

**PATIENT OUTCOME ANALYSIS  
ADENOCARCINOMA OF THE PANCREAS  
“The Marquette General Hospital experience from 1995 to 2006”**

Carcinoma of the pancreas is one of the most refractory problems in cancer medicine. Although it accounts for only about 2% of the new cancer diagnosis each year it accounts for 6% of the cancer deaths each year. Even though we have made great strides in treating, prolonging life, and even curing many other cancers we have unfortunately made fairly little headway in the prevention, early detection and treatment of pancreatic cancer relative to cancers at other sites.

Nationally, in 2007 there is estimated to be 37,170 new cases of cancer of the pancreas and 33,370 deaths due to cancer of the pancreas. It is slightly more frequent in men than in women. In men, of the 18,830 men diagnosed with pancreatic cancer in 2007 and 18,340 women diagnosed with pancreatic cancer and 16,840 men and 16,540 women will die of pancreatic cancer in 2007 (See Table 1).

**Table 1:** Pancreatic Cancer

	<b>New Cases</b>	<b>Deaths</b>
<b>Male</b>	<b>18,830</b>	<b>16,840</b>
<b>Female</b>	<b>18,340</b>	<b>16,540</b>
<b>Total:</b>	<b>37,170</b>	<b>33,370</b>

The etiology of pancreatic cancer in most cases is not known. In about 10% of cases there is a family history of pancreatic cancer and many of these have an inactivating mutation in the P-16 tumor suppressor gene. Many sporadic (non – familial) cases of cancer when studied also have acquired this P-16 inactivation mutation.

Other genetic abnormalities which increase the risk of various non-pancreas cancers can also increase the risk for pancreatic cancer. These include the BRCA-2 breast cancer gene mutation, PRSS1 gene mutation which causes pancreatitis at an early age, the hereditary non-polyposis colorectal cancer gene (HNPCC or Lynch Syndrome) which also increases the risk of colorectal and endometrial cancer and the Peutz-Jeghers Syndrome.

The risk of pancreatic cancer increases with age. The average age at the time of diagnosis of pancreatic cancer is 72 years. 70% of patients are older than 65 at the time of diagnosis. Risk also seems to be slightly higher in African Americans.

Environmental and lifestyle factors can also increase the risk of pancreatic cancer. Tobacco smoking, obesity and diabetes mellitus all seem to increase the risk of pancreatic cancer. There is some evidence that exposure to some pesticides, dyes and chemicals used in metal refining may slightly increase the risk also. There is also some speculation that stomach infection with *Helicobacter pylori* may be associated with an increased risk of pancreatic cancer.

Many other factors such as alcohol consumption, coffee drinking or type of diet have in the past been speculated as risk factors for pancreatic cancer. The evidence for these is very weak and currently they are thought to not be independent risk factors.

Pancreatic adenocarcinoma tends to cause symptoms that occur very late in the natural history of the disease after it has already advanced to an incurable stage. This is because the pancreas is located so deep within the abdomen that it cannot be felt and because it does not have any pain nerves to give an early warning sign until the cancer is already extended beyond the pancreas itself. In general, the only pancreatic cancers that are able to be discovered early enough to be cured are those that occur at the very head of the pancreas where even a small tumor can give an “early warning sign” by obstructing the bile duct which causes jaundice.

At Marquette General Hospital over the years 1995 to 2006 a total 204 patients with adenocarcinoma of the pancreas have been diagnosed and treated. In the last 3 years the number of pancreatic cancer cases diagnosed and or treated at Marquette General Hospital has almost doubled, possibly as a result of referrals to Marquette General Hospital for specialized diagnostic procedures such as CT –guided biopsies, PET Scans or specialized therapies such as the placement of biliary stents, surgery for gastric outlet obstruction, specialized radiation therapy and or chemotherapy.

In Table 2 are listed by decreasing order of frequency the main presenting symptoms of these 204 cases of pancreatic cancer. Unexplained weight loss was the most frequent presenting symptom in 37% followed closely by jaundice in 32%. Loss of appetite, nausea, change of bowel habits and vomiting all occurred in over 10% of patients. Unfortunately, weight loss, decreased appetite and

change in bowel habits are all so non-specific as to often be overlooked by the patient or even the physician until jaundice or pain indicate the severity of the disorder. We still have no good methods for screening or early detection of the vast majority of cancers of the pancreas and this is a continuing area of active research. Theoretically, if pancreatic cancer could be detected before it was symptomatic then it might be much more curable.

