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Gastrointestinal NETs

PANDORA-2 protocol; intervention study to improve the quality of life in patients with small (≤2 cm) pancreatic neuroendocrine tumors

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Introduction

Current guidelines (European Neuro-Endocrine Tumor Society, ENETS 2016 and North American Neuro- Endocrine Tumor Society, NANETS 2018) changed the treatment strategy for small (≤2cm) non-functioning pancreatic neuroendocrine tumors (NF-pNET) from tumor resection to an active surveillance strategy. This treatment change is based on the relatively large number of patients with incidentally detected small pNET, which are indolent tumors, and the knowledge that surgical resection is associated with morbidity and long-term effects such as exocrine- and endocrine insufficiency. To implement this new surveillance strategy, the PANDORA-study (2016) was started, an active surveillance protocol with prospective data collection including clinical outcomes and quality of life (QoL). The PANDORA-study (NL6510) was implemented in all Dutch Pancreatic Cancer Group centers, including all 4 ENETS Centers of Excellence in The Netherlands.

The study showed excellent clinical outcomes after a median follow-up of 17 months, where 89% of patients had pNETs without any tumor growth and only 2/76 (3%) of patients had tumor growth leading to a resection. An unanticipated result of PANDORA was that the QoL of patients was decreased at baseline and during follow-up compared to the reference population. Furthermore, there was suboptimal adherence to the advised surveillance protocol. Reflecting on the preliminary results of PANDORA, two important aspects became clear:

1. PANDORA was designed from a medical perspective, with an effort not to miss pNETs with malignant behavior. Therefore, the surveillance protocol in PANDORA was intense with frequent imaging.

2. PANDORA did not have measures to support patients during their intensive follow-up protocol, apart from the available care in DPCG hospitals.

For this study we strive to improve the QoL for patients with small NF-pNET undergoing active surveillance by reducing the burden of the current active surveillance protocol and by introducing a supportive care intervention.

Methods

This study is a nation-wide multicenter prospective study with currently 12 participating centers. Patients are included if they have a NF-pNET of 2 cm or smaller The diagnosis is made with both a Ga-68 DOTATATE PET-CT and a CT-scan or MRI-scan. Patients are excluded if the tumor shows high-grade dysplasia or tumor growth 3 months after diagnosis, if it has a syndromal origin, if it has hormone overproduction, if there are signs of lymph node metastasis or distant metastasis. Patients will receive a less intensive follow-up protocol at the start of the study with 6 moments of radiological imaging over 10 years, compared to 13 moments in the previous PANDORA-study. At 3 months patients will undergo endoscopic ultrasonography with fine-needle biopsy, to confirm the diagnosis and tumor grade. Patients will be asked to report their QoL through an online questionnaires biannually for the first four years of participation. In the third year of this study, new patients will also be given a supportive care intervention. As a result, three study groups will be available for outcome analysis regarding QoL, clinical outcomes and adherence to the follow-up protocol:

Group 1. Previous PANDORA cohort, which will continue with QoL analysis and will be available as historical control group for both interventions.

Group 2. Phase 1 PANDORA-2 cohort, which will have received a reduced active surveillance program, but without designed supportive care (which is still in development).

Group 3. Phase 2 PANDORA-2 cohort, which will have received both reduced active surveillance as well as the supportive care intervention.

Surgical resection will be recommended if a patient develops symptoms, if a tumor is >2cm, if it shows tumor growth >0.5cm/year, if the pancreatic duct or common bile duct shows dilatation, if lymph nodes show pathological enlargement, if there is vascular involvement or infiltration of surrounding organs, or if a patient expresses a strong preference for surgical treatment.

Results

With PANDORA-2, we are aiming to gain insights in the causes of the decreased QoL of PANDORA-patients and involve partners/family caregivers in the analysis. The less intense surveillance protocol is aimed at improving the patients' QoL while maintaining tumor control and subsequently to implement a supportive care intervention. Furthermore, an analysis of the effect of this regiment on the adherence to the follow-up protocol will be made, as well as a cost-benefit analysis.

The life expectancy of this rare disease is almost unchanged and should therefore be with the best QoL. This study will be dedicated to that goal.

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ENETS Consensus Guidelines Update for Gastroduodenal Neuroendocrine Neoplasms

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Introduction

Gastric neuroendocrine neoplasms (g-NENs) represent the most frequent digestive NENs and are increasingly recognized due to expanding indications of upper gastrointestinal endoscopy. Often silent and benign, g-NENs may however be aggressive when sporadic and may sometimes mimic the course of gastric adenocarcinoma. Duodenal neuroendocrine neoplasms (d-NENs) may be sporadic or associated with multiple endocrine neoplasia type 1 (MEN-1) and present with a functional syndrome (i.e. gastrinoma with Zollinger-Ellison syndrome).

Since the last ENETS guidelines [1], new data have become available, especially focusing on g-NENs, while few changes have been reported concerning d-NENs over the last three years.

For an alphabetical list of all other Vienna Consensus Conference participants, see Appendix.

Epidemiology

New epidemiological data come from a study performed in Argentina [2], showing that g-NENs and d-NENs represent 6.9 and 2.0% of all digestive NENs, respectively. These data are similar to the SEER data, where g-NENs were found to represent 8.7% of all enteric NENs [3], and quite similar to a recent prospective Austrian study by Niederle et al. [4], where g-NENs represented 5.6% of all digestive NENs. The proportions of g-NENs with respect to the overall NEN rates do vary, however; g-NENs represented 23% of all NENs in the Austrian study compared to 6% in the SEER data, 5% in a Canadian study (Ontario) and 7.4% in a Taiwanese study [4–7]. These differences underline the need for multicenter prospective studies with long-term analysis to better describe the European epidemiology of these tumors.

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Table 1. Classification of g-NENs

	Type 1	Type 2	Type 3
Proportion among g-NENs, %	70–80	5–6	14–25
Tumor characteristics	Often small (<1–2 cm), multiple in 65% of cases, polypoid in 78% of cases	Often small (<1–2 cm) and multiple, polypoid	Unique, often large (>2 cm) polypoid and ulcerated
Associated conditions	Atrophic body gastritis	Gastrinoma/MEN-1	None
Pathology	G1–G2 NET	G1–G2 NET	G3 NEC
Serum gastrin levels	↑	↑	Normal
Gastric pH	↑↑	↓↓	Normal
Metastases, %	2–5	10–30	50–100
Tumor-related deaths, %	0	<10	25–30

Clinical and Histological Features

Well-differentiated g-NENs may be divided into three types (table 1): type 1 and 2 are ECLomas, due to chronic hypergastrinemia, associated with chronic atrophic gastritis (CAG) and Zollinger-Ellison syndrome, respectively. Type 3 g-NENs are rare and sporadic and are not a consequence of an underlying gastric mucosal abnormality; they are mostly single large lesions with a high metastatic potential and with a high grade (often G3 NEC) [8, 9]. Some issues remain open with respect to the above definitions, as well-differentiated g-NENs with a range of grades (G1–G3) not associated with CAG have been described [10–12], and thus a further distinction among type 3 g-NENs may be appropriate. Mixed gastric neoplasms as endocrine/exocrine have also been described; 68 cases have been reported in the literature so far, but no data about the patients' survival rate are available [13].

Prognosis and Survival

The overall outcome in type 1 g-NENs is universally excellent; when managed by endoscopic surveillance and lesion resection for larger lesions, recurrence-free survival of approximately 24 months can be achieved with a 100% survival rate. Data on metastatic rates for types 2 and 3 g-NENs have not significantly changed since the last ENETS guidelines [1, 14]. Similarly, no new data regarding d-NENs survival rates have been reported.

Diagnosis and Tumor Staging

Upper gastrointestinal endoscopy with careful appraisal of the tumor(s) and background gastric mucosa is still the gold standard in diagnosing g- and d-NENs. Endoscopic ultrasonography also plays a pivotal role in locoregional evaluation, but the cut-off in terms of size when defining the indication for this examination in type 1 NENs needs to be investigated. Conventional imaging techniques such as CT scan and MRI are of very limited value for small type 1 and 2 tumors of the stomach and duodenum in terms of cost/benefit ratio, while they are needed for disease staging in advanced neoplasms and in type 3 NENs. Data concerning the application of somatostatin receptor imaging (either using somatostatin receptor scintigraphy or ^{68}Ga-PET-DOTANOC) in these patients are scanty. These examinations are rarely useful for type 1 g-NENs that are invariably small and indolent, but they can be useful in type 2 and 3 g-NENs as part of the overall staging and perhaps choosing therapy [15–17]. Larger cohort studies with long-term follow-up are needed to evaluate the clinical usefulness of these tests both in g- and in d-NENs.

Treatment

In patients with type 1 g-NENs (fig. 1), conservative management strategies are to be preferred over surgery. Previously, the ENETS guidelines recommended surveillance after 1–2 years and resection for lesions ≥1 cm or those threatening the deep muscularis propria to avoid

metastatic spread. Some investigators have advocated resecting all visible lesions using biopsy forceps for small lesions and endoscopic mucosal resection (EMR) for lesions >5 mm [18, 19]; however, there are no randomized data comparing an aggressive endoscopic approach (resecting all visible tumors) to more selective endoscopic therapy (resecting only larger lesions). The overall metastatic risk is low in type 1 g-NENs and has been directly correlated with tumor size (10 mm appearing to be the cut-off) [20]. Therefore, the minimal approach should be to resect tumors ≥10 mm. Resection should be performed by experienced endoscopists in gastric tumors using either EMR or endoscopic submucosal dissection (ESD); the latter has the benefit of an en bloc resection for complete histological appraisal and has been shown effective in a total of 96 patients [21–24]. Nonetheless, EMR and ESD do carry risks of bleeding and perforation. A randomized trial comparing a less aggressive therapy to more aggressive endoscopic therapies is needed. It is also important to carefully analyze the non-involved adjacent gastric mucosa for dysplasia in a background of CAG, and mapping biopsies are recommended. For patients with type 1 tumors that are predicted T2 or with positive margins, local excision or partial gastrectomy should be discussed; surgical antrectomy to suppress hypergastrinemia and limit ECL growth is still debated [1] but rarely practiced as completeness of antrectomy remains speculative.

Somatostatin analogues (SSAs) have been used in limited series in patients with type 1 g-NENs; they do lead to regression of tumors but this has not been compared to surveillance strategies and as such cannot be recommended in early disease. SSAs might be useful to treat patients with multiple small lesions that are hard to eradicate endoscopically [25], but RCTs comparing their efficacy to endoscopic management are needed to confirm this hypothesis. Their use can be an option for patients with metastatic disease, proven SSTR2 expression and a low Ki-67 index. The gastrin receptor antagonist netazepide has been shown to have anti-proliferative properties in g-NENs in non-controlled studies [26, 27]. Again, its use cannot be universally recommended and needs to be tested in RCTs.

For type 2 g-NENs, treatment is usually dictated by the possible presence of duodenal or pancreatic NENs as part of MEN-1, and local or limited excision can be recommended, but this should be patient tailored at multidisciplinary NET centers of excellence. Netazepide is also being tested in a trial enrolling patients with type 2 neoplasms [NCT01322542].

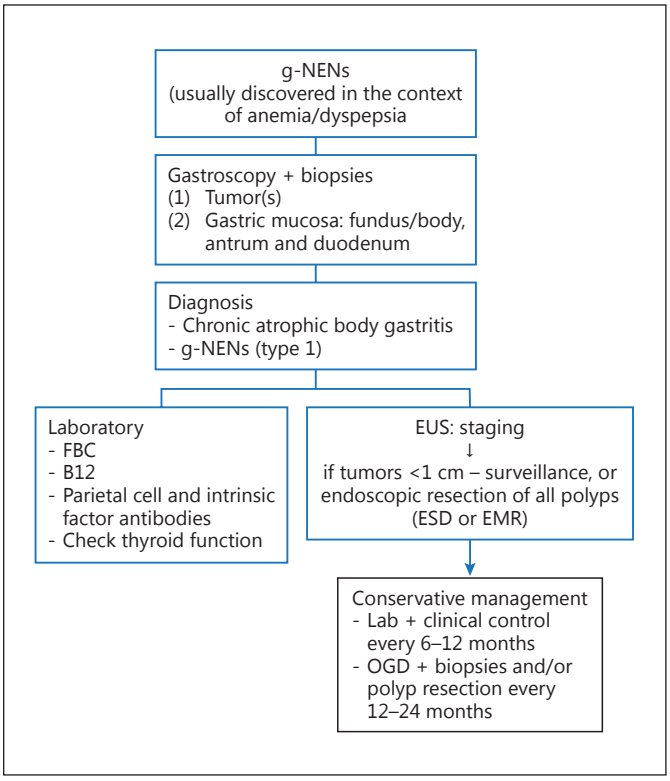

Fig. 1. Algorithm for type 1 g-NEN management. EUS = Endoscopic ultrasonography; FBC = full blood count; OGD = oesophageal gastroduodenal endoscopy.

