TOPIC HIGHLIGHT

2016 Pancreatic Cancer: Global view

Management of pancreatic cancer in the elderly

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Abstract

Currently, pancreatic adenocarcinoma mainly occurs after 60 years of age, and its prognosis remains poor despite modest improvements in recent decades. The aging of the population will result in a rise in the incidence of pancreatic adenocarcinoma within the next years. Thus, the management of pancreatic cancer in the elderly population is gaining increasing relevance. Older cancer patients represent a heterogeneous group with different biological, functional and psychosocial characteristics that can modify the usual management of this disease, including pharmacokinetic and pharmacodynamic changes, polypharmacy, performance status, comorbidities and organ dysfunction. However, the biological age, not the chronological age, of the patient should be the limiting factor in determining the most appropriate treatment for these patients. Unfortunately, despite the increased incidence of this pathology in older patients, there is an underrepresentation of these patients in clinical trials, and the management of older patients is thus determined by extrapolation from the results of studies performed in younger patients. In this review, the special characteristics of the elderly, the multidisciplinary management of localized and advanced ductal adenocarcinoma of the pancreas and the most recent advances in the management of this condition will be discussed, focusing on surgery, chemotherapy, radiation and palliative care.

Key words: Pancreatic ductal adenocarcinoma; Elderly; Management; Treatment; Pancreatic cancer

Core tip: Pancreatic cancer is a disease that mainly affects the elderly. The older patients have different biological, functional and psychosocial characteristics compared with the young population. The infrequent participation of these patients in clinical trials have raised challenges in the management of this disease. In this review, the special features of the elderly as well as the current multidisciplinary management of pancreatic cancer will be discussed.

INTRODUCTION

In the United States, approximately 48960 patients are diagnosed with pancreatic cancer annually, and this disease represents the fourth leading cause of cancer-related death in the United States among both men and women. Advancing age is a high risk factor for cancer, and more than 60% of new cancer cases and over 70% of cancer mortalities occur in elderly people. The incidence of pancreatic cancer increases with age; in the United States, only 13% of all patients with pancreatic cancer are diagnosed before 60 years of age.

Elderly patients represent a special subgroup because of the presence of related pharmacodynamic and pharmacokinetic changes. Hence, a standard clinical evaluation of these patients may not be sufficient to determine individual treatment strategies. New assessment methods have been proposed, and several studies have demonstrated the value of these techniques in routine clinical practice.

At present, surgical resection is the only potentially curative treatment for pancreatic cancer, but only 15%-20% of patients are candidates for pancreatectomy because the majority of them are diagnosed with disseminated or locally advance disease. Although it is the best option, many older patients are not recommended for surgery. In addition, they are also less likely to receive chemotherapy compared with younger patients.

Due to the aging population, it is estimated that the number of elderly patients with pancreatic cancer will continue to rise. Unfortunately, very little data are available regarding the management of these patients; therefore, therapeutic approaches to this subgroup are a daily challenge.

The aim of this review is summarize current knowledge regarding the management and therapeutic approach in elderly patients with pancreatic cancer.

CHARACTERISTICS OF THE ELDERLY AND THEIR EFFECTS ON THERAPEUTIC DECISIONS

The population of western countries is aging, and because the incidence of cancer increases with age, the population of patients with cancer is growing. More than 50% of all newly diagnosed patients with cancer are older than 60 years, and more than one third are over the age of 70[1]. By the year 2030, 70% of all malignancies and 85% of all cancer-related deaths are expected to occur in individuals aged 65 years or older, and therefore, older people will likely represent the prototypical cancer patient in the future[2]. Age is an important risk factor for the development of pancreatic cancer. Whereas the overall incidence rate of pancreatic cancer for all ages is 11.7%, the incidence rate among individuals older than 65 years and older than 80 years is 66.4% and up to as many as 91.1%, respectively[3].