**Table 2: Pancreatic Cancer – Symptoms Present at Time of Diagnosis**

	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	Total
<b>Total # Cases</b>	<b>13</b>	<b>10</b>	<b>15</b>	<b>10</b>	<b>17</b>	<b>20</b>	<b>14</b>	<b>16</b>	<b>12</b>	<b>24</b>	<b>28</b>	<b>25</b>	<b>204</b>
<b>Weight Loss</b>	46%	50%	47%	50%	35%	55%	21%	25%	44%	8%	43%	24%	<b>37%</b>
<b>Jaundice</b>	31%	30%	40%	20%	35%	30%	21%	31%	50%	25%	43%	32%	<b>32%</b>
<b>Loss of Appetite</b>	31%	20%	27%	0%	6%	25%	29%	19%	25%	4%	21%	24%	<b>19%</b>
<b>Nausea</b>	8%	20%	0%	20%	35%	0%	36%	6%	8%	4%	12%	4%	<b>13%</b>
<b>Change in Bowel Habits</b>	15%	0%	20%	20%	0%	15%	29%	6%	17%	0%	18%	12%	<b>13%</b>
<b>Vomiting</b>	15%	20%	0%	30%	12%	15%	21%	6%	8%	4%	4%	12%	<b>12%</b>
<b>Dyspnea</b>	8%	0%	6%	0%	0%	5%	14%	0%	0%	0%	0%	4%	<b>5%</b>
<b>Unexplained Fever</b>	0%	0%	0%	0%	0%	0%	0%	0%	8%	0%	4%	8%	<b>2%</b>
<b>Night Sweats</b>	0%	0%	0%	10%	0%	0%	0%	0%	0%	0%	4%	0%	<b>1%</b>
<b>Anemia</b>	0%	0%	0%	0%	6%	10%	0%	0%	0%	0%	0%	0%	<b>1%</b>
<b>Bone pain</b>	0%	0%	0%	0%	0%	0%	0%	6%	0%	0%	0%	0%	<b>0.5%</b>
<b>Indigestion</b>	0%	0%	0%	0%	0%	10%	0%	0%	0%	0%	0%	0%	<b>.08%</b>
<b>Hemoptysis</b>	0%	0%	0%	0%	6%	0%	0%	0%	0%	0%	0%	0%	<b>.05%</b>

Since other diseases can cause the symptoms listed in Table 2 and can have appearances on radiologic or endoscopic exams suggestive of pancreatic cancer, it is imperative that the diagnosis be confirmed by microscopic examination of the tissue whenever possible. Moreover, there are rare incidences of malignancies arising in the pancreas which are not adenocarcinomas of the pancreas but rather lymphomas or neuro-endocrine cancers. The treatment and prognosis of these lesions is quite different and pathologic diagnosis again is essential whenever possible.

Table 3 shows the definitive diagnostic method used to confirm pancreatic adenocarcinoma in the 204 patients between 1995 and 2006. 127 patients had positive solid tissue histology obtained either operatively or by an image or endoscopic guided core biopsy. 30% or 62 patients had their diagnosis based on fine needle aspiration cytology without the availability of a solid tissue biopsy. 6% (12 patients) were unable to have successful biopsy despite the symptom complex and radiologic picture consistent with the diagnosis of pancreatic cancer. 2% or 3 patients out of the 204 were unable to have diagnostic tissue obtained even though the tumor was directly visualized.

**Table 3:** Diagnostic Method Used in Confirming Pancreatic Cancer at Marquette General Hospital 1995 - 2006

	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	Total (Mean %)
<b>Positive Histology</b>	8 (62%)	6 (60%)	6 (40%)	7 (70%)	8 (47%)	12 (60%)	11 (79%)	13 (82%)	8 (67%)	17 (71%)	15 (53%)	16 (64%)	127 (63%)
<b>Positive Cytology, no Positive Histology</b>	2 (15%)	3 (30%)	7 (46%)	3 (30%)	8 (47%)	7 (35%)	3 (21%)	2 (12%)	4 (33%)	5 (21%)	12 (43%)	6 (24%)	62 (30%)
<b>Direct Visualization w/o microscopic confirmation</b>	1 (8%)	0 (0%)	1 (7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	3 (2%)
<b>Radiographic w/o microscopic confirmation</b>	2 (15%)	1 (10%)	1 (7%)	0 (0%)	1 (6%)	1 (5%)	0 (0%)	1 (6%)	0 (0%)	2 (8%)	1 (4%)	2 (8%)	12 (6%)
<b>Total Cases</b>	13 (100%)	10 (100%)	15 (100%)	10 (100%)	17 (100%)	20 (100%)	14 (100%)	16 (100%)	12 (100%)	24 (100%)	28 (100%)	25 (100%)	204 (100%)

Our experience at Marquette General Hospital as well as elsewhere has been that it can be very difficult to obtain positive or diagnostic tissue even when the cancer can be felt or directly seen. The tumor is often rather indistinct and may not separate itself well from the surrounding normal pancreatic tissue. The pancreatic cancer also often stimulates a fibrous or inflammatory reaction around it and even within it so that much of what appears to be tumor is actually the body's reaction to the cancer rather than cancer cells themselves, making retrieval of diagnostic cancer cells sometimes very difficult. It is apparently for this reason also that in some instances fine needle aspiration cytology is positive even when the core biopsies of the same area are negative.

The relatively recent capability for visualizing and biopsing the pancreas by endoscopic ultrasound may eventually further increase our ability to obtain a tissue diagnosis. Whenever possible, the

intent is to obtain the diagnostic tissue in the least invasive manner and to avoid surgery unless it is necessary for relief of obstruction or if it is thought to be potentially curative.

The American College of Surgeons Commission on Cancer not only inspects and accredits cancer programs, including the Marquette General Cancer Center, it also collects data from all of these cancer programs to form a national cancer database (NCDB) to serve as a benchmark for performance. Table 4 shows the stage (Appendix #1 – AJCC Staging form for carcinoma of the pancreas) of pancreatic cancer at the time of diagnosis at Marquette General Hospital in the 114 cases diagnosed and or treated at Marquette General Hospital from 2000 to 2006 and compares these statistics with those of other hospitals throughout the United States in the NCDB.

