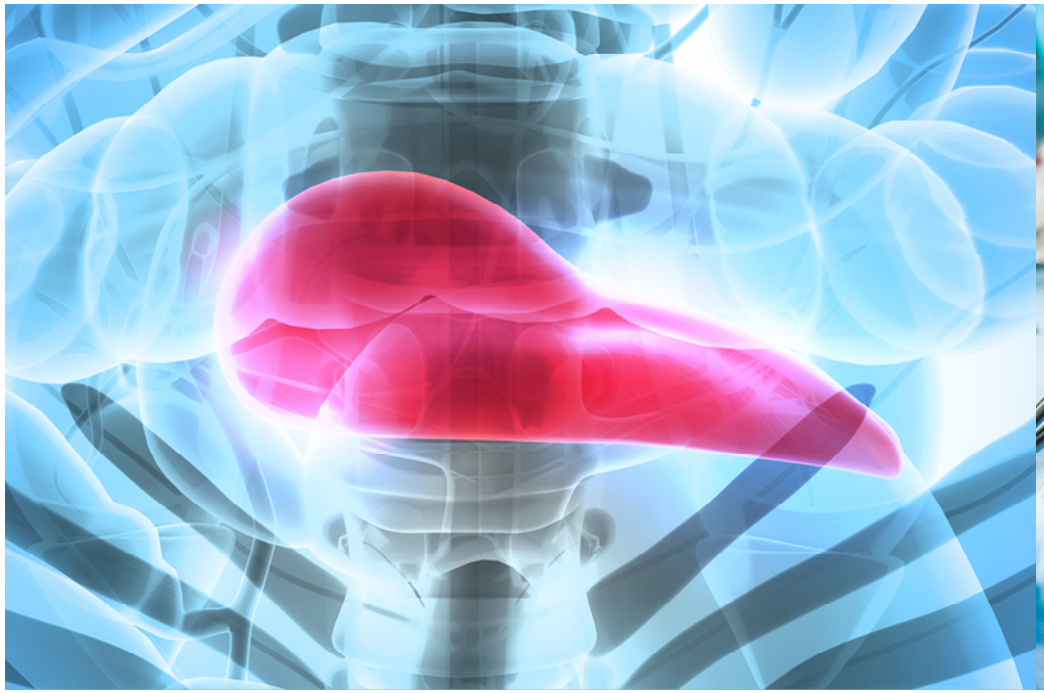
KCE REPORT 286

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

MANAGEMENT OF PANCREATIC CANCER: CAPITA SELECTA – PART 1: INTRODUCTION AND METHODOLOGY



KCE REPORT 286
Good Clinical Practice

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MANAGEMENT OF PANCREATIC CANCER: CAPITA SELECTA – PART 1: INTRODUCTION AND METHODOLOGY

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse event
CA	Coeliac axis
CHA	Common hepatic artery
CI	Confidence interval
CRT	Chemoradiotherapy
CT	Computed tomography
DTA	Diagnostic Test Accuracy
ERCP	Endoscopic retrograde cholangiopancreatography
EUS	Endoscopic ultrasound
FNA	Fine needle aspiration
GCP	Good clinical practice
GDG	Guideline development group
KCE	Belgian health care knowledge centre
LAPC	Locally advanced pancreatic cancer
MA	Meta-analysis
mRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
NCCN	National comprehensive cancer network
NIHDI (RIZIV – INAMI)	National Institute for Health and Disability Insurance
OS	Overall survival
PET	Positron emission tomography
PICO	Population-intervention-comparator-outcome
PIRT	Population - index test - reference test - target disorder
PV	Portal vein
QoL	Quality of life

RCT	Randomised controlled trial
RQ	Research question
SEER	Surveillance, Epidemiology and End Results
SMA	Superior mesenteric artery
SR	Systematic review
SMV	Superior mesenteric vein
UICC	International union against cancer
US	Ultrasonography
WSR	Age standardised rate, using the World Standard Population
yrs	Years

SCIENTIFIC REPORT

1 INTRODUCTION

The development of clinical care pathways is one of the main actions described in the Belgian National Cancer Plan 2008-2010 and one of the assignments of the College of Oncology. For many years the Belgian Health Care Knowledge Centre (KCE) has collaborated with the College of Oncology in providing scientific support in the development of clinical practice guidelines. So far, this collaboration has resulted in the publication of clinical practice guidelines on various cancers. The last guideline on pancreatic cancer was published in 2009[1] and needed an update. This report focuses on the most common variant: pancreatic adenocarcinoma.

1.1 Background

The most common type of pancreatic cancer (95%) are adenocarcinomas that originate from the pancreatic duct. Acinar cell carcinomas are less frequent. Other less common exocrine cancers include adenosquamous carcinomas, squamous cell carcinomas, signet ring cell carcinomas, undifferentiated carcinomas and undifferentiated carcinomas with giant cells. Endocrine pancreatic cancers account for less than 5% of all pancreatic cancers. These are the pancreatic neuroendocrine tumours (NETs) or islet cell tumours. Benign or precancerous masses in the pancreas include serous cystic neoplasms, mucinous cystic neoplasms, intraductal papillary mucinous neoplasms and solid pseudopapillary neoplasms.[2]

Pancreatic cancer is staged according to the 8th edition of the TNM classification proposed by the International Union Against Cancer (UICC) (see Table 8,Table 9).[3] In summary, T1 is a tumour smaller than 2 cm limited to the pancreas, T2 is a tumour also limited to the pancreas but larger than 2 cm, T3 extends beyond the pancreas and T4 invades the coeliac axis or superior mesenteric artery. N1 indicates invasion of regional lymph nodes (Table 10).[4]

In clinical practice and in this report, pancreatic cancer is defined as resectable, borderline resectable and unresectable, including locally advanced pancreatic cancer (LAPC) and metastatic cancer. A tumour is resectable when the surgeon considers that it can be removed entirely. Resectable tumours include stages IA, IB and IIA and B of the TNM system, i.e. lesions confined to the pancreas or having spread just outside the pancreas without invading major blood vessels, nerves or lymph nodes. There is however no absolute link between resectability and TNM classification since even a small local tumour can invade the surrounding vasculature. The extent of resection is confirmed after the operation. R0 indicates that all visible and microscopic tumour was removed, the margins are clean. R1 indicates that the histopathological examination of the margins shows cancer cells. In the case of R2 visible tumour could not be removed.[5] The National Comprehensive Cancer Network (NCCN) guideline[6] proposes criteria defining the resectability status based on a publication by the Society of Abdominal Radiology and the American Pancreatic Association (Table 1).[7]

Table 1 – Resectability criteria defined by NCCN.

