REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Pancreatic Adenocarcinoma

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PANCREATIC DUCTAL ADENOCARCINOMA IS THE MOST LETHAL COMMON cancer because it is usually diagnosed at an advanced stage and is resistant to therapy. In this article, we review current understanding of the biology and treatment of pancreatic adenocarcinoma.

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EPIDEMIOLOGY AND RISK FACTORS

Pancreatic adenocarcinoma is rarely diagnosed in persons younger than 40 years of age, and the median age at diagnosis is 71 years. Worldwide, the incidence of all types of pancreatic cancer (85% of which are adenocarcinomas) ranges from 1 to 10 cases per 100,000 people, is generally higher in developed countries and among men, and has remained stable for the past 30 years relative to the incidence of other common solid tumors.[1] It is the eighth leading cause of death from cancer in men and the ninth leading cause of death from cancer in women throughout the world. In the United States this year, pancreatic cancer is expected to develop in 46,000 people, and 40,000 people are expected to die from it.[2]

The risk factors and established genetic syndromes associated with pancreatic adenocarcinoma are shown in Table 1. Although it is estimated that 5 to 10% of pancreatic cancers have an inherited component, the genetic basis for familial aggregation has not been identified in most cases.[16] Among people with a known family history of pancreatic cancer in a first-degree relative, as compared with the general population, the relative risk of the development of pancreatic cancer is increased by a factor of 2, 6, and 30 in people with one, two, and three affected family members, respectively.[17] There is no effective screening tool to detect asymptomatic premalignant or early malignant tumors, and aspirin has not been proved to have a protective effect against pancreatic cancer, as it does against other types of cancer.[18] Although there is consensus regarding the value of screening patients with an inherited predisposition for pancreatic cancer, there is no consensus on the most effective method of screening or the optimal interval between screenings.[19]

BIOLOGIC FEATURES OF PANCREATIC CANCER

Defining features of pancreatic adenocarcinoma include a very high rate of activating mutations in *KRAS* (>90%), progression from distinct types of precursor lesions, a propensity for both local invasion and distant metastasis, an extensive stromal reaction (desmoplasia) resulting in a hypovascular and hypoxic microenvironment, reprogramming of cellular metabolism, and evasion of tumor immunity.[20]

Molecular pathology studies and extensive genomic analyses have established a model of the progression of pancreatic adenocarcinoma. The signature mutations of pancreatic adenocarcinoma have been identified in microscopic premalignant pancreatic lesions associated with the pancreatic ducts; these findings are referred to as pancreatic intraepithelial neoplasia. As in the model established for the polyp-to-adenocarcinoma sequence in colon cancer, there is a stepwise progression

Table 1. Risk Factors and Inherited Syndromes Associated with Pancreatic Cancer.*

Variable	Approximate Risk
Risk factor	
Smoking[3]	2–3
Long-standing diabetes mellitus[4]	2
Nonhereditary and chronic pancreatitis[5]	2–6
Obesity, inactivity, or both[6]	2
Non–O blood group[7]	1–2
Genetic syndrome and associated gene or genes — %	
Hereditary pancreatitis (*PRSS1, SPINK1*)[8]	50
Familial atypical multiple mole and melanoma syndrome (*p16*)[9]	10–20
Hereditary breast and ovarian cancer syndromes (*BRCA1, BRCA2, PALB2*)[10,11]	1–2
Peutz–Jeghers syndrome (*STK11* [*LKB1*])[12]	30–40
Hereditary nonpolyposis colon cancer (Lynch syndrome) (*MLH1, MSH2, MSH6*)[13]	4
Ataxia–telangiectasia (*ATM*)[14]	Unknown
Li–Fraumeni syndrome (P53)[15]	Unknown

* Values associated with risk factors are expressed as relative risks, and values associated with genetic syndromes are expressed as lifetime risks, as compared with the risk in the general population.

of pancreatic intraepithelial neoplasia from low grade to high grade in types 1, 2, and 3. These types are associated with accumulating genetic alterations. In autopsy series, low-grade pancreatic intraepithelial neoplasia type 1 lesions are readily detectable in the nondiseased pancreas, whereas more advanced lesions are typically detected adjacent to established adenocarcinomas or in the non–tumor-bearing pancreas in patients with a familial predisposition to pancreatic cancer.[21] More than 90% of cases of pancreatic intraepithelial neoplasia of all grades have *KRAS* mutations.[22] The mutational inactivation of the *CDKN2A*, *p53*, and SMAD family member 4 (*SMAD4*) tumor suppressors is detected with increasing frequency in type 2 and type 3 lesions of pancreatic intraepithelial neoplasia, suggesting that *KRAS* mutations contribute to its inception and that the subsequent mutations are rate-limiting events for tumor progression.[23] Genetically engineered mouse models are consistent with this model of genetic progression.[24]

Recent exome-sequencing studies have identified additional loss-of-function mutations encoding components of the SWI/SNF nucleosome remodeling complex, which are cumulatively detected in approximately 10 to 15% of pancreatic adenocarcinomas, as well as other, less frequent alterations.[25] Since these are alterations of tumor-suppressor genes, they have not yet led to hypotheses for therapeutic interventions. Beyond these mutational events, the pancreatic adenocarcinoma genome is characterized by diverse, large-scale chromosomal changes with frequent amplifications, deletions, and rearrangements.

Intraductal papillary mucinous neoplasms are a second type of precursor to pancreatic cancer. These radiographically detectable cystic tumors are relatively common (occurring in approximately 2% of adults and in up to 10% of persons 70 years of age or older), and they have heterogeneous histologic and clinical features. Although most intraductal papillary mucinous neoplasms are asymptomatic, these tumors are associated with an overall risk of invasive cancer of approximately 25%, and those arising from the main pancreatic duct have considerably higher malignant potential than those arising from the branch duct. Like pancreatic epithelial neoplasms, intraductal papillary mucinous neoplasms frequently harbor *KRAS* mutations (in 40 to 65% of cases) (Fig. 1).[26] In addition, 40 to 80% have activating mutations in *GNAS* (encoding the G-protein subunit α_s, which activates adenylate cyclase, leading to cyclic AMP production), and more than 50% have inactivation of *RNF43* (an antagonist of Wnt signaling); the effect of these mutations is unknown.