**Table 4: Stage of Pancreas Cancer Patients Diagnosed 2000 to 2006**

Marquette General Hospital, Marquette, MI vs National Cancer Data Base (NCDB)

STAGE	2000-2006: N (Cases)		2000-2006: % (Percent)	
	NCDB	MGH	NCDB	MGH
0	637	0	0.49	0..00
I	9,665	6	7.40	6.48
II	18,222	29	13.95	25.18
III	15,318	11	11.72	8.63
IV	63,941	56	48.94	46.04
UNKNOWN	22,876	12	17.51	13.67
<b>TOTAL</b>	<b>130,659</b>	<b>114</b>	<b>100.00</b>	<b>100.00</b>

Source: NCDB, Commission on Cancer, AcoS. Benchmark Reports, V9.0

The Marquette General Hospital statistics are very comparable to national statistics. Only 6 to 7% of pancreatic cancers present a very limited stage or small size (Stage 1). Marquette General Hospital has a slightly higher percentage of patients at Stage 2 and conversely a lower percentage of patients at Stage 3 than the national averages. However these are not likely to be statistically significant considering the small numbers of patients at these stages. Unfortunately, almost 50% of patients at Marquette General Hospital and nationally present with pancreatic cancer already disseminated to Stage 4. Again, it is the lack of medical science’s ability to prevent or detect very early the presence of pancreatic cancer that seems to limit our success in curing this disease.

Table 5A and 5B shows us the pathologic types of malignancies found in patients with pancreatic tumors and also shows the grade or differentiation of these cancers. The vast majority of these cancers are adenocarcinomas. Four lymphomas and two neuro-endocrine cancers arising in the pancreas were also diagnosed. A significant minority of cancer cases were diagnosed by fine needle aspiration cytology only and therefore are not assigned a histologic grade.

**Table 5A:** Pathologic Types of Malignancies Found in Patients with Pancreatic Tumors

	Adenocarcinoma	Mucin-producing adenocarcinoma	Adenosquamous carcinoma	Squamous carcinoma	Lymphoma B-cell	Large cell lymphoma	Angiosarcoma	Acinar carcinoma	Neuroendocrine carcinoma	Neuroendocrine neoplasm	Malignancy, nos	Carcinoma nos
1995-2006	161	3	2	2	1	3	1	1	1	1	2	25

**Table 5B:** Pathologic Grades of Malignancies Found in Patients with Pancreatic Tumors

	GRADE 1	GRADE 2	GRADE 3	GRADE 4	NO ASSIGNED GRADE OR CYTOLOGY ONLY
1995 – 2006	10	34	44	5	109

Table 6 demonstrates the general categories of treatment or treatment combinations employed for the 139 pancreatic cancer patients at Marquette General Hospital from 2000 through 2006 compared to the same statistics from the National Cancer Database. The Marquette General Cancer Center statistics are very similar to those of the NCDB. The most frequent modalities or combinations of modalities used were chemotherapy only in 28%, surgery, radiation and chemotherapy in 15% and combined radiation and chemotherapy in 10% of the patients. 24% of patients at Marquette General Hospital and almost 45% of patients in the NCDB had no treatment whatsoever usually indicating either patient wishes or advanced state of cancer spread with such a poor performance status that the patient could not tolerate or benefit from treatment.

**Table 6:** Treatment of Pancreas Cancer Patients Diagnosed 2000 – 2006

Marquette General Hospital, Marquette, MI vs National Cancer Data Base (NCDB)

Treatment	2000 – 2006 Number of Cases (N)		2000 – 2006 Percent (%)	
	NCDB	MGH	NCDB	MGH
<b>Surgery only</b>	12,458	6	9.53	4.31
<b>Radiation only</b>	0	2	0.00	1.43
<b>Rad. &amp; Chemo.</b>	13,306	14	10.18	10.07
<b>Chemo. Only</b>	28,729	39	21.99	28.10
<b>Surg. &amp; Chemo.</b>	0	4	0.00	2.97
<b>Surg., Rad. &amp; Chemo</b>	8,662	21	6.63	15.10
<b>Other Specified Therapy (i.e. Palliative with Chemo.</b>	8,911	8	6.82	5.75
<b>No 1<sup>st</sup> Course Rx</b>	58,593	33	44.84	23.74
<b>Unknown</b>	0	12	0	8.63
<b>Total</b>	<b>130,659</b>	<b>139</b>	<b>100</b>	<b>100</b>

Source: NCDB, Commission on Cancer, ACOS. Benchmark Reports, v9.0

As seen in Graph 7, most patients are treated without major surgical procedures whenever possible. Surgery is usually reserved for those cases that are thought to be potentially curable or those patients with intestinal obstruction. The evolution of relatively non-invasive methods of diagnosis and treatment (including biliary and even gastric outlet stents) has allowed us to avoid major surgery for the majority of patients who do not have potentially surgically curable disease.