Resectability status	Arterial	Venous
Resectable	No arterial tumour contact [coeliac axis (CA), superior mesenteric artery (SMA), or common hepatic artery (CHA)]	No tumour contact with the superior mesenteric vein (SMV), or portal vein (PV) or <180° contact without vein contour irregularity
Borderline resectable	Pancreatic head/uncinate process • Solid tumour with CHA without extension to coeliac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction • Solid tumour contact with the SMA <180° • Presence of variant arterial anatomy (e.g. accessory right • hepatic artery) and the presence and degree of tumour contact should be noted if present as it may affect surgical planning Pancreatic body/tail • Solid tumour contact with the CA of <180° • Solid tumour contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery (some members prefer these criteria to be in the unresectable category)	Solid tumour contact with the SMV or PV of >180°, contact of <180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessels proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction • Solid tumour contact with the inferior vena cava
Unresectable	• Distant metastases Pancreatic head/uncinate process • Solid tumour contact with SMA >180° • Solid tumour contact with the CA >180° • Solid tumour contact with the first jejunal SMA branch Body and tail • Solid tumour contact with the SMA and CA • Solid tumour contact with the CA and aorta	Pancreatic head/uncinate process • Unreconstructible SMV/PV due to tumour involvement or occlusion (can be due to tumour or bland thrombus) • Contact with most proximal draining jejunal branch into SMV Body and tail • Unreconstructible SMV/PV due to tumour involvement or occlusion (can be due to tumour or bland thrombus)

Borderline resectable cancer involves stage III that may be considered resectable by the surgeon. LAPC and metastatic cancer are unresectable. LAPC has not spread to distal sites (metastases) but has invaded the surrounding vasculature to such an extent (see Table 1) that it cannot be entirely removed by surgical intervention. However, attempts may be made to resect LAPC, after chemo(radio)therapy, then called induction therapy. The Guideline Development Group (GDG) underlined that definitions vary and in practice, attempts are made to offer the best chances for resection to an individual patient. Stage IV or metastatic cancer is always unresectable.

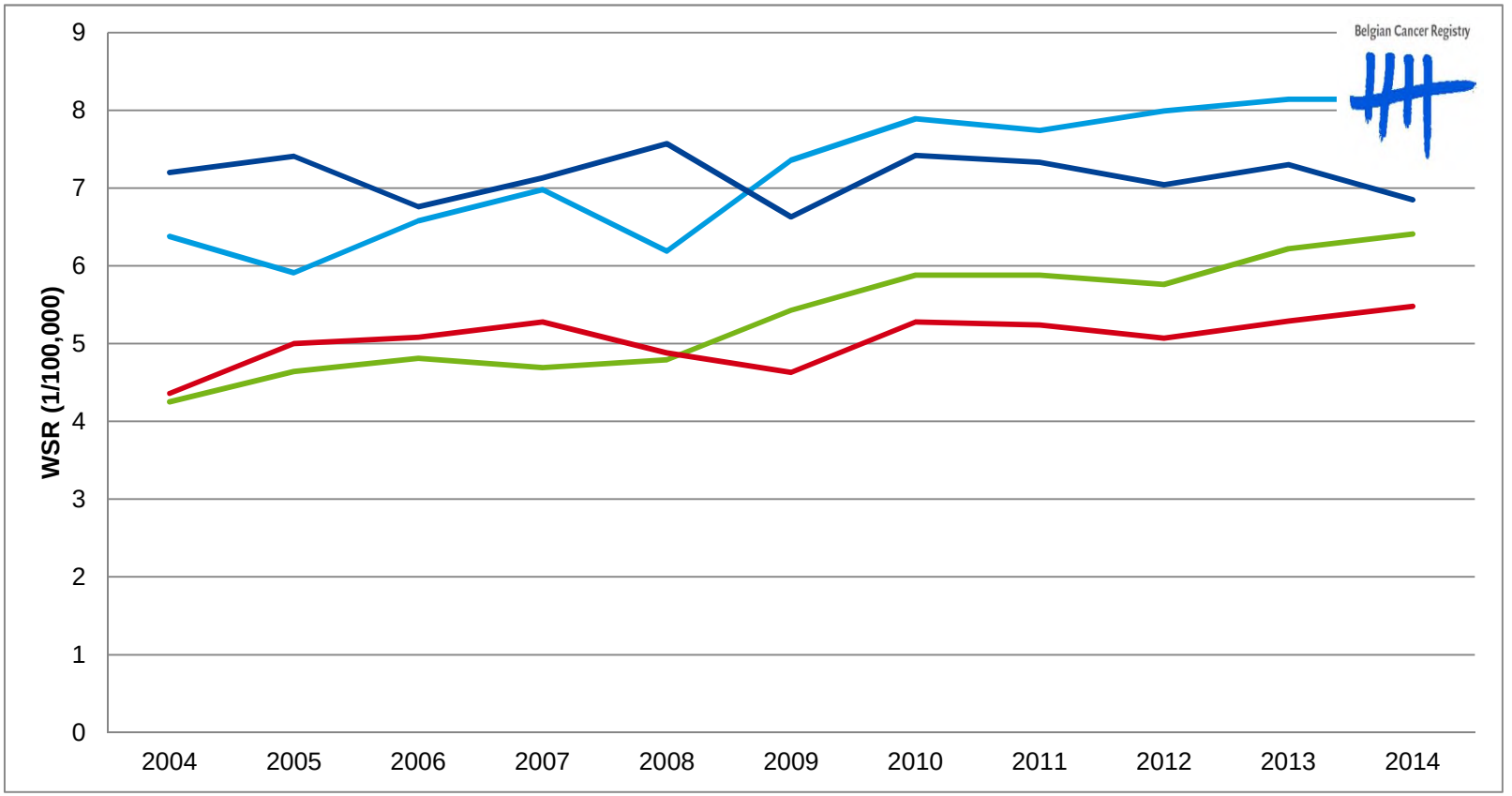
The American Cancer Society estimates the average lifetime risk of pancreatic cancer for both men and women at 1 in 65 (1.5%). Life style (e.g. smoking, obesity) and genetic factors affect individual risk. Estimates in the United States for 2016 are that about 53 070 people (27 670 men and 25 400 women) will be diagnosed with pancreatic cancer and about 41 780 people (21 450 men and 20 330 women) will die of pancreatic cancer. Statistics on pancreatic cancer for the period 2008-2012 state an incidence rate of 12.3 per 100 000, age adjusted to the 2000 United States standard population and death rate of 10.9.[8] The Surveillance, Epidemiology and End Results (SEER) database in the United States also provide informative statistics regarding survival. The proportion of patients surviving five years after diagnosis is as low as 7.7% (time period 2006-2012). For the same time period (2006-2012) the proportion of patients by stage was 9% localised (confined to the primary site), 29% regional (spread to regional lymph nodes), 52% distant (metastasized) and 10% unknown. The five year survival by stage was 29.3% for localised cancer, 11.1% for regional, 2.6% for distant and 4.9% for unstaged cancers.[9]

Pancreatic Cancer Action, based in the United Kingdom reports a five year survival of 5% and stresses that this figure has not improved significantly in almost 50 years.[10]

The Belgian Cancer Registry (www.kankerregister.org) publishes Fact Sheets with overviews on the incidence of pancreatic cancer in the three Belgian Regions and for different age groups up until 2014.[11] For all types of pancreatic cancer the average age at diagnosis was 68.5 years for men and 71.1 years for women in 2014. The age standardised rate, using the World Standard Population per 100 000 person-years was 8.1 for men and 6.4 for women for the entire country with small differences across regions. Between 2004 and 2014 a rise in incidence is noted: from 6.4 to 8.1 for men and 4.3 to 6.4 for women (http://www.kankerregister.org/media/docs/publications/BCR_publicatieCancerBurden2015.pdf).

Figure 1 depicts the rising incidence and mortality for men and women from 2004 until 2014. The lower numbers of the early years may be affected by incomplete registration (personal communication Belgian Cancer Registry).

Figure 1 – Incidence and mortality rates of pancreatic carcinoma in Belgium (2004-2014)



Legend: light blue: incidence men, dark blue: mortality men; green: incidence women, red: mortality women

The number of new diagnoses and incidence per gender and age for pancreatic adenocarcinoma specifically in 2014 were communicated separately (courtesy Belgian Cancer Registry) and are presented in Table 2. The standardised mortality rate for pancreatic adenocarcinoma was 6.85 for men and 5.48 for women in Belgium for the year 2014.

