Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
KCE

Soutien scientifique au Collège d'Oncologie: recommandations pour la pratique clinique dans la prise en charge du cancer du pancréas

KCE reports 105B

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
2009

Le Centre fédéral d'expertise des soins de santé

Présentation : Le Centre fédéral d'expertise des soins de santé est un parastatal, créé le 24 décembre 2002 par la loi-programme (articles 262 à 266), sous tutelle du Ministre de la Santé publique et des Affaires sociales, qui est chargé de réaliser des études éclairant la décision politique dans le domaine des soins de santé et de l'assurance maladie.

Conseil d'administration

Membres effectifs : Gillet Pierre (Président), Cuypers Dirk (Vice-Président), Avontroodt Yolande, De Cock Jo (Vice-Président), De Meyere Frank, De Ridder Henri, Gillet Jean-Bernard, Godin Jean-Noël, Goyens Floris, Maes Jef, Mertens Pascal, Mertens Raf, Moens Marc, Perl François, Van Massenhove Frank (Vice-Président), Vandermeeren Philippe, Verertbruggen Patrick, Vermeyen Karel.

Membres suppléants : Annemans Lieven, Bertels Jan, Collin Benoît, Cuypers Rita, Decoster Christiaan, Dercq Jean-Paul, Désir Daniel, Laasman Jean-Marc, Lemye Roland, Morel Amanda, Palsterman Paul, Ponce Annick, Remacle Anne, Schrooten Renaat, Vanderstappen Anne.

Commissaire du gouvernement : Roger Yves

Direction

Directeur général a.i. : Jean-Pierre Closon

Directeur général adjoint a.i. : Gert Peeters

Contact

Centre fédéral d'expertise des soins de santé (KCE).
Cité Administrative Botanique, Doorbuilding (10ème)
Boulevard du Jardin Botanique, 55
B-1000 Bruxelles
Belgium

Tel: +32 [0]2 287 33 88
Fax: +32 [0]2 287 33 85

Email : info@kce.fgov.be
Web : http://www.kce.fgov.be

Soutien scientifique au Collège d'Oncologie: Recommandation de bonne pratique pour la prise en charge du cancer du pancréas

KCE reports 105 B

MARC PEETERS, JOAN VLAYEN, SABINE STORDEUR, FRANÇOISE MAMBOURG,
TOM BOTERBERG, BERNARD DE HEMPTINNE, PIETER DEMETTER,
PIERRE DEPREZ, JEAN-FRANÇOIS GIGOT, ANNE HOORENS, ERIC VAN CUTSEM,
BART VAN DEN EYNDEN, JEAN-LUC VAN LAETHEM, CHRIS VERSLYPE

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
2009

KCE reports 105B

Titre :	Soutien scientifique au Collège d'Oncologie: recommandations pour la pratique clinique dans la prise en charge du cancer du pancréas
Auteurs :	Marc Peeters (UGent), Joan Vlayen (KCE), Sabine Stordeur (KCE), Françoise Mambourg (KCE), Tom Boterberg (UGent), Bernard de Hemptinne (UGent), Pieter Demetter (ULB), Pierre Deprez (UCL), Jean-François Gigot (UCL), Anne Hoorens (UZ Brussel), Eric Van Cutsem (UZ Leuven), Bart Van den Eynden (UA), Jean-Luc Van Laethem (ULB), Chris Verslype (UZ Leuven)
Experts externes :	Phillipe Coucke (Association Belge de Radiothérapie-Oncologie)2, Claude Cuvelier (Belgian Club for Digestive Pathology)1, Anne Jouret-Mourin (Belgian Society of Pathology)1,2, Max Lonneux (Société Belge de Médecine Nucléaire)1,2, Willem Lybaert (Belgian Society of Medical Oncology)1,2, Marika Rasschaert (Belgian Society of Medical Oncology)2, Christine Sempoux (Belgian Club for Digestive Pathology)1,2, Baki Topal (Koninklijk Belgisch Genootschap Heelkunde)1,2, Daniël Urbain (Belgian Society of Gastrointestinal Endoscopy)2, Joseph Weerts (Belgian Society of Surgical Oncology)2, Dirk Ysebaert (Belgian Society of Surgical Oncology)1,2 1 présents à la réunion générale; 2 évaluation par scores
Remerciements	Sven D'Haese (Collège d'Oncologie), Kris Henau (Fondation Registre du Cancer)
Validateurs externes :	Raymond Aerts (UZ Leuven), Olivier R.C. Busch (AMC Amsterdam), Marc Polus (CHU Sart-Tilman, Liège)
Conflits d'intérêt :	La plupart des auteurs, experts externes et validateurs travaillent dans un centre spécialisé dans la prise en charge du cancer du pancréas. Marc Peeters et Eric Van Cutsem ont reçu des bourses de recherche de différentes firmes pharmaceutiques. Aucun autre conflit d'intérêt n'a été communiqué.
Disclaimer:	Les experts externes ont collaboré au rapport scientifique qui a ensuite été soumis aux validateurs. La validation du rapport résulte d'un consensus ou d'un vote majoritaire entre les validateurs. Le KCE reste seul responsable des erreurs ou omissions qui pourraient subsister de même que des recommandations faites aux autorités publiques.
Mise en page :	Ine Verhulst

Bruxelles, le16 février 2009

Etude n° 2008-70

Domaine : Good Clinical Practice (GCP)

MeSH : Pancreatic Neoplasms ; Practice Guidelines

Classifications : [NLM] WI 810 ; [ICD-10] C25 ; [ICPC] D76

Langage : Français, Anglais

Format : Adobe® PDF™ (A4)

Dépôt légal : D/2009/10.273/11

Comment citer ce rapport?

Peeters M, Vlayen J, Stordeur S, Mambourg F, Boterberg T, de Hemptinne B, et al. Soutien scientifique au Collège d'Oncologie: Recommandation de bonne pratique pour la prise en charge du cancer du pancréas. Good Clinical Practice (GCP). Brussel: Centre fédéral d'expertise des soins de santé (KCE); 2009. KCE reports 105B (D/2009/10.273/11)

PRÉFACE

Dans la série des recommandations de bonne pratique élaborées en collaboration avec le Collège d'Oncologie, la présente qui porte sur le cancer du pancréas, fait directement suite à celles relatives aux cancers gastro-intestinaux, à savoir le cancer colorectal et le cancer de l'œsophage et de l'estomac. Tout le monde sait que le pronostic du cancer du pancréas est sombre. Pour la majorité des patients, la tumeur n'est pas opérable, et la prise en charge palliative est la seule option envisageable. Seuls 5% des patients survivent au-delà de 5 ans.

Ce mauvais pronostic justifie l'attention particulière accordée dans la présente recommandation à la prise en charge palliative et au soutien des patients ayant un cancer du pancréas. Des conseils spécifiques sont notamment donnés pour la prise en charge de la douleur et au support nutritionnel des patients.

Dans le cas du cancer du pancréas, l'élaboration de recommandations de bonne pratique basées sur les preuves n'est pas une sinécure. Les recommandations internationales de haute qualité sur lesquelles s'appuyer sont rares. De plus, certains traitements spécifiques, tels que la combinaison de la chimiothérapie et de la radiothérapie avant et après la chirurgie, restent à ce jour, très controversés. Et pourtant, un document très complet et de grande qualité a été rédigé, grâce à l'apport essentiel d'un large groupe d'experts motivés et enthousiastes.

Comme pour les recommandations précédentes, fruits de la collaboration entre le Collège d'Oncologie et le KCE, la présente recommandation servira d'assise au développement d'indicateurs de qualité. La qualité des soins aux patients cancéreux est un thème crucial dans le Plan National Cancer, et constitue d'ailleurs le sujet d'un projet KCE en cours, dont les résultats sont attendus à la fin de cette année. A suivre avec intérêt.

Gert Peeters
Directeur général adjoint a.i.

Jean-Pierre Closon
Directeur général a.i.

Résumé

INTRODUCTION

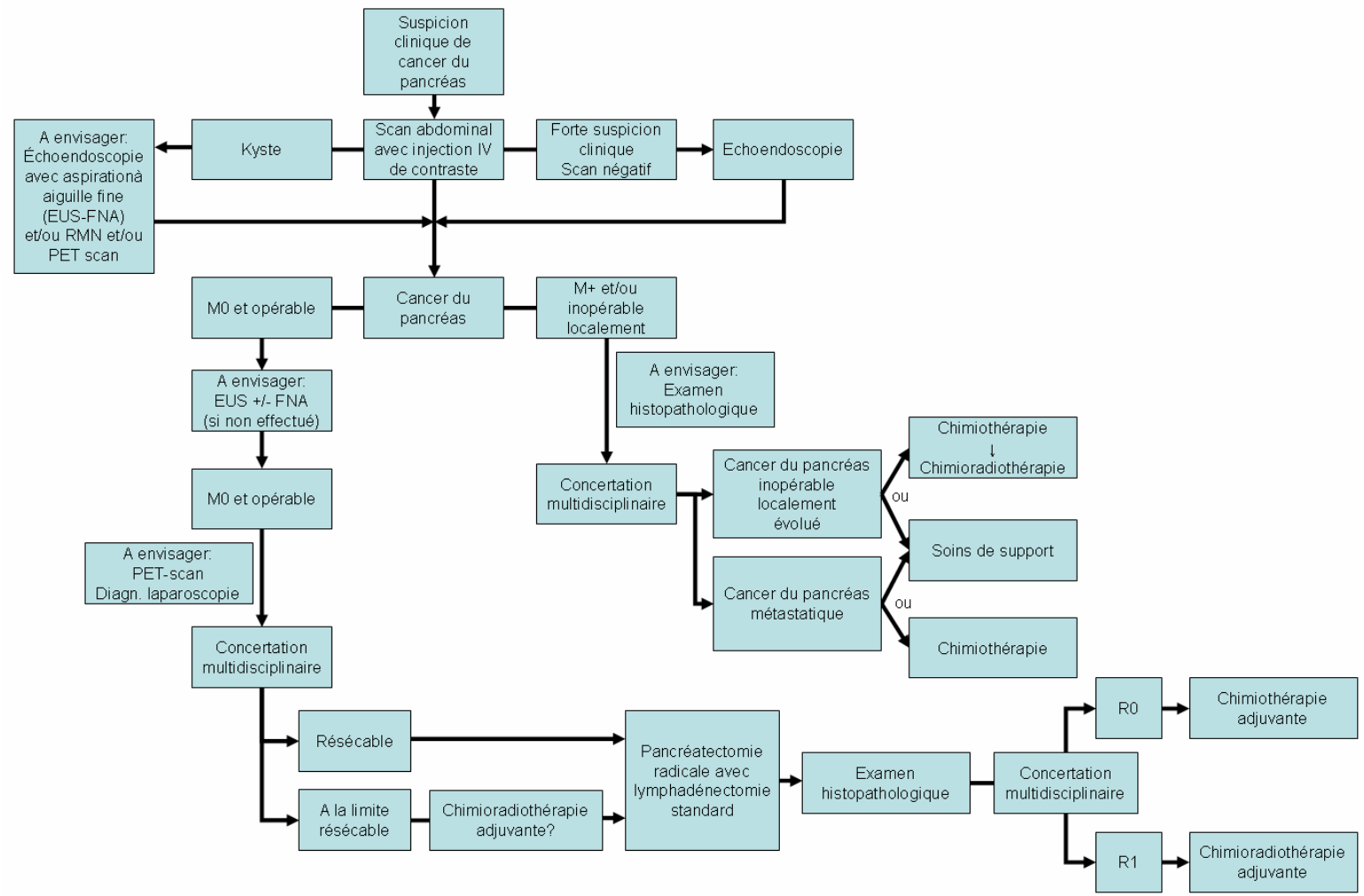
Dans le cadre de la collaboration entre le Collègue d'Oncologie et le KCE, diverses recommandations ont été formulées pour la prise en charge du cancer du pancréas. Lesdites recommandations portent sur l'ensemble du parcours du patient atteint d'un cancer du pancréas, du diagnostic jusqu'au suivi. Ces recommandations sont destinées à tous les dispensateurs de soins impliqués dans la prise en charge de ces patients.

METHODOLOGIE

Pour élaborer ces recommandations, nous avons utilisé la méthodologie ADAPTE. Dans un premier temps, avec l'aide de cliniciens, nous avons formulé les principales questions de recherche cliniques. Les recommandations de bonne pratique (inter)nationales ont été recherchées dans Medline, Embase, The National Guideline Clearinghouse ainsi que sur les sites Internet d'instances publiant des recommandations et d'organisations actives en oncologie. Les 21 recommandations trouvées ont fait l'objet d'une évaluation qualitative, réalisée par deux évaluateurs indépendants, avec l'outil AGREE. Elles ont été retenues ou rejetées sur la base d'une appréciation de leur qualité globale. Ensuite, les 6 recommandations sélectionnées ont été actualisées pour chaque question clinique en recherchant des preuves supplémentaires dans Medline, la Cochrane Database of Systematic Reviews, la Database of Abstracts of Reviews of Effects (DARE) et la Société Américaine d'Oncologie Clinique (ASCO). Pour les matières au sujet desquelles aucune recommandation n'avait été retenue, la recherche de littérature s'est centrée sur les revues systématiques et les études primaires, sans restriction de date.

Sur base des preuves relevées dans la littérature, un groupe pluridisciplinaire a formulé les recommandations de bonne pratique. A chaque recommandation, un niveau de preuve a été attribué ('level of evidence') et un score de recommandation ('grade of recommendation') en utilisant le système GRADE (pour plus de détails : voir le rapport scientifique qui suit ce résumé).

Ces recommandations ont ensuite été soumises de manière formelle à l'appréciation de représentants des associations professionnelles et scientifiques et ont par la suite été débattues en séance publique. Les conflits d'intérêt ont été actés.



IV: intraveineux; RMN: tomographie à résonance magnétique nucléaire; PET: tomographie par émission de positrons; R0: résection complète de la tumeur; R1: résection avec marges positives à l'analyse microscopique.

RECOMMANDATIONS FINALES

ALGORITHME

Voir page précédente.

Les détails des recommandations se trouvent dans le rapport scientifique qui suit le présent résumé.

DÉPISTAGE

Un dépistage systématique du cancer du pancréas n'est pas recommandé. Le suivi des personnes à haut risque de cancer du pancréas doit se dérouler dans le cadre de protocoles scientifiques revus par les pairs.

DIAGNOSTIC

Il convient d'envisager un diagnostic de cancer du pancréas chez les individus présentant : un diabète de type 2 sans facteurs prédisposant ou antécédents familiaux de diabète ; un ictère ; une pancréatite inexpliquée ; une perte de poids rapide ; des dorsalgies inexpliquées.

Outre une anamnèse et un examen clinique, tout patient faisant l'objet d'une suspicion clinique de cancer du pancréas doit passer un scanner diagnostique de l'abdomen (avec injection intraveineuse de produit de contraste, voir 'stadification'). Chez les patients à forte suspicion de cancer du pancréas dont le scanner de l'abdomen se révèle négatif, est en outre recommandée une écho-endoscopie. Lorsqu'une confirmation histopathologique du diagnostic est nécessaire pour définir la suite du traitement, une aspiration à l'aiguille fine sous écho-endoscopie est préconisée.

L'imagerie diagnostique avec échographie transabdominale, tomographie par résonance magnétique nucléaire (RMN), cholangio-pancréatographie rétrograde endoscopique (CPRE) ou une tomographie par émission de positrons (PET scan) peut être envisagée dans des cas spécifiques. Les marqueurs tumoraux sériques ne sont pas appropriés pour diagnostiquer le cancer du pancréas.

Une ponction du liquide kystique avec guidage écho-endoscopique, suivie d'un examen cytologique et d'une détermination des amylases et de l'antigène carcino-embryonnaire (ACE) peut être utile dans le diagnostic différentiel des kystes pancréatiques bénins et (pré)malins.

STADIFICATION

Les patients atteints d'un cancer du pancréas doivent se soumettre en routine à un scanner de l'abdomen avec injection intraveineuse d'un liquide de contraste aux fins d'une stadification locale et d'une stadification à distance. Chez certains patients triés sur le volet souffrant d'un cancer du pancréas, on peut envisager une écho-endoscopie ou une laparoscopie diagnostique. Si, après une stadification conventionnelle, un traitement curatif est considéré comme réalisable, on peut envisager une tomographie par émission de positrons pour une recherche de métastases au niveau des ganglions lymphatiques et d'autres organes. Si l'échographie transabdominale et la RMN ne sont pas préconisées en routine pour la stadification des patients atteints de cancer du pancréas, elles peuvent l'être dans certains cas spécifiques.

Les résultats des examens diagnostiques et de stadification doivent faire l'objet d'une concertation multidisciplinaire afin de définir la prise en charge thérapeutique subséquente.

TRAITEMENT NEO-ADJUVANT

Le traitement néo-adjuvant des patients atteints d'un cancer du pancréas résécable n'est pas recommandé en dehors du cadre des études cliniques. Chez les patients présentant un cancer du pancréas localement évolué de type borderline, un traitement néo-adjuvant avec chimiothérapie ou chimioradiothérapie peut être envisagé. Une réévaluation de la résécabilité est conseillée après 2-3 mois.

TRAITEMENT CHIRURGICAL À VISÉE CURATIVE

Le drainage biliaire préopératoire n'est pas recommandé en routine chez les patients présentant un cancer du pancréas résécable et un ictère obstructif.

Les patients atteints d'un cancer du pancréas résécable et médicalement opérables doivent subir une résection radicale du pancréas (pancréaticoduodénectomie pour les tumeurs de la tête du pancréas, pancréatectomie distale pour les tumeurs du corps et de la queue du pancréas), avec dissection standard des ganglions lymphatiques. L'objectif de cette chirurgie doit être une résection R0 (marges de résection histologiquement indemnes de tumeur ≥ 1 mm). Une dissection radicale et étendue des ganglions lymphatiques n'est pas recommandée.

La résection du pancréas avec reconstruction artérielle n'est pas conseillée chez les patients atteints d'un cancer du pancréas chez qui les artères majeures sont impliquées (artère hépatique, artère mésentérique supérieure et tronc cœliaque). L'invasion veineuse ne constitue pas une contre-indication à la chirurgie. Dans les tumeurs de la partie gauche du pancréas, l'invasion locale de l'artère splénique et/ou veineuse ne constitue pas une contre-indication à la chirurgie.

La chirurgie oncologique du pancréas doit être réservée aux centres qui traitent des volumes importants de cas (selon la littérature, au moins 10 par an) disposant d'une expertise multidisciplinaire et des infrastructures idoines.

EXAMEN HISTOPATHOLOGIQUE

Pour l'examen histopathologique du fragment réséqué d'une tumeur pancréatique, un protocole normalisé est recommandé. L'examen macroscopique comprend un dimensionnement de tous les fragments réséqués, la description de la présence d'une tumeur, la localisation de la tumeur et son origine probable, les dimensions de la tumeur (au minimum son diamètre maximal), le nombre de ganglions lymphatiques et la distance par rapport à la marge de résection la plus proche. L'examen microscopique comprend la détermination du type histologique, la différenciation tumorale, la mesure de la tumeur, le statut des marges de résection, le statut des ganglions lymphatiques, la présence d'une invasion locale, la présence d'une invasion vasculaire ou périneurale et la présence de métastases distales.

TRAITEMENT ADJUVANT

Pour les patients ayant subi une résection pancréatique R0 ou R1, une chimiothérapie postopératoire en monothérapie avec gemcitabine est préconisée. La radiothérapie post-opératoire seule n'est pas recommandée. Dans le cas des patients ayant subi une résection pancréatique R1, on peut envisager une chimiothérapie postopératoire après concertation multidisciplinaire.

SUIVI APRÈS TRAITEMENT CURATIF

Pour les patients ayant subi un traitement curatif pour un cancer du pancréas, des consultations de suivi tous les 3 à 6 mois sont recommandées. Les examens techniques doivent se limiter au minimum chez les patients asymptomatiques.

TRAITEMENT PALLIATIF

Chez les patients atteints d'un cancer métastatique du pancréas, un traitement par chimiothérapie (gemcitabine seule ou en association avec erlotinib) est conseillé.

La chimiothérapie est également recommandée chez les patients souffrant d'un cancer pancréatique localement évolué et inopérable. L'adjonction d'une radiothérapie peut être envisagée sur la base d'une réévaluation après 2 – 3 mois.

Chez les patients atteints d'un cancer du pancréas inopérable et présentant un ictère obstructif, un traitement par stents métalliques est recommandé.

TRAITEMENT DE SOUTIEN

Patients ayant subi une résection du pancréas

Alimentation

Chez les patients devant subir une pancréaticoduodénectomie, il convient d'instaurer un régime préopératoire enrichi, administré par voie orale. Plus généralement, chez les patients qui doivent se soumettre à une chirurgie du pancréas, il faut envisager un soutien nutritionnel postopératoire précoce, de préférence par voie entérale. Une alimentation immunomodulatoire n'est pas conseillée en routine.

Prévention des complications postopératoires de la chirurgie du pancréas

Le traitement préventif avec la somatostatine ou ses analogues n'est pas recommandé en routine, mais peut être envisagé chez des patients à haut risque triés sur le volet devant subir une résection pancréatique.

Les patients présentant une insuffisance pancréatique exocrine symptomatique doivent recevoir une supplémentation en enzymes pancréatiques.

Patients atteints de cancer du pancréas inopérable

On préconise un traitement palliatif et symptomatique optimal chez tous les patients atteints de cancer du pancréas inopérable :

Alimentation

Chez les patients présentant un cancer du pancréas avancé associé à une perte de poids et/ou à une anorexie, il convient d'envisager un conseil en nutrition. Un traitement symptomatique de la douleur, des nausées, des vomissements et de la diarrhée doit être envisagé dans le but de garantir une alimentation orale adaptée.

Douleur

Il convient de respecter une prise en charge en trois étapes pour traiter la douleur consécutive à un cancer du pancréas. C'est ce que l'on appelle l'échelle analgésique proposée par l'Organisation Mondiale de la Santé.

Le blocage neurolytique du plexus cœliaque constitue une option thérapeutique chez les patients souffrant de cancer du pancréas qui sont victimes de violentes douleurs au niveau de la partie supérieure de l'abdomen et ne répondent pas aux autres mesures analgésiques.

Soutien psychologique

Un soutien psychologique spécifique assuré par des professionnels faisant partie d'une équipe multidisciplinaire doit être proposé aux patients souffrant d'un cancer du pancréas.

MISE EN OEUVRE ET IMPLÉMENTATION DE LA RECOMMANDATION

La mise en oeuvre de la présente recommandation sera encouragée grâce à la mise en ligne sur le site Internet du Collège d'Oncologie, d'un outil de mise en œuvre fondé sur l'algorithme général de cette recommandation. Il convient de définir des indicateurs de qualité adéquats sur base des principales consignes de la présente recommandation.

Les preuves étant en évolution constante, une mise à jour de cette recommandation sera vraisemblablement nécessaire à l'horizon de cinq ans, dans la foulée d'une pré-évaluation de la littérature.

Scientific summary

Table of contents

ABBREVIATIONS

95% CI	95 percent confidence interval
5-FU	5-fluorouracil
AGA	American Gastroenterological Association
AHRQ	Agency for Healthcare Research and Quality
APC	Argon plasma coagulation
ARR	Absolute Risk Reduction
ASCO	American Society of Clinical Oncology
ASR	Age-standardised rate
CEA	Carcinoembryonic antigen
CCO	Cancer Care Ontario
CPG	Clinical Practice Guideline
CRT	Chemoradiotherapy
CT	Computed tomography
ERCP	Endoscopic Retrograde Cholangiopancreaticography
EUS	Endoscopic ultrasound
FNA(C)	Fine needle aspiration (cytology)
FNCLCC	Fédération Nationale des Centres de Lutte Contre le Cancer
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard ratio
IMA	Inferior mesenteric artery
IPMN	Intraductal papillary mucinous neoplasm
IPMT	Intraductal papillary mucinous tumour
LN	Lymph node
MDT	Multidisciplinary team
MeSH	Medical Subject Headings
MRCP	Magnetic resonance cholangiopancreaticography
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Clinical Excellence
NNT	Number needed to treat
OR	Odds ratio
PCA	Patient-controlled analgesia
PD	Pancreaticoduodenectomy
PDT	Photodynamic therapy
PET	Positron-emission tomography
PPPD	Pylorus-preserving pancreaticoduodenectomy
QoL	Quality of life

RCT	Randomised Controlled Trial
RT	Radiotherapy
SEER	Surveillance, Epidemiology, and End Results
SIGN	Scottish Intercollegiate Guidelines Network
SMA	Superior mesenteric artery
US	Ultrasonography

1 INTRODUCTION

1.1 SCOPE

In the present report, a clinical practice guideline (CPG) on pancreatic cancer is presented, which is the result of a collaboration of the College of Physicians for Oncology and the KCE. This clinical practice guideline will cover a broad range of topics: screening, diagnosis, staging, treatment, supportive therapy, and follow-up. The guideline primarily concerns individuals with primary exocrine and ductal pancreatic cancer, including cystic tumours and intraductal papillary mucinous tumours (IPMT). It is intended to be used by all care providers involved in the care for these patients.

1.2 EPIDEMIOLOGY

Pancreatic cancer is the fifth leading cause of cancer-related death in Western countries [1]. In 2004, pancreatic cancer was the fourth and fifth most frequent cause of cancer-related death in males (n = 674; 4.6%) and females (n = 627; 5.5%) respectively in Belgium [2].

Pancreatic cancer is the most fatal of all major cancers, with a median survival time of around 6 months and a 5-year relative survival of 5.1% [3]. Although survival rates are highest (21%) when the tumour is localised at diagnosis, less than 10% of tumours are detected at an early stage [3].

Pancreatic cancer is very rare in the first 5 decades of life. After the age of 60, however, incidence rates increase exponentially, peaking in the seventh to eighth decades (56.1 per 100 000 person-years in persons older than 60 years vs. 2.7 per 100 000 person-years in younger age categories) [4].

Men have higher incidence and mortality rates than women (Table 1). Incidence and mortality rates of pancreatic cancer show also important regional disparities. Pancreatic cancer rates are higher in more developed regions, such as Northern America, Europe and Australia, and lower in less developed countries, with some exceptions in Argentina (8.8/100 000) and Uruguay (9.7/100 000). In Europe, the highest incidence is found in Latvia, Estonia, Austria, Italy and Denmark, whereas the lowest incidence is found in Sweden, The Netherlands and Belgium.

Table 1. Age standardised incidence (ASR) and mortality rates by sex in the world (per 100 000 person-years).

	Males		Females	
	ASR incidence	**ASR mortality**	**ASR incidence**	**ASR mortality**
World	4.6	4.4	3.3	3.3
More developed regions	8.1	8.0	5.3	5.4
Less developed regions	2.9	2.6	2.1	2.0
Northern America	8.2	7.7	6.3	6.0
Central and Eastern Europe	8.7	8.5	4.6	4.5
Northern Europe	7.3	7.2	5.7	5.8
Denmark	8.1	8.6	6.9	7.8
Norway	7.6	7.5	5.9	6.4
Sweden	5.6	7.6	4.7	6.8
UK	7.1	6.6	5.8	5.5
Latvia	12.1	11.5	5.8	5.9
Estonia	11.2	10.2	5.7	4.9
Southern Europe	7.5	7.2	4.8	4.7
Italy	8.5	7.7	5.8	5.3
Greece	6.9	6.6	4.3	4.3
Spain	6.6	6.4	3.9	4.0
Western Europe	7.3	8.3	4.9	5.9
Austria	8.9	9.0	7.0	7.3
Belgium	6.0	7.8	4.0	5.5
France	7.2	8.1	3.9	5.1
Germany	7.6	8.7	5.3	6.4
Luxemburg	7.2	8.3	4.6	5.0
The Netherlands	6.0	7.1	5.1	6.1
Switzerland	7.8	7.3	6.1	5.8

Source: Globocan 2002 databases (estimates of the incidence and mortality from 27 cancers for all countries in the world in 2002. Incidence data are available from cancer registries. They cover entire national populations or samples of such populations from selected regions)

Zhang et al. [4] analysed incidence data gathered from nine Surveillance, Epidemiology, and End Results (SEER) registries covering the last three decades (1973–2002) (Table 2). Results indicated that incidence significantly decreased by 0.62% each year from 1973 to 2002 in men. The increase of incidence observed in 1935–1978 in women continued until 1984 and then slightly went down. Importantly, the nine selected SEER registries cover only about 10% of the US population, although almost all representative subsets of the US population are included. Moreover, it is likely that underdiagnosis or misdiagnosis was more common in the 1970s than in the 1980s and 1990s, because computed tomography only became widely available in the 1980s [4].

Table 2. Pancreatic cancer incidence (absolute numbers and age-standardised rates) in the United States, 1973-2002 [4].

Variable	**Incident cases, 1973–2002**	**Incident cases per year**	**ASR 1973–2002**
Age			
< 60	13 983	466	2.70
≥ 60	56 535	1884	56.10
Sex			
Male	35 115	1170	13.53
Female	35 403	1180	10.01
Race			
White	58 841	1961	11.19
Black	7550	252	16.76

In France, a time trend study indicated an increase in age-standardised incidence rate (ASR) of pancreatic cancer between 1980 and 2000 (4.5 vs. 5.8/100 000 for men and 2.1 vs. 3.2/100 000 for women) [5].

In Belgium, the crude incidence rate of pancreatic cancer rose from 7.4 per 100 000 males in 1999 to 10.2 per 100 000 males in 2005, and from 7.6 per 100 000 females in 1999 to 9.6 per 100 000 females in 2005. ASR increased by 5.4% and 7.3% per year (1999-2005) for males and females respectively (Table 3). Compared with incidence rates from The Netherlands between 1999 and 2005, Belgian rates remained lower (probably due to underreporting), but followed the same upwards trend.

Table 3. Age standardised incidence of pancreatic cancer in Belgium and The Netherlands, 1999-2005 (n/100 000 persons-years)

Year	Males		Females	
	The Netherlands	Belgium	The Netherlands	Belgium
1999	5.8	4.3	4.7	3.2
2000	6.6	4.3	4.8	3.4
2001	6.2	4.8	4.5	3.4
2002	6.3	5.5	4.7	3.7
2003	5.9	5.4	4.7	3.8
2004	6.8	6.5	4.8	4.2
2005	6.4	5.7	5.3	4.6

Sources: Belgian Cancer Registry and Kennis Netwerk integrale kanker centra (NL) (http://www.ikcnet.nl/page.php?id=225&nav_id=97)

In Europe, mortality rates have steadily increased between the late 1950s and the 1980s [6]. Trends in 22 European countries, the European Union (EU-15) and 6 selected eastern European countries (Bulgaria, Czech Republic, Hungary, Poland, Romania and Slovakia) have been updated using official death certification data for pancreatic cancer abstracted from the WHO database over the period 1980 to 1999 [6]. An increase in mortality in the 1980s was followed by a levelling off in the 1990s for both sexes among EU countries. In men, a rise from 7.2 to 7.5/100 000 was observed between the early and the late 1980s, followed by a levelling off in the 1990s. For women, rates tended to rise up to the early 1990s, and to level off thereafter around 4.7/100 000. In eastern countries, rates for both sexes rose between the early 1980s and the mid-1990s, and levelled off thereafter around 8.5/100 000 men and 5.0/100 000 women.

2 METHODOLOGY

2.1 GENERAL APPROACH

As for the previous CPGs developed within the collaboration between the College and the KCE, the present CPG was developed by adapting (inter)national CPGs to the Belgian context (www.kce.fgov.be). This approach is currently being structured in a formal methodology by the ADAPTE group, an international group of guideline developers and researchers [7]. The ADAPTE methodology generally consists of three major phases:

1. Set-up Phase: Outlines the necessary tasks to be completed prior to beginning the adaptation process (e.g., identifying necessary skills and resources).

2. Adaptation Phase: Assists guideline developers in moving from selection of a topic to identification of specific clinical questions; searching for and retrieving guidelines; assessing the consistency of the evidence therein, their quality, currency, content and applicability; decision making around adaptation; and preparing the draft adapted guideline.

3. Finalization Phase: Guides guideline developers through getting feedback on the document from stakeholders who will be impacted by the guideline, consulting with the source developers of guidelines used in the adaptation process, establishing a process for review and updating of the adapted guideline and the process of creating a final document.

2.2 CLINICAL QUESTIONS

The clinical practice guideline addresses the following clinical questions (discussed with the multidisciplinary guideline development group during the kick-off meeting on July 9th 2008):

1. Screening:
    a. What is the value of mass screening for pancreatic cancer?
    b. What is the value of surveillance of patients at high risk for developing pancreatic cancer?
2. Diagnosis:
    a. What is the value of symptoms and signs in the diagnosis of pancreatic cancer?
    b. 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. Staging: 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?
4. 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?

5. Surgery:
    a. Is preoperative biliary drainage (PBD) associated with better postoperative outcomes compared to no PBD in patients with obstructive jaundice caused by pancreatic cancer?
    b. 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?
    c. Is pylorus preservation associated with better outcomes compared to no preservation in patients with resectable pancreatic cancer?
    d. Which technique is preferred for pancreaticoenteric anastomosis in patients with resectable pancreatic cancer?
    e. Is vascular resection indicated in patients with pancreatic cancer?
    f. Is laparoscopic pancreatic resection associated with better outcomes than open resection in patients with resectable pancreatic cancer?
    g. Is a high volume of pancreatic resections associated with better outcomes in patients with resectable pancreatic cancer?
6. Pathology: What prognostic factors influencing outcome in patients with pancreatic cancer need to be reported in the pathology report?
7. Adjuvant treatment: 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?
8. Follow-up: Is follow-up after curative treatment of pancreatic cancer associated with better survival compared to no follow-up?
9. Palliative treatment:
    a. Is treatment with chemotherapy, radiotherapy, or both associated with better survival and QoL compared to no such treatment in patients with inoperable pancreatic cancer?
    b. Is palliative surgery indicated in patients with inoperable pancreatic cancer?
    c. Is stenting associated with better survival and QoL compared to surgical bypass or no stenting in patients with inoperable pancreatic cancer and obstructive jaundice?
10. Supportive treatment:
    a. In patients having undergone pancreatic resection, what is the role of nutritional support, somatostatin (analogues) and enzyme replacement in their postoperative care?
    b. In patients with inoperable pancreatic cancer, what is the optimal nutritional strategy and pain treatment? What is the role of enzyme replacement?
    c. In patients with pancreatic cancer, what is the role of psychological support?
11. Recurrent disease: What is the optimal treatment strategy in patients with recurrent pancreatic cancer?

2.3 SEARCH FOR EVIDENCE

2.3.1 Clinical practice guidelines

2.3.1.1 Sources

A broad search of electronic databases (Medline, EMBASE), specific guideline websites and websites of oncologic organisations (Table 4) was conducted in February 2008.

Table 4: Searched guideline websites and websites of oncologic organisations.

Alberta Heritage Foundation For Medical Research (AHFMR)	http://www.ahfmr.ab.ca/
American Society of Clinical Oncology (ASCO)	http://www.asco.org/
American College of Surgeons (ACS)	http://www.facs.org/cancer/coc/
Cancer Care Ontario	http://www.cancercare.on.ca/english/home/
CMA Infobase	http://mdm.ca/cpgsnew/cpgs/index.asp
Guidelines International Network (GIN)	http://www.g-i-n.net/
National Comprehensive Cancer Network (NCCN)	http://www.nccn.org/
National Guideline Clearinghouse	http://www.guideline.gov/
National Cancer Institute	http://www.cancer.gov/
Haute Autorité de Santé (HAS)	http://bfes.has-sante.fr/HTML/indexBFES_HAS.html
BC Cancer Agency	http://www.bccancer.bc.ca/default.htm
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org/index.asp
National Health and Medical Research Council (NHMRC)	http://www.nhmrc.gov.au/
Scottish Intercollegiate Guidelines Network (SIGN)	http://www.sign.ac.uk/
New Zealand Guidelines Group (NZGG)	http://www.nzgg.org.nz/
Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC)	http://www.fnclcc.fr/sor/structure/index-sorspecialistes.html
National Institute for Health and Clinical Excellence (NICE)	http://www.nice.org.uk/

2.3.1.2 Search terms

For Medline the following MeSH terms was used: pancreatic neoplasms. For EMBASE the following Emtree terms were used in combination: pancreas adenocarcinoma, pancreas cancer, pancreas carcinoma, pancreas tumor. These MeSH and Emtree terms were combined with a standardised search strategy to identify CPGs (Table 5).

Table 5: Standardised search strategy for CPGs.

Database	Search strategy
Medline	guideline [pt] OR practice guideline [pt] OR recommendation* [ti] OR standard* [ti] OR guideline* [ti]
EMBASE	'practice guideline'/exp

2.3.1.3 In- and exclusion criteria

Both national and international CPGs on pancreatic cancer were searched. A language (English, Dutch, French) and date restriction (2001 – 2008) were used. CPGs without references were excluded, as were CPGs without clear recommendations.

2.3.2 Additional evidence

For each clinical question, the evidence – identified through the included CPGs – was updated by searching Medline, the Cochrane Database of Systematic Reviews, DARE, and the proceedings of the annual meetings of the American Society of Clinical Oncology (ASCO) from the search date of the CPG on (search date May – August 2008). For those clinical questions where no CPG was available, the search was extended to the inception date of the respective databases. A combination of appropriate MeSH terms and free text words was used (see appendix 8).

An iterative approach was followed. For therapeutic interventions, only systematic reviews and randomized controlled trials (RCT) were included. However, for diagnostic interventions we also searched for observational studies in case no systematic review or RCT was found. Inclusion criteria for the diagnostic studies were: prospective cohort study design (or RCT), ability to construct a 2x2 table, no partial verification, description of standard.

The identified studies were selected based on title and abstract. For all eligible studies, the full-text was retrieved. In case no full-text was available, the study was not taken into account for the final recommendations.

2.4 QUALITY APPRAISAL

2.4.1 Clinical practice guidelines

In total, 21 CPGs were identified. All were quality appraised by two independent reviewers (JV, FM) using the AGREE instrument. Disagreement was discussed face-to-face. At the end, agreement was reached for all CPGs, and 6 CPGs were included (see appendix 2).

2.4.2 Additional evidence

The quality of the retrieved systematic reviews and RCTs was assessed using the checklists of the Dutch Cochrane Centre (www.cochrane.nl).

2.5 DATA EXTRACTION AND SUMMARY

For each included CPG the following data were extracted: search date & publication year, searched databases, availability of evidence tables, recommendations and referenced evidence.

For each systematic review, the search date, publication year, included studies and main results were extracted. For RCTs, the following data were extracted: publication year, study population, study intervention, and outcomes.

For each clinical question, the recommendations from the identified CPGs and the additional evidence were summarized in evidence tables. A level of evidence was assigned to each recommendation and additional study using the GRADE system (see appendix 1).

For selected topics (EUS, tumour markers, pancreaticoenteric anastomosis), a meta-analysis was done using the free software packages Meta-DiSc 10 version 1.4 (Unit of clinical biostatistics, the Ramo y Cajal Hospital, Madrid, Spain) for diagnostic questions and RevMan 4.3 (Cochrane Collaboration, http://www.cc-ims.net/RevMan) for therapeutic questions.

2.6 FORMULATION OF RECOMMENDATIONS

Based on the retrieved evidence, a first draft of recommendations was prepared by a small working group (JV, SS, FM). This first draft together with the evidence tables was circulated to the guideline development group 2 weeks prior to the first face-to-face meeting. The guideline development group met on several occasions (September 10th 2008, October 8th 2008, October 23rd 2008, November 18th 2008) to discuss the first draft. Recommendations were changed if important evidence supported this change. Based on the discussion meetings a second draft of recommendations was prepared.

A grade of recommendation was assigned to each recommendation using the GRADE system (see appendix 1). The second draft was once more circulated to the guideline development group for final approval.

2.7 EXTERNAL REVIEW

The recommendations prepared by the guideline development group were circulated to the Professional Associations (Table 6). Each association was asked to assign 2 key persons to discuss the recommendations during an open meeting. These panellists received the recommendations one week prior to this open meeting. As a preparation of the meeting all invited panellists were asked to score each recommendation on a 5-point Likert-scale to indicate their agreement with the recommendation, with a score of '1' indicating 'completely disagree', '2' indicating 'somewhat disagree', '3' indicating 'unsure', '4' indicating 'somewhat agree', and '5' indicating 'completely agree' (the panellists were also able to answer 'not applicable' in case they were not familiar with the underlying evidence). In case a panellist disagreed with the recommendation (score '1' or '2'), (s)he was asked to provide appropriate evidence. All scores (n = 15) were then anonymized and summarized into a mean score, standard deviation and % of 'agree'-scores (score '4' and '5') to allow a targeted discussion (see appendix 3). The recommendations were then discussed during a face-to-face meeting on December 8th 2008. Based on this discussion a final draft of the recommendations was prepared, and discussed by the guideline development group by email. In appendix 3, an overview is provided of how the comments of the experts were taken into account.

Table 6: List of Professional Associations that were asked to assign two experts.

Belgian Society of Pathology *
Belgian Society of Medical Oncology *
Belgische Vereniging voor Radiotherapie-Oncologie - Association Belge de Radiothérapie-Oncologie *
Royal Belgian Radiological Society *
Belgische Genootschap voor Nucleaire Geneeskunde - Société Belge de Médecine Nucléaire *
Belgian Society of Surgical Oncology *
Koninklijk Belgisch Genootschap Heelkunde - Société Royale Belge de Chirurgie *
Vlaamse Vereniging voor Gastro-enterologie
Belgian Group of Digestive Oncology **
Société Royale Belge de Gastro-entérologie
Domus Medica
Société Scientifique de Médecine Générale
Belgian Group for Endoscopic Surgery
Belgian Society of Gastrointestinal Endoscopy *
Belgian Digestive Pathology Club *

* Two experts assigned and feedback received. ** Two experts assigned, but no feedback received.

3 FINAL RECOMMENDATIONS

3.1 FLOWCHART

See next page.

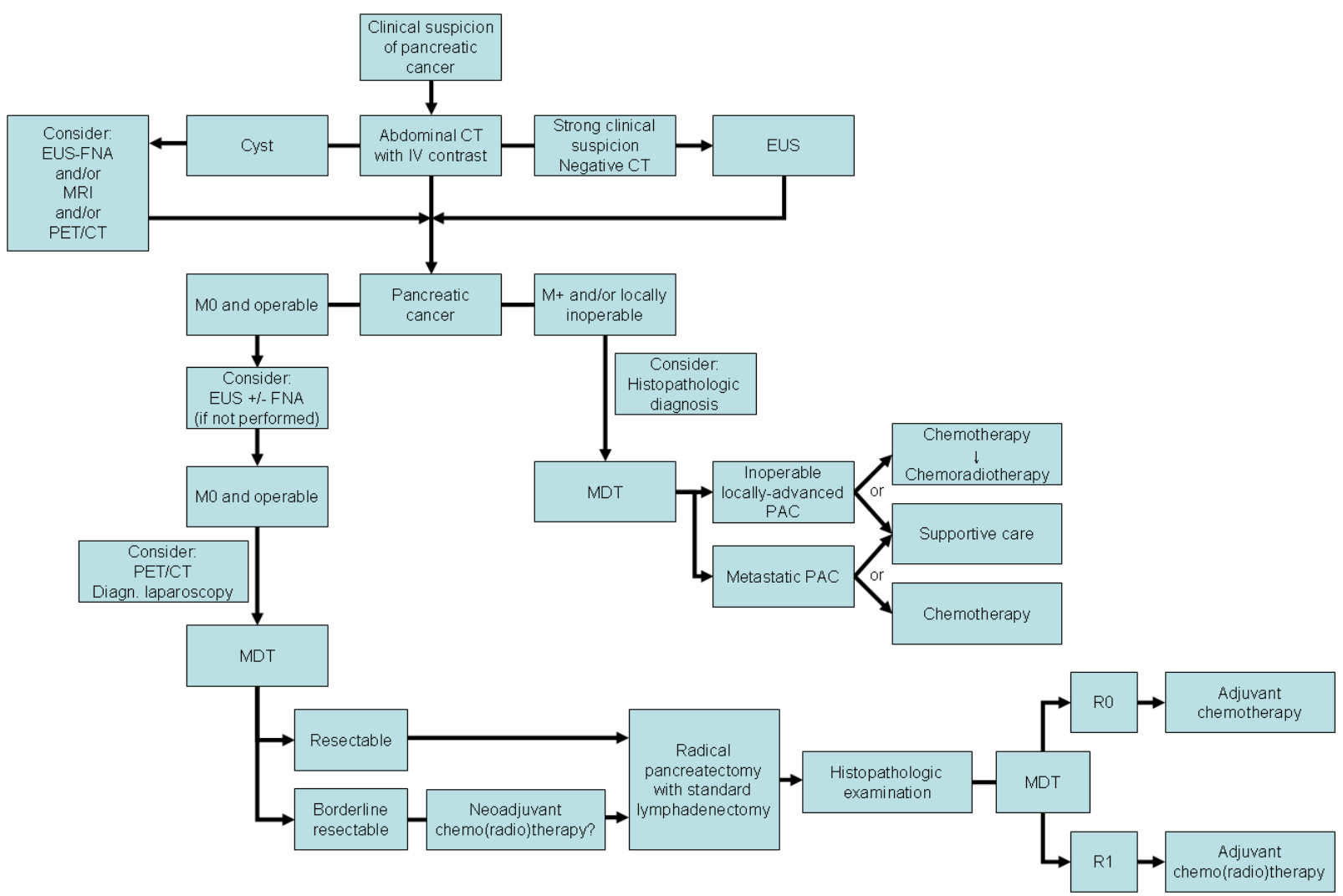
3.2 SCREENING

3.2.1 Principles and goals of screening

Screening is the term used to describe the investigation of asymptomatic individuals in order to detect disease at an early stage when it is more amenable to treatment. The principles underlying an effective screening intervention were originally developed by Wilson and Jungner in 1968, and these are summarized below [8]:

1. The condition should be an important health problem for the individual and community.
2. There should be an accepted treatment or useful intervention for patients with the disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development for latent to declared disease, should be adequately understood.
8. There should be an agreed policy for referring for further examination and whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case finding should be a continuing process and not a "once and for all" project.

The essence of these principles is that the target disease process should be a common problem that has a better outcome when treated at an early stage, and that the test employed is acceptable and sufficiently sensitive, specific, and inexpensive to be cost-effective.



EUS: endoscopic ultrasound; FNA: fine needle aspiration; IV: intravenous; MDT: multidisciplinary team; PAC: pancreatic cancer; PET: positron-emission tomography.

Although these original principles remain largely valid, other considerations need to be made. The Dutch National Health Council extended the Wilson & Jungner criteria, adding additional criteria on practical and ethical issues [8]:

1. Treatment started at an early stage should be of more benefit than treatment started later.
2. The time between test and result and between result and treatment must be as short as possible.
3. The recruitment procedure should not limit people in their freedom to participate or not in the screening program.
4. Potential participants should receive adequate information about pro and cons of participation. Benefits and risks should also be well known to health care providers.
5. Public education should promote a broad accessibility of the program. It should however not include a moral pressure effect.
6. There should be quality assurance (QA) and quality control (QC) procedures for the whole screening program.
7. Screening programs are concerted actions meeting organisational and managerial requirements.

Early disease stage at diagnosis and administration of curative intent surgery (i.e. resection) provide the best opportunities of achieving long-term survival among patients with pancreatic cancer [9] (see chapter 3.2.2). Beyond the generally expected qualities of a screening tool for early stage cancer (inexpensive, non-invasive, sensitive and specific), a screening tool for pancreatic cancer should also have a high positive and negative predictive value, as the screened individual may subsequently choose whether or not to undergo surgery with curative intent, which is associated with significant risks and morbidity [9].

3.2.2 Rationale of screening for pancreatic cancer

A moderate-quality guideline developed by the U.S. Preventive Services Task Force (USPSTF) was identified (developed in 1996, updated in 2004) [10]. For our guideline, additional studies were searched using the same search strategy as the USPSTF, starting from 2001 (end date of USPSTF search).

3.2.2.1 Mass screening

The USPSTF found no evidence that screening for pancreatic cancer is effective in reducing morbidity and mortality [10]. There is a potential for significant harm due to the very low prevalence and incidence of pancreatic cancer, limited accuracy of available screening tests, the invasive nature of diagnostic tests, and the poor outcomes of treatment. As a result, the USPSTF concluded that the harms of screening for pancreatic cancer exceed any potential benefits.

Moreover, Kim et al. [11] conducted a large prospective observational study among 70940 asymptomatic persons in Korea. All persons underwent abdominal ultrasonography and serum CA 19-9 measurement. They concluded that mass screening for pancreatic cancer using CA 19-9 measurement in asymptomatic subjects was ineffective because of a very low positive predictive value (0.9%), despite its high sensitivity (100%) and specificity (98.5%).

Recommendation

- **Mass screening for pancreatic cancer is not recommended (2C recommendation)**

3.2.2.2 Surveillance for patients at high-risk for pancreatic cancer

Although the available techniques for detecting early pancreatic cancer in the general population are unfeasible, impractical or not cost-effective, they may have a use for the surveillance of well-defined, high-risk groups of patients (e.g. hereditary pancreatitis, familial pancreatic cancer, hereditary breast cancer [BRCA1 and BRCA2 positivity], a subset of kindreds with familial atypical multiple mole melanoma [FAMMM] syndrome affected with a p16 germline mutation, Peutz–Jeghers polyposis) [12]. In these patient groups, surveillance, considered as monitoring individuals known to have a disease or to be at increased risk for a disease, is somewhat different to mass screening. For these targeted groups, the potential benefit of surveillance is higher than that of screening in the population at large, because the prevalence of the disease is higher. As a consequence, the benefit-to-risk ratio of surveillance is more favourable than the benefit-to-risk ratio of screening. However, only low-quality observational studies, narrative reviews and consensus reports are available supporting the use of surveillance of high-risk patients.

A screening trial with patients at high risk for pancreatic cancer was conducted at the Johns Hopkins University [13, 14]. The study population was selected according to a strict screening protocol and included 7 patients from kindreds affected with Peutz-Jeghers Syndrome (PJS) and 109 patients from Familial Pancreatic Cancer (FPC) kindreds. Asymptomatic patients were prospectively screened using a combination of endoscopic ultrasound (EUS) and computed tomography (CT). An abnormal EUS led to the use of EUS-guided fine-needle aspiration, multidetector CT and endoscopic retrograde cholangiopancreatography (ERCP). Overall, 29 patients displayed neoplastic lesions (25%) and 15 patients underwent surgery. Final pathologic examination demonstrated 6 high-grade or invasive lesions (PanIN-3, IPMN with carcinoma in situ, pancreatic adenocarcinoma), 11 low-grade lesions (PanIN-2 or IPMN), and 6 non-neoplastic lesions. Additionally, 6 extrapancreatic lesions were detected through screening, including 1 malignant ovarian tumour. However, although abnormalities noted on screening prompted surgery, approximately one half of the malignant or potentially malignant lesions were detected at surgery and not by the initial screening tests.