**Graph 7:** Patients Diagnosed with Pancreatic Adenocarcinoma at Marquette General Hospital 2001 - 2005

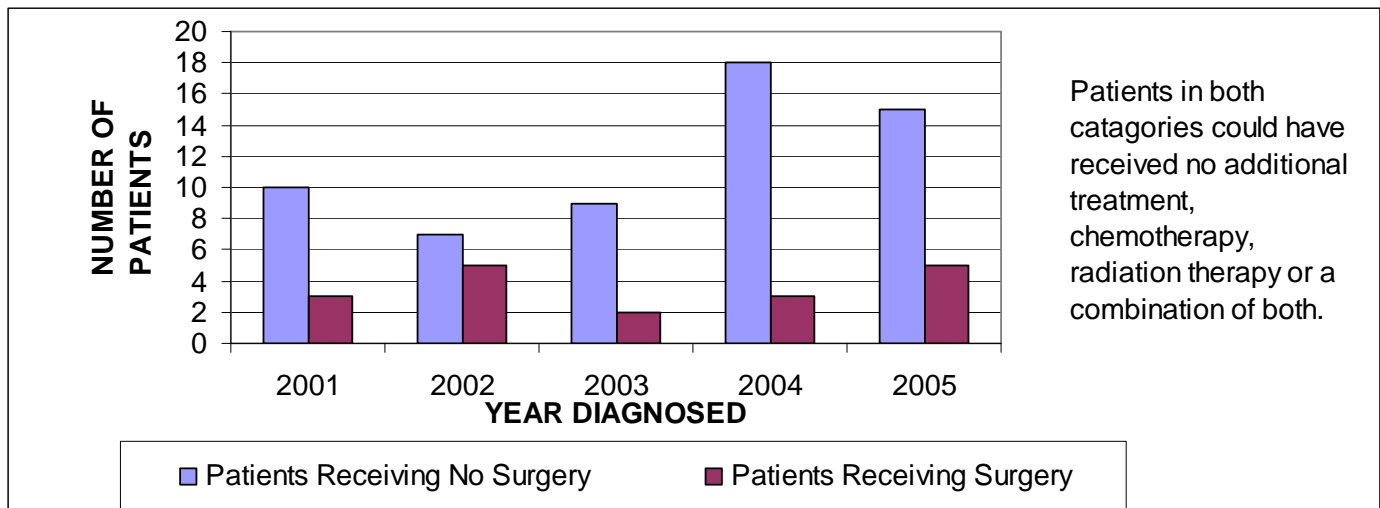


Table 8 details the use of radiation therapy for the Marquette General Hospital and NCDB patients from 2000 to 2006. 75 to 80% of patients with pancreatic cancer did not receive radiation therapy.

For those patients that did receive radiation therapy, external beam radiation was almost universally applied as opposed to brachytherapy or other forms of radioisotopes.

**Table 8:** Radiation of Pancreas Patients Cancer Diagnosed 2000 – 2006 Marquette General Hospital, Marquette, MI vs National Cancer Data Base (NCDB)

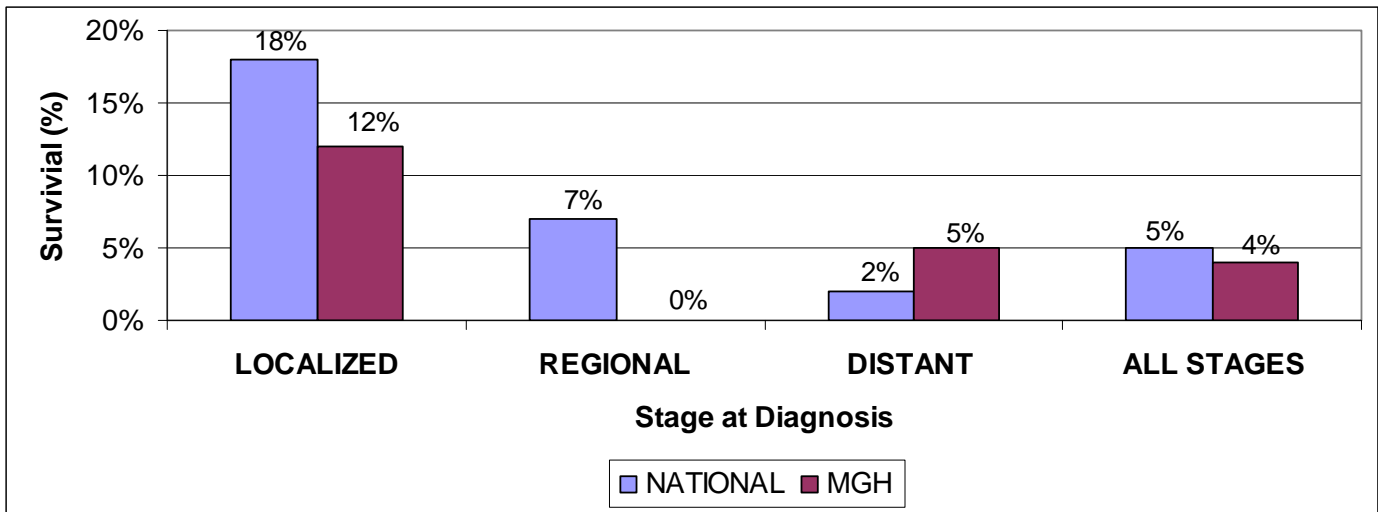
<b>RADIATION</b>	2000 – 2006 N (cases)		2000 – 2006 % (percent)	
	NCDB	MGH	NCDB	MGH
<b>No Radiation</b>	104,440	104	79.93	74.82
<b>Beam Radiation</b>	25,453	35	19.48	25.18
<b>BrachyTherapy</b>	62	0	0.05	0.00
<b>Radioisotopes</b>	30	0	0.02	0.00
<b>Radiation Therapy, NOS</b>	674	0	0.52	0.00
<b>Total</b>	130,659	139	100.00	100.00

Source: NCDB, Commission on Cancer, ACoS. Benchmark Reports, v9.0

We do not have chemotherapy statistics for the NCDB during this time period. At Marquette General Hospital from 1999 through 2006 the most common chemotherapeutic agents used were Gemcitabine and 5-Fluorouracil (5FU) in various forms. 5FU by continuous infusion was most often given concomitantly with radiation therapy. Recently, there is data that Gemcitabine may be as effective as or even more effective than 5FU when given concomitantly with radiation therapy. Recent data has also shown that some newer chemotherapy agents such as Oxaliplatin can also be effective in the palliation of pancreatic cancer and that the use of targeted non-chemotherapeutic biologic agents such as Erlotinib in combination with chemotherapy can also give an added benefit.