Table 2 – Pancreatic adenocarcinoma: new diagnoses and incidence per gender and age in Belgium (2014)

Pancreas (ICD-10:C25): Adenocarcinomen*: incidence by gender, Belgium 2014

Belgian Cancer Registry

Pancreas adenocarcinoma*: new diagnoses diagnoses by age and gender

	Total	00-	05-	10-	15-	20-	25-	30-	35-	40-	45-	50-	55-	60-	65-	70-	75-	80-	85+
both genders	1297	-	-	-	-	1	2	4	5	11	33	71	124	171	215	222	214	169	55
men	683	-	-	-	-	-	1	2	3	7	20	36	78	96	116	113	115	74	22
women	614	-	-	-	-	1	1	2	2	4	13	35	46	75	99	109	99	95	33

Pancreas adenocarcinoma*: incidence by gender, age group and standardized for Belgium 2014

	Total	00-	05-	10-	15-	20-	25-	30-	35-	40-	45-	50-	55-	60-	65-	70-	75-	80-	85+	CR	ESR	WSR	CRi
both genders	1297	-	-	-	-	0.1	0.3	0.5	0.7	1.4	4.1	8.8	16.8	26.1	37.2	52.6	54.1	52.7	19.8	11.6	8.3	5.7	0.7
men	683	-	-	-	-	-	0.3	0.5	0.8	1.8	4.9	8.9	21.2	29.7	41.6	57.9	66.7	58.9	25.8	12.5	9.5	6.5	0.8
women	614	-	-	-	-	0.3	0.3	0.5	0.6	1.0	3.3	8.7	12.4	22.6	33.1	48.0	44.3	48.7	17.2	10.8	7.2	4.9	0.7

CR: crude rate of bruto-incidence (n/100.000 person years)
ESR and WSR: age standardised incidence base on European and World standardpopulation (n/100.000 person years)
CRi: Cumulative Risk for 0-74 yrs (%)

* neuro-endocrine tumors are excluded

Histology according to ICD-O-3:
Adenocarcinoma 8140-8149;8160-8239;8250-8576/3

Source: Courtesy Belgian Cancer Registry

1.2 The need for a guideline

A comprehensive guideline was previously published (2009); scientific evidence was searched up until February 2008. The planned update, foreseen after five years, is now due.[1] The rising incidence and sombre prognosis of pancreatic cancer are all the more motivating to re-assess the evidence providing patients with the best possible outcomes.

A search for existing guidelines on pancreatic cancer published over the previous ten years was performed in February 2016 (Table 3). NCCN was the only recent comprehensive guideline identified. In February 2016 we identified the version 2.2015 but in April 2016 the next version 1.2016 was posted on the website.[6]

However since the methodology used for the production of this guideline was not fully clear, and since it is based on a single database for the systematic searches (Medline) it was not taken into consideration for an ADAPTE procedure (www.adapte.org). In addition, NCCN issued a guideline on pancreatic cancer intended to be used by patients.[12] Integraal Kankercentrum Nederland (IKNL) published a guideline in Dutch in 2011.[13] The National Guideline Clearinghouse reports on asymptomatic neoplastic pancreatic cysts.[14] The Guidelines International Network (GIN) resource yielded two reports published in 2015 with critical appraisals of existing guidelines published until November 2013[15] and April 2014.[16] Both concluded that there is a lack of high quality evidence based guidelines. Finally the National Institute for Health and Care Excellence (NICE) published technology appraisal guidance on specific subjects: paclitaxel,[17] electroporation[18] and cabazitaxel.[19]

1.3 Scope

Based on limited available resources, it was decided to limit the scope of the present update to no more than three research questions (RQs) for *de novo* searches.

In order to select three RQs to update the 2009 KCE guideline [1] a scoping meeting was held with a group of experts, named the scoping group, on March 21st, 2016. The scoping group consisted of members of the GDG and stakeholders (see Colophon). The recommendations extracted from the 2009 KCE guideline were listed and scored (with regard to the presumed need for an update) using an online survey prior to the meeting. The topics with the highest scores were selected and discussed in detail (Table 11).

The ranking was as follows according to the adherence rates:

- 85% for “What is the optimal treatment strategy in patients with recurrent or metastatic pancreatic cancer?”
- 77% for “Neoadjuvant treatment: Is neoadjuvant treatment with chemotherapy, radiotherapy or both associated with better survival, resectability, quality of life (QoL), and complication rate compared to no neoadjuvant treatment: a) in patients with resectable pancreatic cancer? b) in patients with locally advanced or borderline resectable pancreatic cancer, then called induction therapy?”
- 75% for “Is a high volume of pancreatic resections associated with better outcomes in patients with resectable pancreatic cancer?”
- 71% for "What is the value of the following diagnostic procedures in the diagnosis of pancreatic cancer: ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasonography (EUS) + fine needle aspiration (FNA) of the primary tumour, positron emission tomography (PET) scan, endoscopic retrograde cholangiopancreatography (ERCP), tumour markers, and cyst fluid analysis?". Because the question regarding high volume centres is more related to health service research (HSR) than good clinical practice (GCP) guidelines, this RQ was not addressed in the present report. The three remaining questions with the highest scores were retained, discussed, reformulated and proposed in a logical order (diagnosis, therapy, recurrence).

We decided not to consider the volume/outcome relationship in resectable pancreatic cancer since this would need a separate focused study of Belgian practice, which was beyond the available KCE resources for the present report. Moreover, a 2009 KCE report already concluded that for pancreas cancer surgery, there is abundant evidence that results are better in high volume centres. Therefore, KCE recommended “centralising the expertise in a limited number of centres by establishing an annual minimum threshold of pancreatectomies…”. [20]

Table 3 – Websites for guidelines

Institute	Website	Number of hits and reference
GIN guideline resource	http://www.g-i-n.net/	2 [15, 16]
IKNL	www.iknl.nl	1 [13]
National Guideline Clearinghouse	http://www.guideline.gov/	1 [14]
NCCN	www.nccn.org	2 [6, 12]
NICE guidelines	www.nice.org.uk	3 [17-19]
SIGN guidelines	www.sign.ac.uk	0
Unicancer	http://www.unicancer.fr/	0

1.4 Remit of the guideline

1.4.1 Overall objectives

This guideline provides recommendations based on current scientific evidence for three specific RQs about pancreatic cancer. Clinicians are encouraged to interpret these recommendations in the context of the individual patient situation, values and preferences. The guidelines are based on clinical evidence and may not always be in line with the current criteria for National Institute for Health and Disability Insurance (NIHDI-RIZIV/INAMI) reimbursement of diagnostic and therapeutic interventions. The NIHDI may consider to review reimbursement/funding criteria based on the guidelines.

1.4.2 Target users of the guideline

This guideline is intended to be used by all care providers involved in the management of patients with pancreatic cancer, including general practitioners, oncologists, gastroenterologists, surgeons, radiologists, pathologists and nurses. It should also be of interest to patients and their families, hospital managers and policy makers.

1.5 Statement of intent

Clinical Guidelines are designed to improve the quality of health care and decrease the use of unnecessary or harmful interventions. This guideline has been developed by clinicians and researchers for use within the Belgian healthcare context. It provides advice regarding the care and management of patients with pancreatic cancer. The recommendations are not intended to indicate an exclusive course of action or to serve as a standard of care. Standards of care are determined on the basis of all the available clinical data for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Variations, which take into account individual circumstances, clinical judgement and patient choice, may also be appropriate. The information in this guideline is not a substitute for proper diagnosis, treatment or the provision of advice by an appropriate health professional. It is advised, however, that significant deviations from the national guideline are fully documented in the patient's file at the time the relevant decision is taken.

