**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 6444**

**Columns:** **TOPIC HIGHLIGHT**

WJG 20th Anniversary Special Issues (14): Pancreatic cancer

**Pancreatic cancer-improved care achievable**

Buanes TA *et al*. Outcome in pancreatic cancer

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**Received:** October 17, 2013 **Revised:** January 16, 2014

**Accepted:** April 30, 2014

**Published online:**

 **Abstract**

Pancreatic adenocarcinoma is one of the most aggressive cancers, and the decline in mortality observed in most other cancer diseases, has so far not taken place in pancreatic cancer. Complete tumor resection is a requirement for potential cure, and the reorganization of care in the direction of high patient-volume centers, offering multimodal treatment, has improved survival and Quality of Life. Also the rates and severity grade of complications are improving in high-volume pancreatic centers. One of the major problems worldwide is underutilization of surgery in resectable pancreatic cancer. Suboptimal investigation, follow up and oncological treatment outside specialized centers are additional key problems. New chemotherapeutic regimens like FOLFIRINOX have improved survival in patients with metastatic disease, and different adjuvant treatment options result in well documented survival benefit. Neoadjuvant treatment is highly relevant, but needs further evaluation. Also adjuvant immunotherapy, in the form of vaccination with synthetic K-Ras-peptides, has been shown to produce long term immunological memory in cytotoxic T-cells in long term survivors. Improvement in clinical outcome is already achievable and further progress is expected in the near future for patients treated with curative as well as palliative intention.

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**Key words:** Pancreatic cancer; Pathogenesis; Prevention; Diagnosis; Treatment; Evidence-based medicine; Immunotherapy; Adjuvant chemotherapy; Neoadjuvant chemotherapy

**Core tip:** Curative treatment outcome for patients with pancreatic cancer is achievable if early surgical treatment is combined with adjuvant chemotherapy. Nevertheless, most patients end up in a palliative situation, earlier or later. But also palliative therapeutic interventions are improving, but a multidisciplinary team with advanced expertise is a prerequisite for optimal care.

Buanes TA. Pancreatic cancer-improved care achievable. *World J Gastroenterol* 2014; In press

**INTRODUCTION**Pancreatic adenocarcinoma is one of the most aggressive cancers. Despite all advances in cancer treatment it is still the fourth most-frequent tumor-related cause of death in the Western world[[1](#_ENREF_1)]. The reasons for this are challenges associated with the diagnosis, which tend to be late and precarious, but more importantly limited therapeutic options. Therefore, even though cancer mortality in Europe has declined by approximately 10% during recent years, this is not the case for pancreatic cancer[[2](#_ENREF_2)]. The development of new and potent treatment options is therefore strongly needed. In recent years there have been important advances in the organization of care for pancreatic cancer patients, also resulting in more focused studies on preoperative investigation, surgical, oncological and immunological treatment. This review summarizes available evidence, focusing best clinical practice based on the latest translational research.

**RESEARCH**
Search in Pud review articles, relevant to the scope of this review, was prioritized. bMed was performed with the key words: Pancreatic cancer, combined with pathogenesis, prevention, diagnosis and treatment. Reports were selected, based on publication date (preferring recent studies) and conceived internal validity in each single paper. A balanced mix of original papers, preferring randomized trials initiated after 2003, and Cochrane reviews, meta-analyses and review articles, relevant to the scope of this review, were prioritized.

**PATHOGENESIS**

The cause of pancreatic cancer remains unknown. Several environmental factors have been implicated, but a causal role has been shown only for tobacco. The risk of pancreatic cancer in smokers is 2.5 to 3.6 times that in non-smokers, increasing with greater tobacco use and longer duration of exposure[[3](#_ENREF_3)]. Worldwide the proportion of early onset pancreatic cancer is strongly correlated with lung cancer mortality [[4](#_ENREF_4)](r2 = 0.53), suggesting that approximately half of the variation in the proportion of early onset pancreatic cancer can be explained by smoking. The possible roles of moderate intake of alcohol, coffee, and use of aspirin as contributing factors are supported by very limited data. Increased risk of pancreatic cancer among patients with blood type A, B or AB as compared with blood type O has been observed in recent reports[[5](#_ENREF_5), [6](#_ENREF_6)]. Pancreatic cancer also occurs with increased frequency among persons with long-standing diabetes[[7](#_ENREF_7),[8](#_ENREF_8)], but this does not necessarily imply that diabetes is a pathogenetic factor, as it may be a consequence of the cancer. The latter concept is supported by the recent observation that adrenomedullin is upregulated in patients with pancreatic cancer and causes insulin resistance in β cells[[9](#_ENREF_9)]. A recent meta-analysis also favors the association between hepatitis B/C infection and pancreatic cancer[[10](#_ENREF_10)]
 There may be a causal relationship between chronic pancreatitis and pancreatic cancer, but the population attributable fraction was estimated to only 1.34% (95%CI: 0.612-2.07) in a recent study[[11](#_ENREF_11)], suggesting that a relatively small proportion of pancreatic cancers might be avoided if pancreatitis could be prevented. Pancreatitis appearing shortly before the diagnosis of pancreatic cancer is probably the result of tumor-related ductal obstruction. But patients with hereditary pancreatitis , which is a rare subgroup of chronic pancreatitis, have a marked relative and absolute increased risk of pancreatic cancer[[12](#_ENREF_12)] as compared to the general population, especially in smokers. This has been documented in two comprehensive international studies[[13](#_ENREF_13),[14](#_ENREF_14)]. Whitcomb[[15](#_ENREF_15)] identified in 1996 the first genetic defect in patients with hereditary pancreatitis on the cationic trysinogen gene (PRSS1).