The majority of genomics analyses have focused on resected pancreatic adenocarcinoma, which accounts for only approximately 15% of cases. Exome sequencing from a rapid autopsy program in which patients with pancreatic cancer had provided consent for an autopsy to be performed immediately after death has shown considerable intratumoral genomic heterogeneity, with multiple distinct subclones arising from a common originating cell, as has been noted in other types of cancer.[27] Also, the primary tumors and the metastatic deposits obtained from the same patient have largely overlapping genomic features. Nevertheless, metastases arise from distinct subclones within the primary tumor. A high metastatic burden (ranging from 10 to 1000 metastatic nodules) is strongly associated with the presence of inactivating *SMAD4* (*DPC4*) mutations. Studies of resected specimens have shown that these mutations predict shortened survival. In addition, alterations in P53 further subdivide

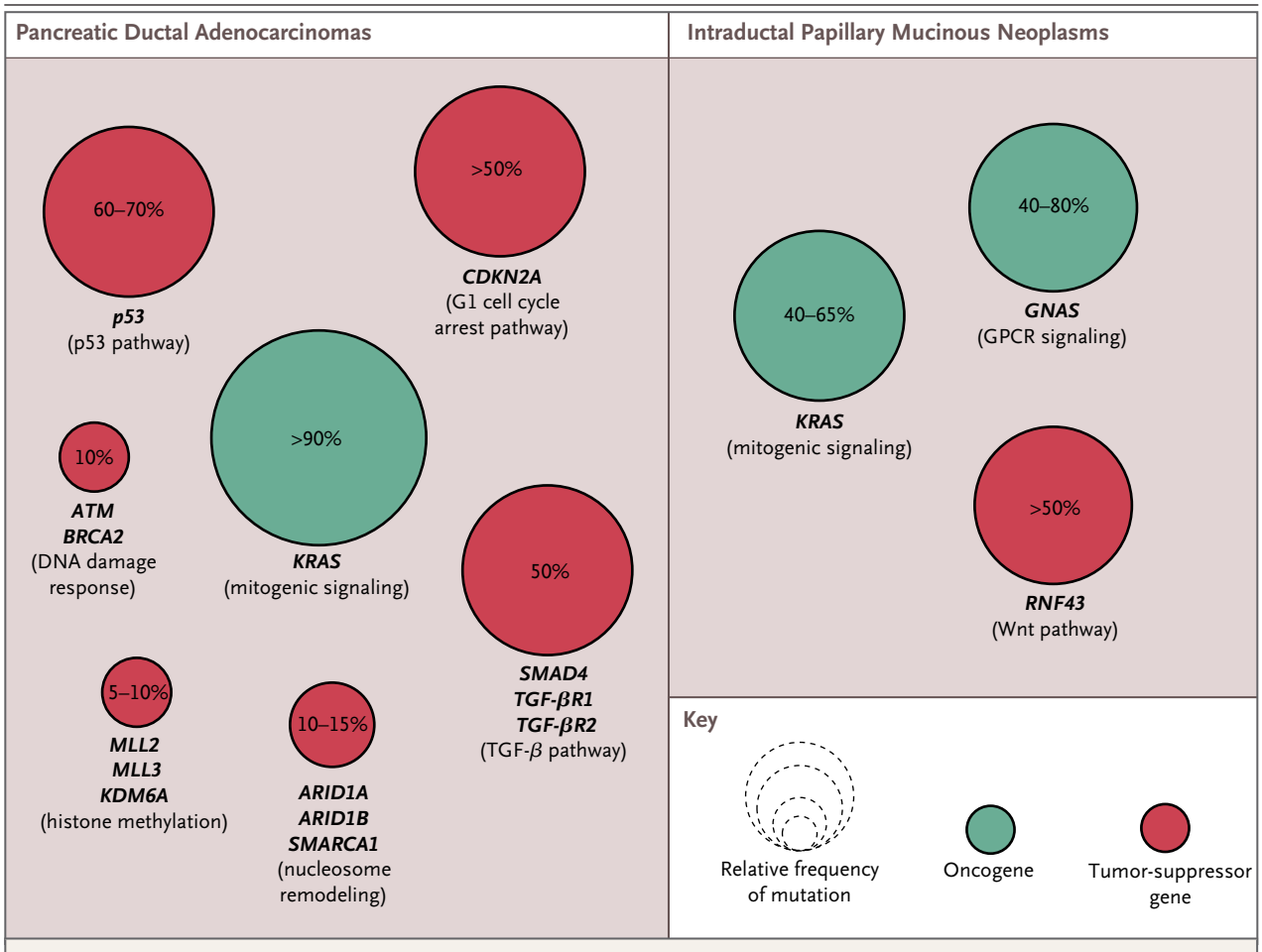

Figure 1. Approximate Frequencies of Mutations in Patients with Pancreatic Ductal Adenocarcinomas and Intraductal Papillary Mucinous Neoplasms.

The two major precursors of pancreatic adenocarcinoma are pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. They have a distinct set of mutational events. Red circles indicate commonly mutated oncogenes, and green circles indicate tumor suppressors. *ARID1A* denotes AT-rich interactive domain 1A; *ARID1B* AT-rich interactive domain 1B; *ATM* ataxia telangiectasia–mutated; *CDKN2A* cyclin-dependent kinase inhibitor 2A; *GNAS* guanine nucleotide binding protein, alpha stimulating; GPCR G-protein–coupled receptor; *KDM6A* lysine (K)-specific demethylase 6A; *KRAS* Kirsten rat sarcoma viral oncogene homologue; *MLL2* mixed-lineage leukemia 2; *MLL3* mixed-lineage leukemia 3; *RNF43* ring-finger protein 43; *SMAD4* SMAD family member 4; *SMARCA1* SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 1; TGF-β transforming growth factor β; *TGF-βR1* TGF-β receptor 1; and *TGF-βR2* TGF-β receptor 2.

the metastatic phenotype into distinct genetic subsets.