1.6 Funding and declaration of interest

KCE is a federal institution funded for the largest part by INAMI – RIZIV, but also by the Federal Public Service of Health, Food chain Safety and Environment, and the Federal Public Service of Social Security. The development of clinical practice guidelines is part of the legal mission of the KCE. Although the development of guidelines is paid by KCE's budget, the sole mission of the KCE is providing scientifically valid information. KCE has no interest in companies (commercial or non-commercial i.e. hospitals and universities), associations (e.g. professional associations, unions), individuals or organisations (e.g. lobby groups) that could be positively or negatively affected (financially or in any other way) by the implementation of these guidelines. All clinicians involved in the GDG, stakeholders and the peer-review process completed a declaration of interest form. Information on potential conflicts of interest is published in the Colophon of this report. All members of the KCE Expert Team make yearly declarations of interest and further details of these are available upon request.

2 GENERAL METHODOLOGY

2.1 Introduction

The KCE guideline is produced according to highly codified principles, based on scientific information regularly updated from the international literature. This guideline was developed using a standard methodology based on a systematic review of the evidence. Further details about KCE and the guideline development methodology are available at https://kce.fgov.be/content/kce-processes.

Several steps were followed to elaborate this guideline. At first, clinical questions were selected and the inclusion and exclusion criteria were defined in collaboration with a scoping group, consisting of members of the GDG and stakeholders. The composition of the different groups is documented in the Colophon. In a second step, a systematic literature review was conducted. The third step involves formulation of recommendations based on the literature review and grading according to the GRADE approach.

2.2 The Guideline Development Group

This guideline was developed as a result of a collaboration between multidisciplinary groups of practising clinicians, the Dutch Cochrane Collaboration (DCC) and KCE experts. Guideline development and literature review expertise, support and facilitation were provided by the KCE expert team assisted by an external team: the Dutch Cochrane Centre (DCC).

The roles assigned to the GDG were:

- To define the clinical questions, in close collaboration with the KCE expert team and stakeholders;
- To identify critical and important outcomes;
- To provide feedback on the selection of studies and identify further relevant manuscripts which may have been missed;
- To provide feedback on the content of the guideline;

- To provide judgement about indirectness of evidence;
- To provide feedback on the draft recommendations;
- To address additional concerns to be reported under a section on 'other considerations'.

2.3 General approach and research questions

As discussed above, the selection of RQs was made by the members of the GDG, representatives of professional organizations and patient representatives, constituting a scoping group. An online survey was held prior to a face to face meeting on March 21, 2016. The following three RQs were selected and re-formulated after discussion:

RQ1: What is the best diagnostic strategy in the following conditions?

1. Suspicion of resectable pancreatic cancer
2. Suspicion of borderline resectable pancreatic cancer
3. Suspicion of locally advanced pancreatic cancer
4. To exclude metastasis in known pancreatic cancer (in order to assess resectability)

The various diagnostic procedures to be considered are: US, CT, MRI including various technologies such as magnetic resonance cholangiopancreatography (mRCP), EUS, PET scan, FNA, tumour markers and laparoscopy.

RQ2: Is neoadjuvant treatment with chemotherapy, radiotherapy or both, followed by surgery, associated with better overall survival (OS), resectability, quality of life (QoL) and complication rate compared to no neoadjuvant treatment?

a. in patients with resectable pancreatic cancer?

b. in patients with borderline resectable pancreatic cancer?

c. in patients with LAPC? Since LAPC patients are by definition not amenable to surgery, the notion "neoadjuvant therapy" was replaced by "induction therapy" indicating that some patients with LAPC might become resectable after chemotherapy.

RQ3: What is the optimal treatment strategy in patients with recurrent or metastatic pancreatic cancer?

2.3.1 RQs, PIRT and PICOs

The RQs were expressed as population - index test - reference test - target disorder (PIRT) for the diagnostic RQ and population-intervention-comparator-outcome (PICO) for the therapeutic RQs as described below.

Table 4 – RQ 1

RQ1: What is the best diagnostic strategy in the following conditions? **1. Suspicion of resectable pancreatic cancer** **2. Suspicion of borderline resectable pancreatic cancer** **3. Suspicion of locally advanced pancreatic cancer**	
P (patient)	a. Patients suspected of resectable pancreatic cancer b. Patients suspected with borderline resectable cancer c. Patients suspected with locally advanced pancreatic cancer
I (Intervention)	CT MRI different technologies, mRCP EUS +/- FNA +/- cyst fluid analysis PET scan Tumour markers: Ca19.9 and CEA Laparoscopy
R (Reference standard)	Histopathology and/or clinical follow-up and/or surgery
T (Target)	Diagnosis, assess resectability

Table 5 – RQ 2 a & b

Is neoadjuvant treatment with chemotherapy, radiotherapy or both, followed by surgery, associated with better survival, resectability, QoL and complication rate compared to no neoadjuvant treatment? a. in patients with resectable pancreatic cancer? b. in patients with borderline resectable pancreatic cancer?	
P	patients with pancreas cancer: a: resectable, b: borderline resectable
I	neoadjuvant chemotherapy, radiotherapy or both
C	upfront surgery and adjuvant therapy for groups a and b systemic therapy only for group b
O	per subgroup and definition: OS, disease free survival (DFS), QoL, resection rate and R0 resections, adverse events (AE)

Table 6 – RQ 2 c

For patients diagnosed with LAPC, is induction treatment with chemotherapy, radiotherapy or both, followed by surgery, associated with better survival, resectability, QoL and complication rate compared to any other type of treatment	
P	patients with LAPC
I	induction with chemotherapy, radiotherapy or both
C	surgery or systemic therapy (any other type of therapy)
O	OS, DFS, QoL, resection rate and R0 resections, AEs

Table 7 – RQ 3

What is the optimal treatment strategy in patients with recurrent/metastatic pancreatic cancer?	
P	Patients presenting with recurrent/metastatic pancreas cancer?
I	chemotherapy radiotherapy chemoradiotherapy (CRT) re - resection
C	best supportive care, including palliative care
O	OS, QoL

2.4 Literature search

For each RQ a search for systematic reviews (SR) was conducted in MEDLINE, Embase and The Cochrane Library (Cochrane Database of Systematic Reviews, DARE and HTA database). If a recent high quality SR was available a search for primary studies published after the search date of the review was performed in MEDLINE, Embase and CENTRAL. If no SR was available, primary studies were searched for in the databases from 2008 onwards. Members of the GDG were also consulted to identify additional relevant evidence that may have been missed by the search. Detailed search strategies per database can be found in the sections related to each particular RQ. Only full articles published in English, German, Dutch and French were included.

2.5 Selection process

Studies were screened on title and abstract using the PICO and PIRT in- and exclusion criteria and irrelevant studies were eliminated. In a second step, the remaining papers were screened by reading the full-text. If no full-text was available, the study was excluded for the final recommendations. Reference lists of the selected studies were hand searched for additional relevant manuscripts. The flow charts illustrating the selection process can also be found in each section.

2.6 Quality appraisal

2.6.1 Systematic reviews

Selected SRs were critically appraised by two DCC researchers independently of each other using the AMSTAR checklist (Table 12) (http://amstar.ca/Amstar_Checklist.php).[21] In doubt, a third KCE expert was consulted.

