

Pancreatic Cancer - Resetting the Standard of Care. An Ode to George Crile Jr.

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Received: November 06, 2020; **Published:** November 28, 2020

Introduction

Cancer of the Pancreas (CaP) is a dismal and lethal malignancy. The annual mortality approaches its incidence [1]. This commentary is prompted by a 2020 analysis of actual long term survivors of pancreatic cancer from the NIH Surveillance, Epidemiology, End Results (SEER) database between 1975-2011, recent observations from the Weizmann institute in Israel regarding how signaling and bacteria in cancer cells facilitate or deter responses to cancer therapy, and 55 years administering care to patients and ministering to families [2-4].

Most reviews of CaP are modest, single institution experiences, with projected, not actual survival, providing bias and misleading, inaccurate outcomes [2,5,15]. The analysis of the SEER data by Bengtsson, Andersson and Anson from Lund provides complete/real world outcomes for 84,275 of 181,392 CaP registry patients [2].

Ninety-seven thousand were excluded because of incomplete data or follow up, leaving 84,00+, an impressive sample size. CaP is the 9th most common malignancy and the fourth cause of cancer deaths, after lung, colorectal and breast cancer [2]. In 2020 an estimated 57,600 US adults (30,400 M and 27,200F) were diagnosed with CaP (458,00 worldwide), with a projected mortality of 47,050 in the US and > 350,000 worldwide [1,6]. Most CaP patients die within 6 months of diagnosis.

Since 1975 there have been numerous diagnostic, therapeutic, technical and technological advances, which have made operations safer, data easier to retrieve and analyze and no lack of provider or institutional hubris on the internet. None of these have improved the actual 5 year survival of CaP; 0.9% in 1975, 4.2% in 2011 and less than 5% today [2]. Cross sectional body imaging and advanced endoscopy were available by 1976 [6]. Before this preoperative diagnosis relied on history and physical exam, fewer and less sensitive laboratory tests and fewer drugs to treat cancer. For pancreatic cancer laparotomy was as much diagnostic as therapeutic [5,7].

Today most resections for CaP are pancreaticoduodenal (PDR) are safe. The operative mortality in the 1970's was 20 - 30% and the morbidity and convalescence were prolonged, and actual 5 year survivors were rare [2,5]. Absent imaging studies, nearly every patient with suspected CaP underwent surgery not to be denied the chance of "cure". This was despite all objective evidence [5].

CT scans were introduced in 1974 - 1975, initially to visualize and diagnose intracranial pathology. In 1976 the first body scans became available in the US and at the Cleveland Clinic. The cross-section CT images were compelling and changed the way patients were evaluated and treated [7]. CT/MRI with angiography followed and facilitated staging, visualization of tumor, its blood supply, and therapy [8]. They did not find de novo pancreatic cancers, or improve cure and 45 years later the overall actual 5year survival remains less than 5% despite universal CT [2,9]. This is because CaP is a systemic disease at the time of diagnosis. It had spread long before the diagnosis [2,5,9]. A 50 - 80% local and systemic recurrence rate within a year of resection, and autopsy findings of cancer near R0 margins affirm that microscopic

metastases disseminate before they are evident and minimize the value of staging and optimism [2,9]. All operations for cancer are local therapy and are curable absent metastasis.

Tumor prognostic factors, as staging, tumor differentiation, and genes all influence prognosis, but most long term survivors survive despite poor prognostic factors [2,5,9,10]. Of 35,628, 2004 - 2111 SEER patients, almost 20,000 had advanced Stage 4 disease and 100 (0.5%) survived 5 years [2].

For all SEER patients (84,275) the overall resection rate was 18.5%, 87% had regional or distant disease, and 46% received adjuvant chemotherapy. Operative mortality and morbidity rates have greatly improved since the database was established and the stage and actual survival of 35,628 patients treated between 2004 - 2011 were separately analyzed to reflect this. The best 5year survival was in Stage 1A lesions, the smallest (< 0.5 cm), "localized" and least common cancers. These lesions were noted in 1.3%, or 463 patients and the 5year survival was 31.7% or 148 patients. Stage 1B tumors (0.5 - 1.0 cm.) occurred in 4.4% (1567 patients) of which 188 (11.8%) survived 5 years. Of 2030 resected Stage 1A and B cancers (< 1 cm), only 336 patients (17%) survived 5 years. The largest percent decline was 20% from stage 1A to 1B. The 5year survival for the remaining stages was 2A (9%), 2B (8.7%), 3 (1.9%) and 4 (0.5%). This suggests metastases are indolent for long periods, even in tumors < 1 cm [12,13].

The quote, "INSANITY doing the same thing over and over and expecting a different outcome." Is likely (mis) attributed to Einstein but is an appropriate description of the long held repetitive surgical treatment of CaP [14,15].