The most recent consensus recommendations were proposed by Participants of the Fourth International Symposium of Inherited Diseases of the Pancreas [12]. Among the participants, there was a strong agreement that screening as surveillance should only be performed within the context of peer-reviewed protocols, with scientific evaluation and human subjects protections. These protocols should strictly define who should be candidates for screening and the sequence of the used screening techniques.

Candidates for pancreatic cancer surveillance are [12]:

- $\geq$ 3 first-degree, second-degree, or third-degree relatives with pancreatic cancer in the same lineage;
- Known mutation carrier for BRCA1, BRCA2 or p16, with at least one first-degree or second-degree relative with pancreatic cancer;
- A member, ideally a verified germline carrier, of a Peutz-Jeghers Syndrome kindred;
- Two relatives in the same lineage (directly connected) affected with pancreatic cancer, at least one a first-degree relative of the candidate;
- An affected individual with hereditary pancreatitis.

No consensus could be reached on the most appropriate approach for the surveillance of high-risk persons [12]. At present, many centres use endoscopic ultrasound (EUS) as their procedure of choice because of its high sensitivity [15]. Above this, EUS is well-tolerated and has few side effects [16]. However, the accuracy of EUS is highly operator-dependent (poor inter-observer agreement concerning the interpretation of pancreatic EUS in high-risk individuals undergoing screening examinations) [17]. Moreover, EUS is not good at distinguishing benign lesions from cancers [18].

No consensus was reached on when to start screening and on the frequency of screening.

In familial pancreatic cancer kindreds, endoscopic surveillance was found to be cost-effective, with an incremental cost-effectiveness ratio of $16,885/life-year saved [19]. Screening was more cost-effective as the probability of dysplasia increased and as the sensitivity of EUS and ERCP increased. Screening remained cost-effective if the prevalence of dysplasia was greater than 16% or if the sensitivity of EUS was greater than 84%. Procedure costs had a limited impact on cost-effectiveness. However, the authors cautiously recommended that such surveillance should be performed in centres that have experience with endoscopic screening for pancreatic dysplasia. The cost-effectiveness of repeated screening remains to be determined.

Recommendation

- **Surveillance of persons at high risk of developing pancreatic cancer should only be performed within the context of peer-reviewed protocols (expert opinion).**

3.3 DIAGNOSIS

3.3.1 History and physical exam

The presenting symptoms of pancreatic cancer may include weight loss, jaundice, floating stools, epigastric pain, back pain, dyspepsia, nausea, early satiety and depression. Sometimes, pancreatic cancer presents as adult-onset diabetes without predisposing features or family history of diabetes, venous thrombosis or acute pancreatitis. However, no early alarm symptoms have been described. In fact, many patients are asymptomatic until the tumour has reached an incurable stage.

One prospective cohort study evaluated the diagnostic accuracy of some common symptoms of pancreatic cancer in 512 patients with suspected pancreatic disease [20]. Jaundice was found to be the most sensitive symptom for pancreatic cancer, while weight loss and malabsorption were found to be very specific.

In a recent Chinese observational trial, preoperative abdominal and/or back pain were found to be independent predictors for poor survival (RR 1.90, 95%CI 1.23-2.93, p = 0.004) [21].

At present, a large population-based trial of the Group Health Center for Health Studies and Kaiser Permanente Northern California is examining the risk factors for pancreatic cancer (http://www.centerforhealthstudies.org/).

Recommendation

- **Diagnosis of pancreatic cancer should be considered with the presence of the following risk factors: adult-onset diabetes without predisposing features or family history of diabetes, jaundice, unexplained pancreatitis, rapid weight loss and unexplained back pain (expert opinion).**

3.3.2 Conventional imaging

3.3.2.1 Computed tomography (CT)

CT scan is considered the cornerstone for the diagnosis (and staging) of pancreatic cancer and intraductal papillary mucinous neoplasm (IPMN). Importantly, adequate information should be provided to the radiologist about the suspicion of pancreatic cancer to allow a correct execution of the CT scan (e.g. with arterial and portal venous phase).

Two systematic reviews were identified examining the role of CT in the diagnosis of pancreatic cancer [22, 23]. The review of Bipat et al. was of good quality and was chosen as starting point for the search for additional evidence (search date December 2003).

Bipat et al. calculated a summary sensitivity and specificity of 91% and 85% respectively for helical CT (23 studies) and 86% and 79% respectively for conventional CT (20 studies) [22]. Three additional prospective observational studies were found [24-26]. Sensitivity ranged from 80% to 98%, while specificity ranged from 23% to 88%. All three studies suffered from important methodological flaws.

3.3.2.2 Ultrasonography (US)

In some cases, US is done for differential diagnostic reasons, which can lead to a final diagnosis of pancreatic cancer (e.g. in the case of a pancreatic mass with clear liver metastases). However, it cannot be considered the standard imaging technique for the diagnosis (and staging) of pancreatic cancer.

For abdominal US, Bipat et al. calculated a summary sensitivity and specificity of 76% and 75% respectively (14 studies) [22]. In 62 consecutive patients with a pancreatic tumour, Okamoto et al. found a sensitivity of 79% and specificity of 67% for the diagnosis of pancreatic cancer by contrast-enhanced US at the vascular image phase (presence of tumour vessels) [27]. Sensitivity and specificity at the perfusion image phase (hypo-enhancement pattern) were 96% and 78% respectively. Rickes et al. found a sensitivity and specificity of 67% and 39% respectively for the diagnosis of cystadenocarcinoma by conventional US in 31 patients with a cystic pancreatic lesion [28]. Sensitivity and specificity were 67% and 96% respectively using echo-enhanced US.

3.3.2.3 Magnetic resonance imaging (MRI)

In cases where CT is impossible or contraindicated, MRI can be useful. Especially in the differential diagnosis of cystic pancreatic lesions, MRI can be considered. Magnetic resonance cholangiopancreaticography (MRCP) followed by dynamic MRI is the radiological test of choice for the diagnosis of IPMN [29].

Bipat et al. included 11 studies on MRI [22]. For diagnosis, summary sensitivity and specificity of MRI was 84% and 82% respectively. One additional observational study found a sensitivity of 100% and a specificity of 76% [30]. Another study examined the diagnostic performance of MRCP for the diagnosis of malignancy in patients with obstructive jaundice [31]. Sensitivity and specificity were 65% and 81% respectively. The combination of MRCP and MRI increased the sensitivity and specificity to 82% and 94% respectively. Finally, Calvo et al. measured MRCP against ERCP as reference standard in 78 patients with suspected biliopancreatic pathology requiring ERCP [32]. Both sensitivity and specificity for the diagnosis of pancreatic malignancy were 100%.

3.3.2.4 Endoscopic ultrasonography (EUS)

In patients with a high suspicion of pancreatic cancer, but with a negative abdominal CT, an EUS is recommended. One systematic review was found comparing the diagnostic value of CT and EUS [23]. Nine studies were found assessing tumour detection. EUS was found to be more sensitive than CT, but no meta-analysis was done. Overall, this systematic review was of low quality. It was therefore decided to search for original prospective cohort studies without a date limit. In total, 15 eligible studies were found (see appendix 4). Six studies on conventional EUS were identified [33-38]. Pooled sensitivity was 85% (95%CI 82 – 88%), while pooled specificity was 94% (95%CI 91 – 96%) (see appendix 4). However, inconsistency between these 6 studies was high. In addition, 3 studies were identified evaluating the use of perfusional imaging with EUS [34, 39, 40]. Sensitivity ranged from 91 to 94%, while specificity ranged from 77 to 100%.

Obtaining a pathological proof of malignancy is advisable in advanced cases or when neoadjuvant treatment is planned. EUS-guided fine needle aspiration (FNA) is preferred to percutaneous (US- or CT-guided) sampling because of the lower associated risk of soiling [41]. However, in patients with advanced disease and liver metastases, US- or CT-guided liver punction can be considered.

Eight studies on EUS-FNA were identified [37, 42-48]. Pooled sensitivity was 89% (95%CI 87 – 91%), again with a high inconsistency (see appendix 4). However, pooled specificity was consistently high (99%, 95%CI 97 – 100%).

3.3.3 Serum tumour markers

Three reviews and one guideline were identified examining the role of tumour markers in the diagnosis of pancreaticobiliary cancer [49-52]. The review of Goonetilleke et al. [49] and the ASCO guideline [52] examined the role of CA 19-9 as a marker of pancreatic cancer. Both identified a different body of evidence. Hathurusinghe et al. [50] and Kumar et al. [51] reviewed the role of Tumour M2-PK, and both found the same 6 published observational studies. No reviews on other tumour markers were identified. Therefore, and because of the difference in evidence between the review of Goonetilleke et al. and the ASCO guideline (which was of low quality, and therefore not included), it was decided to search for original studies without a date limit, focusing on prospective cohort studies only.

In total, 7 eligible prospective cohort studies were identified, of which 2 were included in the review of Goonetilleke et al. [49]. Five studies on CA 19-9 were identified [53-57]. Meta-analysis of the 4 studies using the upper normal limit as cut-off value (40 U/ml in the study of Malesci et al., 37 U/ml in the 3 other studies) showed a summary sensitivity of 82% (95%CI 75 – 88%) and specificity of 81% (95%CI 77 – 84%) (see appendix). Inconsistency between the 4 studies was high, in particular for the specificity. Urgell et al. examined the diagnostic performance of CA 19-9 in 156 patients with a suspicion of pancreatic cancer, using a cut-off of 100 U/ml for patients without a pancreatic mass and 250 U/ml for patients with a pancreatic mass [56]. A sensitivity and specificity of 68% and 88% respectively was found.

In case of obstructive jaundice, the sensitivity of CA 19-9 increases, while the specificity decreases [49]. Indeed, CA 19-9 may be falsely positive in cases of benign biliary obstruction. On the other hand, it can be falsely negative in Lewis a-negative individuals.

Three studies examined the diagnostic performance of carcinoembryonic antigen (CEA) [53, 57, 58]. For the 2 studies using 2.5 ng/ml as cut-off value, summary sensitivity and specificity are 61% (95%CI 48 – 72%) and 85% (95%CI 81 – 88%) respectively (see appendix) [53, 57]. However, important inconsistency was found between the 2 studies. Carr-Locke et al. used a cut-off value of 10 µg/l [58]. Sensitivity was 69%, while specificity was 87%. Both sensitivity and specificity were found to be lower in case of obstructive jaundice [58].

Kuno et al. also studied the diagnostic value of Span-1 and EL-1 [53]. Sensitivity and specificity of Span-1 for the diagnosis of pancreatic cancer were 89% and 80% respectively. For EL-1, sensitivity and specificity were 51% and 87% respectively. Finally, Palsson et al. examined the diagnostic performance of CA 50, and found a sensitivity and specificity of 96% and 48% respectively [20].

In view of this evidence, serum tumour markers cannot be considered part of the routine *diagnostic* work-up of patients with clinically suspected pancreatic cancer. However, in some cases, a reference value at diagnosis can be useful for the monitoring of treatment.

3.3.4 Cyst fluid analysis

In case of differential diagnosis between benign and (pre)malignant pancreatic cysts, EUS-guided cyst fluid analysis (including cytology, amylase and CEA) can be useful. However, the clinical consequences are rather limited.

Van der Waaij et al. published a low-quality systematic review examining the diagnostic value of cyst fluid analysis in patients with pancreatic cystic lesions [59]. The authors included 12 observational studies of varying but overall poor quality. Both CEA < 5 ng/ml and CA 19-9 < 37 U/ml were found to be very specific for serous cystadenoma and pseudocysts (specificity of 95% and 98% respectively). On the other hand, amylase < 250 U/l had a high specificity but low sensitivity for serous cystadenoma, mucinous cystadenoma and mucinous cystadenocarcinoma, and thus almost excluded pseudocysts. Cytologic examination revealed malignant cells in 48% of mucinous cystadenocarcinoma.

Two additional prospective observational studies were identified [60, 61]. However, both trials were found to have serious methodological flaws. Khalid et al. included only patients with available surgical pathology and/or malignant cytology (partial verification) [60], while Shami et al. excluded patients with pseudocysts (important selection bias) [61]. Therefore, these results were not included.

3.3.5 ERCP

ERCP primarily has a therapeutic purpose in case of obstructive jaundice, and is not routinely done for the diagnosis of pancreatic cancer. It can be considered for the diagnosis of IPMN [29]. One good systematic review of the AHRQ was found addressing the role of ERCP in the diagnosis of malignant strictures and pancreatic cancer [62].

For the diagnosis of malignant strictures no significant differences were found in diagnostic performance between ERCP and MRCP (3 studies with independent reference standard, only 1 prospective study; sensitivity 71 – 93% vs. 81 – 86%, specificity 92 – 94% vs. 82 – 100%) and between ERCP and EUS (2 studies with independent reference standard, only 1 prospective study; sensitivity 75 – 89% vs. 85 – 89%, specificity 65 – 92% vs. 80 – 96%) [62].

For the diagnosis of pancreatic cancer only one prospective study was found comparing ERCP to MRCP (sensitivity 70 vs. 84%, specificity 94 vs. 97%) and 2 retrospective studies were found comparing ERCP to EUS (no significant differences) [62]. For the diagnosis of IPMT, one prospective and one retrospective study compared ERCP to EUS. No significant differences were found.

Sensitivity for detecting malignancy was found to be similar or higher for brush cytology vs. bile aspiration cytology (5 studies of which 4 prospective; 33 – 100% vs. 6 – 50%), similar for FNA cytology versus brush cytology (3 studies of which 2 prospective; 25 – 91% vs. 8 – 56%), and similar or higher for forceps biopsy versus brush cytology (6 studies of which 4 prospective; 43 – 81% vs. 18 – 53%) [62].

One additional prospective cohort study, published since the AHRQ report, was found [63]. In 60 patients with painless jaundice and a stricture on ERCP but no mass on CT, ERCP and brushing had a sensitivity of 40% and a specificity of 100% for the differentiation between malignant and benign strictures.

3.3.6 Positron Emission Tomography (PET) scan

PET scan can be useful for the differential diagnosis of cystic lesions, and for the differential diagnosis of pancreatic cancer and chronic pancreatitis. In a recent KCE report, the diagnostic accuracy of PET scan for the detection of pancreatic cancer was analysed [64]. Two systematic reviews were discussed in this report [65, 66]. Based on a meta-analysis of 9 observational studies, Orlando et al. found a summary sensitivity and specificity of 92% (95%CI 87 – 95%) and 68% (95%CI 51% – 81%) respectively after a positive CT, 73% (95%CI 50% – 88%) and 86% (95%CI 75% – 93%) respectively after a negative CT, and 100% and 68% respectively (results based on a single study) after an indeterminate CT [65]. In the HTA-AHRQ 2004 report, PET sensitivity ranged from 71% to 100% and specificity from 50% to 100% [66].

Seven additional prospective cohort studies, published since the meta-analysis of Orlando et al., were identified [24, 25, 55, 67-70]. In the 5 studies that included patients with a solid mass, sensitivity ranged from 75% to 97% and specificity from 65% to 88% [24, 25, 67-69]. The 2 studies that exclusively included patients with a cystic pancreatic mass found a sensitivity of 94% and a specificity of 94 – 97% [55, 70].

The FNCLCC also identified several observational studies examining the diagnostic value of PET scan [71]. Sensitivity ranged from 71 – 92%. Based on the results of these studies, the FNCLCC concluded that PET scan is indicated for the differential diagnosis of pancreatic cancer and chronic pancreatitis.

Recommendations

- **In addition to a history taking and clinical examination, all patients with clinically suspected pancreatic cancer should undergo diagnostic imaging with abdominal CT (1B recommendation).**
- **In patients with a high suspicion of pancreatic cancer and a negative CT scan, an EUS is recommended (1B recommendation).**
- **When tissue diagnosis of pancreatic cancer is needed to guide treatment, imaging-guided FNA is recommended (1B recommendation).**
- **Diagnostic imaging with US, MRI, ERCP or PET scan should be considered in specific cases (see text) of clinically suspected pancreatic cancer (1C recommendation).**
- **Serum tumour markers are not part of the routine diagnostic work-up of patients with clinically suspected pancreatic cancer (1C recommendation).**
- **EUS-guided cyst fluid analysis, including cytology, amylase and CEA, can be useful in the differential diagnosis between benign and (pre)malignant pancreatic cysts (2C recommendation).**

3.4 STAGING

3.4.1 CT

By allowing the detection of liver metastases and/or vascular invasion, CT scan is the definite imaging technique in many cases, provided that the liver is at least imaged in the arterial and portal venous phase. Two systematic reviews were identified assessing the staging accuracy of CT [22, 23]. Bipat et al. found 32 studies with helical CT and 12 studies with conventional CT [22]. For the determination of resectability, a summary sensitivity of 81% and 82% was calculated for helical CT and conventional CT respectively, while the summary specificity was 82% and 76% respectively.

Dewitt et al. identified 11 studies comparing CT to EUS for the staging of pancreatic cancer [23]. For T staging, 4 out of 5 studies found EUS to be superior. Also for N staging, 5 out of 8 studies found EUS to be superior. For determining the resectability, the 4 identified studies found inconsistent results.

In addition to these 2 systematic reviews, 3 recent observational studies were identified. Li et al. found a sensitivity and specificity of 93% and 94% respectively for the determination of resectability [72]. Imbriaco et al. found a comparable sensitivity (92%), but a slightly lower specificity (86%) [26]. For the diagnosis of liver metastases, Satoi et al. found a sensitivity of 88% and a specificity of 89% [73]. All three trials had important methodological limitations.

3.4.2 Ultrasonography

US is sometimes used to identify patients with non-resectable tumours, mainly based on the presence of liver metastases. Bipat et al. identified 6 observational studies examining the diagnostic accuracy for determining the resectability of pancreatic tumours with US [22]. A summary sensitivity of 83% was calculated, while the summary specificity was 63%. The latter was significantly lower compared with the specificity for helical CT ($p = 0.0011$).

No additional studies of acceptable quality were identified.

3.4.3 MRI

As stated above (see chapter 3.3.2.3), MRI can be useful in cases where CT is impossible or contraindicated. Bipat et al. identified 7 trials examining the diagnostic accuracy for determining the resectability of pancreatic tumours with MRI [22]. A summary sensitivity and specificity of 82% and 78% respectively was found.

One additional observational study found a sensitivity and specificity of 75% and 71% respectively for the diagnosis of liver metastases with MRI [30]. Sensitivity for N staging was 15%. This trial had important methodological limitations.

3.4.4 Endoscopic ultrasonography

EUS can be useful for the detection of small tumours or IPMN, especially if uncertainty exists with CT (and/or MRI). Three systematic reviews on EUS were identified. In a Medline search limited to English-language literature, van Vliet et al. identified 11 studies [74]. Median accuracy for T staging was 79% (range 69-93%, 8 studies). For N staging, median sensitivity and specificity both were 63%. Puli et al. identified 29 studies examining the diagnostic accuracy of EUS in the diagnosis of vascular invasion in patients with pancreatic and periampullary cancer [75]. Pooled sensitivity and specificity were 73% and 90% respectively. Finally, Dewitt et al. found EUS to be superior to CT for T and N staging (see chapter 3.4.1) [23].

3.4.5 PET scan

PET scan has only a limited role in the staging of pancreatic cancer. In patients with an option for curative treatment after conventional staging, PET(/CT) scan may be considered for the staging of lymph nodes (loco-regional, distal or all lymph nodes) and distant sites other than lymph nodes. In the KCE report on PET scan [64], one systematic review was discussed on the diagnostic accuracy in detecting pancreatic metastatic disease [66]. A trend towards higher sensitivity (PET: range 46 – 92%; CT: range 18 – 76%; EUS 93%; US 67%) but lower specificity (PET: range 50 – 100%; CT: range 25 – 100%; EUS 75%; US 100%) than the comparators was found. The FNCLCC referenced one observational study, reporting a sensitivity and specificity of 97% and 95% respectively for the detection of liver metastases [71]. Two recent observational studies both found a sensitivity of 81% and specificity between 88% and 100% for the detection of distant metastases [25, 76].

3.4.6 ERCP

No adequate studies or guidelines were identified addressing the role of ERCP in the staging of pancreatic cancer.

3.4.7 Diagnostic laparoscopy and/or laparoscopic ultrasonography

Laparoscopy (and/or LUS) can be useful to detect small peritoneal and/or small liver metastases. It can be considered before resection or if neoadjuvant treatment is planned. One narrative review based on a Medline search was identified [77]. Inconsistent results were reported between the identified studies in this review, which consisted mostly of case series or retrospective studies. Moreover, comparison between the studies was found to be difficult because of different regimens in performing CT scan, leading to different resectability rates.

No additional good prospective cohort studies were found.

3.4.8 Explorative laparotomy

Despite the availability of good diagnostic and staging techniques, final assessment of the resectability of a pancreatic tumour is often only possible during surgery, and an important number of pancreatic cancers will be found to be unresectable [78]. No prospective studies were found evaluating the staging accuracy of explorative laparotomy. In view of the associated morbidity, it cannot be routinely recommended as a staging procedure.

Recommendations

- **In patients with pancreatic cancer, abdominal CT with intravenous contrast should be performed routinely. The liver should at least be imaged in the arterial and portal venous phase (1B recommendation).**
- **In selected patients with pancreatic cancer, EUS and diagnostic laparoscopy can be considered (2C recommendation).**
- **In patients with pancreatic cancer with an option for curative treatment after conventional staging, PET(/CT) scan may be considered for the staging of lymph nodes (loco-regional, distal or all lymph nodes) and distant sites other than lymph nodes (2C recommendation).**
- **Ultrasonography and MRI are not routinely recommended as staging procedures in patients with pancreatic cancer, but can be considered in specific cases (2C recommendation).**
- **In patients with pancreatic cancer, the results of the diagnostic and staging workup should be discussed during a multidisciplinary team meeting to guide further treatment (expert opinion).**

3.5 NEOADJUVANT TREATMENT

The CCO guideline identified only one underpowered RCT published in abstract form [79]. Forty-two patients with potentially resectable pancreatic cancer were randomised to preoperative CRT with gemcitabine and accelerated hyperfractionated RT (n = 23) or surgery alone (n = 19) [80]. No significant survival benefit was detected for patients who received preoperative CRT.

No additional completed RCTs comparing neoadjuvant treatment to surgery alone and published after the CCO guideline were identified. However, one ongoing RCT was found [81].

One phase II trial was found comparing neoadjuvant gemcitabine alone (n = 24) to gemcitabine and cisplatin (n = 26) in patients with potentially resectable pancreatic cancer [82]. Resection rate was higher in the combination group (70% vs. 38%), as was the 1-year survival (62% vs. 42%). No statistics were provided in this study. Observational studies also suggest the potential of CRT to downstage unresectable [83, 84] or borderline resectable locally advanced pancreatic tumours [85, 86]. Evaluation of resectability is recommended after 2 – 3 months of treatment with CRT in these patients.

Recommendation

- **Neoadjuvant treatment is not recommended in patients with resectable pancreatic cancer outside clinical trials (2C recommendation).**
- **In patients with borderline resectable locally advanced pancreatic cancer, treatment with chemotherapy or chemoradiotherapy can be considered. Evaluation of resectability is recommended after 2 – 3 months (2C recommendation).**

3.6 SURGICAL TREATMENT WITH CURATIVE INTENT

No good-quality guidelines were found addressing the role of surgical treatment with curative intent in patients with pancreatic cancer. Therefore, no date limit was used during the search for additional evidence.

3.6.1 Preoperative biliary drainage

Four systematic reviews were found comparing preoperative biliary drainage (PBD) to no drainage in patients with obstructive jaundice resulting from tumours [87-90]. Two reviews only included RCTs on preoperative endoscopic stenting (internal drainage) [87, 88], while the 2 other reviews included RCTs on internal and external drainage [89, 90]. No additional RCTs were identified, but one ongoing RCT was found [91].

Aly et al. [90] and Sewnath et al. [89] found a comparable body of evidence on preoperative internal and external drainage, but the most recent of these 2 reviews was the most complete and of higher quality [89]. Above this, Sewnath et al. performed a meta-analysis [89]. Therefore, only these results will be discussed. Five RCTs were identified, while the study of Lygidakis et al. was not considered a RCT [92]. Meta-analysis of these 5 RCTs showed no difference in overall mortality between PBD and no PBD (OR 1.19, 95%CI 0.63 – 2.23, p = 0.60) [89]. However, the overall complication rate was significantly higher in the PBD group (OR 1.99, 95%CI 1.25 – 3.16, p = 0.004). The authors therefore concluded PBD not to be beneficial [89].

Mumtaz et al. [87] and Saleh et al [88] both identified 2 RCTs comparing preoperative endoscopic stenting to no stenting [92, 93]. No difference was found in the overall, pre-surgical and post-surgical mortality [87]. There were significantly more pre-surgical complications in the stented group (OR 43.75, 95%CI 2.51 – 761.84, p = 0.01), but significantly less post-surgical complications (OR 0.45, 0.22 – 0.91, p = 0.03). Overall complication rate did not differ significantly (OR 0.50, 95%CI 0.01 – 23.68, p = 0.70). Therefore, the authors concluded that the evidence did not support or refute endoscopic biliary stenting [87].

Recommendation

- **Preoperative biliary drainage is not routinely recommended in patients with resectable pancreatic cancer and obstructive jaundice (1B recommendation).**

3.6.2 Radical pancreatic resection and lymphadenectomy

3.6.2.1 Resectability criteria

No universally accepted resectability criteria exist for patients with pancreatic cancer. Therefore, decisions about treatment and resectability always need to involve multidisciplinary discussion. However, although the NCCN guidelines were found to be of insufficient quality, their resectability criteria were considered very relevant and were adopted for our guidelines (Table 7) [94].

Clearly, the following characteristics render a pancreatic tumour unresectable: distant metastases, lymph node metastases beyond the field of resection, superior mesenteric vein (SMV) and/or portal occlusion, and superior mesenteric artery (SMA), celiac and/or hepatic artery encasement. Indeed, the evidence on pancreatic resection with arterial reconstruction in patients with pancreatic cancer and arterial involvement is limited to small (retrospective) case series [95-97] or subsets of case series [98-101]. Reported results are disappointing with a considerable postoperative mortality and a median survival ranging from 12 to 20 months in selected cases (if reported). Therefore, pancreatic resection with arterial reconstruction is not recommended in patients with pancreatic cancer whom major arteries (arteria hepatica, arteria mesenterica superior, truncus coeliacus) are involved. Importantly, in patients with an aberrant right hepatic artery (in up to 12% of cases [102]) running through an otherwise resectable tumour, arterial reconstruction is possible [103].

Venous invasion is not considered a contra-indication for surgery, provided a R0 resection can be achieved. Tumours with limited involvement of the inferior vena cava, severe unilateral SMV and/or portal impingement, or a short segment SMV occlusion are considered borderline resectable (Table 7). Siriwardana et al. pooled the results of 52 studies, including 1 RCT, involving 1646 patients undergoing pancreatic resection with portal–superior mesenteric vein resection for pancreatic cancer [102]. Median survival was 13 months, while 1-year and 5-year survival were 50% and 7% respectively. Median postoperative morbidity rate was 42%. In 67% of patients nodal metastases were found. Siriwardana et al. included data of only 1 RCT (see chapter 3.6.2, Lygidakis et al. [103]). No additional RCTs were identified by our search.

Table 7. NCCN resectability criteria for pancreatic tumours [94].

Resectable tumours
No distant metastases Clear fat plane around celiac and superior mesenteric arteries (SMA) Patent * superior mesenteric vein (SMV)/ portal vein
Borderline resectable tumours
Head/body Severe unilateral SMV/portal impingement * Tumour abutment * on SMA Gastroduodenal artery encasement * up to origin at hepatic artery Tumours with limited involvement of the inferior vena cava (IVC) SMV occlusion, if of a short segment, with open vein both proximally and distally Colon or mesocolon invasion *Tail* Adrenal, colon or mesocolon, or kidney invasion
Unresectable tumours
Distant metastases Metastases to lymph nodes beyond the field of resection *Head* SMA, celiac encasement SMV/portal occlusion Aortic, IVC invasion or encasement Invasion of SMV below transverse mesocolon $ *Body* SMA, celiac, hepatic encasement SMV/portal occlusion Aortic invasion *Tail:* SMA, celiac encasement Rib, vertebral invasion

* No uniform and generally accepted definition exists for patency, impingement, abutment or encasement.
$ I.e. bifurcation of the splanchnic branches.

3.6.2.2 Resectable tumours

No randomised trials compared surgical resection to no resection or to other treatment modalities in patients with resectable pancreatic cancer. However, surgical resection remains the only potentially curative option in patients with resectable pancreatic cancer. The nature and extent of the surgery depend on the localisation and size of the tumour. Tumours of the pancreatic body and tail are treated with a distal pancreatectomy, although many of these tumours cause symptoms late in their development and are therefore advanced at diagnosis and commonly unresectable. Patients with tumours of the pancreatic head are treated with pancreaticoduodenectomy (PD) (the so-called 'Whipple-procedure'). In some cases, more radical procedures, such as total pancreatectomy (e.g. in patients with extensive IPMN involving the whole pancreas), are needed [29, 104, 105].

The extent of lymphadenectomy during PD can be defined as standard, radical or extended radical [106]. According to an international consensus panel, *standard lymphadenectomy* can be defined as a regional lymphadenectomy around the duodenum and pancreas with a partial (right) skeletonization of the superior mesenteric artery and celiac trunk (see appendix 5 for lymph node stations) [107].

During a *radical lymphadenectomy*, a regional (standard) lymphadenectomy is extended with a skeletonization of the hepatic arteries, of the superior mesenteric artery between the aorta and inferior pancreaticoduodenal artery, and of the celiac trunk, and a dissection of the anterolateral aspect of the aorta and of the inferior vena cava including the Gerota's fascia (see appendix 5). Finally, an *extended radical lymphadenectomy* extends a radical lymphadenectomy with a clearance of the anterior aorta between the diaphragmatic hiatus (around the celiac trunk) and the origin of the common iliac arteries (see appendix 5).

One good-quality systematic review comparing standard to (extended) radical lymphadenectomy was identified, including 4 RCTs [106]. Meta-analysis of the 3 RCTs published in full-text – only taking into account patients with pancreatic cancer – revealed no significant differences in overall survival (HR 0.93, 95%CI 0.77 – 1.13, p = 0.48) or postoperative morbidity [106]. Importantly, definitions of standard and (extended) radical lymphadenectomy differed across the included studies. The authors concluded (extended) radical lymphadenectomy not to be beneficial. No additional RCTs were identified by our search.

Based on this evidence, it is also clear that if peroperative exploration shows that a standard lymphadenectomy is insufficient (because of involvement of lymph nodes beyond the resection field), surgery becomes palliative.

3.6.2.3 Borderline resectable tumours

One small Japanese RCT was identified comparing radical resection (pancreaticoduodenectomy or distal pancreatectomy with dissection of the regional lymph nodes) to 5-FU-based CRT in patients with resectable locally advanced pancreatic cancer [108]. Criteria for resectability included invasion of the pancreatic capsule without involvement of the superior mesenteric artery or the common hepatic artery, and absence of distant metastasis. Patients treated with radical resection had a significantly better 1-year survival (62% vs. 32%, p = 0.05) and mean survival (> 17 months vs. 11 months, p < 0.03) [108]. Lygidakis et al. compared radical resection (mono-bloc spleno-pancreatic and vascular resection) to palliative gastro-biliary bypass in patients with pancreatic head carcinoma and portal-mesenteric venous invasion [103]. Both treatment groups were also treated with adjuvant locoregional chemoimmunotherapy. Patients undergoing radical resection had a significantly higher 2-year (81% vs. 0%, p = 0.0001) and 5-year survival (19% vs. 0%, p = 0.0001). No RCTs were found comparing radical resection to other treatment modalities for patients with less advanced pancreatic cancer.

Recommendation

- **Patients with resectable pancreatic cancer who are fit for surgery should undergo radical pancreatic resection (pancreaticoduodenectomy for pancreatic head tumours, distal pancreatectomy for pancreatic body and tail tumours) and standard lymphadenectomy with the intent of a R0 resection (1C recommendation).**
- **Radical and extended radical lymphadenectomy are not recommended during pancreatic resection (1B recommendation).**
- **Pancreatic resection with arterial reconstruction is not recommended in patients with pancreatic cancer in whom major arteries (arteria hepatica, arteria mesenterica superior, truncus coeliacus) are involved (2C recommendation).**
- **Venous invasion is not a contra-indication for surgery (2C recommendation).**
- **In left-sided tumours, local invasion of the splenic artery and/or vein is not a contraindication for resection (expert opinion).**

3.6.3 Reconstruction after pancreaticoduodenectomy

3.6.3.1 Pylorus preservation vs. antrectomy

Compared to a standard Whipple PD, a pylorus-preserving PD involves a less extensive dissection, leaving the stomach and pylorus intact. Theoretically, this may result in decreased blood loss, operating time and postoperative complications. Three systematic reviews were identified comparing standard Whipple to pylorus-preserving PD in patients with pancreatic or periampullary cancer [109-111]. The two most recent reviews are of high quality [109, 110]. Both reviews included the same 6 RCTs and performed a meta-analysis. Although different methods were used to pool the data, both reviews found no difference in overall postoperative mortality and morbidity. However, pylorus-preserving PD was associated with a shorter operating time and reduced blood loss [109, 110]. No additional RCTs published since 2006 were found.

Recommendation

- **The choice between standard and pylorus-preserving pancreaticoduodenectomy (PD), both equivalent techniques, should be based on individual surgeon preference (1B recommendation).**

3.6.3.2 Pancreaticoenteric anastomosis

Pancreaticoduodenectomy is associated with a high postoperative morbidity, with leakage from the pancreatic anastomosis being the most important cause of morbidity [112]. The reported incidence of pancreatic fistula or leakage ranges from 2 to 28%, and the mortality risk from a major pancreatic fistula may be as high as 28%. Several RCTs compared different techniques of pancreatic anastomosis [113-120], with pancreaticojejunostomy (PJS) and pancreaticogastrostomy (PGS) being the most frequently used techniques.

A recent systematic review [113] identified only one RCT comparing PJS to PGS after PD [121]. Pooled analysis of this RCT with the results of 10 observational trials showed a higher rate of pancreatic fistula (RR 2.62, 95%CI 1.91 – 3.60), a higher overall morbidity rate (RR 1.43, 95%CI 1.26 – 1.61) and mortality rate (RR 2.51, 95%CI 1.61 – 3.91) after PJS reconstruction [113]. Two additional RCTs were identified by our search [114, 115]. In contrast to the results of McKay et al. [113], pooled analysis of the 3 published RCTs showed no difference in the rate of pancreatic fistula (RR 1.15, 95%CI 0.74 – 1.80, p = 0.53), postoperative complications (RR 1.03, 95%CI 0.82 – 1.29, p = 0.80) or mortality rate (RR 0.91, 95%CI 0.38 – 2.18, p = 0.83) (see appendix 4 for forest plots).

Recommendation

- **The choice between pancreaticojejunostomy and pancreaticogastrostomy, both equivalent techniques of pancreatic anastomosis after pancreaticoduodenectomy, should be based on individual surgeon preference (1B recommendation).**

3.6.4 Role of laparoscopy

One narrative review based on a Medline search was identified [77]. No RCTs were found. Experiences with laparoscopic pancreaticoduodenectomy were reported to be negative, with longer operative time and hospital stay [77]. Laparoscopic left pancreatectomy seems to be more promising, especially for cystic tumours. Croce et al. reported less operative time and postoperative stay, a faster recovery, and few pancreatic fistulas [77]. However, these data are based on observational studies only.

Recommendation

- **Laparoscopic pancreatic resection with curative intent is strictly investigational (2C recommendation).**

3.6.5 Relation volume-outcome

Two systematic reviews were found examining the relation between volume and outcome for pancreatic surgery [122, 123]. Halm et al. identified 10 trials examining associations between hospital volume and death [122]. Nine of these studies found a significant volume-outcome relation, with a median absolute difference in mortality rate for high vs. low-volume hospitals of 13 deaths per 100 cases (range 3.0 – 17.9). The median number of cases per year in high-volume hospitals was 20 (range 3 – 200).

Killeen et al. also found a large volume effect based on the results of 11 studies [123]. A number-needed-to-treat of 10 – 15 patients was calculated for a high-volume provider to prevent one death.

One Belgian nation-wide study was identified [124]. Analysis of 1794 pancreaticoduodenectomies performed between 2000 and 2004 in all 126 Belgian hospitals showed a significant relationship between the annual number of pancreaticoduodenectomies per hospital and the mortality rate ($p = 0.005$). The mortality rate for hospitals performing more than 10 pancreaticoduodenectomies annually was 5.4% (compared to 10.7% for hospitals performing 10 or fewer pancreaticoduodenectomies annually; $p < 0.001$).

Importantly, the outcome of patients with pancreatic cancer is not only influenced by the volume of pancreaticoduodenectomies, but also by other factors, such as the surgeon's training, the availability of multidisciplinary expertise and adequate facilities.

Recommendation

- **Pancreatic oncologic surgery should be restricted to high-volume centres in which a multidisciplinary expertise and adequate facilities are available (1C recommendation).**

3.7 HISTOPATHOLOGIC EXAMINATION

A limited number of observational studies showed the benefits of a standardized protocol for the examination of a pancreatic carcinoma resection specimen. Standardized pathologic evaluation resulted in a higher rate of R1 resections [125, 126] and improved lymph node identification [127]. Several guidelines were found for the histopathological examination and reporting of pancreatic carcinoma resection specimens [128-130]. Although none of these were found to be of sufficient quality, they were used as starting point for the preparation of this chapter. In contrast to the other search questions, the search for additional primary studies was not restricted to systematic reviews, RCTs or prospective cohort studies.

Importantly, in the literature no uniform definition of R0 resection was found [129, 131-133]. For our guidelines, we adopt the definition of the Royal College of Pathologists [129, 133]: margins histologically positive for disease or with cancer at less than 1 mm from a margin are not considered a R0 resection. This definition is not in line with the UICC's definition (R0: no residual tumour; R1: microscopic residual tumour; R2: macroscopic residual tumour) [138].

3.7.1 Specimen handling

The type of resection specimen (e.g. standard Whipple's pancreaticoduodenectomy [PD], pylorus-preserving PD, left pancreatectomy, etc.) should first be recorded [129]. The specimen should preferably be examined immediately after resection in the fresh and unfixed state, after opening of the duodenum and/or stomach [129, 130]. In case of a Whipple resection, the posterior surface (retroperitoneal margin) of the pancreas and the groove of the vena mesenterica superior (uncinatus margin) should be inked. The anterior surface can also be inked (in a different colour) [128, 129, 133]. Probing of the bile duct and/or main pancreatic duct from the resection margin into the duodenum can aid the section. This will allow cutting the pancreas open horizontally along the probe(s) from the pancreatic resection margin up to the duodenum [130]. This will allow identification of the tumour, which often leads to stenosis of the ducts.

Finally, the specimen should be pinned on a cork plate in an anatomically correct position and fixed at least overnight [128, 129]. Alternatively, serial slicing of the entire pancreatic head perpendicular to the longitudinal axis of the duodenum can be performed [133]. Subsequently, tissue for histological examination is removed.

3.7.2 Gross examination

All components of the resection specimen (pancreas, duodenum, stomach, etc.) should be measured [128-130]. Gross inspection also includes the description of the presence of a tumour, which may be difficult to distinguish macroscopically from chronic pancreatitis [128].

The tumour site, bile duct, pancreatic head, body or tail and probable site of origin should be recorded [128-130] to be sure that it is the pancreas and to exclude ampullary carcinomas (a neoplasm centered in the region of the ampulla), the latter having a significantly better prognosis. The term peri-ampullary carcinoma is used for neoplasms in an advanced stage for which it is not possible to define the precise site of origin. The presence of adenomatous changes in the ampulla can help to make the distinction.

The macroscopic appearance of the tumour should be noted [130]. Features such as cyst formations, papillary (intraductal) tumour components or ectatic, mucin-filled duct segments, should be recorded, since they are diagnostic of specific types of pancreatic tumours with a generally better prognosis, e.g. mucinous cystic tumour, IPMT, etc.

In case of cystic tumours it is important to describe the relationship with the main pancreatic ducts.

Tumour size should be measured at least recording the maximum diameter of the tumour [128-130]. Tumour size is an independent prognostic factor. In a recent meta-analysis, Garcea et al. found a prolonged median survival for tumours less then 2 cm (8 studies; OR 2.52, 95%CI 1.95 – 3.29, $p < 0.001$) [134]. This was confirmed by several additional prognostic studies [21, 131, 135, 136], but not by others [132, 137].

In case of mucinous cystic tumours and IPMT particular care should be taken to sample the tumour extensively, in order not to miss the invasive component.

The number of lymph nodes should be recorded. All dissected lymph nodes should be embedded for adequate staging [128]. Nodes should be classified according to their anatomical site, namely (1) nodes attached to the pancreas (superior/inferior/anterior/posterior), (2) hepatic, celiac artery or superior mesenteric artery nodes, (3) paraaortic nodes and nodes around the inferior mesenteric artery and (4) splenic nodes or perigastric nodes.

Finally, the distance from the tumour to the margins (pancreatic transection margin, retroperitoneal margin, the resection margin of the bile duct) should be assessed macroscopically [129].

3.7.3 Microscopic examination

Microscopic examination includes the histological type (e.g. ductal adenocarcinoma, intraductal papillary-mucinous carcinoma, pancreatoblastoma, etc.), the tumour differentiation (according to the WHO principles), the tumour size (see above), intra- and extrapancreatic extent, the status of the margins, the lymph node status, the presence of vascular or perineural invasion, and the presence of distal spread [128-130].

Histological grading (well, moderately or poorly differentiated) is an independent prognostic factor. Well-differentiated tumours were found to have a prolonged median survival (19 studies; OR 2.40, 95%CI 1.69 – 3.41, $p < 0.001$) [134]. This was confirmed by Howard et al. [131] and Yekebas et al. [138], but not by Tani et al. [139].

Resection margins include pancreatic transection margin, posterior (retroperitoneal) resection margin, the resection margin of the bile duct, and the proximal duodenal margin in case of pylorus-preserving PD. The pancreatic transection margin and/or the common bile duct margin are to be evaluated intraoperatively on frozen sections.

Most important is the posterior resection margin (defined as the retroperitoneal peripancreatic fatty tissue adjacent to the pancreatic tissue). Distance should be recorded microscopically.

After left pancreatectomy the resection margin toward the head of the pancreas should be examined. It should be evaluated intraoperatively on frozen sections to determine whether it is tumour free.

The microscopic resection margin involvement was found to be an independent prognostic factor. Garcea et al. found a prolonged median survival for patients having undergone a R0 resection (11 studies; OR 3.00, 95%CI 2.15 – 4.17, p < 0.001) [134]. Howard et al. found similar although less pronounced results (HR 1.39, 95%CI 1.02 – 1.90, p = 0.03) [131]. However, these results were not confirmed by 3 more recent studies [132, 139, 140]. Westgaard et al. found involvement of the retroperitoneal margin to be an indicator of poor prognosis after resection with curative intent (R0 and R1) (HR 1.89, 95%CI 1.16 – 3.08, p = 0.01) [141]. As stated above, margins histologically positive for disease or with cancer at less than 1 mm from a margin are considered not to be an R0 resection [129, 133].

An additional independent prognostic factor is the lymph node status. A negative lymph node status was found to be associated with a better median survival (24 studies; OR 2.09, 95%CI 1.69 – 2.60, p < 0.001 [134]. This was confirmed by several other studies [21, 132, 136, 137]. Above this, three studies found the lymph node ratio (LNR, proportion of metastatic to examined lymph nodes) to be another prognostic factor [142-144].

Several large population-based studies also found the number of lymph nodes examined to be a prognostic factor, with a minimal number of 10 and an optimal number of lymph nodes examined between 12 and 15 [144-146]. Finally, Yekebas et al. found nodal micro-involvement (immunostaining with Ber-EP4) to be a prognostic factor [138].

Perineural and vascular invasion are less pronounced prognostic factors. Garcea et al. found the absence of perineural invasion to be associated with a prolonged median survival (12 studies; OR 2.37, 95%CI 1.77 – 3.18, p < 0.001) [134]. However, this was not confirmed by Tani et al. [139]. No significant association was found between blood vessel invasion and median survival (OR 1.88, 95%CI 0.89 – 3.49, p = 0.097) [134]. This was confirmed in 2 additional studies [137, 139]. On the contrary, 3 other studies found blood vessel invasion to be a prognostic factor [21, 135, 136].

Many molecular markers are under evaluation at present [147]. Overall, conflicting evidence exists on their use as prognostic indicators. Therefore, their use is strictly investigational.

3.7.4 Frozen section diagnosis

Intra-operative frozen section diagnosis is often used to histologically confirm the primary diagnosis, to assess the resection margins, or to confirm the presence of malignancy in a potentially metastatic nodule in the liver, peritoneum or a lymph node [129]. Observational (retrospective) studies have shown frozen section examination to be accurate in the majority of cases [148, 149]. However, some important pitfalls are associated with frozen section diagnosis. First, it can be difficult to determine malignancy vs. benignity of ductal structures present in the microscopic field, e.g. because of crushing artefacts (in case of stapling) or cautery artefacts [149]. Second, the pathologist can be confronted with true cytologic atypia in a resection margin. An important question than is if the creation of a further margin is necessary. In case of PanIN-3 lesions at the pancreatic resection margin (see definitions in appendix 7), a new margin will need to be taken if technically feasible [149, 150].

Recommendations

- **A standardized protocol for the examination of a pancreatic carcinoma resection specimen is recommended (1C recommendation).**
- **The retroperitoneal margin of the pancreas should be inked before fixation of the resection specimen (expert opinion).**
- **In the literature, no consensus exists on the definition of a R0 resection. In the present guideline, margins histologically positive for disease or with cancer at less than 1 mm from a margin are considered not to be a R0 resection (expert opinion).**
- **Gross examination of the resection specimen includes (1C recommendation):**
  - **the measurement of all components;**
  - **the description of the presence of a tumour;**
  - **the tumour site and probable site of origin;**
  - **tumour size (at least maximum diameter);**
  - **number of lymph nodes;**
  - **distance to the nearest margin.**
- **Microscopic examination includes (1C recommendation):**
  - **histological type;**
  - **tumour differentiation;**
  - **tumour size;**
  - **status of the margins;**
  - **lymph node status;**
  - **presence of local invasion;**
  - **presence of vascular or perineural invasion;**
  - **presence of distal spread.**

3.7.5 Staging systems

Currently, two different staging systems are available for the classification of pancreatic tumours: the International Union Against Cancer (UICC) or TNM classification [151] and the Japanese Pancreas Society (JCS) classification [152] (see appendix 6). Obviously, the most widely used classification in Europe is the UICC classification. The most important differences with the JCS classification are the tumour staging (according to tumour size in the JCS classification vs. according to tumour extension in the UICC classification) and the nodal staging (according to 3 lymph node regions in the JCS classification vs. according to the presence of lymph node metastasis or not in the UICC classification). Retroperitoneal serosal – portal vein invasion is also taken into account in the JCS classification.

In view of the widespread use in Europe, the use of the UICC classification is recommended for the staging of pancreatic cancers in Belgium.

3.8 ADJUVANT TREATMENT

The CCO guideline identified 6 randomised comparisons between surgery followed by adjuvant chemotherapy and surgery alone, including the recently published results of the CONKO-001 trial [79, 153]. Pooled analysis showed a significant reduction in 2-year mortality in favour of adjuvant chemotherapy, with a risk ratio of 0.85 (95%CI 0.75 – 0.98, p=0.03). However, in this pooled analysis the results of the GITSG trial were also included, which is in fact a comparison of postoperative chemoradiotherapy followed by chemotherapy to surgery alone [154].

Moreover, in the ESPAC1 study the 'adjuvant chemotherapy group' comprised both the chemotherapy arm and the chemoradiotherapy + chemotherapy arm, while the 'no adjuvant chemotherapy group' comprised the observation (i.e. surgery only) arm and the chemoradiotherapy arm [155]. These results were included as such in the pooled analysis by the CCO [79].

Finally, the study of Kosuge et al. was not included in the pooled analysis, because of the absence of sufficient survival data at two years [156]. No additional RCTs were identified by our literature search.

Three randomised comparisons of postoperative CRT and surgery alone were identified by the CCO [79]. Pooled analysis of these 3 trials combined with the results of the GITSG trial showed no difference in 2-year mortality, with a risk ratio of 0.94 (95%CI 0.75 – 1.20, p=0.64). Again, in the ESPAC1 study the 'adjuvant chemoradiotherapy group' comprised both the chemoradiotherapy arm and the chemoradiotherapy + chemotherapy arm, while the 'no adjuvant chemoradiotherapy group' comprised the observation (i.e. surgery only) arm and the chemotherapy arm [155]. These results were included as such in the pooled analysis by the CCO [79]. No additional RCTs were identified by our search.

CCO also identified 2 trials comparing postoperative chemoradiotherapy followed by chemotherapy to surgery alone [79]. Kalser et al. reported a significant survival benefit in favour of split-course RT with 5-FU, followed by maintenance 5-FU (2-year overall survival 43% vs. 18%) [154]. In the ESPAC1 trial, 5-year overall survival was 13% for the treatment group compared to 11% for the observation group [155].

One RCT compared postoperative CRT to postoperative chemotherapy [155]. Five-year survival (29% vs. 7%) and median survival (21.6 vs. 13.9 months) were higher in the chemotherapy group [79]. One ongoing RCT was identified, comparing adjuvant gemcitabine to adjuvant gemcitabine-based CRT after R0 resection of pancreatic head cancer [157].

Several additional RCTs were identified, comparing different adjuvant chemotherapy regimens [158], different adjuvant CRT regimens [159], and 2 regimens of chemotherapy before and after adjuvant CRT [160]. One underpowered and low-quality RCT compared adjuvant 5-FU-based CRT to gemcitabine-based CRT [159]. No significant differences in median survival (17.2 vs. 12.1 months, p=0.84) or time-to-progression (14.3 vs. 10.8 months, p=0.80) were found. Gemcitabine-based CRT was associated with more toxicity [159]. Regine et al. compared 5-FU with gemcitabine before and after adjuvant 5-FU-based CRT [160]. A non-significant survival benefit was found in favour of the gemcitabine group (3-year survival 31% vs. 22%; HR 0.82, 95%CI 0.65-1.03; p = 0.09). However, gemcitabine was associated with a higher grade 4 haematologic toxicity [160].

Based on a meta-analysis of individual data from 4 published RCTs (875 patients, 278 with R1 and 591 with R0 resections), Butturini et al. identified a survival benefit with CRT in patients with a R1 resection (HR 0.72, 95%CI 0.47-1.10) [140]. On the contrary, in patients with a R0 resection, a 19% increased risk of death with CRT was found (HR 1.19, 95%CI 0.95-1.49). Based on these results, postoperative CRT can be considered in patients with positive resection margins after discussion in the multidisciplinary team meeting.