2.6.2 Primary studies

Critical appraisal of each study was performed by two DCC researchers independently of each other. In doubt, a third KCE expert was consulted. Retrieved diagnostic studies were assessed for the risk of bias with the QUADAS-2 tool (Table 13).[22] The quality appraisal of randomised controlled trials (RCT) for therapeutic interventions was performed using the "Cochrane Collaboration's tool for assessing risk of bias" (Table 14).[23] If applicable, risk of bias for the items regarding detection bias and attrition bias were assessed per class of outcomes (e.g. subjective and objective outcomes).

For the assessment of the quality of comparative observational studies the Cochrane Collaboration's tool for assessing risk of bias was used, but with the addition of two extra items that apply to potential bias due to the selection of participants: 'Concurrency of the intervention and comparator group' and 'Comparability of the intervention and comparator group'. For the first item low risk of bias was assigned if the participants in the intervention and comparator group were enrolled and followed-up concurrently (i.e. in parallel). For the second item low risk of bias was assigned in case of a matched study design and/or appropriate adjustment for confounders in the analysis (e.g. age, tumour type, stage, performance status). The tools used for the quality appraisal are reported in the appropriate sections related to each particular RQ.

2.7 Data extraction and evidence summary

For each SR the following data were extracted: title and reference, funding sources, search date, databases being searched, number and types of included studies (RCT, comparative cohort study or other study type), details about the statistical analysis, eligibility criteria, exclusion criteria, number of participants, patient and disease characteristics, details of the intervention and comparator groups that have been addressed in the review, results for the outcomes as defined in the various RQs, and limitations and other comments regarding the review.

For each primary study the following data were extracted: title, reference, type of study (RCT, comparative cohort study or other study type), source of funding, country and setting, sample size, duration and follow-up, details about the statistical analysis, eligibility criteria, exclusion criteria, number of participants, patient and disease characteristics (including baseline comparability), details of the intervention and comparator (e.g. type, dose, duration, route of administration) or details of the index test(s) and reference standards, results, and limitations and other comments regarding the study. For observational studies the results that are adjusted for confounders were reported, if presented in the original study. Important confounders (prognostic factors) to be considered depend on the RQ, but may include (amongst others) age, tumour type, tumour stage, performance status.

2.8 Statistical analysis

For each comparison (intervention vs. comparator) separate analyses were performed if data were available. If a recent SR with low risk of bias was available, the results of the review were used and presented in Summary of Findings Tables. If new RCTs were identified, the existing SR and meta-analysis (MA) were updated. This was only feasible if the required data in the review were readily available (i.e. the review reports the 2 by 2 Tables of the included studies). If not feasible, the results of the newly identified RCTs were summarized and presented in Summary of Findings Tables. For diagnostic test accuracy, meta-analyses were performed according to the statistical guidelines described in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (DTA), (http://srdta.cochrane.org/handbook-dta-reviews) while for treatment, meta-analyses were performed according to the statistical guidelines described in the Cochrane Handbook for Systematic Reviews of Interventions (http://www.cochrane.org/training/cochrane-handbook) using Review Manager Software (Review Manager 2014). Heterogeneity was statistically assessed with χ^2 test and I^2 statistic. If heterogeneity was present, a random-effects model was used instead of a fixed-effect model. Possible reasons for heterogeneity were explored post-hoc. Sensitivity analysis was performed by removing outliers from the analysis. Studies that were clinically heterogeneous or did not present the data in sufficient detail to enable statistical pooling were summarized qualitatively. Forest plots were reported in each particular section, when appropriate.

2.9 Grading evidence

For each recommendation, we provided its strength and the quality of the supporting evidence.[24] According to GRADE, we classified the quality of evidence into four categories: high, moderate, low, and very low (Table 16). The quality of evidence reflects the extent to which a guideline panel's confidence in an estimate of the effect was adequate to support a particular recommendation (Table 17).

Quality rating for RCTs was initially considered to be of high level. The rating was then downgraded if needed based on the judgement of the different quality elements. Each quality element considered to have serious or very serious risk of bias was rated down -1 or -2 points respectively. Judgement of the overall confidence in the effect estimate was also taken into account. We considered confidence in estimates as a continuum and the final rating of confidence could differ from that suggested by each separate domain.[25]

Observational studies were considered low level of evidence by default. However, the level of evidence of observational studies with no threats to validity could be upgraded for a number of reasons:

1. Large magnitude of effects: The larger the magnitude of effect, the stronger becomes the evidence. As a rule of thumb, the following criteria were proposed by GRADE:
    a. Large, i.e. RR >2 or <0.5 (based on consistent evidence from at least 2 studies, with no plausible confounders): upgrade 1 level
    b. Very large, i.e. RR >5 or <0.2 (based on direct evidence with no major threats to validity): upgrade 2 levels
2. All plausible confounders from observational studies or randomized trials may be working to reduce the demonstrated effect or increase the effect if no effect was observed
3. Dose-response gradient may increase the confidence in the findings of observational studies and thereby increase the quality of evidence.

The general principles used to downgrade the quality rating are summarized in Table 18. Decisions on downgrading with -1 or -2 points were based on the judgement of the assessors. Reasons for (not) downgrading were summarized in the GRADE profiles in each particular section when applicable. For GRADEing the level of evidence for DTA studies the methods were applied as described in 2008.[26]

2.10 Literature search for patient preferences

There was no search performed on patient preferences for this report.

2.11 Formulation of recommendations

Based on the retrieved evidence, a first draft of recommendations was prepared by KCE experts and circulated with the evidence tables to the GDG two weeks prior to the face-to-face meetings (November 14th, 2016 and February 6th, 2017). Recommendations were changed if important new evidence supported this change. Based on the discussion during the first meeting a second draft of recommendations was prepared and circulated to the GDG for final approval.

The strength of each recommendation was assigned using the GRADE system (Table 19). The strength of recommendations depends on a balance between all desirable and all undesirable effects of an intervention (i.e., net clinical benefit), quality of available evidence, values and preferences and estimated cost (resource utilization) (Table 20). A strong recommendation implies that most patients would want the recommended course of action. A weak recommendation implies that the majority of informed patients would want the intervention but many would not.[27] Specifically, a strong negative recommendation means the harms of the recommended approach clearly exceed the benefits whereas a weak negative recommendation implies that the majority of patients would not want the intervention, but many would. In the case of a weak recommendation, clinicians are especially required to spend adequate time with patients to discuss their values and preferences. Such an in-depth discussion is necessary to empower the patient to make an informed decision.

For policy-makers, a strong recommendation implies that variability in clinical practice between individuals or regions would be inappropriate whereas a weak recommendation implies that variability between individuals or regions may be appropriate, and therefore its application as quality of care criterion would be inappropriate.[27] For interpretation of "strong" and "weak" recommendations (see Table 21). No formal cost-effectiveness study was conducted.

2.12 External review

2.12.1 Healthcare professionals

The recommendations prepared by the GDG were circulated to the stakeholders. Professional associations (Table 22) were contacted and asked to assign one or two key representatives to act as external reviewers (stakeholders) of the draft guideline. The external experts were involved in the evaluation of the clinical recommendations (February 20th, 2017). All invited panellists received the scientific reports for the RQs and were asked to score each recommendation on a 5-point Likert scale indicating their level of agreement with the recommendation, with a score of '1' indicating 'completely disagree', '2' 'somewhat disagree', '3' 'unsure', '4' 'somewhat agree', and '5' 'completely agree' or 'not applicable' if they were not familiar with the underlying evidence. If panellists disagreed with the recommendation (score '1' or '2'), they were asked to provide an explanation supported by appropriate evidence. Scientific arguments reported by these experts led to rephrasing the clinical recommendations. An overview is provided of the scores and comments in each chapter. The comments were addressed under the heading *'other considerations'* in each chapter.

