

**PROTOCOL TITLE:**

**Duodenopancreatectomy versus Best Supportive Care for  
Pancreatic Adenocarcinoma -**

**Measuring Patients' Inclinations Toward Risks and Benefits Before  
Suggesting Treatment Options.**

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<b>Abbreviations:</b>	Pancreatic Ductal Adenocarcinoma	= PDC
	Duodenopancreatectomy	= DP
	Chemotherapy	= CT
	Radiation Therapy	= RT
	Ultrasonography	= US
	Computerized Tomography	= CT scan
	Magnetic Resonance Imaging	= MRI
	Palliative Surgical Bypass	= PSB

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## Duodenopancreatectomy versus Best Supportive Care for Pancreatic Adenocarcinoma

### Measuring Patients' Inclinations toward Risks and Benefits before Suggesting Treatment Options.

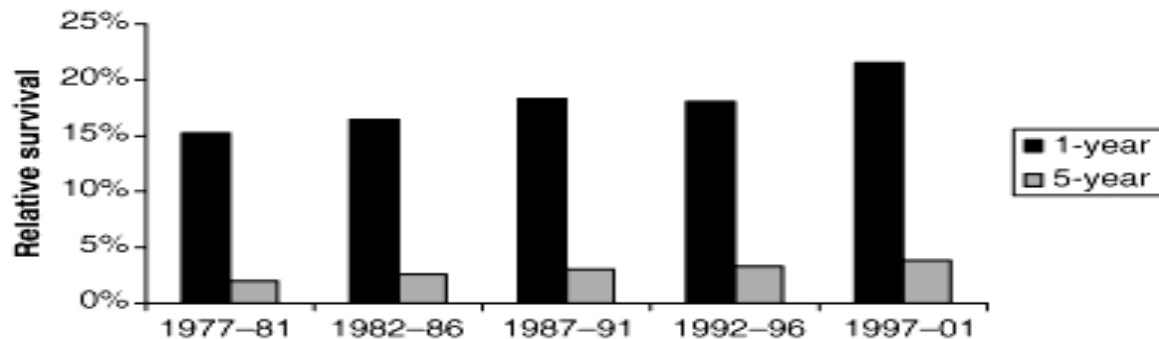
**Introduction:** Pancreatic ductal adenocarcinoma (PDC) is the 5<sup>th</sup> leading cause of cancer death worldwide<sup>1</sup>. The only possible cure for PDC is surgical resection of the tumor and surrounding tissues. Chemotherapy and radiation therapy are used to treat patients who underwent surgery if pathological assessment of the tumor shows neoplastic invasion of the lymph nodes or blood vessels to increase the chances of cure. In addition, chemo and radiation therapy are used to palliate patients with unresectable PDC to prolong their survival and improve their quality of life. Despite recent advances in surgery, chemo and radiation therapy, the prognosis of PDC remains poor with overall 5-year survival rates of less than 5%. On the other hand, when PDC is diagnosed in early stage and treated by surgical resection, 5-year survival rates improve up to 40%<sup>2</sup>. The best chance of reducing the high mortality rates of patients affected by PDC is the identification of individuals affected by early stage cancer.

Various environmental and lifestyle risk factors<sup>3</sup>, occupational exposures<sup>4</sup> and medical conditions<sup>5</sup> predispose to PC and cigarette smoking is the only environmental risk factor that has been consistently associated with the development of PC<sup>6,7</sup>. In addition, several case-control studies demonstrated that a family history of PC is an important risk factor for developing PC, with risks ranging from 2.7-16%, even after adjusting for environmental risk factors and diabetes mellitus<sup>8,9,11,12,11</sup>.

Cancer development is characterized by a complex series of phenomena occurring at the DNA level. Genomic instability, epigenetic factors and a relaxation in cell cycle control might confer growth advantages on transformed cells, thus favoring hyperplasia and the onset of cancer. Genetic instability increases the probability of the activation of oncogenes and the inactivation of tumor suppressor genes, ultimately leading to cancer growth. Since it is inherently unstable, DNA in mammalian cells is commonly damaged, giving rise to some 20,000 lesions per day per cell<sup>15</sup>, the main sources of which are spontaneous depurination, damage from reactive oxygen species and deamidation of bases<sup>1</sup>. The outcome of DNA damage varies, but it is generally adverse. Acute effects arise from a disturbed DNA metabolism, triggering cell cycle arrest or cell death. The long-term effects are due to irreversible mutations that contribute to the formation of cancer cells<sup>17</sup>.

### Epidemiology of pancreatic cancer

PC is a highly lethal and common malignancy, accounting for an annual incidence of 1-10/100,000<sup>14</sup> and a mortality rate of more than 95% at 5 years<sup>18</sup>. During the last decades no significant improvement in patients' survival has been observed as illustrated in **figure 1**<sup>19</sup>.



**Figure 1.** The age-specific incidence rates of pancreatic cancer in five consecutive time periods between 1977 and 2001

Of the approximately 30,000 cases diagnoses each year in the Unites States, approximately 5-10% of patients have a family history of PC <sup>20</sup>.

In Canada, PC is the 9<sup>th</sup> most common malignancy while it is 4<sup>th</sup> for mortality rate<sup>21</sup>. The lifetime probability of developing PC in Canada is 1.2% for males and 1.4% for females and the total number of patients who developed PC in 2006 was 3,449 <sup>42</sup>. Statistics on the incidence of FPC in Canada are currently not available.

In Atlantic Canada, the number of patients diagnosed with PC has been relatively stable during the last decade. In 2006 the total number of patients diagnosed with PC was 145 (5 in Newfoundland, 15 in Princess Edward Island, 65 in Nova Scotia and 55 in New Brunswick) . It is expected that about 12-14 cases of PC diagnosed each year in Atlantic Canada may be familiar <sup>42</sup> (Table 1).