As the most common oncogenic mutation in pancreatic adenocarcinoma, *KRAS* activation has been investigated in depth for its contributions to the tumorigenic growth of established cancers. Several studies have shown that the *KRAS* mutation is a marker of a poor prognosis in both patients with resectable tumors and those with unresectable tumors.[28] Functional studies have shown that *KRAS* is critical for the sustained growth of advanced pancreatic adenocarcinoma. In genetically engineered mouse models in which a mutant *KRAS* allele can be switched off at any time during tumorigenesis, loss of KRAS expression results in massive cell death and arrested proliferation, leading to rapid tumor regression.[29] Similarly, most human pancreatic adenocarcinoma cell lines are highly sensitized to cell death, arrested proliferation, or both on knockdown of mutant *KRAS* with the use of RNA interference.[30] Therefore, the targeting of *KRAS* is the subject of many ongoing preclinical and clinical investigations. In addition, the epidermal growth factor

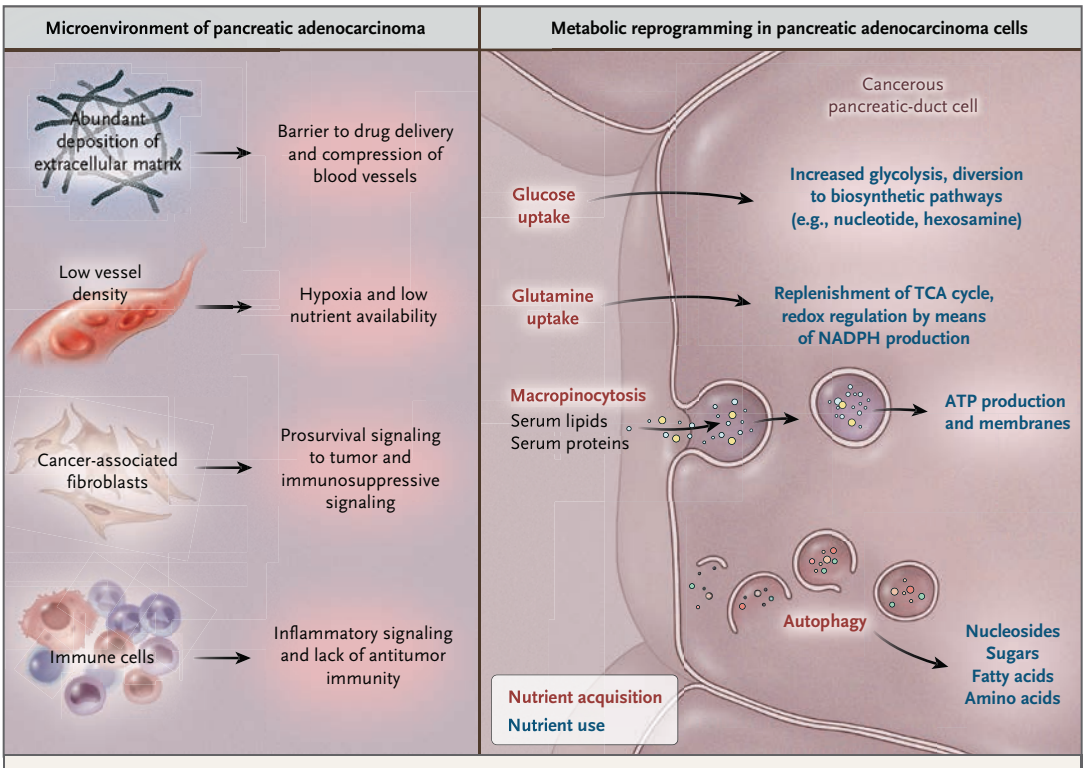

Figure 2. Biologic Features of Pancreatic Cancer.
Pancreatic cancers have a complex microenvironment that might be a target for therapy. TCA denotes tricarboxylic acid.

receptor (EGFR), nuclear factor κB, BCL-XL, and mitogen-activated protein kinase pathways have been shown to contribute to KRAS-mediated pancreatic adenocarcinoma, suggesting alternative combinatorial approaches.[31-35]

NEW INSIGHTS INTO CELLULAR METABOLISM

Alterations in cellular metabolism have emerged as targets for therapeutic intervention. Cancers in general have increased metabolic requirements that need to be coordinated with nutrient supply. Pancreatic adenocarcinoma must contend with particularly severe metabolic stress, since the hypovascular, fibrotic tumor microenvironment results in extreme hypoxia and limited nutrient availability. Consequently, a number of acquired alterations in nutrient acquisition and use are required for the growth and survival of pancreatic adenocarcinomas; several of these alterations are controlled directly or indirectly by oncogenic KRAS. KRAS promotes acquisition of extracellular nutrients, including increased glucose uptake, and directs the scavenging of serum lipids and proteins, the latter by an endocytic process known as macropinocytosis.[36] The tumors with *KRAS* mutations are characterized by constitutively high levels of autophagy, a process by which organelles and protein aggregates are recycled by engulfment in modified membranes (autophagosomes) and degraded in lysosomes.[37] Autophagy can serve both to detoxify the cell by removing damaged components and to provide intermediary metabolites derived from degraded cargo for biosynthesis and energy production. Studies involving cells from both mice and humans show that the growth of pancreatic adenocarcinoma is inhibited by genetic inhibition of autophagy or by chloroquine, which inhibits lysosomal acidification and is currently under investigation in clinical trials.

