The European evidence-based guidelines on pancreatic cystic neoplasms (PCN) in clinical practice: the development of relative and absolute indications for surgery during prospective IPMN surveillance

Vaalavuo Yrjö[1,2], Siiki Antti[1,2], Antila Anne[1,2], Irina Rinta-Kiikka[2,3], Sand Juhani[1,2], Laukkarinen Johanna[1,2]

[1]*Department* of Gastroenterology and Alimentary Tract Surgery, [2]Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland. [3]Dept. of Radiology, Tampere University Hospital, Tampere, Finland,

Correspondence:

Johanna Laukkarinen, MD, PhD

Associate professor in surgery

Head, Dept. of Gastroenterology and Alimentary Tract Surgery

Tampere University Hospital

Teiskontie 35, 33521 Tampere, Finland

Tel. (office) +358 3 311 64314

Tel. (cell) + 358 50 358 6556

Email johanna.laukkarinen@fimnet.fi

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Short title: The European evidence-based guidelines on pancreatic cystic neoplasms (PCN) in clinical practice

Abstract

Introduction

The European evidence-based guidelines on PCN recommend surveillance for IPMN patients who are fit for surgery but who have no indication for immediate surgery. Our aim was to demonstrate the feasibility of the new guidelines in clinical practice.

Methods

This is a prospective cohort study of patients included in the IPMN register in Tampere University Hospital, Finland. IPMN was diagnosed from 1 January 2013 to 31 December 2018. Patients were analyzed for surveillance and indications for surgery according to the European guidelines on PCN.

Results

Out of 128 patients in register 23 was decided to operate upfront and 105 patients were included in the surveillance programme. Invasive carcinoma was found in 4/23 of operated patients. Median follow-up time was 26 months (6-69). Median size of the cyst at the beginning and end of the surveillance was 16mm (4-58mm). During surveillance 0/105 (0.0%) patients had or developed an absolute indication for surgery. Relative indication for surgery was present in 8/105 (7.6%) patients in the beginning surveillance and 9/105 (8.6%) patients developed at least one relative indication for surgery during surveillance. From the surveillance cohort 2/105 patients were operated. Surveillance was abandoned in 15/105 (14.1%) patients all due to poor general condition or other medical conditions.

Conclusions

In clinical practice, surveillance of IPMN according to the European guidelines on PCN is feasible. Among our patients 16% were detected to have relative indications for surgery during the median 26 (range 3-135) months of surveillance. Nearly 15% became surgically unfit during surveillance period.

Introduction

The rate of malignant transformation of branch duct intraductal papillary mucinous neoplasms (BD-IPMN) without risk factors is low (1, 2). Risk factors for malignant transformation have been established in various guidelines, such as the European evidence-based guidelines on pancreatic cystic neoplasms (3), in 2017, the revised international consensus Fukuoka guidelines for the management of IPMN of the pancreas (4) and American Gastroenterological Association guidelines (5). Patterns of surveillance and indication for surgery vary between these guidelines.

The new European evidence-based guidelines on pancreatic cystic neoplasms recommend surveillance for patients who are fit for surgery but who have no indication for immediate surgery. Absolute indications for surgery include positive cytology for malignant/high grade dysplasia, solid mass, jaundice (tumour related), enchancing mutal nodules (≥5mm), main pancreatic duct dilatation ≥10mm. Relative indications for surgery include cyst growth rate ≥5mm/year, cyst diameter ≥40 mm, elevated levels of serum carbohydrate antigen 19-9 (CA 19.9) (>37U/mL), enhancing mural nodule <5 mm, main pancreatic duct (MPD) diameter 5-9.9 mm, acute pancreatitis (caused by IPMN) and new-onset diabetes mellitus. For patients with significant co-morbidities but regarded fit for surgery, the guideline suggests intensive surveillance in a presence of only one relative indication for surgery. If a patient with significant co-morbidities has two or more relative indications, surgery is recommended (3).