**Table1. Canadian data on the most common cancers diagnosed in 2006**

**Actual Data for New Cases for the Most Common Cancers by Sex and Geographic Region, Most Recent Year<sup>1</sup>, Canada**

	New Cases													
	Canada	NL*	PE	NS	NB	QC	ON	MB	SK	AB	BC	YT	NT	NU
<b>Males</b>														
<b>All Cancers</b>	<b>74,800</b>	<b>1,150</b>	<b>410</b>	<b>2,800</b>	<b>2,000</b>	<b>18,800</b>	<b>28,000</b>	<b>2,700</b>	<b>2,700</b>	<b>6,400</b>	<b>9,400</b>	<b>50</b>	<b>40</b>	<b>25</b>
Prostate	19,500	260	120	730	550	3,900*	7,700	680	950	1,950	2,500	10	5	–
Lung	11,600	180	60	450	350	3,700	3,800	410	340	780	1,350	10	5	10
Colorectal	10,000	240	55	390	240	2,600	3,600	390	360	810	1,300	10	10	5
Bladder**	4,600	70	25	180	130	1,450	1,400	170	180	420	610	–	–	–
Non-Hodgkin Lymphoma	3,200	30	20	120	100	720	1,200	110	120	290	440	–	–	–
Kidney	2,600	40	15	100	95	700	1,000	130	90	220	240	–	–	–
Leukemia	2,400	20	20	70	45	560	1,000	80	110	180	280	–	–	–
Oral	2,200	45	5	85	50	560	780	90	65	160	270	–	5	–
Melanoma	2,100	35	10	95	55	290	1,000	70	45	230	360	–	–	–
Stomach	1,900	40	10	65	45	480	710	80	50	140	230	–	–	–
Pancreas	1,650	15	15	60	65	470	530	80	50	120	220	–	–	–

– Fewer than 3 cases

\* Likely an underestimate of the number of cases, see *Appendix II: Methods*.

\*\* Inter-provincial variation. Ontario does not report in situ bladder cases. It is estimated including in situ cases for Ontario would result in 2100 bladder cancer cases among men and 820 among women. See text.

<sup>1</sup> 2003 for Canada, Newfoundland and Labrador, Quebec, Ontario; 2004 for Prince Edward Island, Nova Scotia, New Brunswick, Manitoba, Saskatchewan, Alberta, British Columbia; 2000-2004 average for Yukon, Northwest Territories, Nunavut.

**Note:** Total of rounded numbers may not equal rounded total number and an average is used for the territories. Counts exclude cases of non-melanoma (basal cell and squamous cell) skin cancer.

**Source:** Surveillance Division, CCDPC, Public Health Agency of Canada

Ninety-five percent of pancreatic neoplasms are ductal adenocarcinomas, and 80% of patients with ductal adenocarcinomas present with metastatic disease, leading to an extremely poor 5-year survival rate of 4-6% <sup>42,2</sup>.

The Surveillance Epidemiology and End Results (SEER) Program reports an overall age-adjusted incidence rate of 11 per 100,000 individuals<sup>23</sup>. Individuals of African descent have a higher incidence rate (14.9 per 100,000) than Caucasian (10.9 per 100,000), and the incidence of pancreatic cancer is higher among men (12.5 per 100,000) compared to women (9.8 per 100,000) <sup>44</sup>.

**Diagnosis of pancreatic cancer**

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Advances in technology have meant that the sensitivity for detecting smaller lesions is improving, as is the identification of extra-pancreatic spread <sup>24</sup>.

**a. Tumor markers:** The most commonly used marker in everyday practice CA19-9 has a sensitivity of 70–90% and specificity of 90%, and is better than other markers, including CA-50 and DU-PAN-2 and CEA<sup>25</sup>. False positive results are often obtained in benign obstructive jaundice, chronic pancreatitis even in the absence of bile duct obstruction and ascites. CA19-9 is particularly useful in assessing response to prognosis and treatment in advanced cases, identifying early recurrence in resected cases and as an aid in preoperative staging <sup>26,27</sup>.

**b. Non-invasive imaging techniques:** Transabdominal ultrasound can be the initial investigation and may detect tumors >2 cm in size, dilatation of the biliary and main pancreatic ducts and possible extra-pancreatic spread— notably, liver metastases, with a diagnostic accuracy of 75%<sup>28</sup>, but it is not useful in early disease, if the bile duct is not dilated and in obese patients. Therefore contrast-enhanced multidetector CT scan is the single most useful imaging procedure (using a pancreas protocol CT with 1 mm images) and can achieve diagnostic rates of 97% for PC<sup>29</sup>. The accuracy for predicting an unresectable lesion is 90%, but the accuracy of predicting a resectable lesion is much less at 80–85% <sup>3,31,32</sup>. False negative results before laparotomy are mainly due to small hepatic metastases <1 cm and small peritoneal deposits. Lymph node staging is inaccurate in the absence of systematic biopsy<sup>33</sup>. Magnetic resonance imaging produces similar results to contrast-enhanced multislice CT and is useful for patients who cannot receive intravenous contrast <sup>34,35</sup>. Positron emission tomography (PET) cannot differentiate inflammatory conditions from tumors accurately and the sensitivity is 71–87% with specificity of around 64–80%<sup>36</sup>. The use of fusion CT-PET scanning adds little if anything to the use of CT alone<sup>37</sup>. Measurement of tumor metabolism by nuclear magnetic spectroscopy holds considerable promise as a diagnostic technique but is very much in development<sup>38</sup>.

**c. Invasive imaging techniques:** Endoluminal ultrasonography (EUS) has similar accuracy to CT in the staging of pancreatic cancer but is undoubtedly better for the detection of early pancreatic tumors as small as 2–3 mm <sup>75</sup>. The addition of fine needle aspiration (FNA) cytology to EUS is highly accurate for identifying malignancy in lesions identified on EUS and not seen on CT scan<sup>39</sup>. The drawbacks of EUS are that distant metastases and nodal involvement cannot be accurately assessed. The sensitivity and specificity of endoscopic retrograde cholangiopancreatography (ERCP) alone are 70–82% and 88–94%, respectively, in symptomatic patients or those with suspected pancreatic cancer but should no longer be used as a pure imaging tool given the developments in magnetic resonance cholangiopancreatography and EUS <sup>75,82</sup>. ERCP is used to insert biliary stents for relief of obstructive jaundice <sup>40</sup> and to gain cytological diagnosis by sampling or brushings. These can also be obtained at percutaneous transhepatic cholangiography (PTHC) <sup>117</sup>.

