European Journal of Surgical Oncology 45 (2019) 1770–1777

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Postoperative surveillance of pancreatic cancer patients

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ARTICLE INFO

Article history:
Received 10 April 2019
Received in revised form
21 May 2019
Accepted 31 May 2019
Available online 1 June 2019

Keywords:
Pancreatic cancer
Pancreatectomy
Postoperative surveillance
Follow-up
Recurrence
Systematic review

ABSTRACT

Background: The aim of this study is to collect the best available evidence for diagnostic modalities, frequency, and duration of surveillance after resection for pancreatic ductal adenocarcinoma (PDAC).
Methods: PDAC guidelines published after 2015 were collected. Furthermore, a systematic search of the literature on postoperative surveillance was performed in PubMed and Embase from 2000 to 2019. Articles comparing different diagnostic modalities and frequencies of postoperative surveillance in PDAC patients with regard to survival, quality of life, morbidity and cost-effectiveness were selected.
Results: The literature search resulted in 570 articles. A total of seven guidelines and twelve original clinical studies were eventually evaluated. PDAC guidelines increasingly recommend a combination of tumor marker testing and computed tomography (CT) imaging every three to six months during the first two years after resection. These guidelines are, however, based on expert opinion and other low-level evidence. Prospective studies comparing different surveillance strategies are lacking. According to recent studies, surveillance with tumor markers and imaging at regular intervals results in the detection of PDAC recurrence before the onset of symptoms and more frequent administration of further therapy, such as chemotherapy or radiotherapy.
Conclusion: Current evidence for recurrence-focused surveillance after PDAC resection is limited and contradictory. Consequently, recommendations on surveillance are conflicting. To define the clinical merit of recurrence-focused surveillance, patients who are most likely to benefit from early detection and treatment of PDAC recurrence need to be identified. To this purpose, well-designed prospective studies are needed, accounting for both economical and psychosocial implications of surveillance.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer related mortality in Europe and is expected to rise to second place by 2030 [1,2]. For patients with non-metastasized, resectable disease, radical resection offers the best chances for long-term survival [3]. However, at least 80% of

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https://doi.org/10.1016/j.ejso.2019.05.031
0748-7983/

patients will develop local and/or distant disease recurrence after pancreatectomy, often within two years [4–7]. Although administration of (neo)adjuvant chemotherapy has been shown to result in extended disease-free survival and lower recurrence rates, disease recurrence remains the principal cause of mortality in patients with resected PDAC [8,9].

Patients with PDAC recurrence constitute a significant group that continues to face limited effective treatment possibilities and a poor survival of only 3–9 months after recurrence detection [10–13]. Therefore, even after resection of the primary tumor, PDAC is still associated with a 5-year survival rate of only 12–27% [14–17]. More effective multi-drug regimens, such as FOLFIRINOX and gemcitabine/nab-paclitaxel, and local ablative therapies such as stereotactic body radiation therapy (SBRT), irreversible electroporation (IRE (Nanoknife®)) and radiofrequency ablation (RFA), represent expanded treatment options that could offer improved systemic and/or local control of PDAC recurrence. Several small and non-randomized studies have suggested that patients with recurrent PDAC might benefit from these therapies, both in terms of survival and quality of life [11,18–21]. This has prompted questions on the importance of early detection of recurrent PDAC.

Without recurrence-focused surveillance, disease recurrence is commonly identified after the manifestation of clinical symptoms, which is associated with a more advanced disease stage and worse performance status. Surveillance with serial tumor marker testing and imaging could facilitate earlier detection of PDAC recurrence when the tumor load is still low, arguably increasing the chance of effective systemic and/or local treatment. Furthermore, deterioration of the patients' performance status limits the ability to receive treatment for PDAC recurrence. As a consequence, recurrence-focused surveillance is increasingly recommended. Evidence for this strategy is, however, lacking. Nevertheless, most studies on the potential benefits of postoperative surveillance have been performed before the introduction of recent treatment options.

Potential disadvantages of recurrence-focused surveillance are the introduction of psychological stress and morbidity that may result in an overall decrease in quality of life, while the impact of treatment on survival is yet unclear. Given the lack of high-quality evidence, most European countries including the Netherlands have raised (ethical) concerns regarding recurrence-focused surveillance. Consequently, PDAC guidelines provide minimal guidance on diagnostic modalities and frequency of postoperative surveillance. This has led to widely varying surveillance strategies throughout the world, potentially depriving certain PDAC patients of meaningful surveillance, while wrongfully harming others. We therefore performed the current systematic review to collect the best available evidence for diagnostic modalities, frequency, and duration of surveillance after PDAC resection.

