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**CASE STUDY: ADVANCED UNRESECTABLE PANCREATIC ADENOCARCINOMA  
MANAGEMENT USING GEMCITABINE AND INTEGRATED HEALTH CLINIC  
APPROACH**

**Abstract:**

Pancreatic cancer ranks fourth among cancer-related deaths in the United States. In 2008, the estimated incidence of pancreatic cancer was 37,700 cases, and an estimated 34,300 patients died from the disease<sup>1</sup>. For patients with resectable disease, surgery remains the treatment of choice. However, data from several randomized trials indicate that a more extensive resection does not improve survival but increases post-operative morbidity<sup>1</sup>. Gemcitabine is the clinical standard for most chemotherapy regimens for pancreatic cancer; however, patients have a generally limited response to this therapy. In this report, we present a case of advanced pancreatic adenocarcinoma management at Integrated Health Clinic (IHC), using local hyperthermia in conjunction with chemotherapy and disease-specific dietary, supplementary, injection and intravenous therapies. Current literature has shown that hyperthermia selectively targets cancer cells leading to apoptosis through the application of several mechanisms of action. Studies show the safety and efficacy of hyperthermia combined with chemotherapy and/or radiotherapy and that prognosis is improved in patients with locally advanced cancer<sup>2</sup>. The use of hyperthermia for the treatment of cancer has been well documented. Mechanisms of action of hyperthermia include the stimulation of the immune system acting on the unique morphology of cancer cells<sup>3</sup>

**Case history:**

P.P., a 64 year-old male was diagnosed with pancreatic cancer in September 2012. He initially presented with progressive 30 lbs weight loss, fatigue, weakness and jaundice. Abdominal CT identified a 3.5 x 3.8 cm mass at the pancreatic head along with dilation of the common bile duct. Core biopsy reported moderately and focally poorly differentiated cells. Final staging confirmed locally advanced pancreatic adenocarcinoma with invasion of the peripancreatic lymph nodes and superior mesenteric vein. A Whipple's procedure was attempted but not completed as the pancreatic mass was proven unresectable. He instead underwent a hepaticojejunostomy as well as a Roux-en-Y gastrojejunostomy procedure. Medical history includes hypertension, cardiomyopathy, paroxysmal atrial fibrillation and a history of a silent myocardial infarction. He has a 35-year pack per day smoking history quitting in 2005.

In December 2012, PP began palliative intravenous gemcitabine weekly for 3 weeks on a 4 week cycle, with the goal to control residual disease and prolong life. In March 2012, after completion of three cycles, chemotherapy was halted due an infection after fracture of a biliary stent. Chemotherapy resumed in May 2013 and soon after PP developed a liver abscess and chemotherapy was again halted until January 2014. He remained on periodic gemcitabine treatment until September 2014, with starts and stops due to the aforementioned infections and abscesses which recurred throughout his care.

PP had regular loco-regional hyperthermia (LRHT) treatments in conjunction with chemotherapy, and alone when chemotherapy was halted. LRHT was initiated in November 2012 and continued until October 2014. A large probe was placed over the pancreas and liver. Overall, PP underwent 68 LRHT treatments with no adverse reactions. Intravenous therapies consisted of 50 grams ascorbic acid, 5 grams dichloroacetate (DCA), and/or 600 mg alpha lipoic acid (ALA). These I.V. therapies were administered alone or in conjunction with hyperthermia treatments. *Viscum album* (Iscador) was administered subcutaneously prior to each LRHT treatment. Pharmaceuticals and targeted supplementation were recommended as part of his naturopathic plan (Table 1). No adverse therapeutic reactions were reported.