**d. Diagnostic biopsy:** Percutaneous FNA cytology has a sensitivity and specificity of 69% and 100%, respectively, for tissue diagnosis <sup>117</sup>, but concerns have remained about intraperitoneal seeding, with an incidence of up to 16% <sup>41</sup>. The diagnostic accuracy of EUS with FNA carries a sensitivity and specificity of >90% and ~100%, respectively, but requires an expert team with the presence of a cytologist examining the tissue specimens in the EUS suite, repeating the procedure until the diagnosis is conclusive<sup>42</sup>. The incidence of carcinomatosis is much less after EUS-guided biopsy than percutaneous biopsy<sup>43</sup>. A further development is the use of EUS with an endoscopic trucut biopsy needle<sup>44</sup>. EUS-guided biopsy is thus the preferred procedure if histological confirmation is needed in cases of advanced pancreatic cancer before chemotherapy or to diagnose small uncharacterized lesions.

**e. Laparoscopy and laparoscopic ultrasound:** Laparoscopy with laparoscopic ultrasound enables intraoperative scanning of the liver and pancreas to be performed and is highly predictive of resectability, altering the management of 15% of patients already assessed as resectable by dual-phase helical CT<sup>45</sup>. Selective laparoscopy based on the serum level of CA19-9 is a more efficient strategy, reducing the proportion of patients undergoing laparoscopic ultrasound from 100% to around 45% while increasing the yield from 15% to 25%<sup>46</sup>.

### **Palliative treatment options for pancreatic cancer (inoperable disease)**

The only potential cure for PC is surgical resection with negative margins. This option is possible only for the minority of patients affected by PC. The majority of them are diagnosed when the tumor is already too advanced to be resected. For these patients, palliative therapy is the only option for quality of life improvement. Currently, palliative chemotherapy is administered only for patients with good performance status. Survival benefit for palliative chemotherapy has been shown only in a few randomized trials.

### **Palliative therapy for symptoms caused by pancreatic cancer**

The treatment of patients who have localized advanced disease, metastases or deteriorated performance status is directed at symptom control.

1. **Pain:** Intractable pain is a major problem and often necessitates the use of high-dose opiate analgesia. Complementary approaches include intraoperative, percutaneous radiological guided neurolytic celiac plexus block and bilateral or unilateral thoracoscopic splanchnicectomy. In general, the results are disappointing and are particularly poor for patients with tumors in the body and tail of the pancreas.
2. **Weight loss:** weight loss initially is due to pancreatic exocrine insufficiency owing to obstruction of the main pancreatic duct as well as exclusion of bile acids from obstruction of the main bile duct. Fat maldigestion may also contribute to abdominal pain and bloating. Relief of biliary obstruction and pancreatic enzyme supplementation will alleviate these symptoms. Cachexia can be a marked feature of the later stages of pancreatic cancer, with no good treatment.
3. **Biliary and duodenal obstruction:** Biliary stenting using endoscopic retrograde cholangiography (ERCP) is the preferred option with the combined percutaneous approach employed only if the former is technically not possible. The life of a plastic stent is about 3 months, causing recurrent jaundice. Self-expanding metal (and covered) stents have greatly reduced the risk of obstruction and acute cholangitis. Metal stents should be used for patients with a good performance status and favorable prognosis (locally advanced primary tumor <3 cm) and plastic ones for those patients with metastases and tumors  $\geq 3$  cm in diameter. Expandable metal stents are being increasingly deployed endoscopically for duodenal obstruction (occurs in  $\sim 15\%$ ), with a technical success rate of around 85%, but may be associated with serious complications, including perforation, fistula and bleeding and recurrent obstruction due to stent migration or fracture. Surgical bypass (open and laparoscopic) can be used to relieve jaundice using a Roux-en-Y loop hepatojejunostomy, and duodenal obstruction by gastrojejunostomy, especially in younger patients and both can be achieved laparoscopically.

### **Palliative chemo and radiation therapy**

1. **Chemotherapy:** PC is highly resistant to conventional methods of cytotoxic treatment and radiotherapy. Few chemotherapeutic agents have been shown to have reproducible response rates of more than 10%. 5-Fluorouracil (5FU) is an inhibitor of thymidylate synthetase (essential for synthesis of DNA nucleotides) and has been the most widely used in advanced pancreatic cancer, with a median survival of around 5–6 months and is better than the best supportive care<sup>47</sup>. A pivotal trial in 1997 meant that the nucleoside analogue, gemcitabine, replaced 5FU as the preferred drug<sup>48</sup>. Although the median survival improvement in favor of gemcitabine compared with 5FU was slight (5.7 vs. 4.4 months), the 1-year survival rate was more encouraging (18% vs. 2%), and most importantly, the toxicity was relatively mild and achieved a better clinical response (24% vs. 5%, respectively)<sup>93</sup>.

- 2. Chemo-radiotherapy and follow-on chemotherapy:** Radiotherapy has been widely used for the treatment of PC <sup>49,5</sup>. The main drawback is the limit on the dosage owing to the close proximity of adjacent radiosensitive organs. External beam radiotherapy is routinely used with 5FU as a radiosensitising agent (chemo-radiotherapy), although gemcitabine is now being evaluated as an alternative radiosensitiser. Newer techniques such as conformal radiotherapy are now being used, but these studies almost invariably employ follow-on chemotherapy once the chemo-radiotherapy has been completed. A recent meta-analysis demonstrated that chemo-radiotherapy is better than radiotherapy alone and that there is no survival difference between chemoradiotherapy plus follow-on chemotherapy and chemotherapy alone <sup>95</sup>. A recent phase III study compared chemo-radiotherapy and follow-on gemcitabine with gemcitabine alone in patients with locally advanced disease <sup>51</sup>. The trial was closed prematurely because of significant toxicity in the combination arm and significantly reduced median survival in the combination arm (8.4 vs. 14.3 months;  $p = 0.014$ ).

### **Curative treatment options for pancreatic cancer (resectable disease)**

**1. Selection and staging:** Once the pancreatic cancer has been identified, the patient needs to be assessed for fitness for major surgery and the tumor staged preoperatively for respectability. Venous resection is necessary during the course of a pancreatectomy in 5–10% of patients. Vascular reconstruction in this context results in a median and long-term survival that is similar to that of patients not needing a venous reconstruction<sup>52</sup>. It should be emphasized, however, that routine venous resection in patients with significant venous involvement is not feasible and the results of arterial reconstruction are unacceptably poor<sup>53</sup>. The resection rates and short- and long-term results are significantly better in high-volume centers, and major pancreas cancer surgery should only be undertaken in regional and supraregional centers <sup>54,55</sup>.

