


Surveillance after surgery for pancreatic cancer: a global scoping review of guidelines and a nordic Survey of contemporary practice

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ABSTRACT

Objectives: Most patients with pancreatic cancer who have undergone surgical resection eventually develop disease recurrence. This study aimed to investigate whether there is evidence to support routine surveillance after pancreatic cancer surgery, with a secondary aim of analyzing the implementation of surveillance strategies in the Nordic countries.

Materials and Methods: A scoping review was conducted to identify clinical practice guidelines globally and research studies relating to surveillance after pancreatic cancer resection. This was followed by a survey among 20 pancreatic units from four Nordic countries to assess their current practice of follow-up for operated patients.

Results: Altogether 16 clinical practice guidelines and 17 research studies were included. The guidelines provided inconsistent recommendations regarding postoperative surveillance of pancreatic cancer. The clinical research data were mainly based on retrospective cohort studies with low level of evidence and lead-time bias was not addressed. Active surveillance was recommended in Sweden and Denmark, but not in Norway beyond the post-operative/adjuvant period. Finland had no national recommendations for surveillance. The Nordic survey revealed a wide variation in reported practice among the different units. About 75% (15 of 20 units) performed routine postoperative surveillance. Routine CA 19-9 testing was used by 80% and routine CT by 67% as part of surveillance. About 73% of centers continued follow-up until 5 years postoperatively.

Conclusion: Evidence for routine long-term (i.e. 5 years) surveillance after pancreatic cancer surgery remains limited. Most pancreatic units in the Nordic countries conduct regular follow-up, but protocols vary.

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Introduction

Pancreatic cancer constitutes a substantial global burden in terms of cancer mortality. The incidence is lower than many other cancer types, but pancreatic cancer consistently ranks as one of the leading causes of cancer deaths [1]. This highlights the aggressive nature of the disease and the challenges associated with its early detection and treatment.

Surgical resection remains the cornerstone of curative therapy for pancreatic cancer [2]. Nevertheless, recurrence of the tumor occurs in up to 80% of patients, typically within two years after the operation [3]. The most common site for recurrence is the liver (26.5%), followed by locoregional sites (20.8%), peritoneal dissemination (13.5%) and lungs (11.4%) [4]. There are still no clear treatment strategies for recurrent

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disease, in terms of which treatment to offer and how this may potentially affect survival. Indeed, there is a risk of lead-time-bias (Figure 1) involved in the analyses of patients treated for recurrence. A variety of treatment options are available for recurrent pancreatic cancer, ranging from surgical re-resection, to chemotherapy, radiotherapy and local ablative therapies, with a selection of patients achieving potential clinical benefit [5–7] and also depending on the site of recurrence (e.g. lungs or liver) [8]. These types of data have sparked interest in early detection of disease recurrence to enable salvage therapy while the tumor burden is still limited [9,10]. Therefore, surveillance programs are increasingly recommended, but protocols vary and the clinical benefits remain uncertain [11]. For example, a recent UK study reported a wide variation in surveillance practice after pancreatic cancer surgery between but also within units [12].

The aim of the present study was to examine the available literature on the role of routine surveillance after pancreatic cancer surgery and, as a secondary aim, to assess postoperative surveillance strategies in the Nordic countries using a survey among pancreatic surgeons within the Nordic Pancreatic Cancer Network (NPCN).

Methods

Scoping review

This review was reported according to the PRISMA extension for scoping reviews [13]. Clinical practice guidelines in pancreatic cancer surgery were retrieved from society websites. A search of PubMed was done from 2000 to 2023 using the search string “pancreatic cancer AND (surveillance OR follow-up) AND recurrence” to identify relevant clinical research studies. Studies were considered eligible if they reported on survival, cost-effectiveness or quality of life related to postoperative surveillance after pancreatic cancer surgery. Data points extracted and charted from the studies comprised year of publication, country of origin, study design, number of patients and main findings. No additional data

were required from the authors of the included papers. Results were compiled as a narrative synthesis.

Survey

This was a survey of all 20 Nordic tertiary referral centers providing curative-intent surgery for pancreatic cancer. The Nordic countries cover a population of approximately 27.5 million inhabitants, with Sweden having a population of 10.6 million, Denmark 5.9 million, Norway 5.5 million, and Finland 5.5 million (year 2024). The healthcare systems in the Nordic countries are mainly public-based, especially for treatments requiring specialized level of care, such as pancreatic cancer surgery and oncological management. The participating centers are shown in Figure 2. All surgeon members of the NPCN were sent an online questionnaire distributed *via* email to evaluate whether routine surveillance is performed after pancreatic cancer surgery and requesting the specific surveillance strategy for each center.