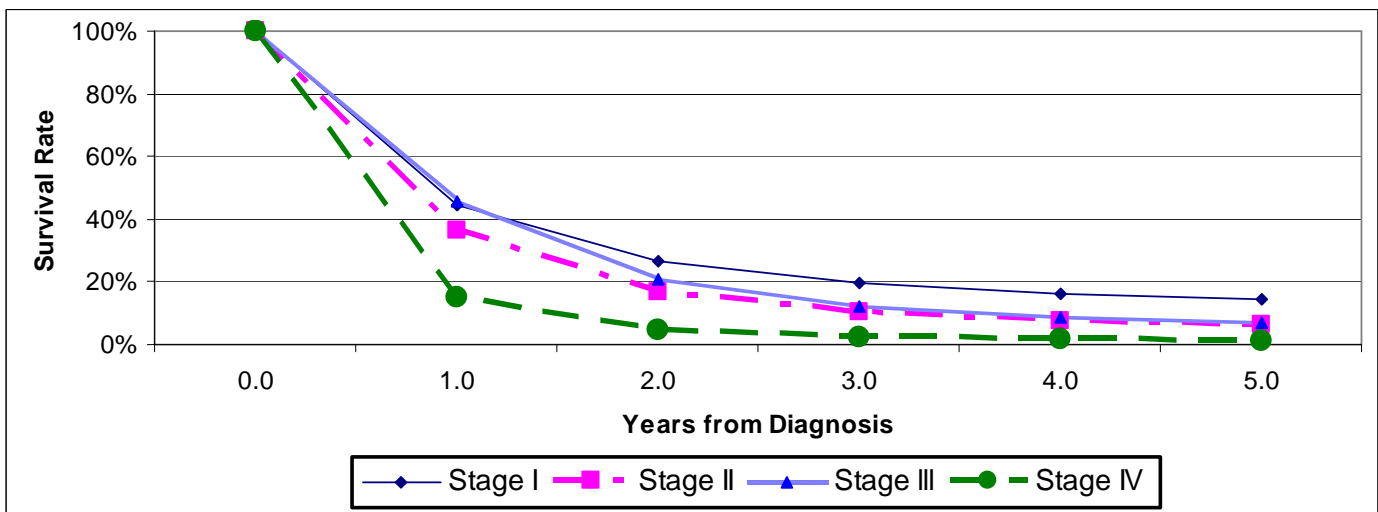
Graph 9 shows the 5-year survival for pancreatic cancer at Marquette General Hospital versus national statistics. While relatively small numbers (compared to the NCDB total) tends to exaggerate statistically insignificant variances, it would appear that our success at treating both localized and distant disease is equivalent to the national data and that our overall survival in patients with pancreatic cancer at 5 years is very comparable to national data.