**Table 1. Prescriptions & Targeted Supplementation**

<b>Medications</b>	<b>Dose</b>	<b>Effects</b>
<b>Prescriptions</b>		
Metformin*	400 mg tablet p.o. BID	Activation of AMPK disrupts crosstalk between insulin/IGF-1 and GCPR signaling in pancreatic cancer cells <sup>4</sup> . Direct inhibitory effect on cancer cell growth and antitumoral action <sup>5</sup> .
Dichloroacetic Acid (DCA)*	500 mg p.o. BID (5 days on & 2 days off)	Inhibits pyruvate dehydrogenase thereby inhibiting glycolysis. Causes favoring of aerobic respiration, which reverses the suppression of apoptotic pathways. Increase tumor apoptosis shrinks

		tumor size <sup>6</sup> . Trigger apoptosis in cancer cells by reducing mitochondrial membrane potential, blocking aerobic glycolysis (Warburg effect) and activating mitochondrial potassium-ion channels <sup>7</sup>
Celebrex*	100 mg capsule p.o. QD	Inhibit cyclooxygenase-2 (Cox2) enzymes. Blocking Cox 2 has been shown to decrease tumor invasiveness <sup>8</sup> . Induce apoptosis and inhibit angiogenesis of tumor cells <sup>9</sup>
Cimetidine*	400 mg tablet p.o. BID	Anti-adhesion and antiangiogenesis, Inhibit tumor cell propagation and metastasis <sup>10</sup> . Enhance host immune response and block cell growth promoting activity of histamine in melanoma cell lines <sup>11</sup>
<b>Supplements</b>		
Can-Arrest* (Curcumin 200mg, Boswellia 200mg, Quercetin 100mg)	2 capsules p.o. BID	Inhibition of the transcription factor NF-κB to arrest tumor growth and its progression <sup>12</sup> . Inhibit cyclooxygenase-2 (COX2) enzymes. Blocking COX 2 has been shown to

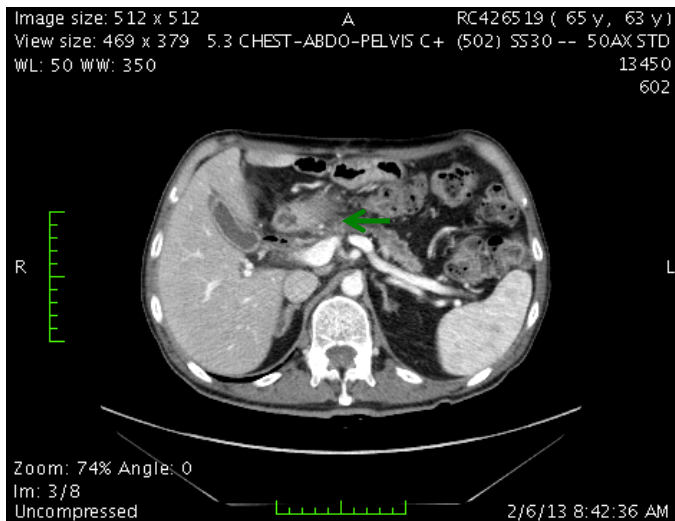
		decrease tumor invasiveness <sup>13</sup>
Avemar*	1 sachet p.o. QD	Anti-tumoral. Immune modulation. Improve quality of life <sup>14</sup> . Induce apoptosis and exert significant antitumor activity <sup>15</sup>
Pectasol-C	3 scoops p.o. QD	Immuno-stimulatory. Activation of functional T cytotoxic cells, B-cell and NK cells <sup>16</sup> . Bind to galectins on cancer cell surface interfering with cancer cell metastatic target site interaction <sup>17</sup>
Fish oil (Omega 3 oil)	1-2 tbsp p.o. QD	Inhibit acute phase protein response and cachexia <sup>18</sup> . Prevent progression of APPR and cachexia in weight losing patients with advanced cancer <sup>19</sup>
Melatonin	20 mg capsule p.o. QHS	Immunomodulatory. Augment production of T-lymphocytes and NK cells. Oncostatic properties in melanomas and tumors of epithelial origin <sup>20</sup> . Multiple anti-cancer actions including; reduces toxicity after chemotherapy, radiotherapy, immuno-hormonal therapy and cancer