In patients with type 3 g-NENs, while endoscopic management for small lesions has been proposed [1, 28], surgical treatment remains the recommended option and follows the strategy employed for gastric adenocarcinomas (partial or total gastrectomy with lymph node dissection). Systemic therapies are required for inoperable or stage 4 disease.

For d-NENs, endoscopic management has been proven to be safe and effective for lesions ≤10 mm in size, confined to the submucosal layer, without lymph node or distant metastasis (fig. 2). In a series of 38 patients diagnosed over a 5-year period, no recurrence was observed at a mean follow-up of 17 months, and ESD achieved a higher rate of radical excision than EMR [24]. Surgery should be performed for suspected T2 tumors or in those with positive margins after resection (local excision and antrectomy or total gastrectomy depending on tumor-histological features and invasion).

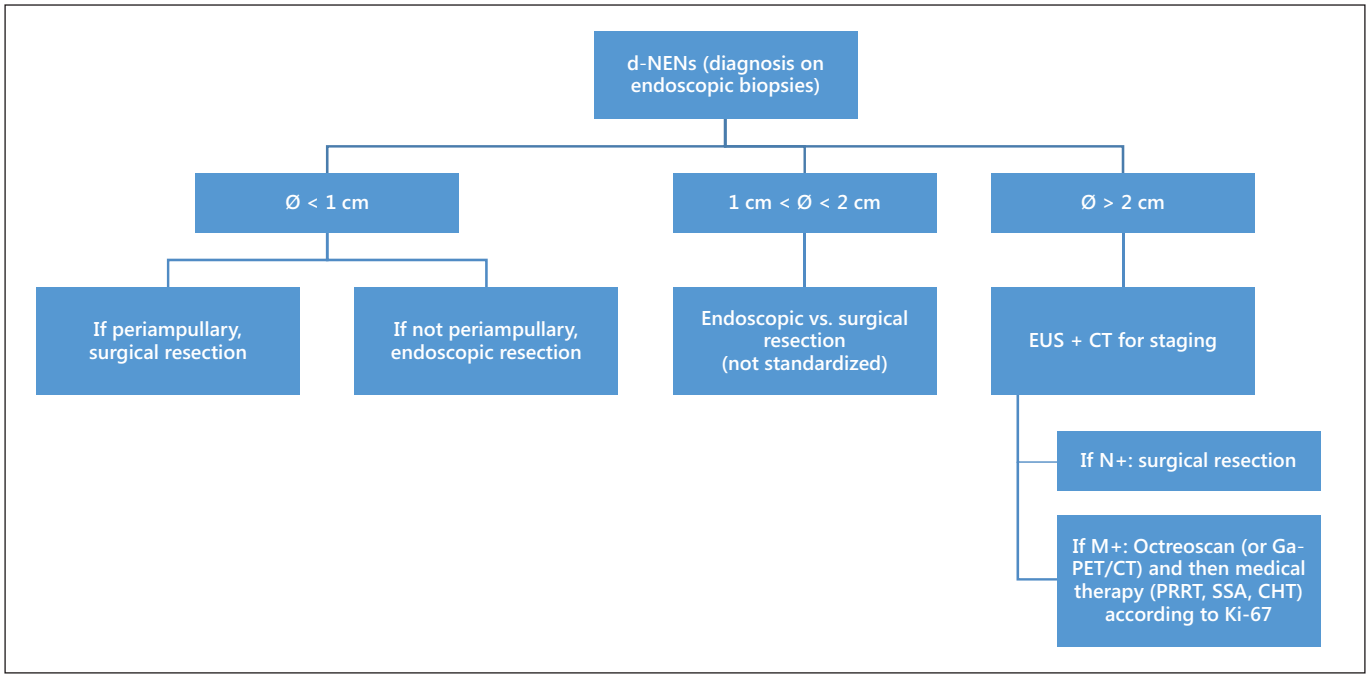

Fig. 2. Algorithm for d-NENs. EUS = Endoscopic ultrasonography; N+ = positive lymph nodes; M+ = positive for metastasis; CHT = chemotherapy.

Follow-Up

Endoscopic follow-up is recommended for patients with g- and d-NENs following excision, but the correct timing has never been defined. It is recommended that patients undergo endoscopy at least every 2 years. For type 1 g-NENs, an approach based on tumor recurrence has been proposed, but it has never been validated in prospective trials. Patients with CAG also require careful surveillance for apparition of intestinal metaplasia and dysplasia using modern endoscopic equipment [29, 30].

Please also refer to the ENETS consensus guideline updates for other gastroenteropancreatic neuroendocrine tumors [31–36, this issue].

Appendix

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Rapid Research Communication

Watchful waiting for small non-functional pancreatic neuroendocrine tumours: nationwide prospective cohort study (PANDORA)

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Introduction

Non-functional pancreatic neuroendocrine tumours (NF-pNETs) are rare neoplasms, often detected incidentally. The prognosis varies and is largely dependent on the Ki-67 proliferation index, presence of a genetic syndrome, lymph node involvement, and tumour size[1–4]. Resection of pancreatic lesions is associated with significant morbidity, and may include long-term complications such as new-onset diabetes and exocrine pancreatic insufficiency[5,6]. Clearly, the potential survival benefit obtained with surgery needs to outweigh the morbidity associated with pancreatic surgery. This explains the current controversy regarding small (2 cm or less) asymptomatic NF-pNETs, for which some advocate surgery and others suggest a conservative approach[7–11].

Based on retrospective data, guidelines advise watchful waiting for NF-pNETs of 2 cm or smaller, but provide no clear recommendation on the required follow-up[4,12]. Therefore, the objective of this study was to prospectively evaluate disease-related outcomes and quality of life (QoL) after implementation of a nationwide, watchful-waiting programme for NF-pNETs no larger than 2 cm. The study also study sought to evaluate the feasibility of the proposed follow-up protocol, as well as adherence to the protocol in participating centres.

Methods

This was an interim analysis of the multicentre prospective PANDORA study of the Dutch Pancreatic Cancer Group. Full details of the study design, methods employed, and statistical analysis can be found in *Appendix* S1. All patients with sporadic, asymptomatic NF-pNETs of 2 cm or smaller were included if they met the eligibility criteria, in particular absence of nodal and/or distant metastases. The trial was registered in the Netherlands Trial Register (NL6510).

Patients were enrolled into a watchful-waiting protocol to monitor tumour progression (*Fig. 1*). Surgical resection was recommended if patients developed symptoms, tumour growth exceeding 0.5 cm/year, total tumour size greater 2 cm, pathological lymph node enlargement, vascular involvement or infiltration into surrounding organs, or pancreatic duct dilatation, or if the patient expressed a strong preference for operation.

Results

Between 1 January 2017 and 29 February 2020, a total of 76 patients with a NF-pNET no larger than 2 cm were included. Baseline characteristics are summarized in *Table S1*. During a median follow-up of 17 (i.q.r. 8–35) months, 68 participants (89 per cent) had no signs of tumour progression. Eight patients (11 per cent) showed tumour progression exceeding 0.5 cm/year, and two also had a final tumour size of more than 2.0 cm. No other tumours larger than 2.0 cm were noted, and 21 patients (28 per cent) had tumours smaller than 1.0 cm. Characteristics of patients with progression are shown in *Table 1* and *Table S1*.

Overall, six patients (8 per cent) underwent surgery during follow-up (*Table S2*). Two patients had surgery because of significant tumour growth, detected after 3 and 10 months of follow-up. One patient had tumour progression of 0.8 cm in 1 year (from 1.8 to 2.6 cm). Gallium-68 DOTATATE PET–CT showed two enlarged lymph

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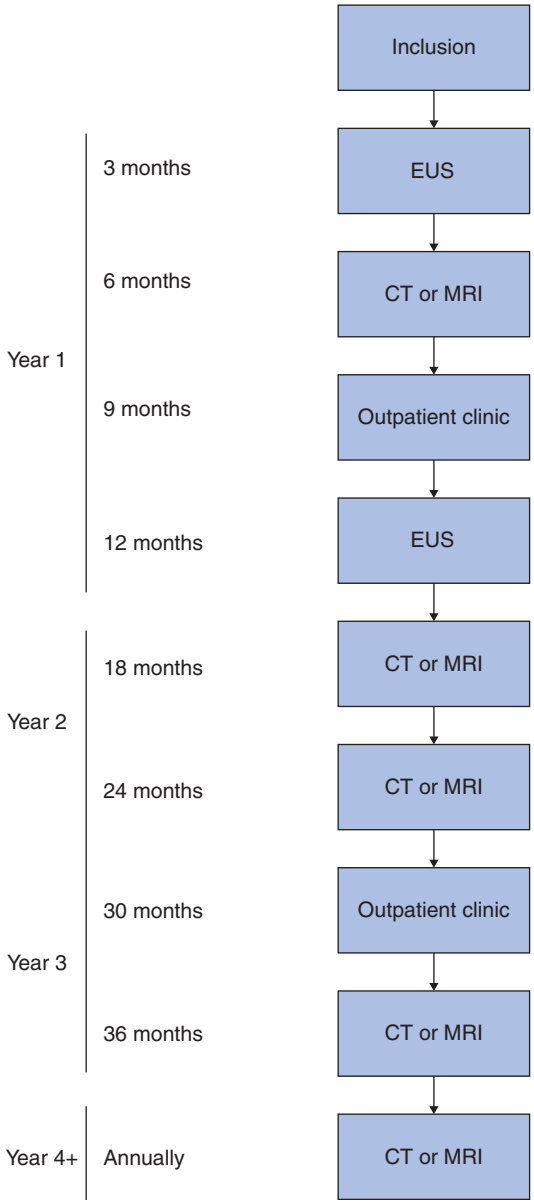

Fig. 1 Follow-up protocol for watchful waiting of patients with a non-functional pancreatic neuroendocrine tumour of 2 cm or smaller included in the PANDORA study

EUS, endoscopic ultrasonography.

nodes (aortocaval and para-aortal). During surgery, one unexpected peritoneal deposit was identified and the patient underwent laparoscopic enucleation of the primary tumour with lymphadenectomy and removal of the peritoneal lesion. The final histopathological diagnosis was a pNET of 2.0 cm, with a Ki-67 index of 5–10 per cent, two positive lymph nodes and, indeed, peritoneal metastasis. Two new lymph nodes were detected 11 months after surgery, for which somatostatin analogue therapy was started.

The second patient showed tumour progression exceeding 0.5 cm (from 1.0 to 1.7 cm) within 3 months of follow-up and as a result underwent surgery. The final histopathological diagnosis showed a pNET of 1.7 cm, R0 resection, with a Ki-67 index of less than 3 per cent, and 0 of 17 positive lymph nodes. The patient is currently asymptomatic at 11 months' follow-up without signs of disease progression.

Table 1 Follow-up of patients with progressive non-functional pancreatic neuroendocrine tumours

	No. of patients* ($n = 8$)
Clinical characteristics	
Tumour size at last follow-up (cm)†	1.2 (0.7)
Time to progression (months)‡	17 (13–30)
Duration of follow-up (months)‡	24 (9–61)
Developed symptoms	0
Developed metastases	
None	7
Lymph node + peritoneal	1
Surgical resection	
Type of surgery	
Spleen-preserving distal pancreatectomy	1
Enucleation	1
Surgical approach	
Open	1
Laparoscopic	0
Clavien–Dindo ≥ grade III complications	1
Postoperative histopathology	
Positive lymph nodes	1
Ki-67 index (%)	
< 3	1
3–20	1
> 20	0

*Unless indicated otherwise; values are †s.d. and ‡median (i.q.r.).

Three patients had a pNET resected despite lacking an indication according to the study protocol. Of these, two underwent spleen-resecting distal pancreatectomy, citing fear of disease progression as the predominant reason for requesting surgery. One patient underwent laparoscopic spleen-resecting distal pancreatectomy because the surgeon did not support the decision for watchful waiting and advocated tumour resection. All three patients had a pNET on final histopathology.

A fourth patient had a pNET enucleated owing to uncertainty regarding the pNET diagnosis on delayed (contrast-enhanced) endoscopic ultrasonography (EUS) at 8 months' follow-up. The final histopathological report showed an intravascular pyogenic granuloma, but no pNET.

In total, four patients died, all from non-pNET-related causes.

Although the study protocol recommended confirmation of the diagnosis to by at least 2 different imaging modalities, only one type of imaging was used at the time of diagnosis in 19 patients (25 per cent). Thirty-two patients (42 per cent) had two, and 25 (33 per cent) had three or more imaging modalities to confirm the diagnosis. Only 17 patients (22 per cent) underwent EUS at the suggested 3-month time point. Instead, patients opted for CT (31, 41 per cent), MRI (16, 21 per cent), or no imaging at all (12, 16 per cent). At 6 and 12 months, 21 (28 per cent) and 11 (15 per cent) patients did not undergo any imaging.