2.12.2 Patient representatives

Associations of patient representatives (Fondation contre le Cancer – Stichting tegen Kanker and Kom op tegen Kanker) were contacted to invite patient representatives to take part in the scoping and stakeholder meetings. A key role for patient representatives is to ensure that patient views and experiences inform the group's work. The views of the patient representatives were included under the heading *'other considerations'* in each chapter.

2.12.3 Final validation

As part of the standard KCE procedures, an external scientific validation of the report was conducted prior to its publication. The scientific content was assessed by three validators on March 2, 2017 (see Colophon).

2.13 Implementation and updating of the guideline

2.13.1 Multidisciplinary approach

In this report we focused on the effectiveness of specific medical interventions, without taking into account the organization of health services. In clinical practice, a multidisciplinary approach by different health care professionals should be encouraged. This approach should not only cover the medical needs of the patient but also their psychosocial needs.

2.13.2 Patient-centered care

The choice of a treatment should not only consider medical aspects but also patient preferences. Patients should always receive timely and comprehensive information about treatment options, advantages and disadvantages.

2.13.3 Barriers and facilitators for implementation

During the stakeholders meeting, the potential barriers and facilitators related to the use of this guideline were discussed. Information on the identification of barriers and facilitators in guidelines implementation can be found in a recent KCE-report (see KCE website: https://kce.fgov.be/fr).

2.13.4 Actors of the implementation of this guideline

Clinical guidelines provide a tool for physicians to consult at different stages of the patient management pathway: screening, diagnosis, treatment and follow-up. They are developed according to highly codified principles, based on scientific information regularly updated from the international literature. KCE formulates recommendations addressed to specific audiences (clinicians, decision-makers, sickness funds, NIHDI, professional organizations, hospital managers…) but is not involved in the decision making process itself nor in the execution of the decisions.

The implementation of this guideline will be facilitated/conducted by the College of Oncology and the professional associations involved. Dissemination of this guideline is intended by scientific and professional organisations. They can make attractive and user-friendly tools tailored to caregivers groups using diverse channels such as websites or continuing education.

2.13.5 Monitoring the quality of care

This guideline should be considered as a starting point to develop quality improvement programs that targets all caregivers concerned. It can be used as a tool to support health policies to improve the quality of care, e.g. through the support of actions to increase caregivers' awareness and to improve their practice, or through the development (or revision) of sets of process and outcome quality indicators. KCE previously recommended to set up an integrative quality system in oncology, covering the development and implementation of clinical practice guidelines, the monitoring of the quality of care with quality indicators, feedback to health care providers and organizations and targeted actions to improve the quality if needed.[28]

2.13.6 Guideline update

In view of the rapidly evolving evidence, guidelines should be updated every five years. Important new evidence would become available in the meantime, this should be taken into consideration. Potential interest for groups of health practitioners is also considered in this process. This appraisal should lead to a decision on whether to update a guideline or specific parts of it to ensure the recommendations stay in line with the latest scientific developments.

3 APPENDIX

3.1 UIAC TNM CLASSIFICATION

Table 8 – TNM Classification of Tumours, Pancreas (ICD-O C25)

T – Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour 2 cm or less in greatest dimension
T1a	Tumour 0.5 cm or less in greatest dimension
T1b	Tumour greater than 0.5 cm and less than 1 cm in greatest dimension
T1c	Tumour greater than 1 cm but no more than 2 cm in greatest dimension
T2	Tumour more than 2 cm in greatest dimension but no more than 4 cm in greatest dimension
T3	Tumour more than 4 cm in greatest dimension
T4	Tumour involves coeliac axis, superior mesenteric artery and/or common hepatic artery
N – Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases in 1 to 3 regional lymph node
N2	Metastases in 4 or more regional lymph node
M – Distant metastases	
M0	No distant metastasis
M1	Distant metastasis

Source: IUAC 8th edition3

Table 9 – pTNM pathological classification

pT – Primary Tumour
pT is the pathological classification corresponding to the T categories
pN – Regional lymph nodes
pN is the pathological classification corresponding to the N categories
pM- Distant metastases
pM1 distant metastasis microscopically confirmed

Table 10 – Stage grouping pancreas cancer - IUAC 8th edition

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1,T2,T3	N1	M0
Stage III	T1,T2,T3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

3.2 Scoping

Table 11 – Scoring research questions by the scoping group

Research Question	Completely disagree (A1)	Somewhat disagree (A2)	Unsure (A3)	Somewhat agree (A4)	Completely agree (A5)	Not applicable to me (A6)	No answer	adherence rate	Comments
What is the value of mass screening for pancreatic cancer?	6	4	0	2	12	1	3	58%	at risk population can be defined
What is the value of surveillance of patients at high risk for developing pancreatic cancer?	0	6	3	5	10	1	3	63%	With credentialing for quality of EUS and MRI-If Prospective registries are part of peer-reviewed, then agree-at risk population are defined, we must sensitize to proper work-up-I agree, but I know that in the field, screening is proposed to a lot of families - it may be interesting to look into the 'guidelines' as suggested by the different genetic groups
What is the value of symptoms and signs in the diagnosis of pancreatic cancer?	5	4	0	4	11	1	0	63%	What about jaundice?-what is the value of jaundice as a frequent symptom?;also painless obstructive jaundice, pain left hemi-abdomen, maybe venous thrombosis
What is the value of the following diagnostic procedures in the diagnosis of pancreatic cancer: ultrasonography (US), CT, MRI, endoscopic ultrasonography (EUS) + fine needle aspiration (FNA) of the primary tumour, PET scan, ERCP, tumour markers, and cyst fluid analysis?	3	4	0	4	13	1	0	71%	protocol for ct scan ercp ?- I think CA 19.9 can be considered as part of the diagnostic work-up, and obviously for follow-up- work-up has to be: - abdominal CT 3-phasic + chest CT - serum tumour markers need to be taken when a lesion is found - tissue is not necessary before surgery (if it would not change the type of surgery) - it is in metastatic disease and has to be taken by EUS-guided FNA or a biopsy in a metastatic lesion - MRI, ERCP, PET-CT can be useful - for cysts: MRI, EUS and CT provide additional information (fluid analysis...: is the evidence that high??)

Research Question	Completely disagree (A1)	Somewhat disagree (A2)	Unsure (A3)	Somewhat agree (A4)	Completely agree (A5)	Not applicable to me (A6)	No answer	adherence rate	Comments
What is the value of the following procedures in the staging of pancreatic cancer: US, CT, MRI, EUS + FNA, PET scan, laparoscopy, laparotomy and ERCP?	1	6	2	2	12	2	0	61%	systematic laparascopy should be strongly suggest clearer definition of what is really resectable disease must be emphasized as neoadjuvant approach is gaining popularity, the term of diagnostic laparoscopy must be reviewed- the place of this exam must be defined and re-evaluated -to my knowledge no indication for PET/CT in this situation;- CT abdomen and chest - 3 phases, not only for liver but also for operability locally -PET-CT low evidence
Neoadjuvant treatment: Is neoadjuvant treatment with chemotherapy, radiotherapy or both associated with better survival, resectability, quality of life (QoL), and complication rate compared to no neoadjuvant treatment: a: in patients with resectable pancreatic cancer? b: in patients with locally advanced borderline resectable pancreatic cancer?	2	3	0	9	8	2	1	77%	see prior question-newer chemotherapeutic possibilities, eg Folfirinox- Role of radiotherapy unclear
Is preoperative biliary drainage (PBD) associated	3	3	2	3	8	4	1	58%	data are valid for a certain level of bilirubinemia and not applicable to all patients, criteria of preoperative drainage must be defined, should