**GENETICS** Pancreatic cancer has been shown to result from a successive accumulation of gene mutations[[16](#_ENREF_16)] in the ductal epithelium, evolving from premalignant lesions to fully invasive cancer. Pancreatic intraepithelial neoplasia is a precursor of pancreatic cancer[[17](#_ENREF_17)], progressing from minimally dysplastic epithelium to invasive carcinoma. During carcinogenesis accumulation of mutations take place, initially activation of the KRAS2 oncogene, then inactivation of the tumor suppressor gene CDKN2A and inactivation of the tumor suppressor gene TP53 and finally deletion of the SMAD family member 4 gene[[18](#_ENREF_18),[19](#_ENREF_19)].

At least one of four genetic defects are present in almost all patients with fully established pancreatic cancer[[20](#_ENREF_20)]. Activated mutations in the KRAS2 oncogene is very frequent in pancreatic cancer cells, making this mutation an appropriate target for immunological attack from vaccine-activated cytotoxic T-cells[[21](#_ENREF_21)]. The abnormal Ras protein, generated from transcription of the mutant KRAS gene, results in permanent activation of proliferative and survival signaling pathways in the cancer cells.

Comprehensive genetic analysis of 24 pancreatic cancers showed that the genetic basis of the tumor is extremely complex and heterogeneous[[22](#_ENREF_22)]. An average of 63 genetic abnormalities per tumor was found, mainly point mutations, classified as likely to be carcinogenetically relevant. These abnormalities can be organized in 12 functional pathways. A model of this carcinogenetic process is presented graphically as the “Components of Pancreatic Cancer” in a clarifying review article by Hidalgo[[19](#_ENREF_19)].

Genomic sequencing, evaluating the clonal relationships among primary and metastatic pancreatic cancer cells, has recently been performed. Based on differential accumulation of mutations, the authors estimated that pancreatic tumors cells are present for 6 to 12 years before development of metastatic disease, suggesting a broad time window for early detection of the primary tumor[[23](#_ENREF_23)].

**PREVENTION**Universal primary screening for pancreatic cancer is currently not recommended, given the tools available and their performance[[24](#_ENREF_24),[25](#_ENREF_25)], even though the time interval when pancreatic cancer cells are present in advance of their dissemination, is probably long[[23](#_ENREF_23),[26](#_ENREF_26)]. Hence, the beneficial potential of a biomarker panel with the required accuracy, is huge. No imaging modality fills this requirement. Sensitivity as well as specificity of endoscopic ultrasound (EUS) examination has been improving during recent years, and enables fine needle aspiration (FNA) during the same procedure. But even screening of high-risk groups by EUS combined with CT, should only be performed in the context of prospective trials[[25](#_ENREF_25),[27](#_ENREF_27)].

The number of patients with incidentally diagnosed cystic pancreatic lesions is rising, most likely due to the increased use of high-resolution imaging[[28](#_ENREF_28)]. The variable degree of malignancy potential in different cystic pancreatic lesions can be clarified by EUS guided aspiration/analysis of cystic fluid, as low levels of CEA (carcinoembryonic antigen) in cyst fluid from serous cystadenoma has been documented[[29](#_ENREF_29)]. Oppositely, cyst fluid from mucinous lesions tends to have high CEA values[[30](#_ENREF_30)]. Intraductal papillary mucinous neoplasms (IPMN) in the main duct develop invasive carcinoma more often than IPMN lesions in side branches[[31](#_ENREF_31)], both supposed to be more indolent than sporadic pancreatic adenocarcinoma. But in patients with lymph node metastasis, long term survival curves are almost identical[[32](#_ENREF_32)]. IPMN-lesions usually have a premalignant time interval of several years duration. Surgical resection of mucinous cystic lesions before they become invasive carcinoma, apparently represents one of the best opportunities to prevent pancreatic cancer. Also when incidentally recognized malignant lesions undergo surgical resection, survival is significantly improved[[33](#_ENREF_33)]. Five year survival above 30% is reported after resection of incidentaloma, even in distal pancreatic carcinoma[[34](#_ENREF_34)]. Prevention of death from pancreatic cancer is therefore increasingly affordable, even though screening programs have not become the way to do it up till now.