QoL scores on the European Organisation for Research and Treatment of Cancer QLQ-C30 questionnaire were statistically significantly worse at baseline for the study population compared with the mean of the reference population regarding emotional functioning (83.9 *versus* 89.0; $P = 0.042$), nausea and vomiting (6.9 *versus* 2.7; $P = 0.037$), dyspnoea (18.8 *versus* 7.1; $P = 0.004$), and insomnia (22.9 *versus* 14.0; $P = 0.046$) (*Fig. S1*).

Discussion

This multicentre prospective cohort study, which evaluated watchful waiting for NF-pNETs no larger than 2 cm, found that

short-term follow-up is both safe and feasible. A small proportion of patients showed tumour progression. Application of a watchful-waiting protocol successfully prevented surgery in over 9 of 10 patients. Furthermore, heterogeneity in pNET management, despite use of a study protocol, was observed in this study, along with poor QoL at the time of diagnosis.

The present finding of slow tumour progression supports previous studies[9,11,13–17] of NF-pNETs of 2 cm or smaller, which advised wait-and-see in certain patients. In contrast, other authors[18] have recommended upfront surgery for all pNETs, as even small lesions may have malignant characteristics that could impair survival. Importantly, patients with malignant tumour features were excluded from the present study, and, even when significant tumour growth occurred, six of eight patients with tumour progression refused surgery and opted to continue watchful waiting. Collectively, these results indicate that, under strict criteria, patients with a NF-pNET no larger than 2 cm can safely be treated conservatively.

In turn, it is clear that implementation of this novel watchful-waiting approach to pNET is challenging[19–21]. As is common in investigator-driven multicentre studies, not all centres adhered strictly to the follow-up protocol. EUS was included at 3 and 12 months of follow-up to reduce the number of scans per patient, and so that multiple imaging modalities could confirm tumour size stability. It also provided an immediate opportunity to perform fine-needle aspiration (FNA) if there was doubt regarding tumour origin. However, EUS was considered a high burden for patients, and was frequently rejected by both patients and physicians. In addition, not all patients underwent the suggested CT or MRI at 6 and 12 months' follow-up, as the interval after diagnosis was deemed too short by some physicians. A reduction in the follow-up protocol has been made by the study group, whereby the EUS examination at 3 months is suggested only for patients who have not undergone EUS previously. In future studies, EUS FNA could also be used to examine other tumour characteristics.

A potential pitfall of a wait-and-see approach is late detection of disease spread. This was the case in one patient in the present study who underwent surgery for rapid tumour progression, in whom peritoneal metastases were diagnosed during surgery. The sensitivity of CT, MRI, and DOTATATE PET–CT is known to be low for (small) peritoneal metastases[22,23]. However, the optimal timing of adjuvant treatment for metastases in pNET is unknown, and treatment in the absence of radiologically measurable disease is usually not recommended. To truly evaluate the oncological safety of watchful waiting of pNET, longer follow-up is necessary. Nevertheless, it is important to report these short-term findings, because they give insight into the obstacles of implementation of new guidelines, as well as the pitfalls regarding treatment indication and sensitivity of imaging techniques. QoL was poorer at baseline in the study population than that of the reference population, but the results are too premature for conclusions to be drawn on the exact reason for this difference.

The authors further recommend improved patient support during the first years of watchful waiting. The PANDORA study is continuing to evaluate long-term outcomes of a wait-and-see approach for NF-pNETs no larger than 2 cm.

Disclosure. The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

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Original Article

Developing an evidence-based and theory informed intervention to involve families in patients care after surgery: A quality improvement project

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ABSTRACT

Objectives: In the post-surgical setting, active involvement of family caregivers has the potential to improve patient outcomes by prevention of surgical complications that are sensitive to fundamental care. This paper describes the development of a theoretically grounded program to enhance the active involvement of family caregivers in fundamental care for post-surgical patients.

Methods: We used a quality improvement project following a multi-phase design. In Phase 1, an iterative method was used to combine evidence from a narrative review and professionals' preferences. In Phase 2, the logic model underlying the program was developed guided by four steps: (1) confirm situation, intervention aim, and target population; (2) documented expected outcomes, and outputs of the intervention; (3) identify and describe assumptions, external factors and inputs; and (4) confirm intervention components.

Results: Phase 1 identified a minimum set of family involvement activities that were both supported by staff and the narrative review. In Phase 2, the logic model was developed and includes (1) the inputs (e.g. educational- and environmental support), (2) the ultimate outcomes (e.g. reduction of postoperative complications), (3) the intermediate outcomes (e.g. behavioural changes), and (4) immediate outcomes (e.g. improved knowledge, skills and attitude).

Conclusions: We demonstrated how we aimed to change our practice to an environment in which family caregivers were stimulated to be actively involved in postoperative care on surgical wards, and how we took different factors into account. The description of this program may provide a solid basis for professionals to implement the family involvement program in their own setting.

What is known?

Family involvement in care has been explored both conceptually and empirically, however there are less accounts of the underlying theoretical rationale for multi-component interventions aimed to improve family involvement in post-surgical patient care.

What is new?

This paper gives insight in the development of an evidence-based and theoretically grounded program to promote family involvement in fundamental care for patients after surgery. It shows how the family involvement program has the potential to influence outcomes on different levels, and improve quality of care. The logic model presented may help other hospitals to make attempts toward a more patient- and family centred environment.

1. Introduction

Attention to the delivery of patient- and family-centred care

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(PFCC) in hospital has increased in recent years. Family-centred care is more than the presence of family during hospitalisation; it includes family participation in all aspects of care delivery [1]. This participation requires a mutual partnership and collaboration among healthcare professionals, patients and their family caregivers in a way that promotes patient satisfaction and self-determination [2].

In the field of surgery, active involvement of family caregivers in fundamental care activities has the potential to improve health-related outcomes (e.g. quality of life (QoL), and discomfort) by prevention of surgical complications. This fundamental care, sometimes referred to as essential or basic care, reflects a diverse range of care processes that combine the physical, psychosocial and relational dimensions of care, traditionally delivered by nursing staff [3,4]. Poorly executed fundamental care threaten patient safety, quality of life, patient empowerment, functioning and satisfaction [3]. This results in higher numbers of complications and poor care experiences [3]. Families often act namely as primary caregivers after discharge, but feel often unprepared for this task and experience a lack of knowledge to deliver proper care [5]. Educating and training these family caregivers could improve the execution of fundamental care, and thereby reducing the risk of complications.

The incidence of complications is 2–4.5 times greater in surgery than in general medicine [6], and the consequences of surgical complications on patients' health can be severe [7]. Some surgical complications such as pneumonia, urinary tract infections, and delirium are believed to be potentially preventable [8–11], and are sensitive to adequate fundamental care. Thus, meeting patients' fundamental care needs in hospital care is crucial, especially when patients are not able to carry out these activities independently (e.g. eating, dressing, washing, mobilising, and oral hygiene) [3]. For that purpose, hospitalisation may provide a unique opportunity to actively stimulate family caregivers to collaborate in care. Family caregivers can learn new skills and knowledge under supervision and, coached by healthcare professionals, they may be motivated to be actively involved in care activities.

Although family involvement in care has been explored both conceptually and empirically, there are less accounts of the underlying theoretical rationale for multi-component interventions aimed to improve family involvement in post-surgical patient care. Gaining this understanding will provides a solid basis for healthcare professionals and policy makers on how they can replicate and implement the intervention in their own setting. Thus, the aim of this project was to develop an evidence-based and theoretically grounded program to promote family involvement in fundamental care for patients after surgery.

2. Material and methods

This project is reported according to applicable criteria of the revised Standards for Quality Improvement Reporting Excellence (SQUIRE) guideline [12].

2.1. Study design

This two-phased study follows a multi-phase design [13]. We used both an empirical approach to initially develop the family involvement program and then a logic model to refine it. The development of the family involvement program was undertaken by an interdisciplinary team of six healthcare professionals (i.e. surgeon, surgical resident, physician assistant, and three nurse scientists). We used the logic model in the development phase of the intervention to bring more clarity in the understanding of our program and to give theoretical insight in the links between inputs, activities, actions, and outcomes.

2.2. Study setting

The setting for this quality improvement project was two surgical wards that provided care to patients after oncological and gastrointestinal surgery. The intervention was created for these two wards involving about 64 full-time equivalent nursing staff in a 1000-bed university hospital (Setting blinded for peer review, the Netherlands). These wards were chosen because staff expressed a willingness to adopt a more family centred approach to their care.

2.3. Procedures, data collection and analysis

2.3.1. Phase 1

In Phase 1, an iterative method was used to combine evidence and healthcare professionals' preferences. Six steps were used (1) narrative review, (2) draft the program, (3) focus group meetings with nurses; (4) group discussion with physicians; (5) surveys of physicians' opinions; (6) redraft the program. We deliberately opted for various data collection methods and tailored these methods to the target group and their preferences.

The first step was to undertake a narrative review. Because this was a quality improvement project, that aimed to get specific evidence into practice in a relatively short time frame [14–16], this review was limited to focusing on family centred care interventions and evidence of their effectiveness as well as on the association between patient outcomes and fundamental care activities. We carried out several searches of the scientific literature in the leading biomedical bibliographic databases (Ovid Medline, Ovid Embase, EBSCO CINAHL, PsychInfo and the Cochrane Library) up to March 2015, and was updated in July 2017. The preferred citations were systematic reviews and randomised clinical trials published in reputable journals. If these types of studies were not available, we included other study designs. No restriction was placed on the year of publication for the included studies.

The second step, drafting the program, was undertaken by the project team. The review findings along with a conceptual understanding about family involvement were used in this process.

During the third step, focus group meetings of seven to eight nurses were carried out to acquire insight in the views of nurses on active family involvement in fundamental activities after surgery, the competences nurses think they should have to stimulate active family involvement, and their preferences regarding educational strategies. Competencies were defined as the functional adequacy and capacity to integrate knowledge and skills with attitudes and values into specific context of practice [17]. Participants were recruited by using convenience sampling. We invited registered nurses who were working on one of the two surgical wards to participate. A topic list (Appendix A) and prompts to were used to structure the discussion. One project team member moderated the focus groups and two others observed and took notes. The focus groups were audiotaped to assist in checking and complete the notes. We used an iterative process to identify themes across the qualitative data [18], first by coding, then grouping codes into preliminary subthemes and themes using an iterative approach. Data saturation was reached after three meetings.

In the fourth step, a 45-min large group discussion was undertaken to gain more understanding physicians' (surgeons and residents) perspectives and experiences regarding the active involvement and family presence on surgical wards. While smaller focus groups may have yielded more rich data, this was not viewed as an option as clinical (operating) schedules and lack of time of physicians hampers the feasibility. The surgeon involved in this project moderated this discussion by using a topic list (Appendix B)

which was created to reflect the literature. Two project members observed and took notes. The group discussion was also audiotaped to assist in ensure the notes were comprehensive. The same thematic analysis approach as was used for the focus groups, was used for these notes.

An opinion survey targeting physicians was used in step 5 because we recognised that the large number of physicians attending the group discussion meant that some may not have had the chance to voice their opinions. As a result, we were not able to determine if data saturation was reached. Survey questions (Appendix C) were developed from a review of the literature [1], and local knowledge but were not psychometrically tested [1,19]. The aim of the survey was to get more insight into factors that potentially facilitated or hindered physicians in involving families in care. The data were analysed descriptively.

Step 6 involved a synthesis of the findings from all of these steps led to redrafting of the program. This activity was undertaken by the project team and occurred over several group meetings.

2.3.2. Phase 2

After Phase 1, the logic model underlying the program was developed. Four steps in logic modelling guided this process: (1) confirm situation, intervention aim, and target population; (2) documented expected outcomes (i.e. immediate (direct changes), intermediate (modifications in manifestations) and ultimate outcomes (improvement of patient condition), and outputs of the intervention; (3) identify and describe assumptions, external factors and inputs; and (4) confirm intervention components [20]. Discussion, reflection and other techniques like brainstorming and theoretical hypothesis testing were used in this process. All these activities were discussed within the interdisciplinary project team, and with other stakeholders (see Acknowledgements).