Recommendations

- **Postoperative chemotherapy with single-agent gemcitabine is recommended for patients with R0 and R1 resected pancreatic cancer (1B recommendation).**
- **Postoperative radiotherapy alone cannot be recommended in patients with R0 and R1 resected pancreatic cancer (expert opinion).**

3.9 FOLLOW-UP AFTER CURATIVE TREATMENT

No guidelines or primary studies were found evaluating the benefit, standard schedule and frequency of follow-up in curatively treated patients with pancreatic cancer. Generally, follow-up is indicated where early detection of tumour recurrence may result in cure. However, in patients with pancreatic cancer, early detection of recurrence only seldom leads to curative therapeutic interventions (see below).

Kim et al. found half of the recurrences to occur within 6 months after surgery and 87% to occur within 12 months after surgery [161]. Most common types of tumour recurrence are hepatic metastases, local recurrences and lymph node metastases [161, 162]. CT was found to be a reliable procedure for detecting tumour recurrence, in particular hepatic metastases [161-163]. FDG-PET proved to be beneficial for the detection of non-locoregional and extra-abdominal recurrences [163]. Tumour markers were found to be of some value in the follow-up of patients with pancreatic cancer [164-166].

In view of this limited evidence, technical examinations should be limited to a minimum in the follow-up of asymptomatic patients.

Recommendation

- **In patients with curatively treated pancreatic cancer, surveillance visits are recommended every 3 – 6 months. Technical examinations should be limited to a minimum in asymptomatic patients (expert opinion).**

3.10 PALLIATIVE TREATMENT

3.10.1 Chemotherapy

3.10.1.1 Chemotherapy vs. best supportive care

Two high-quality systematic reviews were identified comparing best supportive care to chemotherapy in advanced pancreatic carcinoma [167, 168]. Both reviews identified the same 8 RCTs, although Sultana et al. excluded the study of Andersen et al. [169] because it included patients who had undergone prior resection. Overall survival was significantly better in patients who received chemotherapy (HR 0.64; 95%CI 0.42 – 0.98, p = 0.04) [167]. Chemotherapy significantly reduced the one-year mortality (OR 0.37; 95%CI 0.25 – 0.57, p < 0.00001) [168].

Although the advantage of chemotherapy in patients with advanced pancreatic cancer was clearly shown by the 2 identified systematic reviews, unfit patients with a poor performance status (Karnofsky performance status < 70%) only have a marginal benefit from chemotherapy and may often benefit more from optimal supportive care [170].

3.10.1.2 Gemcitabine vs. 5-FU

Sultana et al. identified 2 RCTs comparing gemcitabine to 5-FU in patients with advanced pancreatic cancer [167]. The survival advantage for gemcitabine over 5-FU was not statistically significant (HR 0.75; 95%CI 0.42 – 1.31, p = 0.31). One additional phase II trial (published as an abstract) was identified, comparing folfirinox (5-FU/leucovorin, irinotecan and oxaliplatin) to gemcitabine as first-line treatment for metastatic pancreatic adenocarcinoma [171]. Although partial response was better in the folfirinox group (39% vs. 12%), no statistical analysis or mortality data were provided.

3.10.1.3 Gemcitabine alone vs. gemcitabine combination

Many trials and systematic reviews compared the efficacy of gemcitabine alone to gemcitabine combination regimens in patients with advanced/metastatic pancreatic cancer. Six published systematic reviews [167, 168, 172-175] and 1 CCO guideline [176] identified a total of 28 RCTs. One additional meta-analysis was published as an abstract [177]. In contrast to both Bria et al. [173] and Banu et al. [174], Sultana et al., Yip et al. and Heinemann et al. didn't include trials involving targeted agents [167, 168, 172]. Xie et al. performed a meta-analysis of trials evaluating the combination of gemcitabine and cisplatin [175].

Our search identified 2 updates of RCTs previously published as an abstract [178, 179], 1 new RCT published in full-text [180] and 5 new RCTs published as an abstract [181-185].

Inconsistency in the conclusions was found across the systematic reviews, with 4 reviews favouring gemcitabine combination [167, 172, 174, 177] and 4 reviews finding no differences [168, 173, 175, 176]. The combinations with the highest potential included platinum-based compounds (mainly oxaliplatin) [167, 168, 172-174, 177] and capecitabine [167, 172, 177].

Looking at the individual studies, only a few phase III trials showed an improved survival with gemcitabine combined with cytotoxic agents compared with gemcitabine alone [186]. In an interim analysis published as an abstract, Cunningham et al. showed a significantly improved median (7.4 vs. 6.0 months) and 1-year survival (26% vs. 19%) in favour of the combination of gemcitabine and capecitabine [187]. However, these results were not confirmed by Herrmann et al. [178].

Of the trials evaluating the combination of gemcitabine with targeted agents, only the study of Moore et al. showed a significant survival benefit in favour of the combination of gemcitabine and erlotinib (overall survival: HR 0.82, 95%CI 0.69-0.99, p = 0.038) [179].

3.10.1.4 5-FU alone vs. 5-FU combination

Sultana et al. and Yip et al. [167, 168] identified the same 7 RCTs, although Sultana et al. excluded 2 RCTs on methodological grounds [188, 189]. Nevertheless, both reviews concluded 5-FU-based combinations not to be superior to 5-FU alone in terms of survival (HR 0.94; 95%CI 0.82 – 1.08, p = 0.39) [167]. No additional RCTs were identified.

3.10.1.5 Other chemotherapy regimens

Cytotoxic agents

Yip et al. identified 6 RCTs comparing different chemotherapy regimens, with only 1 trial finding an advantage of one regimen over another [168]. Our search identified 3 additional published RCTs [190-192] and 5 RCTs published as an abstract [193-197]. Only 3 of these trials found an advantage of one regimen over another [191, 195, 196].

Lutz et al. compared docetaxel plus gemcitabine to docetaxel plus cisplatin in 96 patients with advanced pancreatic cancer [191]. Median survival was comparable (7.4 vs. 7.1 months, no p value provided), with a better 1-year survival in the group receiving docetaxel plus gemitabine (30% vs. 16%, no p-value provided). Less severe acute toxicity was experienced with docetaxel plus gemcitabine (9% vs. 16%, no p value provided) [191].

Reni et al. compared cisplatin, capecitabine and gemcitabine plus epirubicin (PEXG) or docetaxel (PDXG) in 64 patients with advanced pancreatic cancer [195]. Progression-free survival at 6 months was higher in the PDXG group (54% vs. 44%, no p value provided, interim analysis with 51 patients).

Andre et al. compared a 'simplified' gemcitabine – oxaliplatin regimen (S-GEMOX, gemcitabine infusion immediately followed by oxaliplatin infusion) to a 'standard' regimen (GEMOX, gemcitabine infusion on day 1 and oxaliplatin infusion on day 2) [196]. Median overall survival was higher in the S-GEMOX group (7.6 vs. 3.2 months, no p value provided).

Targeted agents

Our search identified 1 full-text RCT [198] and 4 RCTs published as an abstract [199-203]. Only 1 of these trials found an advantage of one regimen over another [203].

Vervenne et al. evaluated the efficacy and safety of adding bevacizumab to erlotinib plus gemcitabine in 607 patients with metastatic pancreatic cancer [203]. Addition of bevacizumab did not lead to a significantly longer overall survival (6.0 vs. 7.1 months; HR 0.89, 95%CI 0.74 – 1.07), but there was a significantly improved progression-free survival (3.6 vs. 4.6 months; HR 0.73, 95%CI 0.61 – 0.86; p=0.0002).

3.10.2 Chemoradiotherapy

A CCO guideline was identified describing the treatment of patients with unresectable non-metastatic locally advanced pancreatic cancer [204]. Since patients with metastatic disease were not covered by that guideline, it was decided to expand the date limit of our literature search to beyond that of the CCO guideline (February 2004). Two additional systematic reviews were identified [168, 205]. Overall, and taking into account the respective search dates, the evidence base of these 3 reviews is similar [168, 204, 205].

All three reviews found 1 RCT comparing CRT (radiotherapy plus concurrent 5-FU infusion with weekly 5-FU maintenance post-radiotherapy) to best supportive care [206]. A survival benefit was found in favour of CRT (HR 0.28, 95%CI 0.13 – 0.60) [205]. One other RCT compared high dose radiation alone to high dose radiation plus 5-FU (concurrent and maintenance) or low dose radiation plus 5-FU (concurrent and maintenance) [207]. Again, a survival benefit was found in favour of CRT (HR 0.50, 95%CI 0.29 – 0.84) [205]. No statistically significant differences were found between the 2 CRT arms.

The most recent and most complete systematic review identified 2 RCTs comparing radiotherapy to chemoradiotherapy (without maintenance chemotherapy) [205]. Pooled analysis of these 2 trials showed a significant better overall survival in favour of chemoradiotherapy (HR 0.69, 95%CI 0.51 – 0.94). Haematological toxicity tended to be lower in the radiotherapy arm (RR 2.51, 95%CI 0.96 – 6.54).

Sultana et al. identified 4 RCTs comparing chemotherapy alone to CRT [205]. Overall survival data for time-to-event analysis was available in two trials. Pooled analysis showed no significant difference in overall survival between the 2 treatment arms (HR 0.79, 95%CI 0.32 – 1.95) [205]. In a recent RCT (published as an abstract), a combination of radiotherapy and gemcitabine was compared to gemcitabine alone in 71 patients with localized, unresectable pancreatic cancer [208]. Median survival was significantly better for the CRT arm (11.0 vs. 9.2 months, p=0.044). On the other hand, grade IV toxicity was more common in the CRT arm (41.2% vs. 5.7%, p<0.0001).

Several RCTs were identified comparing different chemotherapeutic agents in combination with radiotherapy [168, 204, 205] (Table 8). Only Li et al. reported a significant survival benefit in favour of gemcitabine-based CRT compared to 5-FU-based CRT [209]. All other comparisons did not find a difference in survival between the treatment arms [207, 210-213]. A recent underpowered and low-quality RCT comparing 5-FU-based CRT to gemcitabine-based CRT also found no difference in median survival between the 2 treatment groups (9.5 vs. 9.1 months, p=0.79) [159].

Table 8. Overview of RCTs comparing different chemotherapeutic agents in combination with radiotherapy.

Study ID	Treatment groups	Source systematic review(s)
McCracken 1980	Group A: radiotherapy + methyl lomustine + 5-FU Group B: same regimen + testolactone 200 mg po daily	CCO 2-7
GITSG 1985	Group A: radiotherapy + 5-FU, followed by maintenance with 5-FU Group B: radiotherapy + doxorubicin, followed by maintenance with 5-FU	CCO 2-7, Yip 2006, Sultana 2007b
Earle 1994	Group A: radiotherapy + 5-FU Group B: radiotherapy + hycanthone	CCO 2-7, Yip 2006; excluded in Sultana 2007b
Li 2003	Group A: radiotherapy + 5-FU, followed by maintenance with gemcitabine Group B: radiotherapy + gemcitabine, followed by maintenance with gemcitabine	CCO 2-7, Yip 2006, Sultana 2007b
Wilkowski 2006	Group A: radiotherapy + 5-FU Group B: radiotherapy + gemcitabine + cisplatin Group C: radiotherapy + gemcitabine + cisplatin, followed by 4 cycles of gemcitabine + cisplatin	Sultana 2007b
Brasiuniene 2007	Group A: radiotherapy + 5-FU Group B: radiotherapy + gemcitabine	-

In patients with inoperable locally advanced pancreatic cancer, addition of radiotherapy after 3 months of induction chemotherapy can be considered. In a retrospective analysis of 128 patients with locally advanced pancreatic cancer and no disease progression after 3 months of chemotherapy, addition of radiotherapy resulted in an improved median progression-free survival (10.8 vs. 7.4 months, p = 0.005) and median survival (15.0 vs. 11.7 months, p = 0.0009) in comparison with continuation of chemotherapy [214]. Currently, prospective phase III trials are ongoing to evaluate this treatment option (http://clinicaltrials.gov/ct2/show/NCT00192712).

3.10.3 Radiotherapy

As stated above (see 3.10.2), radiotherapy alone was associated with worse survival compared to chemoradiotherapy for patients with advanced pancreatic cancer [168, 205]. No RCTs were identified comparing radiotherapy to best supportive care or to chemotherapy. Our search could not identify additional trials on radiotherapy alone or new trials published since the 2 most recent systematic reviews [168, 205].

3.10.4 Palliative surgery

No guideline was found addressing the use of palliative surgery in patients with advanced pancreatic cancer. Three systematic reviews [215-218] and two additional RCTs [219, 220] were found comparing endoscopic and surgical biliary bypass. One other systematic review studied the role of laparoscopic biliary bypass [221]. In addition, four RCTs studied different types of palliative surgery [222-225]. However, no systematic reviews or RCTs were found comparing palliative resection to no resection in patients with advanced pancreatic cancer. Therefore, palliative resection is not recommended in these patients.

The 3 systematic reviews comparing endoscopic and surgical biliary bypass identified the same 3 RCTs [215-218]. Moss et al. found no difference in rates of technical (RR 1.01, 95%CI 0.95 – 1.07) and therapeutic success (RR 1.00, 95%CI 0.93 – 1.08) between stenting and surgery [215]. The relative risk of all complications was significantly reduced in patients receiving stents compared to surgery (RR 0.60, 95%CI 0.45 – 0.81, p = 0.0007). There were no significant differences in survival or quality of life. These results are largely in line with those of the 2 other reviews [217, 218].

In a recent RCT, Artifon et al. randomised 30 patients with metastatic pancreatic cancer and biliary obstruction to endoscopic or surgical treatment [219]. No difference was found in complication rate and survival. The overall total cost of care (including initial care and subsequent interventions and hospitalizations until death) were lower in the endoscopy group compared with the surgical group (US$ 4271 ± 2411 vs. 8321 ± 1821, p = 0.0013). In addition, the quality of life scores at 30 and 60 days were better in the endoscopy group. Nieveen van Dijkum et al. randomised 27 patients with a biopsy-proven unresectable peripancreatic tumour to surgical palliation (retrocolic gastroenterostomy and Roux-en-Y side-to-side hepaticojejunostomy in combination with celiac plexus block) or endoscopic palliation (Wallstent and percutaneous celiac plexus block in case of intractable pain) [220]. No significant differences were found. Based on this body of evidence, surgical biliary bypass cannot be routinely recommended in patients with advanced pancreatic cancer and biliary obstruction. However, in patients who are peroperatively found to be unresectable, surgical (double) biliary bypass can be considered.

Date et al. reviewed the literature on laparoscopic biliary bypass in patients with non-resectable periampullary cancer [221]. Only observational studies were identified, and the authors concluded that these techniques (laparoscopic cholecystoenterostomy, choledochojejunostomy and choledochoduodenostomy) cannot be recommended as routine practice. Navarra et al. compared the results of open and laparoscopic palliative antecolic isoperistaltic gastrojejunostomy in 24 patients with inoperable neoplasms of the distal stomach, duodenum, and biliopancreatic area (including 11 patients with pancreatic cancer) [222]. The laparoscopic group experienced less intraoperative blood loss and postoperative complications. No separate figures were provided for the patients with pancreatic cancer.

Van Heek et al. randomised 70 patients with unresectable periampullary cancer to a double bypass (hepaticojejunostomy and a retrocolic gastrojejunostomy) or a single bypass (hepaticojejunostomy) [223]. Of the 65 patients included in the analysis, 57 had pancreatic head cancer. Postoperative morbidity rates and median survival did not differ significantly between the 2 groups. Reoperation was necessary in more patients with a single bypass (ARR 18%, NNT 6).

Yilmaz et al. compared antecolic, isoperistaltic gastrojejunostomy, jejunojejunostomy, and hepaticojejunostomy after cholecystectomy on the one hand to hepaticojejunostomy and antecolic, antiperistaltic gastrojejunostomy after cholecystectomy on the other hand in 44 patients with unresectable pancreatic head cancer [224]. Again, no significant differences were found.

Finally, Shyr et al. compared 3 types of gastrojejunostomy in 45 patients with unresectable periampullary cancer complicated by gastric outlet obstruction [225]. No differences were found in hospital mortality and complication rates. However, patients receiving a gastrojejunostomy with duodenal partition had a lower incidence of symptomatic gastric outlet obstruction.

3.10.5 Endoscopic treatment

3.10.5.1 Stents

Four systematic reviews examined the role of endoscopic stents in the palliation of patients with pancreatic cancer and biliary obstruction [215-218]. The most recent review was the most complete, and will be discussed in more detail [215].

Moss et al. identified 7 RCTs comparing endoscopic metal to plastic stents [215]. No difference was found in terms of technical success (RR 1.01, 95%CI 0.96 – 1.05), therapeutic success (RR 1.0, 95%CI 0.95 – 1.05) or complications (RR 1.34, 95%CI 0.56 – 3.20). No significant differences were reported for survival or quality of life. Metal stents had a significantly reduced risk of recurrent biliary obstruction.

Our search identified 2 recently published RCTs comparing metal to plastic stents. Katsinelos et al. randomised 47 patients with inoperable malignant distal common bile duct strictures (including 25 patients with pancreatic cancer) to a Tannenbaum stent or an uncovered self-expandable metal stent [226].

No significant difference in survival was found. The median first stent patency was longer in the metal group, but the total cost associated with the Tannenbaum stents was lower than for the metal stents (€ 17700 vs. € 30100; p = 0.001). Soderlund et al. compared plastic stents to covered self-expanding metal stents (SEMS) in patients with unresectable malignant common bile duct strictures (including 78 patients with pancreatic cancer) [227]. Median patency times were significantly longer in the SEMS group, the costs did not differ significantly.

Twelve RCTs were found comparing different types of plastic stents [215]. There was no statistical difference between Tannenbaum Teflon® and polyethylene stents with regard to technical success, 30-day mortality or recurrent biliary obstruction prior to death (5 studies). Teflon stents were associated with a significantly lower therapeutic success and a higher risk of complications (not significant). No differences were found between both stent types for duration of stent patency and patient survival.

Moss et al. also identified 3 trials comparing different types of metal stents [215]. However, the results of these trials do not allow a definite choice of preferred type.

Recommendations

- **In patients with metastatic pancreatic cancer and a good performance status, chemotherapy (gemcitabine alone or gemcitabine combined with erlotinib) is recommended (1B recommendation).**
- **In patients with inoperable locally advanced pancreatic cancer, chemotherapy is recommended. Based on an evaluation after 2 – 3 months, addition of radiotherapy can be considered (expert opinion).**
- **In patients with inoperable pancreatic cancer (based on imaging) and obstructive jaundice, treatment with metal stents is recommended (1A recommendation).**

3.11 SUPPORTIVE TREATMENT

3.11.1 Patients undergoing surgical resection

3.11.1.1 Nutrition

Preoperative nutritional therapy

Initiation of nutritional support prior to surgery may provide additional benefit over postoperative supplementation alone [228]. One of the proposed strategies to reduce morbidity in cancer patients undergoing major elective surgery is the use of enteral diets enriched with specific nutritional compounds (arginine, glutamine, omega-3 fatty acids [fish oil], and nucleotides [ribonucleic acid, RNA]) that have been defined as "immunonutrition" [229]. Immunonutrition is supposed to alter cytokine production and immune function, thereby limiting the undesirable perioperative excessive stimulation of the immune and inflammatory cascade [229]. For example, Glutamine dipeptide (L-alanyl-L-glutamine) has been investigated in patients undergoing abdominal surgery in order to improve their postoperative nitrogen balance and immunonutrition. A recent meta-analysis of 9 RCTs involving 373 patients showed that glutamine dipeptide had a positive effect in improving postoperative cumulative nitrogen balance (weighted mean difference [WMD] 8.35, 95%CI 2.98-13.71, p = 0.002), decreasing postoperative infectious morbidity (OR 0.24, 95%CI 0.06-0.93, p = 0.04), shortening the length of hospital stay (WMD -3.55, 95%CI -5.26 – -1.84, p < 0.00001), without serious adverse effects. However, none of these 9 RCTs involved pancreatic cancer patients [232].

Only one pilot RCT involving 46 candidates for major elective surgery for malignancy (including 30 pancreatic cancer patients) compared a standard preoperative treatment with immunonutrition (Impact) of 5 days with a preoperative feeding period of 2 days using an immunonutrition formula enriched with glycine (Impact plus) [229]. Both treatment groups were compared with a control group that only received postoperative nutritional support.

This pilot study demonstrated that pre-operative administration of an immunoenriched diet significantly reduced systemic perioperative inflammation, postoperative complications and length of postoperative stay in intermediate care unit/intensive care unit for patients undergoing major abdominal cancer surgery, when compared with postoperative diet administration alone. No adverse gastrointestinal effect was recorded in the preoperative period.

In a systematic review conducted by Goonetilleke et al. [228], 1 RCT of moderate quality [230] was included that evaluated combined preoperative and postoperative administration of enteral diets enriched with arginine, omega-3 fatty acids, and nucleotides in 206 patients undergoing major elective surgery for gastrointestinal cancer (including 22 patients with pancreatic cancer). Intent-to-treat analysis showed a lower infectious complication rate in favour of the supplemented group (14% vs. 30%, p=0.009). The mean postoperative length of stay was also shorter in favour of the supplemented group (11.1 ± 4.4 vs. 12.9 ± 4.6 days, p=0.01).

Postoperative nutritional support

Enteral nutrition versus parenteral nutrition

One low-quality systematic review was identified that evaluated the effects of peri-operative nutritional supplementation in patients undergoing pancreaticoduodenectomy [228]. The 10 included studies compared total parenteral nutrition (TPN), enteral nutrition (EN) and immune-enhanced enteral nutrition (I-EN) with each other or with no initial postoperative nutritional support. One study compared cyclical with non-cyclical EN. According to the authors, routine postoperative TPN was associated with a higher incidence of complications (mortality, overall morbidity and length of hospital stay). EN reduced infectious complications. Cyclical nutrition was associated with a lower incidence of postoperative gastric stasis. The optimal route of delivery of enteral feeding remains unestablished. Nasojejunal feeding tubes may avoid the risks of surgical jejunostomy, but can dislodge and can be a source of postoperative discomfort. The evidence for immune-enhanced nutrition in patients undergoing pancreaticoduodenectomy is limited.

One high-quality RCT [231] and 3 moderate-quality RCTs [232-234] also compared TPN and EN (with or without immuno-nutrition). In the RCT of Braga et al., enteral nutrition was safe and well tolerated [231]. Achievement of the full nutritional goal was observed in at least 80% of all patients (after surgery for cancer of the stomach, pancreas or oesophagus). The feasibility and safety, the low prevalence of metabolic adverse effects, the improved gut oxygenation, and the low cost of EN support its use in upper gastrointestinal cancer patients requiring postoperative artificial nutrition.

Early EN represents a rational alternative to TPN and is four-fold less expensive (in Italy). The RCT conducted by Di Carlo et al. [233] among a more homogeneous sample of patients undergoing pancreaticoduodenectomy concluded that best results were obtained with enteral immunonutrition over standard EN and TPN regarding the rate and severity of postoperative complications and length of stay. Similar results were obtained by Gianotti et al. [234] in a heterogeneous sample of 260 patients with gastric or pancreatic cancer (n = 140). Studying the glutamine supplementation both in enteral and parenteral nutrition, Fish et al. [235] found no difference in plasma amino-acid profiles by feeding group.

Enteral nutrition: immuno-modulating diet or standard formula

Immunonutrition has been designed to favourably modulate host immune and inflammatory responses to surgery. So, immunonutrition is supposed to have beneficial effects on postoperative recovery in surgical patients.

Two high-quality RCTs were conducted among large samples of patients undergoing surgery in order to test the impact of postoperative jejunostomy feeding with either an immunomodulating diet or a standard nutrition diet [236, 237]. However, both studies concluded that immunomodulating diets had no benefit over standard EN when a peptide-based diet was used in terms of postoperative complications, treatment tolerance, liver and kidney function and visceral protein synthesis.

While there is an unquestionable need for EN in surgical patients, there is no need to administer more expensive immunomodulatory diets in all surgical patients [236, 237].

Parenteral nutrition with supplementation

A double-blind RCT involving 60 patients with a peri-ampullary tumour undergoing classical or pylorus-preserving PD showed no beneficial effect of Glamin (glutamin) supplementation with a low-dose parenteral regimen on the surgical outcome (median postoperative hospital stay and complication rates) [238]. The authors recognized that the lack of effect of glutamin supplementation could be attributed to the low-dose regimen (0.2 g/kg of glutamin per day), considering that the dose clearly influences the benefit observed from glutamin supplementation.

Another RCT was conducted among 44 patients undergoing elective major abdominal surgery (18 Whipple's procedures) in order to estimate the benefit from parenteral nutrition supplemented with Omega-3 polyunsaturated fatty acid in fish oil [239]. The control group received parenteral nutrition supplemented with soybean oil. However, whatever the type of supplementation, it did not succeed in improving hepatic and pancreatic function. Moreover, after a follow-up at 18 months, results did not show any difference in quality of life, health status or mortality between the 2 treatment groups.

Recommendations

- **In patients undergoing pancreaticoduodenectomy, a preoperative enriched nutritional oral diet should be considered (1B recommendation).**
- **Patients undergoing surgery for pancreatic cancer should be considered for early postoperative nutritional support preferably by the enteral route (1B recommendation).**
- **In patients undergoing surgery for pancreatic cancer, immunomodulatory diets are not routinely recommended (1A recommendation).**

3.11.1.2 Prevention of postoperative pancreas-related complications

Pancreatic surgery is associated with an important mortality and morbidity. Reported perioperative mortality after pancreaticoduodenectomy in high-volume centres ranges from 1 to 4% [112]. A considerable number of patients suffers from postoperative complications, with pancreatic fistula/leakage (2 – 28%), postoperative haemorrhage (2 – 15%), intra-abdominal abscess (1 – 12%), and delayed gastric emptying (14 – 70%) being the most important [112]. Postoperative complications, in particular pancreatic fistula, are known to be associated with an increased length-of-stay and higher hospital costs [240].

Somatostatin and analogues

CCO identified 6 RCTs evaluating the use of octreotide following pancreatic surgery for cancer or inflammatory disease [241]. Three trials found a reduced overall complication rate in favour of octreotide, while the 3 other trials found no statistically significant differences. Only 2 trials reported a reduced rate of pancreatic fistula. No differences were found in postoperative mortality. Based on these results, CCO recommended the use of octreotide in the perioperative management of patients undergoing major pancreatic resection [241]. Importantly, differences in trial design and surgical technique complicate the true treatment effect.

One additional open-label RCT evaluated the use of octreotide in 105 patients undergoing pancreatic surgery and subsequent pancreaticojejunostomy [242]. No significant differences were found in terms of postoperative complications, 30-day mortality and hospital stay.

In addition, 2 RCTs were identified evaluating the use of somatostatin in patients undergoing pancreaticoduodenectomy [243, 244]. Both trials found a significant reduction of the overall complication rate in favour of somatostatin, but found conflicting results in terms of pancreatic fistula and hospital stay.

Finally, 1 RCT evaluated the use of the somatostatin analogue vapreotide in patients undergoing pancreatic resection for presumed pancreatic or periampullary cancer [245].

No differences were found between vapreotide and placebo in terms of pancreas-specific complications and postoperative mortality.

Based on this evidence, postoperative treatment with somatostatin or somatostatin analogues can be considered in selected, high-risk patients (i.e. patients with a soft pancreas and non-dilated ducts) undergoing pancreatic resection.

Recommendation

- **Prophylactic treatment with somatostatin or somatostatin analogues should not be administered routinely, but may be considered in high-risk patients undergoing pancreatic resection (2B recommendation).**

Exocrine supplementation

A large part of the pancreas can be resected before symptoms of exocrine pancreatic insufficiency develop [246]. The clinical signs of exocrine pancreatic insufficiency are mainly dominated by fat malabsorption, including abdominal pain, steatorrhoea, vitamin deficiency and weight loss. Importantly, other causes of diarrhoea, such as celiac disease or rapid intestinal transit should be kept in mind.

No RCTs were found evaluating the use of exocrine supplementation after pancreatic resection for cancer. However, in other conditions associated with pancreatic insufficiency, such as chronic pancreatitis or cystic fibrosis, supplementation with pancreatic enzymes is a well-established treatment [247, 248]. One RCT examined the efficacy of enteric coated pancreatin enzyme supplementation in patients with unresectable pancreatic head cancer and occlusion of the pancreatic duct [249]. Patients treated with exocrine supplementation for 8 weeks experienced a weight gain of 0.7 kg (mean difference 4.9%, 95%CI 0.9 – 8.9%, p = 0.02).

Recommendation

- **Patients with symptomatic exocrine pancreatic insufficiency after radical pancreatic resection should be supplemented with pancreatic enzymes (expert opinion).**

3.11.1.3 Postoperative pain

Postoperative pain is one of the most important problems that confront surgical patients. Particularly in upper abdominal surgery, pain affects the deep breathing and cough. The literature supports the efficacy and safety of three techniques for perioperative pain control used by anaesthesiologists: (1) epidural or intrathecal opioid analgesia; (2) patient-controlled analgesia (PCA) with systemic opioids; and (3) regional analgesic techniques, including but not limited to intercostal blocks, plexus blocks, and local anaesthetic infiltration of incisions [250]. The literature also suggests that two routes of administration, when compared with a single route, may be more effective in providing perioperative analgesia.

The American Society of Anesthesiologists Task Force on Acute Pain Management published guidelines for Acute Pain Management in the perioperative setting [250]. These guidelines were based on a thorough literature review and meta-analysis:

- Anaesthesiologists who manage perioperative pain should utilize therapeutic options such as epidural or intrathecal opioids, systemic opioid PCA, and regional techniques, after thoughtfully considering the risks and benefits for the individual patient. These modalities should be used in preference to intramuscular opioids ordered "as needed."
- Whenever possible, anaesthesiologists should employ multimodal pain management therapy. Unless contraindicated, all patients should receive an around-the-clock regimen of NSAIDs, COXIBs, or acetaminophen. In addition, regional blockade with local anaesthetics should be considered.

In addition to the evidence provided in the ASA guideline, for patients who underwent elective surgery for pancreatic neoplasm, one moderate-quality RCT concluded that epidural analgesia with morphine plus bupivacaine allowed better analgesia, a more rapid return to normal gut activity and early enteral nutrition compared with epidural analgesia with morphine alone [251].

3.11.2 Patients with inoperable disease

Optimal palliative and symptomatic treatment is recommended in all patients with inoperable pancreatic cancer. Patients with pancreatic cancer should have access to a specialist (outpatient and/or inpatient) palliative care team when needed, in particular in relation to comfort and symptom control, and quality of life. This team clearly should involve the general practitioner, who should have a coordinating role in the organisation of the palliative home care.

Recommendations

- **Optimal palliative and symptomatic treatment is recommended in all patients with inoperable pancreatic cancer (expert opinion).**

3.11.2.1 Nutrition

As cancer stage advances, weight loss increases leading to a reduced quality of life [252]. The wasting that frequently accompanies advanced cancers, especially pancreatic cancer, is well-known. One of the goals of nutrition intervention for patients with cancer is to minimise weight loss and prevent or correct nutritional deficiencies. However, efforts to reverse the weight loss process through nutrition intervention for patients with unresectable pancreatic cancer had limited success to improve outcomes such as energy intake, body weight stabilisation, lean body mass increase or quality of life [253]. Only few well-designed studies evaluated the effect of oral nutrition supplements in these patients.

A RCT of 200 cachectic patients with unresectable pancreatic adenocarcinoma compared dietary intake of two types of nutritional supplements for eight weeks. Results suggested that the administration of specialised protein and energy dense oral supplements (whether or not enriched with n-3 fatty acids and antioxidants) was associated with weight stabilisation [254, 255], lean body mass stabilisation [255], increased median survival [254] and better quality of life [254, 255]. The weight gain was closely linked to both an increase in blood phospholipid EPA levels [255] and patient's compliance to dietary intake [256]. Compliance to dietary prescription is a challenge in the presence of the many symptoms experienced by patients with advanced cancer. Strategies to sustain patients' compliance included referral for pain or nausea management, improved pancreatic enzyme use and advice to patient or carers regarding small, frequent, nutrient-dense meals to deal with early satiety [256].

A RCT of moderate quality and small sample size indicated that patients who received n-3 fatty acid oral nutritional supplement had a higher total energy expenditure and physical activity level after 8 weeks without gain in weight or lean body mass [257]. No statistical significant difference was obtained between both treatment groups.

Recommendations

- **In patients with advanced pancreatic cancer who have lost weight or who are anorexic, nutritional advice should be considered (1C recommendation).**
- **Control of symptoms such as pain, nausea, vomiting and diarrhoea should be considered, to enable patients to maintain an oral intake in a form appropriate to their condition (expert opinion).**

3.11.2.2 *Enzyme replacement therapy*

A RCT evaluating enteric coated pancreatin microsphere treatment in 21 patients with unresectable cancer of the pancreatic head region and occlusion of the pancreatic duct indicated that pancreatic enzyme replacement therapy in combination with dietary counselling can (partly) prevent weight loss, at least in the initial period after diagnosis and insertion of a biliary endoprosthesis. Patients on pancreatic enzymes reached a significantly higher daily total energy intake than patients on placebo, whereas the occurrence and severity of steatorrhoea-associated complaints did not differ [249].

Recommendation

- **Pancreatic enzyme replacement therapy can be considered for patients with inoperable advanced pancreatic cancer and proved steatorrhoea (2C recommendation).**

3.11.2.3 *Pain*

The WHO three-step analgesic ladder sets out generic recommendations on cancer pain relief (http://www.who.int/cancer/palliative/painladder/en/index.html). If pain occurs, there should be prompt oral administration of drugs in the following order until the patient is free of pain: nonopioids (aspirin and paracetamol); mild opioids (codeine); strong opioids such as morphine. To maintain pain relief, drugs should be given "by the clock", that is every 3-6 hours, rather than "on demand". This three-step approach of administering the right drug in the right dose at the right time is inexpensive and 80-90% effective. Surgical intervention on appropriate nerves may provide further pain relief if drugs are not sufficiently effective.

In a systematic review comprising five RCTs [258] neurolytic celiac plexus block (NCPB) was associated with a statistically significant improvement in pain control compared with standard treatment (weighted mean difference in VAS score at 8 weeks: –0.60, 95%CI −0.82 to −0.37, p< 0.00001).

However, the benefit in pain control was rather small (a 6% reduction in mean Visual Analogue Scale score compared with baseline). The improvement in pain control translated into a significant decrease in opioid usage (mean reduction 40–80 mg/d) and constipation. No impact on health-related quality of life or survival was demonstrated. These results suggested that while NCPB showed statistical benefit in pain control and reduction of opioid use, it was of limited clinical efficacy as an adjunct to standard pain management. Moreover, in the included RCTs, NCPB did not eliminate the requirement for opioids. The majority of patients required opioids to control pain throughout follow-up until death. Therefore, NCPB cannot be considered effective as a single method to control pain in patients with unresectable pancreatic cancer. Moreover, most studies suggested that NCPB is effective for only 2–3 months [258]. Pooled data from the RCTs showed a low rate of adverse events: diarrhoea (9%), transient hypotension (8%), constipation (40%), nausea and vomiting (41%), and lethargy (49%). No serious NCPB-related adverse events were reported.

A more recent moderate-quality RCT involving 56 patients with chronic pain secondary to unresectable pancreatic cancer confirmed these results, with an additional gain in quality of life [259].

Other RCTs indicated that analgesic results were independent of the techniques used (transaortic celiac plexus block, retrocrural block, bilateral chemical splanchnicectomy) [260], although splanchnic nerves neurolytic blockade obtained higher impact on pain, codeine consumption, patient satisfaction and survival rate [261]. Complete relief of pain was also more frequent when NCPB was performed within 2 months of onset of pain or when the patient already responded to NSAIDS [260].

Different routes of NCPB can be used, including a percutaneous indwelling catheter, EUS- or CT-guided NCPB or surgical NCPB. All identified RCTs used a non-surgical approach.

In view of the palliative setting, such a non-surgical approach is highly preferable. Data from randomised trials in non-oncological patients suggest that EUS-guided NCPB is preferable to CT-guided NCPB [262].

Recommendations

- **A three-step approach of pain drug administration (WHO analgesic ladder) should be followed in patients with pain associated with pancreatic cancer (expert opinion).**
- **Neurolytic celiac plexus block (NCPB) is a treatment option in patients with pancreatic cancer and severe upper abdominal pain that is unresponsive to other analgesic measures (1A recommendation).**

3.11.3 Psychological support

One moderate-quality RCT indicated that patients who benefited from a formal psychotherapeutic support (including educational information, a supportive relationship, and ongoing psychotherapeutic counselling, emotional and cognitive support to foster "fighting spirit" and to diminish "hope and helplessness") had better survival than patients who only received routine care during hospital stay [263].

Recommendation

- **Patients with pancreatic cancer should be offered specific psychological support from professionals belonging to the multidisciplinary team (1C recommendation).**

3.12 RECURRENT DISEASE

In patients with recurrent disease presenting with metastases, the same principles are applicable as discussed in the section on palliative treatment (see chapter 3.10). In these patients, chemotherapy has a central role. Meyers et al. found a significant survival benefit in favour of chemotherapy in patients with recurrent disease [264]. In selected patients with recurrence, CRT can be considered [265].

The evidence on surgery for recurrent disease is limited to case series or case reports. In selected cases, recurrent disease can be treated with reresection [266-268] or metastasectomy [269]. In a retrospective study, Kleeff et al. found a non-significant survival benefit in favour of reresection compared with palliative surgery in 30 patients with recurrent disease (median survival 17.0 vs. 9.4 months, p = 0.084) [266].

3.13 ADDENDUM: INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS (IPMN)

IPMNs represent a well-defined clinical and pathologic entity, separated into different categories according to the degree of cytoarchitectural atypia (see definitions in appendix 7) [150]. On the basis of the anatomic involvement of the pancreatic duct, IPMNs can be subclassified into 'main duct types' (predominant involvement of the main pancreatic duct, 'branch duct types' (predominant involvement of the secondary pancreatic ducts) or 'mixed types'. Branch duct types are known to be less aggressive than main duct IPMNs, with malignancy associated with up to 70% of main duct IPMNs compared to 25% of branch duct types [105].

Presenting symptoms most commonly include: symptoms of acute or chronic relapsing pancreatitis, diarrhoea/steatorrhoea, nausea/vomiting, fatigue, anorexia, an abdominal mass or early satiety [29]. However, about one fourth of patients with IPMN present without symptoms.

Both diagnosis and staging of IPMNs are challenging. For the visualisation of the ductal system, MRCP followed by dynamic MRI is the radiologic test of choice in patients with IPMN [29]. To evaluate extrapancreatic invasion and resectability of invasive IPMNs, abdominal CT is recommended. In case of diagnostic uncertainty, EUS can be considered.

Treatment of IPMNs is difficult, and should be restricted to specialised teams, involving oncologists, gastroenterologists, pathologists and surgeons. In the absence of RCTs, it is difficult to provide clear-cut recommendations. However, based on the available evidence, Belyaev et al. established a treatment algorithm for IPMNs [29]. In selected cases (asymptomatic non-invasive branch duct IPMNs sized < 3cm, no mural nodules, normal pancreatic duct; poor surgical candidates; older patients) 'watchful waiting' can be considered. However, for patients with IPMN who are fit for surgery, surgical resection should be considered and discussed at the multidisciplinary team meeting.

Since recurrence occurs in 50 – 65% of patients after resection of invasive IPMN [105], long-term follow-up is recommended.

4 IMPLEMENTATION AND UPDATING OF THE PANCREATIC CANCER GUIDELINE

4.1 IMPLEMENTATION

The implementation of the present guideline will be led by the College of Oncology. An online implementation tool – similar to the tools accompanying previous guidelines (https://portal.health.fgov.be/portal/page?_pageid=56,10338450&_dad=portal&_schema=PORTAL) – will be developed. The tool will be based on the general algorithm of this guideline.

4.2 QUALITY CONTROL

The implementation of the guideline has to be evaluated with appropriate quality control criteria. These criteria should at least assess the following items of the general algorithm:

- diagnostic work-up
- staging
- treatment according to stage
- follow-up
- multidisciplinary approach

For each of these steps, quality indicators should be developed, which should be preferentially based on the recommendations with a high level of evidence. Additionally, a literature search for existing quality indicators should be done. However, a pre-assessment of the literature (Medline and the National Quality Measures Clearinghouse, http://www.qualitymeasures.ahrq.gov/) only identified a limited number of existing quality indicators (Table 9).

Table 9. Existing quality indicators for pancreatic cancer, identified through pre-assessment of the literature.

Quality Indicator	Source
Pancreatic resection mortality rate	Agency for Healthcare Research and Quality
Pancreatic resection: volume	Agency for Healthcare Research and Quality

4.3 GUIDELINE UPDATE

In view of the changing evidence, and based on a pre-assessment of the literature, this guideline should be fully updated in 5 years. In the meanwhile, when important evidence becomes available, this will be mentioned on the website of the College of Oncology (https://portal.health.fgov.be/portal/page?_pageid=56,10338450&_dad=portal&_schema=PORTAL).

5 APPENDIXES

APPENDIX 1: GRADE SYSTEM

Grade of Recommendation/ Description	Benefit vs. Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A/ Strong recommendation, high quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/ Strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/ Strong recommendation, low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation, but may change when higher quality evidence becomes available
2A/ Weak recommendation, high quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/ Weak recommendation, moderate quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/ Weak recommendation, low quality evidence	Benefits closely balanced with risks and burden	Observational studies or case series	Very weak recommendation, other alternatives may be equally reasonable

APPENDIX 2: IDENTIFIED GUIDELINES AND THEIR QUALITY APPRAISAL

Source	Title	Standardised Methodology Score	Final Appraisal
American Society of Clinical Oncology	ASCO 2006 Update of Recommendations for the Use of Tumor Markers in Gastrointestinal Cancer.	62%	Not recommended
American Society for Gastrointestinal Endoscopy	ASGE guideline: the role of ERCP in diseases of the biliary tract and the pancreas.	33%	Not recommended
American Society for Gastrointestinal Endoscopy	The role of endoscopy in the evaluation and treatment of patients with pancreaticobiliary malignancy.	33%	Not recommended
American Society for Gastrointestinal Endoscopy	Complications of ERCP.	31%	Not recommended
American Society for Gastrointestinal Endoscopy	ASGE guideline: the role of endoscopy in the diagnosis and the management of cystic lesions and inflammatory fluid collections of the pancreas.	26%	Not recommended
Cancer Care Ontario	The Treatment of Locally Advanced Pancreatic Cancer. Practice Guideline Report #2-7.	98%	Recommended with alterations
Cancer Care Ontario	Use of Gemcitabine in the Treatment of Advanced Pancreatic Adenocarcinoma. Practice Guideline Report #2-10.	98%	Recommended with alterations
Cancer Care Ontario	Chemotherapy or Radiotherapy for Resectable Pancreatic Adenocarcinoma: Clinical Practice Guidelines.	95%	Recommended with alterations
Cancer Care Ontario	The Role of Octreotide in the Management of Patients with Cancer. Practice Guideline Report #12-7.	98%	Recommended with alterations
European Society for Medical Oncology	ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of pancreatic cancer.	19%	Not recommended
Fédération Nationale des Centres de Lutte Contre le Cancer	Recommandations pour la pratique clinique : Standards, Options et Recommandations 2003 pour l'utilisation de la tomographie par émission de positons au [18F]-FDG (TEP-FDG) en cancérologie.	79%	Recommended with alterations
Pancreatic Section of the British Society of Gastroenterology, Pancreatic Society of Great Britain and Ireland, Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, Royal College of Pathologists, Special Interest Group for Gastro-Intestinal Radiology	Guidelines for the management of patients with pancreatic cancer periampullary and ampullary carcinomas.	41%	Not recommended
National Comprehensive Cancer Network	Pancreatic Adenocarcinoma. V.I. 2008.	62%	Not recommended
U.S. Preventive Services Task	Screening for Pancreatic Cancer: A Brief Evidence Update for the U.S. Preventive	67%	Recommended with alterations

Source	Title	Standardised Methodology Score	Final Appraisal
Force	Services Task Force.		
Vereniging van Integrale Kankercentra	Pancreascarcinoom.	12%	Not recommended
Society for Surgery of the Alimentary Tract	Surgical Treatment of Pancreatic Cancer.	19%	Not recommended
Fédération Francophone de Cancérologie Digestive	Cancer du pancréas	33%	Not recommended
American College of Gastroenterology	ACG Practice Guidelines for the Diagnosis and Management of Neoplastic Pancreatic Cysts	29%	Not recommended
Verslype et al. 2007	The management of pancreatic cancer. Current expert opinion and recommendations derived from the 8th World Congress on Gastrointestinal Cancer, Barcelona, 2006.	38%	Not recommended
Tanaka et al. 2006	International Consensus Guidelines for Management of Intraductal Papillary Mucinous Neoplasms and Mucinous Cystic Neoplasms of the Pancreas	29%	Not recommended
Society for Surgery of the Alimentary Tract	Cystic Neoplasms of the Pancreas	19%	Not recommended

APPENDIX 3: OVERVIEW OF SCORES OF EXTERNAL EXPERTS

Item	Recommendation(s)	GOR	LoE	Median	Low	High	%4 or 5	Comments	Decision
Screening	Mass screening for pancreatic cancer is not recommended	2	C	5	5	5	100%		
	Surveillance of persons at high risk of developing pancreatic cancer should only be performed within the context of peer-reviewed protocols	Expert opinion		4,5	1	5	75%	2. it should be done routinely in clinic	No evidence: overruled
Diagnosis	Diagnosis of pancreatic cancer should be considered with the presence of the following risk factors: adult-onset diabetes without predisposing features or family history of diabetes, unexplained pancreatitis, rapid weight loss and unexplained back pain	1	C	5	4	5	100%	3. consider also 'jaundice'	Is discussed in the text
	In addition to a history taking and clinical examination, all patients with clinically suspected pancreatic cancer should undergo diagnostic imaging with abdominal CT	1	B	5	2	5	89%	4. I don't understand the overall imaging strategy. In case of high pre-test probability, why not allow for a PET-CT to be performed, provided the CT is contrast-enhanced of course ?	No evidence: overruled
	In patients with a high suspicion of pancreatic cancer and a negative CT scan, an EUS is recommended	1	B	5	3	5	89%	1. MRI ???	Is discussed in the text
	When tissue diagnosis of pancreatic cancer is needed to guide treatment, EUS-guided FNA is recommended	1	B	5	3	5	89%		
	Diagnostic imaging with US, MRI, ERCP or PET scan should be considered in specific cases of clinically suspected pancreatic cancer	1	C	5	2	5	88%	4. what is the meaning of "specific cases" ?	Is discussed in the text
	Serum tumour markers are not part of the routine diagnostic work-up of patients with clinically suspected pancreatic cancer	1	C	3,5	1	5	50%	9. reference value for follow up ?	Will be added in the text
	EUS-guided cyst fluid analysis, including cytology, amylase and CEA, can be useful in the differential diagnosis between benign and (pre)malignant pancreatic cysts	1	C	5	4	5	100%		
Staging	In patients with pancreatic cancer, abdominal CT with intravenous contrast should be performed routinely. The liver should at least be imaged in the arterial and portal venous phase	1	B	5	4	5	100%		
	In selected patients with pancreatic cancer, EUS and diagnostic laparoscopy can be considered	2	C	5	4	5	100%		
	In patients with pancreatic cancer and an option for curative treatment after conventional staging, PET(/CT) scan may be considered for the staging of lymph nodes (loco-regional, distal or all lymph nodes) and distant sites other than lymph nodes	2	C	4	2	5	56%	1. Specificity ?? 4. PET-CT should be standard for the staging due to its whole-body imaging capability and high detection rate of distant metastases.	Data will be provided in the text. No evidence for PET as standard staging procedure: overruled
	Ultrasonography and MRI are not routinely recommended as staging procedures in patients with pancreatic cancer, but can be considered in specific cases	2	C	4	2	5	63%	4. How to adress the vascular invasion without MRI ? 9. depends on radiologist's preference for CT or MRI	
Neoadjuvant	Neoadjuvant treatment is not recommended in patients with resectable pancreatic cancer outside clinical trials	2	C	5	3	5	75%		
	In patients with borderline resectable locally advanced pancreatic cancer, treatment with chemotherapy or chemoradiotherapy is recommended. Evaluation of resectability is recommended after 2 – 3 months	2	C	4,5	4	5	100%		

Item	Recommendation(s)	GOR	LoE	Median	Low	High	%4 or 5	Comments	Decision
Surgery	Preoperative biliary drainage is not routinely recommended in patients with resectable pancreatic cancer and obstructive jaundice	1	B	5	3	5	88%		
	Patients with resectable pancreatic cancer who are fit for surgery should undergo radical pancreatic resection (pancreaticoduodenectomy for pancreatic head tumours, distal pancreatectomy for pancreatic body and tail tumours) and standard lymphadenectomy with the intent of an R0 resection	1	C	5	5	5	100%		
	Radical and extended radical lymphadenectomy are not recommended during pancreatic resection	1	B	5	4	5	100%		
	Pancreatic resection with arterial reconstruction is not recommended in patients with pancreatic cancer and involvement of vital arteries (arteria hepatica, arteria mesenterica superior, truncus coeliacus)	2	C	5	3	5	88%	9. quid, peroperative findings or right hepatic artery from AMS running through otherwise resectable tumor	Will be discussed in the text
	Venous invasion is not a contra-indication for surgery	2	C	5	3	5	88%	3. R0 resection should be obtained; VP resection	Will be added in the text
	In left-sided tumours, local invasion of the splenic artery and/or vein is not a contraindication for resection	Expert opinion		4,5	3	5	75%		
	Standard and pylorus-preserving pancreaticoduodenectomy (PD) are equivalent techniques	1	B	5	4	5	100%		
	Pancreaticojejunostomy and pancreaticogastrostomy are equivalent techniques of pancreatic anastomosis after pancreaticoduodenectomy	1	B	4,5	2	5	83%	3. underpowered RCTs; Am J Surg 2007;193:171-183	Agreement reached
	Laparoscopic pancreatic resection with curative intent is strictly investigational	2	C	5	4	5	100%		
	Pancreatic oncologic surgery should be restricted to high-volume centres	1	C	4,5	1	5	63%	1. High volume centers ??? 9. depends on definition of 'high-volume' centre	Recommendation will be changed
Pathology	A standardized protocol for the examination of a pancreatic carcinoma resection specimen is recommended	1	C	5	5	5	100%		
	The retroperitoneal side of the pancreas should be inked before fixation of the resection specimen	Expert opinion		5	4	5	100%	6. RETROPERITONEAL MARGIN (no " side")	Will be changed
	Margins histologically positive for disease or with cancer at less than 1 mm from a margin are considered not to be a R0 resection	Expert opinion		5	2	5	86%	3. UICC TNM definitions !	Will be discussed in the text
	Gross examination of the resection specimen includes: - the measurement of all components; - the description of the presence of a tumour; - the tumour site and probable site of origin; - tumour size (at least maximum diameter); - number of lymph nodes; - distance to the nearest margin	1	C	5	4	5	100%		
	Microscopic examination includes: - histological type; - tumour differentiation; - tumour size; - status of the margins; - lymph node status; - presence of local invasion; - presence of vascular or perineural invasion; - presence of distal spread	1	C	5	4	5	100%	3. consider also 'LNR, ECLNI & ECLNR'	

Item	Recommendation(s)	GOR	LoE	Median	Low	High	%4 or 5	Comments	Decision
Adjuvant	Postoperative chemotherapy with single-agent gemcitabine is recommended for patients with R0 and R1 resected pancreatic adenocarcinoma	1	B	5	4	5	100%		
	In patients with R1 resected pancreatic adenocarcinoma, postoperative chemoradiotherapy can be considered after discussion in the multidisciplinary team meeting	Expert opinion		4,5	3	5	88%		
	Postoperative chemoradiotherapy is not recommended outside a clinical trial	2	B	4	1	5	63%	1. To be discussed 2. evidence based therapy	Recommendation will be removed
Follow-up	In patients with curatively treated pancreatic cancer, surveillance visits are recommended every 3 – 6 months. Technical examinations should be limited to a minimum in asymptomatic patients	Expert opinion		4	3	5	86%	4. I am surprised by the absence of recommendation related to the evaluation of tumor response to neoadjuvant therapies.	No evidence: overruled
Palliative	In patients with metastatic pancreatic cancer, chemotherapy (gemcitabine alone or gemcitabine combined with erlotinib) is recommended	1	B	5	4	5	100%		
	In patients with inoperable locally advanced pancreatic cancer, chemotherapy is recommended. Based on an evaluation after 2 – 3 months, addition of radiotherapy can be considered	Expert opinion		4	3	5	67%	4. evaluation : on what basis ? Morphologic imaging ? PET-CT ?	No evidence: overruled
	In patients with inoperable pancreatic cancer and obstructive jaundice, treatment with metal stents is recommended	1	A	5	3	5	75%	9. patients should be discussed multidisciplinary with a hpb surgeon before being considered unresectable	Will be added as general recommendation
Supportive	In patients undergoing pancreaticoduodenectomy, a preoperative enriched nutritional oral diet should be considered	1	B	5	4	5	100%		
	Patients undergoing surgery for pancreatic cancer should be considered for early postoperative nutritional support preferably by the enteral route	1	B	5	4	5	100%		
	In patients undergoing surgery for pancreatic cancer, immunomodulatory diets are not routinely recommended	1	A	4	3	5	71%	9. glutamine	Discussion will be added
	Postoperative treatment with somatostatin or somatostatin analogues can be considered in high risk patients undergoing pancreatic resection	2	B	4	2	5	67%	1. Variations +++ in studies	Is already taken into account in the grade of recommendation
	In all patients undergoing pancreatic resection for malignancy, pancreatic insufficiency should be actively searched for	Expert opinion		4	3	5	86%		
	Patients with symptomatic exocrine pancreatic insufficiency after radical pancreatic resection should be supplemented with pancreatic enzymes	Expert opinion		5	4	5	100%		
	Optimal palliative and symptomatic treatment is recommended in all patients with inoperable pancreatic cancer	Expert opinion		5	5	5	100%		
	In patients with advanced pancreatic cancer who have lost weight or who are anorexic, nutritional advice should be considered	1	C	5	3	5	86%		
	Control of symptoms such as pain, nausea, vomiting and diarrhoea should be considered, to enable patients to maintain an oral intake in a form appropriate to their condition	Expert opinion		5	4	5	100%		
	Pancreatic enzyme replacement therapy can be considered for selected patients with inoperable advanced pancreatic cancer and proved steatthorea.	2	C	5	4	5	100%		
	A three-step approach of pain drug administration (WHO analgesic ladder) should be followed in patients with pain associated with pancreatic cancer	Expert opinion		4	3	5	86%		
	Neurolytic celiac plexus block (NCPB) is a treatment option in patients with pancreatic cancer and severe upper abdominal pain that is unresponsive to other analgesic measures	1	A	5	3	5	86%		
	Patients with pancreatic cancer should be offered specific psychological support from professionals belonging to the multidisciplinary team	1	C	5	3	5	88%		

APPENDIX 4: EVIDENCE TABLES BY CLINICAL QUESTION

SCREENING

Mass screening for pancreatic cancer.