Research Question	Completely disagree (A1)	Somewhat disagree (A2)	Unsure (A3)	Somewhat agree (A4)	Completely agree (A5)	Not applicable to me (A6)	No answer	adherence rate	Comments
with better postoperative outcomes compared to no PBD in patients with obstructive jaundice caused by pancreatic cancer?									not be done if bilirubin preoperative < 15 mg/dl. Stenting increases infectious complications postresection- For all stented bile ducts peroperative bile cultures should be taken- Depends on the level of bilirubine-Le drainage peut même être délétère car augmente le risque infectieux.
Is radical resection (including lymphadenectomy) associated with better survival, postoperative mortality, complication rate and recurrence rate compared to no resection in patients with resectable pancreatic cancer?	3	4	2	2	10	2	1	57%	Venous resection is associated with lower survival rate and a surrogate for adverse prognostic factors (Delpero)-indication for laparoscopic surgery must be defined- if well accepted with good results for a left pancreatectomy, the indication for a right pancreatectomy is not clear at all. Should a laparoscopic approach be considered for a right pancreatectomy? - unsure about the lymph nodes
Is pylorus preservation associated with better outcomes compared to no preservation in patients with resectable pancreatic cancer?	4	2	1	3	7	4	3	59%	
Which technique is preferred for pancreaticoenteric anastomosis in patients with	3	3	1	3	5	5	4	53%	PGS has a slightly lower risk for leakage and when there is a leakage the complication rate is lower-This is recommended for soft pancreata. On the other hand there is a higher rate of

Research Question	Completely disagree (A1)	Somewhat disagree (A2)	Unsure (A3)	Somewhat agree (A4)	Completely agree (A5)	Not applicable to me (A6)	No answer	adherence rate	Comments
resectable pancreatic cancer?									exocrine insufficiency due to inactivation of pancreatic enzymes; I know about the recent publication on pancreaticogastrostomy but I am not convinced
Is laparoscopic pancreatic resection associated with better outcomes than open resection in patients with resectable pancreatic cancer?	4	3	1	0	9	4	3	53%	distinction between left and right pancreatectomy must be made- complication rate is not lower after laparoscopic resections
Is a high volume of pancreatic resections associated with better outcomes in patients with resectable pancreatic cancer?	3	2	0	1	14	1	3	75%	Comparison with ProCare must be drawn- the quality of the center is as important as the volume- definition of a high volume center is difficult (do high volume center operate on cancer only or do they also included pancreatitis for the evaluation?) more criteria than postoperative mortality must be evaluated to define a good center (quality of the resection,incidence and gravity of the fistula, survival...),,,,,,,Voir la définition des "high volume". Les centres qui réalisent ce type d'intervention doivent disposer des infrastructures spécifiques : réanimation, radiologie interventionnelle, équipes chirurgicales complètes (2 chirurgiens, assistants, instrumentistes). This statement remains valid, but there is still no adequate tool nor legal obligation for surgeons or hospitals to act accordingly.....?
What prognostic factors influencing outcome in patients	4	2	1	4	10	2	1	67%	need for more guidelines for standardisation- lymph node status: also extracapsular growth is important

Research Question	Completely disagree (A1)	Somewhat disagree (A2)	Unsure (A3)	Somewhat agree (A4)	Completely agree (A5)	Not applicable to me (A6)	No answer	adherence rate	Comments
with pancreatic cancer need to be reported in the pathology report?									
Is adjuvant treatment with chemotherapy, radiotherapy or both associated with better survival, QoL, complication rate and recurrence rate compared to no adjuvant treatment in patients with pancreatic cancer treated with radical resection?	2	4	2	4	8	2	1	60%	5FU is also appropriate-role of radiotherapy in R1 status patients?R1 chemotherapy may be followed by chemoradiotherapy
Is follow-up after curative treatment of pancreatic cancer associated with better survival compared to no follow-up?	3	4	0	6	6	2	2	63%	The answer is not an answer to the question: I do not think it has an impact on survival - however, I believe FU is useful because it allows us to start therapy early (and helps us for trials,... gaining knowledge)
Is treatment with chemotherapy, radiotherapy, or both associated with better survival and QoL compared to no such treatment in patients with inoperable pancreatic cancer?	3	3	0	4	9	2	2	68%	RCT have been published in the field-newer chemotherapeutic options: Gemcitabine/Abraxane? -Folfirinox if possibility of resection after shrinkage?,,there are other options now besides gemcitabine +/- erlotinib-Gemcitabine -No erlotinib -Folfirinox is an option - Other regimen as well new therapeutic options

Research Question	Completely disagree (A1)	Somewhat disagree (A2)	Unsure (A3)	Somewhat agree (A4)	Completely agree (A5)	Not applicable to me (A6)	No answer	adherence rate	Comments
Is stenting associated with better survival and QoL compared to surgical bypass or no stenting in patients with inoperable pancreatic cancer and obstructive jaundice?	6	3	0	1	9	3	1	53%	place of surgical drainage (open or by laparoscopy) must be defined in case of peroperative diagnosis of unresectable cancer -If inoperable during surgical exploration option for surgical bypass -it depends: bypass may be better in jaundice + gastric outlet but mostly stent is the best option
In patients having undergone pancreatic resection, what is the role of nutritional support, somatostatin (analogues), enzyme replacement and pain treatment in their postoperative care?	3	1	3	3	7	3	3	59%	NCPB could be proposed earlier, as demonstrated by the Sahai et al paper, published in JCO-all must be considered in the preoperative setting < nutritional support and "fast track"-coeliac block: abdominal pain but more often back pain
In patients with pancreatic cancer, what is the role of psychological support?	7	2	0	1	8	2	3	50%	
Is vascular resection indicated in patients with pancreatic cancer?	0	3	4	3	7	3	3	59%	Which vascular resection? feasible but associated to worse outcome if predicable treatment with neoadjuvant therapy is advocated, difference between vein and arterial resection must be done type of vascular reconstruction should be discussed, arterial resection and reconstruction is not

Research Question	Completely disagree (A1)	Somewhat disagree (A2)	Unsure (A3)	Somewhat agree (A4)	Completely agree (A5)	Not applicable to me (A6)	No answer	adherence rate	Comments
									recommended unless in selected cases. Venous resection and reconstruction is recommended if R0 is possible- no, I think this question may be considered (belongs in part to one of the first questions on operability)
Is palliative surgery indicated in patients with inoperable pancreatic cancer?	4	5	1	2	5	2	4	41%	answer is NO, place of surgical drainage face to endoscopic drainage, In selected cases - Solitary hepatic metastases detected during operation-Invasion para-aortic lymph nodes detected during operation-yes, It may be considered in very specific cases, but I do not think it is worthwhile addressing -It should not be re-evaluated but it should be clearly said that it is not indicated!
What is the optimal treatment strategy in patients with recurrent pancreatic cancer?	1	0	1	4	7	4	6	85%	obvious: Palliative chemotherapy, to be discussed during the meeting-there is no answer to this question
What is the use of biomarkers in screening or in prognostic evaluation?	3	0	3	7	2	2	6	60%	what kind of biomarker-investigational-there is no existing valuable information (at least not strong enough to put in guidelines)

3.3 Critical appraisal checklists for systematic reviews and primary studies

3.3.1 Systematic reviews

AMSTAR criteria were used to assess systematic reviews.