**DIAGNOSIS**High quality imaging plays a crucial role in the diagnosis of pancreatic tumors. One cross-sectional imaging modality is sufficient for adequate evaluation of tumor diagnosis and resectability in most patients. Multidetector computed tomography (CT) angiography, performed by using a dedicated dual-phase pancreatic protocol [[35](#_ENREF_35)] is the preference of most centers[[36](#_ENREF_36)]. Adoption of a standardized template for radiology reporting in pancreatic neoplasms is strongly recommended in a consensus statement, authored by radiologists, gastroenterologists and hepatopancreaticobiliary surgeons under the sponsorship of the Society of Abdominal Radiologists and the American Pancreatic Association[[35](#_ENREF_35)]. MRI, including magnetic resonance cholangiography, may help to differentiate cystic lesions, but does not add information about resectability. Endoscopic ultrasound (EUS) guided fine-needle aspiration is essential for analysis of cystic fluid, and is the best method for obtaining a tissue diagnosis when needed, *i.e.,* before neoadjuvant or palliative chemotherapy. Routine use of ERCP or 18F-fluorodeoxyglucose (18F-FDG) PET cannot be recommended[[36](#_ENREF_36),[37](#_ENREF_37)]. ERCP should only be used for therapeutic purposes, because of the high frequency of severe complications. Procedure-related mortality rate of 1.4% have recently been published[[38](#_ENREF_38)]. Routine preoperative biopsy of resectable pancreatic tumors is not advisable, because malignant disease cannot be ruled out reliably[[39](#_ENREF_39)]. Seeding of cancer cells along the path of the needle[[40](#_ENREF_40)] after percutaneous biopsy is another reason for avoiding preoperative biopsy in patients with resectable tumors.

**BIOMARKERS**

Numerous biomarkers for cancer have been developed[[41](#_ENREF_41)], but the clinical benefit in pancreatic cancer patients has so far been limited, and the persistent search for a biomarker panel with improved sensitivity/specificity is important. New markers based on analysis of gene expression[[42](#_ENREF_42)], proteomic analysis[[43](#_ENREF_43)], radiolabeling with anti-Claudine 4[[44](#_ENREF_44)] and membrane bound molecules[[41](#_ENREF_41)] are developing, but a panel also including microRNA (miRNA) as a biomarker, seems presently most likely to obtain clinical significance[[45](#_ENREF_45)]. The beneficial role of a secure biomarker panel is obvious for primary diagnosis, as well as monitoring of treatment outcome. Carbohydrate antigen 19-9 (CA 19-9) is in widespread clinical use, even though sensitivity and specificity are low[[46](#_ENREF_46)]. Its clinical usefulness in early detection of recurrent disease and therapeutic monitoring is well documented[[47](#_ENREF_47)].

**STAGING**Pancreatic cancer is staged according to the most recent edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification [[48](#_ENREF_48)]. Treatment of different stages have been changing during recent years, and the outcome, recorded with survival and Quality of life (QoL) as clinical endpoints, changes with the development of revised guidelines. Bilimoria et al reported in 2007[[49](#_ENREF_49)] survival data resulting from treatment according to staging by the 6th edition of AJCC Pancreatic Cancer Staging System, when T1, T2 and T3 tumors are considered potentially resectable, even though locally advanced T3 tumors involve the superior mesenteric veins (SMV), portal vein (PV), or splenic vein (SV). Median survival 24.1 months was reported in stage 1A, decreasing to 4.5 months in stage IV. Details of stage characteristics are given in Bilimorias report from the National Cancer (NCD)-database[[49](#_ENREF_49)] and in Hidalgos review[[19](#_ENREF_19)]. However, the practical consequences of staging, related to assessment of resectability and timing of an operation, is changing after the introduction of the concept of borderline resectable tumors. As indicated in table 1, this question depends on the local handling program of each pancreatic center.