**Graph 9: Pancreatic Cancer Five-year Survival Marquette General vs National 1996 - 2002**

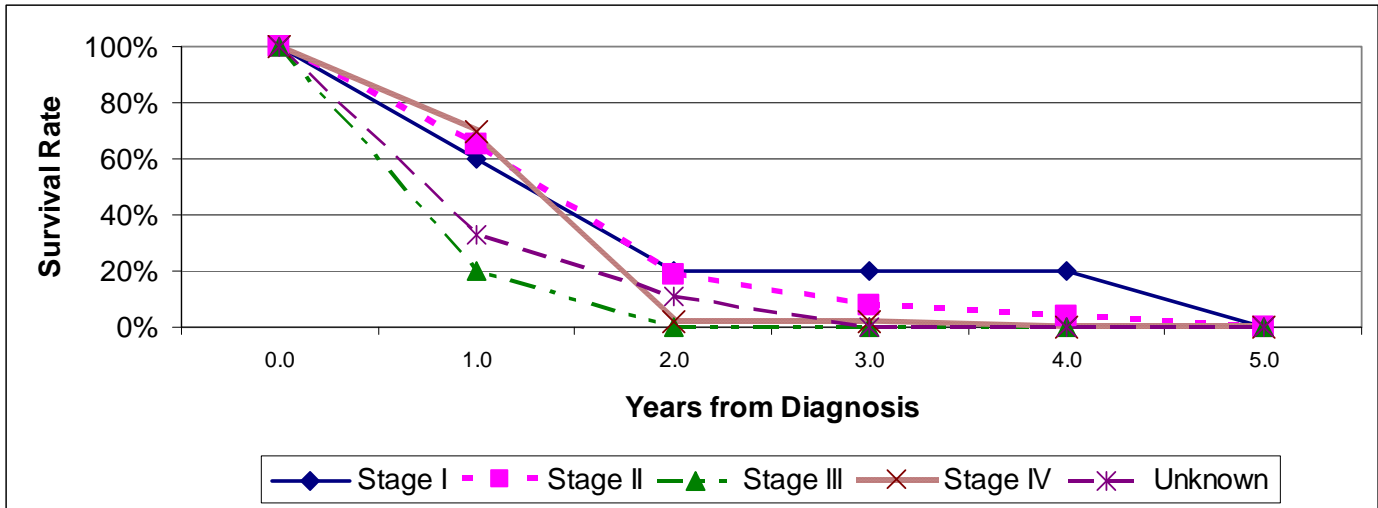


Graph 10A shows the survival curves for the NCDB 1998 through 2000. In Graph 10B the combined data for pancreatic cancer diagnosed from 2001 through 2005 is presented again by the stage at diagnosis. In addition, in Graph 10C the combined experience of Marquette General Hospital from 1995 through 2005 is presented showing survival by stage at diagnosis.

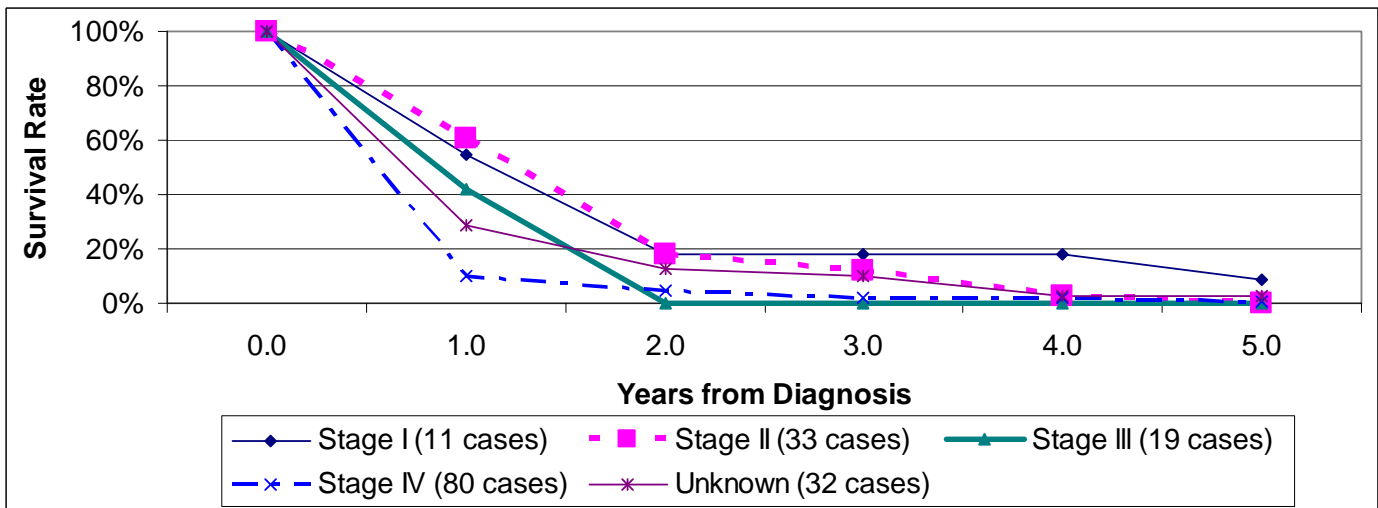
**Graph 10A: Observed survival For Pancreas Nationally 1998 - 2000**



**Graph 10B:** Observed Survival for Pancreas at Marquette General Hospital 2001 - 2005



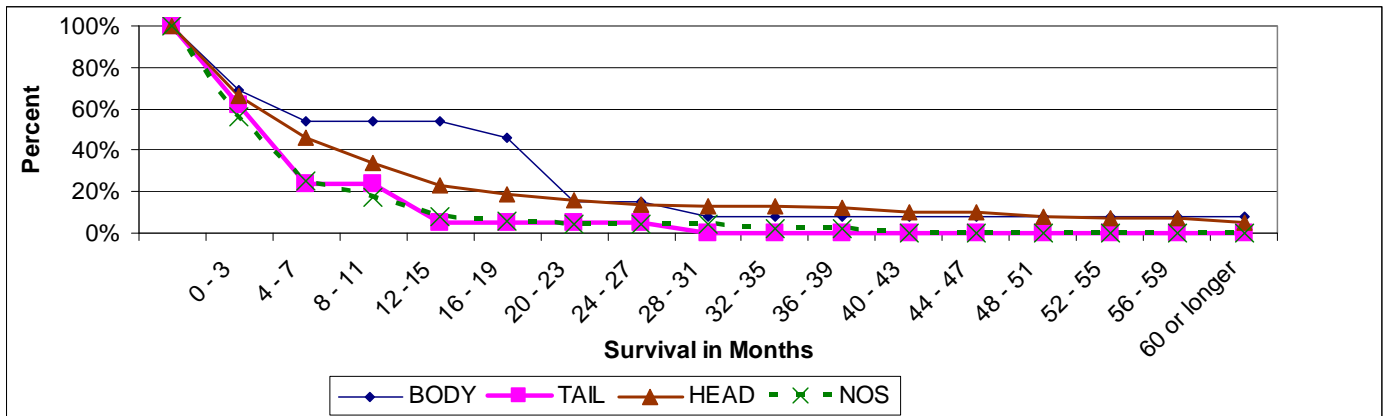
**Graph 10C:** Observed Survival for Pancreas Cancer Diagnosed at Marquette General Hospital 1995 - 2005