		surgery. Adjuvant therapy for cancer <sup>21</sup>
Milk Thistle formula	1 capsule p.o. BID	Cancer chemopreventive and anti-carcinogenic effect <sup>22</sup> . Apoptotic effect, without cytotoxic effects <sup>23</sup> .
Alpha lipoic acid	600 mg capsule p.o. BID	Induce apoptosis in cancer cells. Stabilize NF-κB transcription factor <sup>24</sup> . Inhibit aerobic glycolysis <sup>25</sup>
Curcumin	8000 mg capsule p.o. QD	Inhibit tumor initiation, promotion, invasion, angiogenesis, and metastasis <sup>26</sup> . Inhibition of the transcription factor NF-κB to arrest tumor growth and its progression <sup>27</sup>
Astragalus	2 capsule p.o. BID	Potentiate immune-mediated anti-tumor activity of IL-2, enhance natural killer (NK) cell activity <sup>25</sup> . Anorexia and cachexia control in advanced cancer patients <sup>28</sup>

\* Taken 30-45 minutes prior to loco-regional hyperthermia

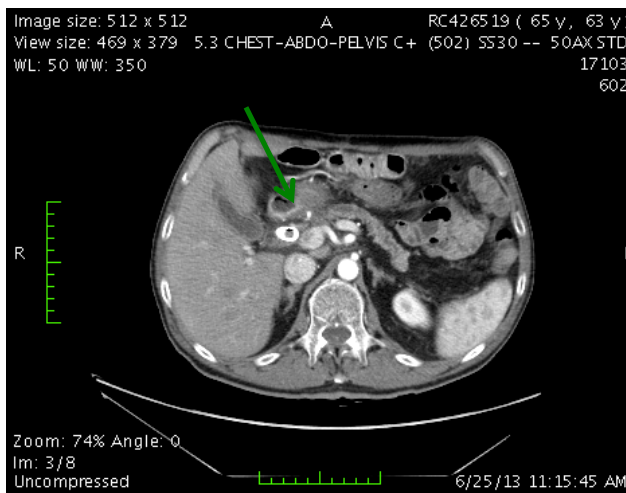
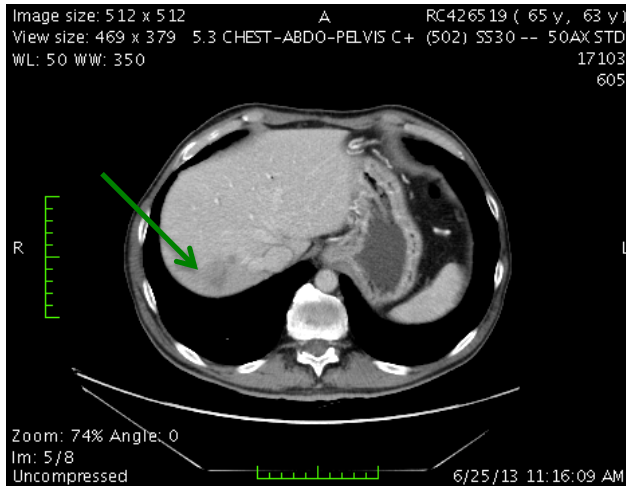
A CT scan of the chest, abdomen and pelvis in February 2013 noted reduction in size of the pancreatic mass and mesenteric nodules. There was no evidence of tumour spread (Fig. 1).

**Figure 1. - CT of the chest, abdomen and pelvis – February 6, 2013**



CT scan from June 2013 found a mass within the liver, presumably remnants of the liver abscess measuring 2.9 x 3.8 cm. There is a decrease in size of the mass in the pancreatic head. Lymph nodes within the porta hepatis were noted and were unchanged in appearance and size. In June 2013, the pancreatic mass had further reduced to 2.3 x 3.2 cm and the liver mass showed further reduction (Fig 2).