The association between aging and cancer is well established: carcinogenesis is a time-consuming process with a final product (cancer) that is more likely to occur late in life; older tissues are more vulnerable to environmental carcinogens; and changes in the environment of the body (chronic inflammation, immunosenescence) may favor the development of cancer[4,5]. Additionally, the immune system plays an important role in the progression of pancreatic cancer[6-8]. Very little data are available regarding pancreatic cancer in the elderly. Kamisawa *et al*[9] compared the pathologic features of pancreatic cancer in elderly *vs* younger patients and found no differences in the grade, location or incidence of the local spread, although elderly patients developed fewer hematogenous metastases. Other reports have indicated that older patients present more diploid tumors or that p53 mutations, which are associated with a worse prognosis[10].

Several studies have shown that older cancer patients are often undertreated and have poorer outcomes compared with younger individuals[11,12]. This outcome may be due to the less aggressive treatment of elderly patients. Focusing on pancreatic cancer, some studies have shown that nearly half of all elderly patients did not receive any treatment for locoregional pancreatic cancer. Moreover, only 11% received a multimodal therapy (surgery +/-chemoradiotherapy)[13].

Despite the rapidly growing oncogeriatric population, older cancer patients are underrepresented in clinical trials[14]. Talarico *et al*[15] analyzed the age-related enrollment of cancer patients in clinical trials and found that the proportions of the overall patient population aged $\geq$ 65, $\geq$ 70, and $\geq$ 75 years were 36%, 20%, and 9% in clinical trials compared with 60%, 46%, and 31% in the United States cancer population, respectively. This under-representation generates challenges because the results from clinical trials in younger patients cannot be extrapolated to the treatment of the elderly. The diverse effects of aging on organ function and the variety of potential comorbid disease results in a heterogeneous elderly population. For example, pharmacokinetic and pharmacodynamic differences between young and elderly patients, and indeed among elderly patients themselves, could result in considerable variability in the efficacy and safety of cancer treatments. The most important pharmacokinetic changes are described in Table 1.

Table 1 Pharmacokinetic changes in the elderly

Physiological process	Situation in the elderly	Changes	Effect
Absorption	Decreased	Atrophy of the intestinal mucosa Decreases in gastrointestinal motility Decreased splanchnic blood flow Decreased secretion of digestive enzymes	Reduced absorption of protein, vitamins and drugs
Metabolism	Decreased	Reduced liver size Reduced hepatic blood flow Reduced activity of cytochrome p450-dependant reactions	Reduced protein synthesis Reduced activation/deactivation of drugs and carcinogens
Drug distribution	Decreased	Reduced total body water Reduced concentration of plasma albumin Reduced red blood cell concentration	Reduced Vd of water-soluble drugs Increased Vd of liposoluble drugs
Excretion	Decreased	Reduced glomerular filtration rate Reduced tubular function	Reduced elimination of drugs and of their active metabolites

Vd: Volume of distribution.

Pharmacodynamic changes may cause resistance to cytotoxic drugs in older individuals due to resistance to apoptosis and poorer oxygenation in these neoplasms[16,17]. Specifically, in patients with advanced pancreatic adenocarcinoma treated with gemcitabine who were aged 75 or older, the median survival time was approximately six to eight weeks shorter than that in trial patients[18]. Another important question concerns the effects of toxicity on older people. While grade 2 adverse events are not important in young people and, in fact, are often not reported, the same level of toxicity may result in a considerable deterioration of functionality in elderly patients.

A widespread occurrence in the management of older individuals is the intake of multiple medications[19]. Polypharmacy is at least as common as it is in age-matched individuals without cancer. Prithviraj et al[20] showed that 80% of newly diagnosed cancer patients aged 65 or older were taking five or more medications. Polypharmacy increases the risk of side effects, drug-drug interactions, and treatment costs and decreases medical adherence. Moreover, it may represent a risk factor for additional complications of cytotoxic chemotherapy and affect patient outcomes[21]. Hence, periodic reviews of prescribed medications is necessary to abolish these challenges associated with polypharmacy.