KRAS also reprograms metabolism by altering the expression of enzymes involved in glucose utilization (Fig. 2). Instead of using glucose to fuel the tricarboxylic acid cycle leading to energy production by oxidative phosphorylation, pancreatic adenocarcinoma cells depend on high levels of glycolysis, which allows for the production of energy and provides the metabolic intermediates for biosynthetic reactions.[29] KRAS in particular directs glucose to be used for nucleotide biosyn-

thesis and protein glycosylation. In addition, KRAS promotes the use of glutamine for both replenishing the tricarboxylic acid cycle and generating NADPH, an antioxidant that mitigates potentially cytotoxic reactive oxygen species generated during cell proliferation.[38] Finally, KRAS maintains the redox state by inducing the nuclear factor erythroid 2–related factor 2 (Nrf2) transcription factor, a master regulator of antioxidant genes.[39] Genetic and pharmacologic studies indicate that many of these adaptive changes in metabolism are required for tumorigenicity of pancreatic adenocarcinoma cells and thus are potential targets for therapeutic intervention.

PANCREATIC STROMA AND IMMUNOMODULATION

The microenvironment of pancreatic adenocarcinoma has a complex role in tumor growth and therapeutic response.[20] These cancers are characterized by a dense stroma consisting of proliferating myofibroblasts (pancreatic stellate cells) and deposition of type I collagen, hyaluronic acid, and other extracellular matrix components, as well as multiple types of inflammatory cells, including macrophages, mast cells, lymphocytes, and plasma cells. Factors that are produced in the stroma, such as connective-tissue growth factor, may directly contribute to the survival of tumor cells.[40] In addition, the microenvironment probably has many indirect effects on disease progression. For example, pancreatic adenocarcinomas have low microvascular density, prominent leaky vasculature, limited perfusion, and consequent intratumoral hypoxia. The fibrous stroma may contribute to this reduced blood flow, and its high interstitial pressure may impair drug delivery.[41] Clinical trials targeting the pancreatic stromal barrier (e.g., ClinicalTrials.gov number, NCT01839487) are currently under way, including studies of recombinant hyaluronidase, which degrades a major component of the extracellular matrix. However, studies in mouse models have shown that reducing the myofibroblast content accelerates tumorigenesis and results in more aggressive histologic features, indicating that some stromal components restrain tumor growth and highlighting the need for further understanding of the tumor microenvironment.[42-44]

An additional important characteristic of the microenvironment of pancreatic adenocarcinoma is restriction of immune surveillance and creation of an inflammatory program that supports tumorigenesis through paracrine cross-talk between tumor cells and immune cells.[45] From the earliest stages of tumor formation, immunosuppressive regulatory T cells and Gr1+CD11b+ myeloid cells are recruited to the tumor stroma, leading to a block in T-cell–mediated antitumor immunity. This recruitment is induced by production of the cytokine granulocyte–macrophage colony-stimulating factor by tumor cells.[46] Moreover, macrophages with tumorigenic potential are recruited to early and advanced lesions through a process requiring the interleukin-6–Janus kinase–signal transducer and activator of transcription 3 (STAT3) signaling pathway.[47] These properties of the tumor microenvironment have important implications for immune-based therapies. Remarkably, studies involving genetically engineered mouse models show that targeting chemokine (C-X-C motif) ligand 12 (CXCL12), which is expressed in a subgroup of stromal fibroblasts, synergizes the checkpoint agonists, restoring cytotoxic T-cell recruitment and leading to tumor regression.[48] An additional approach to reactivating tumor immunity is the use of agonist CD40 antibodies, which have been shown to cause infiltration of pancreatic adenocarcinoma with tumoricidal macrophages in both patients and mouse models.[49] The use of tumor antigen–targeted vaccines (e.g., a vaccine against mutant KRAS), another immunomodulatory strategy, has shown promise in in mouse models of early but not advanced disease.[50] Overall, the rapidly evolving field of tumor immunology holds promise for the development of new and more effective strategies to combat pancreatic adenocarcinoma.

CLINICAL PRESENTATION, DIAGNOSIS, AND STAGING

Approximately 60 to 70% of pancreatic cancers are located in the head of the pancreas, and 20 to 25% are located in the body and tail of the pancreas. The presenting signs and symptoms are related to the location.[51] Patients with pancreatic cancer most commonly present with abdominal pain, weight loss, asthenia, and anorexia.[52] Jaundice is a common manifestation of tumors in the head of the pancreas. Diabetes is present in at least 50% of patients with pancreatic cancer.[53]

Once a pancreatic mass is detected, abdominal computed tomography with both arterial and venous phases is usually sufficient to determine the initial stage and treatment.[54] Pancre-