During the first activity, the interdisciplinary team used all the information gathered to clarify the initial situation prior to the intervention. The initial situation refers to the local context in which the intervention will be implemented, as well as the key issues that the intervention attempts to solve. We used the findings from the previous steps to formulate a clear definition of the situation (i.e. inadequate family participation in post-operative care), and to identify the key issues that we aim to address by implementing our program. In the second activity, we formulated outcome measurements which we expected to influence as a result of the program. We made a distinction between short-term, medium-term, and long-term changes in outcomes (see Fig. 1). To reach the outcomes several activities are required, as well as stakeholders who are involved in the activities. These are the so-called outputs (e.g. training of healthcare professionals). In the third activity, we described our assumptions (e.g. optimising fundamental care activities given by family caregivers after surgery leads to better patient outcomes that are sensitive to fundamental care activities). These assumptions are beliefs about the way we think that the intervention works and are essential, because wrong assumptions often lead to poor results [20]. Once we defined the assumptions, we discussed the inputs (e.g. staff- and family willingness and time). These inputs are all the resources and contributions that we put into the intervention [20]. The success rate of the program is not only influenced by the way of the implementation, but also by the presence of external factors. Although these external factors are often out of control of individual healthcare professionals and can be difficult to influence, they should be mapped and considered carefully. During the last step, we decided which components will be included in the program. In our model, one example of such a component is the active involvement of family caregivers in fundamental care activities. For this, we used the results of our narrative review and the input of the healthcare professionals.

2.4. Ethical considerations

The Medical Ethics Review Committee of a University Hospital (setting blinded for peer review) reviewed the study protocol and concluded that the Medical Research Involving Human Subject Act (WMO) does not apply to this project (reference number W17_067#17.085). Consent to participate in this project was implied by participants' contribution to data collection. All authors declare that no competing interests exist.

3. Results

3.1. Phase 1

The family involvement program comprised fundamental care activities, in which family caregivers can be actively involved. Table 1 provides a summary of the results of each of the 6-step process used in Phase 1 to develop the program and gives a short overview of the evidence-base and healthcare professionals' preferences and beliefs. Baseline characteristics of all respondents are presented in Table 2. Our narrative review identified limited evidence on effective interventions to promote family caregiver involvement in hospital care of adults [21,22]. Despite this, we recognised it was important to focus on complications known to be responsive to fundamental care [3,8,23]. We found several articles that showed an association between patient outcomes and fundamental care activities as summarised below:

- Oral care, coughing and deep breathing exercises [10,24,25].
- Early mobilisation and head-of-bed elevation [10,26–28].
- Encourage oral intake and companionship during meals, and feeding assistant if needed [9,27].
- Active orientation to time, place, and person [26,27].
- Remove visiting hours (i.e. open visiting policy) [1].

These activities became the proposed targets for family caregiver involvement.

In step 2, drafting the program, we selected a minimum set of fundamental care activities that have a known effect on post-operative complications, as well as several tasks that encourage family caregivers to provide fundamental care activities (Table 3). These activities were all related to physical care because of our narrative review findings.

In step 3, the focus group data ($n = 23$) showed that nurses expected positive effects of family presence on clinical outcomes. However, some nurses had some negative personal experiences with managing patients and family caregivers who exhibit aggressive behaviour. Nurses mentioned that adequate communication was important, as are clearly defined responsibilities among patients, family caregivers, and healthcare professionals. Nurses named the following other competencies as important to engage and support the involvement of family caregivers; being persuasive, being honest, listening carefully, being flexible, have self-reflection and be able to negotiate. Nevertheless, there were nurses who doubted the extent to which they possessed these competences. They spoke about the specific need for a number of training courses, preferably focusing on self-reflection and conflict management.

Analysis of the large group discussion from step 4 with 63 physicians showed they expected positive effects of family presence on clinical outcomes. However, they also emphasised that family presence may be more time-consuming, and the patient was their top priority. Physicians sometimes felt hesitant to share

Table 1
Six iterative steps to develop the intervention.

Steps	Main topics	Participants	Main findings
1.Narrative review	• Active involvement of family caregivers in a hospital setting • The association between patients outcomes and fundamental care activities	Literature focusing on adult patients admitted to the hospital (first search up to March 2015, and updated in July 2017)	• Limited evidence on effective interventions to promote family involvement in care on adult acute wards [21,22] • Focusing on complications which are known to be responsive to fundamental care [3,8,23]
2. Drafting the program	• Selection of a minimum set of fundamental care activities known to have an effect on postoperative complications. • Selection of several tasks to encourage family caregivers to provide fundamental care activities: (1) information about basic care activities; (2) goal setting with the patient, family caregiver and nurse; (3) task-oriented training; (4) hands-on participation in basic care; (5) presence of family caregivers during medical ward rounds; (6) rooming-in (at least 8 h a day).		
3. Focus group meetings	• Nurses' needs and expectations regarding active family involvement • Nurses' perceived competence in involving family carers in fundamental activities • Nurses' preferences regarding educational strategies	Three focus group meetings, totalling 23 participants	• Positive effects of family presence on outcomes, but this may be more time-consuming • Nurses needed to be flexible, but as one nurse said: *'how flexible can you be as you need to finish your within a certain time'* • Some had negative personal experiences with managing patients and family caregivers who exbitit aggressive behaviour • There should be clearly defined responsibilities among patients, family caregivers and healthcare professionals • Most important competency mentioned is adequate communication to build trusted relationships and stimulate the involvement of family caregivers • Important communication skills are: persuasiveness, being honest, listening carefully, self-reflection and able to negotiating. • The majority of the nurses mentioned that they have an adequate communication style, and adapt their communication to align with patients and family caregivers. • Nurses had specific preferences for a number of training courses, preferably focusing on self-reflection and conflict management
4. Group discussion with physicians	• Needs and expectations of surgeons and medical residents regarding active family involvement after surgery • Facilitators and barriers for implementation	Discussion was led by one of the project leaders, and 63 participants attended the meeting	• Positive effects of family presence on outcomes, but this may be more time-consuming • They feel that it adds value to the decision-making process • There should be a clear definition of who is a family caregiver • Patient is top priority: patient preferences are prioritised over the preferences of family caregivers • Hidden agenda of family caregivers. • Physicians have some privacy concerns constrain information sharing • Family caregivers should receive adequate education • It is essential that any changes does not influence hospital bed capacity
5. Surgeon opinion survey	• Statements on the active involvement of family caregivers in care and decision-making. There were three answer options possible, namely (1) disagree (2) neutral (3) agree.	Physicians response rate = 75/125; 60% Male: 45 (61%) Female: 29 (39%)	• Family caregivers are seen as respected partner in healthcare team ($n = 40/71$; 56%) • Family caregivers' preferences are taken into account in the decision-making process ($n = 39/69$; 57%) • Convinced that family caregivers' preferences are based on patient preferences (36/70; 53%) • Only supporting the active involvement of family caregivers if the effectiveness on patient outcomes has been demonstrated in scientific research (20/70; 29%) • Trust in competences and skills of family caregivers to adequately deliver fundamental care activities (44/68; 65%)
6. Redrafting the program	• Adding healthcare professionals' education to the program to train physicians and nurses on the core concepts of PFCC, and how to provide family education and coaching		

*Note:*PFCC, patient- and family centred care.

Table 2
Baseline characteristics of the respondents [*n* (%)].

Variable	Step 3:Focus group nurses (*n* = 23)	Step 4: Group discussion physicians (*n* = 63)	Step 5:Survey physicians (*n* = 73)
Sex			
Female	16 (69.57)	–	29 (39.73)
Male	7 (30.43)	–	45 (61.64)
Age, *Median* (range)	33.0 (23–59)	–	–
Education			
Vocational school education	10 (43.48)	–	–
Bachelor degree	13 (56.52)	–	–
Professional role			
Nurse	19 (82.61)	–	–
Senior nurse	1 (4.35)	–	–
Head nurse	2 (8.70)	–	–
Nurse specialist	1 (4.35)	–	–
Surgeon	–	–	19 (26.03)
Surgical residents	–	–	17 (23.29)
Trainees	–	–	10 (13.70)
MD/PhD-students[a]	–	–	25 (34.25)
Physician assistant	–	–	3 (4.11)
Unclear	–	–	1 (1.37)

Note: [a] MD/PhD-student: MD = Medical Doctor, they all finished their medical degree, and are now working on their PhD in the field of surgery.

Table 3
Fundamental care activities targeted for family involvement.

Target	Fundamental care activity	Mode	Postoperative outcome	Evidence base
Personal cleansing and dressing/ safety and prevention	Oral care	Twice a day	Pulmonary complications, pneumonia, surgical site infections	• I cough-program [10] • Perioperative oral hygiene in reduction of postoperative respiratory tract infections after elective thoracic surgery in adults [24]
Respiration	Coughing and deep breathing exercises	Three times a day	Pulmonary complications, pneumonia	• I cough-program [10] • Preoperative inspiratory muscle training for postoperative pulmonary complications in adults undergoing cardiac and major abdominal surgery [25]
Mobility	Early mobilisation Head-of-bed elevation	Minimum of three times a day	Pulmonary complications, pneumonia Delirium	• I cough-program [10] • CareWell in hospital program [26] • Hospital elder life program [27] • Enhanced recovery in gastrointestinal surgery: upper gastrointestinal surgery [28]
Eating and drinking	Encourage oral intake and companionship during meals; feeding assistance if needed	During meal times	Delirium Malnutrition	• Hospital elder life program [27] • Supportive interventions for enhancing dietary intake in malnourished or nutritionally at-risk adults [9]
Safety and prevention	Active orientation; specific time-, place-, and person-related information in the context of the present day, and daily discussions on actual items (e.g. news)	Minimum of three times a day	Delirium	• CareWell in hospital program [26] • Hospital elder life program [27]
Dignity/comfort/ privacy/ communication and education	Physical proximity; rooming-in; presence during medical rounds	Up to 24 h a day	Anxiety, depression, hopelessness, quality of life	• Policy to practice: increased family presence and the impact on patient- and family-centred care adoption [1]

information with family caregivers, because they were not always sure if family caregivers would use for some 'hidden agenda' they might have. While physicians realised families had to have an understanding of patients' condition to be able to assist in fundamental care, they were not sure about how they would actually determine patient's preference for which family members should have access to confidential patient information.

In total, 75 physicians (60%) completed the survey in step 5 (Appendix C). Most of the physicians saw family caregivers as a respected partner in healthcare team, and take their preferences into account in the decision-making process. The majority trusted the competences and skills of family caregivers to adequately deliver fundamental care activities. Almost 30% mentioned that they only support the active involvement of family caregivers if the effectiveness on patient outcomes has been demonstrated in scientific research.

Informed by the findings from the previous steps, in our synthesis (step 6) we added healthcare professionals' education to the program. The education seems to be necessary to train physicians and nurses on the core concepts of patient- and family centred care, and on how to provide family education and coaching.

3.2. Phase 2

Informed by the findings from Phase 1, results of the four guiding steps used in Phase 2 that underpin the program are described next. The various components of the logic model were developed from the body of work, and not individual steps in Phase 1. The family involvement program logic model is displayed in Fig. 1.

3.2.1. Step 1: confirm situation, intervention aim, and target population

3.2.1.1. Situation. PFCC was one of the core priorities within the [full name blinded for peer review] medical centre (a Joint