Results and discussion

The literature search retrieved 4 418 articles. After full-text assessment, 16 clinical practice guidelines (Table 1) and 17 research studies (Table 2) were included. Figure 3 describes the PRISMA flow diagram of study inclusion.

Guidelines

Current guidelines vary widely in their recommendations regarding surveillance after pancreatic cancer surgery, from no routine follow-up to regular clinical examination, tumor markers and computed tomography (CT)/magnetic resonance imaging (MRI) every 3–6 to months for up to 5 years.

Nordic countries

Swedish guidelines recommend postoperative surveillance with clinical examination every 3 months for 1 year, then

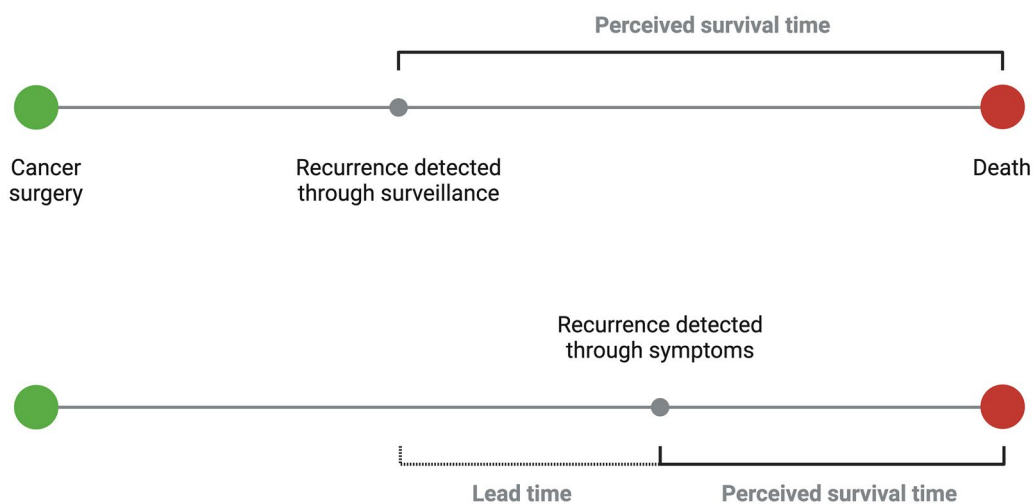


Figure 1. Potential for lead-time bias as a result of systematic surveillance. Recurrence may be detected earlier at an asymptomatic stage in the surveillance group (top part of diagram), leading to a perceived increased survival time attributed to treatment, compared to treatment only initiated after symptoms (bottom panel). Provided the oncological treatment has no or only limited effect, the time of death may remain about the same in both groups, and hence actual survival is similar even if perceived as longer in the surveillance group. Created with BioRender.com.



Figure 2. HPB Centers in the nordic countries. All centers ($n=20$) participated in the survey. Created with www.nordmap.se.

individualized follow-up for up to 5 years; CA 19-9, HbA1C and CT after 6 and 12 months on an individual basis [14]. Danish guidelines recommend follow-up with clinical examination and CA 19-9 every 3 months for 1 year, then every 6 months for up to 2 years; CT after 6 and 12 months on an individual basis [15]. Norwegian guidelines recommend clinical examination, CA19-9 and CT before initiation and after completion of adjuvant chemotherapy (i.e. 2-3 months and 7-8 months after surgery), then clinical follow up in the general practitioner (GP) office [16]. Finland currently has no national guidelines for pancreatic cancer surveillance and each university hospital has its own postoperative strategy.

The rest of Europe

The European Society for Medical Oncology (ESMO) recommends surveillance after resection of pancreatic cancer, but no information is provided regarding method, interval and duration of surveillance. The International Association of Pancreatology/European Pancreatic Club (IAP/EPC) has no recommendation for surveillance. Surveillance is recommended by French [20] and Italian [17] guidelines, with clinical examination, CA 19-9, and CT to monitor recurrence with varying surveillance intervals and duration, while Dutch [18], German [21], Spanish [23] and UK guidelines [24] do not recommend routine surveillance.

Table 1. Guidelines for surveillance after pancreatic cancer surgery.