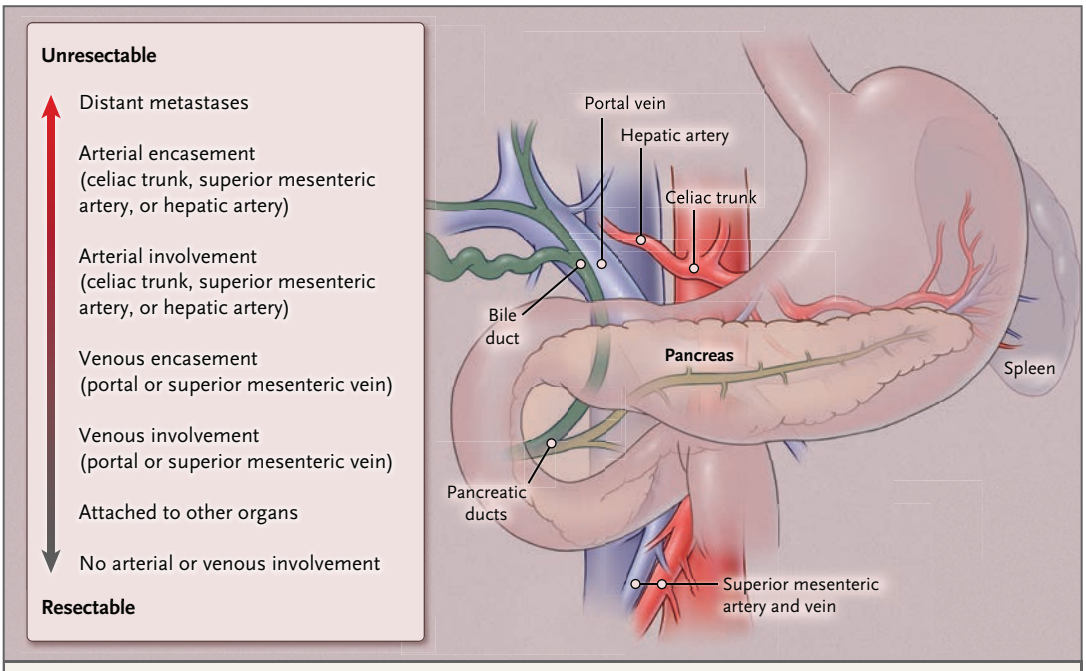

Figure 3. Anatomy and Surgical Resectability of Pancreatic Cancer.
Pancreatic cancers are categorized on a continuum from resectable to unresectable according to the involvement of adjacent structures and the presence of distant metastases.

atic cancer metastasizes primarily to the liver, abdomen, and lungs. A biopsy of the pancreatic mass is most often accomplished by means of endoscopic ultrasonography. Although the tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) have neither sensitivity nor specificity for use in screening to detect pancreatic cancer, if elevated, they are useful in following patients with known disease.

More than 90% of patients who have received a diagnosis of pancreatic cancer die from the disease. Approximately 70% of these patients die from extensive metastatic disease; the other 30% have limited metastatic disease at the time of death, but many of them have bulky primary tumors.[27] Cachexia associated with pancreatic cancer may not directly correlate with the overall disease burden.

MANAGEMENT

SURGICALLY RESECTABLE PANCREATIC CANCER (STAGE I OR II)

Surgery

Surgical resection is the only potentially curative therapy for pancreatic cancer. Assessment of the primary tumor and involvement of the local vessels, including the celiac artery, superior mesenteric artery and vein, portal vein, and hepatic artery, is critical in determining resectability (Fig. 3).[55] Localized tumors are categorized on a continuum from "resectable" to "unresectable (locally advanced)" according to the involvement of the local vessels. The term "borderline resectable" has gained popularity as a catchall for tumors that elude precise categorization. After careful assessment, only 15 to 20% of patients are considered to be candidates for surgical resection, and many of these patients are found to have microscopically positive margins at the time of surgery.[56]

A pancreaticoduodenectomy (the Whipple procedure) is required to remove tumors in the head and neck of the pancreas. No major difference in outcome has been observed with variations on pancreaticoduodenectomy, including pylorus-preserving, subtotal stomach-preserving, and minimally invasive techniques. In addition, more extensive surgery, including extended lymphadenectomy and arterial en bloc resection, does not improve outcomes.[57] Tumors in the body or tail of the pancreas are removed by means of a distal pancreatectomy, which most often includes a splenectomy. Increasingly, distal tumors are

Table 2. Adjuvant Therapy for Pancreatic Cancer.*

Study	No. of Patients	Treatment	Survival	P Value
GITSG[58]	43	Observation Fluorouracil plus radiotherapy	10% at 2 yr 20% at 2 yr	0.007
EORTC[59]	218	Observation Fluorouracil plus radiotherapy	26% at 2 yr 34% at 2 yr	0.10
ESPAC-1[60]	289	Observation Chemoradiotherapy	16.9 mo (median)† 13.9 mo	
		Fluorouracil Chemoradiotherapy plus fluorouracil	21.6 mo 19.9 mo	
CONKO-01[61]	368	Observation Gemcitabine	10.4% at 5 yr 20.7% at 5 yr	0.01
ESPAC 3[62]	1088	Fluorouracil Gemcitabine	23.0 mo (median) 23.6 mo	0.39
RTOG 9704[63]	451	Fluorouracil plus radiotherapy Gemcitabine plus radiotherapy	22% at 5 yr 18% at 5 yr	0.12
JASPAC-01[64]	378	S-1 (oral fluoropyrimidine) Gemcitabine	70% at 2 yr 53% at 2 yr	<0.001

* CONKO-01 denotes Charité Onkologie 01, EORTC European Organization for Research and Treatment of Cancer, ESPAC European Study Group for Pancreatic Cancer, GITSG Gastrointestinal Tumor Study Group, JASPAC-01 Japan Adjuvant Study Group of Pancreatic Cancer, and RTOG 9704 Radiation Therapy Oncology Group 9704.

† The estimated 5-year survival rate was 10% among patients who received chemoradiotherapy and 20% among patients who did not receive chemoradiotherapy (P=0.05). The 5-year survival rate was 21% among patients who received chemotherapy and 8% among patients who did not receive chemotherapy (P=0.009).

being safely resected laparoscopically. A significant correlation between hospital and surgical case volume for pancreatic resection and operative mortality has persisted over time.

Adjuvant Therapy

Because of the poor outcomes associated with surgery alone, the role of adjuvant therapy has been extensively evaluated. Adjuvant therapy includes systemic therapy to reduce the risk of distant metastases and chemoradiotherapy to reduce the risk of locoregional failure. A series of studies has established that 6 months of chemotherapy with either gemcitabine or fluorouracil, as compared with observation, improves overall survival (Table 2). Although there is a clear consensus regarding the value of adjuvant chemotherapy, the role of adjuvant radiation therapy is controversial. Two European studies showed no benefit of adjuvant radiation therapy.[59,60] These studies were criticized for design flaws, and a disagreement has emerged between investigators in Europe and investigators in the United States over the value of radiation therapy for local control. It is the subject of an ongoing randomized trial in the United States (NCT01013649).