CPG ID	Ref	Search date	Recommendation	Supporting evidence	Level of evidence
Mass screening					
USPSTF	[10]	2001	USPSTF recommends against routine screening for pancreatic cancer in asymptomatic adults using abdominal palpation, ultrasonography, or serologic markers.	Neoptolemos et al.	Low D recommendation

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Mass screening									
Kim JE 2004	[11]	NA	70 940 asymptomatic persons visiting the Health Promotion Center at the Samsung Medical Center, Seoul, Korea	Abdominal ultrasonography and serum CA 19-9 measurement	Sensitivity, specificity, and predictive values of CA 19-9 for detecting pancreatic cancer	- Number of subjects with a level of CA 19-9 > cut-off of 37 U/mL was 1063 (1.5%) including 4 cases with pancreatic cancer. - Sensitivity is 100% - Specificity is 98.5%. - Positive predictive value is 0.9%. Mass screening for pancreatic cancer using CA 19-9 levels in asymptomatic subjects is ineffective because of a very low PPV, despite its high Se and Sp.		Prospective study	Low

Screening in high risk patients for pancreatic cancer

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Screening in high-risk patients									
Canto MI 2006	[13]	NA	116 high-risk pancreatic cancer patients who had no symptom referable to the pancreas or suggestive of malignancy: 7 patients from kindreds affected with Peutz-Jeghers Syndrome and 109 patients from Familial Pancreatic Cancer kindreds	Combination of CT and EUS.	An abnormal EUS led to the use of EUS-FNA, multidetector CT, and ERCP.	-29 patients displayed neoplastic-type lesions whom 15 patients underwent surgery. -Final pathologic examination demonstrated 6 high-grade or invasive lesions (PanIN III, IPMN with carcinoma in situ, and 1 frank adenocarcinoma), 11 low-grade lesions (PanIN II or IPMN), and 6 nonneoplastic lesions. Additionally, 6 extrapancreatic lesions were detected via screening, including 1 malignant ovarian tumor.	Selection of positive patients for further examination depends on the assurance coverage of the patients.	Prospective case-control study	Very low

DIAGNOSIS

Symptoms and signs

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
Palsson B 1997	[20]	NA	Patients with clinically suspected pancreatic disease	Clinical exam CA50 Standard: histology/cytology, follow-up	Pain: Sensitivity 58% (102/175) Specificity 51% (172/337) Jaundice: Sensitivity 67% (117/175) Specificity 66% (221/337) Weight loss: Sensitivity 48% (42/88) Specificity 84% (165/197) Malabsorption: Sensitivity 19% (18/97) Specificity 94% (196/208)	Blinded study Differential verification Fewer registrations of weight loss and malabsorption	Prospective cohort study	Low

CT

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
Bipat S 2005	[22]	Dec 2003	Patients with known or suspected pancreatic adenocarcinoma	Helical CT Conventional CT US MRI	Helical CT: sensitivity 91%, specificity 85% (23 studies) Conventional CT: sensitivity 86%, specificity 79%	High-quality SR 23 studies included on helical CT, 20 studies included on conventional CT	SR	Moderate
Dewitt J 2006	[23]	2004	Patients with suspected or established pancreatic cancer	CT EUS	EUS was more sensitive than CT Specificity was superior or equivalent to CT No meta-analysis is provided	Medline only English only Inclusion of 9 studies assessing tumour detection (including 3 retrospective studies)	SR	Low
Bang S 2006	[24]	NA	Patients with suspected primary pancreatic cancer (n=102)	Dynamic CT PET Standard: pathologic findings, follow-up	Sensitivity: 80% (74/93) Specificity: 44% (4/9) PPV: 94% (74/79)	Differential verification Partially blinded	Prospective observational study	Low

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
Heinrich S 2005	[25]	NA	Patients with suspected pancreatic cancer (n=59)	Contrast-enhanced CT Standard: intraoperative findings, histology, follow-up	Sensitivity: 93% (43/46) Specificity: 23% (3/13) PPV: 81% (43/53)	Differential verification No information on blinding	Prospective observational study	Low
Imbriaco M 2006	[26]	NA	Patients with suspected pancreatic cancer (n=78)	Multislice CT Standard: final histopathological results of FNAC with follow-up	Sensitivity: 98% (44/46) Specificity: 88% (28/32) PPV: 92% (44/48)	Differential verification Blinding of pathology results?	Prospective observational study	Low

Ultrasonography

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
Bipat S 2005	[22]	Dec 2003	Patients with known or suspected pancreatic adenocarcinoma	Helical CT Conventional CT US MRI Outcome: diagnosis	US: sensitivity 76%, specificity 75%	High-quality SR 14 studies included	SR	Moderate
Rickes S 2004	[28]	NA	Patients with cystic pancreatic lesion (n=31)	Conventional US Echo-enhanced US Standard: histopathology, follow-up	Conventional US: Sensitivity: 67% Specificity: 39% Echo-enhanced US: Sensitivity: 67% Specificity: 96%	Differential verification Blinded study	Prospective observational study	Low
Okamoto Y 2007	[27]	NA	Patients with pancreatic tumours (n=62)	Contrast-enhanced US Standard: surgery, FNA/biopsy of liver metastases, pancreatic juice cytology, autopsy	Positive vascularity Sensitivity: 79% (42/53) Specificity: 67% (6/9) PPV: 93% (42/45) Hypo-enhancement Sensitivity: 96% (51/53) Specificity: 78% (7/9) PPV: 96% (51/53)	Differential verification Blinded study	Prospective observational study	Low

MRI

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
Bipat S 2005	[22]	Dec 2003	Patients with known or suspected pancreatic adenocarcinoma	Helical CT Conventional CT US MRI	MRI: sensitivity 84%, specificity 82%	High-quality SR 11 studies included	SR	Moderate
Ruf J 2006	[30]	NA	Patients with clinically suspected pancreatic cancer (n=32)	MRI Standard: surgery, laparotomy, biopsy or follow-up	Sensitivity: 100% (15/15) Specificity: 76% (13/17) PPV: 79% (15/19)	Differential verification No information on blinding Prospective??	Prospective observational study	Very low
Zhong L 2003	[31]	NA	Patients with obstructive jaundice (n=82)	MRCP MRCP-MTI Standard: surgical findings and pathology	MRCP: Sensitivity: 65% (22/34) Specificity: 81% (39/48) PPV: 71% (22/31) MRCP + MRI: Sensitivity: 82% (28/34) Specificity: 94% (45/48) PPV: 90% (28/31)	Differential verification No information on blinding	Prospective observational study	Low
Calvo T 2002	[32]	NA	Patients with suspected biliopancreatic pathology requiring ERCP (n=150)	MRCP Standard: ERCP	Sensitivity: 100% (9/9) Specificity: 100% (69/69) PPV: 100% (9/9)	Differential verification Exclusion of 72 patients from analysis (reasons provided in article: 42 didn't need cannulation during ERCP) Blinded study	Prospective observational study	Low

EUS

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
Dewitt J 2006	[23]	2004	Patients with suspected or established pancreatic cancer	CT EUS	EUS was more sensitive than CT Specificity was superior or equivalent to CT No meta-analysis is provided	Medline only English only Inclusion of 9 studies assessing tumour detection (including 3 retrospective studies)	SR	Low
Rocca R 2007	[37]	NA	Patients with pancreatic mass (n=293); pancreatic cysts included (n=88)	EUS EUS-FNA when indicated (n=246)	EUS: Sensitivity: 79% (152/193) Specificity: 93% (93/100)	Differential verification Blinded study	Prospective observational study	Low

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
				Standard: surgery + histopathology, follow-up Outcome: diagnosis of malignancy	PPV: 96% (152/159) 72 results were inconclusive (included as negative result) <u>EUS-FNA:</u> Sensitivity: 80% (155/193) Specificity: 100% (100/100) PPV: 100% (155/155) 16 results were inconclusive (included as negative result) Technical feasibility: 94% (232/246) Inadequate samples: 12% (28/232)			
Eloubeidi MA 2007	[42]	NA	Patients with suspected pancreatic cancer and solid lesion on EUS (n=547)	EUS-FNA Standard: surgical specimen, death from pancreatic cancer, follow-up Outcome: diagnosis of malignancy	Sensitivity: 92% (401/437) Specificity: 97% (100/103) PPV: 99% (401/404) Failures: 1% (7/547) Atypical samples (n=24) included as negative result Suspicious samples (n=25) included as positive result	Differential verification 7 patients with no final diagnosis excluded from analysis (partial verification) No blinding Previous reports: Eloubeidi 2003a & Eloubeidi 2003b	Prospective observational study	Low
Iglesias-Garcia J 2007	[47]	NA	Patients with solid pancreatic mass (n=62)	EUS-FNA (cytology & histology) Standard: surgical specimen, follow-up Outcome: diagnosis of malignancy	<u>Cytology:</u> Sensitivity: 68% (26/38) Specificity: 71% (17/24) PPV: 79% (26/33) Inadequate samples: 18% (11/62) <u>Histology:</u> Sensitivity: 68% (26/38) Specificity: 100% (24/24) PPV: 100% (26/26) Inadequate samples: 16% (10/62) <u>Both:</u> Sensitivity: 84% (32/38) Specificity: 100% (24/24) PPV: 100% (32/32)	Differential verification No information on blinding	Prospective observational study	Low
Hocke M 2006	[34]	NA	Patients with undifferentiated pancreatic lesions (n=120)	EUS Contrast-enhanced EUS Standard: EUS-FNA, surgical specimen, follow-up	<u>EUS:</u> Sensitivity: 73% (41/56) Specificity: 83% (25/30) PPV: 89% (41/46)	Differential verification Blinded study Exclusion of patients with premalignant lesions,	Prospective observational study	Low

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
				Outcome: diagnosis of malignancy	CE-EUS: Sensitivity: 91% (51/56) Specificity: 93% (28/30) PPV: 96% (51/53)	neuro-endocrine tumours, heart failure and lesions unreachable by needle (n=34)		
Horwhat JD 2006	[46]	NA	Patients with high clinical suspicion of pancreatic cancer (n=84)	EUS-FNA (n=42) CT/US-FNA (n=42) Standard: histology, surgical data, follow-up Outcome: diagnosis of malignancy	EUS-FNA: Sensitivity: 84% (21/25) Specificity: 100% (11/11) PPV: 100% (21/21)	Differential verification No information on blinding RCT comparing EUS-FNA to CT/US-FNA 12 patients excluded (reasons provided in article): 2 patients because of technical failure	RCT	Low
Mishra G 2006	[48]	NA	Patients with solid (n=52) or cystic pancreatic lesion (n=19)	EUS-FNA Telomerase activity Standard: surgical data, follow-up Outcome: diagnosis of malignancy	EUS-FNA: Sensitivity: 85% (40/47) Specificity: 100% (5/5) PPV: 100% (40/40)	Differential verification No information on blinding 9 patients excluded from original sample (reasons provided in article): 2 patients because of technical failure Results only presented for solid lesions	Prospective observational study	Low
Saftoiu A 2006	[40]	NA	Patients with suspicion of pancreatic cancer (n=42)	Power-Doppler EUS Standard: imaging + FNA + FU, surgical specimen Outcome: diagnosis of malignancy	Sensitivity: 93% (27/29) Specificity: 77% (10/13) PPV: 90% (27/30)	Differential verification Blinded study Results for EUS-FNA cannot be interpreted, because FNA was also used as gold standard	Prospective observational study	Low
Harewood GC 2002	[45]	NA	Patients with known or suspected solid pancreatic mass (n=185)	EUS-FNA Standard: surgical pathology, malignant cytology, follow-up Outcome: diagnosis of malignancy	Sensitivity: 94% (154/164) Specificity: 100% (21/21) PPV: 100% (154/154) 13 results were atypical (n=7) or inadequate (n=6, 3%) (included as negative result) In 1 patient with malignancy, the tumour was not visualised with EUS	Differential verification No information on blinding	Prospective observational study	Low

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
Becker D 2001	[39]	NA	Patients with solid pancreatic mass (n=23)	Echo-enhanced colour- and power-Doppler EUS Standard: surgery, histology, follow-up Outcome: diagnosis of malignancy (hypoperfusion)	Sensitivity: 94% (15/16) Specificity: 100% (7/7) PPV: 100% (15/15)	Differential verification Blinded study	Prospective observational study	Low
Fritscher-Ravens A 2001	[43]	NA	Patients with solid focal pancreatic lesions (n=30)	EUS-FNA: Wilson-Cook needle vs. GIP assembly Standard: surgical specimen, bacteriology, follow-up Outcome: diagnosis of malignancy	Wilson-Cook: Sensitivity: 85% (17/20) Specificity: 100% (7/7) PPV: 100% (17/17) One inadequate sample (excluded because of lost-to-follow-up) GIP: Sensitivity: 55% (11/20) Specificity: 100% (7/7) PPV: 100% (11/11) Inadequate samples: 11% (3/27) (included as negative result)	Differential verification Blinded study Exclusion of 3 patients (reasons provided in article)	Prospective observational study	Low
Gress F 2001	[44]	NA	Patients with suspected pancreatic cancer and negative CT-FNA or ERCP sampling (n=102)	EUS-FNA Standard: surgical specimen, follow-up Outcome: diagnosis of malignancy	Sensitivity: 93% (57/61) Specificity: 100% (41/41) PPV: 100% (57/57) 8 results were inconclusive or non-diagnostic (included as negative result)	Differential verification Not blinded	Prospective observational study	Low
Glasbrenner B 2000	[33]	NA	Patients with pancreatic head mass scheduled for surgery (M0) (n=95)	EUS ERCP Standard: surgical specimen, cytology/histology, follow-up Outcome: diagnosis of malignancy	Sensitivity: 78% (38/49) Specificity: 93% (39/42) PPV: 93% (38/41) Technical failure: 4% (4/95) (excluded from analysis)	Differential verification Blinded study	Prospective observational study	Low
Legmann P 1998	[35]	NA	Patients with suspected pancreatic tumour (n=51)	EUS Dual-phase helical CT Standard: pathologic specimen, surgical record, biopsy (including metastases), follow-up Outcome: diagnosis of malignancy	EUS: Sensitivity: 100% (27/27) Specificity: 33% (1/3) PPV: 93% (27/29)	Differential verification Not blinded 21 patients excluded (reasons provided in article)	Prospective observational study	Low

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
Nakaizumi A 1995	[36]	NA	Patients with suspected and/or confirmed pancreatic cancer (n=232)	EUS Standard: histology/cytology, follow-up Outcome: diagnosis of malignancy	Sensitivity: 94% (46/49) Specificity: 97% (177/183) PPV: 88% (46/52)	Differential verification No information on blinding	Prospective observational study	Low

Figure 1. Pooled sensitivity of conventional EUS for the diagnosis of pancreatic malignancy.

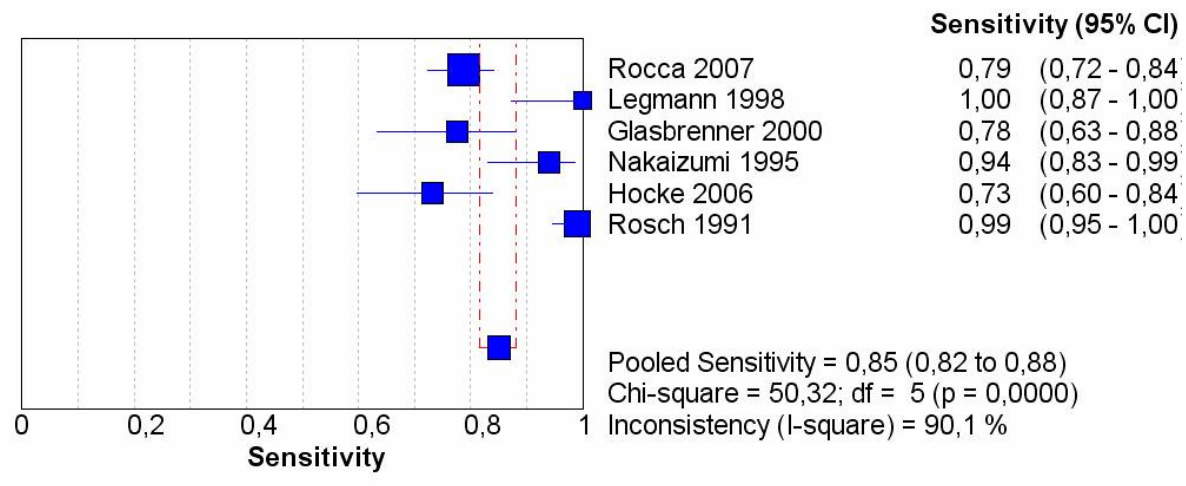


Figure 2. Pooled specificity of conventional EUS for the diagnosis of pancreatic malignancy.

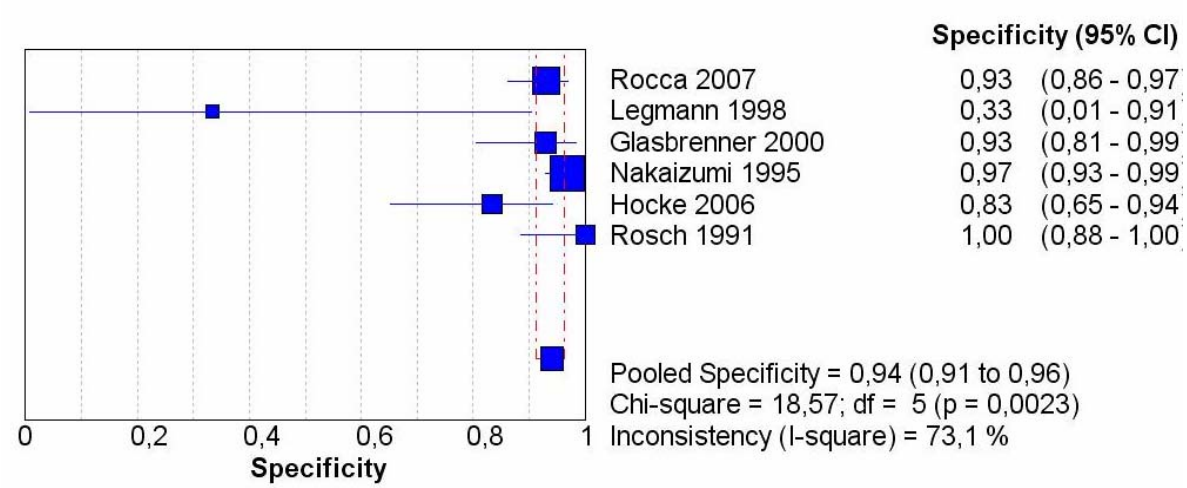


Figure 3. Pooled sensitivity of EUS-FNA for the diagnosis of pancreatic malignancy.

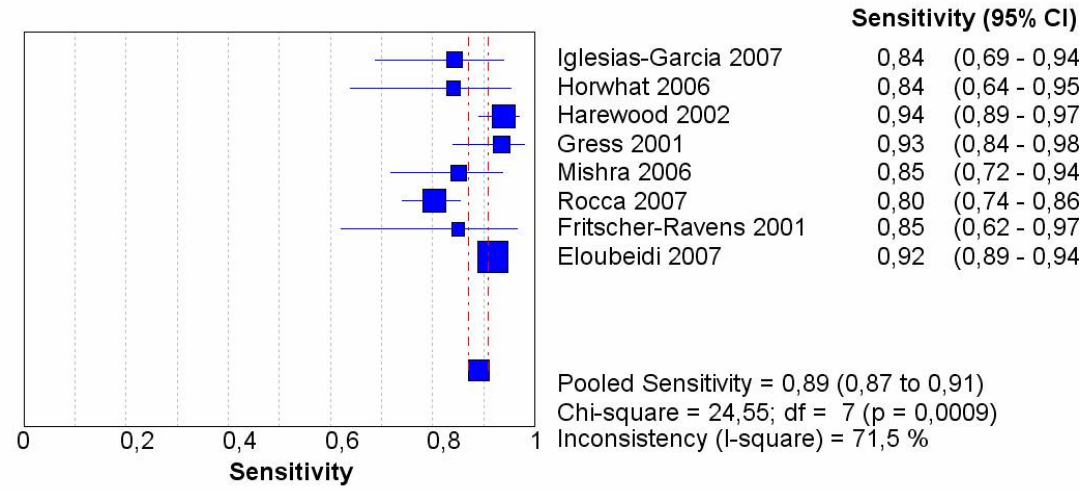
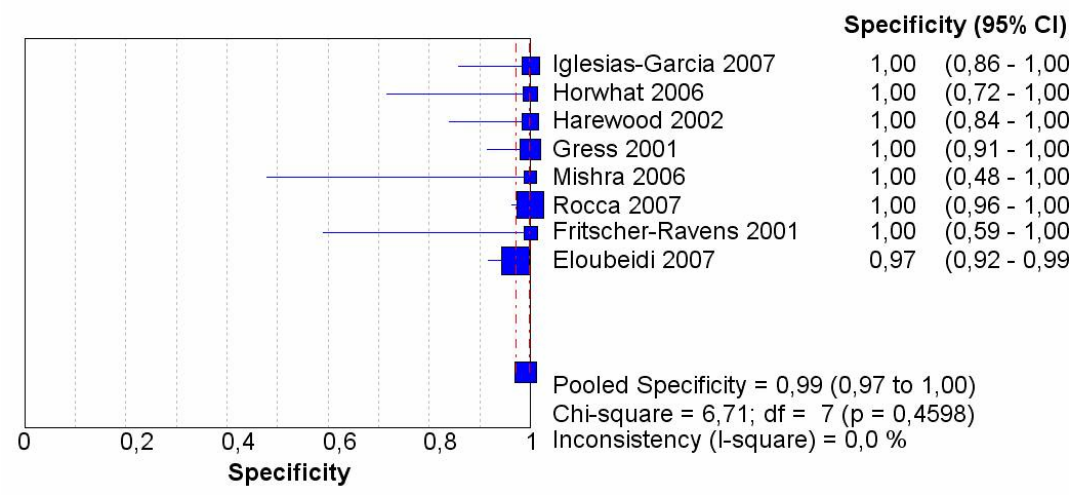


Figure 4. Pooled specificity of EUS-FNA for the diagnosis of pancreatic malignancy.



Tumour markers

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
Goonetilleke KS 2007	[49]	Dec 2005	Patients with suspected pancreatic cancer	CA 19-9	Median sensitivity: 79% (range 70-90%) Median specificity: 82% (68-91%) Median PPV: 72% (41-95%) Median NPV: 81% (65-98%) In case of jaundice, sensitivity increases and specificity decreases	Medline only English only No quality assessment 22 studies included, involving 2283 patients	SR	Low
Hathurusinghe HR 2007	[50]	Aug 2006	Patients with suspected pancreatic cancer	Tumor M2-PK	Sensitivity: range 71 – 85% Specificity: 41 – 97% Sensitivity increases in combination with CA 19-9 (96%)	English only No quality assessment 6 studies included (no pooling)	SR	Low
Kumar Y 2007	[51]	2005	Patients with suspected pancreatic cancer	Tumor M2-PK	Meta-analysis of 2 studies with diagnostic cut-off value of 15 U/ml: Sensitivity 72% Specificity 89%	Search of Medline and NeLH English only No quality assessment 7 studies included (incl. one abstract)	SR	Very low
Carr-Locke DL 1980	[58]	NA	Patients referred for ERCP (n=144)	CEA (cut-off 10 µg/l) Standard: standard investigations, ERCP, operation, follow-up, or post-mortem findings Outcome: diagnosis of pancreatic cancer	Sensitivity: 69% (20/29) Specificity: 87% (98/113) PPV: 58% (15/26) Obstructive jaundice (n=64): Sensitivity: 64% (14/22) Specificity: 74% (31/42) PPV: 58% (11/19)	Differential verification No information on blinding CEA not available in 2 patients	Prospective observational study	Low
Wang TH 1986	[57]	NA	Patients with suspected pancreatic cancer (n=151)	CA 19-9 (cut-off 37 U/ml) CEA (cut-off 2.5 ng/ml) Standard: imaging, pathology Outcome: diagnosis of pancreatic cancer	CA 19-9: Sensitivity 83% (20/24) Specificity 91% (105/116) PPV 65% (20/31) CEA: Sensitivity 71% (17/24) Specificity 78% (90/116) PPV 40% (17/43)	Differential verification No information on blinding	Prospective observational study	Low
Malesci A 1992	[54]	NA	Patients with suspected pancreatic cancer (n=110)	CA 19-9 (cut-off 40 U/ml) Standard: histology, diagnostic imaging + follow-up	Sensitivity: 83% (45/54) Specificity: 68% (38/56) PPV: 71% (45/63)	Differential verification Blinded study	Prospective observational study	Low

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
Kuno N 1994	[53]	NA	Patients with suspected pancreatic cancer (n=423)	CA 19-9 (cut-off 37 U/ml) CEA (cut-off 2.5 ng/ml) Span 1 (cut-off 30 U/ml) EL-1 (cut-off 400 ng/dl) Standard: histology, follow-up Outcome: diagnosis of pancreatic cancer	CA 19-9: Sensitivity 87% (41/47) Specificity 78% (279/356) PPV 35% (41/118) CEA: Sensitivity 57% (26/46) Specificity 87% (310/356) PPV 36% (26/72) Span 1: Sensitivity 89% (42/47) Specificity 80% (284/356) PPV 37% (42/114) EL-1: Sensitivity 51% (24/47) Specificity 87% (311/356) PPV 35% (24/69)	Differential verification No information on blinding 20 patients excluded (reasons provided in article)	Prospective observational study	Low
Palsson B 1997	[20]	NA	Patients with clinically suspected pancreatic disease	Clinical exam CA50 (cut-off 20 U/ml) Standard: histology/cytology, follow-up Outcome: diagnosis of pancreatic cancer	Sensitivity 96% (168/175) Specificity 48% (162/337) PPV 49% (168/343)	Blinded study Differential verification	Prospective cohort study	Low
Urgell E 2000	[56]	NA	Patients with clinical suspicion of pancreatic cancer (n=156)	CA 19-9 (reference value 37 U/ml; cut-off value 250 U/ml in presence of pancreatic mass, 100 U/ml otherwise) Standard: FNA cytology, clinical criteria, death Outcome: diagnosis of pancreatic cancer	Sensitivity 68% (51/75) Specificity 88% (72/81) PPV 85% (51/60)	Differential verification No information on blinding 15 patients excluded (incomplete clinical information and/or inadequate sample collection)	Prospective observational study	Low
Sperti C 2001	[55]	NA	Patients with cystic tumour of the pancreas (n=56)	CA 19-9 (cut-off 37 U/ml) Standard: pathology, biopsy, follow-up	Sensitivity: 65% (11/17) Specificity: 90% (35/39) PPV: 73% (11/15)	Differential verification Blinded study	Prospective observational study	Low

Figure 5. Pooled sensitivity of CA 19-9 for the diagnosis of pancreatic malignancy.

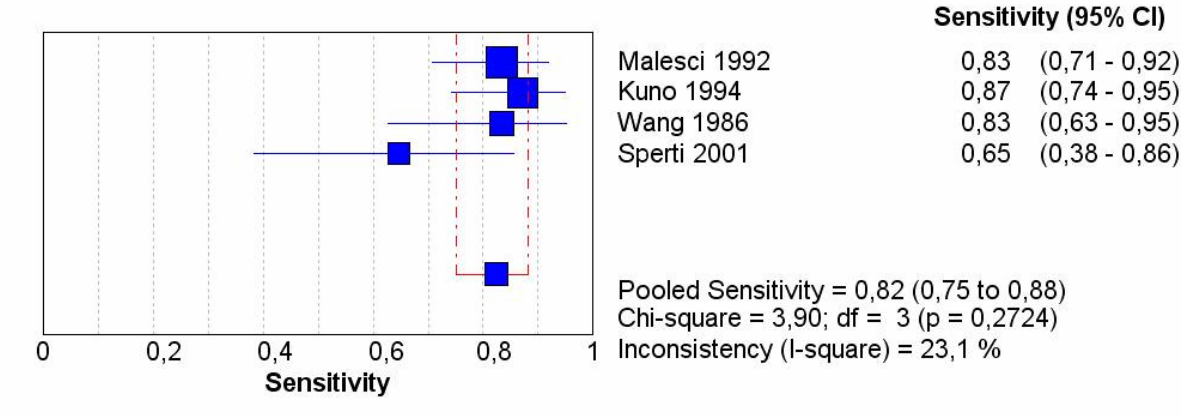


Figure 6. Pooled specificity of CA 19-9 for the diagnosis of pancreatic malignancy.

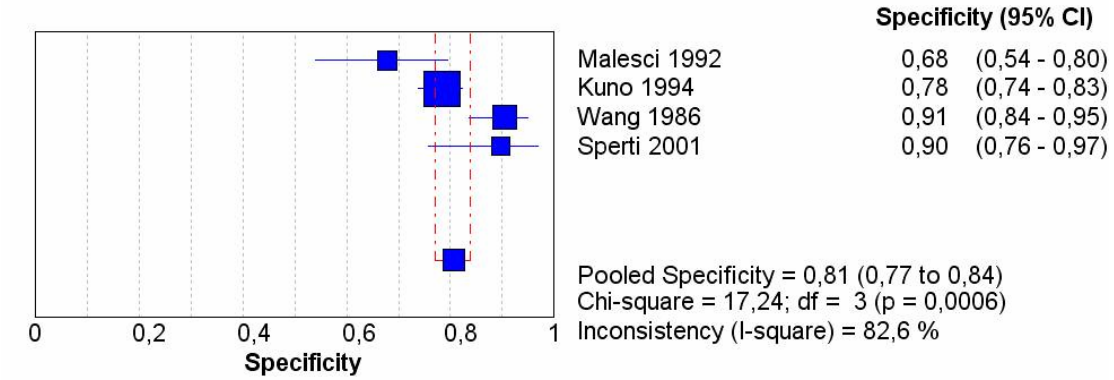


Figure 7. Pooled sensitivity of CEA for the diagnosis of pancreatic malignancy.

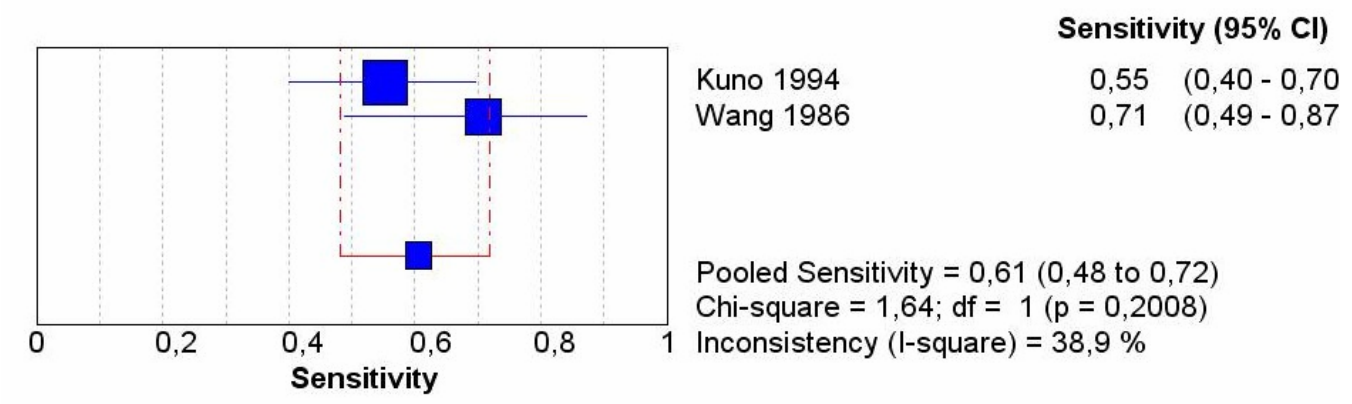
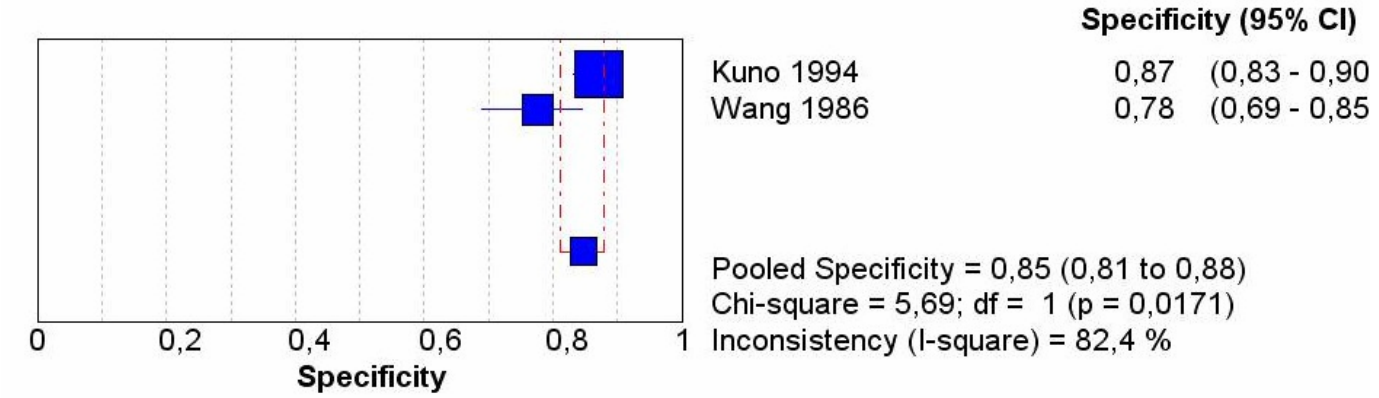


Figure 8. Pooled specificity of CEA for the diagnosis of pancreatic malignancy.



Cyst fluid analysis

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
van der Waaij LA 2005	[59]	June 2004	Patients with pancreatic cystic lesions	Cyst fluid analysis with amylase, CEA, CA 19-9 and cytology for the differentiation between benign and premalignant/malignant lesions	Amylase < 250 U/l, serous cystadenoma (SCA) + mucinous cystadenoma (MCA) + mucinous cystadenocarcinoma (MCAC) vs. pseudocyst (PC): sensitivity 44%, specificity 98%, PPV 98% CEA < 5 ng/ml, SCA + PC vs. MCA + MCAC: sensitivity 50%, specificity 95%, PPV 94% CA 19-9 < 37 U/ml, SCA + PC vs. MCA + MCAC: sensitivity 19%, specificity 98%, PPV 94%	Medline only No quality assessment 12 observational studies included, overall low quality	SR	Low – very low

ERCP

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
AHRQ 2002	[62]	Aug 2001	(1) common bile duct stones (2) pancreaticobiliary malignancy (3) pancreatitis (4) abdominal pain of possible pancreaticobiliary origin	Endoscopic retrograde pancreatography (ERCP)	Twelve studies comparing at least two tissue sampling techniques were identified in this systematic review. The available studies are limited by small size and do not consistently compare techniques in the same group of patients. Most studies do not report statistical tests, so it is not possible to determine with confidence whether reported differences in sensitivity are significantly different. While available evidence is suggestive, larger studies are needed to draw conclusions on relative performance of tissue sampling techniques. The available evidence suggests that sensitivity for detecting malignancy is similar or higher for brush cytology vs. bile aspiration cytology, similar for fine needle aspiration (FNA) cytology vs. brush cytology, and similar or higher for forceps biopsy vs. brush cytology. Using	Good-quality SR	SR	Moderate - high

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
					combinations of two or more sampling techniques may increase overall sensitivity. No comparative studies evaluated whether incremental improvement could also be achieved by repeated sampling using the same technique. In the absence of comparative studies of endoscopic ultrasound (EUS)-FNA and ERCP-FNA, indirect comparison of single-arm studies was attempted. Results from 10 studies including at least 400 subjects with pancreatic mass suggest a range of sensitivity in detecting pancreatic malignancy of 60-94 percent with a specificity of 100 percent. Two studies of ERCP-FNA including 164 subjects with various pancreatobiliary tumors reported sensitivities ranging from 25 percent to 62 percent. While sensitivity reported in these studies appears to be lower than that for EUS-FNA, such a comparison is not valid due to differences in study populations, cytology techniques, and study settings. The available evidence directly comparing ERCP with either MRCP or EUS is modest in size and of varying methodologic quality. The evidence comparing ERCP with MRCP is some what stronger than that comparing ERCP with EUS. Individual studies do not demonstrate statistically significant differences in diagnostic performance for ERCP vs. MRCP or for ERCP vs. EUS for characterizing malignant strictures. In sum, the available studies suggest that both MRCP and EUS provide similar diagnostic performance as ERCP in			

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
					detecting pancreaticobiliary malignant obstruction.			
Stavropoulos S 2005	[63]	NA	Patients with painless jaundice and no mass on CT and stricture on ERCP (n=61)	ERCP + brushing Standard: histopathology, follow-up	Sensitivity: 40% (17/42) Specificity: 100% (18/18) PPV: 100% (17/17)	Differential verification 1 patient excluded from analysis because no brushing possible Blinded study	Prospective observational study	Low

PET scan

CPG ID	Ref	Search date	Recommendation	Supporting evidence	Level of evidence
FNCLCC 2003	[71]	Oct 2002	Sous réserve d'une glycémie < 7,2 mmol.L-1, la TEP-FDG est indiquée pour établir le diagnostic différentiel entre cancer et pancréatite chronique (niveau de preuve B2).	Shreve 1999 Diederichs 2000 Sendler 2000 Jadvar 2001 Sperti 2001 Papos 2002	Low

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
Orlando LA 2004	[65]	2003	Patients with suspected pancreatic cancer	PET	PET after positive CT: Summary sensitivity: 92% (95%CI 87 – 95%) Summary specificity: 68% (95%CI 51% – 81%) PET after negative CT: Summary sensitivity: 73% (95%CI 50% – 88%) Summary specificity: 86% (95%CI 75% – 93%) PET after indeterminate CT: Summary sensitivity: 100% Summary specificity: 68% (results based on a single study)	Meta-analysis of 9 observational studies	SR	Low
Singer E 2007	[69]	NA	Patients with mass-forming lesion of the pancreas (n=41)	PET Standard: histology (biopsy, surgery, autopsy), follow-up	Sensitivity: 86% (19/22) Specificity: 79% (15/19) PPV: 83% (19/23)	Differential verification Blinded study	Prospective observational study	Low

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
Bang S 2006	[24]	NA	Patients with suspected primary pancreatic cancer (n=102)	Dynamic CT PET Standard: pathologic findings, follow-up	Sensitivity: 97% (90/93) Specificity: 78% (7/9) PPV: 98% (90/92)	Differential verification Blinded study	Prospective observational study	Low
Heinrich S 2005	[25]	NA	Patients with focal lesion in pancreas (n=59)	PET/CT Standard: intraoperative findings, histology, follow-up	Sensitivity: 89% (41/46) Specificity: 69% (9/13) PPV: 91% (41/45)	Differential verification No information on blinding	Prospective observational study	Low
Nishiyama Y 2005a	[67]	NA	Patients with suspected pancreatic cancer (n=86)	PET Standard: histology/cytology, follow-up	Sensitivity: 89% (49/55) Specificity: 65% (20/31) PPV: 82% (49/60)	Differential verification Blinded study	Prospective observational study	Low
Rasmussen I 2004	[68]	NA	Patients with recently diagnosed pancreatic mass (n=20)	PET Standard: histopathology, biopsies	Sensitivity: 75% (9/12) Specificity: 88% (7/8) PPV: 90% (9/10)	Differential verification Blinded study	Prospective observational study	Low
Sperti C 2005	[270]	NA	Patients with suspected cystic tumour of the pancreas (n=50)	PET Standard: pathology, biopsy, follow-up	Sensitivity: 94% (16/17) Specificity: 94% (31/33) PPV: 89% (16/18)	Differential verification Blinded study	Prospective observational study	Low
Sperti C 2001	[55]	NA	Patients with cystic tumour of the pancreas (n=56)	PET Standard: pathology, biopsy, follow-up	Sensitivity: 94% (16/17) Specificity: 97% (38/39) PPV: 94% (16/17)	Differential verification Blinded study Included in FNCLCC guideline	Prospective observational study	Low

STAGING

CT

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
Bipat S 2005	[22]	Dec 2003	Patients with known or suspected pancreatic adenocarcinoma	Helical CT Conventional CT US MRI Outcome: resectability	Helical CT: sensitivity 81%, specificity 82% Conventional CT: sensitivity 82%, specificity 76%	High-quality SR 32 studies on helical CT included, 12 studies on conventional CT	SR	Moderate
Dewitt J 2006	[23]	2004	Patients with suspected or established pancreatic cancer	CT EUS	No meta-analysis is provided T staging: 5 studies, of which 4 found EUS to be superior (different TNM staging systems across studies) N staging: 8 studies, of which 5 founds EUS to be superior Resectability: 4 studies, inconsistent results	Medline only English only	SR	Low
Imbriaco M 2006	[26]	NA	Patients with histologically confirmed pancreatic cancer (n=46)	Multislice CT Standard: final histopathological results of FNAC with follow-up Outcome: resectability	Sensitivity: 92% (36/39) Specificity: 86% (6/7) PPV: 97% (36/37)	Differential verification Unsure if partial verification (for unresectable patients) Blinding of pathology results?	Prospective observational study	Low
Li H 2005	[72]	NA	Patients with pancreatic cancer (n=101)	Tri-phase MDCT Standard: pathology, follow-up Outcome: resectability	Sensitivity: 93% (78/84) Specificity: 94% (16/17) PPV: 99% (78/79)	Differential verification No information on blinding	Prospective observational study	Low
Satoi S 2007	[73]	NA	Patients with pancreatic cancer (n=43)	Contrast-enhanced MDCT Standard: liver biopsy, follow-up Outcome: detection of liver metastasis	Sensitivity: 88% (22/25) Specificity: 89% (16/18) PPV: 92% (22/24)	Differential verification Partially blinded	Prospective observational study	Low

Ultrasonography

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
Bipat S 2005	[22]	Dec 2003	Patients with known or suspected pancreatic adenocarcinoma	Helical CT Conventional CT US MRI Outcome: resectability	US: sensitivity 83%, specificity 63% (significantly lower than specificity of helical CT: 82%, p=0.011)	High-quality SR 6 studies included	SR	Moderate

MRI

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
Bipat S 2005	[22]	Dec 2003	Patients with known or suspected pancreatic adenocarcinoma	Helical CT Conventional CT US MRI Outcome: resectability	MRI: sensitivity 82%, specificity 78%	High-quality SR 7 studies included	SR	Moderate
Ruf J 2006	[30]	NA	Patients with pancreatic cancer (n=32)	MRI Standard: surgery, laparotomy, biopsy or follow-up	Liver metastasis: Sensitivity: 75% (6/8) Specificity: 71% (5/7) PPV: 75% (6/8) N staging: Sensitivity: 15% (2/11)	Differential verification No information on blinding Prospective??	Prospective observational study	Very low

EUS

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
van Vliet EP 2007	[74]	Feb 2006	Patients with pancreatic adenocarcinoma	EUS	T staging: Median accuracy: 79% (range 69-93%) (8 studies) N staging: Median accuracy: 69% (range 50-88%) (10 studies) Median sensitivity: 63% (range 33%-92%) Median specificity: 63% (range 26%-100%)	Medline only English only No quality assessment 11 studies identified	SR	Low
Puli SR 2007	[75]	?	Patients with pancreatic and periampullary cancer	EUS Outcome: vascular invasion	Pooled sensitivity: 73% (95%CI 69-77%) Pooled specificity: 90% (95%CI 88-92%)	No quality assessment 29 studies identified	SR	Low

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
Dewitt J 2006	[23]	2004	Patients with suspected or established pancreatic cancer	CT EUS	No meta-analysis is provided T staging: 5 studies, of which 4 found EUS to be superior (different TNM staging systems across studies) N staging: 8 studies, of which 5 founds EUS to be superior Resectability: 4 studies, inconsistent results	Medline only English only	SR	Low

PET scan

CPG ID	Ref	Search date	Recommendation	Supporting evidence	Level of evidence
FNCLCC 2003	[71]	Oct 2002	La TEP complète utilement le bilan d'extension des cancers du pancréas (niveau de preuve B2) et permet de ne pas proposer une chirurgie radicale aux patients déjà porteurs de métastases (accord d'experts).	Frohlich 1999	Low

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
Heinrich S 2005	[25]	NA	Patients with pancreatic cancer (n=46)	PET/CT Standard: intraoperative findings, histology, follow-up	M-staging: Sensitivity: 81% (13/16) Specificity: 100% (30/30) PPV: 100% (13/13)	Differential verification Partial verification for N staging No information on blinding	Prospective observational study	Low
Nishiyama Y 2005b	[76]	NA	Patients with pancreatic cancer (n=42)	PET Standard: histology/cytology, follow-up	M-staging: Sensitivity: 81% (13/16) Specificity: 88% (23/26) PPV: 81% (13/16)	Differential verification Blinded study	Prospective observational study	Low

ERCP

No adequate evidence identified.

Laparoscopy

No adequate evidence identified.

Explorative laparotomy

No adequate evidence identified.