By 1986 I had sufficient experience with PDR to confirm that cure or 5year survival was remote. With Howard Bruckner MD and Harry Snady MD, we undertook a trial of multi drug chemo and radiation therapy for borderline resectable CaP [9,16]. The outcomes were much better than for resection and adjuvant therapy. Improved outcomes followed in resectable lesions first treated by chemo and radiation, and it became my preferred option for all CaP patients [9]. In the initial study 1990 half of the 5,10 and 20+ year survivors were initially unresectable [9]. Neoadjuvant therapy has its advocates and sceptics [17]. Part of this discrepancy may lie in the length of time neoadjuvant therapy is given. Believing the evidence that CaP is a systemic disease that originates IN the pancreas and not a surgical disease OF the pancreas, we treated to maximum response and benefit as evidenced by tumor markers, imaging, and patient status rather than for a fixed time before considering surgery. Some patients were treated for 11 months, in others disease progressed or became evident during treatment precluding any thought of unnecessary surgery.

George Crile jr MD known as "Barney" to distinguish him from his father, who was a founder of The Cleveland Clinic, questioned poor outcomes and ineffective traditions in surgery and was a champion of common sense [18]. He was responsible for minimal procedures for thyroid, rectal and breast cancer [18]. After one stage PDR resection was reported, Crile did several successful resections and to the chagrin of the surgical establishment affirmed that resection was more likely to harm than cure, and more would benefit from gastric and biliary bypass than resection [19]. He was unique in many ways. A graduate of Yale, where he played football and ran track, he then attended and graduated from Harvard Medical school (first in his class). After internship at Barnes Hospital and surgical training at The Cleveland Clinic, he was a navy surgeon for 4 years in WW 2 where he showed that appendicitis at sea was better treated by antibiotics not surgery, and pilonidal sinus(es) could be drained and heal by granulation, not excised [18].

When I joined the surgical staff at The Cleveland Clinic Dr. Crile was an emeritus surgeon, who saw and referred women with breast cancer to his 3 younger colleagues. He was vital, insightful, smart and enthusiastic. I sought his advice often. He cautioned that diseases with poor outcomes often had popular but ineffective treatment, "think for 2 or 3 minutes of reasons why treatment is ineffective and you will be right most times". He wrote "I came home from WW 2 convinced that operations in many fields of surgery were either too radical or not even necessary. Universal acceptance of a procedure does not necessarily make it right" [20]. More than espouse a contrary position he showed in clinical studies that subtotal thyroidectomy with "node picking" was wiser than more radical dissections; that simple

mastectomy or lumpectomy had outcomes equal to or better than radical mastectomy; that fulguration of some rectal cancers was simple, minimal, better appreciated and the equivalent of abdominal perineal resection; and finally that biliary bypass operations provided a better quality and longer life than the riskier resection for cancer of the pancreas [21]. Some habits relapse. How else to explain today's resurgence of total thyroidectomy, and bilateral mastectomy for prophylaxis against new cancers.

Thought by many to be a contrarian, his views, experience, outcomes and publications were later praised, and emulated [21,22].

Finally, it is perplexing why similar cancers respond differently to chemotherapy. Until recently matching drugs and tumors involved looking for gene mutations on tumor cells. The response was not predictable as many drugs do not target mutations. A newer approach relies on existing cancer datasets and signaling pathways; chains of signals that transmit cellular messages to predict cell division, growth and how cell metabolism may be altered. This involves genes that transmit messages along these pathways. Analyzing the datasets provides information on the sensitivity of cancer cells to nearly 500 drugs [3].

A second innovation involves targeting bacteria that live in cancer cells. Investigators at The Weizmann Institute sampled more than 1000 human cancer cells and found specific bacteria in each cancer and suggested relations between cancer cells, bacteria and treatment [4]. Dr. R Strausman suggested bacteria in pancreatic cancer cells could protect the cancer by digesting or inactivating treating drugs. Each cancer had unique bacterial species. The greatest number of and most diverse bacterial species were in breast cancer. Bacteria are more prevalent in tumor cells than surrounding tissues. This is the infancy of study for the cancer microbiome.

Isolating bacteria in tumor cells is tedious and requires filtration of contaminating bacteria outside tumor cells. The ultimate value and significance of these studies is unknown but if comparable to the gut microbiome, could be a game changer.

Disease is old and many approaches and treatments are outdated, traditional, ineffective and unimaginative. When the bottom line is dismal, new directions and thoughts are needed rather than to reenergize old customs. The reality is that CaP is a systemic disease and surgery is far less effective than the theoretical reasons to continue its initial use. Since metastases occur before cancers are diagnosed screening may find smaller but still incurable lesions.

Preventing cancer and pancreatic cancer may be easier, more predictable, economical and wiser than early detection by screening. Prevention requires lifestyle changes that are best started in childhood. A healthy lifestyle may prevent or eliminate chronic inflammation, the common cause and ignitor of most chronic diseases including cancer [23]. Chronic inflammation and chronic diseases account for 80% of deaths in the developed world. Other beneficiaries of prevention are land animals, fish, climate change, forests, and rainforests, the atmosphere, and waistlines, which will shrink, and lifespan which will lengthen. Simply modifying eating habits to favor whole foods and plant based diets including vegetables and fruits. Reducing and eliminating animal protein (meat and dairy) will improve health and extend longevity. Improving health by prevention or reversal will reduce unsustainable health care costs. This would be a welcome if not astonishing change. Perhaps this is what Mark Twain inferred when he said "Always do right, this will gratify some and astonish the rest" [24].

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Volume 7 Issue 12 December 2020

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