**2. Surgical techniques:** The aim of surgery is to achieve complete clearance of macroscopic tumor with clear microscopic resection margins, even if there are lymph node metastases. In practical terms a large proportion of patients (at least 35%) are histologically staged complete clearance of macroscopic tumor with positive resection margins <sup>74</sup>. The standard operation for tumors of the head of the pancreas is the Kausch–Whipple partial pancreatoduodenectomy (KW-PPD) <sup>56</sup>. Patients with tumors of the pancreatic body or tail undergo left pancreatectomy usually with en bloc resection of the spleen and hilar lymph nodes <sup>98</sup>. There is no role for total pancreatectomy unless this is the only means by which a radical resection can be achieved <sup>98</sup>. Postoperative morbidity remains high at around 40% even in supraregional units<sup>57</sup>. Independent risk factors are age >70 years, extended resections and small main pancreatic duct diameter measuring less than 3 mm<sup>58</sup>.

### **Adjuvant treatment after surgical resection**

**1. Chemotherapy:** Radical resection alone will result in a 5-year survival of only 10% owing to recurrence after surgery <sup>98</sup>. Nearly all patients develop metastatic disease, most commonly of the liver and peritoneum but also the lungs, and this may occur with or without local recurrence <sup>98,59,60</sup>. Although chemo-radiation to the area of the resection may reduce the local failure rate, survival length is the same as with systemic chemotherapy<sup>61</sup>. After pancreatic resection, the most important independent prognostic markers are lymph node status, tumor size and tumor grade <sup>62,6</sup>. The results from two large randomized trials show that adjuvant systemic chemotherapy will increase the 5-year survival from 9% to 12% with resection alone to 21–29% and 23% with either 5FU and folinic acid or gemcitabine, respectively<sup>64</sup>. The survival benefit of adjuvant chemotherapy is maintained irrespective of the type of operation used and whether or not patients develop postoperative complications<sup>65</sup>. Adjuvant chemo-radiotherapy has been used in the USA on the basis of a small randomized trial <sup>66,67</sup>, as well as apparently improving survival as reported in a non-randomized series of patients <sup>68,69</sup>, but these results have not been confirmed in large randomized trials <sup>70,7</sup>, so the focus has moved to whether chemo-radiotherapy and follow-on chemotherapy represents a better alternative than chemotherapy alone. The results of meta-analysis using individual patient data reject the use of chemo-radiation and provide powerful

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evidence for systemic chemotherapy <sup>116</sup>.

### **Prognostic factors of pancreatic cancer**

The key factors relating to the overall prognosis of PC are<sup>72</sup>:

- tumor grade (cellular differentiation)
- maximal diameter of the tumor mass (tumor size)
- lymph-node metastasis (lymphovascular invasion) at the moment of diagnosis.

The microscopic resection margin status is also an important survival factor after surgical treatment, although less so if the patient is treated with postoperative adjuvant chemotherapy<sup>73</sup>. A positive microscopic resection margin (R1) is operationally defined as at least one cancer cell within 1 mm of any surface of the resected specimen. A positive R1 margin is unrelated to tumor diameter but rather to histological grade and lymph node status, indicating that this has more to do with the biology of the tumor than with physical factors <sup>63</sup>.

### **Limitations of the current literature**

Pancreatico-duodenectomy (PD) is the only potentially curative treatment for cancer of the head of the pancreas, but is feasible in less than 10% of cases <sup>74,75</sup>. After resection, a 5-year survival rate of 15e20% has been reported in large series<sup>7,77</sup>. Whilst similar survival figures were reported as long as 20 years ago, improvement in perioperative management during the last three decades has caused a significant reduction of complications<sup>78</sup>, with two studies reporting no deaths <sup>76,79</sup>. With the decrease in perioperative morbidity and mortality, surgery has clearly established its role in the treatment of patients with pancreatic cancer when performed with curative intent. Curative PD (R0 resection) is associated with better survival than surgical or medical palliation <sup>80,81</sup>. However, when the tumour is found to be locally advanced at operation, the surgeon has frequently to face the dilemma of what procedure should be performed, as it is not clear whether microscopically incomplete resection (R1) can confer a survival benefit when compared with palliative surgical bypass (PSB). This question was initially addressed in 1995 by Reinders et al. who found a better survival in patients undergoing R1 resection compared to those undergoing PSB, but did not include long-term follow-up<sup>82</sup>. One year later, in 1996, the Johns Hopkins group reported similar results including patients with macroscopically residual disease (R2) as well <sup>83</sup>. More recently, Kuhlmann et al. also demonstrated a significant survival difference <sup>84</sup>, but this has been questioned by others who found no difference between palliative bypass and non-radical resection<sup>85,86</sup>. Residual microscopic disease is also widely considered as the main independent prognostic factor, with resection recommended only if tumour clearance is anticipated <sup>87,88,89</sup>. Even if there was a survival benefit, should we resect locally advanced tumours with a high risk of incomplete microscopic clearance or perhaps consider PD as a more aggressive form of palliation? Can PD be compared to PSB and be performed with similar complication rate and mortality?

### **Current status of practice**

The vast majority of patients affected by PDC presents to medical attention with new onset of painless jaundice. These patients usually are diagnosed with suspected PDC after undergoing imaging tests that show the presence of biliary duct dilatation and the presence of tissue density abnormalities in the head of the pancreas or affecting the distal bile duct. When the diagnosis of PDC is contemplated, patients are referred to a specialist surgeon for possible surgical resection. Surgical therapy is usually recommended if negative margins are feasible, if the patients are fit to undergo surgery and the imaging modalities show absence of extra-pancreatic cancer spread.