Methods

First, PDAC guidelines published after 2015 by different medical societies were collected. Second, to evaluate the current evidence on diagnostic modalities (e.g. serum tumor marker testing and imaging procedures), frequency (e.g. every 3 or 6 months) and duration (e.g. 2 years) of surveillance after resection of PDAC, a systematic search of the literature was performed in PubMed and Embase from 2000 to 2019 (Appendix I). Synonyms, medical subject headings (MeSH) terms and keywords for 'pancreatic cancer' were combined with different terms for 'postoperative surveillance'. The Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines were followed [22]. The search was restricted to title and abstract, and English or Dutch language. Titles, abstracts, and subsequently full-text articles were screened for relevance, based on predefined in- and exclusion criteria. Conference abstracts and 'Letter to the Editor'-papers were excluded.

Articles were considered eligible when reporting on survival, quality of life, morbidity, and cost-effectiveness of postoperative surveillance. A study-population of patients with PDAC who underwent pancreatic resection with or without (neo)adjuvant chemo- and/or radiotherapy was deemed representative. Articles reporting on postoperative surveillance in patients with different pancreatic tumors, such as benign neoplasms, neuroendocrine tumors, or pancreatic metastases were excluded. No restriction in study design was made. Of original clinical studies, type of study, study period, methods, results and conclusions were extracted and summarized.

Results

Search results

Five guidelines from different continents were evaluated, as well as the recently revised French, UK and Dutch guidelines (Table 1). The literature search resulted in 570 titles and abstracts, which were screened for eligibility. After full-text assessment, twelve original studies were included (Table 2).

Guidelines on surveillance after resection of PDAC

Recommendations on surveillance after radical resection of PDAC are conflicting, and based on expert opinion and other low-level evidence (Table 1) [23–30]. The European Society for Medical Oncology (ESMO) explicitly recommends no surveillance with regular additional testing, based on the poor prognosis upon diagnosis of disease recurrence and limited effective treatment options [24]. The International Association of Pancreatology/European Pancreatic Club (IAP/EPC) has, according to the 2016 guidelines, no recommendations for surveillance [25]. Recently, both the French and UK guidelines were revised [26,27]. In contrast to the ESMO guidelines, the French guidelines now state that it might be beneficial to detect recurrence at an early stage, using serum CA 19-9 measurement when elevated at diagnosis, and a CT-scan of the chest, abdomen and pelvis every 3 months for 2–3 years, then every 6–12 months up to 5 years [26]. Within the guidelines of the UK National Institute for Health and Care Excellence on diagnosis and management of pancreatic cancer, it was stated that the committee was not able to make any recommendations about the method, frequency or duration of postoperative surveillance. Herewith, the guideline committee acknowledged the lack of evidence on whether detecting recurrence improves overall survival [27]. Similar to the UK guidelines, recurrence-focused surveillance was not recommended within the revised 2019 National Dutch Guideline for pancreatic cancer, considering the current lack of high-quality evidence on postoperative surveillance and recurrence treatment. Contrastingly, the National Comprehensive Cancer Network (NCCN; United States) and Japan Pancreas Society both recommend routine testing of serum carbohydrate antigen (CA) 19-9 levels and computed tomography (CT) imaging of the abdomen and pelvis, every 3–6 months for the first 2 years after surgery [28,29]. The American Society of Clinical Oncology (ASCO), however, states that the benefit of imaging is unclear. They recommend a surveillance existing of history and physical evaluation every 3–6 months, with addition serum CA 19–9 testing if this tumor marker was elevated pre-operatively [30].

Table 1
Current guidelines and recommended surveillance strategies.