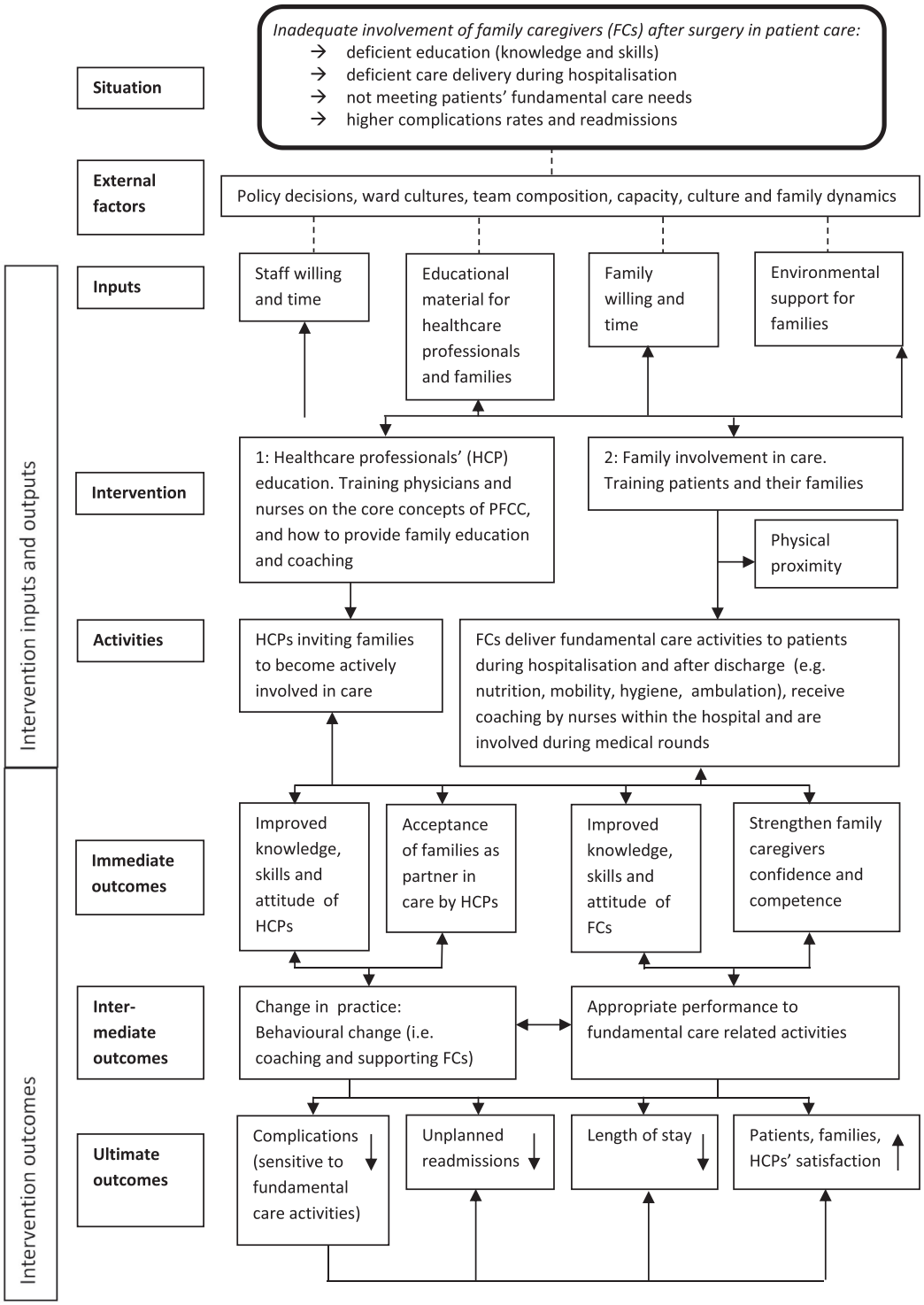

Fig. 1. Active involvement of family caregivers in surgical care logic model.

Commission International (JCI) accredited Organisation), further supported by the JCI quality standards for PFCC. They stated that 'hospitals must embed effective communication, cultural competence, and PFCC practices into the core activities of its system of care delivery—not considering them stand-alone initiatives—to truly meet the needs of the patients, families, and communities served' [29]. But in translating this to the surgical departments' policy, we found out families were not encouraged to actively participate in many aspects of care delivery, and they were not involved as partners in the healthcare team.

3.2.1.2. Intervention aim. The main aim of the intervention was to support the active involvement of family caregivers in fundamental care activities related to patients' physical care needs after surgery during hospitalisation. Achieving this aim will improve the knowledge, skills and the self-confidence in care delivery of family

caregivers, and subsequently has the potential to reduce readmissions related to postoperative complications sensitive to fundamental care activities.

3.2.1.3. Target population. The program will be offered to all adult patients undergoing elective surgery who have a suitable family caregiver who is up for training and care delivery. A potential family caregiver who meets any of the following criteria will be seen as suitable:

- Age 18 years or older;
- Able to be present during hospitalisation during the first 5 postoperative days on the nursing ward;
- Is nominated by the patient as a family caregiver;
- Is able to undertake care activities by themselves without support from healthcare professionals.

We targeted this population for several reasons. First, patients undergoing elective surgery frequently experience complications sensitive to fundamental care and unplanned readmissions [8,19]. Second, most have an expected hospital stay of at least five days which make adequate training and coaching of family caregivers possible. Finally, the majority of patients undergoing elective surgery experience difficulties in carrying out self-care activities in the postoperative phase and it is known that fundamental care activities are often deficient carried out in acute settings [3].

3.2.2. Step 2: document expected outcomes and outputs of the intervention

3.2.2.1. Outcomes. The ultimate outcomes of the family involvement program are a reduction of postoperative complications (i.e. potentially preventable complications sensitive to fundamental care activities), as well as a reduction of unplanned hospital readmissions related to these complications, shorter length of hospital stay, and improved patient- family- and healthcare professional's satisfaction. To achieve these outcomes, it is essential that first the intermediate outcomes are reached. Therefore, healthcare practice needs to become more family-centred, which involves healthcare professionals (i.e. physicians and nurses) changing their behaviours to facilitate active involvement of family caregivers. Furthermore, family caregivers should have opportunities to deliver fundamental care in an appropriate way as incorrect execution can negatively influence patient outcomes. To facilitate these intermediate outcomes immediate outcomes were defined. First, knowledge, skills and attitudes of healthcare professionals should be optimised, and healthcare professionals need to accept family caregivers as a respected partner in the care team. Second, family caregivers need to have the knowledge, skills and willingness to undertake fundamental care activities. Besides this, they also need to feel confidence about care delivery about themselves.

3.2.2.2. Outputs. The desired outputs consist of activities related to the main components of the intervention, namely education and the active involvement of family caregivers. The first defined output is to train physicians and nurses to provide FC education and coaching. The second focuses on the training of family caregivers to support them in the delivery of fundamental care to their loved ones during hospitalisation and after discharge if still needed (i.e. early mobilisation, encouraging oral intake, breathing exercises, oral care and supporting active orientation).

3.2.3. Step 3: identify and describe assumptions, external factors and inputs

3.2.3.1. Assumptions. Based on Phase 1 findings, we made three assumptions. First, optimising fundamental care activities given by family caregivers after surgery leads to better patient outcomes that are sensitive to fundamental care activities. Second, family caregivers are willing to receive training and to participate in delivering fundamental care activities. Third, healthcare professionals are willing to encourage and coach family caregivers during hospitalisation.

3.2.3.2. External factors. External factors that should be considered and may influence the implementation and the outcomes of the intervention were related to hospital policies regarding family involvement in care, ward cultures, team composition, the capacity to learn and coach family caregivers, and family dynamics.

3.2.3.3. Inputs. The inputs of the family involvement program are (1) willingness of staff and family caregivers; (2) adequate educational material to support nurses, physicians and family caregivers; (3) environmental support (e.g. a comfortable room with an extra bed and meals for the family caregiver).

3.2.4. Step 4: confirm intervention components

The family involvement program is a multi-component intervention, comprised two main components: (1) training and coaching of physicians and nurses; (2) the active involvement of family caregivers in fundamental care activities. The main components, barriers, tasks and persons in charge are outlined in Table 4.

The training and coaching of physicians and nurses is mainly focused on the four core concept of PFCC: (1) dignity and respect; (2) information sharing; (3) participation; and (4) collaboration [30].

Several tasks to encourage family caregivers to provide fundamental care activities were planned (Table 4). While we used the Fundamentals of Care (FOC) framework to select possible tasks which family members can perform if they want to participate, these tasks cover all dimensions (i.e. physical, relational and psychosocial) (Tables 3 and 4) [31]. A minimum set of fundamental care activities known to have an effect on postoperative complications were selected (see Table 3).

Optional care activities for the family caregiver to participate in included wound dressing, taking care of abdominal drains or nasogastric tubes, and administration of medication. It was planned that a qualified nurse would supervise all activities until family caregivers were competent to carry out the activities on their own.

4. Discussion

This two-phased study, using both an empirical approach to initially develop the family involvement program and then a logic model to refine it, provides guidance on how to actively involve family caregivers in fundamental care activities in post-surgical care. We linked a quality improvement project with an evidence-based approach. These two approaches have similar overall goals, but focus on different parts of the problem [32]. A quality improvement approach is focusing on ‘doing the things right [32], i.e. how can we make it possible that family caregivers are stimulated to be actively involved in fundamental care activities. Whereas the evidence-based approach was used to focus more on ‘doing the right things’ based on the best available evidence [32]. Therefore, we selected fundamental care activities known to be effective in reducing some postoperative complications, and explored healthcare professionals' preferences and beliefs in Phase 1. Based on Phase 1 findings, we developed the logic model underlying the family involvement program in Phase 2.

To enhance a more patient- and family centred approach within hospitals, we propose the logic model as a useful framework for interdisciplinary teams to engage family caregivers as respected

Table 4
Main components of the program.

Component	Targeted barrier	Tasks	In charge
Training and coaching of healthcare professionals	Physicians and nurses' knowledge, skills, attitude and acceptance of families as partner in care towards a PFCC approach	- Explain the purpose, benefits, and goals of the involvement of family caregivers and the core concepts of PFCC - Explain the difference between passive and active involvement of family caregivers - Discuss facilitators and barriers regarding the involvement of family caregivers on surgical wards - Additional attention to support the nursing staff to integrate coaching competencies in clinical practice to facilitate the active involvement of family caregivers	Educators
Family involvement in fundamental care activities	Family caregivers' knowledge, skills, attitude, confidence, and competence towards a PFCC approach	- Invite family caregivers to participate in fundamental care activities - Give information about fundamental care activities - Set shared goals with patient and family caregivers - Train family caregivers to deliver fundamental care activities to patients during hospitalisation - Physical proximity of family caregivers/patients (e.g. rooming-in for at least 8 h a day)	Nurses/ family caregiver
		- Invite family caregivers by medical rounds - Mutual agreement between healthcare professionals and family caregivers	Physicians and nurses

Note: PFCC, patient- and family centred care.

and active partners in care.

An obstacle we faced in developing the intervention was the lack of rigorous evidence regarding family involvement in hospitalised adults [21,22]. Furthermore, despite good will, practices do not always align with a more family-centred approach [33]. Involving families as respected partners seems to be simple, but is not easy. For example healthcare professionals miss opportunities to share information with patients and family members, and do not regularly check if their information given was understood or meaningful for them [34]. This constrained families from participation in care processes [34]. In our project, we focused on active family participation in fundamental care activities to reduce the number of postoperative complications, and the number of unplanned hospital readmissions related to these complications. However, other more general interventions to stimulate patient- and family participation, and optimise patient outcomes may be useful too (e.g. participation in bedside handover, and medication communication [35,36].

Besides the implementation challenges, the burden on FCs is another emerging obstacle. Family caregivers are confronted with a new range of tasks and responsibilities related to the patients' need [37], at a stressful time. Furthermore, some healthcare professionals may see this intervention as a justification to lower numbers of nursing staff and to save money, or an abduction of nurses' responsibilities [38,39]. Yet, if healthcare leaders condoned this rationing of nursing staff, it may directly affects the patient outcomes in a negative way as nurse staffing is associated with the quality of care [40]. Finally, in creating this intervention, we focused mainly on physicians and nurses, with special attention to the important role of nurses, instead of other healthcare professionals. This because approximately 70% of all in-hospital care is delivered by nurses [41], and they are therefore in an ideal position to actively involve and coach family caregivers. Clearly, other healthcare professionals such as physiotherapists, dieticians, and social workers should also contribute to the active involvement of family members, and be preferably involved in the drafting of such a program.

In addition to the limitations mentioned thus far, some others include the context and theoretical underpinnings of the program. That is, the family involvement program was designed for use in two Dutch surgical units that employed staff willing to adopt a more family centred approach to their care. It is possible this program may not be appropriate in other surgical settings or with less willing staff, however, the process we used, and some of the program components may be feasible in other settings. Second, there are a plethora of theories that can be used to underpin both family centred care interventions and their implementation. Modifying or tailoring our program to varying contexts will likely be required. Additionally, we used a range of data collection methods to develop the program, and each method has his limitations. A narrative review was used to get insight in the existing evidence in a timely fashion; a comprehensive systematic review was not undertaken. As a result, we may have missed some relevant information. Regarding the focus groups, there is a possibility that some participants were overwhelmed and dominated by other participants, and therefore did not feel confident enough to give their own opinion. This may particularly occurred in the group of physicians, as the group was large, which made it more difficult for the moderator to involve everyone. To overcome this limitation, we sent out an additional survey and achieved a high response rate. Therefore, we consider our results to be robust. A very important limitation of our project is that we did not actively involve family caregivers in the design of the program, but used in-direct family input by using work of other researchers. Patient and public involvement in service delivery, quality improvement and research is relatively new in The Netherlands, and thus it is not an entrenched in our culture. Although we did not yet create a full partnership with patient- and family caregivers in the development of this program [42], we recognise the need for an extensive evaluation of this program in which we need to encourage patients and family caregivers to share their experiences and input for further refinement of the program. Additionally, given our learnings from this project, we will aim to involve them in planning for the evaluation.

The focus towards a more patient- and family centred environment has consequences to hospital policies regarding family involvement in care, ward cultures, team composition, the capacity to learn and coach family caregivers, and family dynamics. Although we developed the family involvement program with an interdisciplinary team, it is mainly focusing on direct nursing care because nurses traditionally carry out or support most of the fundamental care activities in-hospital.