As previously discussed, the survival curves for Marquette General Hospital are very similar to those of the NCDB. It is evident from all three figures that more localized disease (Stage 1) does better than disease that presented with metastases at the time of diagnosis (Stage 4). It is also demonstrated that by one year over half of all patients with pancreatic cancer have died but that after two years there are anywhere from 9 to 14% of patients who presented with non-metastatic disease who are still alive and who may live for at least a few more years. 9 to 14% of patients treated for Stage 1 disease are still alive at 5 years. Graph 11 shows the survival of the cancer

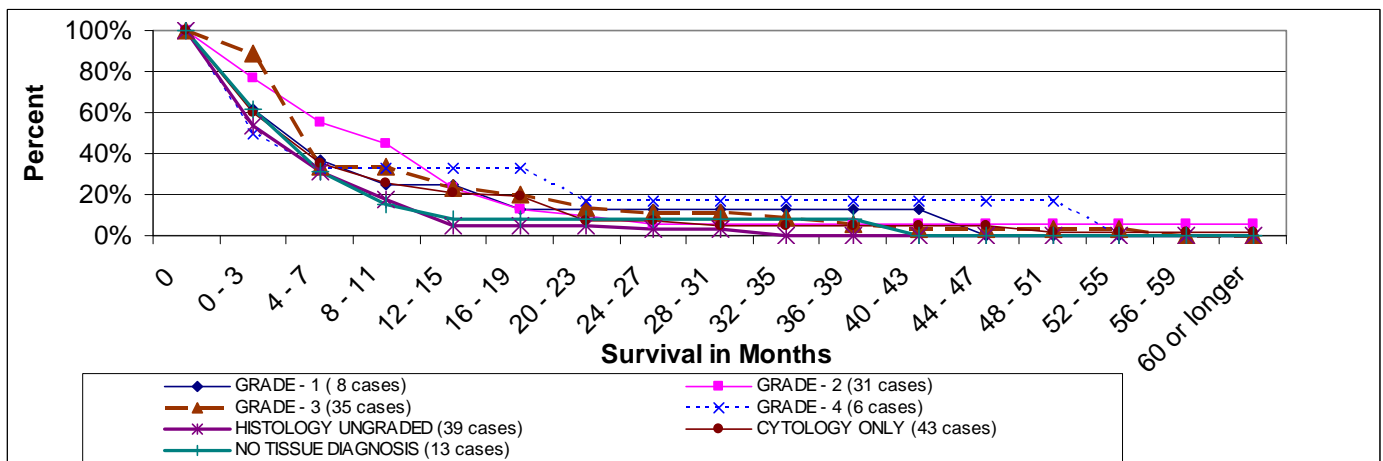
patients by the location of the primary within the pancreas. It would appear that, as expected, the cancers arising in the head or proximal body of the pancreas have the best survival since they are often detected the earliest.

**Graph 11:** Survival by Location within Pancreas at Time of Diagnosis at Marquette General Hospital 1995 - 2006



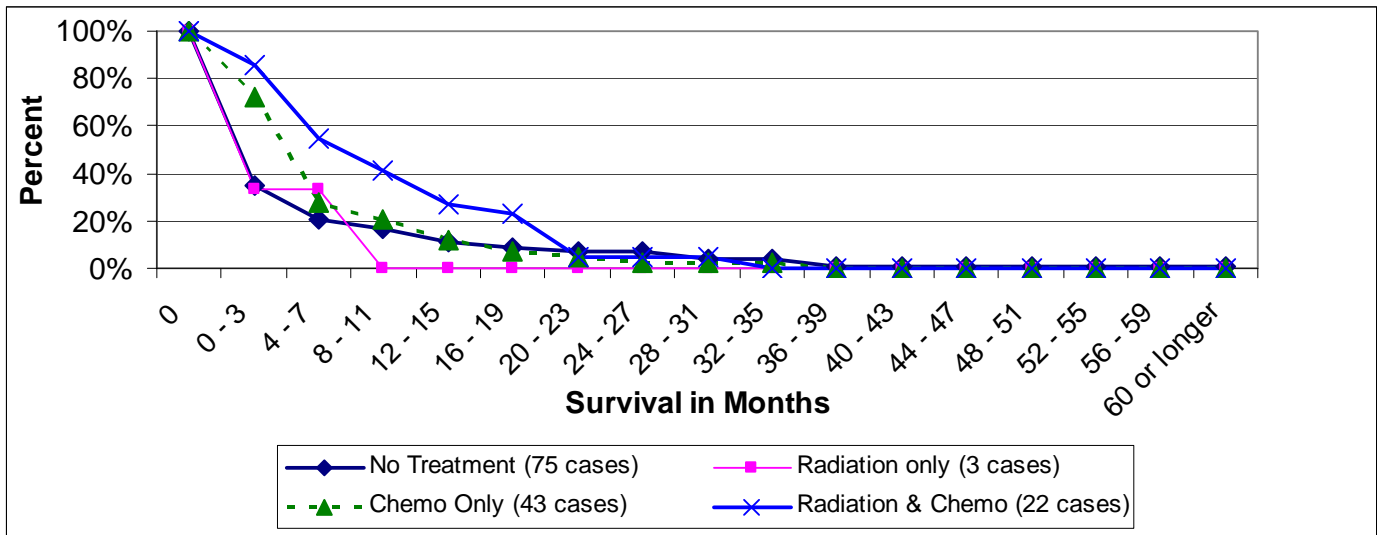
Graph 12 shows the survival of pancreatic cancer patients according to the histologic grade of the cancer. For those cancers that could be assigned to histologic grade it appears that there is a very loose correlation of survival with grade or differentiation of the cancer. This is minimally evident most obvious for the “tail” of the curve showing those patients that live beyond 20 months. It is here that the grade or differentiation of the cancer seems to have the greatest correlation with how long our patients live.

