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Editorial Open Access

Cancer of the Pancreas (Cap) New Thoughts, New Approaches for the New Year

Avram M Cooperman*

The Pancreas and Biliary Center Mount Sinai Beth Israel New York, New York, USA

***Corresponding author:** Avram M Cooperman, The Pancreas and Biliary Center Mount Sinai Beth Israel New York, New York, United States, Tel: +13522739474; E-mail: Avram.cooperman@gmail.com

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Editorial

"Insanity: Doing the same thing over and over and expecting a different outcome"- Albert Einstein.

Although Einstein was not referring to CaP he was prescient. Embracing and continuing a century of failed experience raises unambiguous questions about the wisdom and common sense (or lack of) applied to CaP, which remains insoluble [1].

CaP is the 12th most common malignancy, but the most lethal [2]. When diagnosed it is a systemic disease, as micro metastasis have disseminated long before tumor detection. Even when CaP is discovered incidentally survival is limited because of metastases. Despite public awareness and campaigns to promote early detection the 5 year survival has improved little since the 1970's, a period before body imaging, advanced endoscopy or multi drug systemic therapy was available. In England and Wales between 1971- 1975 the relative 1 year survival for CaP was 6% which increased to 17.4% between 2005-2009, while during the same time the relative 5 year survival was 2% and 3.6% [3,4]. Relative survival is the percent survival of cancer patients compared to a healthy cohort. Relative 1 year survival is an expression of stage of disease at diagnosis while relative 5 year survival reflects efficacy of therapy. While CaP is detected sooner, therapy has little impact on disease outcome. This is reflected in the misleading way we express survival, utilizing projected, or actuarial and not actual survival. The less dismal actuarial survival statistics encourage a continued emphasis to cure by surgery despite the very few cures. Actuarial survival may overstate actual survival by 20 + percent [5].

Resectability rates in hospital patients have remain unchanged (15-20%) for 50 years and are lower in population based studies (4-6%) Median survival after resection (11-20 mos.) is longer than" locally unresectable" (6-11 mos.) or metastatic disease (2-6 mos.), reflective of extent of disease rather than treatment [2- 6].

Many believe that the "best" therapy is surgical resection, a formidable procedure with significant morbidity (30-50%), albeit declining mortality (1-5%). All technical modifications, including more radical operations, vascular and RO resections, and radical lymph node dissection cannot and do not improve the cure rate for a systemic disease [2,4].

Neoadjuvant therapy has had a positive impact on cancers of the stomach and rectum and is generating similar interest for CaP [5]. The largest study (327 CaP patients) with impressive actual 5 (27%) and 10 (14%) year survival utilized neoadjuvant therapy for resectable and borderline resectable lesions [6]. Beginning in the 1980's we altered our approach to CaP based on the dismal outcomes with existing therapy and acceptance of its systemic nature [7]. Keeping Einsteins adage in mind and contrary to the then existing culture, survival was better in 68 regionally unresectable patients who received chemo radiation therapy (CMT) as primary treatment (23 mos) vs 91 patients post Whipple resection (13.5 mos), and was even longer in a subset who after CMT underwent resection (33mos) [7]. We extended upfront CMT to all patients who consented. Half of our 10 -20 + year survivors were initially unresectable [8]. There was a low incidence of tumor recurrence after 5 years. which was unusual. Whether this was due to the long length of CMT before surgery (10 + mos), a small sample (20 pts), both, or neither is unclear but meriting additional studies.

"Early detection" of CaP is a misleading, failed concept, as it is dependent on cross sectional imaging studies. When malignant lesions are detected they are most always advanced and metastatic [1,4,6].

Two screening studies for CaP, one in asymptomatic patients at risk, and the other in patients who with upper abdominal symptoms yielded a high number of pancreatic lesions (40%). Nearly all were small intraductal papillary mucinous lesions, and most were followed and observed [9,10]. The few resected lesions were benign,or "premalignant", with atypia, dysplasia, and high grade PanIN .The National Familial Pancreas Tumor Registry follows first degree asymptomatic relatives when 3 or more family members have/ had CaP, and has detected 56 relatives with pancreatic cancer, almost all with metastatic disease [11-17].

Since cure of CaP is unusual, and early diagnosis by body imaging is an ineffective guessing game, an emphasis on prevention would be logical and attractive. There is sufficient evidence that lifestyle and nutrition lower the incidence of CaP. Cigarette smoking, a diet high in fat, chicken, meat, fish, and processed foods and low in fruit , fiber and vegetables promote many" Western Diseases" including CaP [12]. India, a country where 20% of the population is impoverished has a much lower incidence of malignant disease. This has been attributed in part to spices, particularly turmeric which has a direct effect in vitro on malignant cells. At least one clinical trial showed a direct benefit in 2/21 advanced CaP patients [13]. While prevention will not affect the 45,000 patients who are diagnosed with CaP annually it could lower the number of new cases and other common illnesses, which would be welcome and long overdue. Yet few physicians are knowledgeable, interested or relate this data to patients. This approach is neither expensive nor toxic and places responsibility on the patient, not the food or pharmaceutical industry.

Finally, the quest for a preclinical, accurate and specific marker to detect pinpoint cancers (millions of cells) rather than evident lesions (billions of cells) is being addressed. Studies of the ENOX2 cancer marker have indicated that this cell surface enzyme is produced after malignant transformation and its activity promotes cancer cell growth.

Interestingly, tissue-specific isoforms of ENOX2 are produced by cancer cells and subsequently shed into circulation, allowing for the detection and identification of up to 26 primary cancers. Natural compounds found within both green tea and peppers of the genius Capsicum inhibit ENOX2 activity, indicating these compounds may possess anticancer properties. While preliminary, and needing additional clinical trials and verification, it is an exciting concept [14].

As the 16th year of the new millennium starts, a fresh start or look at the customs, and "standard of care" applied to CaP are warranted. At the least, an honest open appraisal of actual outcomes is overdue and needed. The long standing emphasis on local measures to treat a systemic disease should be re-examined. An openminded look at prevention including lifestyle, and biochemical markers, to detect and reverse preclinical disease would be a relief when prevention is neglected or fails.

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