Continent	Organization	Recommendation	Level of evidence
Europe	ESMO (2015) [24]	No recurrence-focused surveillance.	No evidence (4D)
	IAP/EPC (2016) [25]	No recommendation.	Not applicable
	French clinical practice guidelines (2018) [26]	(i) clinical examination, (ii) serum CA 19–9 testing when elevated at diagnosis, (iii) thoraco-abdomino-pelvic CT, every 3 months for 2–3 years, then every 6–12 months up to 5 years.	Non-uniform expert opinion (2B)
	UK National Institute for Health and Care Excellence guidelines (2018) [27]	No recurrence-focused surveillance.	Low (C)
	Dutch national guidelines (2019)	No recurrence-focused surveillance.	Very low*
North America	NCCN (2018) [28]	History and physical examination for symptom assessment every 3–6 months for 2 years, then every 6–12 months as clinically indicated.	Uniform expert opinion (2A)
		CA 19-9 and follow-up CT scans (chest, abdomen, and pelvis) with contrast every 3–6 months for 2 years.	Non-uniform expert opinion (2B)
	ASCO (2017) [29]	History and physical examination every 3–6 months after completion of therapy. Additional serum CA 19-9 if elevated pre-operatively. No recommendations regarding the use of imaging procedures, surveillance intervals and duration.	Low (C)
Asia	JPS (2016) [30]	Measurement of tumor markers and a dynamic CT scan every 3–6 months for 2 years postoperatively and every 6–12 months subsequently, at least for 5 years.	Low (C)
Australia	AGITG (2016) [59]	No recommendation.	Not applicable

ESMO, European Society for Medical Oncology; IAP/EPC, International Association of Pancreatology/European Pancreatic Club; UK, United Kingdom; NCCN, National Comprehensive Cancer Network; ASCO, American Society of Clinical Oncology; JPS, Japan Pancreas Society; AGIGT, Australasian Gastro-Intestinal Trials Group.
*Grading of Recommendations, Assessment, Development and Evaluations (GRADE) rating.

Surveillance modalities

Serum tumor marker testing

In current clinical practice, the most widely assessed serum biomarker after resection of PDAC is CA 19–9 [31,32]. For the detection of PDAC recurrence, postoperative serum CA 19-9 has a moderate value with a sensitivity of 68–89% and a specificity of 77–89% [33]. It was found that CA 19–9 elevation could precede radiographic evidence of recurrence by 3–6 months [34,35]. In this context, it was suggested that CA 19-9 patterns during surveillance could be used in patient counselling, and benefits of tumor marker-guided treatment were shown [34,35]. Nevertheless, patient interviews have demonstrated that patients perceive detection of recurrence through CA-19-9 as the focal point of postoperative surveillance, hampering discussions about other treatment-related problems [36]. As such, some authors consider not using this relatively unprecise tumor marker [36]. More recently, there has been increasing interest in the use of liquid biopsies in the form of circulating tumor DNA as potential novel biomarkers that could aid in the detection of PDAC recurrence [37,38]. A joint review by the ASCO and College of American Pathologists, however, state the evidence for clinical validity and utility for liquid biopsy assays in oncology care outside of study purposes currently is insufficient [39].

Imaging procedures

During both pre-operative assessment and post-operative surveillance, CT imaging is stated to be the preferred imaging modality [28,40,41]. A meta-analysis on the diagnostic performance of CT and PET-CT imaging for the detection of PDAC recurrence showed that CT alone has a moderate diagnostic value with a sensitivity of 70% and a specificity of 80%; PET-CT alone showed a sensitivity and specificity of 88% and 89%, respectively, and for a combination of PET-CT and CT, a sensitivity of 95% and specificity of 81% was found [42]. Only a few small retrospective cohort studies reported on imaging as part of a standardized surveillance strategy; most studies used imaging procedures only when recurrent disease was clinically suspected [43–45]. In the context of standardized surveillance with regular imaging, diagnostic accuracy values of CT and PET-CT were found to be similar, as compared to values of imaging procedures performed when recurrence was clinically suspected [42].

In a study by Balaj et al., early local recurrence of PDAC was detected in the first 12 months following surgery in 69% of patients (n = 33), with an average of 1.5 scans (range 1–3). The authors suggested that routine CT monitoring during the first year after surgery, using an interval of three months, may be appropriate to detect early local PDAC recurrence and provide treatment for local recurrence [40].