5. Conclusion

In conclusion, while PFCC should be the norm, this is not always the case. In this paper, we demonstrate how we aimed to change

our practice to an environment in which family caregivers were stimulated to be actively involved in postoperative care on surgical wards, and how we took these different factors into account. We undertook a formal process to create a theory and evidence informed program to involve family caregivers actively in hospital care in which nurses play a central role as they deliver the largest amount of in-hospital care. The family involvement program using logic modelling presented here may help others, and especially nurses, to make an earnest attempt toward achieving this goal. It may provide a solid basis for healthcare professionals and policy makers to implement the program in their own setting, while recognising that research on the effectiveness of this model is still needed. Therefore, we are working on an evaluation of our quality improvement work, and plan to undertake a randomised clinical trial afterwards to obtain rigorous evidence of effectiveness.

Conflicts of interest

The authors declare no conflict of interest.

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Authors contribution

All authors made a substantial contribution to this work and gave approval for submission. In more detail: Anne Maria Eskes drafted the manuscript. All authors contributed to the design of this project and were involved in the analysis of the results. Anne Marthe Schreuder, Hester Vermeulen, Els Jacqueline Maria Nieveen van Dijkum and Wendy Chaboyer commented on several drafts of the manuscript. Lastly, Els Jacqueline Maria Nieveen van Dijkum and Wendy Chaboyer supervised the work.

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Appendices. Supplementary data

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Clinical and Economic Outcomes of Patients Undergoing Guideline-Directed Management of Pancreatic Cysts

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INTRODUCTION: **Numerous guidelines exist for the management of pancreatic cysts. We sought to compare the guideline-directed management strategies for pancreatic cysts by comparing 2 approaches (2017 International Consensus Guidelines and 2015 American Gastroenterological Association Guidelines) that differ significantly in their thresholds for imaging, surveillance, and surgery.**

METHODS: **We developed a Monte Carlo model to evaluate the outcomes for a cohort of 10,000 patients managed per each guideline. The primary outcome was mortality related to pancreatic cyst management. Secondary outcomes included all-cause mortality, missed cancers, number of surgeries, number of imaging studies, cumulative cost, and quality-adjusted life years.**

RESULTS: **Deaths because of pancreatic cyst management and quality-adjusted life years were similar in both guidelines at a significantly higher cost of $3.6 million per additional cancer detected in the Consensus Guidelines. Deaths from "unrelated" causes (1,422) vastly outnumbered deaths related to pancreatic cysts (125). Secondary outcomes included more missed cancers in the American Gastroenterological Association guideline (71 vs 49), more surgeries and imaging studies in the Consensus guideline (711 vs 163; 116,997 vs 68,912), and higher cost in the Consensus guideline ($168.3 million vs $89.4 million). As the rate of malignant transformation increases, a more-intensive guideline resulted in fewer deaths related to pancreatic cyst management.**

DISCUSSION: **Our study demonstrates trade-offs between more- and less-intensive management strategies for pancreatic cysts. Although deaths related to pancreatic cyst management were similar in each strategy, fewer missed cancers in the more-intensive surveillance strategy is offset by a greater number of surgical deaths and higher cost. In conclusion, our study identifies that if the rate malignant transformation of pancreatic cysts is low (0.12% annually), a less-intensive guideline will result in similar deaths to a more-intensive guideline at a much lower cost.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B564,http://links.lww.com/AJG/B565, http://links.lww.com/AJG/B569, http://links.lww.com/AJG/B570

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INTRODUCTION

Pancreatic cysts are frequently found incidentally at cross-sectional imaging performed for unrelated symptoms, identifying a large population of asymptomatic lesions with an uncertain natural history (1). Because of the small but quantifiable risk of malignant transformation of pancreatic cystic neoplasms (2), surveillance and further investigation, including potentially invasive procedures, are often recommended. Surveillance recommendations are based on limited data and driven mostly by expert opinion, particularly given the lack of prospective data on the risk of malignant transformation. Numerous guidelines have been published regarding the management of pancreatic cystic lesions and vary significantly in the intensity of surveillance and management recommendations (3–7).

Because there is no currently known way to predict malignant transformation of pancreatic cysts, guidelines have relied on imaging characteristics to drive recommendations for further surveillance, invasive testing, or surgical management. The differences in more- vs less-intensive surveillance and management recommendations remain controversial. We sought to compare the guideline-directed management strategies for pancreatic cysts between 2 approaches that differ significantly in their thresholds for imaging, surveillance, and surgery by quantifying the outcomes of each approach. We specifically compared the 2015 American

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Gastroenterological Association (AGA) Guidelines (4) with the 2017 International Consensus Guidelines (7) using simulated outcomes of a model-based cohort of patients with pancreatic cysts.

METHODS

Simulation model

We developed a Monte Carlo simulation model to evaluate outcomes for the management of pancreatic cysts excluding cysts that were either overtly malignant or benign on imaging. The cohort was modeled based on pancreatic cysts commonly seen in clinical practice that would undergo longitudinal surveillance. The patient-level simulation model was used to compare the Consensus Guidelines (7) and the AGA Guidelines (4) for imaging surveillance, cancer outcomes, surgical outcomes, mortality, costs, and quality-adjusted life years (QALYs). We simulated 10,000 individuals progressing through each guideline with paired sample runs to minimize variation (8). We also ran the simulation independent of guideline-directed management to identify the natural history outcomes for the cohort. Each simulation was replicated 30 times to account for stochastic parameters. We used the base-case starting age of 55 years for all patients, and 50% of patients were men. Patients were followed for 15 years at 6-month intervals to assess outcomes. The primary outcome was mortality related to pancreas cyst management (cancer-related death and surgical deaths). Secondary outcomes included all-cause mortality, missed cancers (patients who had malignant transformation of pancreatic cysts not identified during guideline-directed management), number of surgeries, number of imaging studies, cumulative cost, and QALYs.

Cohort and model inputs

As with all models, the base-case assumptions play an integral role in the overall utility of the model. When possible, we used the data-driven estimates for factors such as growth rate, size of cyst, and mortality related to surgery. We made assumptions based on expert opinion on various factors to develop a base-case model that includes a breadth of cyst sizes, growth characteristics, high-risk features, and heterogeneity that one would expect in a large population (Table 1). Costs were based on Medicare reimbursement estimates. Two key inputs that are worth further discussion are the rate of malignant transformation of cysts and surgical mortality.

The rate of malignant transformation for pancreatic cysts is not well known, given the lack of natural history studies. We estimated the base rate of malignant transformation (to high grade dysplasia or cancer) for the cohort of individuals in our study (aged 55–70 years) to be 0.12% per year and also performed a sensitivity analysis for the rate of malignant transformation. This rate of malignant transformation is on the low end of the 95% confidence interval in the recent technical review for all individuals with pancreatic cysts (2). However, our model only assessed a cohort between ages 55–70 years; thus, the overall rate of malignant progression will be lower than an estimate for "all comers" for this younger population.

Furthermore, the Surveillance, Epidemiology, and End Results database (https://seer.cancer.gov/statfacts/html/pancreas.html) estimates that there are 56,770 new cases of pancreatic cancer in 2019 with 37% of them from individuals between 55 and 70 years (our cohort age range), suggesting a total of 315,073 cases of pancreatic cancer over 15 years for this age group. If we assume a "worst case scenario" that 50% of these pancreatic cancer cases come from pancreatic cysts and 60 million persons in the United States aged 55–70 years with 15% having pancreatic cysts, then the risk of malignant transformation to result in 157,500 cases of pancreatic cancer is estimated to be 0.12% per year. If we used the malignant transformation estimate of 0.24% annually from the recently published technical review, this would result in all cases of pancreatic cancers in this age group to be from pancreatic cysts which is not realistic nor true. Based on this calculation, a rate of malignant transformation of 0.12% seems to be a reasonable baseline rate. Although some will consider this to be too low (supporting a higher transformation rate as presented in the AGA Technical review), others will consider this to be too high (50% of pancreatic cancers arising from pancreatic cysts seems inconsistent with clinical experience).

Overall mortality for pancreatic surgery for pancreatic cysts based on 74 studies in a recent review was 2.1%; however, there is likely publication bias suggesting that this overall mortality is probably underestimated (2). A Surveillance, Epidemiology, and End Results database study estimated mortality for pancreatic cyst surgery to be 6.6% (9). For our model, we chose a conservative 2.5% overall mortality (4% for Whipple procedure and 1% for distal pancreatectomy) associated with pancreatic surgery. Sensitivity analysis is also performed on this variable.

QALYs were estimated by using a base utility value for the patient depending on the disease state (before cancer, early cancer, late cancer, or postoperative) with a one-time disutility subtracted for each endoscopic ultrasound (EUS) procedure and surgery (Table 1). We did not include disutilities for potential long-term complications (e.g., diabetes mellitus) because our model did not incorporate such complications.

Guideline-directed management

Figure 1 diagrams the modeled Consensus and AGA Guidelines management algorithms.

It is important to recognize that the Consensus Guidelines, although written for intraductal papillary mucinous neoplasms, are used in clinical practice for lesions with this presumptive diagnosis, recognizing that imaging and EUS even with fine needle aspiration may misclassify cysts. Our model recognizes this consideration, given our goal to provide a "real-word" assessment of current approaches. Therefore, we have applied the Consensus Guidelines to the cohort of individuals with pancreatic cysts undergoing longitudinal surveillance. For the Consensus Guidelines, we assume that all individuals with cysts >3.5 cm would undergo surgical resection that is approximately 50% of those who had cysts >3 cm. Simplifications were made to both guidelines, given the patient factors we were able to model. For example, in the Consensus Guidelines, we omit the first high-risk stigmata "obstructive jaundice in a patient with cystic lesion of the head of the pancreas" because we do not model jaundice, and this is extremely rare in pancreatic cysts.

We have provided the following interpretation of the AGA Guidelines in our model regarding the presence of a solid component and when to stop surveillance. Specifically, we include the solid component (mural nodule) as an indication for EUS even if this was the only high-risk feature. We based our decision on the AGA guideline statement "Some clinicians and patients may elect to evaluate the cyst with just 1 high-risk feature present, such as a solid component, if this is particularly prominent (4)." In addition, regarding stopping the surveillance, we stopped only if there was <3 mm cyst growth over a 5-year cycle. This decision is an interpretation of "significant change" and supported by the AGA

Table 1. Summary of model inputs for the simulation model and sensitivity analysis ranges

Input	Value	Citation
Starting age	Base case: 55; *sensitivity range: (50–60)*	Assumption
Percent male	50%	Noone et al. (22)
Percent in head of pancreas	50%	Scheiman et al. (2)
Probability of death from other causes	Age- and sex-dependent values	CDC mortality tables
Percentage of patients progressing to cancer over 15-yr horizon	Base case: 1.75% over 15 yr (0.12% annually) *Sensitivity range: [1%–3.5%]*	Scheiman et al. (2)
Rate of death from cancer	5% within 3 yr; *Sensitivity range: [2.5%–10%]* 20% 3–6 yr; *Sensitivity range: [10%–40%]* 90% after 6 yr	Assumption
Initial cyst size	3–25 mm, 70% were ≤10 mm	Assumption
Benign growth rate	50%: Minimal linear growth, UNIF(0,0.04) mm per 6 mo 50%: Moderate linear growth, UNIF(0.04,0.06) mm per 6 mo *Sensitivity range: ±10%*	Kang et al. (23), assumption
Malignant growth rate	30%: Slow linear growth, UNIF(0.15,0.25) mm per 6 mo 70%: Fast linear growth, UNIF(1.7,2.3) mm per 6 mo *Sensitivity range: ±10%*	Kang et al. (23), assumption
Presence of solid component	Can be present up to 1 yr before cyst is defined as malignant Solid components appear in 75% of patients with cancer; *Sensitivity range: [50%–85%]* Solid components appear in 1% of patients without cancer; *Sensitivity range: [0.5%–5%]*	Assumption
Pancreatic duct	Dilation occurs in 15% of patients Increase of 0.25 mm per 6 mo Starts growing up to 3 yr before malignancy	Assumption
Consensus guideline size surgery cutoff	Base case: 3.5 cm	Assumption
Surgical mortality	Whipple procedure: 4%; *Sensitivity range: [2%–6.6%]* Distal pancreatectomy: 1%; *Sensitivity range: [0.5%–2.5%]*	Kneuertz et al. (24), assumption
Imaging costs	MRI: $1,200, EUS: $1,500; *Sensitivity range: ±20%*	Das et al. (25)
Surgical costs	Whipple procedure: $40,000 Distal pancreatectomy: $25,000 *Sensitivity range: ±20%*	Das et al., O'Neill et al. (25,26)
Utility values	1.0 before cancer 0.9 early cancer, 0.5 late cancer (after 1 yr of cancer) 0.95 postoperative 0.0048 disutility for each EUS 0.27 one-time disutility for surgery	Das et al., Gregor et al., Huang et al. (12,27,28), assumption

CDC, Center for Disease Control and Prevention; EUS, endoscopic ultrasound; MRI, magnetic resonance imaging; UNIF, uniform distribution.
Ranges used in sensitivity analysis are presented in italics.