Because aging is a highly individualized process, chronological age is not adequate to estimate the individual life expectancy and functional reserve. In other words, "biological age" is more important than "chronological age" to define who is an old patient. In medical oncology, treatment decisions are mostly based on clinical judgment and performance scales such as the Karnofsky performance score (KPS). However, in older cancer patients, these scales are not as sensitive as in the adult population because relevant information is not taken into account, such as comorbidities, the functionality of the patients and support from family. To improve the assessment and to determine individual treatment strategies for an optimal outcome, one concept of geriatric medicine is being incorporated in geriatric oncology: the comprehensive geriatric assessment (CGA). CGA is defined as a multidimensional, interdisciplinary diagnostic process that focuses on the determination of medical, psychosocial, and functional capabilities in older people to develop an integrated treatment plan. CGA has been shown to improve overall survival, quality of life and physical functioning in the non-oncologic geriatric population. Several recent reports have strongly suggested that different components of comprehensive geriatric assessment can be useful in oncology to predict early death, functional decline, toxicity and overall survival[22,23]. Important domains in a geriatric assessment are functional status, comorbidities, cognition, mental health status and support, fatigue, and the assessment of polypharmacy and presence of geriatric syndromes[24]. Many tools are available to assess these domains (Table 2). Despite the recommendations for a CGA by The International Society of Geriatric Oncology (SIOG), it is not widely implemented in the practice of oncology likely because it is a time- and resource-consuming endeavor[25]. In addition, true CGA is conducted by an experienced geriatrician; nonetheless, they are rarely available in most cancer structures. A suitable tool is one that is performed quickly by a trained nurse or physician and that has a high sensitivity and specificity to discriminate patients who require a more detailed assessment and possible geriatric interventions. The most widely used screening tool for older cancer patients is the VES-13 (vulnerable elders survey-13), which has a sensitivity range from 68%-87%[26].

Because elderly patients are a heterogeneous group, routine individual assessments of frailty and fitness are required. Such assessments may guide treatment decisions through evaluations of the balance of benefits and harms associated with performing or omitting specific oncologic interventions.

Table 2 Elements of a comprehensive geriatric assessment

Parameter assessed	Elements and tools of the assessment
Demographic and social status	Questions on living situation, marital status, educational level, safety of the environment, financial resources, caregiver burden
Functional status	Performance status index
	ADLs
	IADLs
	Barthel index
	Pepper assessment tool for disability
	Visual and/or hearing impairment, regardless of use of glasses or hearing aid
	Mobility problem (requiring help or use of walking aid)
	Timed Get Up and Go
	One-leg standing balance test
	Walking problems, gait assessment, and gait speed
	Karnofsky health care professional-rated performance rating scale
Comorbidity	Charlson comorbidity index
	CIRS
	No. of comorbid conditions
	Summary of comorbidities
	NYHA
Cognition	Mini Mental State Examination Informant
	Questionnaire on Cognitive Decline in the Elderly
	Modified Mini Mental State Examination
	Clock-drawing test
	Blessed Orientation-Memory-Concentration
Emotional conditions (Depression)	Geriatric Depression Scale
	Hospital Anxiety and Depression Scale
	Mental health index
	Presence of depression (as a geriatric syndrome)
Nutrition	Weight loss (unintentional loss in 3 or 6 mo)
	Mini Nutritional Assessment Short Nutritional
	DETERMINE Nutritional Index
Polypharmacy	Number of medications
	Appropriateness of medications
	Risk of drug interactions
Geriatric syndromes	Dementia
	Delirium
	Depression
	Falls
	Neglect and abuse
	Spontaneous bone fractures and osteoporosis
	Incontinence (fecal and/or urinary)
	Constipation
	Sarcopenia

Data adapted from Wildiers *et al*[25]. ADL: Activity of daily living; CIRS: Cumulative Illness Rating Scale; CIRS-G: Cumulative Illness Rating Scale-Geriatrics; DETERMINE: Disease, Eating poorly, Tooth loss/mouth pain, Economic hardship, Reduced social contact, Multiple medicines, Involuntary weight loss/gain, Needs assistance in self-care, Elder years > 80; ECOG: Eastern Cooperative Oncology Group; IADL: Instrumental activity of daily living; PS: Performance status; NYHA: New York Heart Association.