**TREATMENT** Long term survival is not achieved in pancreatic cancer patients without surgical resection of the tumor. This is true even when chemoradiation is used in early stage disease[[50](#_ENREF_50),[51](#_ENREF_51)]. The superiority of surgery over chemoradiotherapy has even been documented in a randomized controlled trial (one year survival 62% *vs* 32%, *P* < 0.05)[[52](#_ENREF_52)]. In the Surveillance Epidemiology and End Result (SEER) database, curative intent surgery was found to be the strongest predictor of prolonged survival[[53](#_ENREF_53)]*.* In high-volume centers, resection of mesenteric vessels and even multivisceral resection are performed in patients with locally advanced disease [[54-58](#_ENREF_54)] to enable long term survival.

**MULTIDISCIPLINARY APPROACH**

A multidisciplinary approach is mandatory, already at the time of primary diagnosis of pancreatic cancer. The impact was evaluated in 203 consecutive patients at the Johns Hopkins pancreatic multidisciplinary clinic in 2006/2007[[59](#_ENREF_59)], and a comprehensive and coordinated evaluation led to changes in therapeutic recommendations in almost one-quarter of patients. Patient logistics and care was organized around a nurse navigator in an “All-in-One Resort”[[60](#_ENREF_60),[61](#_ENREF_61)], and high degree of patient satisfaction has been reported. The continuous ongoing development of oncological and surgical treatment algorithms in patients with borderline resectable and locally advanced disease, further underlines the importance of close cooperation within the multidisciplinary team in order to maximize short- and long-term oncological outcomes[[62](#_ENREF_62)].

**SURGERY – FOR WHOM, HOW AND WHEN?**

Improved quality of preoperative staging has enabled radiological classification of pancreatic tumors as resectable, borderline resectable (a concept which has been defined by a consensus panel[[63](#_ENREF_63),[64](#_ENREF_64)]) and locally advanced unresectable tumors. Borderline resectable tumors may be treated by neoadjuvant chemoradiation, which has been shown to result in high rates of R0 resections, and 5 year survival in the same range as primary resectable tumors[[63](#_ENREF_63)]. But the downside of the neoadjuvant protocol was that significant numbers of included patients with potentially resectable tumors at inclusion (approximately ¼), progressed during neoadjuvant treatment and could never be resected[[63](#_ENREF_63),[65](#_ENREF_65)]. These patients have the disadvantage of median survival 8 months[[66](#_ENREF_66)]. Future development of care for patients with pancreatic cancer is obviously emerging towards more advanced surgery for new patient groups combined with oncological efforts after surgery, probably also preoperatively. Further prospective clinical studies, focusing clinical outcome, are mandatory. But the underutilization of surgery in patients with localized pancreatic cancer is a major ethical problem: Numerous patients without any contraindication against surgery never receive surgical treatment of their serious disease[[50](#_ENREF_50),[67](#_ENREF_67)].

The best outcome of surgical treatment is histologically free resection margin (R0) and it has been unclear whether an R1 resection confers any survival benefit at all over no surgical removal of locally advanced tumors. Even the predictive value of an R0 resection has been queried: In 360 consecutive patients, undergoing pancreaticoduodenectomy, R0 was found in 300 (83.3%), but R0 status did not come out as survival predictor in multivariate analyses[[68](#_ENREF_68)]. Patients who underwent an R1 resection had a median overall survival of 21.5 mo compared with 27.8 mo after R0 resection, which was found not significantly different. This might in part be explained by the fact that up till 2006, pathological examination of pancreaticoduodenectomy specimens were not standardized between different pancreatic centers[[69](#_ENREF_69),[70](#_ENREF_70)]. Verbeke *et al*[[71](#_ENREF_71)] published a systematic, detailed technique for handling and evaluation of resected specimens with colouring of the resectional margins, redefining R1 resection as tumor cells within 1 mm of the resection margin. The Heidelberg group documented that R0 resection came out as predictor of long term survival in multivariate analyses after the introduction of this standardized handling of resected specimens[[54](#_ENREF_54)]. Accordingly, refinement of surgical technique, aiming at increased rates of R0 resection, defined by new standards, is mandatory. This may require increased rates of resection of the SMV/PV[[72](#_ENREF_72)], altered dissection strategy[[73](#_ENREF_73)] or it might be advantageous to alter the whole treatment algorithm, introducing neoadjuvant chemoradiotherapy in patients with borderline resectable tumours, as described in the United States National Comprehensive Cancer Network guidelines[[36](#_ENREF_36),[74](#_ENREF_74)]. European guidelines are different, as neoadjuvant chemoradiotherapy is not recommended in patients with resectable pancreatic cancer[[75](#_ENREF_75)]. The intention behind the neoadjuvant treatment algorithm is to avoid surgery in patients with rapidly progressive disease, and to achieve better local tumour control for the residual group, potentially even to down-size unresectable locally advanced tumours to allow secondary resection. Chemoradiotherapy before any surgical resection selects patients with more stable disease for surgery and putative micrometastasis may be treated at an earlier stage. On the other hand significant numbers of primary resectable patients become unresectable during neoadjuvant treatment and the outcome of primary resection followed by adjuvant chemotherapy is lost in many of these cases. A median survival of 23[[76](#_ENREF_76)] to 28 months[[77](#_ENREF_77)] has been documented in two recent randomized controlled trials. This life expectancy is replaced by the prospects of an unresectable tumor, being less than a year, ie. significantly shorter[[78](#_ENREF_78)].