Table 12 – AMSTAR checklist

Question	Answer
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	□ Yes □ No □ Can't answer □ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	□ Yes □ No □ Can't answer □ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	□ Yes □ No □ Can't answer □ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	□ Yes □ No □ Can't answer □ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	□ Yes □ No □ Can't answer □ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	□ Yes □ No □ Can't answer □ Not applicable

7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	□ Yes □ No □ Can't answer □ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	□ Yes □ No □ Can't answer □ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	□ Yes □ No □ Can't answer □ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	□ Yes □ No □ Can't answer □ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	□ Yes □ No □ Can't answer □ Not applicable

3.3.2 Diagnostic accuracy studies

The quality assessment tool used for the quality assessment of diagnostic accuracy studies was QUADAS Tool.

Table 13 – The QUADAS tool

Item	Label	Yes	No	Unclear	Not applicable
1.	Was the spectrum of patients representatives of the patients who will receive the test in practice?				
2.	Were selection criteria clearly described?				
3.	Is the reference standard likely to correctly classify the target condition?				
4.	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?				
5.	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?				
6.	Did patients receive the same reference standard regardless of the index test result?				
7.	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?				
8.	Was the execution of the index test described in sufficient detail to permit replication of the test?				
9.	Was the execution of the reference standard described in sufficient detail to permit its replication?				
10.	Were the index test results interpreted without knowledge of the results of the reference standard?				
11.	Were the reference standard results interpreted without knowledge of the results of the index test?				
12.	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?				
13.	Were uninterpretable/ intermediate test results reported?				
14.	Were withdrawals from the study explained?				

3.3.3 Primary studies for therapeutic interventions

To assess risk of bias of RCTs we used Cochrane Collaboration's tool.

Table 14 – Cochrane Collaboration's tool for assessing risk of bias

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment
Performance bias		
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias		
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessors
Attrition bias		
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any reinclusions in analyses performed by the review authors	Attrition bias due to amount, nature or handling of incomplete outcome data
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	Reporting bias due to selective outcome reporting
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were pre specified in the review's protocol, responses should be provided for each question/entry	Bias due to problems not covered elsewhere in the table

To conduct the quality appraisal of comparative cohort studies, the following tool was used.

Table 15 – Additional items for assessing risk of bias of comparative observational primary studies (cohort studies)

Additional item	Review authors' judgement
Concurrency of the intervention and comparator group	Low risk of bias will be assigned if the participants in the intervention and comparator group were enrolled and followed-up concurrently (i.e. in parallel)
Comparability of the intervention and comparator group	Low risk of bias will be assigned in case of a matched study design and/or appropriate adjustment for confounders in the analysis (e.g. age, tumour type, stage, performance status)

3.4 Grading evidence

Table 16 – A summary of the GRADE approach to grading the quality of evidence for each outcome.

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias	1. Large effect 2. Dose-response 3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	High (⨁⨁⨁⨁) Moderate (⨁⨁⨁⊖) Low (⨁⨁⊖⊖) Very low (⨁⊖⊖⊖)
Observational studies	Low			

Source: Guyatt GH [29]

Table 17 – Levels of evidence according to the GRADE system.

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Source: Balshem[24]

Table 18 – Downgrading the quality rating of evidence using GRADE.

Quality element	Reasons for downgrading
Limitations	For each study reporting the selected outcome, possible risk of bias introduced by lack of allocation concealment, lack of blinding, lack of intention-to-treat analysis, loss of follow-up and selective outcome reporting were assessed. Additionally, other limitations such as stopping early for benefit and use of unvalidated outcome measures were taken into consideration. Level of evidence was downgraded if studies were of sufficiently poor quality. Downgrading was omitted if studies with low risk of bias were available that lead to similar conclusions as the studies with a high risk of bias.
Inconsistency	Downgrading the level of evidence for inconsistency of results was considered in the following situations: point estimates vary widely across studies, confidence intervals show minimal or no overlap, the statistical test for heterogeneity shows a low p-value or the I^2 is large. If large variability in magnitude of effect remained unexplained, the quality of evidence was rated down.
Indirectness	Quality rating was downgraded for indirectness in case the trial population or the applied intervention differed significantly from the population or intervention of interest. Also, the use of surrogate outcomes could lead to downgrading. A third reason for downgrading for indirectness occurred when the studied interventions were not tested in a head-to-head comparison.
Imprecision	Evaluation of the imprecision of results was primarily based on examination of the 95% confidence interval (CI). Quality was rated down if clinical action would differ if the upper versus the lower boundary of the 95%CI represented the truth. In general, 95%CIs around relative effects were used for evaluation, except when the event rate was low in spite of a large sample size. To examine the 95%CIs, the clinical decision threshold (CDT) was defined. When the 95%CI crossed this clinical decision threshold, the quality level was rated down. A relative risk reduction (RRR) of 25% was defined as CDT by default and adapted if deemed appropriate e.g. in case of a low risk intervention. Even if 95%CIs appeared robust, level of evidence could be rated down because of fragility. To judge fragility of results, it is suggested to calculate the number of patients needed for an adequately powered (imaginary) single trial, also called the optimal information size (OIS). If the total number of patients included in a systematic review was less than the calculated OIS, rating down for imprecision was considered. For calculations, a RRR of 25% was used, unless otherwise stated. When the OIS could not be calculated, a minimum of 300 events for binary outcomes and a minimum of 400 participants for continuous outcomes were used as a rule of thumb.
Reporting bias	Quality rating was downgraded for reporting bias if publication bias was suggested by analysis using funnel plots or searching of trial registries. Publication bias was also suspected if results came from small, positive industry-sponsored trials only.

3.5 Formulation of recommendations

3.5.1 Evaluation of the recommendations

Table 19 – Strength of recommendation according to the GRADE system

Grade	Definition
Strong	The desirable effects of an intervention clearly outweigh the undesirable effects *(the intervention is to be put into practice)*, or the undesirable effects of an intervention clearly outweigh the desirable effects *(the intervention is not to be put into practice)*
Weak	The desirable effects of an intervention probably outweigh the undesirable effects *(the intervention probably is to be put into practice)*, or the undesirable effects of an intervention probably outweigh the desirable effects *(the intervention probably is not to be put into practice)*

Source: Andrews[27]

Table 20 – Factors that influence the strength of a recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention, i.e. the greater the resources consumed, the lower the likelihood that a strong recommendation is warranted

Sources: Schünemann[30] and Guyatt[31]

Table 21 – Interpretation of strong and conditional (weak)* recommendations

Implications	Strong recommendation	Weak recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

** The terms "conditional" and "weak" can be used synonymously. Source: Andrews JC [27]*

3.5.2 Stakeholder meeting

Table 22 – List of contacted professional associations

Belgian Society of Medical Oncology - Belgische Vereniging voor Medische Oncologie - Société Belge d'Oncologie Médicale (BSMO)
Belgische Vereniging voor Radiotherapie-Oncologie - Association Belge de Radiothérapie-OncoloSgie (BVRO - ABRO)
Belgian Group of Digestive Oncology (BGDO)
Belgian Society of Surgical Oncology (BSSO)
Royal Belgian Society of Surgery - Koninklijk Belgisch Genootschap voor Heelkunde (KBGH) - Société Royale Belge de Chirurgie (SRBC)
Belgian Society of Radiology (BSR)
Belgische Vereniging voor Nucleaire Geneeskunde - Société Belge de Médecine Nucléaire
Belgian Society of Pathology - Belgische Vereniging Anatomopathologie - Société Belge d'Anatomopathologie
Société Royale Belge de Gastroentérologie
Société Scientifique de Médecine Générale (SSMG)
The Belgian Society of Gastrointestinal Endoscopy (BSGIE)
The Belgian Group for Endoscopic Surgery (BGES)
Vlaamse Vereniging voor Gastro-enterologie (VVGE)

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