Survival

Few studies have been published evaluating the consequences of radiologic surveillance on survival after resection of PDAC (Table 2). Existing studies were retrospective, small and often reported contradictory results. Witkowski et al. performed a retrospective study to determine the potential survival benefit of abdominal imaging after pancreatic cancer resection [46]. In 222 patients with a superior OS of more than 51 months, survival was not improved in patients who received annual abdominal CT scans (n = 72) compared to those who did not (n = 150). For this subgroup, no survival data or hazard ratios were reported [46]. Furthermore, Tzeng et al. evaluated the cost-effectiveness of five surveillance strategies using a Markov model, populated with data from patients who had received intensive surveillance. They

Table 2
Results of articles reporting on the consequences of routine imaging and tumor marker surveillance.

Author	Design	n	Methods	Results	Conclusion	Final remark
Witkowski et al. (2011) [46]	Retrospective cohort study (1991–2005)	2217	Mean number of imaging procedures (1991 vs. 2005). Mean annual rate of CT scans (1991 vs. 2005), adjusted for number of months of survival. Survival analysis was performed in patients with superior OS (>51 months; n = 222); patients who received annual abdominal CT scans (n = 72) were compared to those who did not (n = 150).	3.0 vs. 6.0 procedures ($P < 0.0001$) 2.9 vs. 5.1 procedures ($P < 0.0001$) NA, $P = 0.008$	Substantial increase in application of complex imaging. No survival benefit of routine imaging.	Unfavorable
Tzeng et al. (2012) [19]	Retrospective cohort study (1998–2008)	327	All patients had imaging surveillance. OS and further therapy were compared in patients with asymptomatic (n = 118) vs. symptomatic recurrence (n = 98). PROS was compared in treated (n = 157) vs. untreated patients (n = 59).	Median OS: 29.6 vs. 18.0 months ($P = 0.003$) Further therapy was administered in 91.2% vs. 61.4% ($P < 0.001$) Median PROS: 11.8 vs. 2.6 months ($P < 0.001$)	OS was longer in asymptomatic patients. Treatment was administered more frequently to asymptomatic patients. Administration of further therapy was associated with longer PROS.	Favorable
Tzeng et al. (2013) [47]	Retrospective cohort study (1998–2008)	254	The cost-effectiveness of 5 surveillance strategies was compared using a Markov model, populated with data from patients who had received intensive surveillance.	A limited 6-month strategy* has a significantly lower ICER than other standardized strategies	Increased frequency and intensity of surveillance beyond 6-monthly clinical evaluation and CA 19-9 tests increases costs, without survival benefits.	Unfavorable
Nordby et al. (2015) [18]	Retrospective cohort study (2000–2010)	164	All patients underwent imaging every 6 months or in case of suspicious symptoms. OS and further therapy were compared in patients with asymptomatic (n = 29) vs. symptomatic (n = 115) recurrence.	Median OS was 24.5 vs. 11.0 months ($P < 0.0001$) Treatment was administered in 72% vs. 37%	Patients with asymptomatic recurrence have an improved survival. Detection of asymptomatic recurrence may facilitate patient eligibility for treatment.	Favorable
Deobald et al. (2015) [50]	Qualitative longitudinal descriptive study with semi-structured interviews	15	Individual interviews were undertaken to assess patient and clinician attitudes towards surveillance, as well as perceived benefits and challenges.	FU visits help patients to fulfil their need for reassurance and desire to know whether recurrence occurs, without experiencing difficulties with the FU process. Clinicians recognize their desires. A considerable contrast exists between patients' understanding and expectations, and clinicians' perspectives regarding disease and prognosis.		Neutral
Tjaden et al. (2016) [51]	Prospective cohort study (2012)	184	All patients underwent imaging every 3 months for 2 years and every 6 months thereafter. FU data was analysed with a focus on symptoms, radiological findings and therapeutic consequences in terms of supportive and cancer-directed therapies.	In 49% of FU visits, oncological or diabetes management was changed, or symptom-directed therapy was induced or modified to improve QoL. PDAC recurrence was asymptomatic in 55/75 patients (74%). All patients with recurrence underwent cancer-directed treatment.	Structured surveillance is important to optimize (symptom-directed) treatment and outcome. FU imaging is important because recurrence is often asymptomatic, although its detection allows for treatment and potentially improved prognosis.	Favorable
Elmi et al. (2017) [20]	Retrospective cohort study (2005–2011)	229	Survival was compared in patients who underwent regular imaging surveillance (IS) (n = 163) vs. those with clinical FU only (C) (n = 66) in a multivariable model.	Median OS: 30.4 ± 3.85 vs. 17.1 ± 2.42 months ($P = 0.002$)	Routine imaging surveillance is associated with prolonged OS in a multivariable model.	Favorable
Groot et al. (2017) [49]	Prospective cohort study (2011–2015)	85	The number of imaging procedures to detect PDAC recurrence was determined in a setting where imaging was not performed routinely (symptomatic FU). The pattern, timing, and treatment of recurrent PDAC during symptomatic FU were assessed.	74 patients (87%) underwent at least one imaging procedure, with a mean amount of 3.1 ± 1.9 imaging procedures. 85% of patients with recurrence had symptoms. 25% of patients underwent treatment for recurrence, which was associated with a longer PROS (HR 0.32, 95% CI 0.16–0.65, $P = 0.002$).	Although symptomatic FU does not include routine imaging, most patients underwent imaging for the detection of recurrence at least once. Most recurrences were detected at a late stage and after the manifestation of clinical symptoms, potentially limiting patients to undergo additional treatment for recurrence.	Favorable
Rieser et al. (2018) [35]	Prospective cohort study (2010–2016)	525	CA 19-9 was measured at 6-monthly intervals. Recurrence was defined by radiographic evidence. CA 19-9 levels were correlated with RFS and OS.	CA 19-9 had a poor PPV (35%) but a high NPV (92%) for radiographic recurrence. CA 19-9 elevation predicted subsequent RFS at each time point.	High CA 19-9 frequently may precede recurrence on imaging by more than 6 months. CA 19-9 patterns predict RFS and OS, which could be used in patient counselling and to direct protocols of salvage chemotherapy.	Favorable
Dengsø et al. (2018) [36]	Qualitative longitudinal descriptive study with semi-structured interviews	12	Interviews were undertaken to explore patients' experiences of and perspectives on surveillance within the first year after curative treatment of cancer in the pancreas, duodenum or bile-duct.	Patients experienced monitoring of CA 19-9 for the detection of recurrence as the main point of FU. Consultations were influenced considerably by the test results and implications of these, leaving discussions of other potential patient-important symptoms insufficiently addressed. The authors consider not using this relatively unprecise tumor marker for relapse in the future.		Unfavorable