**COMPARISON OF OUTCOME**

Table 2 puts together core data from four studies illustrating principal difficulties, arising when outcome of neoadjuvant treatment is compared with upfront surgery followed by adjuvant chemotherapy. Katz *et al*[65] published 2008 median postoperative survival 40 mo and 94% R0 resections, which is the best outcome for resected patients. But most patients included in the study could never be respected, and it is an open question what the clinical outcome of an earlier operation would have been in these cases. On the other hand, Nordby *et al*[72] published in 2013, that almost 90% of patients scheduled for upfront surgery were actually resected, but the rate of R0 resection was low, and it is underlined that alteration of surgical technique might be an opportunity of improvement: Increased frequency of resection of the PV/SMV and/or artery first dissection strategy. Finally, ESPAC centers resected PV/SMV in 17 % of operated patients, and obtained similar oncological outcome in the whole group of included patients, when surgery was performed first. Also the Heidelberg group (Schmidt 2012) has reported equivalent survival after upfront surgery. The different outcome in these series is probably explained by diverse patient selection, differences in preoperative and intraoperative criteria for resectability and variable surgical technique. These parameters illustrate important confounding factors when outcome is compared between neoadjuvant and upfront surgical treatment algorithms. Further efforts are therefore needed to standardize and clarify critical determining factors of outcome in advance of future randomized clinical trials. According to the current available evidence, neoadjuvant therapy is usually not recommended for patients with curatively resectable pancreatic cancer[[36](#_ENREF_36),[75](#_ENREF_75)], but the prospective evaluation in well-designed controlled trials is mandatory. A synthesis of the considerations above is summarized in Figure 1A, suggesting upfront surgery for all patients with resectable tumor, followed by adjuvant chemotherapy. However, the inclusion of resectable as well as borderline resectable tumors in a neoadjuvant protocol is the preference of MD Anderson Cancer Center[[79](#_ENREF_79)] as shown in Figure 1B. Further details on tumor biology, enabling personalized medical treatment plans would significantly improve outcome in both arms of these trials, and probably reduce health care costs[[80](#_ENREF_80),[81](#_ENREF_81)].

The purpose of surgical resection of pancreatic tumors is radicality, but final R1 status occurs in all centers. Already in 1996 Lillemoe published data, suggesting a survival benefit of R1 resection over locally advanced unresectable tumours[[82](#_ENREF_82)]. Two recent publications have verified increased survival after R1 resection. Konstantinidis *et al*[[83](#_ENREF_83)] found median survival 14 months in 157 R1 resected patients versus 11 months in 286 locally advanced, unresectable cases. Nordby *et al*[[84](#_ENREF_84)] found median 18 months survival after R1 resection versus 8.1 months in the locally advanced unresectable group and also QoL, recorded longitudinally, was found improved in the resected group. Collective evidence supports the concept that there is a significant clinical benefit of removing the pancreatic tumor, even if the resectional status is R1.

**ONCOLOGICAL TREATMEN**

Pancreatic adenocarcinoma tend to be chemoresistant and for a long period little progress has been obtained by traditional anti-tumor treatment, illustrated by the fact that gemcitabine has been standard of care since 1997[[85](#_ENREF_85)]. But Conroy et al published 2011[[86](#_ENREF_86)] a randomized controlled trial including 342 metastatic patients, comparing FOLFIRINOX (oxaliplatin, irinotecan, leucoverin and fluouracil) with gemcitabine, and found significantly increased survival (11.1 *vs* 6.8 mo). The objective response rate was 31.6% in the FOLFIRINOX group versus 9.4% in the gemcitabine group (*P* < 0.001). During ASCO 2012 the FOLFIRINOX regimen was characterized as a paradigm shift in oncological treatment of pancreatic cancer, and this regimen is now under evaluation in potentially curative subgroups, as those with borderline resectable tumours[[87](#_ENREF_87)]. The results are positive, but the toxicity of FOLFIRINOX generates significant limitations, as only patients with relatively good health can be included.