NEOADJUVANT TREATMENT

CPG ID	Ref	Search date	Recommendation	Supporting evidence	Level of evidence
CCO 2-23	[79]	Nov 2007	There is insufficient evidence to support the use of preoperative chemotherapy or radiotherapy or the use of intraoperative radiotherapy.	Nakamori S 2006: RCT in abstract form	

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
Palmer D 2007	[82]	NA	Patients with potentially resectable pancreas cancer (n = 50)	Gemcitabine (1000 mg/m²) every 7 days for 43 days: n = 24 Gemcitabine (1000 mg/m²) and cisplatin (25 mg/m²): n = 26; 7 to the original schedule (omitting day 22) and 19 to a revised schedule due to neutropenia (omitting days 15 and 36)	Resection rate (primary outcome): 38% vs. 70% 1-year survival: 42% vs. 62% Toxicity: 10 episodes of grade III/IV haematological toxicity in each group	Patients who were allocated to gemcitabine received a median of 85% of the planned dose. Patients who were allocated to combination treatment received a median of 88% and 92% of the planned gemcitabine and cisplatin doses, respectively. Methodological flaws: no information on randomisation procedure, no blinding, no statistics provided. Phase II trial	RCT	Low
Brunner TB 2007	[81]	NA	Patients with locally resectable or potentially resectable pancreatic carcinoma without distant metastasis	Arm A: partial pancreaticoduodenectomy + adjuvant chemotherapy Arm B: same treatment + neoadjuvant CRT (cisplatin/ gemcitabine)	Ongoing trial	Ongoing phase II trial	RCT	NA

SURGICAL TREATMENT WITH CURATIVE INTENT

Preoperative biliary drainage

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
Mumtaz K 2007	[87]	Oct 2006	Patients awaiting surgical procedure for a pancreatico-biliary stricture confirmed or suspected to be malignant	Preoperative endoscopic biliary stenting (EBS)	EBS: n = 62; no EBS: n = 63 Pre-surgical mortality: OR 3.14 (95%CI 0.12-79.3; NS) Pre-surgical complications: OR 43.75 (95%CI 2.51-761.8; p=0.01) in favour of no EBS Post-surgical mortality: OR 0.75 (95%CI 0.25-2.24; NS) Post-surgical complications: OR 0.45 (95%CI 0.22-0.91; p=0.03) in favour of EBS Overall mortality: OR 0.81 (95%CI 0.17-3.89; NS) Overall complications: OR 0.50 (95%CI 0.01-23.68; NS)	2 RCTs included (Lai 1994, Lygidakis 1987), both of moderate quality	SR	Moderate
Saleh MM 2002	[88]	Dec 2001	Patients with obstructive jaundice due to peripapillary pancreatic tumours undergoing radical surgery	Preoperative endoscopic biliary stenting (EBS)	EBS: n = 337; no EBS: n = 412 Postoperative complications: OR 0.79 (95%CI 0.36-1.73; NS) Mortality: OR 0.81 (95%CI 0.33-1.99; NS)	2 RCTs included (Lai 1994, Lygidakis 1987) Meta-analysis is done using the results from the 2 RCTs + 4 observational studies Medline search only No quality assessment of included studies	SR	Moderate
Sewnath ME 2002	[89]	Sept 2001	Patients with obstructive jaundice resulting from tumours	Preoperative biliary drainage (PBD)	Overall death rate: 15.9% vs. 13.5%; OR 1.19 (95%CI 0.63 – 2.23, p=0.60) Overall complication rate: 57.3% vs. 41.9%; OR 1.99 (95%CI 1.25-3.16, p=0.004) in favour of no PBD	5 RCTs included (Hatfield 1982, McPherson 1984, Smith 1985, Pitt 1985, Lai 1994), heterogeneous quality Included Lygidakis 1987 as a retrospective cohort analysis Mixture of RCTs with internal and external drainage	SR	Moderate
Aly EA 2001	[90]	Oct 2000	Patients with malignant	Preoperative biliary drainage	No meta-analysis done.	5 RCTs included (Hatfield	SR	Moderate

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
			obstructive jaundice	(PBD)	Conclusion: no evidence to support routine PBD	1982, McPherson 1984, Smith 1985, Pitt 1985, Lai 1994), heterogeneous quality Medline only, English only		
Van der Gaag NA 2007	[91]	NA	Patients with periampullary tumours causing obstructive jaundice, scheduled to undergo curative resection	'Early' surgical treatment vs. preoperative biliary drainage for 4 weeks and subsequent surgical treatment	Ongoing trial	Ongoing trial	RCT	NA

Radical resection

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
Imamura M 2004	[271]	NA	Patients with resectable locally advanced pancreatic cancer	Radical resection (pancreaticoduodenectomy or distal pancreatectomy with dissection of the regional lymph nodes) (n=20) vs. 5-FU-based CRT (n=22)	1-year survival: 62% vs. 32%, p = 0.05 in favour of surgery Mean survival: > 17 months vs. 11 months, p < 0.03 in favour of surgery Mean hospital stay: 66 +/- 29 days vs. 102 +/- 57 days, p=0.03 in favour of surgery	Prematurely terminated trial due to accrual difficulties No information on blinding	RCT	Moderate
Lygidakis NJ 2004	[103]	NA	Patients with pancreatic head carcinoma and portal-mesenteric venous invasion	Radical resection (mono-bloc spleno-pancreatic and vascular resection) (n=27) vs. palliative gastro-biliary bypass (n=29)	Group A: 1-, 2-, 3-, 4- and 5-year survival was 89%, 81%, 60%, 34% and 19% respectively Group B: 1-year survival was 45%, 2-year survival 0% (p=0.0001) 1-, 2-, 3-, 4- and 5-year disease-free survival in group A: 85%, 61%, 30%, 14% and 0% respectively	4 patients in group B had negative histology	RCT	Moderate
Riall TS 2005	[272]	NA	Patients with periampullary adenocarcinoma (57% pancreatic cancers) (n=299)	Standard pancreaticoduodenectomy (n=146) vs. extended pancreaticoduodenectomy (standard PD + distal gastrectomy + retroperitoneal lymphadenectomy) (n=148)	5-year survival: 25% vs. 31%, NS Median survival: 25 vs. 28 months, NS Overall complication rate: 43% vs. 29%, p=0.01 in favour of standard group FACT-Hep total QOL scores (in subgroup of 105 patients): 143.5 vs. 147.3	5 patients excluded based on histology	RCT	High

Lymphadenectomy

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
Michalski CW 2007	[106]	Feb 2006	Patients with pancreatic cancer	Extended vs. standard lymphadenectomy	Survival: weighted mean log HR = 0.93 (95%CI 0.77 – 1.13, p = 0.48; I^2 59.3%) Meta-analysis of the single morbidities with a random effects model revealed no significant differences	Good quality SR 4 RCTs included (Farnell 2005, Riall 2005, Nimura 2004 [abstract], Pedrazzoli 1998)	SR	Moderate

Vascular resection

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
Siriwardana HP 2006	[102]	June 2005	Patients with pancreatic cancer	Portal–superior mesenteric vein resection during pancreatectomy	Postoperative morbidity rate: 9 – 78%, median 42% Median survival: 13 months 1-year survival 50%; 5-year survival 7% Positive nodes in 67% of patients	English only No quality assessment 52 trials included, of which 1 RCT (Lygidakis 2004)	SR	Low

Pylorus preservation vs. antrectomy

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
Karanicolas PJ 2007	[109]	Jan 2006	Patients with pancreatic or periampullary cancer	Pylorus-preserving pancreaticoduodenectomy vs. standard Whipple pancreaticoduodenectomy	Postoperative mortality: RR 0.40 (95%CI 0.14-1.13, p=0.09) in favour of PPPD Operative time: WMD 72.3 minutes (95%CI 52.9-91.8, p<0.001) in favour of PPPD Blood loss: WMD 283.7 ml (95%CI 176.0-391.4, p<0.001) in favour of PPPD 5-year mortality: RR 0.98 (95%CI 0.87-1.11)	6 RCTs included (Lin 2005, Seiler 2005, Tran 2004, Bloechle 1999, Wenger 1999, Paquet 1998); heterogeneous quality	SR	Moderate
Diener MK 2007	[110]	Dec 2005	Patients with pancreatic or periampullary cancer	Pylorus-preserving pancreaticoduodenectomy vs. standard Whipple pancreaticoduodenectomy	Mortality: OR 0.49 (95%CI 0.17-1.40, p=0.18) Overall morbidity: OR 0.89 (95%CI 0.48-1.65, p=0.69) Operating time: WMD -68.26 minutes (95%CI -105.70 to -30.83, p=0.0004) in favour of PPPD Blood loss: WMD -766.0 ml (95%CI -965.26 to -566.74, p<0.00001) in favour of PPPD	6 RCTs included (Lin 2005, Seiler 2005, Tran 2004, Bloechle 1999, Wenger 1999, Paquet 1998); heterogeneous quality	SR	Moderate

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
Paraskevas KI 2006	[111]	?	Patients with pancreatic or periampullary cancer	Pylorus-preserving pancreaticoduodenectomy vs. standard Whipple pancreaticoduodenectomy	Focus on delayed gastric emptying: heterogeneous results across studies (no meta-analysis performed)	Narrative review based on Medline search for English RCTs	SR	Low

Pancreaticoenteric anastomosis

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
McKay A 2006	[113]	?	Patients undergoing pancreaticoduodenectomy	Reconstruction by pancreaticojejunostomy vs. pancreaticogastrostomy	Pancreatic fistula: RR 2.62 (95%CI 1.91-3.60) in favour of PGS Postoperative morbidity: RR 1.43 (95%CI 1.26-1.61) in favour of PGS In-hospital mortality: RR 2.51 (95%CI 1.61-3.91) in favour of PGS	1 RCT (Yeo 1995), 2 non-randomised prospective clinical trials and 8 observational cohort studies	SR	Moderate
Bassi C 2005	[114]	NA	Patients with periampullary neoplasms undergoing pancreaticoduodenectomy; soft parenchyma on histology (n = 163)	Reconstruction by pancreaticojejunostomy (n=82) vs. pancreaticogastrostomy (n=69)	Postoperative complications: 39% vs. 29% (NS) Pancreatic fistula: 16% vs. 13% (NS) Biliary fistula: 9% vs. 0% (p=0.02)	Twelve patients excluded because of different degrees of fibrosis No information on blinding	RCT	Moderate
Duffas JP 2005	[115]	NA	Patients undergoing pancreaticoduodenectomy (n = 149)	Reconstruction by pancreaticojejunostomy (n=68) vs. pancreaticogastrostomy (n=81)	Intra-abdominal complications: 34% in both groups Pancreatic fistula: 20% vs. 16% Postoperative mortality: 10% vs. 12% (p=0.67) Length of hospital stay: 21 vs. 20 days (NS)	19% benign disorders	RCT	High
Poon RT 2007	[273]	NA	Patients undergoing pancreaticoduodenectomy with end-to-side pancreaticojejunal anastomosis (n = 120)	External stent inserted across the anastomosis (n=60) vs. no stent (n=60)	Pancreatic fistula rate: 6.7% vs. 20%, p=0.032 Clinical leakage: 3.3% vs. 15%, p=0.027 Postoperative mortality: 1.7% vs. 5% (NS) Length of hospital stay: 17 vs. 23 days , p=0.039	Randomisation with sealed envelope No information on blinding of patients or assessors	RCT	Moderate
Peng SY 2007	[117]	NA	Patients undergoing pancreaticoduodenectomy for benign and malignant diseases of the pancreatic head and the periampullary region (n = 217)	Binding pancreaticojejunostomy (n=106, 43 with pancreatic adenoCA) vs. conventional pancreaticojejunostomy (n=111, 47 with pancreatic adenoCA)	Pancreatic anastomotic leakage: 0% vs. 7.2%, p=0.014 Postoperative mortality: 2.8% vs. 6.3% (NS) Length of hospital stay: 18 vs. 22 days, p=0.0005	Good quality RCT Also other types of tumours and benign diseases included	RCT	High
Bassi C 2003	[120]	NA	Patients who underwent a	Duct-to-mucosa anastomosis	Pancreatic fistula: 13% vs. 15% (NS)	No information on	RCT	Moderate

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
			pancreaticoduodenectomy with soft residual tissue (n = 144)	(n=72) vs. 1-layer end-to-side pancreaticojejunostomy (n=72)	Postoperative complications: 54% vs. 53% (NS) Postoperative death: 2% vs. 0% (NS) Length of hospital stay: 16 vs. 17 days (NS)	blinding 33% with pancreatic adenoCA, 21% with IPMT, 18% adenoCA of papilla of Vater		
Tran K 2002	[119]	NA	Patients undergoing a pancreaticoduodenectomy for suspected pancreatic cancer and periampullary cancer (n = 169)	Occlusion of the pancreatic duct (n=86) vs. pancreaticojejunostomy (n=83)	Absence of surgical complications: 64% vs. 76% (NS) Pancreatic fistula: 17% vs. 5%, p=0.013 Postoperative mortality: 8% vs. 5% (NS) Diabetes at 1y: 34% vs. 14%, p=0.001 Median hospital stay: 17 vs. 16 days (NS)	No information on blinding 59% with pancreatic adenoCA; 11% focal pancreatitis	RCT	Moderate
Chou FF 1996	[116]	NA	Patients with periampullary cancer undergoing Whipple's operation (n = 93)	Invaginating pancreaticojejunostomy (n=46) vs. duct-to-mucosa anastomisis (n=47)	Major complications: 33% vs. 21% (NS) Postoperative mortality: 9% vs. 6% (NS) Leakage: 15% vs. 4%, p=0.09 Mean hospital stay (no ITT): 22 vs. 20 days (NS)	No information on blinding 16% pancreatic head cancer, 65% cancer of papilla of Vater or duodenum, 19% cancer of distal common bile duct	RCT	Moderate
Reissman P 1995	[118]	NA	Patients who were scheduled for pancreaticoduodenectomy for periampullary carcinoma (n = 35)	End-to-end pancreaticojejunostomy (n=18) vs. controlled pancreaticocutaneous fistula (n=17)	Overall postoperative morbidity: 56% vs. 24%, p<0.01 Postoperative mortality: 11% vs. 0% (NS) Mean postoperative hospital stay: 42 vs. 26 days, p<0.01	No information on blinding 49% pancreatic adenoCA	RCT	Moderate

Figure 9: Pooled analysis of pancreatic fistula after pancreaticojejunostomy vs. pancreaticogastrostomy.

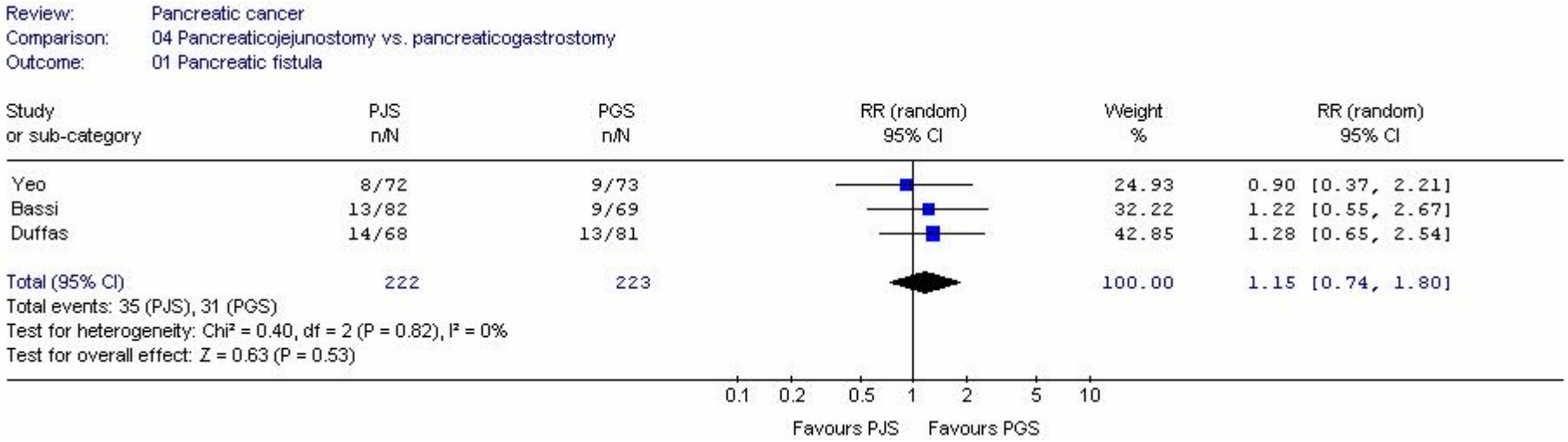


Figure 10. Pooled analysis of postoperative complication rate after pancreaticojejunostomy vs. pancreaticogastrostomy.

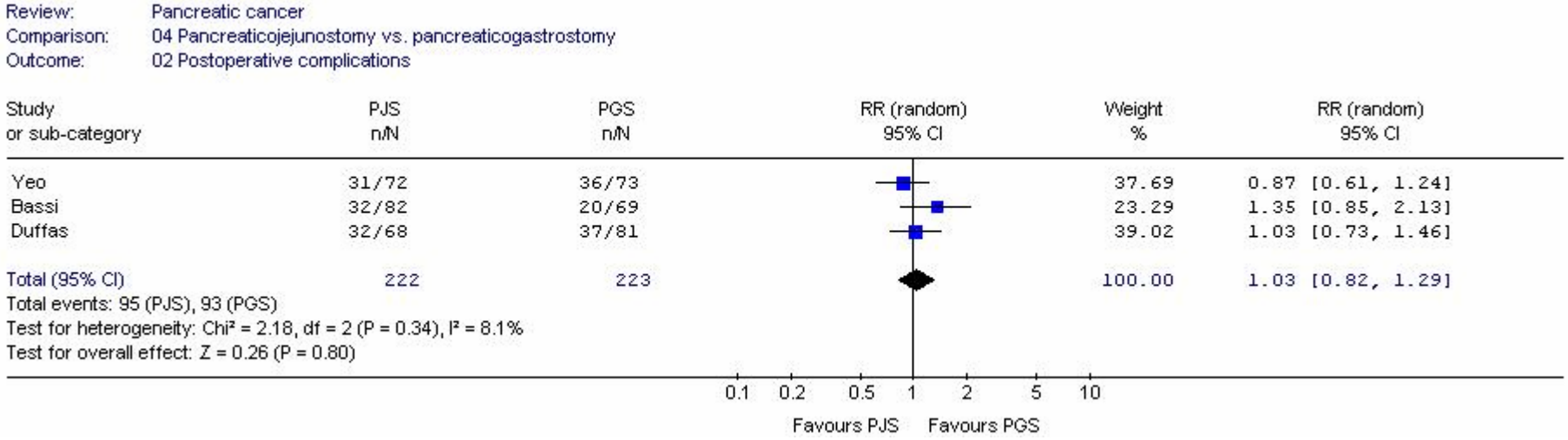
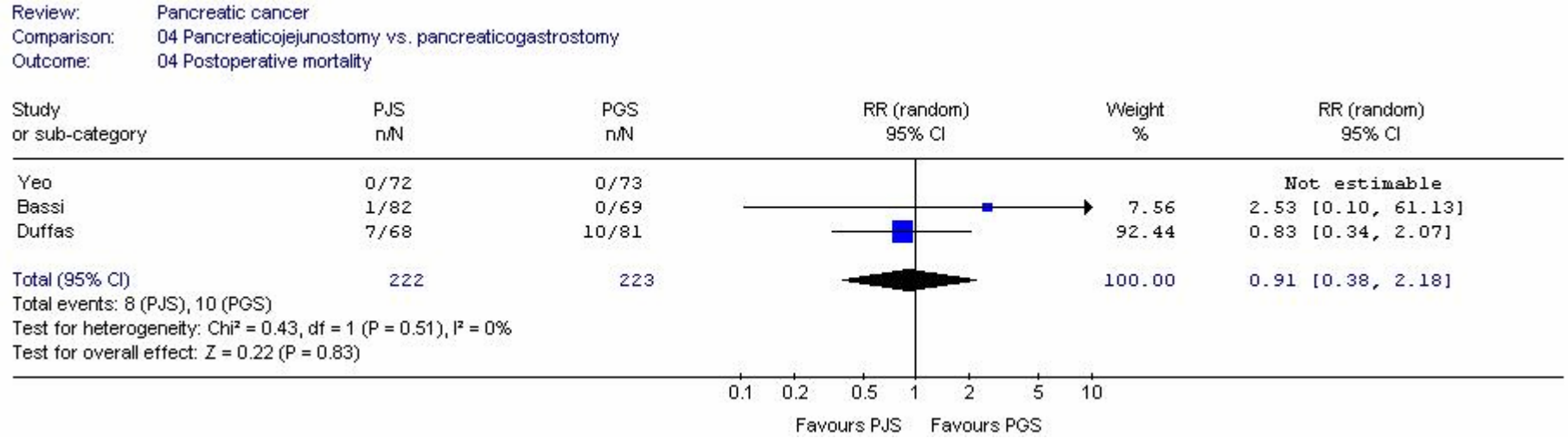


Figure 11. Pooled analysis of postoperative mortality after pancreaticojejunostomy vs. pancreaticogastrostomy.



Laparoscopy

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
Croce E 2005	[77]	?	Patients with pancreatic cancer	Laparoscopic pancreatic resection	Laparoscopic pancreaticoduodenectomy: long operative time, long postoperative stay Laparoscopic left pancreatectomy: fast recovery, comparable complication rate to open approach, shorter postoperative stay, few pancreatic fistulas	Narrative review based on Medline search. No search data available.	SR	Very low

HISTOPATHOLOGIC EXAMINATION

Prognostic factors

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
Garcea G 2008	[134]	Not stated (most recent study included: 2006)	Patients having undergone resection for pancreatic ductal adenocarcinoma	Prognostic factors: patient demographics, operative details and tumour characteristics (such as example tumour size, lymph node metastases and tumour differentiation)	Tumour size: Yearly survival rates: OR=0.32, 95%CI 0.18-0.56; P<0.001 (8 studies) Median survival: OR=2.52, 95%CI 1.95-3.29; P<0.001 (8 studies) Both in favour of tumour < 2 cm Lymph node status: Yearly survival rates: OR=0.32, 95%CI: 0.24-0.42; P<0.001 (26 studies) Median survival: OR=2.09, 95%CI 1.69-2.60; P<0.001 (24 studies) Both in favour of negative LN status Tumour grade: Yearly survival rates: OR=0.26, 95%CI 0.15-0.45 (14 studies) Median survival: OR=2.40, 95%CI 1.69-3.41 (19 studies) Both in favour of well-differentiated tumours Perineural invasion: Yearly survival rates: OR=0.53, 95%CI 0.16-1.74, P=0.296 Median survival: OR=2.37, 95%CI 1.77-3.18, P<0.001 (in favour of no invasion) Blood vessel invasion: Yearly survival rates: OR=0.58, 95%CI 0.26-1.31, P=0.191 Median survival: OR=1.88, 95%CI 0.89-3.49, P=0.097 Resection margin: Yearly survival rates: OR=0.26, 95%CI 0.16-0.42, P<0.001 (16 studies)	Medline & Web of Science English only No quality appraisal	SR + MA	Low

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
					Median survival: OR=3.00, 95%CI 2.15-4.17, P<0.001 (11 studies) Both in favour of R0 resection			
Garcea G 2005	[147]	Not stated	Patients with pancreatic cancer	Molecular prognostic markers	p53 expression (16 studies): only 3 studies found significant correlation with decreased survival p16 expression (6 studies): 3 studies found decreased survival associated with p16 expression Loss of DPC4 expression (2 studies): conflicting results K-ras mutations (11 studies): 6 studies showed no correlation with survival Conflicting results were also found for: p21 expression, cyclin D1 expression, BCL-2 positivity, etc.	Medline search only No information on quality appraisal	SR	Low
Butturini G 2008	[140]	Not stated	Patients with resected pancreatic ductal adenocarcinoma undergoing adjuvant treatment (n = 875)	Prognostic factors (survival)	R0 resections: n = 591, R1 resections: n = 278 Resection margin involvement: HR 1.10, 95%CI 0.94-1.29, p = 0.24	4 RCTs included Medline search only No information on quality appraisal	Meta-analysis	Low
Slidell MB 2008	[144]	NA	Patients with pancreatic cancer having undergone surgical resection and having complete lymph node data (n = 3868)	Prognostic factors: total lymph node count, lymph node ratio (LNR)	Median number of lymph nodes examined: n = 7 (range 0-90) 5-year survival: 4.3% (N1) vs. 11.3% (N0), p<0.001 Multiple logistic regression analyses confirmed 12 lymph nodes as the most appropriate cut-off value in N0 patients. Multivariate analysis (outcome = survival): - Lymph node status: HR 1.30, 95%CI 1.16-1.47, p<0.001 - LNR >0.4: HR 1.82, 95%CI 1.59-2.07, p<0.001		Retrospective population-based study (SEER data)	Very low

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
Li Q 2008	[21]	NA	Patients with pancreatic head cancer having undergone R0 resection (n = 134)	Prognostic factors (survival)	Multivariate analysis: - abdominal and/or back pain: RR 1.901, 95%CI 1.233-2.932, p=0.004 - tumour size > 2cm: RR 2.178, 95%CI 1.179-4.203, p=0.013 - lymph node status: RR 1.296, 95%CI 1.296-2.968, p=0.001 - vascular invasion: RR 2.134, 95%CI 1.278-2.549, p=0.032	Chinese population	Cohort study (prospective?)	Very low
Westgaard A 2008a	[136]	NA	Patients with periampullary adenocarcinoma having undergone pancreaticoduodenectomy with macroscopically free margins (n = 114)	Prognostic factors (survival)	Multivariate analysis: - Pancreatobiliary type differentiation: HR 3.1, 95%CI 1.8-5.1, p < 0.001 - Regional lymph node involvement: HR 2.5, 95%CI 1.5-4.4, p < 0.001 - Vessel involvement: HR 1.9, 95%CI 1.2-3.1, p = 0.012 - Tumour diameter: HR 1.3, 95%CI 1.1-1.5, p = 0.011		Case-control study (with historical control group)	Very low
Westgaard A 2008b	[141]	NA	Patients with macroscopically margin-free periampullary adenocarcinomas (n = 114)	Prognostic factors: R0 resection	Involvement of the retroperitoneal margin in 32 of 40 cases with R1 resection. Indicator of poor prognosis after presumed curative (R0 and R1) resection: HR 1.89, 95%CI 1.16-3.08, p = 0.01).	Same cohort as in Westgaard 2008a	Retrospective cohort study	Very low
Mitsunaga S 2007	[135]	NA	Patients with pancreatic cancer having undergone curative pancreaticoduodenectomy (n = 75)	Prognostic factors (survival)	Multivariate analysis: Tumour size >3cm: HR 2.3, 95%CI 1.3-3.9, p=0.004 Tumour necrosis: HR 2.3, 95%CI 1.3-3.9, p=0.049 Distance of nerve plexus invasion to pancreatic capsule: HR 2.8, 95%CI 1.5-5.3, p=0.001	Japanese population	Cohort study (prospective?)	Very low
Tani M 2007	[139]	NA	Patients with locally-invasive pancreatic cancer having undergone extensive surgery, M0 (n = 55)	Prognostic factors (survival)	Multivariate analysis: Adjuvant chemotherapy: RR 0.428, 95%CI 0.232-0.789, p=0.007	Japanese population	Retrospective cohort study	Very low
Tomlinson JS 2007	[146]	NA	Patients with pancreatic cancer having undergone pancreaticoduodenectomy	Prognostic factor: lymph node cut point	Median number of lymph nodes examined: n = 7 (range 0-54)		Retrospective population-based study	Very low

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
			and pN0 or single-node positive (pN1a) (n = 3505)		Multivariate analysis (outcome = survival): - pN0, lymph node cut point ≥15: HR 0.63, 95%CI 0.494-0.802, p<0.001		(SEER data)	
Pawlik TM 2007	[143]	NA	Patients with pancreatic cancer having undergone pancreaticoduodenectomy with curative intent (n = 905)	Prognostic factors: total number of lymph nodes evaluated, number of positive nodes, LNR	Median number of lymph nodes examined: n = 17 (range 6-28) No significant association of number of lymph nodes examined and survival Multivariate analysis (outcome = survival): - LNR >0.4: HR 2.55, 95%CI 1.75-2.70, p=0.001	Single-centre study	Retrospective analysis of prospective data	Very low
House MG 2007	[142]	NA	Patients with pancreatic cancer having undergone surgical resection (n = 696)	Prognostic factors: lymph node status, absolute number of pathologically assessed LN, LNR	Mean number of lymph nodes examined: n = 17 No association between total number of assessed lymph nodes and survival. Linear relationship between the number of metastatic lymph nodes and median survival for patients with node-positive disease. Linear relationship between LNR and median survival (LNR = 0.18 was best cut-off value).	Single-centre study	Retrospective analysis of prospective data	Very low
Raut CP 2007	[132]	NA	Patients with pancreatic cancer having undergone pancreaticoduodenectomy (n = 360)	Prognostic factors (survival & recurrence)	Multivariate analysis: Lymph node status: HR 1.55, 95%CI 1.21-1.99, p=0.001		Retrospective analysis of prospective data	Very low
Doi R 2007	[137]	NA	Patients with pancreatic head cancer having undergone surgical resection with curative intent, M0 (n = 133)	Prognostic factor: para-aortic lymph node metastasis	Multivariate analysis: HR 2.90, 95%CI 1.60-5.02, p=0.001	Japanese population	Retrospective series	Very low
Yekebas E 2006	[138]	NA	Patients with resectable pancreatic cancer having undergone curative surgery (n = 106)	Prognostic factors: nodal and bone-marrow microinvolvement (immunostaining with Ber-EP4)	5-year overall survival: - pN0 + EP4-: 61% - pN0 + EP4+: 0% (p=0.012) - pN1: 0% (p=0.059) Independent prognostic factors: *Nodal microinvolvement*: RR 2.92, 95%CI 1.39-6.13, p=0.005 (recurrence-free		Cohort study (prospective?)	Very low

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
					survival) *Tumour grade*: RR 3.14, 95%CI 1.74-5.68, p=0.000 (recurrence-free survival) *Nodal stage*: RR 2.18, 95%CI 1.19-4.00, p=0.012 (overall survival)			
Schwarz R 2006	[145]	NA	Patients with pancreatic cancer having undergone surgical resection, M0, <T4, at least 1 lymph node examined (n = 1666)	Prognostic factors: lymph node numbers	Median number of lymph nodes examined: n = 7 (range 1-52) Best cut-off value: n = 16 Multivariate analysis: - Number of lymph nodes examines: RR 0.98, 95%CI 0.97-0.99, p<0.001 - Number of positive lymph nodes: RR 1.08, 95%CI 1.06-1.10, p<0.001		Retrospective population-based study (SEER data)	Very low
Howard TJ 2006	[131]	NA	Patients with pancreatic cancer having undergone surgery (n = 226)	Prognostic factors (survival)	Multivariate analysis: - Tumour size <3cm: HR 1.38, 95%CI 1.02-1.87, p=0.03 - Tumour differentiation: HR 0.76, 95%CI 0.60-0.95, p=0.02 - R0 resection: HR 1.39, 95%CI 1.02-1.90, p=0.03		Retrospective cohort study	Very low

Staging systems

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
Kobari M 1998	[274]	NA	Patients with pancreatic head cancer undergoing resection (n = 1689)	Comparison of JPS (3rd and 4th ed.) and UICC (4th ed.) staging systems	<u>3-year survival</u>: *JPS*: Stage I: 66.2%; Stage II: 37.2%; Stage III: 25.4%; Stage IV: 12.7% *UICC*: Stage I: 44.3%; Stage II: 22.5%; Stage III: 16.3%; Stage IV: 9.6% <u>5-year survival</u>: *JPS*: Stage I: 48.1%; Stage II: 27.7%; Stage III: 22.3%; Stage IV: 8.8% *UICC*:	Japanese population Single-centre study	Retrospective study	Very low

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
					Stage I: 32.5%; Stage II: 11.5%; Stage III: 12.0%; Stage IV: 6.6%			
Balzano G 1997	[275]	NA	Patients with pancreatic cancer undergoing resection (n = 228)	Comparison of JPS (3rd ed.) and UICC (4th ed.) staging systems	Median survival: *JPS*: Stage I: 34 mo; Stage II: 18 mo; Stage III: 14 mo; Stage IV: 7 mo Overall significant difference ($p < 0.001$), even when comparing survival curves by couple. *UICC*: Stage I: 17 mo; Stage II: 12 mo; Stage III: 12 mo; Stage IV: 6 mo Overall significant difference ($p < 0.001$), but not between survival curves of stage II and III ($p = 0.74$). Modification of the UICC classification improved the differentiation between stage II and III, however still not significantly. Better correlation between stages and survival classes for the JPS classification.	Italian study Probably overlap with Zerbi 1994	Retrospective study	Very low
Bakkevold KE 1995	[276]	NA	Patients with histologically or cytologically verified pancreatic cancer (n = 442)	UICC staging system (4th ed.)	Comparable survival of T1a and T1b tumours ($p = 0.68$-0.95). No statistically significant difference in survival between stage II and III ($p = 0.07$-0.40).	Norwegian study Comprised from 2 RCTs	Prospective cohort study	Low
Zerbi A 1994	[277]	NA	Patients with pancreatic cancer undergoing resection (n = 74)	Comparison of JPS (3rd ed.) and UICC (4th ed.) staging systems	Median survival: *JPS*: Stage II: 29 mo; Stage III: 14 mo; Stage IV: 7 mo Overall significant difference ($p < 0.01$), no overlapping confidence intervals. *UICC*: Stage I: 17 mo; Stage II: 10 mo; Stage III: 12 mo; Stage IV: 6 mo Overall significant difference ($p < 0.05$), but overlapping confidence intervals between stage II and III.	Italian study Probably overlap with Balzano 1997	Retrospective study	Very low
Tsunoda T	[278]	NA	Patients with pancreatic	Comparison of JPS (3rd ed.) and	Significantly higher curative resection	Japanese population	Retrospective	Very low

Study ID	Ref	Search date	Population	Intervention(s)	Results	Comments	Study type	Level of evidence
1991			cancer encountered at surgical department (n = 229)	UICC (4th ed.) staging systems	rates in JPS Stage II and III compared to UICCC.		study	

ADJUVANT TREATMENT

CPG ID	Ref	Search date	Recommendation	Supporting evidence	Level of evidence
CCO 2-23	[79]	Nov 2007	Postoperative chemotherapy is recommended for patients with resectable pancreatic adenocarcinoma. Patients should be referred to a medical oncologist to discuss chemotherapy after gross complete excision of a pancreatic adenocarcinoma. Acceptable regimens include six months of 5-fluorouracil (5FU) plus folinic acid or single-agent gemcitabine.	Bakkevold 1993 Neoptolemos JP 2001 & 2004 Takada 2002 Kosuge 2006 Oettle 2007	High
			The role of postoperative radiotherapy is not clear and warrants further study. Postoperative radiotherapy is not recommended when used in a split-course schedule for patients with negative margins. In margin-positive patients, there may be a role for postoperative radiotherapy.	Kalser 1985 Klinkenbijl 1999 Neoptolemos JP 2001 & 2004	High

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
Chemotherapy								
Maeda A 2008	[158]	NA	Patients with curatively resected pancreatic cancer	Adjuvant orally administered S-1 vs. intravenous gemcitabine	Ongoing trial	Ongoing trial	RCT	NA
Yoshitomi H 2007	[279]	NA	Patients with invasive ductal pancreatic cancer who underwent radical surgery	UFT and gemcitabine (n = 50) vs. gemcitabine alone (n = 50)	1-year DFS: 50.3% vs. 45.5% (NS) Median overall survival: 20 vs. 28 months (NS) No grade 4 or more toxicity; grade 2 or more toxicity: 67.3% vs. 56.3% (NS)	Ongoing trial	RCT (abstract)	NA
Chemotherapy vs. chemoradiotherapy								
Van Laethem J 2008	[157]	NA	Patients with R0 resection of pancreatic head cancer	Gemcitabine alone (n = 45) vs. gemcitabine-based CRT (n = 45)	Treatment completion per protocol: 86.7% vs. 73.3% Grade 4 toxicity: 0% vs. 2.2%	Phase II trial	RCT (abstract)	NA
Chemoradiotherapy								
Brasiuniene B 2007	[159]	NA	Patients with resectable pancreatic cancer (n = 41)	5-FU-based CRT (n = 23) vs. gemcitabine-based CRT (n = 18)	Median survival: 17.2 vs. 12.1 months (p = 0.84) Time-to-disease-progression: 14.3 vs. 10.8 months (p = 0.80)	Methodological flaws (sealed envelopes for randomisation; no information on blinding of patients or assessors; no information on ITT	RCT	Low

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
						analysis; comparable groups?)		
Butturini G 2008	[140]	Not stated	Patients with resected pancreatic ductal adenocarcinoma undergoing adjuvant treatment (n = 875)	Chemoradiotherapy, chemotherapy	R0 resections: n = 591, R1 resections: n = 278 Chemoradiotherapy: - R1 patients: 28% reduction in the risk of death (HR 0.72, 95%CI 0.47-1.10) - R0 patients: 19% increased risk of death (HR 1.19, 95%CI 0.95-1.49) Chemotherapy: - R1 patients: 4% increased risk of death (HR 1.04, 95%CI 0.78-1.40) - R0 patients: 35% reduction in risk of death (HR 0.65, 95%CI 0.53-0.80).	4 RCTs included Medline search only No information on quality appraisal Subanalysis	Meta-analysis	Low
Chemotherapy + chemoradiotherapy + chemotherapy								
Regine WF 2008	[160]	NA	Patients with complete gross total resection of pancreatic adenocarcinoma and no prior radiation or chemotherapy (n = 451)	Chemotherapy with 5-FU continuous infusion of 250 mg/m² per day (n = 230) or gemcitabine 30-minute infusion of 1000 mg/m² once per week (n = 221) for 3 weeks prior to chemoradiation therapy and for 12 weeks after chemoradiation therapy. Chemoradiation with a continuous infusion of 5-FU (250 mg/m² per day) was the same for all patients (50.4 Gy).	<u>Pancreatic head tumours</u>: Median survival: 20.5 vs. 16.9 months in favour of gemcitabine 3-year survival: 31% vs. 22% in favour of gemcitabine (HR 0.82; 95%CI 0.65-1.03; p = 0.09) <u>All tumours</u>: Grade 4 haematologic toxicity: 1% (5-FU) vs. 14% (gemcitabine) (p < .001)	Methodological flaws (blinded randomisation? blinding of patients and assessors? differences in T stage)	RCT	Moderate

PALLIATIVE TREATMENT

Palliative treatment with chemotherapy, radiotherapy or both

CPG ID	Ref	Search date	Recommendation	Supporting evidence	Level of evidence
CCO 2-7	[204]	Feb 2004	For medically suitable patients with unresectable, non-metastatic locally advanced pancreatic cancer, current conventional practice is to offer combined chemotherapy and radiotherapy.	Moertel 1969 Moertel 1981 Klaassen 1985 GITSG 1988	High

CPG ID	Ref	Search date	Recommendation	Supporting evidence	Level of evidence
			Outside a clinical trial, 5-fluorouracil (5-FU) given as bolus or infusion is the preferred chemotherapeutic agent to combine with radiotherapy. The optimal mode and duration of 5-FU delivery is unclear, however infusional therapy appears to give better treatment outcome.	GITSG 1985 Earle 1994	High

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
Chemotherapy								
Sultana A 2007a	[167]	?	Patients with locally advanced/metastatic pancreatic adenocarcinoma	Chemotherapy vs. best supportive care	Overall survival: HR 0.64, 95%CI 0.42-0.98, p=0.04, in favour of chemotherapy (6 studies; results of Andren-Sandberg 1983 not included). Significant heterogeneity between studies (p=0.0005; I^2=77.4%).	Good-quality SR, but no search date provided 7 RCTs included involving 432 patients (Andersen 1981 was excluded)	SR	Moderate
				Gemcitabine vs. 5-FU	Overall survival: HR 0.75, 95%CI 0.42-1.31, p=0.31. Marked heterogeneity (p=0.06; I^2=70.9%)	2 RCTs included involving 197 patients		Moderate
				Gemcitabine alone vs. combination	Overall survival: HR 0.91, 95%CI 0.85-0.97, p=0.004 No heterogeneity (p=0.42, I^2=2.6%)	19 RCTs included involving 4697 patients		High
				5-FU alone vs. combination	Overall survival: HR 0.94, 95%CI 0.82-1.08, p=0.39 No heterogeneity (p=0.73, I^2=0%)	5 RCTs included involving 700 patients		High
Yip D 2006	[168]	Jan 2005	Patients with inoperable advanced pancreatic cancer	Chemotherapy vs. best supportive care	Mortality at 6 months: OR 0.46 (7 studies; 95%CI 0.25-0.84, p=0.01). Significant heterogeneity (p=0.02, I^2=71.5%) Mortality at 12 months: OR 0.37 (7 studies; 95%CI 0.25-0.57, p< 0.00001). No heterogeneity (p=0.33, I^2=12.6%)	8 RCTs included (including Andersen 1981)	SR	Moderate
				Gemcitabine vs. other	Mortality at 6 months: OR 1.10 (4 studies; 95%CI 0.80-1.51, p=0.55). Significant heterogeneity (p=0.006, I^2=76%) Mortality at 12 months: OR 1.34 (95%CI 0.88-2.02, p=0.17). Heterogeneity: p=0.03, I^2=79.7%	4 RCTs included		Moderate
				Gemcitabine alone vs.	Mortality at 6 months: OR 0.88 (14	16 RCTs included		Moderate

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
				combination	studies; 95%CI 0.77-1.02, p=0.08). Significant heterogeneity (p=0.009, I^2=53.7%) Mortality at 12 months: OR 0.89 (95%CI 0.76-1.05, p=0.17). No significant heterogeneity (p=0.64, I^2=0%) The drugs combined with gemcitabine were divided into the subgroups: fluropyrimidines, irinotecan, platinums and other combinations. Only for the platinums, there was a suggestion of a statistically significant improvement in the 6-month mortality: OR 0.59 (95%CI 0.43-0.81, p=0.001).			
				5-FU vs. other	Mortality at 6 months: OR 0.58 (95%CI 0.37-0.92, p=0.02). No significant heterogeneity (p=0.07, I^2=57.9%). Mortality at 12 months: OR 0.67 (95%CI 0.34-1.31, p=0.24). No significant heterogeneity (p=0.06, I^2=60%).	4 RCTs included		High
				5-FU alone vs. combination	Mortality at 6 months: OR 0.79 (95%CI 0.59-1.05, p=0.10). No significant heterogeneity (p=0.32, I^2=13.7%). Mortality at 12 months: OR 0.90 (95%CI 0.62-1.30, p=0.57). No significant heterogeneity (p=0.06, I^2=47.7%).	8 RCTs included		High
				Other combinations	No pooled analysis because of heterogeneity. Only 1 trial found advantage of one regimen over another (Kelsen 1991).	6 RCTs included		
Heinemann V 2008	[172]	2006	Patients with histologically confirmed locally	First-line chemotherapy with gemcitabine alone vs.	Significant survival benefit for GEM+X: HR 0.91 (95%CI 0.85-0.97, p=0.004).	Medline, ASCO abstracts and ECCO abstracts	SR	High

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
			advanced or metastatic pancreatic cancer	gemcitabine-based two-drug combinations	No heterogeneity (p=0.82, I^2=0%). Platinum-based combinations: HR 0.85 (95%CI 0.76-0.96, p=0.010). Fluoropyrimidine-based combinations: HR 0.90 (95%CI 0.81-0.99, p=0.030). No risk reduction in the group of trials combining GEM with irinotecan, exatecan or pemetrexed (HR=0.99).	15 RCTs included for MA		
Bria E 2007	[173]	Nov 2006	Patients with advanced pancreatic cancer	Gemcitabine alone vs. gemcitabine-based combinations	Overall survival: RR 0.93 (95%CI 0.84-1.03; p=0.17). No heterogeneity. Progression-free-survival: RR 0.91 (95%CI 0.84-0.98; p=0.015), in favour of combinations. No heterogeneity. Overall response rate: RR 1.57 (95%CI 1.31-1.86; p<0.0001). Significant heterogeneity. Platinum-containing combinations: - PFS: RR 0.67 (95%CI 0.53-0.83; p=0.0004) - ORR: RR 1.77 (95%CI 1.32-2.37; p=0.0001)	Medline, ASCO abstracts, ESMO abstracts and ECC abstracts 20 RCTs included, involving 6296 patients	SR	High
Banu E 2007	[174]	Dec 2005	Patients with advanced and metastatic cancer	First-line chemotherapy with gemcitabine alone vs. gemcitabine-based doublets	OS at 6 months: RR 0.92 (23 studies; 95%CI 0.87-0.97, p=0.003), in favour of doublets. No significant heterogeneity. OS at 12 months: RR 0.96 (21 studies; 95%CI 0.93-0.98, p=0.003), in favour of doublets. No significant heterogeneity. OS at 18 months: RR 0.97 (16 studies; 95%CI 0.95-0.99, p=0.005). No significant heterogeneity. Platinum salts: - 6 months: RRR = 14%; 95%CI 0-25%; p=0.04 - 18 months: RRR = 8%; 95%CI 2-13%; p=0.01	Broad search 23 trials included, involving 5886 patients	SR	High
Xie DR 2006	[280]	March 2005	Patients with advanced stage pancreatic cancer	Gemcitabine alone vs. gemcitabine + cisplatin	Objective remission rate: RD 6% (5 studies; 95%CI 0.00-0.12, p=0.05), in favour of GEM-CIS. No significant	Broad search 6 RCTs included, involving 560 patients	SR	High

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
					heterogeneity. Clinical benefit response: RD 4% (3 studies; 95%CI -0.18-0.10, p=0.58). No heterogeneity. 6-month survival: RD 5% (6 studies; 95%CI -0.03-0.13, p=0.24). No significant heterogeneity. 6-month time-to-progression: RD 9% (4 studies; 95%CI 0.01-0.17, p=0.02), in favour of GEM+CIS. No heterogeneity.			
Yang Q 2008	[177]	2007	Patients with advanced stage pancreatic cancer	Gemcitabine alone vs. gemcitabine-based combinations	GEM+CIS: - 6-month OS: RD 5% (p=0.24) - 12-month OS: RD 7% (p=0.37) GEM+5FU: - 6-month OS: RD 2% (p=0.46) - 12-month OS: RD 4% (p=0.19) GEM+irinotecan: - 6-month OS: RD -1% (p=0.88) - 12-month OS: RD 0% (p=0.97) GEM+oxaliplatin: - 6-month OS: RD 11% (p=0.0007) - 12-month OS: RD 5% (p=0.06) GEM+capecitabine: - 6-month OS: RD 7% (p=0.03) - 12-month OS: RD 5% (p=0.08)	Broad search No information on quality assessment 18 RCTs included in MA, involving 3881 patients	SR (abstract)	NA
Boeck S 2008	[190]	NA	Patients with a histologically confirmed diagnosis of locally advanced (stage III) or metastatic (stage IV) (n=190)	Capecitabine plus oxaliplatin (CapOx) vs. capecitabine plus gemcitabine (CapGem) vs. gemcitabine plus oxaliplatin (mGemOx)	Progression free survival (PFS) rate at 3 months: 51% (CapOx) vs. 64% (CapGem) vs. 60% (mGemOx) Median PFS: 4.2 vs. 5.7 vs. 3.9 months, p = 0.67 Median survival: 8.1 vs. 9.0 vs. 6.9 months, p = 0.56	No information on randomization procedure and blinding	RCT	Moderate
Cascinu S 2008	[198]	NA	Patients with advanced pancreatic cancer (n=84)	Cetuximab plus gemcitabine and cisplatin vs. gemcitabine and cisplatin alone	Objective response: no significant difference (5.3% higher in the cetuximab group; p=0.549) Disease control: no significant (3.5% higher in the non-cetuximab group;	Phase II study Good-quality RCT	RCT	High

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
					p=0.504). Median progression-free survival: 3.4 vs. 4.2 months (HR 0.96, 95%CI 0.60-1.52, p=0.847). Median overall survival: 7.5 vs. 7.8 months (HR 0.91, 95%CI 0.54-1.55, p=0.739). Thirty-three patients from both groups had at least one grade 3-4 toxic effect.			
Herrmann R 2007	[178]	NA	Patients with advanced/metastatic pancreatic cancer (n=319)	Gemcitabine plus capecitabine (GemCap) vs. single-agent Gemcitabine (Gem)	Median overall survival: 8.4 vs. 7.2 months (p=0.234). Post hoc analysis in patients with good Karnofsky Performance Status (score of 90 to 100) showed a significant prolongation of median OS time in the GemCap arm compared with the Gem arm (10.1 vs. 7.4 months, p=0.014). The overall frequency of grade 3 or 4 adverse events was similar in each arm.	Phase III study No information on randomization procedure or blinding	RCT	Moderate
Richards DA 2006	[180]	NA	Patients with advanced pancreatic cancer (n=174)	Gemcitabine plus CI-994 (CG) vs. Gemcitabine plus placebo (PG)	Median survival: 194 vs. 214 days, p=0.908 (HR 0.98, 95%CI 0.701-1.370). Objective response rate: 12% vs. 14% when investigator-assessed and 1% vs. 6% when assessed centrally. QoL scores at 2 months were worse with CG than with PG.	Double-blind placebo-controlled trial Phase II study No information on randomisation procedure Not clear if ITT analysis	RCT	Moderate
Lutz MP 2005	[191]	NA	Chemotherapy-naive patients with advanced pancreatic cancer (n=96)	Docetaxel plus Gemcitabine vs. Docetaxel plus Cisplatin	Confirmed responses: 19.4% vs. 23.5% (overlapping 95%CI). Median progression-free survival: 3.9 vs. 2.8 months (overlapping 95%CI). Median survival: 7.4 vs. 7.1 months (overlapping 95%CI). 1-year survival: 30% vs. 16% (overlapping 95%CI).	Phase II study Central randomisation No information on blinding of patients and/or clinicians/assessors	RCT	Moderate
Alberts SR 2005	[192]	NA	Patients with metastatic pancreatic adenocarcinoma (n=87)	PS-341 alone vs. PS-341 and gemcitabine	Median survival: 2.5 vs. 4.8 months. Median time to progression: 1.2 vs. 2.4 months	Phase II study No information on randomisation procedure or blinding of patients and/or clinicians/assessors Not clear if ITT analysis	RCT	Moderate
Mitry E 2008	[197]	NA	Patients with metastatic	LV5FU2-cisplatin followed by	Median OS: 6.6 vs. 8.2 months (p=0.72).	Phase III trial	RCT	NA

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
			pancreatic cancer (n=202)	gemcitabine vs. gemcitabine followed by LV5FU2-cisplatin	1- year survival: 29.5% vs. 34.5% 2-year survival: 8% vs. 3.5%		(abstract)	
Vervenne W 2008	[203]	NA	Chemotherapy-naive patients with metastatic pancreatic adenocarcinoma (n=607)	Erlotinib (E) and gemcitabine (G) with or without bevacizumab (B)	Median OS: 6.0 vs. 7.1 months (HR 0.89, 95%CI 0.74-1.07). Median PFS: 3.6 vs. 4.6 months (HR 0.73, 95%CI 0.61-0.86; p=0.0002).	Phase III trial Double-blind placebo-controlled trial	RCT (abstract)	NA
Tuinmann G 2008	[184]	NA	Patients with advanced pancreatic cancer	Gemcitabine vs. mitomycin C vs. gemcitabine/mitomycin C	Medium time to progression: 3 vs. 1.7 vs. 1.8 months. Medium overall survival: 7 vs. 3.1 vs. 2.8 months	Phase II trial Interim analysis of 69 patients	RCT (abstract)	NA
Ychou M 2007	[171]	NA	Chemotherapy-naive patients with metastatic pancreatic cancer (n=88)	Folfirinox (5FU/leucovorin, irinotecan and oxaliplatin) vs. gemcitabine	Confirmed partial response: 38.7% vs. 11.7 %. Median duration of response: 6.3 vs. 4.6 months	Phase II trial Interim analysis	RCT (abstract)	NA
Spano J 2007	[183]	NA	Patients with advanced pancreatic cancer (n=103)	Axitinib and gemcitabine vs. gemcitabine	Most commonly reported adverse events: anemia (48%), alk phos elevations (48%), leukopenia (45%), neutropenia (42%), LFT elevations (39%), and thrombocytopenia (27%). Most common non-hematologic adverse events: nausea (24%), vomiting (20%), fatigue (19%), diarrhea (18%), anorexia (18%), constipation (13%), dyspnea (12%), and pyrexia (12%). Pooled median OS: 203 days	Phase II trial No comparative data provided	RCT (abstract)	NA
Kindler HL 2007	[181]	NA	Patients with advanced pancreatic cancer (n=602)	Gemcitabine (G) plus bevacizumab (B) vs. gemcitabine plus placebo (P)	Median OS: 5.7 vs. 6.0 months Median failure-free survival: 4.8 vs. 4.3 months	Double-blind placebo-controlled trial Phase III trial Interim analysis	RCT (abstract)	NA
Philip PA 2007	[182]	NA	Patients with locally advanced or metastatic pancreatic adenocarcinoma (n=766)	Gemcitabine (G) plus cetuximab (C) versus gemcitabine alone	Median survival: 6 (G) vs. 6.5 months (G+C) (HR 1.09, 95%CI 0.93-1.27, p=0.14). Median progression-free survival: 3 vs. 3.5 months (HR 1.13, 95%CI .97-1.3, p=0.058).	Phase III trial	RCT (abstract)	NA
Astsaturov IA 2007	[199]	NA	Patients with previously treated metastatic pancreatic cancer (n=30)	Bevacizumab alone vs. bevacizumab plus docetaxel	Median PFS: 43 vs. 45 days (p=0.5) Median OS: 181 vs. 123 days (p=0.8)	Phase II trial	RCT (abstract)	NA
Andre T 2007	[196]	NA	Patients with metastatic pancreatic cancer (n=57)	First-line simplified GEMOX (D1-D1) vs. classical GEMOX (D1-D2)	Median PFS: 4.0 vs. 2.5 months. Median OS: 7.6 and 3.2 months.	Phase II trial	RCT (abstract)	NA