Guideline	Recommendation
Nordic countries	
Sweden [14]	Clinical examination every 3 months for 1 year, then individualized follow-up for up to 5 years. CA 19-9, HbA1C and CT after 6 and 12 months on an individual basis.
Denmark [15]	Clinical examination and CA 19-9 every 3 months for 1 year, then every 6 months for up to 2 years. CT after 6 and 12 months on an individual basis.
Norway [16]	Clinical examination, CA 19-9 and CT before initiation and after completion of adjuvant chemotherapy (i.e. 2-3 months and 7-8 months after surgery), then clinical follow up in the general practitioner (GP) office.
Finland	No national guidelines.
Rest of Europe	
AIOM [17]	Clinical examination, CA19-9, CEA and CT may be considered, but surveillance intervals and duration not specified.
Dutch national guidelines [18]	No surveillance.
ESMO [19]	Surveillance recommended, but method not specified.
French national guidelines [20]	Clinical examination, CA 19-9 and CT every 3 months for 2-3 years, then every 6-12 months up to 5 years.
German national guidelines [21]	No surveillance.
IAP/EPC [22]	No recommendation.
SEOM [23]	No surveillance.
UK NICE [24]	No surveillance.
North America	
ASCO [25]	Clinical examination and CA 19-9 every 3-6 months. No recommendation regarding imaging tests and surveillance duration.
NCCN [26]	Clinical examination, CA 19-9 and CT every 3-6 months for 2 years, then every 6-12 months for 2 years, then every 6-12 months as clinically indicated.
Asia	
CSCO [27]	Clinical examination, tumor markers and CT/MRI every 3 months for 1 year, then every 3-6 months for 2 years, then every 6 months up to 5 years.
JPS [28]	Tumor markers and CT every 3-6 months for 2 years, then every 6-12 months up to 5 years.
Oceania	
AGITG [29]	No recommendation.

AGITG, Australasian Gastro-Intestinal Trials Group; AIOM, Italian Association of Medical Oncology; ASCO, American Society of Clinical Oncology; CSCO, Chinese Society of Clinical Oncology; ESMO, European Society for Medical Oncology; IAP/EPC, International Association of Pancreatology/European Pancreatic Club; JPS, Japan Pancreas Society; NCI, National Cancer Institute; NICE, National Institute for Health and Care Excellence; NCCN, National Comprehensive Cancer Network; SEOM, Sociedad Española de Oncología Médica.

Table 2. Studies evaluating surveillance after pancreatic cancer surgery.

Author	Country	Type of Study	N	Major Findings	Level of Evidence
Witkowski 2012 [30]	USA	RCS	2217	No survival benefit of routine imaging surveillance.	2B
Tzeng 2012 [31]	USA	RCS	327	Patients with asymptomatic recurrence have improved survival.	2B
Tzeng 2013 [32]	USA	RCS	254	Increased frequency and intensity of surveillance beyond clinical evaluation and CA 19-9 testing increases costs, without survival benefits.	2B
Nordby 2013 [33]	Norway	RCS	164	Patients with asymptomatic recurrence have improved survival.	2B
Deobald 2015 [34]	Canada	QS	15	Follow-up helps fulfil patients need for reassurance whether disease has recurred.	4
Tjaden 2016 [35]	Germany	PCS	184	Structured follow-up is important to optimize treatment and outcome.	2B
Elmi 2017 [36]	USA	RCS	229	Routine imaging surveillance associated with improved survival.	2B
Groot 2018 [37]	The Netherlands	RCS	85	Setting with symptomatic follow-up. Most recurrences detected at late stage. Treatment of recurrence associated with prolonged survival.	2B
Rieser 2018 [38]	USA	RCS	525	CA 19-9 patterns predicts survival. Elevated CA 19-9 levels precedes imaging by more than 6 months.	2B
Samawi 2018 [39]	Canada	RCS	147	Surveillance tests detect recurrences earlier, but do not results in survival differences.	2B
Elberg Dengso 2019 [12]	Denmark	QS	12	Patients perceive CA 19-9 as the focus of surveillance, leaving important symptoms to go unaddressed.	4
Li 2019 [40]	China	RCS	80	Starting salvage treatment immediately upon elevated CA 19-9 levels improves survival.	2B
Wu 2019 [41]	Taiwan	RCS	319	Surveillance does not improve survival.	2B
Halle-Smith 2021 [42]	UK, the Netherlands	SRMA	1596	Surveillance more often detects asymptomatic recurrence, leading to a higher rate of treatment and increased survival	2A
Daamen 2022 [43]	The Netherlands	RCS	836	Treatment of recurrence prolongs survival, with asymptomatic patients having a higher probability to receive recurrence treatment. Surveillance programs aimed at detecting asymptomatic recurrence may improve survival.	2B
Zhang 2023 [44]	Germany	RCS	368	Regular follow-up increases survival.	2B
Elberg Dengso 2023 [45]	Denmark	PCS	104	Physical and psychological symptoms are common after pancreatic cancer surgery and symptom management should be prioritized during the follow-up period.	2B

PCS, prospective cohort study; QS; qualitative study; RCS, retrospective cohort study; SRMA, systematic review and meta-analysis.