**Figure 2. - CT of the chest, abdomen and pelvis - June 25, 2013**



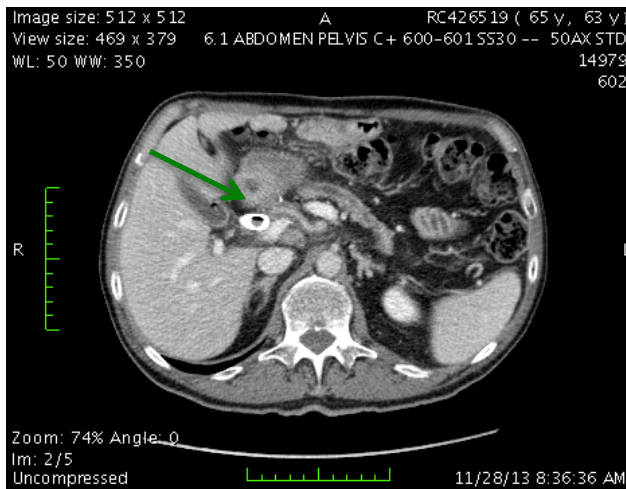
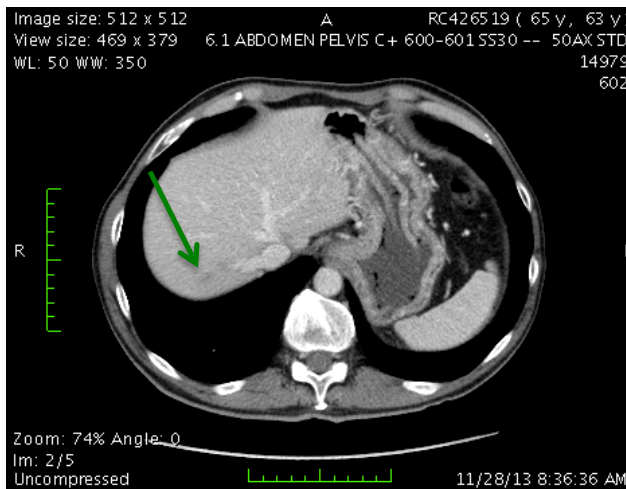
CT images on July 23, 2013 with the stent in place are shown below (Fig. 3).