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
Reni M 2007	[195]	NA	Patients with advanced pancreatic adenocarcinoma (n=64)	PEXG (cisplatin, epirubicin, capecitabine, gemcitabine) or PDXG (docetaxel)	Partial response: 62% vs. 48%. PFS at 6 months: 54% vs. 44%	Phase II trial Interim analysis	RCT (abstract)	NA
Wright JA 2006	[185]	NA	Chemotherapy-naïve patients with advanced pancreatic cancer (n=434)	Virulizin plus gemcitabine vs. gemcitabine alone	Median overall survival: 6.3 vs. 6 months (NS)	Phase III trial Subgroup analysis	RCT (abstract)	NA
Kindler HL 2006 & 2008	[201, 202]	NA	Patients with advanced pancreatic cancer (n=139)	Bevacizumab (B) and gemcitabine (G) plus cetuximab (C) or erlotinib (E)	Median overall survival: 7.8 vs. 7.2 months Median progression-free survival: 5.0 vs. 5.1 months	Phase II trial	RCT (abstract)	NA
Cheverton P 2004	[194]	NA	Chemotherapy-naive patients with advanced pancreatic cancer (n=339)	Exatecan (DX-8951f) vs. gemcitabine (Gem)	Median survival: 151 vs. 197 days 6-month survival: 44.1% vs. 51.1% 12-month survival: 17.9% vs. 22.1%	Phase III trial	RCT (abstract)	NA
Kulke 2004	[193]	NA	Patients with metastatic pancreatic cancer (n=251)	Gemcitabine/cisplatin vs. gemcitabine fixed dose rate infusion vs. gemcitabine/docetaxel vs. gemcitabine/irinotecan	Neutropenia : 51% vs. 47% vs. 26% vs. 15% Thrombocytopenia: 45% vs. 19% vs. 7% vs. 17%	Phase II trial Interim analysis	RCT (abstract)	NA
Ebert 2004	[200]	NA	Patients with advanced pancreatic cancer (n=24)	Gemcitabine vs. imatinib	Median survival: 12 vs. 11.2 weeks (NS) Quality of life was similar in both treatment groups.		RCT (abstract)	NA
Chemoradiotherapy								
Sultana A 2007b	[205]	?	Patients with locally advanced pancreatic cancer	Chemoradiation followed by chemotherapy (combined modality therapy) vs. best supportive care	Survival (1 trial, 31 patients): HR 0.28, 95%CI 0.13–0.60, in favour of CRT followed by CT	Good-quality SR, but no search date provided 1 RCT included	SR	Moderate
				Radiotherapy vs. chemoradiation	Overall survival (two trials, 168 patients): HR 0.69, 95%CI 0.51–0.94, in favour of CRT. No heterogeneity.	2 RCTs included		High
				Radiotherapy vs. combined modality therapy	Survival (1 trial, 56 patients): HR 0.50, 95%CI 0.29–0.84, in favour of CRT followed by CT Time to progression: HR 0.51, 95%CI 0.32–0.81, in favour of CRT followed by CT	1 RCT included		Moderate
				Chemotherapy vs. combined modality therapy	Overall survival (2 trials, 134 patients): HR 0.79, 95%CI 0.32–1.95, in favour of CRT followed by CT. Significant heterogeneity between the two trials analysed.	4 RCTs included		Moderate

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
				5FU-based combined modality treatment vs. another-agent-based combined modality therapy	Only 1 RCT found significantly improved overall survival (14.5 vs. 6.7 months), time to progression (7.1 vs. 2.7 months) and response rate (50 vs. 13%) in patients treated with gemcitabine-based CRT followed by gemcitabine compared to 5FU-based CRT followed by gemcitabine	3 RCTs included (256 patients), no meta-analysis done		Moderate
Yip D 2006	[168]	Jan 2005	Patients with inoperable advanced pancreatic cancer	Same as Sultana A 2007b	10 RCTs included No meta-analysis performed, only qualitative overview	Good-quality SR	SR	Moderate
Loehrer PJ 2008	[208]	NA	Patients with localized, unresectable non-metastatic pancreatic cancer (n = 71)	Gemcitabine alone vs. gemcitabine-based CRT	Median survival: 9.2 vs. 11.0 months (p = 0.044) Grade 4 toxicity: 5.7% vs. 41.2% (p<0.0001) Progression-free-survival: 6.1 vs. 6.3 months (p = 0.34)		RCT (abstract)	NA
Brasiuniene B 2007	[159]	NA	Patients with unresectable pancreatic cancer, stage III-IVA (n = 19)	5-FU-based CRT (n = 10) vs. gemcitabine-based CRT (n = 9)	Median survival: 9.5 vs. 9.1 months (p = 0.79) Progression-free-survival: 8.6 vs. 5.6 months (p = 0.80)	Methodological flaws (sealed envelopes for randomisation; no information on blinding of patients or assessors; no information on ITT analysis; comparable groups?)	RCT	Low
Radiotherapy								
Sultana A 2007b	[205]	?	Patients with locally advanced pancreatic cancer	Radiotherapy vs. chemoradiation	Overall survival (two trials, 168 patients): HR 0.69, 95%CI 0.51–0.94, in favour of CRT. No heterogeneity.	Good-quality SR, but no search date provided 2 RCTs included	SR	High
				Radiotherapy vs. combined modality therapy	Survival (1 trial, 56 patients): HR 0.50, 95%CI 0.29–0.84, in favour of CRT followed by CT Time to progression: HR 0.51, 95%CI 0.32–0.81, in favour of CRT followed by CT	1 RCT included		Moderate
Yip D 2006	[168]	Jan 2005	Patients with inoperable advanced pancreatic cancer	Same as Sultana A 2007b	3 RCTs included No meta-analysis performed, only qualitative overview	Good-quality SR	SR	Moderate

Palliative surgery

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
Moss AC 2007	[215]	June 2006	Patients with obstructive jaundice due to malignant distal biliary obstruction	Surgical bypass vs. endoscopic stents (plastic)	Risk of complications: RR 0.60, 95%CI 0.45–0.81 in favour of plastic stents Risk of recurrent biliary obstruction: RR 18.59, 95%CI 5.33 –64.86 in favour of traditional surgical bypass No difference in rates of technical success (RR 1.01, 95%CI 0.95-1.07) and therapeutic success (RR 1.00, 95%CI 0.93-1.08)	Good-quality SR 3 RCTs identified	SR	High
Hammarstrom L 2005	[217]	April 2004	Patients with malignant biliary obstruction	Surgical bypass vs. endoscopic stents (plastic)	The outcome of endoscopic and percutaneous drainage was similar, but data were few and inconsistent. Due to fewer late complications, surgical bypass is an alternative to metal stents (Wallstent™) which remain patent longer than plastic stents (large-bore polyethylene), with an overall median of 180 and 109 days, respectively, in patients who survive longer than about 6 months, which cannot be accurately predicted though.	3 RCTs identified No meta-analysis	SR	Moderate
Taylor MC 2000	[218]	May 1999	Patients with malignant obstructive jaundice	Surgical bypass vs. endoscopic stents (plastic)	More treatment sessions were required after stent placement than after surgery, and a common OR was estimated to be 7.23 (95%CI 3.73-13.98). Thirty-day mortality was not significantly different (OR 0.522; 95%CI, 0.263-1.036).	3 RCTs identified Medline only English only	SR	High
Artifon EL 2006	[219]	NA	Patients with metastatic pancreatic cancer and obstructive jaundice	Surgical bypass (n = 15) vs. covered self-expandable metal stent (n = 15)	The cost of biliary drainage procedure (US$ 2832 ± 519 vs. 3821 ± 1181, p = 0.031), the cost of care during the first 30 days after drainage (US$ 3122 ± 877 vs. 6591 ± 711, p = 0.001), and the overall total cost of care that included initial care and subsequent interventions and hospitalizations until death (US$ 4271± 2411 vs. 8321 ± 1821, p = 0.0013) were lower in the endoscopy group compared with the surgical group. In addition, the quality of life scores	No information on randomisation procedure or blinding	RCT	Moderate

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
					were better in the endoscopy group at 30 days (p = 0.042) and 60 days (p = 0.05).			
Date RS 2005	[221]	Dec 2003	Patients with non-resectable peri-ampullary cancer	Laparoscopic biliary bypass	Current evidence does not justify the incorporation of laparoscopic biliary bypass techniques into contemporary evidence-based management algorithms for patients with non-resectable periampullary cancer.	Medline only No information on quality appraisal Only observational studies	SR	Low
Navarra GC 2006	[222]	NA	Patients with gastric outlet obstruction resulting from inoperable neoplasms (n = 24, of which 11 with pancreatic cancer)	Open vs. laparoscopic palliative antecolic isoperistaltic gastrojejunostomy	Mean duration of surgery: 145 vs. 150 min (p = 0.75) Mean intraoperative blood loss: 170 vs. 38 ml (p = 0.0001), in favour of laparoscopic approach. Mean postoperative stay: 12 vs. 11 days (p = 0.65).	No information on blinding	RCT	Moderate
Van Heek NT 2003	[223]	NA	Patients with unresectable periampullary cancer (n = 70, of which 57 with pancreatic head cancer)	Double (hepaticojejunostomy + retrocolic gastrojejunostomy) vs. single bypass (hepaticojejunostomy)	Postoperative morbidity rates, including delayed gastric emptying, were 31% in the double vs. 28% in the single bypass group (p=0.12). Median postoperative length of stay was 11 days (range 4–76 days) in the double vs. 9 days (range 6–20 days) in the single bypass group (p=0.06); median survival was 7.2 months in the double vs. 8.4 months in the single bypass group (p=0.15). No differences were found in the quality of life between both groups.	No information on blinding 5 patients lost to follow-up	RCT	Moderate
Nieveen van Dijkum EJ 2003	[220]	NA	Patients with biopsy-proven unresectable peripancreatic tumour, identified by diagnostic laparoscopy (n = 27)	Surgical (retrocolic gastroentero-stomy and Roux-en-Y side-to-side hepaticojejunostomy + celiac plexus block) vs. endoscopic palliation (Wallstent)	Average survival: 192 vs. 116 days Hospital-free survival: 164 vs. 94 days	No information on blinding	RCT	Moderate
Yilmaz S 2001	[224]	NA	Patients with unresectable cancer of the pancreatic head without duodenal obstruction (n = 44)	Antecolic, isoperistaltic gastrojejunostomy, jejunojejunostomy, and hepaticojejunostomy after cholecystectomy vs. hepaticojejunostomy and antecolic, antiperistaltic	No significant differences between the groups in the incidence of postoperative complications, time until restoration of oral diet, relaparotomy rate, late upper gastrointestinal bleeding, mortality, duration of hospital stay, and survival. The isoperistaltic operation took signifi	No information on blinding	RCT	Moderate

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
				gastrojejunostomy procedure after cholecystectomy	cantly longer than the antiperistaltic operation ($p < 0.001$) and there was less delayed gastric emptying in the antiperistaltic group but not significantly so. Both operations caused a significant lengthening in the postoperative gastric emptying time ($p = 0.04$ and $p = 0.01$, respectively).			
Shyr YM 1997	[225]	NA	Patients with unresectable periampullary cancer complicated by gastric outlet obstruction (n = 45)	Type I gastrojejunostomy: performed at the jejunum 20 cm distal to the ligament of Treitz. Type II: similar to type I except that in type II a duodenum partition was done by linear stapler 1 cm beyond the pylorus. Type III gastrojejunostomy: performed at the Roux-limb jejunum 60 cm distal to biliojejunostomy.	When patients were evaluated immediately after oral diet intake resumed, the incidence (27%) of clinical GOO symptoms and mean value of gastric emptying time (GET1/2, 118.1 +/- 39.2 min) were significantly lower in type II patients than in types I and III patients. When evaluated 1 month after operation, the incidence (7% and 17%, respectively of clinical symptoms of GOO and 'mean value of GET1/2 (42.0 +/- 23.0 and 35.6 +/- 5.4 min respectively) were significantly lower in both type II and type III patients than in type I patients. The type II patients resumed oral diet after operation 3.5 days earlier than. Type I patients, $p < 0.05$.	No information on blinding	RCT	Moderate

Endoscopic treatment

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
Moss AC 2007	[215]	June 2006	Patients with obstructive jaundice due to malignant distal biliary obstruction	Surgical bypass vs. endoscopic stents (plastic)	Risk of complications: RR 0.60, 95%CI 0.45–0.81 in favour of plastic stents Risk of recurrent biliary obstruction: RR 18.59, 95%CI 5.33 –64.86 in favour of traditional surgical bypass No difference in rates of technical success (RR 1.01, 95%CI 0.95-1.07) and therapeutic success (RR 1.00, 95%CI 0.93-1.08)	3 RCTs identified	SR	High
				Self-expanding metal stents vs. plastic stents	Risk of recurrent biliary obstruction: - at 4 months: RR 0.44, 95%CI 0.3-0.63 - prior to death or end of study: RR 0.52, 95%CI 0.39–0.69 both in favour of SEMS. No difference in terms of technical success, therapeutic success, mortality or complications. Heterogeneity between the included studies.	7 RCTs identified		Moderate
				Plastic stents	No statistical difference between Tannenbaum Teflon and polyethylene stents with regard to technical success (RR 0.99, 95%CI 0.96-1.03), 30-day mortality (RR 1.27, 95%CI 0.77-2.11) or recurrent biliary obstruction prior to death (RR 0.99, 95%CI 0.78-1.24) (5 studies).	12 RCTs identified		High
Moss AC 2006	[216]	Dec 2005	Patients with pancreatic carcinoma deemed unsuitable for curative resection	Biliary bypass surgery (choledochoduodenostomy, choledochojejunostomy or hepapticojejunostomy) Endoscopic metal stents of different materials and construction Endoscopic plastic stents of different materials and construction	Based on meta-analysis, endoscopic stenting with plastic stents appears to be associated with a reduced risk of complications (RR 0.60, 95%CI 0.45-0.81), but with higher risk of recurrent biliary obstruction prior to death (RR 18.59, 95%CI 5.33-64.86) when compared with surgery. There was a trend towards higher 30-day mortality in the surgical group (p=0.07, RR 0.58, 95%CI 0.32-1.04). There was no evidence of a difference in technical or	21 RCTs identified Good-quality SR, updated in Moss 2007	SR	High

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
					therapeutic success. Other outcomes were not suitable for meta-analysis. No trials comparing endoscopic metal stents to surgery were identified. In endoscopic stent comparisons, metal biliary stents appear to have a lower risk of recurrent biliary obstruction than plastic stents (RR 0.52, 95%CI 0.39 - 0.69). There was no significant statistical difference in technical success, therapeutic success, complications or 30-day mortality using meta-analysis. A narrative review of studies of the cost-effectiveness of metal stents drew conflicting conclusions, but results may be dependent on the patients' length of survival. Neither Teflon, hydrourethane, or hydrophilic coating appear to improve the patency of plastic stents above polyethylene in the trials reviewed. Only perflouro alkoxy plastic stents had superior outcome to polyethylene stents in one trial. The single eligible trial comparing types of metal stents reported higher patency with covered stents, but also a higher risk of complications. These results are based on review of the trials individual results only.			
Hammarstrom L 2005	[217]	April 2004	Patients with malignant biliary obstruction	Surgical bypass vs. endoscopic stents (plastic)	The outcome of endoscopic and percutaneous drainage was similar, but data were few and inconsistent. Due to fewer late complications, surgical bypass is an alternative to metal stents (Wallstent™) which remain patent longer than plastic stents (large-bore polyethylene), with an overall median of 180 and 109 days, respectively, in patients who survive longer than about 6 months, which cannot be accurately	3 RCTs identified No meta-analysis	SR	Moderate

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
					predicted though.			
Taylor MC 2000	[218]	May 1999	Patients with malignant obstructive jaundice	Surgical bypass vs. endoscopic stents (plastic)	More treatment sessions were required after stent placement than after surgery, and a common OR was estimated to be 7.23 (95%CI 3.73-13.98). Thirty-day mortality was not significantly different (OR 0.522; 95%CI, 0.263-1.036).	3 RCTs identified Medline only English only	SR	High
Katsinelos 2006	[226]	NA	Patients with inoperable malignant distal common bile duct strictures (n = 47)	Tannenbaum stent (n = 24) Vs. uncovered self-expandable metal stent (n = 23)	The median first stent patency was longer in the metal group than in the Tannenbaum stent group (255 vs. 123.5 days; p = 0.002). There was no significant difference in survival between the two groups. The total cost associated with the Tannenbaum stents was lower than for the metal stents (17700 vs. 30100 euros; p = 0.001), especially for patients with liver metastases (3000 vs. 6900 euros; p < 0.001).	No information on blinding	RCT	Moderate
Soderlund 2006	[227]	NA	Patients with unresectable malignant common bile duct strictures (n = 100)	Plastic stents vs. covered SEMS	Median survival: 5.3 vs. 3.9 months in the SEMS and PE groups, respectively (p=0.28). Median patency time: 3.6 vs. 1.8 months (p=0.002). In the PE group, the extra cost for failure was €17410 for the stents, €31200 for hospitalization and ERC procedures, for a total of €48610. The cost of the initial SEMS for the SEMS group was €46060, more than for the plastic EPs.	2 protocol violations	RCT	High

SUPPORTIVE TREATMENT

Nutrition

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
Nutritional support for inoperable patients with advanced cancers								
Bauer J 2005	[256]	NA	200 patients with unresectable adenocarcinoma of the pancreas	Enteral administration of 2 cans/day of: - either a protein and energy dense, n-3 fatty acid (1.1 g EPA) oral nutritional supplement (n = 95) - either an isocaloric, isonitrogenous control supplement without n-3 fatty acids (n = 105). 1 can = 310 kcal and 16g protein Dietary intake : 8 weeks Comparison between compliant and non compliant patients. Compliance = min. 1.5 cans of either oral nutrition supplement /day over a 4-week period (465 kcal and 24 g protein)	Significant differences in **total energy intake** by 501 (SEM±80) kcal/day (Wald F_1 = 39.1, p<0.0001) and **total protein intake** by 25.4 (SEM±3.5) g/day (Wald F_1 = 53.0, p<0.0001) between patients compliant with the nutrition prescription compared to noncompliant patients. No significant difference in the **mean energy intake from meals** of the total group at baseline, week 4 and 8 which was 1513 (SEM±43), 1440 (SEM±48) and 1441 (SEM±49) kcal/day, respectively (Wald F_2 = 0.96, p = 0.38). On average, significant difference in **body weight** by a mean of 1.7 (SEM±0.4) kg (Wald F_1 = 19.1, P<0.0001) in compliant group relative to the noncompliant group. Over the 8-week period, (p = 0.052) - compliant patients : + 0.5 kg - noncompliant patients : - 0.7 kg No significant difference in **Lean body mass** (p=0.56) and in QOL measured by EORTC QLQC30 **Global Quality of Life** Score (p=0.075)	Assessment of dietary intake was made over 3 days 1X/month + other verifications Post-hoc analysis	International Multi-centre RCT Same study than Fearon KCH (2003) and Davidson W (2004)	Moderate
Moses AWG 2004	[257]	NA	24 patients with unresectable pancreatic cancer	Enteral administration of 2 cans/day of: - either a n-3 fatty acid (1.1 g EPA) oral nutritional supplement (n = 9) - an isocaloric, isonitrogenous	Outcomes : total **energy expenditure** (TEE), resting energy expenditure (REE) and physical activity level (PAL= TEE/REE=1.5 for healthy adults), weight, lean body mass	Lost to follow-up : 2 in the EPA group, 3 in the control group Very small sample size Imbalance in group sizes	International Multi-centre RCT	Moderate

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
				control supplement without n-3 fatty acids (n = 15). 1 can = 310 kcal, 16g protein, 6g fat, with or without 1.1g EPA Dietary intake : 8 weeks	After 8 weeks, the REE, TEE and PAL (in kcal/day^{-1}) of patients who received the control supplement did not change significantly: -15 (SEM 25), 99 (SEM 132), and 0.01 (SEM 0.1) respectively (p>0.05) In contrast, although REE did not change (-1; SEM 42; p>0.05), TEE (286; SEM 79) and PAL (0.18; SEM 0.05) increased significantly in those who received the n-3 (EPA) enriched supplement (p<0.05). No statistically significant differences between groups. No significant changes in weight or LBM in either group over the 8-week period.			
Davidson W 2004	[254]	NA	200 patients with unresectable adenocarcinoma of the pancreas	Enteral administration of 2 cans/day of: - either a protein and energy dense, n-3 fatty acid (1.1 g EPA) oral nutritional supplement (n = 95) - either an isocaloric, isonitrogenous control supplement without n-3 fatty acids (n = 105). 1 can = 310 kcal and 16g protein Dietary intake : 8 weeks	At Week 8, patients with weight stabilisation : - **survived** longer from baseline : median survival was 259 days (95% CI: 229–289 days) compared to 164 days (95% CI: 97–231 days) (log rank test 5.53, p= 0.019). - reported higher **QoL** scores : 55.0±19.5 vs 47.1±17.4 (p= 0.037) - reported a greater mean **energy intake** (P<0.001) than those who continued to lose weight. The absence of nausea and vomiting (OR 6.5, p= 0.010) and female gender (OR 5.2, p= 0.020) were independent determinants of weight stabilisation.	Post-hoc analysis (n=107)	International Multi-centre RCT	Moderate
Fearon KCH 2003	[255]	NA	200 patients with unresectable adenocarcinoma of the pancreas	Enteral administration of 2 cans/day of: - either a protein and energy dense, n-3 fatty acid (1.1 g EPA) oral nutritional supplement (E group, n = 95)	Intake of the supplements averaged 1.4 cans/day in both groups. Over 8 weeks, patients stopped losing **weight** (☐weight E: 20.25 kg/month vs C: 20.37 kg/month; p = 0.74) and **LBM**	Loss of 90 patients (45 patients in each group) Compliance was low in both groups.	International Multi-centre RCT	High

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
				- either an isocaloric, isonitrogenous control supplement without n-3 fatty acids (C group, n = 105). 1 can = 310 kcal, 16g protein and 6g fat with or without 1.1g EPA Dietary intake : 8 weeks	(☐LBM E: +0.27 kg/month vs C: +0.12 kg/month; p = 0.88) (change from baseline E and C, p<0.001). E patients demonstrated significant correlations between their supplement intake and weight gain (r = 0.50, p<0.001) and increase in LBM (r = 0.33, p = 0.036). Such correlations were not statistically significant in C patients. Increased **plasma EPA levels** in the E group were associated with weight and LBM gain (r = 0.50, p<0.001; r = 0.51, p = 0.001). Weight gain was associated with improved **QoL** measured by $EQ5D_{index}$(p<0.01) in the E group. Median duration of survival from study enrolment for all patients was 130 days and there was no significant difference between the treatment groups (E: 142 (6–587) days; C: 128 (8–626) days (median (range)).			
Peri-operative nutritional supplementation								
Goonetilleke KS 2006	[228]	November 2004	(1) Studies of patients undergoing pancreaticoduodenectomy for suspected malignancy and (2) studies of patients with upper gastrointestinal cancer that included some patients undergoing pancreaticoduodenectomy Ten studies (n=1 264) were included: 8 RCTs (n=1022), 1 observational study (n=62) and 1 retrospective study	Nutritional supplementation of total parenteral nutrition (TPN), enteral nutrition (EN) and immune-enhanced enteral nutrition (I-EN) with each other or no initial post-operative nutritional support; one study compared cyclical versus non-cyclical EN.	(1) ***TPN*** was associated with a higher **mortality** (based on two RCTs): the increase was not statistically significant in one study (6.7% versus 1.8% in the control group) and statistical significance was not reported in the other (5.9% versus 1.4% for EN and 2.8% for I-EN). TPN was associated with significantly higher **overall morbidity** compared with no nutritional support (45% versus 22.8%, p=0.02) in one RCT and with EN and I-EN (58.8% versus 43.5% and 33.8%, p=0.005) in	Search in MEDLINE (1994 to November 2004) and EMBASE (1974 to 2004); Many review's limitations (search, reporting, methods, validity assessment); Part of the conclusion was based on one small RCT of unknown quality The authors' conclusion may not be reliable.	SR	Low

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
			(n=180).		another RCT. TPN was associated with a longer **hospital stay** compared with no TPN (mean stay 16 versus 14 days; one RCT) and EN or I-EN (18.8 versus 17.0 or 15.1 mean days, p<0.02; one RCT). ***EN*** was associated with an increased rate of **overall morbidity** compared with no nutritional supplementation in one observational study (43.3% versus 28.1%, p not reported), but was associated with a lower morbidity rate in one retrospective study (65.3% versus 92.7%, p not reported). EN was associated with a shorter duration of **hospital stay** (13.9 versus 14.8 mean days, statistical significance not reported) compared with the control. (2) None of the studies reported outcome data separately for different types of surgery. ***Cyclical EN*** was associated with significantly fewer mean days to **resumption of normal diet** (12.2 versus 15.7, p=0.04) compared with continuous EN (one RCT, n=57), but there was no significant difference between treatments in the number of days of nasogastric intubation (p=0.82).			
Preoperative enteral immunonutrition								
Giger U 2007	[229]		46 candidates for major elective surgery for cancers of - the stomach (n = 12), - the pancreas (n = 30) or	Triple-arm study using oral administration: 1) 1 L/day of an immunoenriched formula (Impact) for 5 days preoperative (IEF group, n =	**Preoperative and postoperative tolerance** of the liquid diet formulas was excellent (no adverse gastrointestinal effect in preoperative; diarrhoea and/or abdominal bloating was	1 patient in the IEF group died in postoperative day 7 due to cardiac arrest	Randomized controlled pilot study (not blind)	Moderate

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
			- periampullary (n = 4)	14) ; 2) 1 L/day of Impact plus (Impact enriched with glycine) for 2 days preoperative (IEF plus group, n = 17). 3) no preoperative treatment in the control group (CON group, n = 15), patients only received Impact for 7 days postoperatively; Patients belonging to both IEF and IEF Plus groups received the same product as they received preoperatively, for 7 days postoperatively by jejunostomy. Nutritional goal : 25 kcal/kg/day	reported in postoperative by some patients). **Inflammatory response :** In the two treatment groups, perioperative endotoxin levels, CRP(postoperative day 7), and TNF-□ (postoperative days 1 and 3) levels were significantly lower compared to the CON group ($p < .01$). The **length of postoperative IMU/ICU stay** (Impact 1.9 ± 1.3 days; Impact plus 2.2 ± 1.1 days; control group 5.9 ± 0.8 days) and **length of hospital stay** (Impact 19.7 ± 2.3 days; Impact plus 20.1 ± 1.3 days; control group 29.1 ± 3.6 days) were both reduced in the treatment groups compared to the control group ($p < 0.05$). **Infectious complications** (Impact 2/14 (14%); Impact plus 5/17 (29%); control group 10/15 (67%)) showed a trend toward reduction in the treatment groups ($p > 0.05$).			
Postoperative enteral nutrition								
Klek S 2008	[236]		196 patients undergoing subtotal and total gastric resection with lymphadenectomy and pancreatoduodenectomy/total pancreatectomy with lymphadenectomy This large sample included 69 patients undergoing pancreatoduodenectomy or total pancreatectomy	Jejunostomy feeding with a Standard Enteral Nutrition Group (SEN Group, n = 96, n analyzed = 91) or an Immunostimulating Enteral Nutrition (IMEN Group, n = 96, n analyzed = 92) for 7 days SEN Group, n = 35 IMEN Group, n = 34 Enteral feeding was commenced 6h after operation using 5%	There were no significant differences between the two groups as far as the volume of tube feeding delivered was considered. Median postoperative **hospital stay** was 12.4 days (SD 5.9) in SEN and 12.9 days (SD 8.0) in IMEN group ($p= 0.42$). **Complications** were observed in 21 patients (23.1%) in SEN and 23 (25.2%) in IMEN group ($p > 0.05$). **Infectious complications** occurred in 23 patients in SEN group and 21 in IMEN group ($p >$	13 excluded from analysis (4 refused consent, 5 unresectable disease, 4 protocol violation)	RCT	High

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
				glucose solutions, followed by infusion of Peptisorb (SEN group, Nutricia Ltd., Poland) or Reconvan (IMEN group, Fresenius Kabi, Poland) until 7th day.	0.05). Four (4.4%) patients in SEN group and 4 (4.4%) in IMEN had **surgical complications** (p > 0.05). There were no differences in **liver and kidney function, visceral protein turnover** and **treatment tolerance**.			
Lobo DN 2006	[237]		A total of 120 patients undergoing resection for cancers of the pancreas, oesophagus and stomach 108 patients were analyzed after their intervention on following sites : oesophagus (n = 64), stomach (n = 29) and pancreas (n = 15)	Jejunostomy feeding with an immune modulating diet (Stresson, Group A) or an isonitrogenous, isocaloric feed (Nutrison High Protein, Group B) for 10–15 days.	**Feed delivery**, although less than targeted, was similar in both groups. There were 6 (11%) **deaths** in each group. Median (IQR) postoperative **hospital stay** was 14.5 (12–23) days in Group A and 17.5 (13–23) days in Group B (p = 0.48). A total of 24 (44%) patients in each group had **infective complications** (p = 1.0). A total of 21 (39%) patients in Group A and 28 (52%) in Group B had **non-infective complications** (p = 0.18). Jejunostomy-related complications occurred in 26 (48%) patients in Group A and 30 (56%) in Group B (p = 0.3). Early postoperative feeding with an immune modulating diet conferred no outcome advantage when compared with a standard feed.	12 patients were excluded from the analysis (3 protocol violations and 9 unresectable diseases)	RCT	High
Postoperative parenteral nutrition								
Jo S 2006	[238]		143 patients admitted to undergo operations for alleged or suspected periampullary tumors : classical pancreaticoduodenectomy (PD) or pylorus-preserving PD (PPPD)	Parenteral nutrition with Glamin (Glutamine supplementation containing 2.0g/100 ml of Glm, Gln Group, n = 32) or a isonitrogenous amino acid solution (1.3 g/kg per day amino acid, Control Group, n = 28) for 7 days	The **time to soft diet** was 12.9 days (SD 10.5) in Gln group and 11.5 days (SD 7.4) in Control group (p= 0.56). Median postoperative **hospital stay** was 14.0 days (9-54) in Gln group and 14.5 days (9-41) in Control group (p= 0.20).	83 patients were excluded: 44 for preoperative criteria, 33 for operative exclusions and 6 for pathologic exclusion criteria Low-dose regimen of Glutamine (0.2g/kg/day)	RCT	Moderate

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
			60 patients enrolled and analyzed	Total parenteral nutrition (30 kcal/kg/day with 1.3 g/kg/day amino acid)	The **overall and PD-related complication** rates of the Gln group (37.5% and 25.0%) and the control group (28.6% and 14.3%) were not statistically different (p = 0.46 and p = 0.30). **No significant beneficial effect** of Gln supplementation with a low-dose parenteral regimen was demonstrated on the surgical outcome after a PD for periampullary tumors	whereas higher doses are recommended for critical illness (>0.2-0.3 g/kg/day or ≥ 30 g/day) (see Kelly and Wischmeyer, 2003; Dejong, 2006) A power calculation had shown that 67 patients had to be enrolled in each treatment arm. But the trial had to be stopped for practical reasons when only sixty patients had been enrolled, of which 32 in the glutamine group and 28 controls		
Heller AR 2004	[239]		44 patients undergoing elective major abdominal surgery : oesophagectomy (n=7), gastrectomy (n=18), whipple procedure (n=18), total colectomy (n=1)	TPN supplemented with either soybean oil (SO 1.0 g/kg body weight daily, n= 20) for 5 days or a combination of Omega-3 PUFAs in fish oil (FO) and SO (FO 0.2 + SO 0.8 g/kg body weight daily, n=24).	No statistical difference in either **length of ICU stay** or **length of hospital stay** (SO 18.8 ± 8.4 days, SO+FO 19.1 ± 9.6 days), except for the subsample 'gastrectomy + Whipple' (–1.3 ± 0.5 days, p= 0.02). FO significantly reduced aspartate aminotransferase **ASAT** [0.8 ± 0.1 *vs.* 0.5 ± 0.1 mmol/(l . sec)], alanine aminotransferase **ALAT** [0.9 ± 0.1 *vs.* 0.6 ± 0.1 mmol/(l . sec)], **bilirubin** (16.1 ± 5.3 *vs.* 6.9 ± 0.6 mmol/l), **LDH** (7.7 ± 0.4 *vs.* 6.7 ± 0.4 mmol/(l . sec) and **lipase** (0.6 ± 0.1 *vs.* 0.4 ± 0.1_mol/(l. sec). **Weight loss** as encountered after the SO emulsion of 1.1 ± 2.2 kg was absent in the FO group (not statistically significant). Follow-up data at 18 months did not		RCT	High

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
					show any difference in **quality of life**, **health status** or **mortality** between the groups.			
Postoperative parenteral vs enteral nutrition								
Braga M 2001	[231]		257 patients with cancer of the stomach (n=121), pancreas (n=110), or oesophagus (n=26)	- total parenteral nutrition (TPN group, n=131) - early enteral nutrition through jejunostomy (EEN group, n=126). Nutritional goal: 25 kcal/kg/day. The two nutritional formulas were isocaloric and isonitrogenous; they were continued until oral intake was at least 800 kcal/day	**Nutritional goal** reached in 100/126 (79.3%) patients in the EEN group and in 128/131 (97.7%) patients in the TPN group (p < .001). Mean **duration of artificial nutrition** was 13.2 +/-4.9 days in the TPN group and 12.8 +/-5.5 days in the EEN group. No significant difference in nutritional, immunologic, and inflammatory variables between the two groups. The **overall complication** rate was similar (40.4% for TPN vs. 35.7%, for EEN; p= .52). No difference was detected for either infectious or noninfectious complications, **length of hospital stay, and mortality**. In the EEN group, **hyperglycemia** (serum glucose, >200 mg/dL) was observed in 4.7% of the patients vs. 9.1% in the TPN group (p = NS). Alteration of **serum electrolyte levels** was 3.9% in the EEN group vs. 13.7% in the TPN group (p < .01). From PO day 5, **intestinal oxygen tension** recovered faster in the EEN group than in the TPN group (43 ± 5 mm Hg vs. 31 ± 4 mm Hg at day 7; p < .001). EEN was four-fold less expensive than TPN ($25 vs. $90.60/day,		RCT	High

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
					respectively).			
Di Carlo V 1999	[233]		101 patients undergoing pancreaticoduodenectomy for adenocarcinoma of the pancreatic head	- standard enteral formula (SEN group, n=35) - enteral diet supplemented with arginine, omega-3 fatty acids, and RNA (IEN group, n=33) - total parenteral nutrition (TPN, n=32) The two nutritional formulas were isocaloric and isonitrogenous; they were continued until oral intake was at least 800 kcal/day + octreotide (0.1 mg) : 1 dose 1h before surgery and 3 doses/day until the 1st day of oral diet resumption	**Nutritional goal** reached in 84% of enterally fed patients and in 96% of patients in the TPN group (p = NS). Mean **duration of artificial nutrition** was 12.2 +/-4.6 days in the TPN group, 11.8 +/-4.2 days in the SEN group and 9.3 +/-3.6 days in the IEN group Rate of **postoperative complications**: IEN group (33%) < SEN group (40%) < TPN group (59%) (p<0.005 Severity of **infectious complications** (sepsis score): IEN (5.5) < SEN (7.9) < TPN (10.4) (p<0.05) **Length of stay**: IEN (16.3 days) < SEN (17.8) < TPN (19.3) (p<0.05)	Randomization process not explained	RCT	Moderate
Braga M 1998	[232]		166 consecutive patients undergoing curative surgery for gastric (n = 92) or pancreatic cancer (n = 74)	At operation, the patients were randomized into three groups to receive: a) a standard enteral formula through jejunostomy (control group; n = 55); b) the same enteral formula enriched with arginine, RNA, and omega-3 fatty acids through jejunostomy (enriched group; n = 55); c) total parenteral nutrition (TPN group; n = 56). The three regimens were isocaloric and isonitrogenous.	Early enteral infusion was well tolerated. **Side effects** were recorded in 22.7% of the patients, but only 6.3% did not reach the nutritional goal. Control group had a similar rate of **postoperative infections** compared with the group receiving TPN (23.6% vs. 28.5%). The **length of postoperative stay** (LOS) was 13.7 ± 4.8 days in the enriched group, 16.1 ± 5.9 days in the control group, and 17.5 ± 6.1 days in the TPN group (p = 0.09, enriched vs. TPN	Randomisation process not explained; no ITT analysis. Lack of sub-groups analysis.	RCT	Moderate

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
				Enteral nutrition was started within 12 hrs following surgery. Nutritional goal (25 kcal/kg/day) on postoperative day 4.	group).			
Gianotti L 1997	[234]		260 consecutive patients undergoing curative surgery for gastric (n = 120) or pancreatic cancer (n = 140)	At operation, the patients were randomized into three groups to receive: a) a standard enteral formula through jejunostomy (standard group; n = 87); b) the same enteral formula enriched with arginine, RNA, and omega-3 fatty acids through jejunostomy (immunonutrition group; n = 87); c) total parenteral nutrition (TPN group; n = 86). During 7 days Nutritional goal (105 kj/kg/day)	- Recovery of **immune parameters**: significant correlation between Interleukine 6 and preambulin levels (r=-0.77; p=0.02) only in the immunonutrition group. - Post-operative **infection rates** were 14.9% in the immunonutrition group, 22.9% in the standard group and 27.9% in the TPN group (p=0.06) - Mean± SD length of **hospital stay** was 16.1±6.2, 19.2±7.9, 21.6±8.9 days in the immunonutrition group, in the standard group and in the TPN group, respectively (p=0.01 vs standard group; p=0.004 vs TPN group)	- Enteral groups received calories and nitrogen by parenteral route until Day 3 - Randomisation process not explained; no ITT analysis. - Lack of sub-groups analysis.	RCT	Moderate-low
Fish J 1997	[235]		20 patients requiring gastric or pancreatic surgery for malignancy	Pre-operatively, patients were randomized to receive: - Glutamine enriched enteral feeding through jejunostomy (Vivonex Plus) - Parenteral feeding for 10 days Tube-feeding and total parenteral nutrition (TPN) formulas were closely matched for energy, protein, nitrogen, and glutamine	**Plasma amino acids**: Total indispensable amino acids, branched-chain amino acids, and glutamine declined 25% on Day 1 compared with baseline. Indispensable and branched-chain amino acid concentrations were restored with 5 d of either EN or TPN (p<0.05). Glutamine concentrations did not differ significantly by feeding group.	- 17 patients were included for analysis: 7 for EN and 10 for TPN	RCT	Moderate

Peri- and postoperative somatostatin analogues

CPG ID	Ref	Search date	Recommendation	Supporting evidence	Level of evidence
CCO 12-7	[241]	July 2004	Octreotide, administered at a dose of 100 □g subcutaneously three times daily starting one hour prior to surgery and continuing for seven days is recommended as part of the standard management for patients undergoing pancreatic surgery.	6 RCTs: Bassi 1994, Friess 1994, Montorsi 1995, Lowy 1997, Yeo 2000, Suc 2004	Moderate

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
Hesse UJ 2005	[242]	NA	Patients subjected to pancreatic surgery and subsequent pancreaticojejunostomy	Octreotide 0.1 mg SC 3 times/day for 7 days (n=55) vs. no octreotide (n=50)	General complications: 11% vs. 12% (NS) Pancreatic fistula: 9% vs. 8% (NS) 30-day mortality: 2% vs. 0% (NS) Hospital stay: 23 vs. 20 days (NS)	Open-label study Unsure if intention-to-treat-analysis was used 69% cancer	RCT	Moderate
Shan YS 2003	[243]	NA	Patients undergoing elective pancreaticoduodenectomy for pancreatic and periampullary lesions	Somatostatin IV 250 □g/hr for 7 days (n=27) vs. placebo (n=27)	Postoperative mortality: 3.7% in both groups (NS) Overall complication rate: 26% vs. 52% (p<0.05) Pancreatic stump-related complications: 22% vs. 48% (p<0.05) Pancreatic fistula: 7.4% in both groups (NS) Hospital stay: 28 vs. 30 days (NS) Average cost of care with or without complications: $12,233 ± 3912 and $7112±1787 vs. $20467 ± 6171 and $7862 ± 1652 (p<0.05)	No information on blinding 22% pancreatic cancer	RCT	Moderate
Sarr MG 2003	[245]	NA	Patients undergoing an elective pancreatic resection because of a presumed pancreatic or periampullary neoplasm	Vapreotide 0.6 mg twice daily for 7 days (n=135) vs. placebo (n=140)	Pancreas-specific complications: 30% vs. 26% (NS) Mortality: 0% vs. 1.4% (NS)	No information on blinding	RCT	Moderate
Gouillat C 2001	[244]	NA	Patients undergoing pancreaticoduodenectomy for presumed tumour (chronic pancreatitis excluded on preoperative imaging)	Somatostatin IV 6 mg/d on day 1-6 and 3 mg/d on day 7 (n=38) vs. placebo (n=37)	Overall complication rate: 21% vs. 35% (NS) Clinical pancreatic fistula: 5% vs. 22% (p<0.05) Hospital stay: 18 vs. 26 days (p=0.01)	No information on blinding 11% chronic pancreatitis in placebo group	RCT	Moderate

Enzyme replacement

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
Enzyme replacement therapy for inoperable patients with advanced cancers								
Bruno MJ 1998	[249]		21 patients with unresectable cancer of the pancreatic head region with suspected pancreatic duct obstruction	Patients were randomized into two groups to receive: - The pancreatic enzyme preparation (Panzytrat 25 000), an enteric coated pancreatin microsphere preparation containing 25 000 PhEur units of lipase, 1250 PhEur units of proteases, and 22500 PhEur units of amylase per capsule. - A placebo (same appearance, taste, and weight) containing pharmacologically inactive substances. 2 capsules during main meals and 1 capsule during in between snacks. + dietary counselling	- The mean difference in the percentage change of **body weight** was 4.9% (p=0.02, 95% CI: 0.9 to 8.9). Patients on pancreatic enzymes gained 1.2% (0.7 kg) body weight whereas patients on placebo lost 3.7% (2.2 kg). - The **fat absorption coefficient** in patients on pancreatic enzymes improved by 12% whereas in placebo patients it dropped by 8% (p=0.13, 95% CI: –6 to 45). - The daily total **energy intake** was 8.42 MJ in patients on pancreatic enzymes and 6.66 MJ in placebo patients (p=0.04, 95% CI: 0.08 to 3.44). - The mean changes in the severity and occurrence of **steatorrhoea** associated complaints between both groups were not significantly different.	- No adverse event - 21 patients were available for analysis of the double blind treatment period - Randomisation process not explained - No ITT	RCT	Moderate

Pain

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
Neurolytic celiac plexus block for patients with advanced pancreatic cancer								
Zhang CL 2008	[259]		56 patients with chronic upper-abdominal pain secondary to unresectable pancreatic cancer	- Neurolytic celiac plexus block (group 1, n = 29) guided by CT, with MS Contin if NCPB could not control pain - Pharmacological therapy with MS Contin (group 2, n = 27)	- **Pain**: Visual analogue scale (0 = 'no pain' → 10 = 'the worst possible pain'). Group 1: 9.4 ± 0.7 before treatment, decreasing to 1.3 ± 0.8 day 1, and 3.9 ± 1.2 at day 90, p < 0.01). At day 1, 7, and 14, the VAS scores in group 1 were significantly lower than those in group 2 (p < 0.01); at day 30, 60, and 90, pain levels were similar in both groups - **QoL** based on interference with appetite, sleep, communication (0 =	- No precision about randomisation process, no ITT approach - Complications related to block: orthostatic hypotension, drunkenness symptoms, diarrhea, and burning pain in the puncturing position (relieved in few days)	RCT	Moderate

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
					'no interference' → 10 = 'most severe interference'). Improvements statistically significant in both groups but not between groups - **Consumption of analgesics** : dose of opioids significantly lower in group 1 (Day 7: 11±23 vs 81±34; Day 14: 13±25 vs 94±38; Day 30: 54±50 vs 133±53; Day 60: 99±59 vs 161±73; Day 90: 105±65 vs 169±71) (p < 0.01)			
Yan BM 2007	[258]	2005	5 RCTs involving 302 pancreatic cancer patients (NCPB, n = 147; control, n = 155)	- NCPB *versus* control (standard treatment and/or sham NCPB)	- Compared with control, NCPB was associated with lower **VAS** scores (0 = 'no pain' and 10 = 'severe pain') for pain at 2, 4, and 8 wk (weighted mean difference [WMD] = 0.60, 95% CI ☐0.82 to ☐0.37). - **Opioid use** (in mg/day oral morphine) was also reduced at 2, 4, and 8 wk (WMD = ☐85.9, 95% CI ☐144.0 to ☐27.9). - NCPB was associated with a reduction in **constipation** (RR 0.67, 95% CI 0.49–0.91), but not other **adverse events** (nausea, vomiting, diarrhea, sedation, hypotension). - No differences in **survival** were observed (RR 1.08, 95%CI 0.96–1.22). - **QOL** could not be adequately analyzed due to differences in outcome scales among the 2 studies that assessed it.	- Electronic search was completed on OVID/ - PubMed Medline, EMBASE, HealthStar, and the Cochrane Library (1966 through August, 2005) - Restriction to English - Quality assessment of the included studies based on the generation of the allocation sequence, allocation concealment, and method of blinding (the quality of the RCTs cannot be confirmed).	SR	Moderate
Süleyman NO 2004	[261]		47 patiens with an adenocarcinoma of pancreas, located on tail and/or body	Neurolytic coeliac plexus blockade (NCPB, n = 19) [40 ml of ethanol approx. 75% (30 ml of ethanol 96%+10 ml of lidocaine 10 mg/ml) *versus* bilateral splanchnic nerves neurolytic blockade (SNB, n = 20) [6 ml of ethanol approx. 75% solution (4.5 ml ethanol 96% + 1.5 ml of	- Compared with NCPB, SNB was associated with lower **VAS** scores (0 = 'no pain' and 10 = 'severe pain') for pain at 2, 4, 6, 8, 10 and 12 w (respectively; p < 0.001, p < 0.001, p < 0.001, p = 0.001, p = 0.001, and p = 0.002). - Compared with NCPB, SNB was associated with lower **codeine**	- No ITT analyse - Celiac group: 2 patients had severe pain during injection, 5 patients had intractable diarrhea and 2 patients had haemodynamic disturbances, which required inotropic	RCT	Moderate

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
				lidocaine 10 mg/ml) was administered bilaterally (a total of 12 ml)] All patients were treated with analgesics according WHO guideline for cancer patients; on the second step, using codeine 40 mg as needed (max 160 mg/d) and tenoxicam 20 mg/d, 25 mg/d amitriptyline and still had pain on VAS higher than 4.	**consumption** (in mg) at 2, 4, 6, 8, 10 weeks) controls (respectively; p = 0.003, p = 0.041, p = 0.005, p = 0.021, p = 0.028). - Compared with NCPB, SNB was associated with higher **patient satisfaction** at 4 weeks (p = 0.003) - **Survival rate** for NCPB: mean 45.37±SE 5.82 (min: 11–max: 90) days [95% CI: 33.96–56.78]; Median: 47.00±SE 11.61 [95% CI: 24.25–69.75] which were significantly lower than SNB: mean 68.85±SE 7.3 (min: 19–max: 122) days [95% CI: 54.54–83.16]. Median: 70.00±SE 13.42, [95% CI: 43.70–96.30] (p=0.0072) - No significant difference in **performance status** between groups	support for 24 h - Splanchnic group: 1 patient had severe pain during procedure while introducing the needle tangent to posterolateral aspect of vertebral corpus		
Ischia S 1992	[260]		61 patients with unresectable pancreatic cancer patients	3 different NCPB approaches: - transaortic celiac plexus block with absolute alcohol 30 ml (TCPB, n = 20) - retrocrural block with absolute alcohol 15 ml (RB, n = 20) - bilateral chemical splanchnicectomy with absolute alcohol 7 ml (BCS, n = 21)	- Analgesic results are independent of the **techniques** used in this study - NCPB performed within 2 months of the onset of pain, complete **relief of pain** is observed in 72% of patients vs 37% in patients with duration > 2 months (p<0.05) - Success of NCPB when good **response to NSAIDs** : 78% vs 35% if partial or no response to NSAIDs (p<0.01)	No ITT analyse Randomisation process not explained	RCT	Moderate
Peridural analgesia for post-operative pain relief								
Barzoi G 2000	[251]		60 patients having hepato-biliary-pancreatic neoplasm and candidates for major surgery.	Non-stop postoperative epidural analgesia with morphine 0.0017 mg/kg/h)and bupivacaine 0.125% (0.058 mg/kg/h) (group A, n= 30) versus morphine bolus every 12 hours (0.035-mg/kg/12h) (group B, n = 30). Each medication was	- **Pain**: Visual analogic pain scores from 0 to 10 with score **1** 'no pain' and score 10 'maximum bearable pain'. VAS at rest was ≤ 3 with a statistically significant difference only between the two groups in the first survey, with better analgesia in Group A (no more details) - **Effective peristalsis** was present in	No detail about randomisation process; no ITT	RCT	Moderate

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
				administered by means of a thoracic epidural catheter for the control of postoperative pain.	all patients in Group A within the first six postoperative hours; in Group B, after 30 hours. Bowel motions were recorded sooner in group A ($p<0.05$ in 1st, 2nd, 4th and 5th days). - **Pneumonia** occurred in 2 patients of Group A, and in 10 of Group B ($p < 0.05$).			