Neoadjuvant (Preoperative) and New Approaches

The high rate of positive lymph nodes and surgical margins at the time of resection has prompted investigators to evaluate preoperative chemoradiotherapy approaches, which have had limited efficacy. Recently, there has been growing interest in incorporating multiagent chemotherapy regimens such as the combination of fluorouracil, irinotecan, oxaliplatin, and leucovorin (FOLFIRINOX) and gemcitabine plus albumin-bound paclitaxel particles (nab-paclitaxel) in preoperative and postoperative regimens on the basis of their activity in patients with metastatic disease (see below).[65] Clinical trials with these regimens are currently under way (NCT01591733, NCT01688336, and NCT01560949).

Investigators have also sought to enhance the immune response against pancreatic cancer with the use of adjuvant therapy. Early trials showed the ability to induce an immune response against pancreatic cancer cells, but this response has not translated into a survival benefit.[66] Newer trials incorporating immune checkpoint inhibitors such as the inhibitors to programmed death 1 (PD-1) and the PD-1 ligand PD-L1 are under way.

LOCALLY ADVANCED, UNRESECTABLE PANCREATIC CANCER (STAGE III)

As with resectable pancreatic adenocarcinoma, the use of radiation therapy as part of the standard management of locally advanced or unresectable pancreatic cancer is controversial because of the conflicting results of randomized studies.[67,68] Preliminary results of the international LAP-07 (Gemcitabine with or without Capecitabine and/or Radiation Therapy or Gemcitabine with or without Erlotinib in Treating Patients with Locally Advanced Pancreatic Cancer That Cannot Be Removed by Surgery) study (NCT00634725) were presented at the annual meeting of the American Society of Clinical Oncology in 2013 (http://meetinglibrary.asco.org/content/116391-132). In this trial, 269 patients with stable disease or disease that responded to treatment after 4 months of chemotherapy were randomly assigned to receive chemoradiotherapy or continue chemotherapy. There was no significant difference in overall survival between the groups. Although the final analysis of the study data, including adherence to guidelines for administration of radiation therapy, is ongoing, the initial results have markedly lessened enthusiasm for the use of radiation therapy for locally advanced disease.

Progress in treating localized pancreatic cancer has been limited by inadequate systemic control and poor response rates. FOLFIRINOX and gemcitabine–nab-paclitaxel were recently shown to have a benefit in patients with metastatic disease; thus, there has been increasing interest in evaluating FOLFIRINOX and gemcitabine–nab-paclitaxel in patients with locally advanced disease. Early studies suggest that the likelihood of a radiographic response in patients with an unresectable primary tumor is similar to that seen in patients with metastatic disease.[65] There has been considerable interest in the identification of biomarkers that could be used to predict the nature of disease progression in a particular patient. Tumors in which *SMAD4* has been deleted are associated with widespread disease, whereas tumors with intact SMAD4 are associated with more locally destructive disease and fewer metastases.[27]

METASTATIC PANCREATIC CANCER (STAGE IV)

Patients with pancreatic cancer often have multiple symptoms, and integrated supportive care is critical in helping patients remain well for as long as possible. Fluorouracil-based chemotherapy, as compared with best supportive care alone, improves survival by approximately 3 months.[69] In 1996, a study comparing gemcitabine with fluorouracil in patients with advanced pancreatic cancer showed an improvement in overall survival of 1 month among patients receiving gemcitabine.[70] Over the next 10 years, multiple randomized studies compared single-agent gemcitabine with combination therapy and did not show a consistent improvement in survival.[71] In one exception, the addition of the EGFR inhibitor erlotinib was associated with a significant improvement in overall survival of approximately 2 weeks.[71] Because of its limited effect and added

Table 3. Key Clinical Trials in Metastatic Pancreatic Cancer.*

Trial	No. of Patients	Treatment	Median Survival	P Value
			mo	
Burris et al.[70]	126	Fluorouracil Gemcitabine	4.4 5.6	0.002
NCIC[71]	569	Gemcitabine Gemcitabine plus erlotinib	5.9 6.2	0.04
Ueno et al.[72]	834	Gemcitabine S-1	8.8 9.7	<0.001 for non-inferiority
Conroy et al.[73]	342	Gemcitabine FOLFIRINOX	6.8 11.1	<0.001
Von Hoff et al.[74]	861	Gemcitabine Gemcitabine plus nab-paclitaxel	6.7 8.5	<0.001

* FOLFIRINOX denotes fluorouracil, irinotecan, oxaliplatin, and leucovorin; and NCIC National Cancer Institute of Canada.

toxicity, adoption of this regimen has not been widespread.

Two clinical trials recently changed the standard of care from single-agent gemcitabine to combination chemotherapy (Table 3).[73,74] In the first study, FOLFIRINOX, as compared with gemcitabine alone, was associated with a significant improvement in median survival, global health status, and quality of life. In the second study, gemcitabine and nab-paclitaxel, as compared with gemcitabine alone, was also associated with a prolongation of overall survival. At present, FOLFIRINOX or a combination of gemcitabine and nab-paclitaxel is considered standard treatment for patients with good performance status who do not have coexisting conditions. Survival for 2 years was previously rare among patients with metastatic pancreatic cancer and is now seen in approximately 10% of patients who have received either FOLFIRINOX or gemcitabine–nab-paclitaxel. Unfortunately, data are lacking from randomized studies comparing these two regimens to help guide patients and physicians, but there are considerable differences in the route of administration, side-effect profile, and cost.