**Figure 3. CT of abdomen & pelvis - July 23, 2013**

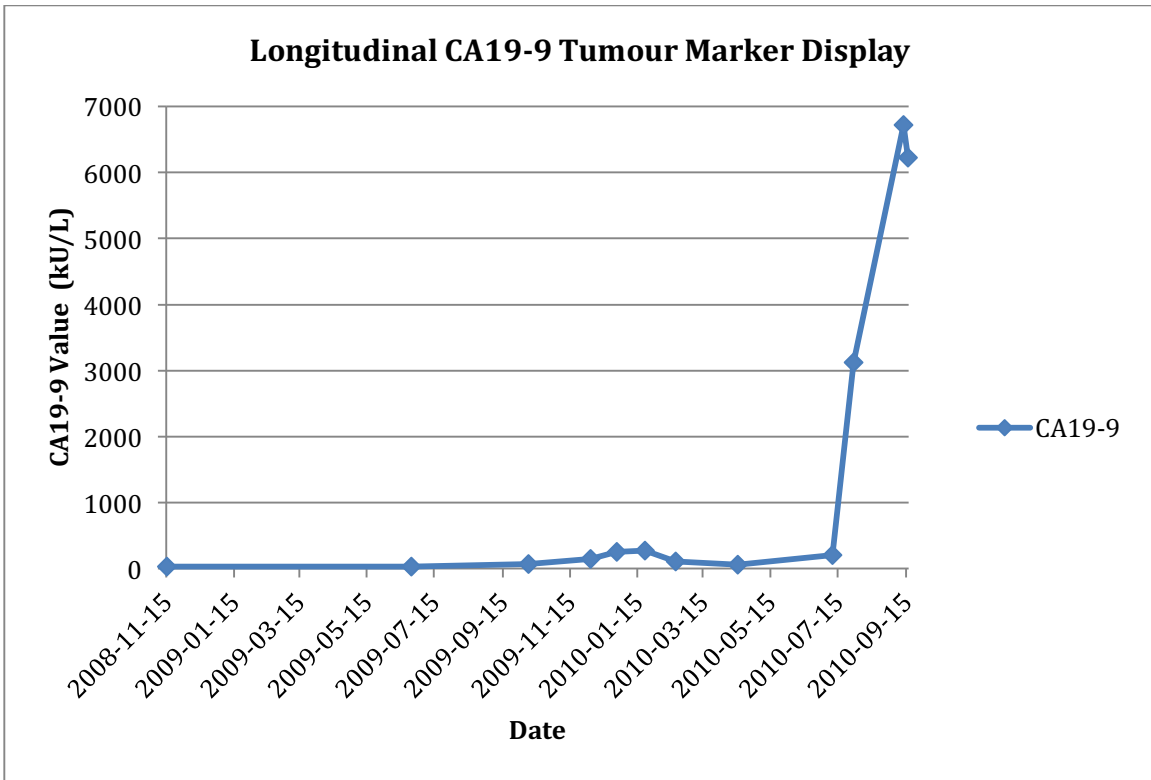


By November 2013, there was complete resolution of the liver abscess. Enlarged lymph nodes within the porta hepatis and portacaval spaces remained stable. (Fig. 4)

**Figure 4. – CT of the chest, abdomen and pelvis – November 28, 2013**



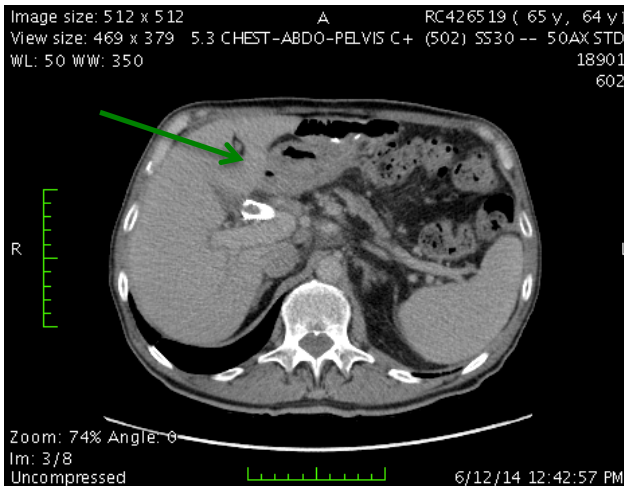
On August 2014, the mass within the pancreatic head measured 7.3 x 4.3 cm. CA 19-9 remained stable until July 2014, when PP started to experience abdominal pain, bloating, cachexia, and ascites and significant rise in tumour markers. (Chart.1).

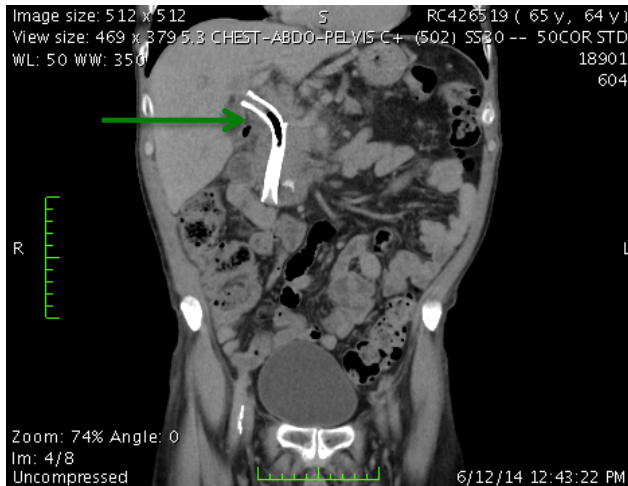


**Chart 1. - CA 19-9**

In June 2014, PP was admitted to the hospital where CT scans showed further enlargement of the pancreatic head and metastases to the liver (Fig. 5)

**Figure 5. - CT of the chest, abdomen and pelvis - June 12, 2014**





Despite these results, he continued regular follow-ups with his naturopathic physician as well as his medical and surgical oncologists. Chemotherapy was discontinued on September 2014 due to abscess around the stent area accompanied by symptoms of infection. PP lived for 2 years and 3 months after first being diagnosed with locally advanced pancreatic cancer, despite receiving relatively limited chemotherapy treatments over the course of his disease. PP had a relatively good quality of life, and survived longer than what is statistically expected of this disease.