Our aim was to demonstrate the feasibility of the new guidelines in clinical practice by describing our IPMN surveillance programme and by analysing the development of relative and absolute indications for surgery during prospective IPMN surveillance.

Methods

This is a retrospective analysis of a prospective cohort. On 1 October 2015 a register for all IPMN patients under surveillance in Tampere University Hospital was established. Starting on 1 January 2013 the data was augmented by patient files retrospectively until 2015, since that the follow-up it has been prospective. For this study, the data was

gathered until 31 December 2018. Patients were analyzed for surveillance and indications for surgery according to the European experts consensus statement on cystic tumours of the pancreas published 2013 (6).

MRI was used as the primary method of cross-section imaging if not contra-indicated. Computed Tomography (CT) were used if necessary. Use of EUS is not routinely considered necessary as a method of surveillance in our center. In selected cases, use of EUS can be useful diagnostic tool and number of EUS studies has been increasing in our hospital. Serum level of Ca19-9 was measured. For first year follow-up was performed at 6-month intervals and yearly after that. If necessary, patients were assessed in multidisciplinary meetings (MDT). For the first follow-up, the patients were asked to attend our outpatient clinic. Whenever a patient was no longer fit for surgery, the surveillance was terminated.

The following data was gathered at baseline: Demographics, comorbidities, symptoms and radiological findings. The database was augmented at each follow-up point to include possible surgical procedures, final histopathological diagnoses and survival. Radiological findings as follows were gathered from radiological reports: radiological diagnosis, size and number of cysts, possible worrisome features (main pancreatic duct dilatation, mural nodules/solid component, calcification and septation), speed of progression in the growth rate the size of cyst and main pancreatic cyst dilatation. A second opinion was elicited from an experienced radiologist for cases with suspected MPD dilatation.

Statistical analyses were performed using SPSS 22.0 for Windows (IBM Inc., Somers, USA). Unless otherwise specified descriptive statistics are reported using count, percentage, median and range.

Permission to review patient files was obtained from the Chief Medical Director of Tampere University Hospital.

Results

Baseline findings

During the study period (1 January 2013-31 December 2018) 128 patients with suspected IPMN and fit for surgery were evaluated in our hospital. Twenty-three patients were assigned to be operated upfront and 105 patients were included in the surveillance programme if the radiological diagnosis was suspected IPMN. At the beginning of the

surveillance all patients had BD-IPMN. Median age of the patients was 69 years (range 28-84) and 82/129 (63.6%) were female. Baseline characteristics of the patients and tumours are described in Table 1. The group designated for upfront resection and the surveillance programme group had significant differences in incidence of symptoms 14/23 patients (60.9%) vs. 1/105 patients (0.9%) ($p<0.05$), and maximum diameter of the cyst 40mm vs. 15mm ($p<0.05$). There were no other statistically significant differences between the groups (Table1, Figure 1).

Patients assigned to upfront surgery

Five patients had an absolute indication; two patients had suspicion of malignancy in histology, two patients had MPD diameter ≥10 mm and one patient had Jaundice. Seven patients had two relative indications for surgery; cyst diameter ≥40 mm and MPD diameter 5-9.9 mm (4 patients), cyst diameter ≥40 mm and elevated levels of CA 19.9 (>37U/mL) (one patient), MPD diameter 5-9.9 mm and elevated levels of CA 19.9 (>37U/mL) (one patient), cyst diameter ≥40 mm and cyst growth rate ≥5mm/year (one patient). Relative indications for surgery in patients with singe indication were; cyst diameter ≥40 mm (6 patients) and main pancreatic duct (MPD) diameter 5-9.9 mm (5 patients) (Table 2a).