North America

The National Comprehensive Cancer Network (NCCN) recommends routine clinical examination, CA 19-9 and CT every

3-6 months for 2 years, then every 6-12 months for 2 years, then every 6-12 months as clinically indicated. The American Society of Clinical Oncology (ASCO) also recommends surveillance, but provides no clear role for imaging tests.

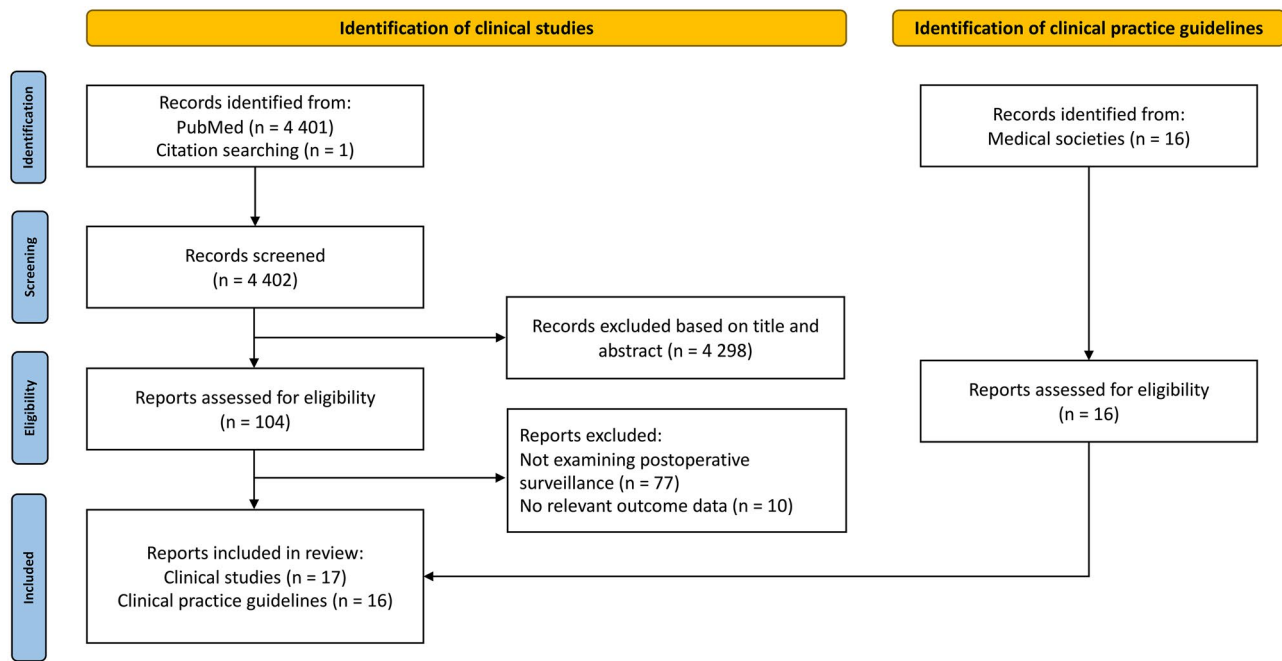


Figure 3. PRISMA flow diagram.

Table 3. Diagnostic performance of postoperative serum tumor markers and imaging modalities for the detection of local and/or distant disease recurrence after pancreatic cancer resection.

Surveillance method	Sensitivity	Specificity	Reference
CA 19-9	68-89%	77-89%	[46–50]
CEA	50%	65%	[46, 48]
CT	70%	80%	[51]
PET-CT	88%	89%	[51]
MRI	42-70%	80-86%	[52,53]
MRI with DWI	85-100%	73-100%	[52,53]

CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CT, computed tomography; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; PET, positron emission tomography.

Asia

The Chinese guidelines recommend clinical examination, CA 19-9 and CT/MRI to monitor for recurrence up to 5 years after surgery. The frequency and method of surveillance may be adjusted according to the regional differences and the accessibility of healthcare resources. The Japanese guidelines recommend CA 19-9 and CT every 3-6 months for 2 years, then every 6-12 months up to 5 years post-surgery.