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Table 2 (*continued*)

Author	Design	n	Methods	Results	Conclusion	Final remark
Samawi et al. (2018) [48]	Retrospective cohort study (2001–2015)	147	Surveillance strategies were classified: 1) Surveillance at cancer centers (CC, 66%) with regular lab tests, and/or imaging. 2) Surveillance at primary care (PCP, 44%). Patient and disease characteristics, percentage of patients receiving chemotherapy for recurrence, OS and RFS were compared in the CC vs. the PCP group.	Percentage of patients with T3/4 tumors was 78% vs. 62% ($P = 0.03$). Percentage of patients receiving chemotherapy for recurrence was 58% vs. 34% ($P = 0.03$). No difference in OS (HR 1.23; 95% CI 0.74 −2.04, $P = 0.40$); RFS favoured the PCP group (HR 1.62; 95% CI 1.01−2.56, $P = 0.04$ for the CC group).	Patients with more advanced tumors were more likely to be seen at CC. Surveillance tests and imaging performed by CC detected recurrences earlier, but did not result in OS differences. PCP may play a larger role in the FU care of selected low risk patients.	Unfavorable
Li et al. (2019) [34]	Prospective cohort study (2014–2017)	80	All patients underwent CA 19-9 testing and imaging every 3 months. RFS and OS were compared in patients who started treatment based on rising CA 19-9 (without radiographic confirmation) vs. patients who did not start until radiographic confirmation of recurrence.	60 patients (75%) had CA 19-9 elevation that preceded radiographic recurrence by ± 3 months. Median RFS: 23.6 vs. 12.1 months ($P < 0.001$) Median OS: 28.1 vs. 20.7 months ($P = 0.049$)	CA 19-9 could precede recurrence confirmed by radiographic examinations. Tumor marker-guided treatment can significantly prolong RFS and OS in patients under surveillance after pancreatic resection.	Favorable