CONCLUSIONS

Pancreatic adenocarcinoma remains one of the most common and deadly cancers. Recent advances in the treatment of metastatic disease are being evaluated in patients with resectable and locally advanced disease. In addition, new insights into the biology and genetics of pancreatic cancer, including new findings regarding *KRAS* mutations, tumor metabolism, and tumor immunology, may be of value in the development of new treatments.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90. [Erratum, CA Cancer J Clin 2011;61:134.]
2. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9-29.
3. Bosetti C, Lucenteforte E, Silverman DT, et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). Ann Oncol 2012;23:1880-8. [Erratum, Ann Oncol 2012;23:2773.]
4. Ben Q, Xu M, Ning X, et al. Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies. Eur J Cancer 2011;47:1928-37.
5. Duell EJ, Lucenteforte E, Olson SH, et al. Pancreatitis and pancreatic cancer risk: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). Ann Oncol 2012;23:2964-70.
6. Aune D, Greenwood DC, Chan DS, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. Ann Oncol 2012;23:843-52.
7. Klein AP, Lindström S, Mendelsohn JB, et al. An absolute risk model to identify individuals at elevated risk for pancreatic cancer in the general population. PLoS One 2013;8(9):e72311.
8. Rebours V, Boutron-Ruault MC, Schnee M, et al. Risk of pancreatic adenocarcinoma in patients with hereditary pancreatitis: a national exhaustive series. Am J Gastroenterol 2008;103:111-9.
9. Vasen HF, Gruis NA, Frants RR, van Der Velden PA, Hille ET, Bergman W. Risk of developing pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion of p16 (p16-Leiden). Int J Cancer 2000;87:809-11.
10. Iqbal J, Ragone A, Lubinski J, et al. The incidence of pancreatic cancer in BRCA1 and BRCA2 mutation carriers. Br J Cancer 2012;107:2005-9.
11. Jones S, Hruban RH, Kamiyama M, et al. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. Science 2009;324:217.
12. Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology 2000;119:1447-53.
13. Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. JAMA 2009;302:1790-5.
14. Swift M, Morrell D, Massey RB, Chase CL. Incidence of cancer in 161 families affected by ataxia–telangiectasia. N Engl J Med 1991;325:1831-6.
15. Ruijs MW, Verhoef S, Rookus MA, et al. TP53 germline mutation testing in 180 families suspected of Li-Fraumeni syndrome: mutation detection rate and relative frequency of cancers in different familial phenotypes. J Med Genet 2010;47:421-8.
16. Klein AP, Brune KA, Petersen GM, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res 2004;64:2634-8.
17. Jacobs EJ, Chanock SJ, Fuchs CS, et al. Family history of cancer and risk of pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). Int J Cancer 2010;127:1421-8.
18. Cook NR, Lee IM, Gaziano JM, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. JAMA 2005;294:47-55.
19. Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut 2013;62:339-47.
20. Feig C, Gopinathan A, Neesse A, Chan DS, Cook N, Tuveson DA. The pancreas cancer microenvironment. Clin Cancer Res 2012;18:4266-76.
21. Canto MI, Hruban RH, Fishman EK, et al. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. Gastroenterology 2012;142:796-804.
22. Kanda M, Matthaei H, Wu J, et al. Presence of somatic mutations in most early-stage pancreatic intraepithelial neoplasia. Gastroenterology 2012;142:730-3.
23. Hustinx SR, Leoni LM, Yeo CJ, et al. Concordant loss of MTAP and p16/CDKN2A expression in pancreatic intraepithelial neoplasia: evidence of homozygous deletion in a noninvasive precursor lesion. Mod Pathol 2005;18:959-63.