Oceania

The Australian guidelines have no recommendation on surveillance.

Diagnostic performance

CA 19-9 is the most widely used serum marker for pancreatic cancer. However, approximately 5-10% of the population have a Lewis-negative phenotype and cannot produce the CA 19-9 tumor antigen. Postoperative CA 19-9 has a sensitivity of 68-89% and a specificity of 77-89% for the detection of pancreatic cancer

recurrence (Table 3) [46–50]. Interestingly, it has been shown that elevation in CA 19-9 levels can precede radiological evidence of recurrence by 3-6 months [38, 40]. CEA has a lower diagnostic yield with a sensitivity of 50% and a specificity of 65% [46, 48]. CT is the imaging method most frequently used for postoperative surveillance. However, the sensitivity is moderate at 70% with a specificity of 80% [51]. PET-CT is less frequently employed, but the sensitivity is higher at 88% with a specificity of 89% [51]. FDG-PET reliably detects locoregional tumor recurrences, while CT or MRI is more sensitive for the detection of hepatic metastases [54]. MRI with diffusion-weighted imaging (DWI) has shown higher sensitivity than MRI alone for detecting postoperative tumor recurrence [52,53].

Survival

The effects of routine surveillance on survival after resection of pancreatic cancer remains largely unclear due to conflicting results (Table 2).

A retrospective cohort study among 327 patients reported that regularly scheduled clinical and radiographic surveillance program may aid in the detection of asymptomatic recurrence, especially within the first 2 years [31]. Asymptomatic patients more often received treatment and demonstrated improved post-diagnosis overall survival (29.6 vs 18.0 months; $p=0.003$), as well as post-recurrence overall survival (13.0 months vs 5.1 months; $p<0.001$).

Another retrospective cohort study among 229 patients found that routine imaging surveillance detected recurrent disease earlier and more patients received chemotherapy for recurrent disease and had longer postoperative overall survival (30.4 months vs 17.1 months; $p=0.002$) [36].

One retrospective cohort study among 525 patients [38] demonstrated that an elevated CA 19-9 level was associated with significantly reduced overall survival when measured at

six monthly intervals for the first 24 months after resection [38]. A retrospective cohort study among 80 patients [40] reported that patients who started salvage treatment only based on rising CA19-9 levels had a significantly longer postoperative overall survival than patients with treatment changes based on radiological examinations (28.1 vs 20.7 months; $p=0.049$) [40].

A Dutch multicenter observational study among 836 patients [43] reported that routine follow-up imaging, as compared with symptomatic follow-up, was associated with improved survival (25 vs 15 months; $p<0.001$). Using propensity-score matching, treatment of recurrence was found to be independently associated with longer overall survival for both asymptomatic and symptomatic recurrences. The median postoperative overall survival was 20 months among patients with asymptomatic tumor recurrence and 15 months among symptomatic patients ($p<0.001$).

Similarly, a recent retrospective cohort study of 368 patients found that tumor recurrence detected within a scheduled follow-up compared to relapse at an unplanned visit was associated with a significantly improved survival [44]. Compared to patients with recurrence detected by clinical deterioration, patients with recurrence detected by routine imaging or laboratory tests had longer postoperative overall survival (24.8 vs 15.1 months; $p=0.007$).

A retrospective cohort study of 85 patients evaluated the consequences of a symptomatic surveillance strategy without routine imaging [37]. Although imaging testing was not part of the symptomatic follow-up strategy, most patients underwent additional imaging procedures to detect recurrence. Most of the recurrences were diagnosed at a late stage and after the manifestation of clinical symptoms, with only a minority of patients receiving additional treatment for their relapse. Importantly, post-recurrence overall survival was significantly longer for patients receiving salvage therapy compared to the group receiving best supportive care (7 vs 3 months; $p=0.016$).

In contrast, a retrospective cohort study among 2217 patients found no significant survival benefit among patients who received annual CT scans on a routine basis [30]. Similarly, another retrospective cohort study among 147 patients found no survival benefit from surveillance despite earlier detection of tumor recurrence [39].

