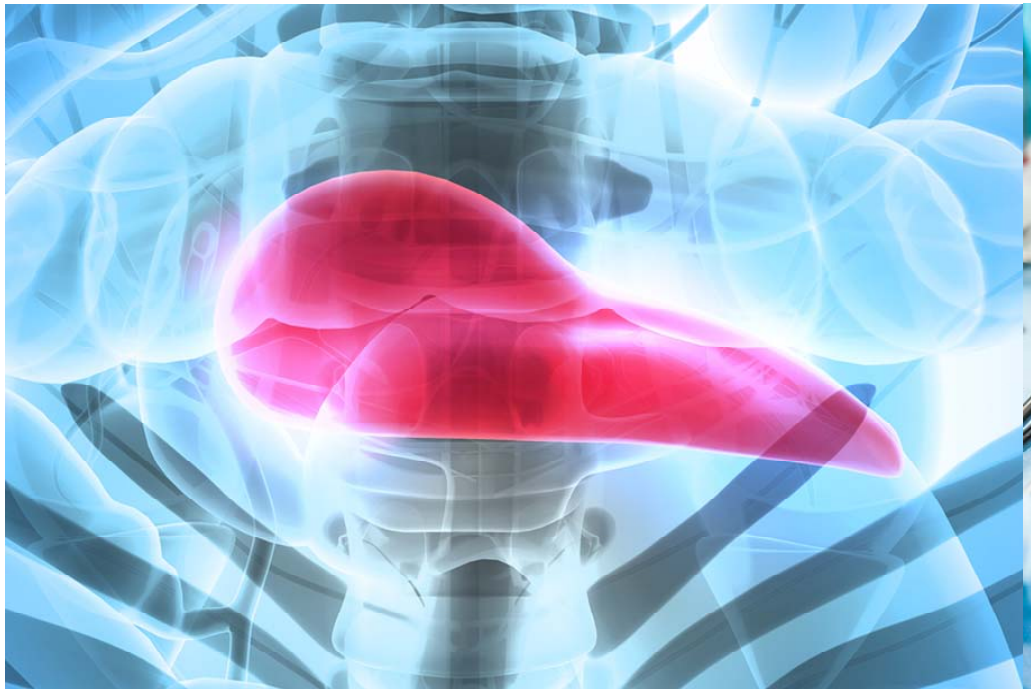
KCE REPORT 286Cs

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

SUMMARY

MANAGEMENT OF PANCREATIC CANCER: CAPITA SELECTA



KCE REPORT 286Cs
GOOD CLINICAL PRACTICE

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SUMMARY

MANAGEMENT OF PANCREATIC CANCER: CAPITA SELECTA

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FOREWORD

Every scientist who applies himself to the development of clinical practice guidelines should accept the fact that these guidelines will be outdated even before they are published. There are two reasons for this. Thousands of new studies are published on a daily basis and the there is a high probability that new insights will be published in the time between completing a study and publishing it. The second reason is more fundamental in nature. Evidence-based medicine demands a statistical approach, with sufficient numbers of patients, and preferably also an observation time of sufficient length. Consequently, it takes years to collect enough evidence to prove the efficacy of any “breakthrough” in the field of diagnosis or treatment.

Every board member of an institution that applies itself to the development of clinical practice guidelines should also accept the fact that a time will come when it is physically impossible to continue regularly updating the growing number of guidelines that were published in the past. It is therefore important to be very selective in this regard and to focus on the hot issues and the most important developments.

Therefore, this document contains an update of only three clinical questions that the guideline development group awarded the highest priority and not a completely new version of our guideline from 2009. Unfortunately we do not have any spectacular breakthroughs to report, but every inch of ground that we can gain on this very malignant tumour is worth the effort. We hope that our work will contribute to moving the prognosis for these patients in the right direction.

Christian LÉONARD
Deputy general director

Raf MERTENS
General director

SUMMARY

TABLE OF CONTENTS

1. INTRODUCTION AND SCOPE

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 (KCE report 105A) and needed update. The present report focuses on a limited number of clinical questions, related to pancreatic adenocarcinoma, which is the most common variant of pancreatic cancer.

For all types of pancreatic cancer registered in Belgium, 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).

The scope of the present update was limited to three research questions (RQs). 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 guideline development group (GDG) and stakeholders (see colophon). The recommendations extracted from the 2009 KCE guideline were listed and scored using an online survey prior to the meeting (see Appendix). The following RQs were selected:

1. 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?
2. 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?
3. What is the optimal treatment strategy in patients with recurrent pancreatic cancer?

2. TARGET USERS

This report is intended for 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.

3. METHODS

3.1. Systematic review of the literature

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 or French were included.

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. Reference lists of the selected studies were hand searched for additional relevant manuscripts. Selected SRs were critically appraised by two researchers independently of each other using the AMSTAR checklist (http://amstar.ca/Amstar_Checklist.php). In doubt, a third expert was consulted.

Critical appraisal of each primary study was performed by two researchers of the Dutch Cochrane Centre independently of each other. In doubt, a third expert was consulted. Retrieved diagnostic studies were assessed for the risk of bias with the QUADAS-2 tool. The quality appraisal of randomised controlled trials (RCT) for therapeutic interventions was performed using the "Cochrane Collaboration's tool for assessing risk of bias". 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.

3.2. Patient preferences

Patient organisations were as stakeholders involved in the development of this guideline.

3.3. Formulation of recommendations

Based on the retrieved evidence, a first draft of recommendations was prepared 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.