OS, overall survival; CT, computed tomography; PROS, post-recurrence overall survival; ICER, incremental cost-effectiveness ratio; FU, follow-up; QoL, Quality of Life; PDAC, pancreatic ductal adenocarcinoma; RFS, recurrence-free survival, PPV, positive predictive value; NPV, negative predictive value.
*A limited 6-month strategy existed of clinical evaluation and CA 19-9 testing with a 6-monthly interval, and imaging in case of symptoms, clinical findings or elevation of CA 19-9Conflict of interest.

showed that an increased frequency and intensity of postoperative surveillance beyond 6-monthly clinical evaluation and CA 19−9 testing increased the costs, without survival benefits [47]. Samawi et al. found that multimodality surveillance in specialized cancer centers resulted in earlier detection of PDAC recurrence, although a survival benefit could not be demonstrated [48]. It was also shown, however, that patients with more advanced tumors were more likely to be seen in expert centers, potentially having a worse *a priori* prognosis compared to patients who received follow-up at primary care physicians. Nevertheless, the authors stated that primary care physicians may play a larger role in postoperative surveillance for selected low risk patients [48].

Conversely, other studies reported data that could support a surveillance strategy with regular CT imaging. Two retrospective observational studies by Nordby et al. and Tzeng et al. showed that patients with asymptomatic PDAC recurrence, detected during systematic CT-based surveillance, had an improved survival and received oncological treatment more frequently [18,19]. Nordby et al. found a median OS of 24.5 months in patients with asymptomatic PDAC recurrence, compared to 11.0 months in patients with symptomatic recurrence ($P < 0.0001$), with respectively 72% and 37% of patients undergoing further treatment [18]. Moreover, Tzeng et al. showed a median OS of 29.6 and 18.0 months in asymptomatic and symptomatic patients ($P = 0.003$). Further therapy was administered in 91.2% of patients with asymptomatic recurrence and in 61.4% of patients with symptomatic recurrence [19]. They both stated that the detection of asymptomatic recurrence on CT surveillance might identify patients with good performance status and tumor biology who are most likely to benefit from subsequent treatment. Furthermore, it was mentioned that detection of recurrent disease by CT may facilitate patient inclusion in clinical trials [18,19].

Moreover, an observational study among 85 patients in whom PDAC was resected showed that even when a symptomatic surveillance strategy without routine imaging was utilized, the majority of patients underwent additional imaging procedures for the detection of recurrence at least once. Although patients received an average of three imaging procedures, most recurrences were detected at a late stage and after the manifestation of clinical symptoms. In this observational cohort study, only 17 of 68 patients (25%) underwent treatment for recurrence, which was found to be an independent predictor for prolonged survival after recurrence [49]. It was argued that the imaging procedures could be used more effectively in the context of a recurrence-focused surveillance, with a 3- or 6-monthly interval, possibly increasing the number of patients eligible for treatment of PDAC recurrence [49].

Recently, a comparative retrospective study by Elmi and colleagues found that routine imaging surveillance after pancreatectomy, as compared to symptom-oriented imaging surveillance, was associated with a prolonged overall post-operative survival in a multivariable model (30.4 months vs. 17.1 months; $P = 0.002$) [20]. The mean interval for diagnosis of recurrent disease in the routine imaging surveillance group was significantly shorter and more patients received chemotherapy for recurrent disease. The authors argue that the possibility for more aggressive treatment at an early stage could therefore have contributed to improved survival rates, and consequently suggested that CT-imaging at 3−4 months interval can be beneficial [20].

Quality of life

Previous studies showed that patients undergoing post-operative surveillance with regular diagnostic testing exhibit significant anxiety and fear of cancer recurrence, with a substantial impact on quality of life (QoL) [50]. In general, however, patients

seem to desire active surveillance after resection of PDAC, and clinicians support an active surveillance as well [50]. Unfortunately, no studies were found to evaluate the direct impact of recurrence-focused surveillance on QoL in PDAC patients. Only one study by Tjaden et al. reported on a potential QoL benefit of standardized surveillance. They found that in 49% of all surveillance-related visits, symptom-directed, oncological or diabetes treatment was induced or modified to improve QoL [52]. Lastly, management of symptoms resulting from post-pancreatectomy exocrine and endocrine insufficiency could be optimized, by frequent evaluation of the patients' nutritional status and their proper use of medication and supplements during standardized surveillance [51].

