrine cancer. As pancreatic cancer progresses, it can cause complications such as:

Weight loss. A number of factors may cause weight loss in people with pancreatic cancer. Weight loss might happen as the cancer consumes the body's energy. Nausea and vomiting caused by cancer treatments or a tumor pressing on your stomach may make it difficult to eat. Or your body may have difficulty processing nutrients from food because your pancreas isn't making enough digestive juices.Jaundice. Pancreatic cancer that blocks the liver's bile duct can cause jaundice. Signs include yellow skin and eyes, dark-colored urine, and pale-colored stools. Jaundice usually occurs without abdominal pain. Pancreatic cancer has an extremely poor prognosis, due to not only being a highly complex and aggressive malignancy (higher invasion and metastasis) but also is resistant to most therapies. Stem cell based treatments are being increasingly explored especially for those cancers that cannot be treated with targeted therapy. In the last decade, Mesenchymal Stem Cells (MSCs) have attracted significant attention as a result of their accessibility, tumor-oriented homing capacity and the transplantation feasibility. We propose a novel strategy of using MSCs as a cell-based anticancer therapeutic option. Till date, MSC-based therapy for pancreatic cancer has not been demonstrated. Our study demonstrates the

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feasibility using the pancreatic cell-line-based model (MiaPaCa-2 and PanC1). Expression of classical pancreatic cancer stem-cell markers i.e., CD44+/CD24+ in MiaPaCa-2 was 71.7±5.5% and PanC-1 showed 64.6±5.2% as compared to fibroblast cell line NIH-3T3 (19.1±1.4%) (p=0.0001). Sensitivity (IC50 dose response) towards Gemcitabine (Gem) and 5-Fluorouracil (5FU) was derived from MTT assay. PanC-1 showed relatively more resistance than MiaPaCa-2 (Gem-600 nM vs. 350 nM and 5-FU ≥1000 nM vs. 400 nM) respectively suggesting PanC1 is more resistant. To study the interaction between human Wharton's Jelly-derived Mesenchymal Stem Cells (hWJMSCs) and pancreatic cancer cells, co-culture assays were performed (ratio of 1:1; 48 hours). Markers of pro-apoptosis (Bax) and proliferation (Ki-67) were assessed by immunofluorescence. An inverse proportionate expression of Bax and Ki67 was observed when MiaPaCa-2/PanC-1 was treated with hWJMSCs (32.5% and 13% respectively). To verify these results, PKH-26-labeled hWJMSCs were overlaid on pancreatic tumor cells (1D). It was observed microscopically that PKH-26-labeled hWJMSCs proliferated two-fold in comparison to tumor cells. The effect of MSCs directly affecting the pancreatic tumor cell was reconfirmed with a proliferative marker Ki67. Functional properties EpCAM/CXCR4 (metastatic markers), Vimentin and E-cadherin (EMT markers) were evaluated using flow cytometry and qPCR. EpCAM was significantly (p=0.0002) decreased when treated with hWJMSCs in comparison to untreated tumor cells (MiaPaCa-2- 23% vs. 37%; PanC1-20% vs. 50%). However, no significant change in CXCR4 expression was observed. To understand the cellular cross-talk between hWJMSCs and pancreatic tumor cells, the conditioned media derived from hWJMSC (CM) was studied. Expression of Bax was significantly further increased (58%) when treated with CM in comparison to hWJMSCs alone (32.5%). However, inhibition of EpCAM expression did not differ from hWJMSCs alone treatment. Migration and invasion potential of tumor cells were inhibited when treated with CM (MiapaCa-2-2.2 vs. 9 cells/field; PanC-1-5 vs. 10.5 cells/field), compared to untreated tumor cells. On frequency distribution histograms (flow cytometry) apoptotic events were characterized by a distinctive sub-G1 peak that represents oligonucleosomal DNA fragments. MiaPaCa-2 and PanC1 cells treated with CM showed significant ($p<0.005$) reduced number of cells entering G1 phase of the cell cycle i.e., at G0 M phase. This result was also evident as per DNA-fragmentation assay. Thus, our results suggest that Wharton's jelly-derived mesenchymal stem cells secretome can modulate the proliferation and migratory (oncogenic) capabilities of pancreatic tumor cells. In other words, paracrine factors released by hWJMSC might act as a cytotoxic biological agent. Hence, CM could be a novel cell-free therapeutic candidate. Presently, under investigation is the proteomic analysis of CM treated pancreatic tumor cells using 2D and MALDI/MS techniques.

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