In the final histopathological analysis two patients had adenocarcinoma, 2 IPMN-carcinoma, 1 BD-IPMN and 1 main duct (MD)-IPMN high grade dysplasia. In addition, 3 BD-IPMN, 3 MD-IPMN and 7 mixt type (MT)-IPMN with low grade dysplasia were detected. Three patients had serous cystic neoplasm (SCN) and 1 chronic pancreatitis was discovered. Pancreaticoduodenectomy was performed on nine, distal resection on seven, total pancreatectomy on six and surgical exploration on one patients (Table 2). Rate of 90-day mortality was 2/23 (8.7%) (Table 2b, Figure 1).

Follow-up data

Follow up imaging was performed by MRI if not contra-indicated (contra-indications being, for example, having a pacemaker or allergy to contrast media). MRI was performed on 100/105 (95.2%), CT on 65/105 (61.9%) and both modalities on 60/105 (57.1%) of the patients. Of the cases 78/105 (74.3%) visited in the outpatient clinic, rest of the patient were contacted by phone or letter. MDT meeting was used in 37/105 (35.2%) cases. Median follow-up time in this study was 26 months (6-69). Median number of follow-up visits was three (2-7), with median frequency being one visit per every 8.6 months. Surveillance was cancelled in 15/105 (14.1%) patients due to poor general condition or other

medical conditions. Mean age for patients whom surveillance was cancelled was 78.8 (range 61-84) years. Mortality was 4/105 (3.8%); 2/105 (1.9%) patients died during surveillance and 2/105 (1.9%) patients died after cancellation of surveillance. None of the patients in the follow-up cohort were diagnosed with or died of pancreatic cancer. From the surveillance cohort 2/105 patients were operated on. The final histopathological analysis was MT-IPMN with low grade dysplasia in both cases (Table 3).

Indications for surgery

Median size of the cyst at the beginning and end of the surveillance was 16mm (4-58mm). Median value of ca19-9 at the beginning and end of the surveillance was 9 U/mL (1-417). Mean value of ca19-9 increased from 16.22 to 20.11 U/ml. Among the patients 84/105 (80%) experienced no increase in size. Mean rate of size increase was 1.39 mm/year in 21/105 (20%) patients which experienced any increase in size. Ca19-9 values didn't increase in 85/105 (81%) patients and 71/105 (68%) of the patients didn´t have increase either Ca19-9 value or cyst size (Table 3).

In the surveillance programme 0/105 (0.0%) patients had absolute indications at the beginning or developed them during the surveillance period and 8/105 (7.6%) of the patients had relative indications for surgery at the beginning of the surveillance.

In the European guidelines, a relative indication for surgery is cyst diameter ≥40 mm. At the beginning of the surveillance cyst diameter was over this threshold in 1/105 (0.95%) patients, cyst diameter being 58mm. Because of the poor general condition of the patient surveillance was opted for over surgery. Size of the cyst remained stable during follow-up. At the beginning of the surveillance 6/105 (5.7%) patients had elevated ca19-9 levels (>37U/mL). In the absence of other worrisome features none of the patients were operated on. Acute pancreatitis (caused by IPMN) was diagnosed in 1/105 (0.95%) patients. It was decided not to operate on this patient.

During surveillance, 9/105 (8.6%) patients developed at least one relative indication for surgery. Rapid growth of the cyst (cyst growth rate ≥5mm/year) was seen in 3/105 (2.9%) patients. Two of them patients had a growth of 9mm and 5mm/year without any other relative indications for surgery. Control MRI was advanced to six months and after that

there was no growth in the cyst. These patients were not operated on. A third patient had cyst growth of 6mm but as this patient was no longer fit for surgery surveillance was terminated.

Elevation of ca 19-9 above 37U/mL (from 29 to 81 U/mL) during surveillance was detected in 2/105 (1.9%) of patients, being a relative indication for surgery. One patient had no other relative indications for surgery and ca 19-9 value fell to 29 U/mL in nine months. The patient was not operated on and surveillance was continued. Other patient with elevated ca 19-9 had two relative indications (discussed below).