Evaluation of adjuvant chemotherapy, combined with radiotherapy or alone, was first analysed in well-designed randomized trials in the ESPAC 1 study which showed no survival benefit for adjuvant chemoradiotherapy but a significant prolonged survival in patients treated by fluouracil and folic acid[[88](#_ENREF_88),[89](#_ENREF_89)]. However, a meta-analysis suggests that further studies with chemoradiation is warranted in patients with positive resection margins, as chemotherapy appears relatively ineffective in this subgroup[[90](#_ENREF_90)]. Another important observation in the ESPAC 1 study was that also QoL, recorded prospectively, was not negatively affected by adjuvant chemotherapy compared to surgery alone[[91](#_ENREF_91)]. Also adjuvant gemcitabine was found to delay recurrence after complete resection of pancreatic cancer[[92](#_ENREF_92)]. Finally adjuvant gemcitabine was compared with fluouracil/folic acid in the ESPAC 3 trial, which did not find any difference[[76](#_ENREF_76)].

Neoadjuvant chemoradiotherapy seems to have an obvious place in patients with locally advanced unresectable tumors, who may become resectable after downstaging[[93](#_ENREF_93)]. However, downstaging filling the RECIST (Response Evaluation Criteria in Solid Tumors) criteria, was found very rare in a recent review[[79](#_ENREF_79)]. In patients with resectable or borderline resectable tumors, the role of gemcitabine is controversial[[94](#_ENREF_94)] due to objective response rates below 10%. But potent new regimens like FOLFIRINOX may expand this window of opportunity.

***Immunotherapy***

After decades of disappointment, the recent success of immunotherapy in metastatic melanoma, including proof-of concept trials[[95](#_ENREF_95)], have renewed the interest in this form of therapy also against pancreatic cancer. In fact, the concept of immune attach against pancreatic tumor cells by CD4+/CD8+ T-lymphocytes was published already in 1997[[96](#_ENREF_96)]. A second treatment protocol was initiated simultaneously, utilizing adjuvant vaccination with synthetic ras peptides encompassing residues 5-21 of p21 ras in patients operated for pancreatic cancer[[21](#_ENREF_21)]. This phase I/II trial included 23 resected patients, receiving adjuvant vaccination, subsequently followed till death or for more than ten years. Three patients mounted a memory response immunologically up to nine years after vaccination. Recurrence was found in a fourth patient six years after the Whipple procedure, and her T-cells had then lost their reactivity. After baseline vaccination (1998), she mounted a strong immune response. The evaluation of K-ras peptides in phase II/III trials are ongoing, so far in the Targovax-study, but numerous other basic and translational efforts are in progress[[97](#_ENREF_97)].

Also the catalytic subunit of telomerase, hTERT, expressed in 85%-90% of human cancer tissue[[98](#_ENREF_98)], is an attractive “universal” tumour antigen. A synthetic peptide, GV1001, has been tested in unresectable pancreatic cancer patients, with promising outcome: Vaccination initiated CD4+/CD8+ immune response[[99](#_ENREF_99)] *via* multiple MHC class II alleles. The intermediate dose of GV1001 resulted in immune response in ¾ of included patients, with significantly increased survival (median 7.2 mo *vs* 2.9 mo) in responding patients. This resulted in a following phase III trial, the Primovax Study, evaluating GV1001 as monotherapy in one arm, compared with standard gemcitabine in the other arm. The intention was to randomize 520 patients to each arm. But the study was closed after inclusion of 360 patients when preliminary data on the deaths of 174 patients showed no survival benefit in the GV1001 group[[100](#_ENREF_100)]. Another randomized trial with three arms, comparing survival in metastatic pancreatic cancer after gemcitabine plus capecitabine, versus gemcitabine plus capecitabine followed by GV 1001 in the second arm and concurrent gemcitabine/capecitabine in the third arm, could neither improve outcome by adding the vaccine[[101](#_ENREF_101)].

**PALLIATIVE SURGERY/ENDOSCOPY**

The majority of patients with pancreatic cancer are not resectable at the time of presentation, with life expectancy less than one year for approximately 80%-90%. Palliative interventions for these patients intend to solve problems associated with biliary occlusion and/or duodenal obstruction. The advantage of surgical palliation with double bypass has been to obtain lifelong palliation with one single procedure[[102](#_ENREF_102)]. But improved radiological staging enables secure prediction of resectability in most cases, and the advantage of avoiding surgical exploration of unresectable patients favors endoscopic stenting, also of patients with duodenal obstruction[[103](#_ENREF_103)]. The development of defined quality indicators for the different aspects of the handling of pancreatic cancer patients[[104](#_ENREF_104)] enables better focus on clinical outcome in future treatment guidelines. The symptom profile of advanced pancreatic cancer is dominated by fatigue and pain[[105](#_ENREF_105)] and appropriate treatment of nausea and vomiting is important[[106](#_ENREF_106)]. The palliative functions of the multidisciplinary team have to be closely integrated to offer well-timed help when treatment aspirations change from curative to palliative ambitions[[107](#_ENREF_107)]: Endoscopic and radiological interventions, together with nutritional support may significantly improve clinical outcome[[108](#_ENREF_108)].