Psychological support

Study ID	Ref	Search date	Population	Intervention	Results	Comments	Study type	Level of evidence
Psychological support for patients with advanced pancreatic cancer								
Kuchler T 2007	[263]		Patients (N = 271) with a preliminary diagnosis of cancer of the oesophagus, stomach, liver/gallbladder, pancreas (n = 40), or colon/rectum and scheduled for surgery	- Standard care as provided on the surgical wards (Control group) - Formal psychotherapeutic support in addition to routine care during the hospital stay (experimental group): educational information, a supportive relationship, and ongoing psychotherapeutic counselling, emotional and cognitive support to foster "fighting spirit" and to diminish "hope and helplessness.	- Kaplan-Meier survival curves demonstrated better **survival** for the experimental group than the control group. The unadjusted significance level for group differences was p = 0.0006 for survival to 10 years. Cox regression models that took TNM staging or the residual tumor classification and tumor site into account also found significant differences at 10 years. Secondary analyses found that differences in favour of the experimental group occurred in patients with stomach, pancreatic, primary liver, or colorectal cancer.	Not specifically for pancreatic cancer.	RCT	Moderate

APPENDIX 5: LYMPH NODE STATIONS

Number	Name
1	Right cardiac
2	Left cardiac
3	Gastric lesser curve
4	Gastric greater curve
5	Superior pyloric
6	Inferior pyloric
7	Left gastric artery
8	**Common hepatic artery**
8a	Anterosuperior
8p	Posterior
9	Celiac origin
10	Splenic hilum
11	Splenic artery
12	**Hepatoduodenal ligament**
12a1	Along hepatic artery, superior
12a2	Along hepatic artery, inferior
12b1	Along bile duct, superior
12b2	Along bile duct, inferior
12c	Around cystic duct
12h	Hepatic hilum
12p1	Retro portal vein, superior
12p2	Retro portal vein, inferior
13	**Posterior pancreaticoduodenal**
13a	Superior to ampulla of Vater
13b	Inferior to ampulla of Vater
14	**Proximal mesenteric lymph nodes**
14a	Origin of SMA
14b	Right side of SMA
14c	Anterior SMA at middle colic artery
14d	Left side of SMA at first jejunal branch
14v	SMV nodes
15	Middle colic vessels
16	**Aorta-caval nodes**
16a1	Aortic hiatus of diaphragm
16a2	Celiac to left renal vein
16b1	Left renal vein to IMA
16b2	IMA to aortic bifurcation
17	**Anterior pancreaticoduodenal**
17a	Superior to ampulla of Vater
17b	Inferior to ampulla of Vater
18	Inferior border of pancreatic body and tail

(source: Japanese Pancreas Society [JCS] classification [152])

APPENDIX 6: STAGING SYSTEMS

UICC TNM CLASSIFICATION

(source: International Union Against Cancer [UICC] [151])

T categories

TX: Primary tumour cannot be assessed

T0: No evidence of primary tumour

Tis: Carcinoma in situ

T1: Tumour limited to the pancreas, 2 cm or less in greatest dimension

T2: Tumour limited to the pancreas, more than 2 cm in greatest dimension

T3: Tumour extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery

T4: Tumour involves the celiac axis or the superior mesenteric artery (unresectable primary tumour)

N categories

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

N1: Regional lymph node metastasis

M categories

MX: Distant metastasis cannot be assessed.

M0: No distant metastasis

M1: Distant metastasis

Stage grouping for pancreatic cancer

Stage 0 (Tis, N0, M0): The tumor is confined to the top layers of pancreatic duct cells and has not invaded deeper tissues. It has not spread outside of the pancreas. These tumors are sometimes referred to as pancreatic carcinoma in situ or pancreatic intraepithelial neoplasia III (PanIn III).

Stage IA (T1, N0, M0): The tumor is confined to the pancreas and is less than 2 cm in size. It has not spread to nearby lymph nodes or distant sites.

Stage IB (T2, N0, M0): The tumor is confined to the pancreas and is larger than 2 cm in size. It has not spread to nearby lymph nodes or distant sites.

Stage IIA (T3, N0, M0): The tumor is growing outside the pancreas but not into large blood vessels. It has not spread to nearby lymph nodes or distant sites.

Stage IIB (T1-3, N1, M0): The tumor is either confined to the pancreas or growing outside the pancreas but not into nearby large blood vessels or major nerves. It has spread to nearby lymph nodes but not distant sites.

Stage III (T4, Any N, M0): The tumor is growing outside the pancreas into nearby large blood vessels or major nerves. It may or may not have spread to nearby lymph nodes. It has not spread to distant sites.

Stage IV (Any T, Any N, M1): The cancer has spread to distant sites.

JAPANESE PANCREAS SOCIETY

(source: Japanese Pancreas Society [JCS] classification [152])

T categories

T1: Tumour size 0 – 2 cm.

T2: Tumour size 2.1 – 4 cm.

T3: Tumour size 4.1 – 6 cm.

T4: Tumour size >6 cm.

N categories

N0: No lymph node involvement.

N1: Involvement of regional lymph nodes close to the primary tumour.

N2: Involvement of regional lymph nodes distant from the primary tumour.

N3: Involvement of lymph nodes other than regional.

Invasion of peripancreatic tissues

Rp-S-PV 0: Absence of retroperitoneal serosal – portal vein system invasion

Rp-S-PV 1: Suspected retroperitoneal serosal – portal vein system invasion

Rp-S-PV 2: Definite retroperitoneal serosal – portal vein system invasion

Rp-S-PV 3: Severe retroperitoneal serosal – portal vein system invasion

Stage grouping for pancreatic cancer

The most advanced factor determines the stage. Distant metastasis is stage IV.

Stage I: T1 and N0 and Rp0 and S0 and PV0

Stage II: T2 and/or N1 and/or Rp1 and/or S1 and/or PV1

Stage III: T3 and/or N2 and/or Rp2 and/or S2 and/or PV2

Stage IV: T4 and/or N3 and/or Rp3 and/or S3 and/or PV3

APPENDIX 7: CLASSIFICATION OF PANCREATIC INTRAEPITHELIAL NEOPLASIA AND INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

PANCREATIC INTRAEPITHELIAL NEOPLASIA NOMENCLATURE [150]

Normal: The normal ductal and ductular epithelium is a cuboidal to low-columnar epithelium with amphophilic cytoplasm. Mucinous cytoplasm, nuclear crowding, and atypia are not seen.

Squamous (transitional) metaplasia: A process in which the normal cubiodal ductal epithelium is replaced by mature stratified squamous or pseudostratified transitional epithelium without atypia.

PanIN-1A (pancreatic intraepithelial neoplasia 1-A): These are flat epithelial lesions composed of tall columnar cells with basally located nuclei and abundant supranuclear mucin. The nuclei are small and round-to-oval in shape. When oval, the nuclei are oriented perpendicular to the basement membrane. It is recognized that there may be considerable histologic overlap between nonneoplastic, flat, hyperplastic lesions and flat, neoplastic lesions without atypia. Therefore, some may choose to designate these entities with the modifier term "lesion" ("PanIN/L-1A") to acknowledge that the neoplastic nature of many cases of PanIN-1A has not been unambiguously established.

PanIN-1B (pancreatic intraepithelial neoplasia 1-B): These epithelial lesions have a papillary, micropapillary, or basally pseudostratified architecture but are otherwise identical to PanIN-1A.

PanIN-2 (pancreatic intraepithelial neoplasia 2): Architecturally, these mucinous epithelial lesions may be flat but are mostly papillary. Cytologically, by definition, these lesions must have some nuclear abnormalities. These abnormalities may include some loss of polarity, nuclear crowding, enlarged nuclei, pseudostratification, and hyperchromatism. These nuclear abnormalities fall short of those seen in PanIN-3. Mitoses are rare, but when present are nonluminal (not apical), and are not atypical. True cribriform structures with luminal necrosis and marked cytologic abnormalities are generally not seen and, when present, should suggest the diagnosis of PanIN-3.

PanIN-3 (pancreatic intraepithelial neoplasia 3): Architecturally, these lesions are usually papillary or micropapillary; however, they may rarely be flat. True cribriforming, the appearance of "budding off" of small clusters of epithelial cells into the lumen, and luminal necrosis should all suggest the diagnosis of PanIN-3. Cytologically, these lesions are characterized by a loss of nuclear polarity, dystrophic goblet cells (goblet cells with nuclei oriented toward the lumen and mucinous cytoplasm oriented toward the basement membrane), mitoses that may occasionally be abnormal, nuclear irregularities, and prominent (macro) nucleoli. The lesions resemble carcinoma at the cytonuclear level, but invasion through the basement membrane is absent.

WHO DEFINITION OF IPMNS [150]

An intraductal papillary mucin-producing neoplasm, arising in the main pancreatic duct or its major branches. The papillary epithelial component and the degree of mucin secretion, cystic dilatation, and invasiveness are variable. Intraductal papillary-mucinous neoplasms are divided into benign, borderline, and malignant noninvasive or invasive lesions.

WHO GRADING OF IPMNS [150]

IPMN adenoma: The epithelium is comprised of tall columnar mucin-containing cells that show slight or no dysplasia (i.e. the epithelium maintains a high degree of differentiation in adenomas).

IPMN borderline: IPMNs with moderate dysplasia are placed in the borderline category. The epithelium shows no more than moderate loss of polarity, nuclear crowding, nuclear enlargement, pseudostratification, and nuclear hyperchromatism. Papillary areas maintain identifiable stromal cores, but pseudopapillary structures may be present.

Intraductal papillary mucinous carcinoma: IPMNs with severe dysplastic epithelial change (carcinoma in situ) are designated as carcinoma even in the absence of invasion. They can be papillary or micropapillary. Cribriform growth and budding of small clusters of epithelial cells into the lumen support the diagnosis of carcinoma in situ. Severe dysplasia is manifest cytologically as loss of polarity, loss of differentiated cytoplasmic features including diminished mucin content, cellular and nuclear pleomorphism, nuclear enlargement, and the presence of mitoses (especially if suprabasal or luminal). Severely dysplastic cells may lack mucin.

APPENDIX 8: MEDLINE SEARCH TERMS

PANCREATIC CANCER

1. exp Pancreatic Neoplasms/
2. (pancrea$ adj5 neoplas$).tw.
3. (pancrea$ adj5 cancer$).tw.
4. (pancrea$ adj5 carcin$).tw.
5. (pancrea$ adj5 tumo$).tw.
6. (pancrea$ adj5 metasta$).tw.
7. (pancrea$ adj5 malig$).tw.
8. or/1-7

SYSTEMATIC REVIEWS AND RANDOMISED TRIALS

1. meta-analysis.pt,ti,ab,sh.
2. 1 or (meta anal$ or metaanal$).ti,ab,sh.
3. (methodol$ or systematic$ or quantitativ$).ti,ab,sh.
4. ((methodol$ or systematic$ or quantitativ$) adj (review$ or overview$ or survey$)).ti,ab,sh.
5. (medline or embase or index medicus).ti,ab.
6. ((pool$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
7. 3 or 4 or 5 or 6
8. 7 and review.pt,sh.
9. 2 or 8
10. Randomized controlled trials/
11. Randomized controlled trial.pt.
12. Random allocation/
13. Double blind method/
14. Single blind method/
15. Clinical trial.pt.
16. exp clinical trials/
17. or/10-16
18. (clinic$ adj trial$1).tw.
19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
20. Placebos/
21. Placebo$.tw.
22. Randomly allocated.tw.
23. (allocated adj2 random).tw.
24. or/18-23
25. 17 or 24
26. Case report.tw.

27. Letter.pt.
28. Historical article.pt.
29. Review of reported cases.pt.
30. Review, multicase.pt.
31. or/26-30
32. 25 not 31
33. 9 or 32

DIAGNOSTIC STUDIES

1. exp "Sensitivity and Specificity"/
2. sensitivity.tw.
3. specificity.tw.
4. ((pre-test or pretest) adj probability).tw.
5. post-test probability.tw.
6. predictive value$.tw.
7. likelihood ratio$.tw.
8. Prospective Studies/
9. or/1-8

SCREENING

1. exp Mass Screening/

SIGNS AND SYMPTOMS

1. Jaundice, Obstructive/ or Jaundice/
2. Anorexia/
3. Weight Loss/
4. sign$.ab,ti.
5. symptom$.ab,ti.
6. Dyspepsia/
7. or/1-6

DIAGNOSIS AND STAGING

1. tomography scanners, x-ray computed/
2. tomography, x-ray computed/
3. magnetic resonance imaging/
4. positron-emission tomography/
5. tomography, spiral computed/ or tomography/
6. Endosonography/
7. Laparoscopy/
8. Ultrasonography/
11. Cholangiopancreatography, Endoscopic Retrograde/
12. Neoplasm Staging/
13. or/1-12

EUS

1. Endosonography/
2. endoscopic ultrasonography.mp.
3. eus.mp.
4. Biopsy, Fine-Needle/
5. or/1-4

ERCP

1. Cholangiopancreatography, Endoscopic Retrograde/
2. endoscopic retrograde cholangiopancreatogr$.tw.
3. endoscopic retrograde cholangio-pancreatogr$.tw.
4. endoscopic retrograde pancreatocholangiogr$.tw.
5. endoscopic retrograde pancreato-cholangiogr$.tw.
6. ERCP$.tw.
7. endoscopic retrograde cholangiogr$.tw.
8. (ERC and endoscop$).tw.
9. (ERC and cholangiogr$).tw.
10. endoscopic cholangiogr$.tw.
11. endoscopic retrograde pancreatogr$.tw.
12. (ERP and endoscop$).tw.
13. (ERP and pancreatogr$).tw.
14. endoscopic pancreatogr$.tw.
15. endoscopic cholangiopancreatogr$.tw.
16. endoscopic cholangio-pancreatogr$.tw.
17. (ECP and endoscop$).tw.
18. (ECP and cholangiogr$).tw.
19. endoscopic pancreatocholangiogr$.tw.
20. endoscopic pancreato-cholangiogr$.tw.
21. (EPC and endoscop$).tw.
22. (EPC and pancreatogr$).tw.
23. or/1-22

CHEMO- AND/OR RADIOTHERAPY

1. adjuvant.mp.
2. Chemotherapy, Adjuvant/
3. Radiotherapy, Adjuvant/
4. Antineoplastic Combined Chemotherapy Protocols/
5. Neoadjuvant Therapy/
6. neoadjuvant.mp.
7. chemothera$.tw.
8. Drug Therapy/

9. radiothera$.tw.
10. Radiotherapy/
11. antineoplastic agents combined/
12. drug therapy combination/
13. combined modality therapy/
14. chemoradiotherap$.tw.
15. or/1-14

SURGERY

1. exp biliary tract surgical procedures/
2. (bypass adj10 surg$).tw.
3. (operat$ adj10 bypass).tw.
4. (bil$ adj10 anastomosis).tw.
5. (bil$ adj10 bypass).tw.
6. exp choledochoduodenostomy/
7. choledochoduoden$.tw.
8. exp choledochojejunostomy/
9. choledochojejun$.tw.
10. hepaticojejun$.tw.
11. Carcinoma, Pancreatic Ductal/su [Surgery]
12. Pancreatic Diseases/su [Surgery]
13. Pancreatic Ducts/su [Surgery]
14. Pancreatic Neoplasms/su [Surgery]
15. Pancreas/su [Surgery]
16. exp Surgical Procedures, Operative/
17. exp Surgical Procedures, Elective/
18. exp Digestive System Surgical Procedures/
19. or/1-18

RELATION VOLUME AND OUTCOME

1. Surgical Procedures, Operative/sn [Statistics & Numerical Data]
2. Health Facility Size/
3. Workload/sn [Statistics & Numerical Data]
4. or/1-3

HISTOPATHOLOGIC EXAMINATION

1. "prognos*".ti,ab.
2. first.ti,ab.
3. episode.ti,ab.
4. 2 and 3
5. cohort.ti,ab.
6. 1 or 4 or 5

7. pathology.mp. or Pathology/ or Pathology, Clinical/ or Pathology, Surgical/
8. Lymph Nodes/
9. (resection adj margin$).mp.
10. Neoplasm Invasiveness/
11. Neoplasm Staging/ or TNM.mp.
12. Neoplasm Recurrence, Local/
13. R0.mp.
14. R1.mp.
15. Frozen Sections/
16. or/7-15
17. 6 and 16

ENDOSCOPIC TREATMENT

1. exp Endoscopy/
2. exp Endoscopy, Gastrointestinal/
3. exp Endoscopy, Digestive System/
4. exp stents/
5. stent$.tw.
6. endoprosthesis.tw.
7. wallstent$.tw.
8. exp Argon/
9. photodynamic.mp.
10. Lasers/
11. laser$.tw
12. Brachytherapy/
13. or/1-12

SOMATOSTATIN (ANALOGUES)

1. octreotide/
2. octreotide.mp.
3. somatostatin.mp.
4. sandostatin.mp.
5. SMS-201-995.mp.
6. or/1-5

EXOCRINE SUPPLEMENTATION

1. Exocrine Pancreatic Insufficiency/
2. Pancreas, Exocrine/
3. Pancrelipase/
4. or/1-3

PAIN

1. exp Pain, Intractable/
2. exp Pain/
3. exp Pain Treshold/
4. exp Pain Measurement/
5. or/1-4

NUTRITION

1. nutritional status/
2. nutritional support/
3. (nutrition* or vitamin* or diet* or supplement*).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4. diet therapy/
5. nutrition therapy/
6. parenteral nutrition/
7. enteral nutrition/
8. or/1-7

PSYCHOLOGICAL SUPPORT

1. exp psychoanalytic therapy/
2. exp psychotherapeutic processes/
3. exp psychotherapy/
4. exp Psychotherapy, Brief/
5. exp Psychotherapy, Multiple/
6. Psychotherapy, rational-emotive/
7. exp reality therapy/
8. exp socioenvironmental therapy/
9. exp autogenic training/
10. Behavior therapy/
11. exp gestalt therapy/
12. exp hypnosis/
13. (symptom adj5 score$).tw.
14. (psychoanalytic adj5 therapy).tw.
15. (psychotherapeutic adj5 process).tw.
16. (socio$ adj3 environment adj5 therapy).tw.
17. psychotherapy.tw.
18. (autogenic adj5 training).tw.
19. (behaviour$ adj5 therapy).tw.
20. (gestalt adj5 therapy).tw.
21. (reality adj5 therapy).tw.
22. (non?directive adj5 therapy).tw.

23. hypnosis.tw.
24. or/1-23

FOLLOW-UP

1. Follow-Up Studies/
2. follow-up.ti,ab.
3. followup.ti,ab.
4. follow up.ti,ab.
5. monitoring.ti,ab.
6. surveillance.ti,ab.
7. or/1-6
8. office visit.ti,ab.
9. physician visit.ti,ab.
10. physical examination.ti,ab.
11. frequency.ti,ab.
12. length.ti,ab.
13. Office Visits/
14. Physical Examination/
15. or/8-14
16. 7 and 15

RECURRENT DISEASE

1. Recurrence/
2. Neoplasm Recurrence, Local/
3. recurren$.tw.
4. or/1-3

6 REFERENCES

[1] Ghadirian P, Lynch H, Krewski D. Epidemiology of pancreatic cancer: an overview. Cancer Detection & Prevention. 2003;27:87-93.

[2] Belgian Cancer Registry. Cancer Incidence in Belgium, 2004-2005. Brussels: Fondation Registre du Cancer; 2008.

[3] Ries LAG, Melbert D, Krapcho M, Stinchcomb DG, Howlader N, Horner MJ, et al. SEER Cancer Statistics Review, 1975-2005. 2008 2007 [cited 2008 12-10-2008]; Available from: http://seer.cancer.gov/csr/1975_2005/

[4] Zhang J, Dhakal I, Yan H, Phillips M, Kesteloot H. Trends in pancreatic cancer incidence in nine SEER Cancer Registries, 1973–2002. Ann Oncol. 2007;18:1268-79.

[5] Lepage C, Remontet L, Launoy G, Tretarred B, Grosclaude P, Colonna M, et al. Trends in incidence of digestive cancers in France. European Journal of Cancer Prevention. 2008;17(13-7).

[6] Levi F, Lucchini F, Negri E, La Vecchia C. Pancreatic Cancer Mortality in Europe: The leveling of an Epidemic. Pancreas. 2003;27(2):139-42.

[7] Fervers B, Burgers JS, Haugh MC, Latreille J, Mlika-Cabanne N, Paquet L, et al. Adaptation of clinical guidelines: literature review and proposition for a framework and procedure. Int J Qual Health Care. 2006 Jun;18(3):167-76.

[8] De Laet C, Neyt M, Vinck I, Lona M, Cleemput I, Van De Sande S. Health Technology Assessment. Colorectale Kankerscreening: wetenschappelijke stand van zaken en budgetimpact voor België. Brussel: Federaal Kenniscentrum voor de Gezondheidszorg (KCE) 2006.

[9] Greer JB, Brand R. Screening for pancreatic cancer: current evidence and future directions. Gastroenterol & hepatol. 2007;3(12):929-38.

[10] U.S. Preventive Services Task Force. Screening for Pancreatic Cancer. *Recommendation Statement*. Rockville: AHRQ 2004.

[11] Kim J-E, Lee KT, Lee JK, Paik SW, Rhee JC, Choi KW. Clinical usefulness of carbohydrate antigen 19-9 as a screening test for pancreatic cancer in an asymptomatic population.[see comment]. J Gastroenterol Hepatol. 2004;19(2):182-6.

[12] Brand RE, Lerch MM, Rubinstein WS, Neoptolemos JP, Whitcomb DC, Hruban RH, et al. Advances in counselling and surveillance of patients at risk for pancreatic cancer. Gut. 2007;56(10):1460-9.

[13] Canto MI, Goggins M, Hruban RH, Petersen GM, Giardiello FM, Yeo C, et al. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2006 Jun;4(6):766-81.

[14] Canto MI, Goggins M, Yeo CJ, Griffin C, Axilbund JE, Brune K, et al. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. Clinical Gastroenterology & Hepatology. 2004;2(7):606-21.

[15] Tamm EP, Loyer EM, Faria SC, Evans DB, Wolff RA, Charnsangavej C. Retrospective analysis of dual-phase MDCT and follow-up EUS/EUS-FNA in the diagnosis of pancreatic cancer. Abdom Imaging. 2007;32(5):660-7.

[16] Mortensen MB, Fristrup C, Holm FS, Pless T, Durup J, Ainsworth AP, et al. Prospective evaluation of patient tolerability, satisfaction with patient information, and complications in endoscopic ultrasonography. Endoscopy. 2005 Feb;37(2):146-53.

[17] Topazian M, Enders F, Kimmey M, Brand R, Chak A, Clain J, et al. Interobserver agreement for EUS findings in familial pancreatic-cancer kindreds. Gastrointest Endosc. 2007 Jul;66(1):62-7.

[18] Grocock CJ, Vitone LJ, Harcus MJ, Neoptolemos JP, Raraty MGT, Greenhalf W. Familial pancreatic cancer: a review and latest advances. Advances in medical sciences. 2007;52:37-49.

[19] Rulyak SJ, Kimmey MB, Veenstra DL, Brentnall TA. Cost-effectiveness of pancreatic cancer screening in familial pancreatic cancer kindreds. Gastrointest Endosc. 2003;57(1):23-9.

[20] Palsson B, Masson P, Andren-Sandberg A. Tumour marker CA 50 levels compared to signs and symptoms in the diagnosis of pancreatic cancer. Eur J Surg Oncol. 1997 Apr;23(2):151-6.

[21] Li Q, Gao C, Li H, Juzi JT, Chen H, Hao X. Factors associated with survival after surgical resection in Chinese patients with ductal adenocarcinoma of the pancreatic head. Dig Surg. 2008;25(2):87-92.

[22] Bipat S, Phoa SSKS, van Delden OM, Bossuyt PMM, Gouma DJ, Lameris JS, et al. Ultrasonography, computed tomography and magnetic resonance imaging for diagnosis and determining resectability of pancreatic adenocarcinoma: a meta-analysis. 2005 Jul-Aug;29(4):438-45.

[23] Dewitt J, Devereaux BM, Lehman GA, Sherman S, Imperiale TF. Comparison of endoscopic ultrasound and computed tomography for the preoperative evaluation of pancreatic cancer: a systematic review. 2006 Jun;4(6):717-25; quiz 664.

[24] Bang S, Chung HW, Park SW, Chung JB, Yun M, Lee JD, et al. The clinical usefulness of 18-fluorodeoxyglucose positron emission tomography in the differential diagnosis, staging, and response evaluation after concurrent chemoradiotherapy for pancreatic cancer. J Clin Gastroenterol. 2006 Nov-Dec;40(10):923-9.

[25] Heinrich S, Goerres GW, Schafer M, Sagmeister M, Bauerfeind P, Pestalozzi BC, et al. Positron emission tomography/computed tomography influences on the management of resectable pancreatic cancer and its cost-effectiveness. Ann Surg. 2005 Aug;242(2):235-43.

[26] Imbriaco M, Smeraldo D, Liuzzi R, Carrillo F, Cacace G, Vecchione D, et al. Multislice CT with single-phase technique in patients with suspected pancreatic cancer. La Radiologia medica. 2006 Mar;111(2):159-66.

[27] Okamoto Y, Kawamoto H, Takaki A, Ishida E, Ogawa T, Kuwaki K, et al. Contrast-enhanced ultrasonography depicts small tumor vessels for the evaluation of pancreatic tumors. Eur J Radiol. 2007 Jan;61(1):163-9.

[28] Rickes S, Wermke W. Differentiation of cystic pancreatic neoplasms and pseudocysts by conventional and echo-enhanced ultrasound. J Gastroenterol Hepatol. 2004 Jul;19(7):761-6.

[29] Belyaev O, Seelig MH, Muller CA, Tannapfel A, Schmidt WE, Uhl W. Intraductal papillary mucinous neoplasms of the pancreas. 2008 Mar;42(3):284-94.

[30] Ruf J, Lopez Hanninen E, Bohmig M, Koch I, Denecke T, Plotkin M, et al. Impact of FDG-PET/MRI image fusion on the detection of pancreatic cancer. Pancreatology. 2006;6(6):512-9.

[31] Zhong L, Yao Q-Y, Li L, Xu J-R. Imaging diagnosis of pancreato-biliary diseases: a control study. World J Gastroenterol. 2003 Dec;9(12):2824-7.

[32] Calvo MM, Bujanda L, Calderon A, Heras I, Cabriada JL, Bernal A, et al. Comparison between magnetic resonance cholangiopancreatography and ERCP for evaluation of the pancreatic duct. Am J Gastroenterol. 2002 Feb;97(2):347-53.

[33] Glasbrenner B, Schwarz M, Pauls S, Preclik G, Beger HG, Adler G. Prospective comparison of endoscopic ultrasound and endoscopic retrograde cholangiopancreatography in the preoperative assessment of masses in the pancreatic head. Dig Surg. 2000;17(5):468-74.

[34] Hocke M, Schulze E, Gottschalk P, Topalidis T, Dietrich CF. Contrast-enhanced endoscopic ultrasound in discrimination between focal pancreatitis and pancreatic cancer. World J Gastroenterol. 2006 Jan 14;12(2):246-50.

[35] Legmann P, Vignaux O, Dousset B, Baraza AJ, Palazzo L, Dumontier I, et al. Pancreatic tumors: comparison of dual-phase helical CT and endoscopic sonography. AJR American journal of roentgenology. 1998 May;170(5):1315-22.

[36] Nakaizumi A, Uehara H, Iishi H, Tatsuta M, Kitamura T, Kuroda C, et al. Endoscopic ultrasonography in diagnosis and staging of pancreatic cancer. Dig Dis Sci. 1995 Mar;40(3):696-700.

[37] Rocca R, Daperno M, Crocella L, Lavagna A, Salvetto M. Endoscopic ultrasound-fine needle aspiration (EUS-FNA) for pancreatic lesions: effectiveness in clinical practice. 2007 Aug;98(4):339-42.

[38] Rosch T, Lorenz R, Braig C, Feuerbach S, Siewert JR, Schusdziarra V, et al. Endoscopic ultrasound in pancreatic tumor diagnosis. Gastrointest Endosc. 1991 May-Jun;37(3):347-52.

[39] Becker D, Strobel D, Bernatik T, Hahn EG. Echo-enhanced color- and power-Doppler EUS for the discrimination between focal pancreatitis and pancreatic carcinoma. 2001 Jun;53(7):784-9.

[40] Saftoiu A, Popescu C, Cazacu S, Dumitrescu D, Georgescu CV, Popescu M, et al. Power Doppler endoscopic ultrasonography for the differential diagnosis between pancreatic cancer and pseudotumoral chronic pancreatitis. 2006 Mar;25(3):363-72.

[41] Micames C, Jowell PS, White R, Paulson E, Nelson R, Morse M, et al. Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosed by EUS-guided FNA vs. percutaneous FNA. Gastrointest Endosc. 2003 Nov;58(5):690-5.

[42] Eloubeidi MA, Varadarajulu S, Desai S, Shirley R, Heslin MJ, Mehra M, et al. A prospective evaluation of an algorithm incorporating routine preoperative endoscopic ultrasound-guided fine needle aspiration in suspected pancreatic cancer. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2007 Jul;11(7):813-9.

[43] Fritscher-Ravens A, Topalidis T, Bobrowski C, Krause C, Thonke E, Jackle S, et al. Endoscopic ultrasound-guided fine-needle aspiration in focal pancreatic lesions: a prospective intraindividual comparison of two needle assemblies. 2001 Jun;33(6):484-90.

[44] Gress F, Gottlieb K, Sherman S, Lehman G. Endoscopic ultrasonography-guided fine-needle aspiration biopsy of suspected pancreatic cancer. Annals of internal medicine. 2001;134(6):459-64.

[45] Harewood GC, Wiersema MJ. Endosonography-guided fine needle aspiration biopsy in the evaluation of pancreatic masses. Am J Gastroenterol. 2002 Jun;97(6):1386-91.

[46] Horwhat JD, Paulson EK, McGrath K, Branch MS, Baillie J, Tyler D, et al. A randomized comparison of EUS-guided FNA versus CT or US-guided FNA for the evaluation of pancreatic mass lesions.[see comment]. 2006 Jun;63(7):966-75.

[47] Iglesias-Garcia J, Dominguez-Munoz E, Lozano-Leon A, Abdulkader I, Larino-Noia J, Antunez J, et al. Impact of endoscopic ultrasound-guided fine needle biopsy for diagnosis of pancreatic masses. World J Gastroenterol. 2007 Jan 14;13(2):289-93.

[48] Mishra G. DNA analysis of cells obtained from endoscopic ultrasound-fine needle aspiration in pancreatic adenocarcinoma: Fool's Gold, Pandora's Box, or Holy Grail? Am J Gastroenterol. 2006 Nov;101(11):2501-3.

[49] Goonetilleke KS, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. 2007 Apr;33(3):266-70.

[50] Hathurusinghe HR, Goonetilleke KS, Siriwardena AK. Current status of tumor M2 pyruvate kinase (tumor M2-PK) as a biomarker of gastrointestinal malignancy. 2007 Oct;14(10):2714-20.

[51] Kumar Y, Gurusamy K, Pamecha V, Davidson BR. Tumor M2-pyruvate kinase as tumor marker in exocrine pancreatic cancer a meta-analysis. Pancreas. 2007 Aug;35(2):114-9.

[52] 2006 Update of ASCO Recommendations for the Use of Tumor Markers in Gastrointestinal Cancer. J Oncol Pract. 2006 November 1, 2006;2(6):314-6.

[53] Kuno N, Kurimoto K, Fukushima M, Hayakawa T, Shibata T, Suzuki T, et al. Effectiveness of multivariate analysis of tumor markers in diagnosis of pancreatic carcinoma: a prospective study in multiinstitutions. Pancreas. 1994 Nov;9(6):725-30.

[54] Malesci A, Montorsi M, Mariani A, Santambrogio R, Bonato C, Bissi O, et al. Clinical utility of the serum CA 19-9 test for diagnosing pancreatic carcinoma in symptomatic patients: a prospective study. Pancreas. 1992;7(4):497-502.

[55] Sperti C, Pasquali C, Chierichetti F, Liessi G, Ferlin G, Pedrazzoli S. Value of 18-fluorodeoxyglucose positron emission tomography in the management of patients with cystic tumors of the pancreas. Ann Surg. 2001 Nov;234(5):675-80.

[56] Urgell E, Puig P, Boadas J, Capella G, Queralto JM, Boluda R, et al. Prospective evaluation of the contribution of K-ras mutational analysis and CA 19.9 measurement to cytological diagnosis in patients with clinical suspicion of pancreatic cancer. 2000 Oct;36(16):2069-75.

[57] Wang TH, Lin JT, Chen DS, Sheu JC, Sung JL. Noninvasive diagnosis of advanced pancreatic cancer by real-time ultrasonography, carcinoembryonic antigen, and carbohydrate antigen 19-9. Pancreas. 1986;1(3):219-23.

[58] Carr-Locke DL. Serum and pancreatic juice carcinoembryonic antigen in pancreatic and biliary disease. Gut. 1980 Aug;21(8):656-61.

[59] van der Waaij LA, van Dullemen HM, Porte RJ. Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. Gastrointest Endosc. 2005 Sep;62(3):383-9.

[60] Khalid A, McGrath KM, Zahid M, Wilson M, Brody D, Swalsky P, et al. The role of pancreatic cyst fluid molecular analysis in predicting cyst pathology. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2005 Oct;3(10):967-73.

[61] Shami VM, Sundaram V, Stelow EB, Conaway M, Moskaluk CA, White GE, et al. The level of carcinoembryonic antigen and the presence of mucin as predictors of cystic pancreatic mucinous neoplasia. Pancreas. 2007 May;34(4):466-9.

[62] Agency for Healthcare Research and Quality. Endoscopic Retrograde Cholangiopancreatography. Summary, Evidence Report/Technology Assessment: Number 50. Rockville, MD: AHRQ 2002.

[63] Stavropoulos S, Larghi A, Verna E, Battezzati P, Stevens P. Intraductal ultrasound for the evaluation of patients with biliary strictures and no abdominal mass on computed tomography. 2005 Aug;37(8):715-21.

[64] Cleemput I, Dargent G, Poelmans J, Camberlin C, Van den Bruel A, Ramaekers D. HTA Positronen Emissie Tomografie in België. Report. Brussel: Federaal Kenniscentrum voor de Gezondheidszorg (KCE); 2005. Report No.: D2005/10.273/29.

[65] Orlando LA, Kulasingam SL, Matchar DB. Meta-analysis: the detection of pancreatic malignancy with positron emission tomography. 2004 Nov 15;20(10):1063-70.

[66] Agency for Healthcare Research and Quality. Positron Emission Testing For Six Cancers (Brain, Cervical, Small Cell Lung, Ovarian, Pancreatic and Testicular). Rockville, MD: AHRQ 2004.

[67] Nishiyama Y, Yamamoto Y, Monden T, Sasakawa Y, Tsutsui K, Wakabayashi H, et al. Evaluation of delayed additional FDG PET imaging in patients with pancreatic tumour. Nucl Med Commun. 2005 Oct;26(10):895-901.

[68] Rasmussen I, Sorensen J, Langstrom B, Haglund U. Is positron emission tomography using 18F-fluorodeoxyglucose and 11C-acetate valuable in diagnosing indeterminate pancreatic masses? Scandinavian journal of surgery : SJS : official organ for the Finnish Surgical Society and the Scandinavian Surgical Society. 2004;93(3):191-7.

[69] Singer E, Gschwantler M, Plattner D, Kriwanek S, Armbruster C, Schueller J, et al. Differential diagnosis of benign and malign pancreatic masses with 18F-fluordeoxyglucose-positron emission tomography recorded with a dual-head coincidence gamma camera. Eur J Gastroenterol Hepatol. 2007 Jun;19(6):471-8.

[70] Sperti C, Pasquali C, Chierichetti F, Ferronato A, Decet G, Pedrazzoli S. 18-Fluorodeoxyglucose positron emission tomography in predicting survival of patients with pancreatic carcinoma. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2003 Dec;7(8):953-9; discussion 9-60.

[71] Fédération Nationale des Centres de Lutte Contre le Cancer. Recommandations pour la pratique clinique: Standards, Options et Recommandations 2003 pour l'utilisation de la tomographie par émission de positons au [18F]-FDG (TEP-FDG) en cancérologie. Paris: FNCLCC 2003.

[72] Li H, Zeng MS, Zhou KR, Jin DY, Lou WH. Pancreatic adenocarcinoma: the different CT criteria for peripancreatic major arterial and venous invasion. J Comput Assist Tomogr. 2005 Mar-Apr;29(2):170-5.

[73] Satoi S, Yamamoto H, Takai S, Tanigawa N, Komemushi A, Yanagimoto H, et al. Clinical impact of multidetector row computed tomography on patients with pancreatic cancer. 2007 Mar;34(2):175-9.

[74] van Vliet EPM, Eijkemans MJC, Kuipers EJ, Poley JW, Steyerberg EW, Siersema PD. Publication bias does not play a role in the reporting of the results of endoscopic ultrasound staging of upper gastrointestinal cancers. Endoscopy. 2007 Apr;39(4):325-32.

[75] Puli SR, Singh S, Hagedorn CH, Reddy J, Olyaee M. Diagnostic accuracy of EUS for vascular invasion in pancreatic and periampullary cancers: a meta-analysis and systematic review. Gastrointest Endosc. 2007 May;65(6):788-97.

[76] Nishiyama Y, Yamamoto Y, Yokoe K, Monden T, Sasakawa Y, Tsutsui K, et al. Contribution of whole body FDG-PET to the detection of distant metastasis in pancreatic cancer. 2005 Sep;19(6):491-7.

[77] Croce E, Olmi S, Bertolini A, Magnone S. Laparoscopic surgery of pancreatic cancer: state of the art. 2005 Nov-Dec;52(66):1889-94.

[78] Ong SL, Garcea G, Thomasset SC, Mann CD, Neal CP, Abu Amara M, et al. Surrogate markers of resectability in patients undergoing exploration of potentially resectable pancreatic adenocarcinoma. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2008 Jun;12(6):1068-73.

[79] Jonker D, Bouttell E, Kamra J, Spithoff K, and the Gastrointestinal Cancer Disease Site Group. Chemotherapy or Radiotherapy for Resectable Pancreatic Adenocarcinoma: Clinical Practice Guidelines. Evidence-based Series #2-23. Ottawa, Ontario: CCO 2007.

[80] Nakamori S, Nakahira S, Miyamoto A, Marubashi S, Nagano H, Dono K, et al. Long-term outocomes of preoperative chemoradiation therapy with gemcitabine and accelerated hyperfractionated radiation for respectable pancreatic cancer. J Clin Oncol (Meeting Abstracts). 2006 June 20, 2006;24(18_suppl):14004-.

[81] Brunner TB, Grabenbauer GG, Meyer T, Golcher H, Sauer R, Hohenberger W. Primary resection versus neoadjuvant chemoradiation followed by resection for locally resectable or potentially resectable pancreatic carcinoma without distant metastasis. A multi-centre prospectively randomised phase II-study of the Interdisciplinary Working Group Gastrointestinal Tumours (AIO, ARO, and CAO). BMC Cancer. 2007;7(41).

[82] Palmer DH, Stocken DD, Hewitt H, Markham CE, Hassan AB, Johnson PJ, et al. A randomized phase 2 trial of neoadjuvant chemotherapy in resectable pancreatic cancer: gemcitabine alone versus gemcitabine combined with cisplatin. 2007 Jul;14(7):2088-96.

[83] Lind PA, Isaksson B, Almstrom M, Johnsson A, Albiin N, Bystrom P, et al. Efficacy of preoperative radiochemotherapy in patients with locally advanced pancreatic carcinoma. Acta Oncol. 2008;47(3):413-20.

[84] Sa Cunha A, Rault A, Laurent C, Adhoute X, Vendrely V, Bellannee G, et al. Surgical resection after radiochemotherapy in patients with unresectable adenocarcinoma of the pancreas. J Am Coll Surg. 2005 Sep;201(3):359-65.

[85] Katz MHG, Pisters PWT, Evans DB, Sun CC, Lee JE, Fleming JB, et al. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. J Am Coll Surg. 2008 May;206(5):833-46; discussion 46-8.

[86] Massucco P, Capussotti L, Magnino A, Sperti E, Gatti M, Muratore A, et al. Pancreatic resections after chemoradiotherapy for locally advanced ductal adenocarcinoma: analysis of perioperative outcome and survival. Ann Surg Oncol. 2006 Sep;13(9):1201-8.

[87] Mumtaz K, Hamid S, Jafri W. Endoscopic retrograde cholangiopancreaticography with or without stenting in patients with pancreaticobiliary malignancy, prior to surgery. Cochrane Database Syst Rev. 2007;3.

[88] Saleh MMA, Norregaard P, Jorgensen HL, Andersen PK, Matzen P. Preoperative endoscopic stent placement before pancreaticoduodenectomy: a meta-analysis of the effect on morbidity and mortality. Gastrointest Endosc. 2002 Oct;56(4):529-34.

[89] Sewnath ME, Karsten TM, Prins MH, Rauws EJA, Obertop H, Gouma DJ. A meta-analysis on the efficacy of preoperative biliary drainage for tumors causing obstructive jaundice. Ann Surg. 2002 Jul;236(1):17-27.

[90] Aly EA, Johnson CD. Preoperative biliary drainage before resection in obstructive jaundice. Dig Surg. 2001;18(2):84-9.

[91] van der Gaag NA, de Castro SMM, Rauws EAJ, Bruno MJ, van Eijck CHJ, Kuipers EJ, et al. Preoperative biliary drainage for periampullary tumors causing obstructive jaundice; DRainage vs. (direct) OPeration (DROP-trial). BMC Surgery. 2007;7(3).

[92] Lygidakis NJ, van der Heyde MN, Lubbers MJ. Evaluation of preoperative biliary drainage in the surgical management of pancreatic head carcinoma. Acta chirurgica Scandinavica. 1987 Nov-Dec;153(11-12):665-8.

[93] Lai EC, Mok FP, Fan ST, Lo CM, Chu KM, Liu CL, et al. Preoperative endoscopic drainage for malignant obstructive jaundice.[see comment]. British Journal of Surgery. 1994 Aug;81(8):1195-8.

[94] National Comprehensive Cancer Network. Pancreatic Adenocarcinoma. V.I. 2008.: NCCN 2008.

[95] Kondo S, Katoh H, Hirano S, Ambo Y, Tanaka E, Okushiba S, et al. Results of radical distal pancreatectomy with en bloc resection of the celiac artery for locally advanced cancer of the pancreatic body. Langenbecks Arch Surg. 2003 Apr;388(2):101-6.

[96] Konishi M, Kinoshita T, Nakagori T, Inoue K, Oda T, Kimata T, et al. Distal pancreatectomy with resection of the celiac axis and reconstruction of the hepatic artery for carcinoma of the body and tail of the pancreas. J Hepatobiliary Pancreat Surg. 2000;7(2):183-7.

[97] Stitzenberg KB, Watson JC, Roberts A, Kagan SA, Cohen SJ, Konski AA, et al. Survival after pancreatectomy with major arterial resection and reconstruction. Ann Surg Oncol. 2008 May;15(5):1399-406.

[98] Nakano H, Bachellier P, Weber J-C, Oussoultzoglou E, Dieng M, Shimura H, et al. Arterial and vena caval resections combined with pancreaticoduodenectomy in highly selected patients with periampullary malignancies. Hepatogastroenterology. 2002 Jan-Feb;49(43):258-62.

[99] Nakao A, Takeda S, Inoue S, Nomoto S, Kanazumi N, Sugimoto H, et al. Indications and techniques of extended resection for pancreatic cancer. World Journal of Surgery. 2006 Jun;30(6):976-82; discussion 83-4.

[100] Tseng JF, Raut CP, Lee JE, Pisters PWT, Vauthey J-N, Abdalla EK, et al. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2004 Dec;8(8):935-49; discussion 49-50.

[101] Li B, Chen F-Z, Ge X-H, Cai M-Z, Jiang J-S, Li J-P, et al. Pancreatoduodenectomy with vascular reconstruction in treating carcinoma of the pancreatic head. Hepatobiliary & pancreatic diseases international : HBPD INT. 2004 Nov;3(4):612-5.

[102] Siriwardana HPP, Siriwardena AK. Systematic review of outcome of synchronous portal-superior mesenteric vein resection during pancreatectomy for cancer. British Journal of Surgery. 2006 Jun;93(6):662-73.

[103] Lygidakis NJ, Singh G, Bardaxoglou E, Dedemadi G, Sgourakis G, Nestoridis J, et al. Mono-bloc total spleno-pancreaticoduodenectomy for pancreatic head carcinoma with portal-mesenteric venous invasion. A prospective randomized study. Hepatogastroenterology. 2004 Mar-Apr;51(56):427-33.

[104] Schmidt CM, White PB, Waters JA, Yiannoutsos CT, Cummings OW, Baker M, et al. Intraductal papillary mucinous neoplasms: predictors of malignant and invasive pathology. Ann Surg. 2007 Oct;246(4):644-51; discussion 51-4.

[105] Bassi C, Sarr MG, Lillemoe KD, Reber HA. Natural history of intraductal papillary mucinous neoplasms (IPMN): current evidence and implications for management. 2008 Apr;12(4):645-50.

[106] Michalski CW, Kleeff J, Wente MN, Diener MK, Buchler MW, Friess H. Systematic review and meta-analysis of standard and extended lymphadenectomy in pancreaticoduodenectomy for pancreatic cancer. 2007 Mar;94(3):265-73.

[107] Pedrazzoli S, DiCarlo V, Dionigi R, Mosca F, Pederzoli P, Pasquali C, et al. Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study. Lymphadenectomy Study Group. Ann Surg. 1998 Oct;228(4):508-17.

[108] Imamura M, Doi R. Treatment of locally advanced pancreatic cancer: should we resect when resectable? 2004 Apr;28(3):293-5.

[109] Karanicolas PJ, Davies E, Kunz R, Briel M, Koka HP, Payne DM, et al. The pylorus: take it or leave it? Systematic review and meta-analysis of pylorus-preserving versus standard whipple pancreaticoduodenectomy for pancreatic or periampullary cancer. 2007 Jun;14(6):1825-34.

[110] Diener MK, Knaebel H-P, Heukaufer C, Antes G, Buchler MW, Seiler CM. A systematic review and meta-analysis of pylorus-preserving versus classical pancreaticoduodenectomy for surgical treatment of periampullary and pancreatic carcinoma. 2007 Feb;245(2):187-200.

[111] Paraskevas KI, Avgerinos C, Manes C, Lytras D, Dervenis C. Delayed gastric emptying is associated with pylorus-preserving but not classical Whipple pancreaticoduodenectomy: a review of the literature and critical reappraisal of the implicated pathomechanism. 2006 Oct 7;12(37):5951-8.

[112] Alexakis N, Halloran C, Raraty M, Ghaneh P, Sutton R, Neoptolemos JP. Current standards of surgery for pancreatic cancer. British Journal of Surgery. 2004 Nov;91(11):1410-27.

[113] McKay A, Mackenzie S, Sutherland FR, Bathe OF, Doig C, Dort J, et al. Meta-analysis of pancreaticojejunostomy versus pancreaticogastrostomy reconstruction after pancreaticoduodenectomy. British Journal of Surgery. 2006 Aug;93(8):929-36.

[114] Bassi C, Falconi M, Molinari E, Salvia R, Butturini G, Sartori N, et al. Reconstruction by pancreaticojejunostomy versus pancreaticogastrostomy following pancreatectomy: results of a comparative study. Ann Surg. 2005 771-3, 2005 Dec;242(6):767-71.

[115] Duffas J-P, Suc B, Msika S, Fourtanier G, Muscari F, Hay JM, et al. A controlled randomized multicenter trial of pancreatogastrostomy or pancreatojejunostomy after pancreatoduodenectomy. Am J Surg. 2005 Jun;189(6):720-9.

[116] Chou FF, Sheen-Chen SM, Chen YS, Chen MC, Chen CL. Postoperative morbidity and mortality of pancreaticoduodenectomy for periampullary cancer. Eur J Surg. 1996 Jun;162(6):477-81.

[117] Peng SY, Wang JW, Lau WY, Cai XJ, Mou YP, Liu YB, et al. Conventional versus binding pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized trial. 2007 May;245(5):692-8.

[118] Reissman P, Perry Y, Cuenca A, Bloom A, Eid A, Shiloni E, et al. Pancreaticojejunostomy versus controlled pancreaticocutaneous fistula in pancreaticoduodenectomy for periampullary carcinoma. 1995 Jun;169(6):585-8.

[119] Tran K, Van Eijck C, Di Carlo V, Hop WCJ, Zerbi A, Balzano G, et al. Occlusion of the pancreatic duct versus pancreaticojejunostomy: a prospective randomized trial. 2002 Oct;236(4):422-8; discussion 8.

[120] Bassi C, Falconi M, Molinari E, Mantovani W, Butturini G, Gumbs AA, et al. Duct-to-mucosa versus end-to-side pancreaticojejunostomy reconstruction after pancreaticoduodenectomy: results of a prospective randomized trial. Surgery. 2003 Nov;134(5):766-71.

[121] Yeo CJ, Cameron JL, Maher MM, Sauter PK, Zahurak ML, Talamini MA, et al. A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. Ann Surg. 1995 Oct;222(4):580-8; discussion 8-92.

[122] Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. Annals of internal medicine. 2002 Sep 17;137(6):511-20.

[123] Killeen SD, O'Sullivan MJ, Coffey JC, Kirwan WO, Redmond HP. Provider volume and outcomes for oncological procedures. British Journal of Surgery. 2005 Apr;92(4):389-402.

[124] Topal B, Van de Sande S, Fieuws S, Penninckx F. Effect of centralization of pancreaticoduodenectomy on nationwide hospital mortality and length of stay. British Journal of Surgery. 2007 Nov;94(11):1377-81.

[125] Esposito I, Kleeff J, Bergmann F, Reiser C, Herpel E, Friess H, et al. Most pancreatic cancer resections are R1 resections. Ann Surg Oncol. 2008 Jun;15(6):1651-60.

[126] Verbeke CS, Leitch D, Menon KV, McMahon MJ, Guillou PJ, Anthoney A. Redefining the R1 resection in pancreatic cancer. British Journal of Surgery. 2006 Oct;93(10):1232-7.

[127] Staley CA, Cleary KR, Abbruzzese JL, Lee JE, Ames FC, Fenoglio CJ, et al. The need for standardized pathologic staging of pancreaticoduodenectomy specimens. Pancreas. 1996 May;12(4):373-80.

[128] Demetter P, Cuvelier CA, Working Party for GIc. Guidelines for adequate histopathological reporting of pancreatic ductal adenocarcinoma resection specimens. Acta Gastroenterol Belg. 2004 Jan-Mar;67(1):46-9.

[129] Royal College of Pathologists. Standards and Minimum Datasets for Reporting Cancers. *Minimum dataset for the histopathological reporting of pancreatic, ampulla of Vater and bile duct carcinoma*. London: Royal College of Pathologists 2002.

[130] Luttges J, Zamboni G, Kloppel G. Recommendation for the examination of pancreaticoduodenectomy specimens removed from patients with carcinoma of the exocrine pancreas. A proposal for a standardized pathological staging of pancreaticoduodenectomy specimens including a checklist. Dig Surg. 1999;16(4):291-6.

[131] Howard TJ, Krug JE, Yu J, Zyromski NJ, Schmidt CM, Jacobson LE, et al. A margin-negative R0 resection accomplished with minimal postoperative complications is the surgeon's contribution

to long-term survival in pancreatic cancer. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2006 Dec;10(10):1338-45; discussion 45-6.

[132] Raut CP, Tseng JF, Sun CC, Wang H, Wolff RA, Crane CH, et al. Impact of resection status on pattern of failure and survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. Ann Surg. 2007 Jul;246(1):52-60.

[133] Verbeke CS. Resection margins and R1 rates in pancreatic cancer--are we there yet? Histopathology. 2008 Jun;52(7):787-96.