### **Controversy**

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Physicians are generally unable to capture the preferences of patients who need to make decisions regarding their own care strategy [10,11]. As reported by Bruera and Degner, the agreement on decision making preferences between patients and physicians is only 38% and just 42% of the patients reach their preferred level of control in deciding about their care strategy [12]. For these reasons it seems of extreme importance to assess the patients' inclinations regarding their willingness to undergo interventions associated with less toxicity even if associated with inferior chances of cure. Currently there is no accepted gold standard to measure the strength of preference for the patients choosing different treatments [14]. Probability Trade Off (PTO) is one of the possible techniques. It is a qualitative and intuitive tested methodology that allows the patients to be presented with information about options, outcomes and associated probabilities. The efficacy of the treatments is systematically varied until the patients switch their treatment preferences during a formal prewritten interview [14]. It is as individuals participating in PTO techniques are "standing at the decision-point of the treatment selection and looking down the decision tree towards the possible outcomes of treatment" [15]. PTO is considered an exhaustive technique because it makes the patients compare all aspects of treatment, its side effects, and probability of success and measure the strength of preference for either treatment by systematically adjusting the success of one treatment over the other. It is for this reasons that the investigators are proposing to use PTO to study the patients' preferences for the therapeutic options of PDC.

### **Study design**

A formal decision analysis technique named Probability-Trade-Off (PTO) will be applied during a structured interview with patients with suspected PDC at QEll Health Science Center. As opposed to the techniques measuring utilities, as would be required for a formal decision analysis, the "Probability-Trade-Off" (PTO) is designed to measure the strength of preference for different treatments according to the perceptions of an individual. As opposed to formal decision analysis techniques which frequently compare the preference of a health state compared to death, the PTO makes the patient compare all aspects of treatment, its side effects, and probability of success, and measures the strength of preference for either treatment by systematically adjusting the success of one treatment over the other, and asking the patient which treatment they prefer. The toxicity of treatments is often kept constant or varied based on the aim of the study. This arrives at a Probability-Trade-Off score, which quantifies the amount of survival, morbidity, mortality, hospital stay, pain etc. that a patient would be willing to give up in order avoiding a potentially more toxic regimen.

### **Probability trade – off and MRIS**

The PTO technique, as proposed by Llewellyn – Thomas is an alternative to traditional decision analysis techniques. Using standardized instructions that begin with explaining to the participants that the PTO is a technique for determining how strongly they adhere to their original choice, the participants are presented visual and verbal information about 2 or more treatments. The information presented covers the type and duration of therapy, side effects and the probability of their occurrence, and the probability of success and/or failure at a given time after treatment. This information is presented side-by-side on the same page for ease of comparison. Additional props may be used to explain probabilities better (i.e. a ninety percent chance of survival may be illustrated by a diagram with ten people, with one darkened in to represent the ten percent who die). Patients are then asked to choose which treatment they prefer after considering the treatment, the side effects, and the treatment efficacy. In the situation of equal treatment efficacy, the treatment that is usually chosen is the least toxic regimen. The next step in the PTO is to change one of the probabilities in the least preferred treatment, in a predetermined, systematic way in order to make it more attractive (i.e. more efficacious, or less toxic), and the patient is then asked again to choose which treatment is preferable. At some incremental change in probability, the patient will switch their preference of treatment (i.e. chose the more toxic regimen, for a greater treatment efficacy), and the probability during which this transition occurs (i.e. the "switch point") is a measure of the strength of preference for the originally chosen treatment regimen, or in decision analysis terms, the point of uncertainty in the decision making process. One can then

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subtract the “switch point” percentage from the starting percentage in the scenario, and arrive at an absolute difference in probability that is required to change a patients’ preference from one treatment regimen to another. This value has also been termed the minimally required increment in survival (MRIS) (H. Llewellyn – Thomas, personal communication, 2003). An example of this task is described next. A participant is shown two treatment regimens, regimen A and B, for the adjuvant treatment of Breast cancer. At the beginning of the PTO task, Regimen A has no side effects and results in a 75% 5 year survival. Regimen B has a 5% risk of deep venous thrombosis (DVT), and results in a 75% 5 year survival. The participant is asked to choose which treatment they prefer, and they will naturally choose regimen A. To show the strength of preference for their original choice, which was based on equal efficacy, and a desire to avoid a risk of DVT, the survival is then increased in predetermined increments (i.e. 1% increments), and at each step, the patient is asked which treatment they prefer. So the next step in this example is to increase the survival of regimen B to a 76% 5 year survival, and ask the participant which treatment they prefer. At some probability (i.e. when regimen B provides an 82% survival) the participant will switch their preference to regimen B, and accept a 5% risk of DVT for a gain in survival. Assuming a 1% incremental change, the “switch point” percentage is therefore 81.5% (the midpoint between 81 % and 82%). The MRIS in this example is therefore 81.5% minus 76%, which is 5.5%. Therefore, this participant would prefer regimen B, when it provides a MRIS of 5.5%, occurring at a probability of 81.5% 5 year survival.

The PTO technique has demonstrated validity, one aspect of which being the ability to show test – retest reliability. Coefficients of reliability have ranged from 0.78 to 0.94 [61, 62]. Additional evidence of validity, criterion validity, is demonstrated by the fact that the correlation between PTO and Time Trade Off (TTO), as assessed by Pearson’s correlation coefficient, was quite high in the study by Singer [63], with a value of  $r$  of 0.86.

#### **Aims of the study:**

- 1) To determine the minimal required increment in survival (MRIS) that patients with suspected PDC require to accept the consequences of surgical therapy compared to best supportive care, when asked to place themselves in the position of a hypothetical patient with resectable PDC.
- 2) To determine the minimal required increment in disease free survival that patients with suspected PDC require to accept the consequences of surgery compared to best supportive care, when asked to place themselves in the position of a hypothetical patient with potentially resectable PDC. Disease free survival is defined as the interval between the intervention (surgical excision) and the time when recurrent tumor is diagnosed in the same patients.
- 3) To determine the minimal required increment in perioperative morbidity and mortality rates that patients with suspected PDC require to accept the consequences of surgery compared to best supportive care, when asked to place themselves in the position of a hypothetical patient with resectable PDC

**Hypothesis:** Physicians are generally unable to capture the preferences of patients who need to make decisions regarding their own health care strategy [41,42]. Currently, there are no publications on the specific patients’ preferences between surgical therapy and best supportive care for patients with PDC. Because PDC usually affects individuals in their sixth decade of life with comorbidities, we expect that the patients will prefer best supportive care if the overall expected survival of radical surgery is in average only 24-36 months. Less invasive procedures are in fact more attractive to elderly individuals and patients with system dysfunction (diabetes, hypertension, renal insufficiency).