During surveillance, 1/105 (0.95%) of patients developed an enhancing mural nodule <5 mm and underwent distal pancreatic resection. In the final histological analysis, MT-IPMN with low grade dysplasia was detected.

MPD dilatation 5-9.9 mm was detected in 3/105 (2.9%) of patients. One of them with progressive MPD dilatation from 4mm to 8mm underwent total pancreatectomy. In the final histological analysis, MT-IPMN with low grade dysplasia was detected. Two other patients had 5mm and 6mm pancreatic duct dilatations with only minimal (1mm and 2mm) growth. The patient had no other relative indications for surgery and surveillance was continued.

One patient developed two relative indications for surgery: Ca 19-9 increased from 25 to 417 U/ml and cyst size increased from 37mm to 41mm However, the patient was not considered to be fit for surgery, and it was decided not to operate him. Surveillance was terminated.

The median time for developing new relative indications for surgery during follow-up was 18 (7-49) months from the beginning of the surveillance. Overall, it was decided to operate on 2/17 (11.8%) of patients with one relative indication for surgery; one patient with MPD dilatation from 4 mm to 8 mm and one with an enhancing septa. No surgery was performed on 15/17 (88.2%) of patients with relative indications. (Figure 1, Table 4).

Discussion

Because of increasing incidence and prevalence of PCN patients under surveillance and consequent intolerable burden to health care system, lifelong intensive surveillance protocols need to be critically evaluated (7-12). On the other hand, surveillance provides a method to proceed to pancreatic surgery in pre-malignant phase instead of poor prognosis when managed in cancer stage (13). Our aim was to demonstrate the feasibility of the European evidence-based guidelines in clinical practice in our hospital. Series of resected tumors for validating the new European guidelines have been published before (14), but only few of these studies focus on surveillance. In this study we describe our surveillance programme using the European evidence-based guidelines.

It was decided to operate upfront on 23 out of 128 (17.9%) patients. Our rate of primary resection is comparable to those reported in other studies although rates of primary resections vary greatly (1). Malignant tumour was detected in 4/23 (17.4%) of patients, which is also in line with the most recent literature (15, 16). All patients had indications for surgery according European evidence-based guideline; 18 patients had relative indications and 5 patients had absolute indications for surgery. Type of surgery was decided based on preoperative imaging or frozen section biopsies perioperatively. Biopsies were taken from resection margin of the pancreas and if needed on other locations. Based on these findings, total pancreatectomy was performed if there were suspicion of tumour involvement in the whole length of the pancreas. In this group of patients perioperative pancreatoscopy was not yet available, but since that it has been added to our diagnostic tools. One hundred and five patients were included in our surveillance programme. None of these patients had absolute indications for surgery at the beginning of the surveillance.

Surveillance was performed primarily by using MRI. EUS was not used routinely but, for selected cases EUS was available as a diagnostic tool. The quality of results obtained seems not to be influenced by the non-application of EUS.

Most of the patients (68%) did not have any increase in cyst size or in ca 19-9 level. Median size of the cysts (16mm) did not increase during the study period although there was minimal growth in the mean size of the cysts. Slow growth (less than 1mm/year) rates of cyst size has been reported in larger series (15, 17). Our surveillance period was relatively short, over a longer period of time slow growth in median size would be expected.

A total of eight patients had one relative indication of surgery at the beginning of the surveillance and 6/8 of these patients had elevated levels of ca 19-9 as relative indication for surgery. In the absence of other relative indications for surgery it was decided not to operate on two patients otherwise fit for surgery. A further six patients also had relative indications

for surgery, but also had significant co-morbidities. It was also decided not to operate on these six patients. Risk for malignancy or high-grade dysplasia (HGD) varies between relative indications for surgery. Evidence for risk of malignancy is well established with features like MPD dilatation, enhancing nodules, growth rate of the cyst and size of the cyst (16-23). In our cohort no patients were operated on for relative indication of raised Ca 19-9 level in spite of a growing number of papers showing raised level of ca 19-9 as an independent risk factor for cancer in IPMN patients (15, 24-26).