Technical Review (p. 835) (2) that states "further surveillance beyond 4 years may be warranted, particularly for presumed mucinous lesions in fit patients younger than 70 years of age and in patients who may have an equivocal change in cyst appearance and/or size." We interpreted growth of at least 3 mm to be an equivocal change in size in our patient cohort who are all younger than 70 years.

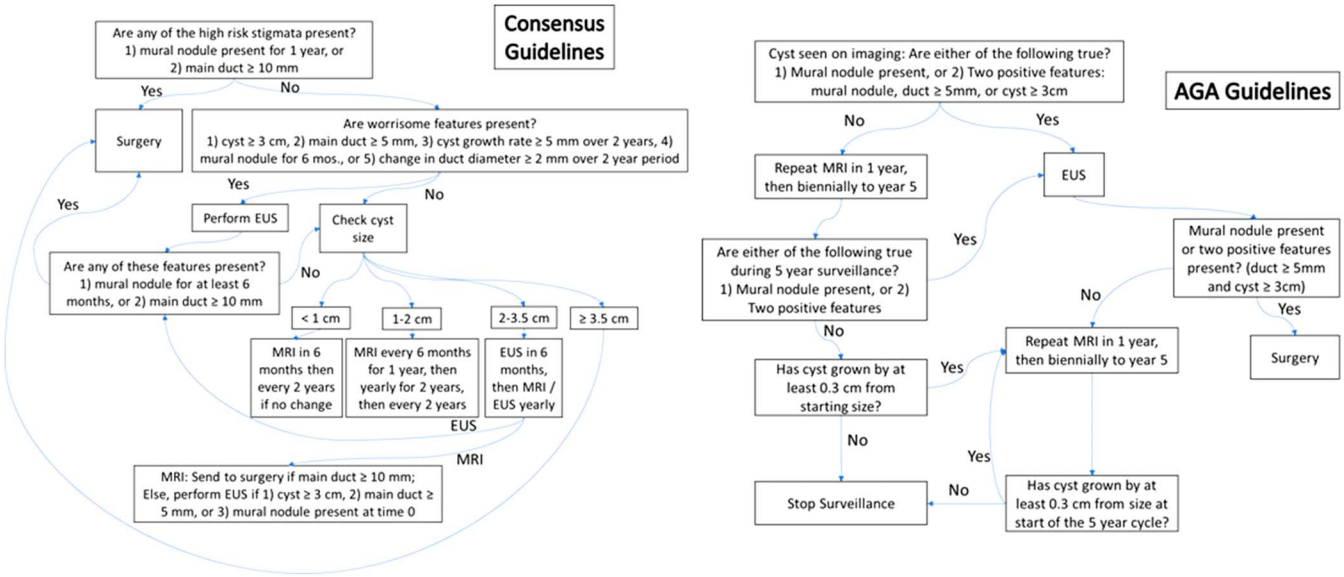

Figure 1. Depiction of how the AGA and consensus guidelines were applied in the model. AGA, American Gastroenterological Association; EUS, endoscopic ultrasound.

Sensitivity analysis

We performed sensitivity analysis to determine the impact of different assumptions on the model outcomes as per Table 1. The starting age of the cohort was also modeled for ages 50 and 60 years. The rate of malignant transformation was tested between 0.07% and 0.24% with the base case at 0.12%. We also varied the surgical mortality rates because these values may vary widely by institution. Tornado diagrams were generated to display differences in deaths related to pancreatic cysts (see Figure 5, Supplementary Digital Content 1, http://links.lww.com/AJG/B564) and costs (see Figure 6, Supplementary Digital Content 2, http://links.lww.com/AJG/B565) from the base case when varying inputs over the sensitivity range, holding all other variables at their base-case values. These figures allow for relative comparison of the effect of changes in the inputs.

RESULTS

Natural history outcomes

During the 15-year follow-up period of the 10,000 patients modeled in the cohort (with 30 replications), an average of 1,422 patients (95% confidence interval: 1,411–1,433) died of "unrelated" causes and an average of 125 patients (121–129) died of pancreatic cancer. Pancreatic cancers developed in 172 (167–176) patients. The pancreatic cysts had an average starting size of 9.26 mm (9.24 mm–9.29 mm). At the end of the 15-year horizon, 6% of patients had cysts <1 cm, 47% had cysts 1–2 cm, 37% had cysts 2–3 cm, and 10% had cysts ≥3 cm. Of the patients with cysts ≥3 cm, 12.4% were malignant and 50.1% had cysts ≥3.5 cm. When the cohort of 10,000 persons was managed according to the AGA Guideline, 40% of the cohort stopped surveillance for pancreatic cysts at 5 years.

Death, cancers diagnosed, and surgeries

Deaths from pancreatic cyst management were similar for each guideline (AGA: 50.8 deaths and Consensus: 50.6 deaths), as per Table 2. In Figure 2, we compare the mortality from cyst management for each guideline, broken out by cancer deaths and deaths from surgery. The comparison is provided for the base case and with varied rates of malignant conversion. The Consensus Guidelines always result in a larger number of surgical deaths, but the AGA Guidelines has more deaths from cancer because of a greater number of missed cancers compared with the Consensus Guidelines. Table 2 presents the base-case results for each guideline for cancers diagnosed, surgeries, deaths from cyst management and other causes, number of imaging studies (MRI and EUS), and costs of surveillance. Following the Consensus Guidelines resulted in an average of 711 patients (700–722) undergoing surgery, of whom 17.8% had cancer. The AGA Guidelines led to fewer operations with an average of 163 patients (158–168) and 61.5% of these having cancer.

Imaging studies, cost, and QALYs

Patients managed according to the Consensus Guidelines had a significantly higher average number of imaging studies compared with patients followed according to the AGA Guidelines (11.7 vs 6.9 per person). The cost of using the AGA Guideline in the cohort over a 15-year period was estimated to be $89.4 million, at an average cost of $8,938 per patient ($8,915–$8,960), considering imaging and surgery costs. For the Consensus Guidelines, the cost was $168.3 million with an average cost of $16,825 per patient ($16,783–$16,868). By using the Consensus Guidelines, there was a cost of $3.6 million per additional cancer identified compared with the AGA Guideline. Expected QALYs were 13.93 years for the AGA Guideline (13.92–13.94) and 13.90 years for the Consensus Guidelines (13.89–13.91).

Sensitivity analysis

As the rate of malignant transformation of pancreatic cysts increases above 2% for the 15-year horizon, fewer deaths were noted in the more-intensive Consensus Guidelines. Figure 3 depicts the death outcomes and costs related to cysts in comparing the 2 guidelines varying the rate of malignant transformation. Figure 5 (see Supplementary Digital Content 1, http://links.lww.com/AJG/B564) presents a tornado diagram to show how

Table 2. Average model outcomes and 95% confidence intervals for the AGA and Consensus Guidelines for cancers diagnosed, surgeries, deaths, imaging studies, QALYs, and costs

Outcome	AGA guideline	Consensus guideline
Cancers per 10,000 persons	171.5 (166.8–176.3)	
Cancers diagnosed per guideline	100.2 (96.8–103.6)	122.4 (118.4–126.4)
Cancers not identified during surveillance	71.3 (68.7–73.9)	49.1 (46.8–51.5)
Missed cancers that began after year 5	37.4 (35.4–39.3)	18.6 (17.2–20.1)
Percentage of cancers diagnosed	58.4%	71.4%
Surgeries (total)	163.0 (158.2–167.7)	711.2 (700.4–721.9)
Patients with cancer	100.2 (96.8–103.6)	126.3 (122.1–130.5)
Patients without cancer	62.7 (59.3–66.2)	584.9 (576.2–593.5)
Deaths		
Total from cyst management	50.8 (48.6–52.9)	50.6 (48.3–53.0)
Cancer deaths	47.3 (45.1–49.5)	32.1 (30.2–34.0)
Surgery deaths	3.5 (2.8–4.1)	18.5 (17.0–20.1)
Imaging studies		
Total for cohort, MRI and EUS	68,912 (68,780–69,044)	116,997 (116,886–117,108)
Imaging studies per patient	6.89 (6.88–6.90)	11.70 (11.69–11.71)
QALYs	13.93 (13.92–13.94)	13.90 (13.89–13.91)
Cost of surveillance for 10,000-person cohort	$89.4 million	$168.3 million
Cost per patient	$8,938 ($8,915–$8,961)	$16,825 ($16,783–$16,868)
Cost per cancer identified	$898,760 ($868,521–$928,999)	$1,384,896 ($1,339,595–$1,430,197)
Cost per additional cancer identified (CG only)		$3.6 million

AGA, American Gastroenterological Association; CG, Consensus Guidelines; EUS, endoscopic ultrasound; QALY, quality-adjusted life year.

pancreatic cyst deaths for each guideline are affected when we vary key inputs over the sensitivity ranges in Table 1. Pancreatic cyst deaths are most affected by the assumed cancer rate and the percentage of cancer patients with nodules. Figure 6 (see Supplementary Digital Content 2, http://links.lww.com/AJG/B565) presents a tornado diagram for cost per patient. Costs are grossly affected by changes in the assumed costs of imaging and surgery, with lesser changes for other variables. Complete results for the sensitivity analysis are shown in Supplementary Tables 1 and 2 (see Supplementary Digital Content 3 and 4, http://links.lww.com/AJG/B569 and http://links.lww.com/AJG/B570).

Four patient outcomes: an illustration of trade-offs

The outcomes for 4 patients followed according to each guideline in the model are presented in Figure 4. The first 2 cases represent similar health outcomes for the patient, regardless of the guideline applied. In case A, the patient develops cancer at the age of 58 years, and the cancer was diagnosed at an early stage by each guideline and was successfully treated by surgery. This patient benefited from surveillance under both strategies with a similar number of imaging studies. In case B, the patient did not develop cancer before death from other causes occurred. The AGA guideline called for surveillance to be stopped after 5 years during which 4 imaging studies were performed. The Consensus Guidelines continued until the patient's death at the age of 66 years, with 12 imaging studies performed.

The final 2 cases represent situations where following one of the guidelines resulted in harm to the patient, either through undetected cancer or surgical death for a false positive. In case C, the patient stopped surveillance at the age of 60 years according to the AGA Guidelines, and cancer developed at the age of 63 years resulting in death from cancer at the age of 67 years. When the same patient followed the Consensus Guidelines, the cancer was detected and treated successfully. Finally, in case D, the patient did not have cancer develop over the 15-year horizon. Given cyst growth, the AGA Guidelines continued surveillance for the entire 15 years with 9 imaging studies performed. The Consensus Guidelines recommended surgery at the age of 63 years, and a surgical complication led to the patient's death. These 4 cases demonstrate potential trade-offs between a more- and less-intensive management protocol.

DISCUSSION

We have explicitly identified numerous trade-offs that exist between more-intensive and less-intensive management strategies for pancreatic cysts using a modeling approach, both of which had similar deaths related to pancreatic cyst management. In particular, the less-intensive AGA Guidelines had more missed cancers but fewer deaths related to surgery, whereas the more-intensive International Consensus Guidelines had fewer missed cancers but more deaths related to surgery. Although our inclination as physicians is "not to miss"

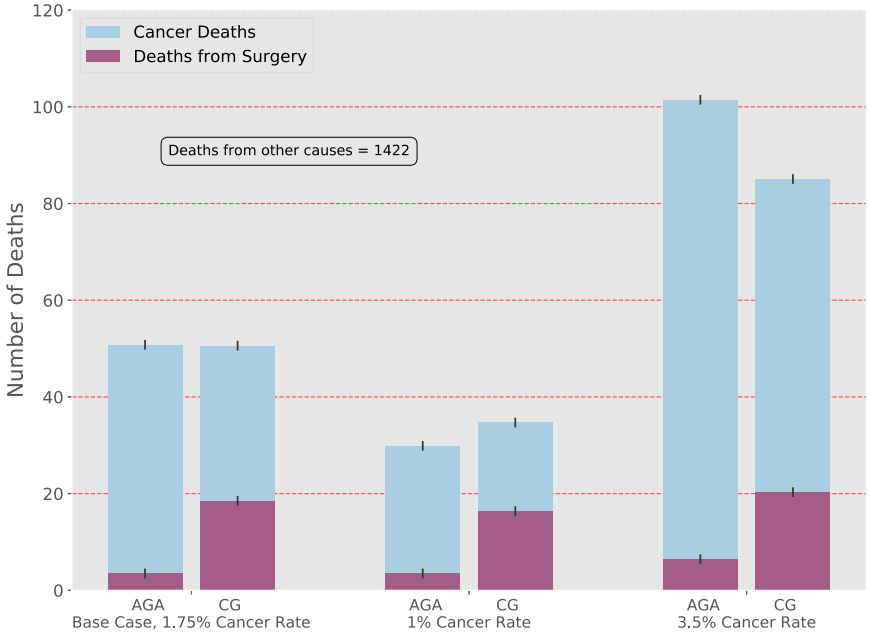

Figure 2. Comparison of AGA and CG for the base case and changes to the cohort for the assumed rate of cancer over the 15-year horizon (these rates correspond to annual cancer rates of 0.07% and 0.24%). The y-axis presents the number of deaths due to cancer and surgery. AGA, American Gastroenterological Association; CG, Consensus Guidelines.

a potentially curative lesion, we also have to consider the potential consequences of aggressive surveillance and treatment which may result in harm including mortality. Furthermore, the more-intensive strategy had significantly higher costs spending nearly $8,000 more per patient when extremely modest imaging and surgical costs are applied. The more-intensive surveillance strategy costs an additional $3.6 million per additional cancer detected, a cost which is unlikely sustainable when applied to the US population. Finally, we demonstrate that the most deaths in the cohort population are unrelated to pancreatic cyst management (1,422 vs 125) as has been shown elsewhere (10).