**Graph 12:** Survival by Tumor Grade/Differentiation at Time of Diagnosis at Marquette General Hospital 1995 - 2005

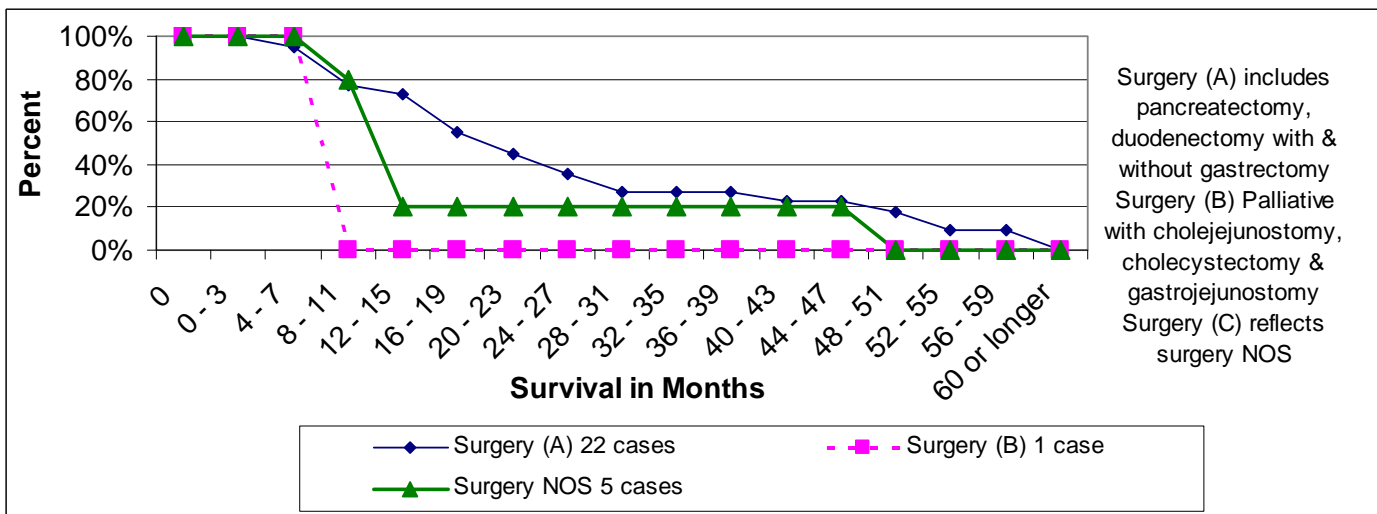


Graph 13A & B show the survival of patients with pancreatic cancer related to the type of treatment they receive. Interpretation of this data is fraught with difficulties. Patients receiving surgery generally fall into two categories, either those with early localized disease who were potentially surgically curable and those who present with advanced disease that which is already causing obstruction of the small bowel and who are expected to do poorly.

**Graph 13A:** Survival by First Course of Treatment at Time of Diagnosis at Marquette General Hospital 1995 - 2005



**Graph 13B:** Survival by First Course of Treatment of Time of Diagnosis at Marquette General Hospital 1995 - 2005



We have therefore divided surgery into “curative” including Whipple procedures, partial pancreatectomies and duodenectomies, etc. and “palliative” which would include such procedures as gastrojejunostomies or choledoco or cholectysto-jejunostomies without attempted removal of the primary tumor. Patients receiving combined radiation and chemotherapy without surgery are generally patients with localized but surgical unresectable disease. Patients receiving chemotherapy only generally have disease that has spread beyond the range of radiation therapy. Also some patients who have extensive local and or regional disease may receive chemotherapy only without radiation. For those patients that do have potentially curative surgery, it is felt that addition of post-operative chemo radiation or at least chemotherapy alone will decrease the risk of recurrence. As expected, those patients receiving curative-intent surgery have the longest survival, suggesting a treatment benefit for properly selected patients.

Palliation of symptoms of incurable disease such as pain can often be achieved by skillful use of pain medicines. Injection of the pain nerves around the pancreas (celiac axis block) is done at Marquette General Hospital with increasing frequency. Overall, the outlook for patients with pancreatic cancer remains poor unless they present with very limited early disease and are capable of withstanding major surgery, radiation and chemotherapy. Marquette General Hospital numbers match up well with those of the NCDB. It would appear that future investigations in pancreatic cancer will need to address either the earliest end of the spectrum at the points of prevention, screening and early detection or at the later stages of cancer with development of new and more effective systemic therapies for established disease.

The Marquette General Cancer Center through its weekly multidisciplinary Tumor Boards, it's participation in cancer clinical trials and it's affiliation with the Karmanos Cancer Institute offers state-of-the-art care to all its cancer patients.

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