During the surveillance, 8/105 (7.6%) patients developed one relative indication for surgery and 6/8 of these patients were treated conservatively. Three patients had a rapid growth of the cyst, two patients had new dilatation on MPD and one had elevated level of ca 19-9. All patients had been under surveillance for several years and the decision not to operate on them was based on the minimal progression of the cyst and absence of other relative indications. One patient developed two relative risk factors for surgery. Multiple relative indications for surgery present a higher risk for malignancy and therefore surgery should be considered also for patients with elevated risk for complications (27, 28). In the case of our patient with two relative indications for surgery, the operative risks were too high because of other medical conditions and therefore the patient was not operated on.

During surveillance no invasive cancer or even HGD were detected. Overall, 2/105 (1.9%) patients in this surveillance cohort underwent surgery. A male aged 74 years and a female aged 68 years. Both of these patients had an MT-IPMN with low grade dysplasia in final histopathological analysis. The indication for and timing of the operation can be questioned. The patients did not have significant co-morbidities, but each of them had only one relative indication for surgery. Pancreatic surgery is associated with significant mortality and this disease carries a fairly good prognosis when treated conservatively even in the presence of relative indications for surgery (2, 29-31). A systematic review conducted by G. Vanella et al. (2018) concludes that mortality due to causes other than pancreatic cancer is much higher in patients with worrisome features but not fit for surgery (32). On the other hand, the patients resected for IPMN have significantly

better prognosis when operated on before malignant transformation or even before transformation to HGD (33, 34). None of the patients died of pancreatic cancer during the surveillance period. In selected cases opting to continue surveillance rather than operate is a feasible option. Positive predictive value of detecting malignancy is low when using European or any other current guideline for managing IPMN patients. It is essential to further study this disease to minimize the number of unnecessary surgical interventions.

Surveillance was cancelled in a relatively high number of patients, 15/105, which relates to the patients' relatively high age (median 69 years) at the beginning of the surveillance. A surveillance programme causes significant costs to the healthcare system and also creates a burden on patients (10, 35). It is essential to select only those patients likely to benefit from the surveillance offered on the programme.

Median time for developing new relative indications for surgery was 18 (7-49) months. In this cohort surveillance was organized according to the European guidelines. However, time to developing a new relative indication is long. Some recent studies suggest that longer intervals for the control of stable disease would be safe (36, 37). Also study by Marchegiani et al. suggest that discontinuation of surveillance for selected patients over 65 years might not increase risk of developing pancreatic cancer (28).

The limitations of this study include the relatively short follow-up time and small patient cohort. In this database we are not able to make suggestions as to whether the indications for surgery are valid or whether we are monitoring the right patients. Most of the studies in this field are series of resected PCNs. The strength of this study is that it aims to describe the whole pathway of the patient with diagnosed IPMN.

Conclusion

We conclude that in clinical practice, surveillance of BD-IPMN according to the European guidelines on PCN is feasible. Upfront surgery was performed on 18 per cent of the patients in this cohort. Among our patients 16 per cent were detected to have relative indications for surgery during the median 26 (range 3-135) months of surveillance. Out of 105 patients in the total study population, two were operated on during the surveillance period. In 5 year surveillance time, nearly 15%

became surgically unfit: It is thus crucial to evaluate not only cyst progression but also changes in patient´s condition as surgical candidate, to promptly terminate surveillance in unfit patients.