In 2021, a systematic review [42] was conducted regarding postoperative surveillance based on 10 studies [12, 31–35, 37,38, 40, 43], with 5 studies suitable for meta-analysis [31, 33, 35, 37, 43] and 3 studies included in the survival analysis [31, 33, 43]. Routine surveillance more frequently detected asymptomatic recurrence, leading to higher treatment rates and longer survival. However, the longer survival may be a result of lead-time bias, i.e. detecting a recurrence earlier, and hence starting a treatment, may project a longer survival time, even if the patient's actual survival time is not extended by the treatment (Figure 1).

Cost-effectiveness of surveillance

A retrospective cohort study [32] evaluated the cost-effectiveness of five surveillance strategies using a Markov model, including no scheduled surveillance and clinical evaluation and CA 19-9 without/with routine radiological examination at either 3 or 6 month intervals. Limited surveillance was found to be the most cost-effective strategy, consisting of clinical evaluation and serum CA 19-9 testing every 6 months and imaging in case of symptoms, clinical findings or increased CA 19-9 levels.

Another retrospective cohort study [30] estimated the average costs for CT-scans associated with surveillance. On average, in 1991 the costs per patient were approximately \$879 compared to \$1797 in 2005, in 2011 monetary terms. The increase in costs reflected the increase in the amount of CT-imaging during surveillance. The study found no significant survival benefit among patients who received more CT scans.

Quality of life during surveillance

Patients are generally positively inclined towards routine surveillance after surgery [34]. They feel safe participating in follow-up appointments and report few difficulties with the overall follow-up process [34]. It has been shown that patients often overemphasize the importance of CA 19-9 and essential symptoms may go unaddressed [12]. Structured postoperative surveillance frequently leads to initiation or modifications of symptom-directed, oncological or diabetic

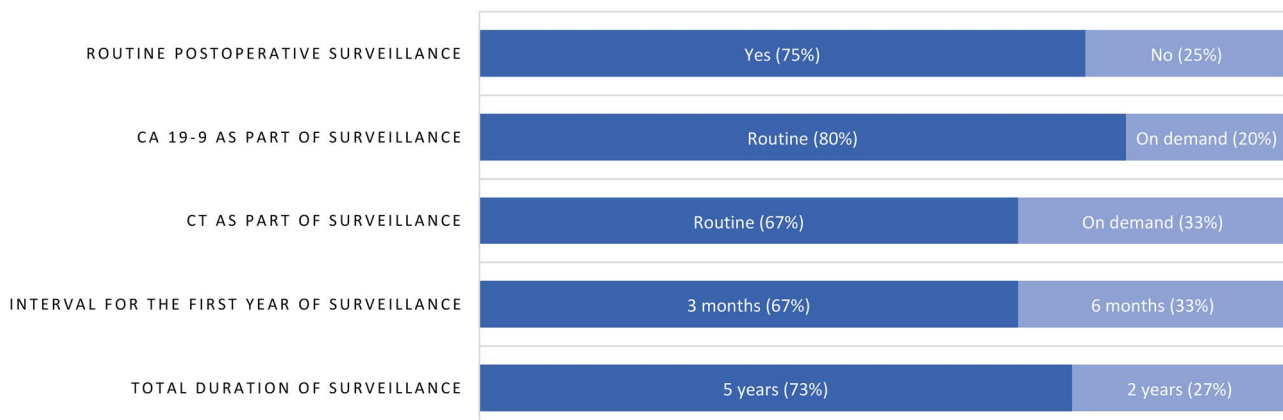


Figure 4. Survey results among nordic referral centers for pancreatic cancer ($N=20$).

treatments for the benefit of quality of life [35]. This is supported by a recent Danish study which also highlights the importance of symptom management after pancreatic cancer surgery [45].

Nordic Survey results

All 20 consultant surgeons from the 20 pancreatic units responded to the survey. The reported practice between the pancreatic units demonstrated wide variation (Figure 4). About 75% had routine postoperative surveillance after pancreatic cancer surgery. Routine CA 19-9 testing was used by 80% and routine CT by 67% as part of surveillance. Most common interval for the first year of follow-up was 3 months (67%). About 73% of centers continued follow-up until 5 years postoperatively.

Conclusion

Current guidelines provide conflicting recommendations regarding postoperative surveillance of pancreatic cancer. Some guidelines favor surveillance based on evidence suggesting that routine surveillance can detect asymptomatic disease, allowing earlier start of recurrence treatment and longer survival. The optimal surveillance method and duration remains to be determined. Further development of existing or novel liquid biopsy methods may lead to more accurate tumor detection and guidance of treatment. However, the subject of lead-time bias remains a major concern and whether postoperative cancer surveillance can be translated into improved survival rates remains to be evaluated in prospective trials.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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