## Discussion:

Pancreatic adenocarcinoma remains a devastating disease with poor clinical prognosis<sup>29,30</sup>. Surgical resection is the only potential for cure, however only 15% of patients diagnosed are suitable candidates for surgery and only 30% of those who undergo resection are alive 3 years post surgery<sup>17</sup>. Roughly 40% of patients diagnosed have unresectable locally advanced pancreatic cancer where tumour cells have invaded critical adjacent structures<sup>31</sup>. The optimal management for unresectable pancreatic cancer remains controversial and usually consists of chemotherapy (commonly gemcitabine) alone or in combination with radiation therapy<sup>32</sup>. Response remains dismal with median survival rates ranging from 10-11 months using gemcitabine as a monotherapy<sup>33</sup>

There have been numerous attempts to improve the efficacy of gemcitabine in unresectable locally advanced pancreatic cancer, however combining gemcitabine with other cytotoxic and targeted agents have shown little benefit<sup>34</sup>. Hyperthermia has shown benefit as a cancer therapy displaying both cytotoxic and immune modulating effects<sup>21-24</sup>. When used in combination with cytotoxic agents, hyperthermia can aid in drug penetration throughout tissues leading to thermal destruction of cancer cells<sup>20</sup>. Furthermore, in vitro studies demonstrate improved cytotoxic activities when gemcitabine is combined with heat treatment<sup>25</sup>. In an overview of methods for drug delivery to tumors, research shows that reduction of

TIFP (Tumor Interstitial Flow Pressure) was temperature and time dependent. The reduction of TIFP was associated with an increase in perfusion and a sustained reduction of hypoxia, which led to an improvement in antitumoral effects when associated with chemotherapy and radiotherapy<sup>35</sup>.

Studies using gemcitabine in conjunction with hyperthermia have shown benefit in overall survival. Ishikawa et al. reported a 17.7 months median overall survival (N=6) in locally advanced unresectable pancreatic cancer with gemcitabine and hyperthermia use<sup>20</sup>. Maluta et al. reported a median overall survival of 15 months (N=60) with chemoradiation therapy (CRT) and hyperthermia in comparison to 11 months with CRT monotherapy<sup>26</sup>. Hyperthermia was well tolerated and no reported adverse effects in both studies<sup>20, 26</sup>. The addition of hyperthermia to a patient's treatment regimen, as in this case for example, shows a potential benefit. Both LRHT and FR-WBHT were administered in conjunction with naturopathic treatments. When cancer cells are subjected to high temperatures (40-43° C) they are susceptible to irreversible damage, in a time and dose dependent way<sup>36</sup>.

This patient was prescribed gemcitabine over 21 months from November 2012 through September 2014. Due to complications, chemotherapy was withdrawn for a total of 9 months where he continued with hyperthermia, IV therapies, targeted supplementation and pharmaceuticals (table 1.). It cannot be discerned which therapy had the most impact on tumour control and it is possible that synergistic actions between therapies occurred. Although his disease ultimately progressed, PP lived for 25 months after first being diagnosed with locally advanced unresectable pancreatic cancer. This report provides information on additional therapeutic strategies with good safety profiles that could be combined with conventional treatment for locally advanced unresectable pancreatic cancer.

## **Conclusion:**

This case report shows that integrative oncology treatment is safe and effective for the management of advanced unresectable pancreatic adenocarcinoma. The use of naturopathic treatment seems to have played an important role in the improvement to this patient's overall survival, significantly beyond that offered by conventional measures alone. Hyperthermia in combination with chemotherapy and targeted supplementation has shown to be effective in the management of advanced unresectable pancreatic adenocarcinoma with fewer side effects.

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