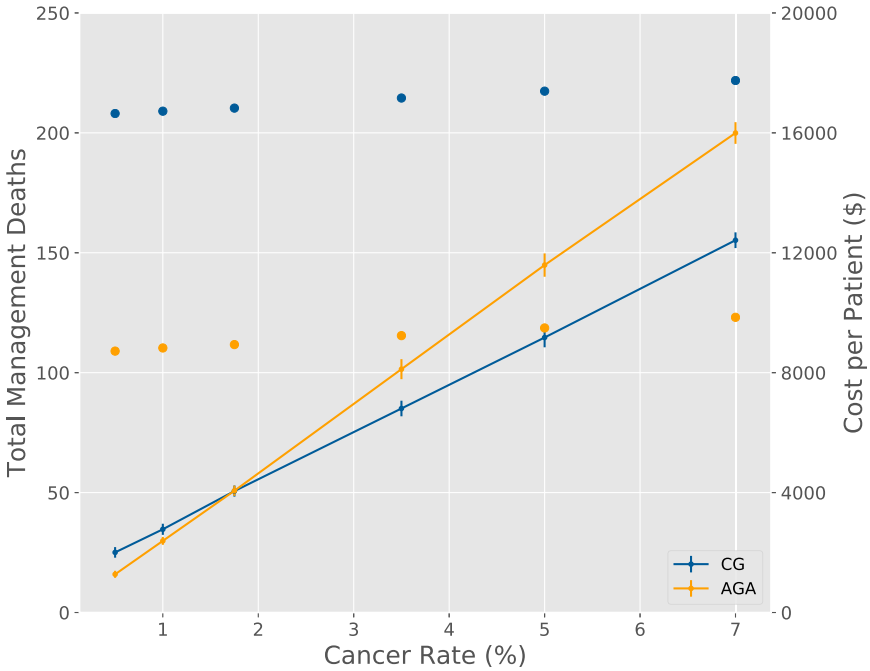

Figure 3. Comparison of AGA and CG total deaths due to cyst management (cancer deaths and surgery deaths) when the cancer rate is varied (these rates correspond to annual cancer rates between 0.035% and 0.48%). Error bars represent the 95% confidence intervals for total management deaths. The dots depict cost per patient for each cancer rate, corresponding to the costs on right y-axis. AGA, American Gastroenterological Association; CG, Consensus Guidelines.

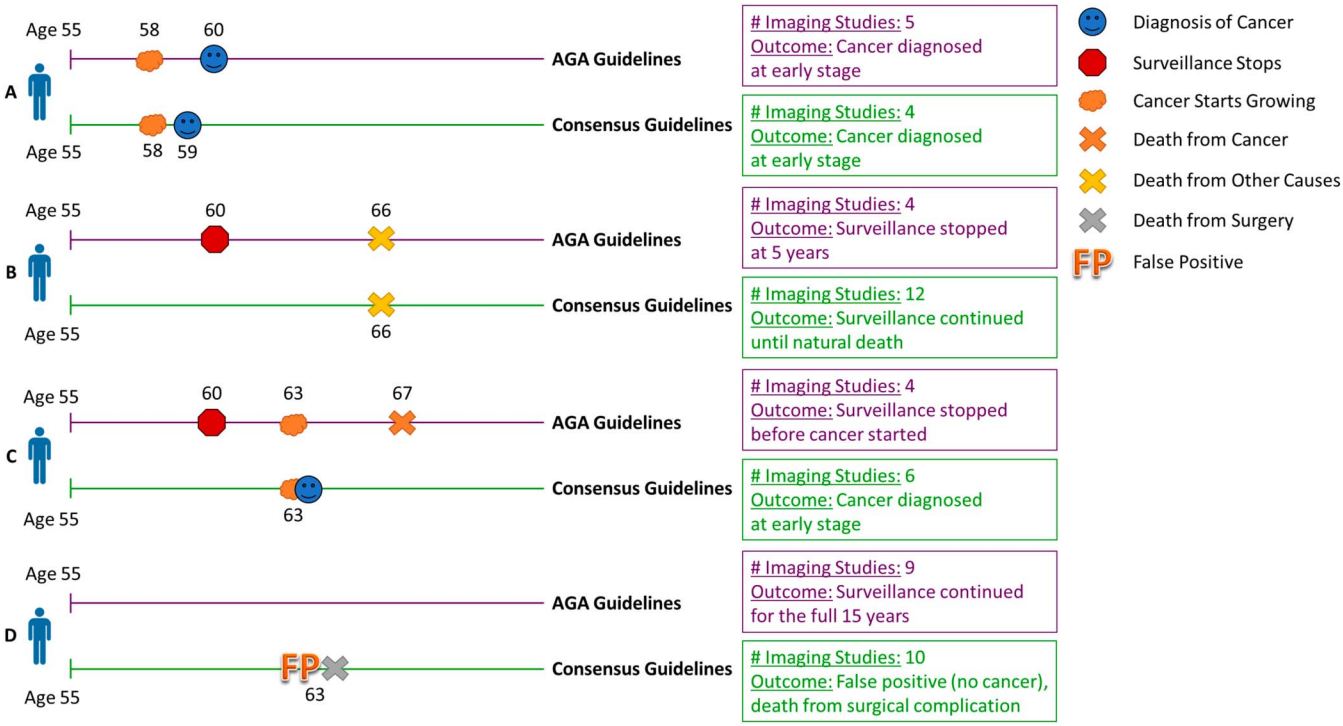

Figure 4. Simulated patient trajectories showing imaging and health outcomes according to the AGA and consensus guidelines. AGA, American Gastroenterological Association.

Several studies have attempted to model the complex nature of pancreatic cysts (11,12), although none have compared various guidelines. One study modeled the cost-effectiveness of a conservative approach (watch and wait), an aggressive approach (surgery for all surgical candidates), and a risk-stratification approach based on EUS and concluded that a risk-stratification approach was the most cost-effective (12). Another study modeled 4 iterations of aggressiveness (from "do nothing" to initial pancreaticoduodenectomy) for cyst surveillance and treatment. Their results suggested that best management depended on clinical features and patients' value for overall survival vs quality-adjusted survival (11), suggesting a trade-off between surgery and surveillance, including quality of life after surgery to include morbidity. Both of these studies differ significantly from our study because they started with a broad treatment strategy and not guideline-directed management as is used in clinical practice. In our study, we started with a pancreatic cyst cohort population (i.e., our cohort model of 10,000 persons) and moved each individual through 2 commonly used guidelines for the management of pancreatic cysts. By doing so, we are able to more accurately describe clinical and economic outcomes of the typical clinical care of individuals with pancreatic cysts.

One major input into our model is the rate of malignant transformation of pancreatic cysts. There are few data that accurately predict the rate of malignant transformation particularly because most studies are cohort studies of high-risk populations often referred for surgery or endoscopic ultrasound. We chose to use a rate of malignant transformation of 0.12% per year as previously discussed but have also performed a sensitivity analysis varying the rate between 0.07%–0.24% per year. As the malignant transformation rate increases, the more intensive guideline performs better than a less intensive guideline with higher costs as a trade-off. Overall, we believe that the risk of malignant transformation is similar to the experience of Barrett's esophagus where malignant transformation was initially believed to be very high based on referral populations and when studied in a larger cohort was found to be significantly lower (13). Furthermore, newer technology in cross-sectional imaging techniques has resulted in greater detection of cysts (14) which will increase those with pancreatic cysts (i.e., denominator), thereby reducing the actual percentage of malignant transformation.

Previous studies have sought to evaluate the AGA Pancreatic Cyst guidelines regarding diagnostic accuracy of high grade dysplasia and cancer (15,16) and suggest that cancers are missed. Other studies showed more missed cancers but greater specificity in the AGA Guidelines (17–20) when compared with other guidelines. These studies are all retrospective in nature and use highly selected cohorts with significant referral bias. It is difficult to interpret these data in clinical care, given the inherent bias associated with each cohort. Regardless, these studies do demonstrate a significant trade-off between different guideline-based approaches. Our model confirms these studies that more cancers are missed in the AGA Guidelines; however, we also are able to identify and quantify the trade-offs of fewer mortalities related to surgery and significantly lower cost when the AGA Guidelines are applied. Our model is more robust than previous studies because we evaluated a cohort of 10,000 persons with pancreatic cysts of various sizes and provide a base population that mimics an overall population rather than a referral population.

We chose conservative estimates for numerous factors which should bias against the less-intensive guideline. For instance, the mortality that we used in our model for pancreatic surgery is likely

lower than that experienced in most centers. Furthermore, we did not consider the morbidity associated with the surveillance strategies. There is likely to be lower morbidity in a less-aggressive approach, whereas a more-aggressive approach is likely to lead to invasive procedures that have associated morbidity related to invasive tests and surgery. One analysis of 49 studies suggested the morbidity rate associated with pancreatic surgery was 30% (2), and a recent publication from an expert referral center documented 46% morbidity rate after pancreas surgery (21), which does not include long-term morbidity from resultant diabetes in some after surgical management. Finally, the costs used on our study were based on Medicare reimbursement and are significantly lower than the full market costs. Therefore, the cost difference between the 2 guidelines modeled is likely far greater than our published results.

Our study has numerous limitations. First and foremost, there is an inherent limitation of all modeling studies because they attempt to simulate real-life scenarios. Given the limited natural history studies related to pancreatic cysts, our model required some expert opinions on initial cyst size and growth rates that were adapted based on the known literature and clinical experience. The true rate of progression to cancer is difficult to ascertain, and therefore, we present data with a sensitivity analysis that include extremely high and low risks of cancer progression. The model however, once created, has been uniformly applied to each guideline and can provide an overall insight into the relative performance characteristics of each guideline for comparison. Furthermore, we performed sensitivity analysis to determine the effect of varying inputs on model outcomes and conclusions. Regarding these limitations, we believe that this study adds significantly to the literature because it clearly defines the trade-offs of strategies in pancreatic cyst surveillance. There have been no randomized controlled trials comparing various pancreatic cyst guidelines to date and none are registered currently at clinicaltrials.gov (Accessed October 14, 2019, Search: pancreatic cyst, 79 registered trials). Therefore, modeling a sample cohort is likely to be the best-available data for understanding guideline-directed management of pancreatic cysts.

In conclusion, our study identifies that if the rate malignant transformation of pancreatic cysts is low (0.12% annually), a less-intensive guideline will result in similar deaths to a more-intensive guideline at a much lower cost. We recommend large prospective trials to further study surveillance of pancreatic cysts.

CONFLICTS OF INTEREST

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Specific author contributions: J.M.L. and J.M.S.: study concept and design, model build and editing, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. V.M.Z. and V.M.S.: study concept and design, model editing, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. B.G.S.: study concept and design, model build and editing, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content.

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Study Highlights

WHAT IS KNOWN

- ✓ Numerous guidelines exist on the management of pancreatic cysts that differ in the intensity of surveillance and treatment recommendations.
- ✓ No study has evaluated the clinical and economic outcomes of guideline-directed management.

WHAT IS NEW HERE

- ✓ Overall mortality from pancreatic cyst management is similar when comparing 2 commonly applied guidelines.
- ✓ Clinical and economic trade-offs exist between more-intense and less-intense guidelines in the management of pancreatic cysts.
- ✓ Deaths from "unrelated" causes vastly outnumber deaths related to pancreatic cysts.
- ✓ Our study identifies that if the rate malignant transformation of pancreatic cysts is low (0.12% annually), a less-intensive guideline will result in similar mortality to a more-intensive guideline at a much lower costs.

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