## **Eligibility**

### **Inclusion criteria**

All Individuals who satisfy the following conditions:

1. Patients diagnosed with painless jaundice, older than 18 years, fit to undergo surgery.
2. Patients able to provide independent informed consent.

### **Exclusion criteria**

Patients who satisfy at least one of the following conditions:

1. Patients unable to comply with the protocol for medical or socio-economic impairments.
2. patients with significant visual, hearing or communication disability
3. Patients on current therapy that could interfere with cognitive function (antidepressants, sedatives, antihistaminics).
4. Patients with previous treatments for other primary or secondary pancreatic tumors to avoid cognitive dissonance reduction bias

**Sample size calculation:** The sample size of the patients required for our PTO technique analysis is based on the assumption of a clinical significant relative difference in 5-year survival of  $\pm 7.5\%$  with standard deviation of 15% (worst case scenario where the data have a large range of dispersion). To detect a significant MRIS of 0.15 at five years the number of individuals to be recruited for interview would be 100 (Dupont's function analysis; Power and Sample Size Calculation Software® (University of Vanderbilt, Nashville, Tennessee, USA) [45]. The parameters necessary for the computation of the sample size are: 1) 5 overall survival; 2) follow-up time equal to 5 years; 3) probability of type I error equal to 0.05; 5) probability of type II error equal to 0.20. If during the course of this study some of the patients are not able to successfully complete the interview, we will proceed to recruit further individuals to reach the necessary number of patients to power our study.

### **Feasibility**

Although PDC is a relatively rare cancer in North America (5/100,000), the QEII Health Science Center is a referring center for complex pancreatic diseases in Nova Scotia, Princess Edward Island, New Brunswick, Newfoundland and Labrador. In these settings, clinicians and basic science investigators are able to perform advanced research in the field of medical and surgical oncology. In average, 2 to 4 patients are assessed for suspected pancreatic and biliary cancer every week at the Queen Elizabeth II Health Sciences Centre. The great majority of them have suspected peri-pancreatic cancer and would be candidates for the formal interview for PTO research. Considering that we estimate a recruitment of 50% of the potential candidates, we estimate that over a period of 10 – 12 months we would be able to collect the entire body of data necessary to complete this study.

### **Recruitment**

During the inpatients daily hospital care and outpatient clinic hours of three different services, (surgery, gastroenterology and oncology at the QEII Health Sciences Centre), eligible individuals will be approached by the primary investigator or assistants and asked whether they would be interested in participating in a study that is designed to understand what are the patients' preferences regarding the treatment of PDC. The patients will be explained the nature of the investigation (formal interview), that participation to this study is completely voluntary, that would not modify any of their future care and that they will be able to withdraw at any time if they decided to do so. In addition, the patients will be informed that participation in the study would

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only require one session of 45 minutes to one hour period and that the results of the study will be made available to them after final analysis if they are interested. The time of recruitment of the expected number of patients required for this study is 12 months.

#### **Protocol Phases**

Demographic data, level of education and comorbidities will be collected for all eligible patients to identify if there are possible differences between the participating cohort members and the patients who refuse to be enrolled.

*Interview-* the patients will undergo a formal interview the use of a Comorbidity questionnaire. They will be given Educational Material on pancreatic cancer to review and then the PTO questions will be asked, supported by visual aids (Pie Charts) to clarify percentages and probabilities associated with best supportive care and surgical resection.

#### **Definitions used during the PTO interview:**

Follow-up- Interval of 5 years after each specific intervention.

Overall disease specific 5-year survival rate- The proportion of survivors in both cohorts of patients treated surgery of best supportive care at the end of 5 years after the original treatment.

Time of recurrence- Interval of time between the day of the intervention and the day when the diagnosis of recurrent PDC is made.

Major complication- Each complication that:

- A. Require therapy, minor hospitalization (less than 48 hours admission to the hospital)
- B. Require major therapy, unplanned hospitalization (more than 48 hours admission to the hospital),
- C. Have permanent adverse sequelae

This classification follows the Society of Interventional Radiology Standard of Practice Committee Classification of Complication by Outcome.

Disease specific death- Death caused by the progression of PDC.

#### **Measurements:**

Independent variables: For each patient enrolled in this study the following parameters will be measured: 1)-Gender, Age (using date of birth reported on personal documents), formal education level and current or previous job activities. 2) Comorbidities as the presence or absence of any condition affecting the overall health as defined by the American Medical Society. The presence of comorbidities will be assessed using a questionnaire derived by the Charlson Comorbidity Index. The Charlson index is perhaps the most well known and widely used comorbidity measure, it is reliable and has been previously validated. The questionnaire is simple to administer and has a high correlation index with the Cumulative Illness Rating Scale (0.8) [52]. Test-retest reliability, assessed with the interclass correlation coefficient, was 0.91 for the questionnaire and 0.92 for the chart-based Charlson index.

Dependent variables: The following dependent variables will be measured for each patient:

1)-Minimal Required Increment Overall Survival at 5 years: the minimal life expectancy difference between the two interventions accepted by the patients as a trade-off for the less invasive procedure

2)-Minimal Required Increment of Disease Free Survival: the minimal difference between cancer free life expectancy between the two interventions accepted by the patients as a trade-off for the less invasive treatments for PDC

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3)-Minimal Required Post intervention Increment Complication Rate: the minimal difference of the probability of any adverse event occurring during the first 30 days of recovery after the intervention as defined by the Society of Interventional Radiology accepted by the patients for the most effective procedure.

4)-Minimal Required Post Intervention Increment Mortality: the minimal difference of the probability of death occurring during the first 30 days due to the intervention by direct or indirect cause as defined by the American College of Surgeons and accepted by the patients for the most effective procedure.

**Confounders and effect modifiers:** In the literature it is well known that the overall 5-year survival after surgery for PDC depends on several independent variables. Age, sex, presence of comorbidities have been previously described as effect modifiers. The presence of comorbidities at the time of the intervention, the degree of organ dysfunction and failure of performing a radical excision of the tumor are associated with increased morbidity and worse overall survival. Therefore, because confounders and effect modifiers have a significant role for the final analysis of the data, our protocol is designed to capture them by collecting the data in a prospective standardized fashion as reported in the data collection form.