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Figure 1. Flowchart of IPMN surveillance in Tampere University Hospital 1.1.2013-31.12.2018

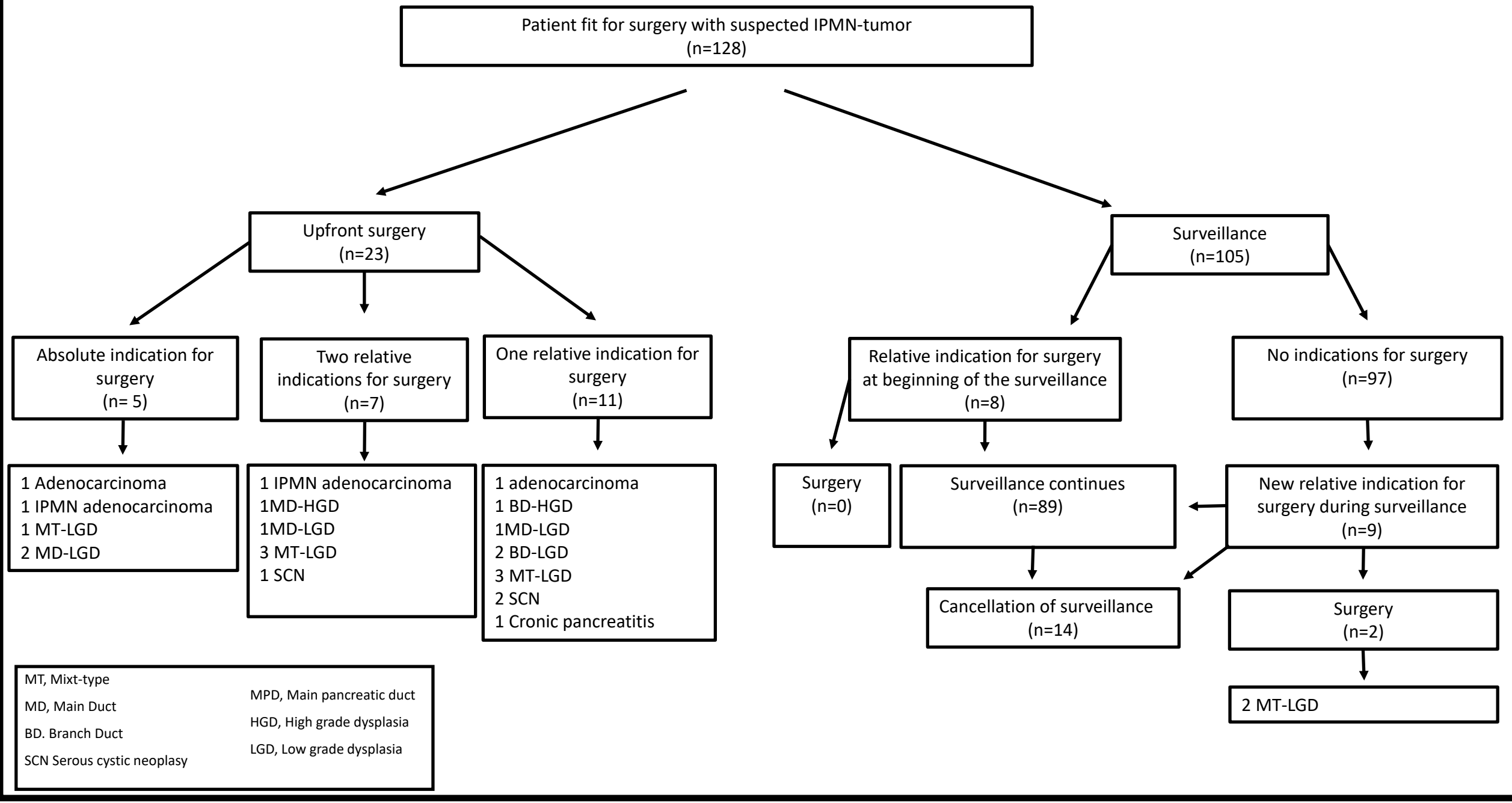

Table 1. Baseline characteristics of IPMN patients and tumours: Upfront operated and follow-up groups.