**QUALITY OF LIFE /PATIENT REPORTED OUTCOME**

The short survival in most patients with pancreatic cancer makes clinical research difficult due to limited follow-up before transition into a general palliative stage. The symptom profile adds to this problem, because fatigue is a major problem for the majority of patients already at the time of primary diagnosis[[105](#_ENREF_105)], and several patients are unable to fill comprehensive report forms. Available knowledge about health-related QoL in pancreatic cancer patients is constrained – for these and several other reasons. The lack of disease-specific tools for QoL-registration in patients with pancreatic cancer is one of the main reasons for shortage of information about clinical outcome. Several self-reported measures have been used in research, but only the European Organisation for Research and Treatment in Cancer (EORTC) has developed a disease-specific instrument for pancreatic cancer[[109](#_ENREF_109)]. The QoL module for pancreatic cancer (EORTC QLQ-PANC26) has 26 questions and must be used in conjunction with the generic instrument EORTC Quality of Life Questioinnaire-C30 (EORTC C-30). Ultimately, altogether 56 questions have to be completed, strongly restricting the feasibility of the instrument both in research and clinical practice. This applies particularly for patients with severe, disabling disease[[105](#_ENREF_105)]. The Edmonton Symptom System (ESAS) form is short and hence feasible, but generic. A recent new instrument is now developed, which is short and disease-specific, the pancreatic cancer disease impact (PACADI) score[[110](#_ENREF_110)]. The methodology behind the PACADI score utilized experience from rheumatology, where the Rheumatoid Arthritis Impact of Disease (RAID) score, based on patients’ selection of dimensions where the disease has the most important impact on their QoL, has been developed and validated[[111](#_ENREF_111), [112](#_ENREF_112)]. The RAID score is proven to be feasible and is now widely used in research. Similarly, the PACADI score asked for the patients’ priorities. The three dimensions with most severe negative impact on pancreatic cancer patients QoL, was pain/discomfort, fatigue and problems with bowel/digestion. But patients with severe icterus reported itching as their most important problem. In order to characterize clinical outcome of therapeutic interventions in a cohort with the short life expectancy of pancreatic cancer patients, it is of utmost importance to obtain valid data on patient reported outcome (PRO). Figure 2 illustrates the difference between a generic (ESAS) and disease-specific (PACADI) instrument in this regard.

**IMPORTANCE OF PATIENT VOLUME**

Pancreatic surgery has now been accepted as one of the most recognized high-risk, low-volume surgical procedures, but this has not taken place without widespread reluctance in the medical community. One early comprehensive analysis of the relationship between a hospitals patient volume and outcome, was published in 2002 by Birkemeyer *et al*[[113](#_ENREF_113)], focused on selected cardiovascular and cancer procedures. Absolute differences in adjusted postoperative mortality rates after pancreatic resections ranged from 16.3% (low volume) and 3.8% (high volume). Several subsequent reports supported the concept that outcome is best in high-volume hospitals, first because complications are recognized earlier and handled better, second because better oncological surgery and chemotherapy is offered[[114-116](#_ENREF_114)]. The statement that postoperative mortality rates as well as long-term survival are improved with high patient volume, is now clearly evidence-based[[117](#_ENREF_117)]. The aggressiveness of the tumor combined with the rates and severity grade of complications associated with pancreatic surgery, resulted in an almost nihilistic therapeutic attitude for several years[[118](#_ENREF_118)]. The fact that most patients with pancreatic cancer die shortly after diagnosis was for years a “self-verifying prophecy”, uphold by negative expectations in most of the medical world. This was a real observation – nevertheless, evidence-based medicine is something very different.

**FUTURE PERSPECTIVES**

The room for improvement is huge in diagnostic as well as therapeutic aspects of pancreatic cancer. The development of a panel of biomarkers enabling early detection of small and localized cancerous lesions is still only a dream, but progress is speeding up, particularly the stability of free miRNA in serum[[119](#_ENREF_119)] has fostered optimism. Even the recurrence risk after surgery and the probable response to anti-tumor therapy may be predicted and become a key to individualized treatment plans in the near future. Novel chemotherapy regimens with documented improved survival are now available[[86](#_ENREF_86)], and even chemo- and radiotherapy resistance may be reversed through utilization of the regulatory effect of miRNA on essential molecular pathways[[120](#_ENREF_120)].