24. Aguirre AJ, Bardeesy N, Sinha M, et al. Activated Kras and Ink4a/Arf deficiency cooperate to produce metastatic pancreatic ductal adenocarcinoma. Genes Dev 2003;17:3112-26.
25. Biankin AV, Waddell N, Kassahn KS, et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. Nature 2012;491:399-405.
26. Wu J, Matthaei H, Maitra A, et al. Recurrent GNAS mutations define an unexpected pathway for pancreatic cyst development. Sci Transl Med 2011;3:92ra66.
27. Iacobuzio-Donahue CA, Fu B, Yachida S, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. J Clin Oncol 2009;27:1806-13.
28. Ogura T, Yamao K, Hara K, et al. Prognostic value of K-ras mutation status and subtypes in endoscopic ultrasound-guided fine-needle aspiration specimens from patients with unresectable pancreatic cancer. J Gastroenterol 2013;48:640-6.
29. Ying H, Kimmelman AC, Lyssiotis CA, et al. Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. Cell 2012;149:656-70.
30. Singh A, Greninger P, Rhodes D, et al. A gene expression signature associated with "K-Ras addiction" reveals regulators of EMT and tumor cell survival. Cancer Cell 2009;15:489-500.
31. Ling J, Kang Y, Zhao R, et al. KrasG12D-induced IKK2/β/NF-κB activation by IL-1α and p62 feedforward loops is required for development of pancreatic ductal adenocarcinoma. Cancer Cell 2012;21:105-20.
32. Corcoran RB, Cheng KA, Hata AN, et al. Synthetic lethal interaction of combined BCL-XL and MEK inhibition promotes tumor regressions in KRAS mutant cancer models. Cancer Cell 2013;23:121-8.
33. Collisson EA, Trejo CL, Silva JM, et al. A central role for RAF→MEK→ERK signaling in the genesis of pancreatic ductal adenocarcinoma. Cancer Discov 2012;2:685-93.
34. Navas C, Hernández-Porras I, Schuhmacher AJ, Sibilia M, Guerra C, Barbacid M. EGF receptor signaling is essential for K-ras oncogene-driven pancreatic ductal adenocarcinoma. Cancer Cell 2012;22:318-30.
35. Ardito CM, Grüner BM, Takeuchi KK, et al. EGF receptor is required for KRAS-induced pancreatic tumorigenesis. Cancer Cell 2012;22:304-17.
36. Commisso C, Davidson SM, Soydaner-Azeloglu RG, et al. Macropinocytosis of protein is an amino acid supply route in Ras-transformed cells. Nature 2013;497:633-7.
37. Yang S, Wang X, Contino G, et al. Pancreatic cancers require autophagy for tumor growth. Genes Dev 2011;25:717-29.
38. Son J, Lyssiotis CA, Ying H, et al. Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway. Nature 2013;496:101-5. [Erratum, Nature 2013;499:504.]
39. DeNicola GM, Karreth FA, Humpton TJ, et al. Oncogene-induced Nrf2 transcription promotes ROS detoxification and tumorigenesis. Nature 2011;475:106-9.
40. Neesse A, Frese KK, Bapiro TE, et al. CTGF antagonism with mAb FG-3019 enhances chemotherapy response without increasing drug delivery in murine ductal pancreas cancer. Proc Natl Acad Sci U S A 2013;110:12325-30.
41. Provenzano PP, Cuevas C, Chang AE, Goel VK, Von Hoff DD, Hingorani SR. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer Cell 2012;21:418-29.
42. Rhim AD, Oberstein PE, Thomas DH, et al. Stromal elements act to restrain, rather than support, pancreatic ductal adenocarcinoma. Cancer Cell 2014;25:735-47.
43. Özdemir BC, Pentcheva-Hoang T, Carstens JL, et al. Depletion of carcinoma-associated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival. Cancer Cell 2014;25:719-34.
44. Lee JJ, Perera RM, Wang H, et al. Stromal response to Hedgehog signaling restrains pancreatic cancer progression. Proc Natl Acad Sci U S A 2014;111(30):E3091-E3100.
45. Vonderheide RH, Bayne LJ. Inflammatory networks and immune surveillance of pancreatic carcinoma. Curr Opin Immunol 2013;25:200-5.
46. Pylayeva-Gupta Y, Lee KE, Hajdu CH, Miller G, Bar-Sagi D. Oncogenic Kras-induced GM-CSF production promotes the development of pancreatic neoplasia. Cancer Cell 2012;21:836-47.
47. Lesina M, Kurkowski MU, Ludes K, et al. Stat3/Socs3 activation by IL-6 transsignaling promotes progression of pancreatic intraepithelial neoplasia and development of pancreatic cancer. Cancer Cell 2011;19:456-69.
48. Feig C, Jones JO, Kraman M, et al. Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti-PD-L1 immunotherapy in pancreatic cancer. Proc Natl Acad Sci U S A 2013;110:20212-7.
49. Beatty GL, Chiorean EG, Fishman MP, et al. CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice and humans. Science 2011;331:1612-6.
50. Keenan BP, Saenger Y, Kafrouni MI, et al. A Listeria vaccine and depletion of T-regulatory cells activate immunity against early stage pancreatic intraepithelial neoplasms and prolong survival of mice. Gastroenterology 2014;146:1784-94.
51. Modolell I, Guarner L, Malagelada JR. Vagaries of clinical presentation of pancreatic and biliary tract cancer. Ann Oncol 1999;10:Suppl 4:82-4.
52. Porta M, Fabregat X, Malats N, et al. Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage. Clin Transl Oncol 2005;7:189-97.
53. Chari ST, Leibson CL, Rabe KG, Ransom J, de Andrade M, Petersen GM. Probability of pancreatic cancer following diabetes: a population-based study. Gastroenterology 2005;129:504-11.
54. American Joint Committee on Cancer. AJCC cancer staging manual. 7th ed. New York: Springer, 2010.
55. Vauthey JN, Dixon E. AHPBA/SSO/SSAT Consensus Conference on Resectable and Borderline Resectable Pancreatic Cancer: rationale and overview of the conference. Ann Surg Oncol 2009;16:1725-6.
56. Konstantinidis IT, Warshaw AL, Allen JN, et al. Pancreatic ductal adenocarcinoma: is there a survival difference for R1 resections versus locally advanced unresectable tumors? What is a "true" R0 resection? Ann Surg 2013;257:731-6.
57. Martin RC II, Scoggins CR, Egnatashvili V, Staley CA, McMasters KM, Kooby DA. Arterial and venous resection for pancreatic adenocarcinoma: operative and long-term outcomes. Arch Surg 2009;144:154-9.
58. Gastrointestinal Tumor Study Group. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Cancer 1987;59:2006-10.
59. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg 1999;230:776-82.
60. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004;350:1200-10. [Erratum, N Engl J Med 2004;351:726.]
61. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA 2013;310:1473-81.
62. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine fol-

lowing pancreatic cancer resection: a randomized controlled trial. JAMA 2010;304:1073-81.
63. Regine WF, Winter KA, Abrams R, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. Ann Surg Oncol 2011;18:1319-26.
64. Fukutomi A, Uesaka K, Boku N, Kanemoto H, Konishi M, Matsumoto I. JASPAC 01: randomized phase III trial of adjuvant chemotherapy with gemcitabine versus S-1 for patients with resected pancreatic cancer. J Clin Oncol 2013;31:Suppl:4008. abstract.
65. Faris JE, Blaszkowsky LS, McDermott S, et al. FOLFIRINOX in locally advanced pancreatic cancer: the Massachusetts General Hospital Cancer Center experience. Oncologist 2013;18:543-8.
66. Lutz E, Yeo CJ, Lillemoe KD, et al. A lethally irradiated allogeneic granulocyte-macrophage colony stimulating factor-secreting tumor vaccine for pancreatic adenocarcinoma: a phase II trial of safety, efficacy, and immune activation. Ann Surg 2011;253:328-35.
67. Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer: definitive results of the 2000-01 FFCD/SFRO study. Ann Oncol 2008;19:1592-9.
68. Loehrer PJ Sr, Feng Y, Cardenes H, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. J Clin Oncol 2011;29:4105-12.
69. Sultana A, Smith CT, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. J Clin Oncol 2007;25:2607-15.
70. Burris HA III, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997;15:2403-13.
71. Moore MJ, Goldstein D, Hamm J, 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. J Clin Oncol 2007;25:1960-6.
72. Ueno H, Ioka T, Ikeda M, et al. Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. J Clin Oncol 2013;31:1640-8.
73. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-25.
74. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691-703.