### **Statistical analysis**

Bivariate analysis of statistical significance of continuous variables will be performed using 2 tail Student's t test. Proportions will be compared by Pearson's Chi Square with Yate's correction factor or Fisher's exact test whenever appropriate. Multivariable linear regression and logistic regression analysis will be performed to determine statistical significance of continuous or dichotomous variables adjusted for covariates and interaction terms. Continuous variables will be tested for normal distribution using the Kolmogorov-Smirnov test and log transformation will be performed for statistical analysis when appropriate. The null hypothesis will be rejected fixing the probability of type I error at 0.05 and a type II error at 0.20. Two-tail probability distribution will be used for all the statistical analysis unless specified. SAS® statistical software (SAS software, North Carolina) will be used to assist all the statistical computations.

**Data management and quality monitoring:** All the relative data will be collected on paper Protocol Form (PF1) and computer input information will be performed by the primary investigator and research assistants. Cross analysis of random variables of the databases will be performed to assess the existence of potential transcription errors. If data entry errors are detected in one category, the corresponding paper copy of the data collection form will be retrieved and corrections made. At the end of each correction process, a new random sample of data will be retrieved and cross-examined until no more errors are detected. Back up copy of the databases will be performed after each updating session. Strategy for protecting confidentiality will include limiting the access to the computers and cabinets containing the primary data only to personnel responsible to update and collect the patients' information and the primary investigators. Each patient will be assigned a unique number to identify them and no links will be able to be made between the patient and any information in any published material.

**Ethics:** After obtaining ethical approval from the QEII Health Science Center Institutional Review Board, permission to conduct formal PTO interviews will be obtained by the primary physicians of the respective outpatients' clinics where the data collection takes place. Written consent will be required from each patient before enrolling in the study. As suggested by the International Ethical Guidelines for Biomedical Research Involving Human Subjects, five fundamental principles were satisfied in the design of this protocol: equipoise of treatments, respect for the patient's autonomy, non-maleficence, beneficence and justice [60].

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**Timeline:** The recruitment of the patients will occur during the first 10-12 months of this study. Data collection and entry will be performed during the entire duration of the protocol. The completion of the data analysis and final publication of the results of the research will be performed within one year from the time of the last patient's data collection.

**Budget:** A part time research assistant would be trained by the primary investigator to perform PTO interviews.

**Personnel Costs**

One research assistant

Classification: research fellow

Role: to coordinate the contact with participating individuals and their primary physicians if necessary.

The research assistant will work closely with the primary investigator and she / he will share the responsibility of educating the participants and their primary physicians about the PTO interview, distribute the educational material necessary to inform the participants about the natural history of HCC and the available therapeutic options and finally to perform PTO interviews.

The research assistant will share the duties of data entry in the computerized database.

Position: part time

Working Week Hours: 16-20

Hourly Wage: \$ 30

Number of weeks: 48

**Total: \$ 28,800**

**Office Costs**

Laptop Computer: \$ 1,200

Statistical Software License: \$ 500

Telephone expenses: \$ 500

Travel expenses for interviews: \$ 5,000

Photocopies \$ 200

Other: \$ 2,000-3,000

**Total: \$ 10,400**

**Other Expenses**

Parking ticket coupons for participating individuals:  
\$ 1000

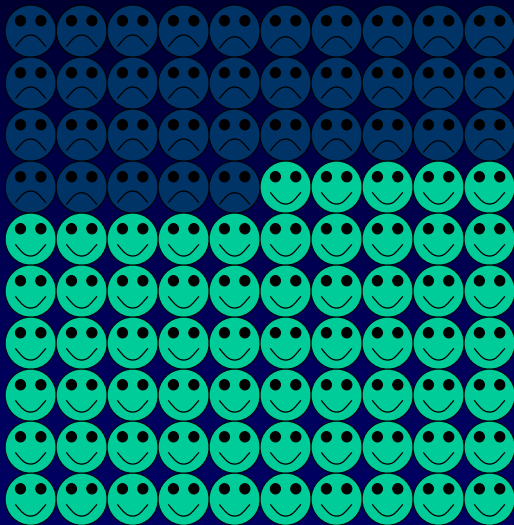
(Each participating individual would receive a coupon of \$ 10 to cover the expenses of parking their car inside the QEII parking lot at the VG Hospital)

**Total: \$40,200**

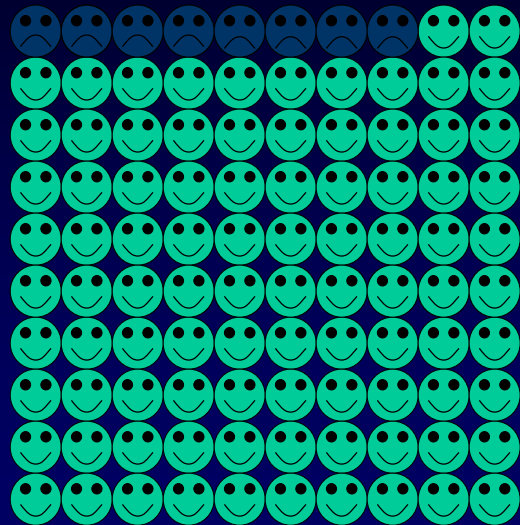
## Example of visual aid used in the PTO exercise

### Post operative complications

Hepatic Resection (35%)



RFA (8%)



*Man-Son-Hing M, Laupacis A, O'Connor A et al. Patient preference-based treatment thresholds and recommendations. A comparison of decision-analytic modeling with the probability-tradeoff technique. Decis Making 2000; 20: 394-403*

**Figure 1:** One of the examples of visual aid used during the formal PTO interview to better explain the interviewed the difference between the probability of an outcome for two therapeutic options.

Patient's name \_\_\_\_\_

Date: \_\_\_\_\_

## Comorbidity Questionnaire

This questionnaire includes a list of questions regarding the participant's present and past health conditions. This questionnaire is asked by the interviewer to the study participant.

Yes

No

1. Have you ever had a heart attack?

Yes

No

2. Have you ever been treated for heart failure?

*(Example: You may have been short of breath and the doctor may have told you that you had fluid in your lungs or that your heart was not pumping well.)*

3. A Have you ever had an operation to unclog or bypass the arteries in your legs, arms, neck or any other part of your body to improve the circulation of your blood?