[134] Garcea G, Dennison AR, Pattenden CJ, Neal CP, Sutton CD, Berry DP. Survival following curative resection for pancreatic ductal adenocarcinoma. A systematic review of the literature. Jop. 2008;9(2):99-132.

[135] Mitsunaga S, Hasebe T, Kinoshita T, Konishi M, Takahashi S, Gotohda N, et al. Detail histologic analysis of nerve plexus invasion in invasive ductal carcinoma of the pancreas and its prognostic impact. The American journal of surgical pathology. 2007 Nov;31(11):1636-44.

[136] Westgaard A, Tafjord S, Farstad IN, Cvancarova M, Eide TJ, Mathisen O, et al. Pancreatobiliary versus intestinal histologic type of differentiation is an independent prognostic factor in resected periampullary adenocarcinoma. BMC Cancer. 2008;8:170.

[137] Doi R, Kami K, Ito D, Fujimoto K, Kawaguchi Y, Wada M, et al. Prognostic implication of para-aortic lymph node metastasis in resectable pancreatic cancer. World Journal of Surgery. 2007 Jan;31(1):147-54.

[138] Yekebas E-F, Bogoevski D, Bubenheim M, Link B-C, Kaifi J-T, Wachowiak R, et al. Strong prognostic value of nodal and bone marrow micro-involvement in patients with pancreatic ductal carcinoma receiving no adjuvant chemotherapy. World J Gastroenterol. 2006 Oct 28;12(40):6515-21.

[139] Tani M, Kawai M, Terasawa H, Ina S, Hirono S, Shimamoto T, et al. Prognostic factors for long-term survival in patients with locally invasive pancreatic cancer. J Hepatobiliary Pancreat Surg. 2007;14(6):545-50.

[140] Butturini G, Stocken DD, Wente MN, Jeekel H, Klinkenbijl JHG, Bakkevold KE, et al. Influence of resection margins and treatment on survival in patients with pancreatic cancer: meta-analysis of randomized controlled trials. Arch Surg. 2008 Jan;143(1):75-83; discussion

[141] Westgaard A, Tafjord S, Farstad IN, Cvancarova M, Eide TJ, Mathisen O, et al. Resectable adenocarcinomas in the pancreatic head: the retroperitoneal resection margin is an independent prognostic factor. BMC Cancer. 2008;8:5.

[142] House MG, Gonen M, Jarnagin WR, D'Angelica M, DeMatteo RP, Fong Y, et al. Prognostic significance of pathologic nodal status in patients with resected pancreatic cancer. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2007 Nov;11(11):1549-55.

[143] Pawlik TM, Gleisner AL, Cameron JL, Winter JM, Assumpcao L, Lillemoe KD, et al. Prognostic relevance of lymph node ratio following pancreaticoduodenectomy for pancreatic cancer. Surgery. 2007 May;141(5):610-8.

[144] Slidell MB, Chang DC, Cameron JL, Wolfgang C, Herman JM, Schulick RD, et al. Impact of total lymph node count and lymph node ratio on staging and survival after pancreatectomy for pancreatic adenocarcinoma: a large, population-based analysis. Ann Surg Oncol. 2008 Jan;15(1):165-74.

[145] Schwarz RE, Smith DD. Extent of lymph node retrieval and pancreatic cancer survival: information from a large US population database. Ann Surg Oncol. 2006 Sep;13(9):1189-200.

[146] Tomlinson JS, Jain S, Bentrem DJ, Sekeris EG, Maggard MA, Hines OJ, et al. Accuracy of staging node-negative pancreas cancer: a potential quality measure. Arch Surg. 2007 Aug;142(8):767-23; discussion 73-4.

[147] Garcea G, Neal CP, Pattenden CJ, Steward WP, Berry DP. Molecular prognostic markers in pancreatic cancer: a systematic review. 2005 Oct;41(15):2213-36.

[148] Doucas H, Neal CP, O'Reilly K, Dennison AR, Berry DP. Frozen section diagnosis of pancreatic malignancy: a sensitive diagnostic technique. Pancreatology. 2006;6(3):210-3; discussion 4.

[149] Lechago J. Frozen section examination of liver, gallbladder, and pancreas. Arch Pathol Lab Med. 2005 Dec;129(12):1610-8.

[150] Hruban RH, Takaori K, Klimstra DS, Adsay NV, Albores-Saavedra J, Biankin AV, et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. The American journal of surgical pathology. 2004 Aug;28(8):977-87.

[151] UICC. Classification of Malignant Tumours. 6th ed. New York: Wiley-Liss 2002.

[152] Japan Pancreas Society. Classification of Pancreatic Carcinoma. 2nd English ed. Tokyo: JCS 2003.

[153] Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial.[see comment]. 2007 Jan 17;297(3):267-77.

[154] Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg. 1985 Aug;120(8):899-903.

[155] Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer.[see comment][erratum appears in N Engl J Med. 2004 Aug 12;351(7):726]. 2004 Mar 18;350(12):1200-10.

[156] Kosuge T, Kiuchi T, Mukai K, Kakizoe T, Japanese Study Group of Adjuvant Therapy for Pancreatic C. A multicenter randomized controlled trial to evaluate the effect of adjuvant cisplatin and 5-fluorouracil therapy after curative resection in cases of pancreatic cancer. 2006 Mar;36(3):159-65.

[157] Van Laethem J, Van Cutsem E, Hammel P, Mornex F, Azria D, Van Tienhoven G, et al. Adjuvant chemotherapy alone versus chemoradiation after curative resection for pancreatic cancer : feasibility results of a randomised EORTC/FFCD/GERCOR phase II/III study (40013/22012/0304). ASCO Meeting Abstracts. 2008 May 20, 2008;26(15_suppl):4514-.

[158] Maeda A, Boku N, Fukutomi A, Kondo S, Kinoshita T, Nagino M, et al. Randomized phase III trial of adjuvant chemotherapy with gemcitabine versus S-1 in patients with resected pancreatic cancer: Japan Adjuvant Study Group of Pancreatic Cancer (JASPAC-01). 2008 Mar;38(3):227-9.

[159] Brasiuniene B, Juozaityte E. The effect of combined treatment methods on survival and toxicity in patients with pancreatic cancer. Medicina. 2007;43(9):716-25.

[160] Regine WF, Winter KA, Abrams RA, Safran H, Hoffman JP, Konski A, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial.[see comment]. 2008 Mar 5;299(9):1019-26.

[161] Kim JK, Ha HK, Han DJ, Auh YH. CT analysis of postoperative tumor recurrence patterns in periampullary cancer. Abdom Imaging. 2003 May-Jun;28(3):384-91.

[162] Coombs RJ, Zeiss J, Howard JM, Thomford NR, Merrick HW. CT of the abdomen after the Whipple procedure: value in depicting postoperative anatomy, surgical complications, and tumor recurrence. AJR American journal of roentgenology. 1990 May;154(5):1011-4.

[163] Ruf J, Lopez Hanninen E, Oettle H, Plotkin M, Pelzer U, Stroszczynski C, et al. Detection of recurrent pancreatic cancer: comparison of FDG-PET with CT/MRI. Pancreatology. 2005;5(2-3):266-72.

[164] Banfi G, Bravi S, Ardemagni A, Zerbi A. CA 19.9, CA 242 and CEA in the diagnosis and follow-up of pancreatic cancer. The International journal of biological markers. 1996 Apr-Jun;11(2):77-81.

[165] Beretta E, Malesci A, Zerbi A, Mariani A, Carlucci M, Bonato C, et al. Serum CA 19-9 in the postsurgical follow-up of patients with pancreatic cancer. Cancer. 1987 Nov 15;60(10):2428-31.

[166] Micke O, Bruns F, Schafer U, Kurowski R, Horst E, Willich N. CA 19-9 in the therapy monitoring and follow-up of locally advanced cancer of the exocrine pancreas treated with radiochemotherapy. Anticancer Res. 2003 Mar-Apr;23(2A):835-40.

[167] Sultana A, Smith CT, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. 2007 Jun 20;25(18):2607-15.

[168] Yip D, Karapetis C, Strickland A, Steer CB, Goldstein D. Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer. Cochrane Database Syst Rev. 2006;3.

[169] Andersen JR, Friis-Moller A, Hancke S, Roder O, Steen J, Baden H. A controlled trial of combination chemotherapy with 5-FU and BCNU in pancreatic cancer. Scandinavian journal of gastroenterology. 1981;16(8):973-5.

[170] Boeck S, Hinke A, Wilkowski R, Heinemann V. Importance of performance status for treatment outcome in advanced pancreatic cancer. World J Gastroenterol. 2007 Jan 14;13(2):224-7.

[171] Ychou M, Desseigne F, Guimbaud R, Ducreux M, Bouche O, Becouarn Y, et al. Randomized phase II trial comparing folfirinox (5FU/leucovorin [LV], irinotecan [I] and oxaliplatin [O]) vs gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA). First results of the ACCORD 11 trial. ASCO Meeting Abstracts. 2007 June 20, 2007;25(18_suppl):4516-.

[172] Heinemann V, Boeck S, Hinke A, Labianca R, Louvet C. Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. BMC Cancer. 2008;8(82).

[173] Bria E, Milella M, Gelibter A, Cuppone F, Pino MS, Ruggeri EM, et al. Gemcitabine-based combinations for inoperable pancreatic cancer: have we made real progress? A meta-analysis of 20 phase 3 trials. 2007 Aug 1;110(3):525-33.

[174] Banu E, Banu A, Fodor A, Landi B, Rougier P, Chatellier G, et al. Meta-analysis of randomised trials comparing gemcitabine-based doublets versus gemcitabine alone in patients with advanced and metastatic pancreatic cancer. Drugs & Aging. 2007;24(10):865-79.

[175] Xie DR, Liang HL, Wang Y, Guo SS. Meta-analysis of inoperable pancreatic cancer: gemcitabine combined with cisplatin versus gemcitabine alone. Chin J Dig Dis. 2006;7(1):49-54.

[176] Germond C, Maroun J, Moore M, Zwaal C, Wong S, and members of the Gastrointestinal Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Use of Gemcitabine in the Treatment of Advanced Pancreatic Adenocarcinoma. Practice Guideline Report #2-10. Ottawa, Ontario: CCO 2005.

[177] Yang Q, Xie DR, Liang HL, Jiang ZM, Bi ZF, Chen SL. A meta-analysis of randomized controlled trials comparing gemcitabine (GEM)-based combination chemotherapy with gemcitabine alone in advanced pancreatic cancer: An updated subgroup analysis of overall survival. ASCO Meeting Abstracts. 2008 May 20, 2008;26(15_suppl):15661-.

[178] Herrmann R, Bodoky G, Ruhstaller T, Glimelius B, Bajetta E, Schuller J, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group.[see comment]. 2007 Jun 1;25(16):2212-7.

[179] Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group.[see comment]. 2007 May 20;25(15):1960-6.

[180] Richards DA, Boehm KA, Waterhouse DM, Wagener DJ, Krishnamurthi SS, Rosemurgy A, et al. Gemcitabine plus CI-994 offers no advantage over gemcitabine alone in the treatment of patients with advanced pancreatic cancer: results of a phase II randomized, double-blind, placebo-controlled, multicenter study. 2006 Jul;17(7):1096-102.

[181] Kindler HL, Niedzwiecki D, Hollis D, Oraefo E, Schrag D, Hurwitz H, et al. A double-blind, placebo-controlled, randomized phase III trial of gemcitabine (G) plus bevacizumab (B) versus gemcitabine plus placebo (P) in patients (pts) with advanced pancreatic cancer (PC): A preliminary analysis of Cancer and Leukemia Group B (CALGB. ASCO Meeting Abstracts. 2007 June 20, 2007;25(18_suppl):4508-.

[182] Philip PA, Benedetti J, Fenoglio-Preiser C, Zalupski M, Lenz H, O'Reilly E, et al. Phase III study of gemcitabine [G] plus cetuximab [C] versus gemcitabine in patients [pts] with locally advanced or metastatic pancreatic adenocarcinoma [PC]: SWOG S0205 study. ASCO Meeting Abstracts. 2007 June 20, 2007;25(18_suppl):LBA4509-.

[183] Spano J, Chodkiewicz C, Maurel J, Wong RP, Wasan HS, Pithavala YK, et al. A randomized phase II study of axitinib (AG-013736) and gemcitabine versus gemcitabine in advanced pancreatic cancer, preceded by a phase I component. ASCO Meeting Abstracts. 2007 June 20, 2007;25(18_suppl):4551-.

[184] Tuinmann G, Mueller L, Hossfeld D, Bokemeyer C. A randomised phase II study of gemcitabine versus mitomycin C versus gemcitabine/mitomycin C in patients with advanced pancreatic cancer. ASCO Meeting Abstracts. 2008 May 20, 2008;26(15_suppl):15658-.

[185] Wright JA, Osterlee J, Fekete S, Lee Y, Young AH. A phase III trial of virulizin plus gemcitabine vs. gemcitabine alone in advanced pancreatic cancer: Results of subgroup analysis. ASCO Meeting Abstracts. 2006 June 20, 2006;24(18_suppl):4116-.

[186] Van Cutsem E, Verslype C, Grusenmeyer PA. Lessons learned in the management of advanced pancreatic cancer. J Clin Oncol. 2007 May 20;25(15):1949-52.

[187] Cunningham D, Chau I, Stocken D, Davies C, Dunn J, Valle J, et al. Phase III randomised comparison of gemcitabine (GEM) versus gemcitabine plus capecitabine (GEM-CAP) in patients with advanced pancreatic cancer. Eur J Cancer Suppl. 2005;3(4):4 (PS11).

[188] Ducreux M, Mitry E, Ould-Kaci M, Boige V, Seitz JF, Bugat R, et al. Randomized phase II study evaluating oxaliplatin alone, oxaliplatin combined with infusional 5-FU, and infusional 5-FU alone in advanced pancreatic carcinoma patients.[see comment]. 2004 Mar;15(3):467-73.

[189] Levi FA, Tubiana-Mathieu N, Focan C, Brezault-Bonnet C, Coudert B, Carvalho C, et al. Chronomodulated (Chrono) vs constant (Cst) rate infusional 5-fluorouracil (FU) with or without cisplatin (CDDP) in patients with advanced or metastatic pancreatic cancer. A multicenter randomized trial of the Chronotherapy Group of the European Organisation for Research and Treatment of Cancer (EORTC 05962). ASCO Meeting Abstracts. 2004 July 15, 2004;22(14_suppl):4117-.

[190] Boeck S, Hoehler T, Seipelt G, Mahlberg R, Wein A, Hochhaus A, et al. Capecitabine plus oxaliplatin (CapOx) versus capecitabine plus gemcitabine (CapGem) versus gemcitabine plus oxaliplatin (mGemOx): final results of a multicenter randomized phase II trial in advanced pancreatic cancer. 2008 Feb;19(2):340-7.

[191] Lutz MP, Van Cutsem E, Wagener T, Van Laethem J-L, Vanhoefer U, Wils JA, et al. Docetaxel plus gemcitabine or docetaxel plus cisplatin in advanced pancreatic carcinoma: randomized phase II study 40984 of the European Organisation for Research and Treatment of Cancer Gastrointestinal Group. 2005 Dec 20;23(36):9250-6.

[192] Alberts SR, Foster NR, Morton RF, Kugler J, Schaefer P, Wiesenfeld M, et al. PS-341 and gemcitabine in patients with metastatic pancreatic adenocarcinoma: a North Central Cancer Treatment Group (NCCTG) randomized phase II study. 2005 Oct;16(10):1654-61.

[193] Kulke MH, Niedzwiecki D, Tempero MA, Hollis DR, Mayer RJ. A randomized phase II study of gemcitabine/cisplatin, gemcitabine fixed dose rate infusion, gemcitabine/docetaxel, or gemcitabine/irinotecan in patients with metastatic pancreatic cancer (CALGB 89904). ASCO Meeting Abstracts. 2004 July 15, 2004;22(14_suppl):4011-.

[194] Cheverton P, Friess H, Andras C, Salek T, Geddes C, Bodoky G, et al. Phase III results of exatecan (DX-8951f) versus gemcitabine (Gem) in chemotherapy-naive patients with advanced pancreatic cancer (APC). ASCO Meeting Abstracts. 2004 July 15, 2004;22(14_suppl):4005-.

[195] Reni M, Cereda S, Passoni P, Rognone A, Mazza E, Nicoletti R, et al. A randomized phase II trial of PEXG (cisplatin, epirubicin, capecitabine, gemcitabine) or PDXG (docetaxel) regimen in advanced pancreatic adenocarcinoma. ASCO Meeting Abstracts. 2007 June 20, 2007;25(18_suppl):4628-.

[196] Andre T, Afchain P, Lledo G, Nguyen S, Paitel J, Mineur L, et al. First-line simplified GEMOX (D1-D1) versus classical GEMOX (D1-D2) in metastatic pancreatic adenocarcinoma (MPA). A GERCOR randomized phase II study. ASCO Meeting Abstracts. 2007 June 20, 2007;25(18_suppl):4592-.

[197] Mitry E, Dahan L, Ychou M, Arthaud J, Gasmi M, Raoul J, et al. LV5FU2-cisplatin followed by gemcitabine or the reverse sequence in metastatic pancreatic cancer: Preliminary results of a randomized phase III trial (FFCD 0301). ASCO Meeting Abstracts. 2008 May 20, 2008;26(15_suppl):4513-.

[198] Cascinu S, Berardi R, Labianca R, Siena S, Falcone A, Aitini E, et al. Cetuximab plus gemcitabine and cisplatin compared with gemcitabine and cisplatin alone in patients with advanced pancreatic cancer: a randomised, multicentre, phase II trial.[see comment]. 2008 Jan;9(1):39-44.

[199] Astsaturov IA, Meropol NJ, Alpaugh RK, Cheng JD, Lewis NL, Beard M, et al. A randomized phase II and coagulation study of bevacizumab alone or with docetaxel in patients with

previously treated metastatic pancreatic adenocarcinoma. ASCO Meeting Abstracts. 2007 June 20, 2007;25(18_suppl):4556-.

[200] Ebert M, Nitsche B, Roecken C, Fahlke J, Hosius C, Gschaidmeier H, et al. A prospective and randomised clinical trial of the tyrosine kinase inhibitor imatinib mesylate as an initial therapy of advanced pancreatic cancer. ASCO Meeting Abstracts. 2004 July 15, 2004;22(14_suppl):4151-.

[201] Kindler HL, Bylow KA, Hochster HS, Friberg G, Micetich K, Locker G, et al. A randomized phase II study of bevacizumab (B) and gemcitabine (G) plus cetuximab (C) or erlotinib (E) in patients (pts) with advanced pancreatic cancer (PC): A preliminary analysis. ASCO Meeting Abstracts. 2006 June 20, 2006;24(18_suppl):4040-.

[202] Kindler HL, Gangadhar T, Karrison T, Hochster HS, Moore MJ, Micetich K, et al. Final analysis of a randomized phase II study of bevacizumab (B) and gemcitabine (G) plus cetuximab (C) or erlotinib (E) in patients (pts) with advanced pancreatic cancer (PC). ASCO Meeting Abstracts. 2008 May 20, 2008;26(15_suppl):4502-.

[203] Vervenne W, Bennouna J, Humblet Y, Gill S, Moore MJ, Van Laethem J, et al. A randomized, double-blind, placebo (P) controlled, multicenter phase III trial to evaluate the efficacy and safety of adding bevacizumab (B) to erlotinib (E) and gemcitabine (G) in patients (pts) with metastatic pancreatic cancer. ASCO Meeting Abstracts. 2008 May 20, 2008;26(15_suppl):4507-.

[204] Earle CC, Agboola O, Maroun J, Zuraw L, Cancer Care Ontario Practice Guidelines Initiative's Gastrointestinal Cancer Disease Site G. The treatment of locally advanced pancreatic cancer: a practice guideline. 2003 Mar;17(3):161-7.

[205] Sultana A, Tudur Smith C, Cunningham D, Starling N, Tait D, Neoptolemos JP, et al. Systematic review, including meta-analyses, on the management of locally advanced pancreatic cancer using radiation/combined modality therapy. 2007 Apr 23;96(8):1183-90.

[206] Shinchi H, Takao S, Noma H, Matsuo Y, Mataki Y, Mori S, et al. Length and quality of survival after external-beam radiotherapy with concurrent continuous 5-fluorouracil infusion for locally unresectable pancreatic cancer. 2002 May 1;53(1):146-50.

[207] Moertel CG, Frytak S, Hahn RG, O'Connell MJ, Reitemeier RJ, Rubin J, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. Cancer. 1981 Oct 15;48(8):1705-10.

[208] Loehrer PJ, Sr., Powell ME, Cardenes HR, Wagner L, Brell JM, Ramanathan RK, et al. A randomized phase III study of gemcitabine in combination with radiation therapy versus gemcitabine alone in patients with localized, unresectable pancreatic cancer: E4201. ASCO Meeting Abstracts. 2008 May 20, 2008;26(15_suppl):4506-.

[209] Li C-P, Chao Y, Chi K-H, Chan W-K, Teng H-C, Lee R-C, et al. Concurrent chemoradiotherapy treatment of locally advanced pancreatic cancer: gemcitabine versus 5-fluorouracil, a randomized controlled study.[see comment]. 2003 Sep 1;57(1):98-104.

[210] Radiation therapy combined with Adriamycin or 5-fluorouracil for the treatment of locally unresectable pancreatic carcinoma. Gastrointestinal Tumor Study Group. Cancer. 1985 Dec 1;56(11):2563-8.

[211] Earle JD, Foley JF, Wieand HS, Kvols LK, McKenna PJ, Krook JE, et al. Evaluation of external-beam radiation therapy plus 5-fluorouracil (5-FU) versus external-beam radiation therapy plus hycanthone (HYC) in confined, unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys. 1994 Jan 1;28(1):207-11.

[212] McCracken JD, Ray P, Heilbrun LK, Vaitkevicius VK, Saiki JH, Rivkin SE, et al. 5-Fluorouracil, methyl-CCNU, and radiotherapy with or without testolactone for localized adenocarcinoma of the exocrine pancreas: a Southwest Oncology Group Study. Cancer. 1980 Oct 1;46(7):1518-22.

[213] Wilkowski R, Thoma M, Bruns C, Wagner A, Heinemann V. Chemoradiotherapy with gemcitabine and continuous 5-FU in patients with primary inoperable pancreatic cancer. Jop. 2006;7(4):349-60.

[214] Huguet F, Andre T, Hammel P, Artru P, Balosso J, Selle F, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. J Clin Oncol. 2007 Jan 20;25(3):326-31.

[215] Moss AC, Morris E, Leyden J, MacMathuna P. Do the benefits of metal stents justify the costs? A systematic review and meta-analysis of trials comparing endoscopic stents for malignant biliary obstruction. Eur J Gastroenterol Hepatol. 2007 Dec;19(12):1119-24.

[216] Moss AC, Morris E, Mac Mathuna P. Palliative biliary stents for obstructing pancreatic carcinoma. Cochrane Database Syst Rev. 2006(1):CD004200.

[217] Hammarstrom L-E. Role of palliative endoscopic drainage in patients with malignant biliary obstruction. Dig Surg. 2005;22(5):295-304; discussion 5.

[218] Taylor MC, McLeod RS, Langer B. Biliary stenting versus bypass surgery for the palliation of malignant distal bile duct obstruction: a meta-analysis. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2000 May;6(3):302-8.

[219] Artifon ELA, Sakai P, Cunha JEM, Dupont A, Filho FM, Hondo FY, et al. Surgery or endoscopy for palliation of biliary obstruction due to metastatic pancreatic cancer. 2006 Sep;101(9):2031-7.

[220] Nieveen van Dijkum EJM, Romijn MG, Terwee CB, de Wit LT, van der Meulen JHP, Lameris HS, et al. Laparoscopic staging and subsequent palliation in patients with peripancreatic carcinoma. 2003 Jan;237(1):66-73.

[221] Date RS, Siriwardena AK. Current status of laparoscopic biliary bypass in the management of non-resectable peri-ampullary cancer. Pancreatology. 2005;5(4-5):325-9.

[222] Navarra G, Musolino C, Venneri A, De Marco ML, Bartolotta M. Palliative antecolic isoperistaltic gastrojejunostomy: a randomized controlled trial comparing open and laparoscopic approaches. 2006 Dec;20(12):1831-4.

[223] Van Heek NT, De Castro SMM, van Eijck CH, van Geenen RCI, Hesselink EJ, Breslau PJ, et al. The need for a prophylactic gastrojejunostomy for unresectable periampullary cancer: a prospective randomized multicenter trial with special focus on assessment of quality of life. Ann Surg. 2003 Dec;238(6):894-902; discussion -5.

[224] Yilmaz S, Kirimlioglu V, Katz DA, Kayaalp C, Caglikulekci M, Ara C. Randomised clinical trial of two bypass operations for unresectable cancer of the pancreatic head. Eur J Surg. 2001 Oct;167(10):770-6.

[225] Shyr YM, Su CH, King KL, Wang HC, Lo SS, Wu CW, et al. Randomized trial of three types of gastrojejunostomy in unresectable periampullary cancer. Surgery. 1997 May;121(5):506-12.

[226] Katsinelos P, Paikos D, Kountouras J, Chatzimavroudis G, Paroutoglou G, Moschos I, et al. Tannenbaum and metal stents in the palliative treatment of malignant distal bile duct obstruction: a comparative study of patency and cost effectiveness. 2006 Oct;20(10):1587-93.

[227] Soderlund C, Linder S. Covered metal versus plastic stents for malignant common bile duct stenosis: a prospective, randomized, controlled trial.[see comment]. 2006 Jun;63(7):986-95.

[228] Goonetilleke KS, Siriwardena AK. Systematic review of peri-operative nutritional supplementation in patients undergoing pancreaticoduodenectomy. Jop. 2006;7(1):5-13.

[229] Giger U, Buchler M, Farhadi J, Berger D, Husler J, Schneider H, et al. Preoperative immunonutrition suppresses perioperative inflammatory response in patients with major abdominal surgery-a randomized controlled pilot study. Ann Surg Oncol. 2007 Oct;14(10):2798-806.

[230] Braga M, Gianotti L, Radaelli G, Vignali A, Mari G, Gentilini O, et al. Perioperative immunonutrition in patients undergoing cancer surgery: results of a randomized double-blind phase 3 trial.[see comment]. Arch Surg. 1999 Apr;134(4):428-33.

[231] Braga M, Gianotti L, Gentilini O, Parisi V, Salis C, Di Carlo V. Early postoperative enteral nutrition improves gut oxygenation and reduces costs compared with total parenteral nutrition.[see comment]. Crit Care Med. 2001 Feb;29(2):242-8.

[232] Braga M, Gianotti L, Vignali A, Cestari A, Bisagni P, Di Carlo V. Artificial nutrition after major abdominal surgery: impact of route of administration and composition of the diet.[see comment]. Crit Care Med. 1998 Jan;26(1):24-30.

[233] Di Carlo V, Gianotti L, Balzano G, Zerbi A, Braga M. Complications of pancreatic surgery and the role of perioperative nutrition. Dig Surg. 1999;16(4):320-6.

[234] Gianotti L, Braga M, Vignali A, Balzano G, Zerbi A, Bisagni P, et al. Effect of route of delivery and formulation of postoperative nutritional support in patients undergoing major operations for malignant neoplasms. Arch Surg. 1997 Nov;132(11):1222-9; discussion 9-30.

[235] Fish J, Sporay G, Beyer K, Jones J, Kihara T, Kennedy A, et al. A prospective randomized study of glutamine-enriched parenteral compared with enteral feeding in postoperative patients. Am J Clin Nutr. 1997 Apr;65(4):977-83.

[236] Klek S, Kulig J, Sierzega M, Szczepanek K, Szybinski P, Scislo L, et al. Standard and immunomodulating enteral nutrition in patients after extended gastrointestinal surgery--a prospective, randomized, controlled clinical trial. Clin Nutr. 2008 Aug;27(4):504-12.

[237] Lobo DN, Williams RN, Welch NT, Aloysius MM, Nunes QM, Padmanabhan J, et al. Early postoperative jejunostomy feeding with an immune modulating diet in patients undergoing resectional surgery for upper gastrointestinal cancer: a prospective, randomized, controlled, double-blind study. Clin Nutr. 2006 Oct;25(5):716-26.

[238] Jo S, Choi S-H, Heo J-S, Kim E-M, Min M-S, Choi D-W, et al. Missing effect of glutamine supplementation on the surgical outcome after pancreaticoduodenectomy for periampullary tumors: a prospective, randomized, double-blind, controlled clinical trial. World Journal of Surgery. 2006 Nov;30(11):1974-82; discussion 83-4.

[239] Heller AR, Rossel T, Gottschlich B, Tiebel O, Menschikowski M, Litz RJ, et al. Omega-3 fatty acids improve liver and pancreas function in postoperative cancer patients. International Journal of Cancer. 2004 Sep 10;111(4):611-6.

[240] Topal B, Peeters G, Vandeweyer H, Aerts R, Penninckx F. Hospital cost-categories of pancreaticoduodenectomy. Acta Chir Belg. 2007 Jul-Aug;107(4):373-7.

[241] Major P, Figueredo A, Tandan V, Bramwell V, Charette M, Oliver T, et al. The Role of Octreotide in the Management of Patients with Cancer. Practice Guideline Report #12-7. Ontario: CCO 2003.

[242] Hesse UJ, DeDecker C, Houtmeyers P, Demetter P, Ceelen W, Pattyn P, et al. Prospectively randomized trial using perioperative low-dose octreotide to prevent organ-related and general complications after pancreatic surgery and pancreatico-jejunostomy.[erratum appears in World J Surg. 2006 Apr;30(4):641]. World Journal of Surgery. 2005 Oct;29(10):1325-8.

[243] Shan Y-S, Sy ED, Lin P-W. Role of somatostatin in the prevention of pancreatic stump-related morbidity following elective pancreaticoduodenectomy in high-risk patients and elimination of surgeon-related factors: prospective, randomized, controlled trial. World Journal of Surgery. 2003 Jun;27(6):709-14.

[244] Gouillat C, Chipponi J, Baulieux J, Partensky C, Saric J, Gayet B. Randomized controlled multicentre trial of somatostatin infusion after pancreaticoduodenectomy. British Journal of Surgery. 2001 Nov;88(11):1456-62.

[245] Sarr MG, Pancreatic Surgery G. The potent somatostatin analogue vapreotide does not decrease pancreas-specific complications after elective pancreatectomy: a prospective, multicenter, double-blinded, randomized, placebo-controlled trial. J Am Coll Surg. 2003 Apr;196(4):556-64; discussion 64-5; author reply 65.

[246] Bruno MJ. Maldigestion and Exocrine Pancreatic Insufficiency after Pancreatic Resection for Malignant Disease. Pancreatology. 2001;1, suppl.1:55-61.

[247] Safdi M, Bekal PK, Martin S, Saeed ZA, Burton F, Toskes PP. The effects of oral pancreatic enzymes (Creon 10 capsule) on steatorrhea: a multicenter, placebo-controlled, parallel group trial in subjects with chronic pancreatitis. Pancreas. 2006 Aug;33(2):156-62.

[248] Stern RC, Eisenberg JD, Wagener JS, Ahrens R, Rock M, doPico G, et al. A comparison of the efficacy and tolerance of pancrelipase and placebo in the treatment of steatorrhea in cystic fibrosis patients with clinical exocrine pancreatic insufficiency. Am J Gastroenterol. 2000 Aug;95(8):1932-8.

[249] Bruno MJ, Haverkort EB, Tijssen GP, Tytgat GN, van Leeuwen DJ. Placebo controlled trial of enteric coated pancreatin microsphere treatment in patients with unresectable cancer of the pancreatic head region. Gut. 1998 Jan;42(1):92-6.

[250] American Society of Anesthesiologists Task Force on Acute Pain M. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology. 2004 Jun;100(6):1573-81.

[251] Barzoi G, Carluccio S, Bianchi B, Vassia S, Colucci G, Mangiante GL. Morphine plus bupivacaine vs. morphine peridural analgesia in abdominal surgery: the effects on postoperative course in major hepatobiliary surgery. HPB Surg. 2000 Aug;11(6):393-9.

[252] Ravasco P, Monteiro-Grillo I, Camilo ME. Does nutrition influence quality of life in cancer patients undergoing radiotherapy? Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2003 May;67(2):213-20.

[253] Capra S, Bauer J, Davidson W, Ash S. Nutritional therapy for cancer-induced weight loss. Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition. 2002 Aug;17(4):210-3.

[254] Davidson W, Ash S, Capra S, Bauer J, Cancer Cachexia Study G. Weight stabilisation is associated with improved survival duration and quality of life in unresectable pancreatic cancer. Clin Nutr. 2004 Apr;23(2):239-47.

[255] Fearon KCH, Von Meyenfeldt MF, Moses AGW, Van Geenen R, Roy A, Gouma DJ, et al. Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial.[see comment]. Gut. 2003 Oct;52(10):1479-86.

[256] Bauer J, Capra S, Battistutta D, Davidson W, Ash S, Cancer Cachexia Study G. Compliance with nutrition prescription improves outcomes in patients with unresectable pancreatic cancer. Clin Nutr. 2005 Dec;24(6):998-1004.

[257] Moses AWG, Slater C, Preston T, Barber MD, Fearon KCH. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. British Journal of Cancer. 2004 Mar 8;90(5):996-1002.

[258] Yan BM, Myers RP. Neurolytic celiac plexus block for pain control in unresectable pancreatic cancer. Am J Gastroenterol. 2007 Feb;102(2):430-8.

[259] Zhang C-L, Zhang T-J, Guo Y-N, Yang L-Q, He M-W, Shi J-Z, et al. Effect of neurolytic celiac plexus block guided by computerized tomography on pancreatic cancer pain. Dig Dis Sci. 2008 Mar;53(3):856-60.

[260] Ischia S, Ischia A, Polati E, Finco G. Three posterior percutaneous celiac plexus block techniques. A prospective, randomized study in 61 patients with pancreatic cancer pain. Anesthesiology. 1992 Apr;76(4):534-40.

[261] Suleyman Ozyalcin N, Talu GK, Camlica H, Erdine S. Efficacy of coeliac plexus and splanchnic nerve blockades in body and tail located pancreatic cancer pain. Eur J Pain. 2004 Dec;8(6):539-45.

[262] Gress F, Schmitt C, Sherman S, Ikenberry S, Lehman G. A prospective randomized comparison of endoscopic ultrasound- and computed tomography-guided celiac plexus block for managing chronic pancreatitis pain.[see comment]. Am J Gastroenterol. 1999 Apr;94(4):900-5.

[263] Kuchler T, Bestmann B, Rappat S, Henne-Bruns D, Wood-Dauphinee S. Impact of psychotherapeutic support for patients with gastrointestinal cancer undergoing surgery: 10-year survival results of a randomized trial.[see comment][erratum appears in J Clin Oncol. 2007 Sep 20;25(27):4328]. J Clin Oncol. 2007 Jul 1;25(19):2702-8.

[264] Meyers MO, Meszoely IM, Hoffman JP, Watson JC, Ross E, Eisenberg BL. Is reporting of recurrence data important in pancreatic cancer? Ann Surg Oncol. 2004 Mar;11(3):304-9.

[265] Wilkowski R, Thoma M, Bruns C, Duhmke E, Heinemann V. Combined chemoradiotherapy for isolated local recurrence after primary resection of pancreatic cancer. Jop. 2006;7(1):34-40.

[266] Kleeff J, Reiser C, Hinz U, Bachmann J, Debus J, Jaeger D, et al. Surgery for recurrent pancreatic ductal adenocarcinoma. Ann Surg. 2007 Apr;245(4):566-72.

[267] Miura F, Takada T, Amano H, Yoshida M, Isaka T, Toyota N, et al. Repeated pancreatectomy after pancreatoduodenectomy. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2007 Feb;11(2):179-86.

[268] Nakeeb A, Lillemoe KD, Cameron JL. The role of pancreaticoduodenectomy for locally recurrent or metastatic carcinoma to the periampullary region. J Am Coll Surg. 1995 Feb;180(2):188-92.

[269] Moriya T, Kimura W, Hirai I, Mizutani M, Yamamoto T, Toya R, et al. Twelve years survival with repeated hepatectomy and lung resection for metastasis from carcinoma of the papilla of Vater after pancreaticoduodenectomy. Hepatogastroenterology. 2007 Sep;54(78):1652-4.

[270] Sperti C, Pasquali C, Decet G, Chierichetti F, Liessi G, Pedrazzoli S. F-18-fluorodeoxyglucose positron emission tomography in differentiating malignant from benign pancreatic cysts: a prospective study. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2005 Jan;9(1):22-8; discussion 8-9.

[271] Imamura M, Doi R, Imaizumi T, Funakoshi A, Wakasugi H, Sunamura M, et al. A randomized multicenter trial comparing resection and radiochemotherapy for resectable locally invasive pancreatic cancer. Surgery. 2004 Nov;136(5):1003-11.

[272] Riall TS, Cameron JL, Lillemoe KD, Campbell KA, Sauter PK, Coleman J, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma--part 3: update on 5-year survival. Journal of Gastrointestinal Surgery. 2005 Dec;9(9):1191-204; discussion 204-6.

[273] Poon RTP, Fan ST, Lo CM, Ng KK, Yuen WK, Yeung C, et al. External drainage of pancreatic duct with a stent to reduce leakage rate of pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized trial. Ann Surg. 2007 Sep;246(3):425-33; discussion 33-5.

[274] Kobari M, Matsuno S. Staging systems for pancreatic cancer: differences between the Japanese and UICC systems. J Hepatobiliary Pancreat Surg. 1998;5(2):121-7.

[275] Balzano G, Bassi C, Zerbi A, Falconi M, Calori G, Butturini G, et al. Evaluation of UICC TNM classification for pancreatic cancer. A study of 228 patients. Int J Pancreatol. 1997 Apr;21(2):111-8.

[276] Bakkevold KE, Kambestad B. Staging of carcinoma of the pancreas and ampulla of Vater. Tumor (T), lymph node (N), and distant metastasis (M) as prognostic factors. Int J Pancreatol. 1995 Jun;17(3):249-59.

[277] Zerbi A, Balzano G, Bottura R, Di Carlo V. Reliability of pancreatic cancer staging classifications. Int J Pancreatol. 1994 Feb;15(1):13-8.

[278] Tsunoda T, Ura K, Eto T, Matsumoto T, Tsuchiya R. UICC and Japanese stage classifications for carcinoma of the pancreas. Int J Pancreatol. 1991 Apr;8(3):205-14.

[279] Yoshitomi H, Togawa A, Kimura F, Shimizu H, Yoshidome H, Miyazaki M, et al. A randomized phase II trial of adjuvant chemotherapy with uracil / tegafur (UFT) and gemcitabine (GEM) vs. gemcitabine alone in patients with resected pancreatic cancer. ASCO Meeting Abstracts. 2007 June 20, 2007;25(18_suppl):4542-.

[280] Xie D-R, Liang H-L, Wang Y, Guo S-S, Yang Q. Meta-analysis on inoperable pancreatic cancer: a comparison between gemcitabine-based combination therapy and gemcitabine alone. World J Gastroenterol. 2006 Nov 21;12(43):6973-81.

This page is left intentionally blank.

Dépôt légal : D/2009/10.273/11

KCE reports

1. Efficacité et rentabilité des thérapies de sevrage tabagique. D/2004/10.273/2.
2. Etude relative aux coûts potentiels liés à une éventuelle modification des règles du droit de la responsabilité médicale (Phase 1). D/2004/10.273/4.
3. Utilisation des antibiotiques en milieu hospitalier dans le cas de la pyélonéphrite aiguë. D/2004/10.273/6.
4. Leucoréduction. Une mesure envisageable dans le cadre de la politique nationale de sécurité des transfusions sanguines. D/2004/10.273/8.
5. Evaluation des risques préopératoires. D/2004/10.273/10.
6. Validation du rapport de la Commission d'examen du sous financement des hôpitaux. D/2004/10.273/12.
7. Recommandation nationale relative aux soins prénatals: Une base pour un itinéraire clinique de suivi de grossesses. D/2004/10.273/14.
8. Systèmes de financement des médicaments hospitaliers: étude descriptive de certains pays européens et du Canada. D/2004/10.273/16.
9. Feedback: évaluation de l'impact et des barrières à l'implémentation – Rapport de recherche: partie 1. D/2005/10.273/02.
10. Le coût des prothèses dentaires. D/2005/10.273/04.
11. Dépistage du cancer du sein. D/2005/10.273/06.
12. Etude d'une méthode de financement alternative pour le sang et les dérivés sanguins labiles dans les hôpitaux. D/2005/10.273/08.
13. Traitement endovasculaire de la sténose carotidienne. D/2005/10.273/10.
14. Variations des pratiques médicales hospitalières en cas d'infarctus aigu du myocarde en Belgique. D/2005/10.273/12
15. Evolution des dépenses de santé. D/2005/10.273/14.
16. Etude relative aux coûts potentiels liés à une éventuelle modification des règles du droit de la responsabilité médicale. Phase II : développement d'un modèle actuariel et premières estimations. D/2005/10.273/16.
17. Evaluation des montants de référence. D/2005/10.273/18.
18. Utilisation des itinéraires cliniques et guides de bonne pratique afin de déterminer de manière prospective les honoraires des médecins hospitaliers: plus facile à dire qu'à faire.. D/2005/10.273/20
19. Evaluation de l'impact d'une contribution personnelle forfaitaire sur le recours au service d'urgences. D/2005/10.273/22.
20. HTA Diagnostic Moléculaire en Belgique. D/2005/10.273/24, D/2005/10.273/26.
21. HTA Matériel de Stomie en Belgique. D/2005/10.273.28.
22. HTA Tomographie par Emission de Positrons en Belgique. D/2005/10.273/30.
23. HTA Le traitement électif endovasculaire de l'anévrysme de l'aorte abdominale (AAA). D/2005/10.273.33.
24. L'emploi des peptides natriurétiques dans l'approche diagnostique des patients présentant une suspicion de décompensation cardiaque. D/2005/10.273.35
25. Endoscopie par capsule. D2006/10.273.02.
26. Aspects médico-légaux des recommandations de bonne pratique médicale. D2006/10.273/06.
27. Qualité et organisation des soins du diabète de type 2. D2006/10.273/08.
28. Recommandations provisoires pour les évaluations pharmacoéconomiques en Belgique. D2006/10.273/11.
29. Recommandations nationales Collège d'oncologie : A. cadre général pour un manuel d'oncologie B. base scientifique pour itinéraires cliniques de diagnostic et traitement, cancer colorectal et cancer du testicule. D2006/10.273/13.
30. Inventaire des bases de données de soins de santé. D2006/10.273/15.
31. Health Technology Assessment : l'antigène prostatique spécifique (PSA) dans le dépistage du cancer de la prostate. D2006/10.273/18.
32. Feedback: évaluation de l'impact et des barrières à l'implémentation - Rapport de recherche: partie II. D2006/10.273/20.
33. Effets et coûts de la vaccination des enfants Belges au moyen du vaccin conjugué antipneumococcique. D2006/10.273/22.
34. Trastuzumab pour les stades précoces du cancer du sein. D2006/10.273/24.

35. Etude relative aux coûts potentiels liés à une éventuelle modification des règles du droit de la responsabilité médicale – Phase III : affinement des estimations. D2006/10.273/27.
36. Traitement pharmacologique et chirurgical de l'obésité. Prise en charge résidentielle des enfants sévèrement obèses en Belgique. D/2006/10.273/29.
37. Health Technology Assessment Imagerie par Résonance Magnétique. D/2006/10.273/33.
38. Dépistage du cancer du col de l'utérus et recherche du Papillomavirus humain (HPV). D/2006/10.273/36
39. Evaluation rapide de technologies émergentes s'appliquant à la colonne vertébrale : remplacement de disque intervertébral et vertébro/cyphoplastie par ballonnet. D/2006/10.273/39.
40. Etat fonctionnel du patient: un instrument potentiel pour le remboursement de la kinésithérapie en Belgique? D/2006/10.273/41.
41. Indicateurs de qualité cliniques. D/2006/10.273/44.
42. Etude des disparités de la chirurgie élective en Belgique. D/2006/10.273/46.
43. Mise à jour de recommandations de bonne pratique existantes. D/2006/10.273/49.
44. Procédure d'évaluation des dispositifs médicaux émergeants. D/2006/10.273/51.
45. HTA Dépistage du Cancer Colorectal : état des lieux scientifique et impact budgétaire pour la Belgique. D/2006/10.273/54.
46. Health Technology Assessment. Polysomnographie et monitoring à domicile des nourrissons en prévention de la mort subite. D/2006/10.273/60.
47. L'utilisation des médicaments dans les maisons de repos et les maisons de repos et de soins Belges. D/2006/10.273/62
48. Lombalgie chronique. D/2006/10.273/64.
49. Médicaments antiviraux en cas de grippe saisonnière et pandémique. Revue de littérature et recommandations de bonne pratique. D/2006/10.273/66.
50. Contributions personnelles en matière de soins de santé en Belgique. L'impact des suppléments. D/2006/10.273/69.
51. Besoin de soins chroniques des personnes âgées de 18 à 65 ans et atteintes de lésions cérébrales acquises. D/2007/10.273/02.
52. Rapid Assessment: Prévention cardiovasculaire primaire dans la pratique du médecin généraliste en Belgique. D/2007/10.273/04.
53. Financement des soins Infirmiers Hospitaliers. D/2007/10 273/06
54. Vaccination des nourrissons contre le rotavirus en Belgique. Analyse coût-efficacité
55. Valeur en termes de données probantes des informations écrites de l'industrie pharmaceutique destinées aux médecins généralistes. D/2007/10.273/13
56. Matériel orthopédique en Belgique: Health Technology Assessment. D/2007/10.273/15.
57. Organisation et Financement de la Réadaptation Locomotrice et Neurologique en Belgique D/2007/10.273/19
58. Le Défibrillateur Cardiaque Implantable.: un rapport d'évaluation de technologie de santé D/2007/10.273/22
59. Analyse de biologie clinique en médecine général. D/2007/10.273/25
60. Tests de la fonction pulmonaire chez l'adulte. D/2007/10.273/28
61. Traitement de plaies par pression négative: une évaluation rapide. D/2007/10.273/31
62. Radiothérapie Conformationelle avec Modulation d'intensité (IMRT). D/2007/10.273/33.
63. Support scientifique du Collège d'Oncologie: un guideline pour la prise en charge du cancer du sein. D/2007/10.273/36.
64. Vaccination HPV pour la prévention du cancer du col de l'utérus en Belgique: Health Technology Assessment. D/2007/10.273/42.
65. Organisation et financement du diagnostic génétique en Belgique. D/2007/10.273/45.
66. Drug Eluting Stents en Belgique: Health Technology Assessment. D/2007/10.273/48.
67. Hadronthérapie. D/2007/10.273/51.
68. Indemnisation des dommages résultant de soins de santé - Phase IV : Clé de répartition entre le Fonds et les assureurs. D/2007/10.273/53.
69. Assurance de Qualité pour le cancer du rectum – Phase I: Recommandation de bonne pratique pour la prise en charge du cancer rectal D/2007/10.273/55
70. Etude comparative des programmes d'accréditation hospitalière en Europe. D/2008/10.273/02
71. Recommandation de bonne pratique clinique pour cinq tests ophtalmiques. D/2008/10.273/05
72. L'offre de médecins en Belgique. Situation actuelle et défis. D/2008/10.273/08

73. Financement du programme de soins pour le patient gériatrique dans l'hôpital classique : Définition et évaluation du patient gériatrique, fonction de liaison et évaluation d'un instrument pour un financement approprié. D/2008/10.273/12
74. Oxygénothérapie Hyperbare: Rapid Assessment. D/2008/10.273/14.
75. Guideline pour la prise en charge du cancer oesophagien et gastrique: éléments scientifiques à destination du Collège d'Oncologie. D/2008/10.273/17.
76. Promotion de la qualité de la médecine générale en Belgique: status quo ou quo vadis ? D/2008/10.273/19.
77. Orthodontie chez les enfants et adolescents D/2008/10.273/21
78. Recommandations pour les évaluations pharmacoéconomiques en Belgique. D/2008/10.273/24.
79. Remboursement des radioisotopes en Belgique. D/2008/10.273/27.
80. Évaluation des effets du maximum à facturer sur la consommation et l'accessibilité financière des soins de santé. D/2008/10.273/36.
81. Assurance de qualité pour le cancer rectal – phase 2: développement et test d'un ensemble d'indicateurs de qualité. D/2008/10.273/39
82. Angiographie coronaire par tomodensitométrie 64-détecteurs chez les patients suspects de maladie coronarienne. D/2008/10.273/41
83. Comparaison internationale des règles de remboursement et aspects légaux de la chirurgie plastique D/2008/10.273/44
84. Les séjours psychiatriques de longue durée en lits T. D/2008/10.273/47
85. Comparaison de deux systèmes de financement des soins de première ligne en Belgique. D/2008/10.273/50.
86. Différenciation de fonctions dans les soins infirmiers :possibilités et limites D/2008/10.273/53
87. Consommation de kinésithérapie et de médecine physique et de réadaptation en Belgique. D/2008/10.273/55
88. Syndrome de Fatigue Chronique : diagnostic, traitement et organisation des soins. D/2008/10.273/59.
89. Evaluation des certains nouveaux traitements du cancer de la prostate et de l'hypertrophie bénigne de la prostate. D/2008/10.273/62
90. Médecine générale: comment promouvoir l'attraction et la rétention dans la profession ? D/2008/10.273/64.
91. Appareils auditifs en Belgique: health technology assessment. D/2008/10.273/68
92. Les infections nosocomiales en Belgique : Volet I, Etude Nationale de Prévalence. D/2008/10.273/71.
93. Détection des événements indésirables dans les bases de données administratives. D/2008/10.273/74.
94. Soins maternels intensifs (Maternal Intensive Care) en Belgique. D/2008/10.273/78.
95. Implantation percutanée des valvules cardiaques dans le cas de maladies valvulaires congénitales et dégénératives: A rapid Health Technology Assessment. D/2007/10.273/80.
96. Construction d'un index médical pour les contrats privés d'assurance maladie. D/2008/10.273/83.
97. Centres de réadaptation ORL/PSY : groupes cibles, preuves scientifiques et organisation des soins. D/2009/10.273/85.
98. Évaluation de programmes de vaccination généraux et ciblés contre l'hépatite A en Belgique. D/2008/10.273/89.
99. Financement de l'hôpital de jour gériatrique. D/2008/10.273/91.
100. Valeurs seuils pour le rapport coût-efficacité en soins de santé. D/2008/10.273/95.
101. Enregistrement vidéo des interventions chirurgicales par endoscopie : une évaluation rapide. D/2008/10.273/98.
102. Les infections nosocomiales en Belgique: Volet II: Impact sur la mortalité et sur les coûts. D/2009/10.273/100.
103. Réformes dans l'organisation des soins de santé mentale : étude d'évaluation des 'projets thérapeutiques' - 1er rapport intermédiaire. D/2009/10.273/05.
104. Chirurgie assistée par robot: health technology assessment. D/2009/10.273/08
105. Soutien scientifique au Collège d'Oncologie: recommandations pour la pratique clinique dans la prise en charge du cancer du pancréas. D/2009/10.273/11

106.