Surgical performance has improved significantly in large volume centers and the laparoscopic technique is well established for distal resections[[121](#_ENREF_121),[122](#_ENREF_122)]. Skepticism remains for laparoscopic resection of adenocarcinoma but the rate of R0 resection was 91% and five year survival 30% in a recent report[[34](#_ENREF_34)]. Accordingly, oncological results are equal or may even be better after laparoscopic than open resection. Also pancreaticoduodenectomy (Whipple-procedures) may be performed laparoscopically, but available data on outcome are scarce[[123](#_ENREF_123)]. Robotic surgery might generate security advantages in this field[[124](#_ENREF_124)], and it seems reasonable to assume that the immunosuppressive effect of surgery can be significantly reduced when an open Whipple-procedure is replaced by a laparoscopic operation. This might represent a greater window of opportunity for adjuvant immunotherapy, becoming more effective when inhibitory immunoregulation is downgraded or even eliminated.

The need of well-designed prospective trials clarifying the role of neoadjuvant chemotherapy is underlined also by other authors[[125](#_ENREF_125),[126](#_ENREF_126)]. Important stadardization of staging and treatment is incorporated in the Intergroup trial (Alliance A021101)[[79](#_ENREF_79)], which is conducted as a single arm pilot study, intended to serve as paradigm for future randomized comparative trials.

**CONCLUSION**Curative treatment outcome for patients with pancreatic cancer is achievable if early surgical treatment is combined with adjuvant chemotherapy. Nevertheless, most patients end up in a palliative situation, earlier or later. But also palliative therapeutic interventions are improving, but a multidisciplinary team with advanced expertise is a prerequisite for optimal care. Translational research is the key to personalized treatment plans, which is strongly needed in patients with pancreatic cancer[[127](#_ENREF_127)].

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**P-Reviewers:** Lee KT, Talukdar R **S-Editor:** Qi Y **L-Editor: E-Editor:**

**Table 1 Staging of pancreatic cancer according to the American Joint Committee on Cancer[**[**48**](#_ENREF_48)**], together with clinical implication for resectability, illustrating that T3 and even T4 tumors may be considered borderline resectable**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Stage** | **Tumor grade1** | **Nodal status1** | **Distant metastases1** | **Resectability** |
| IA | T1 | N0 | M0 | Resectable |
| IB | T2 | N0 | M0 |
| IIA | T3 | N0 | M0 | Borderline resectable2 |
| IIB | T1, T2 or T3 | N1 | M0 |
| III | T4 | Any N | M0 |
| IV | Any T | Any N | M1 | Unresectable, independent of T-grade |

1N denotes regional lymph nodes, M distant metastases, and T primary tumor. 2The concept “borderline resectable”, related to T3 and T4 tumors, is not uniformly conceived between pancreatic centers.

**Table 2 Core data, characterizing outcome of neoadjuvant chemoradiation and surgery, versus upfront surgery plus adjuvant chemotherapy in patients with resectable and/or borderline resectable pancreatic tumor**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Patientsincluded** | **Inclusion periode** | **Treatmentalgorithm** | **Propor-tion not resected** | **R0****stat-us** | **Fre-quency of vascu-lar resec-tion** | **Median survival****in months** |
| Katz 2008[[63](#_ENREF_63)] | 160 | 1999-2006 | Neo-adjuvant | 59 % | 94% | 27 % | 40 |
| Nordby 2013[[84](#_ENREF_84)] | 135 | 2008-2010 | Upfront surgery+ adjuvance | 11 % | 42 % | 6 % | Na1 |
| Neop-tolemos 2010[[76](#_ENREF_76)] | 1088 | 2000-2007 | Upfront surgery+ adjuvance | Only resected patients included | 65 % | 17 % | 23 |
| Schmidt 2012[[77](#_ENREF_77)] | 132 | 2004-2007 | Upfront surgery+ adjuvance | Only resected patients included | 61 % | Na2 | 28 |

Na1: Too short follow up; Na2: Not given in the paper.

**Figure 1 Treatment algorithm for pacreatic tumors including only patients with borderline resectable lesions in randomized controlled trial (A), alternative model, including primary resectable and borderline resectable tumors in RCT, comparing outcome of upfront surgery and neoadjuvant chemotherapy (B).**

**Figure 2 ESAS and pancreatic cancer disease impact form in a patient with serum bilirubin 550 µmol/L, illustrating that only the disease specific instrument enables report on the patient’s most severe problem.**