Baseline characteristics and tumor spesifics			
Features	Operated upfront	Follow up	p
Number of patients	23	105	
Age median (range)	66 (37-79)	69 (28-84)	0.559
Gender female	12 (52.2%)	71 (67%)	0.85
Diabetes	11 (47.8%)	21 (19.8%)	0.07
Previous cancer	4 (17.4%)	29 (27.4)	0.23
Symptomatic	14 (60.9%)	1 (0.9%)	<0.05
Smoking	7 (30.4%)	18 (17.0%)	0.152
Ca 19-9 (kU/L)	9 (1-177)	9 (1-140)	0.832
Diameter of cyst (mm)	40 (4-58)	15 (4-54)	<0.05
MPD diameter (mm)	6 (2-20)	na	
MT[1]	13	0	
MD[1]	5	0	
BD[1]	5	105	

[1]MT, Mixt-type MD, Main duct BD. Branch duct. Preopreative diagnose.

Table 2a. Indication for surgery, upfront operated patients

Indication for surgery	n
Absolute indication	
Malignant histology	2
MPD diameter ≥10 mm	2
Jaundice	1
Two relative indications	
Cyst diameter ≥40 mm and MPD diameter 5-9.9 mm	4
cyst diameter ≥40 mm and elevated levels of CA 19.9 (>37U/mL)	1
MPD diameter 5-9.9 mm and elevated levels of CA 19.9 (>37U/mL)	1
cyst diameter ≥40 mm and cyst growth rate ≥5mm/year	1
One relative indication	
cyst diameter ≥40 mm	6
MPD diameter 5-9.9 mm	5

Table 2b. Histology and type of surgery, upfront operated patients

Histology	n
Adenocarcinoma	2
IPMN-carcinoma	2
MD-IMPN HGD	1
BD-IMPN HGD	1
MX-IPMN LGD	7
MD-IPMN LGD	3
BD-IPMN LGD	3
SCN	3
Chronic pancreatitis	1
Type of surgery	
Pancreaticoduodenectomy	9
Distal pancreatic resection	7
Total pancreatectomy	6
Surgical exploration	1

MPD, Main pancreatic duct

HGD, High grade dysplasia

LGD, Low grade dysplasia

SCN, Serous cystic neoplasy

Table 3. follow-up data of BD-IPMN surveillance patients

Follow-up modality	
MRI	100 (95.2%)
CT	65 (61.9%)
MRI+CT	60 (57.1%)
Follow up characteristics	
Outpatiet visit	78 (74.3%)
MDT-meeting	37 (35.2%)
Follow-up period months, median (range)	26 (3-69)
Number of follow-ups median (range)	3 (2-7)
Follow up termination	15 (14.1%)
Mortality of study up population	4/105(3.8%)
Operated patients	2/105 (1.9%)
Follow-up values	
Cyst size mm median (range)	16 (4-58)
Ca 19-9 U/ml median (range)	9 (1-392)
Patients with no progression during surveillance	
Cyst size mm	84/105 (80%)
Ca 19-9 U/ml	85/105 (81%)
Cyst size and Ca 19-9 U/ml	71/105 (68%)

Table 4. Absolute and relative and indications for surgery in BD-IPMN surveillance

Indications for surgery				
Absolute indication[1]	**Beginning of the surveillance**	**During surveillance**	**All**	**Operated during surveillance**
Solid mass	0	0	0	0
Jaundice	0	0	0	0
Enhancing mural nodule ≥5 mm	0	0	0	0
MPD diameter ≥10 mm	0	0	0	0
Relative indication[1]				
Cyst growth rate ≥5mm/year	0	3	3	0
Cyst diameter ≥40 mm	1	1	1	0
Increased levels of serum CA 19.9 (>37U/mL)	6	2	8	0
Enhancing mural nodule <5 mm	0	1	1	1
Main pancreatic duct (MPD) diameter 5-9.9 mm	0	3	3	1
Acute pancreatitis (caused by IPMN)	1	0	1	0
ALL	8	10	17	2

[1]One patient had two relative indications