To determine the level of evidence and strength of each recommendation, the GRADE methodology was followed (Table 1 and Table 2). The strength of a recommendation depends on the balance between all desirable and all undesirable effects of an intervention (i.e., net clinical benefit), the quality of available evidence, values and preferences, and the estimated cost (resource utilisation). For this guideline, no formal cost-effectiveness study was conducted.

Table 1 – 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, 2011

Table 2 – 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 JC, 2013

The recommendations prepared by the GDG were submitted to key representatives of the relevant stakeholders (see colophon), who acted as external reviewers of the draft guideline. Finally, as part of the standard KCE procedures, the current guideline was reviewed prior to its publication by three independent validators (cf. colophon). Declarations of interest of GDG members, validators and stakeholders were formally recorded and listed in the colophon.

4. CLINICAL RECOMMENDATIONS

The details of the evidence used to formulate the recommendations below are available in the four modules of the scientific report. The tables follow the same sequence as the modules of the scientific report.

4.1. Diagnosis of pancreatic cancer

The research question on diagnostic procedures in the diagnosis of pancreatic cancer was subdivided into two parts. The first relates to differentiating benign from malignant pancreatic lesions, and the second to assessing the surgical resectability of a malignant lesion. A tumour is considered not resectable if it is locally advanced (precluding complete resection), and/or if there are distant metastases (e.g. in the lungs, liver, peritoneum). A borderline resectable cancer is a stage III cancer that may be considered resectable by some surgeons.

In patients suspected of pancreatic cancer, no firm conclusions can be drawn regarding the accuracy of imaging tests to differentiate malignant from benign lesions. Serum biomarkers CA 19-9 and CEA lack sensitivity as single test to diagnose malignancy of pancreatic cancer lesions. In patients with potentially resectable pancreatic cancer lesions based on imaging tests, no firm conclusions can be drawn regarding the accuracy of endoscopic ultrasound (EUS) for predicting curative resectability

The GDG stressed that the diagnostic procedures discussed in this report are part of the general diagnostic assessment of patients with pancreatic cancer and that tumour staging was not part of the present guideline update. Regarding laparoscopy, the GDG reported that in some centres laparoscopic exploration and subsequent laparotomy or laparoscopic resection are performed as one procedure. Due to differences in logistics and organisation this practice is not universal.

Recommendations	Level of Evidence	Strength of recommendation
1. All patients suspected of pancreatic cancer should undergo diagnostic imaging with abdominal CT.	very low	strong
2. Diagnostic imaging with EUS, MRI, or PET scan should not routinely be used for differentiating benign from malignant lesions.	very low	weak
3. In cases in whom CT is inconclusive EUS (+/- FNA) or MRI should be used in an attempt to differentiate benign from malignant lesions.	very low	strong
4. Serum tumour markers CA 19-9 and CEA on their own are not indicated for the primary diagnosis of pancreatic cancer.	very low, to low	strong
5. Laparoscopy should be considered in pancreatic cancer deemed resectable after high quality imaging, in order to avoid unnecessary laparotomies due to liver or peritoneal metastases.	very low	strong
6. EUS is not indicated for assessing resectability of pancreatic cancer.	very low	strong

4.2. Neoadjuvant therapy in pancreatic cancer

Recommendations related to neoadjuvant therapy depend on the resectability status of the tumour at diagnosis. A tumour is resectable when the surgeon considers that it can be removed entirely. Resectable tumours include stages IA, IB and IIA of the TNM system, i.e. lesions confined to the pancreas or having spread just outside the pancreas without invasion of major blood vessels, nerves or lymph nodes. There is no link between resectability and TNM classification because a small local tumour can invade the surrounding vasculature.

Borderline resectable cancer involves stage III that may be considered resectable by the surgeon. Locally advanced pancreatic cancer (LAPC) and metastatic cancer are considered unresectable. However, attempts may be made to resect LAPC, especially after chemotherapy, then called induction therapy.

Recommendations	Level of Evidence	Strength of recommendation
1. Neoadjuvant chemotherapy is not recommended for resectable pancreatic cancer.	very low to low	strong
2. Neoadjuvant chemotherapy for resectable pancreatic cancer is recommended only in the context of a clinical trial.	NA	strong
3. Neoadjuvant chemotherapy for borderline resectable pancreatic cancer should be considered.	very low	strong
4. Chemotherapy or radiotherapy with the intention to bring the patient to surgery is not recommended for LAPC (clearly not resectable).	very low	strong

4.3. Recurrent and metastatic pancreatic cancer

Recurrent and metastatic pancreatic cancer carry a grim prognosis with a 5-year survival of less than 10%. This chapter focusses on the recommendations regarding various current therapeutic attempts in case of recurrent pancreatic cancer or metastatic cancer.

Recommendations	Level of Evidence	Strength of recommendation
1. If patients with advanced pancreatic cancer (LAPC or metastatic) are treated with chemotherapy, gemcitabine in monotherapy is to be preferred over 5-FU in monotherapy.	moderate	strong
2. If fit patients with metastatic pancreatic cancer are treated with chemotherapy, combination therapy with gemcitabine and taxane, or the FOLFIRINOX chemotherapy combination are preferred over gemcitabine in monotherapy.	high	strong
3. Do not recommend re-resection in patients with recurrent or metastatic pancreatic cancer.	NA	strong

4.4. Implementation and updating of the guideline

4.4.1. Multidisciplinary approach

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

4.4.2. 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.

The patient organisations underlined that the poor prognosis of pancreatic cancer presses for high level coordinated research programs on the causes and treatment of pancreatic cancer.

4.4.3. Guideline update

In view of the rapidly evolving evidence, guidelines should be updated every five years. A partial update may be necessary if important new evidence becomes available.

COLOPHON

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