Discussion

The introduction of improved systemic and local treatment options for PDAC might warrant early diagnosis of cancer recurrence, with early retrospective studies suggesting both survival and QoL benefits of standardized postoperative surveillance. Since it can be difficult to obtain histological evidence of PDAC recurrence, a combination of a rise in serum tumor markers and suspicious, progressive findings on imaging could aid in the early clinical diagnosis. Current evidence for potential survival benefits of early detection and treatment of PDAC recurrence is, however, limited and contradictory. High-quality evidence is lacking to provide recommendations for surveillance.

The hypothesis that recurrence-focused surveillance has survival benefits follows the assumption that detection of disease recurrence at an early stage improves the eligibility to undergo treatment and allows for a timely start of further treatment while the tumor burden is still low. However, as the efficacy of recent treatments is poorly evaluated in patients with PDAC recurrence, survival benefits of treatment for recurrence are yet unclear. Given this lack of evidence showing beneficial effect, ethical concerns remain that the early detection of recurrent PDAC may compromise quality of life and patient reported outcomes. A survey undertaken by the Dutch Pancreatic Cancer Group among Dutch pancreatic surgeons assessed their current practice of surveillance and motivation to participate in new studies concerning the detection and treatment of PDAC recurrence [52]. It was shown that current surveillance strategies of Dutch pancreatic surgeons mainly consist of regular outpatient visits with physical examination, in accordance with the European guidelines. The omission of standard tumor marker testing and imaging resulted from the belief that there exists a lack of effective therapies for local and distant recurrence. Because therapeutic consequences of recurrence diagnosis were stated to be minimal, mentally burdensome surveillance was not deemed justifiable [52]. On the other hand, it has been shown that a standardized surveillance can contribute to the induction or modification of symptom-directed clinical management to improve quality of life for symptomatic patients [50,53,54]. Furthermore, early detection of (asymptomatic) PDAC recurrence could facilitate patient recruitment in intervention studies to evaluate the potential benefits of (early) treatment. This might contribute to the expansion of treatment possibilities for patients with recurrent PDAC. To diminish unrealistic expectations of treatment benefits, however, it is highly important that patients are aware of the current limitations of the detection and treatment of PDAC recurrence [18].

Potential benefits of recurrence-focused surveillance have been investigated in patients who underwent treatment with curative intent for different types of cancer, such as epithelial ovarian cancer and colorectal cancer [55–57]. In these cancer types, prospective studies showed no clear disease-specific survival benefit of multimodality surveillance with a certain intensity, and the cost-effectiveness of recurrence-focused surveillance remains unclear. Therefore, the importance and consequences of active surveillance in these patients is increasingly being questioned. An individualized approach to identify patients who potentially benefit most from early detection and treatment of colorectal or ovarian cancer recurrence was recommended. Furthermore, it was concluded that surveillance should be terminated if the likely benefits no longer outweigh the potential risks and disadvantages, such as morbidity from diagnostic testing, emotional distress and monetary costs [56]. For PDAC patients, unfortunately, the risk of disease recurrence after primary resection is relatively high when compared to these other cancers. Therefore, if treatment of PDAC recurrence actually improves survival, recurrence-focused surveillance might be more advantageous for these patients. As prospective studies on surveillance after PDAC resection are currently lacking, however, definite conclusions about the utility of a recurrence-focused surveillance in these patients cannot be made. This absence of evidence reflects a need of high-quality studies to help guide surveillance recommendations.

Current research focuses on the development of new tests to improve the detection of PDAC, such as circulating tumor DNA and new biomarkers like ADAM12 [39,58]. These promising techniques might be helpful during postoperative surveillance as well, as they can potentially contribute to the identification of patients with a high risk of recurrence, who possibly benefit most from an intensified surveillance. For clinical applicability, further development of these detection methods is needed.

In conclusion, expert and high-volume pancreatic centers worldwide increasingly implement standardized postoperative surveillance with serum tumor marker testing and routine imaging in PDAC patients. However, the risk-benefit and cost-effectiveness of recurrence-focused surveillance is still unclear. Therefore, potential side-effects have to be considered, including psychosocial harm, as well as the economic burden that comes with frequent additional testing and treatment. In this context, patients who are most likely to benefit from early detection of recurrent disease, i.e. patients who are able and willing to undergo treatment, need to be identified. Future well-designed prospective studies are exceedingly needed to define the clinical merit as well as economical and psychosocial implications of recurrence-focused surveillance after resection of PDAC.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.05.031.

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