Yes

No

4. Have you had a stroke, cerebrovascular accident, blood clot or bleeding in the brain, or transient ischemic attack (TIA)?

*(Example: Transient ischemic attack is a temporary condition that resolves spontaneously. People with TIA experience one or more of these problems: slurred speech, trouble to move one or more limbs, sensation loss in any part of your body, confusions and sometimes conscience loss)*

Yes

No

If no, go to question number 5

---

**4a. Do you have difficulty moving an arm or leg or speaking as a result of the stroke or cerebrovascular accident?**

Yes	No
<input type="checkbox"/>	<input type="checkbox"/>

---

**5. Do you have asthma?**

*(Example: Asthma is a condition that affects your ability to breath. People with asthma experience episodes where they are short of breath and have wheeze when breathing)*

Yes	No
<input type="checkbox"/>	<input type="checkbox"/>

---

If no, go to question number 6

---

**5. A. If yes, do you take medicines for your asthma?**

A. No.....	<input type="checkbox"/>
B. Yes, only with flare-ups of my asthma.....	<input type="checkbox"/>
A. Yes, I take medicines regularly, even when I'm not B. having a flare-up.....	<input type="checkbox"/>

---

**6. Do you have any of the following conditions?**

	Yes	No
<b>A] emphysema</b>	<input type="checkbox"/>	<input type="checkbox"/>
<b>B] chronic bronchitis</b>		
<b>C] chronic obstructive lung disease</b>		

If no, go to question number 7

---

**6. A. If yes, do you take medicines for your lung disease?**

- A. No.....
- B. Yes, only with flare-ups of my asthma.....
- C. Yes, I take medicines regularly, even when I'm not having a flare-up.....
- 

**7. Do you have stomach ulcers or duodenal ulcer disease?**

- | Yes                      | No                       |
|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> |

*If no, go to question number 8*

---

**7. A. If yes, has this condition been diagnosed by endoscopy?**

*Example: where a doctor looks into your stomach through a scope or an upper gastro-intestinal or barium swallow study (where you swallow chalky dye and then x-rays are taken)?*

- | Yes                      | No                       |
|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> |
- 

**8. Do you have diabetes (high blood sugar)?**

- A. No.....
- B. Yes, treated by modifying my diet.....
- C. Yes treated by medications taken by mouth.....

D. Yes, treated by insulin injections.....

**8a. If you have diabetes, has the diabetes caused any of the following problems?**

	<b>Yes</b>	<b>No</b>
A. Problems with your kidneys	<input type="checkbox"/>	<input type="checkbox"/>
B. Problems with your eyes, treated by an ophthalmologist?	<input type="checkbox"/>	<input type="checkbox"/>

---

**9. Have you ever had any of the following problems with your kidneys?**

	<b>Yes</b>	<b>No</b>
A. Poor kidney function <i>(Example: blood tests show high creatinine)</i>	<input type="checkbox"/>	<input type="checkbox"/>
B. Have used hemodialysis or peritoneal dialysis	<input type="checkbox"/>	<input type="checkbox"/>
C. Have received kidney transplantation	<input type="checkbox"/>	<input type="checkbox"/>

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	<b>Yes</b>	<b>No</b>
<b>10. A. Do you have rheumatoid arthritis?</b>	<input type="checkbox"/>	<input type="checkbox"/>
<i>(Example: Rheumatoid arthritis is a disease of your joints. This condition is caused by an inflammation of your fingers, knees hips and toes)</i>		

	<b>Yes</b>	<b>No</b>
-If yes do you take medications for it regularly?	<input type="checkbox"/>	<input type="checkbox"/>

	<b>Yes</b>	<b>No</b>
<b>10. B. Do you have a condition called Lupus Erythematosus ?</b>	<input type="checkbox"/>	<input type="checkbox"/>

*(Example: Lupus is an autoimmune disease that affect almost all the tissues of*

*PTO for pancreatic cancer*

*your body. This is caused by a general inflammation that your body is building against itself. Lupus can affect your kidneys, eyes, skin and other organs )*

-If yes, do you take medications for it regularly? **Yes**  **No**

**10. C. Do you have polymyalgia rheumatica?** **Yes**  **No**

*(Example: Polymyalgia rheumatica is an autoimmune disease that affect the muscles of your body causing general inflammation in your muscles)*

-If yes, do you take medications for it regularly? **Yes**  **No**

---

**11. Did any of your doctors say that you have any of the following conditions?**

A. Alzheimer's Disease? **Yes**  **No**

*(Example: A condition of your brain that may cause memory loss and confusion)*

B. Any other form of dementia? **Yes**  **No**

*(Example: A disease of your brain that may causes memory loss, confusion, and inappropriate behavior)*

C. Leukemia or polycythemia vera? **Yes**  **No**

*(Example: A disease of your blood cells that causes increased white or red blood cells in your system)*

D. Lymphoma? **Yes**  **No**

*(Example: A disease of your blood cells that causes enlargement of the lymph-nodes in your body)*

**Yes** **No**

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E. Cancer, other than skin cancer, leukemia or lymphoma?

**Yes**

**No**

-If yes, has the cancer spread to other parts of your body?

**Yes**

**No**

F. AIDS or HIV infection?

**Yes**

**No**

G. Have you ever undergone surgery?

-If yes, on what part of your body?

Head	<input type="checkbox"/>	Neck	<input type="checkbox"/>
Throat	<input type="checkbox"/>	Lungs	<input type="checkbox"/>
Esophagus	<input type="checkbox"/>	Stomach	<input type="checkbox"/>
Liver	<input type="checkbox"/>	Gallbladder	<input type="checkbox"/>
Duodenum	<input type="checkbox"/>	Small Intestine	<input type="checkbox"/>
Colon	<input type="checkbox"/>	Rectum	<input type="checkbox"/>
Pancreas	<input type="checkbox"/>	Hernia	<input type="checkbox"/>
Other parts	<input type="checkbox"/>		

-Have you ever had surgery performed to remove a tumor anywhere in your body?

**Yes**

**No**

-If yes, when was the surgery done? Year \_\_\_\_\_

(If less than 5 years the patient will be excluded from this study)

*End of the questionnaire*