SURGERY FOR PANCREATIC CANCER IN THE ELDERLY

Surgical resection is the only potentially curative treatment for pancreatic cancer. Unfortunately, only 15% to 20% patients are candidates for pancreatectomy due to the late presentation of symptoms and/or detection of the disease[27-29]. Furthermore, the rate of resectability diminishes with age. Likewise, some authors reported

that 40% of patients between the ages of 66-70 years are candidates for a pancreatectomy, but by the age of 85 years, only 7% are eligible candidates[30,31].

Resection of the pancreas, either by pancreaticoduodenectomy (PD) (the Whipple procedure), total or by partial pancreatectomy, is a complex surgical procedure with a high rate of morbidity and mortality. Mortality rates after pancreatic surgery have dropped to less than 2%-5% at experienced centers, but complication rates are high, reaching at least 30% in many centers[29]. Mortality also increases proportionally with age: 6.7% of patients aged 65-69 years, 9.3% of patients aged 70-79 years, and 15.5% of patients aged 80 years or older. However, hospitals with a low pancreatic surgery volume (< 11 resections per year) have higher mortality rates than high volume hospitals (7.3% *vs* 3.2%, $P < 0.0001$)[32,33]. These differences were accentuated with each increasing age group. The Hopkins study showed that 33% of patients older than 80 years presented delayed gastric emptying compared with 18.6% of the patients younger than 80 years ($P = 0.03$)[34]. Other studies reported a similar trend in the occurrence of delayed gastric emptying but without statistical significance[35]. Ito *et al*[36] showed a higher incidence of pancreatic fistulas in the elderly, but the results were not significant (45.1% *vs* 29.9%, respectively, $P = 0.14$). In the study by Hodul *et al*[35] the rate of neurologic complications was 9.4% in the older group and 0% in the younger group. The length of hospital stay was also proportionally increased according to age[29].

The number of patients requiring ongoing inpatient nursing care at the time of discharge increased significantly with age. The proportion of patients who could not be discharged home was 10.6%, 19.2% and 36.7% for ages 65-69, 70-79 and 80 years or older, respectively ($P < 0.0001$)[34].

The Memorial Sloan Kettering Group showed a significant difference in 5-year survival between patients aged 70 years or older (21%, median = 18 mo) and < 70 years (29%, median = 24 mo, $P = 0.03$)[37]. Finlayson *et al*[34] evaluated the 5-year survival of patients following surgery for pancreatic cancer and demonstrated a decrease from 16.4% in patients aged 65-69 years to 15.6% in patients aged 70-79 years and 11.3% in patients aged 80 years or older, but this difference did not achieve statistical significance. Patients with more than two comorbidities undergoing pancreatectomy for pancreatic cancer had a 5-year-survival rate of 10% compared with 14% in patients with fewer than two comorbidities (P = NS).

To reduce the rates of morbidity and mortality in elderly patients undergoing pancreatic surgery, an accurate pre-anesthesia and cardiovascular risk assessment is needed. The perioperative management should also be standardized. Patients should be routinely admitted to the intensive care unit (ICU) or to recovery for the first 48-72 h post-surgery. All patients must receive broad-spectrum antibiotics for

two to three days and an H₂ blocker during the entire postoperative hospital stay[38].

Minimally invasive surgery is associated with a lower rate of cardio-respiratory complications, diminished post-operative pain, shorter hospital stays, and a faster reincorporation into daily activities. Therefore, it is a very good option for elderly patients.

In summary, surgery is the only curative treatment in patients with pancreatic cancer. The benefits of surgery do not diminish with age, and therefore, elderly patients should not be denied the surgery a priori based on their age[39]. Although the elderly have a higher surgical mortality rate, this depends, among other factors, on the presence of comorbidities and the experience of the surgeon. Consequently, a proper preoperative assessment must be performed, as well as strict post-operative monitoring. Furthermore, this surgery must be conducted in a center with a high volume of pancreatic surgery patients. Under these conditions, surgical resection can be performed safely in older individuals.

ADJUVANT THERAPIES FOR PANCREATIC CANCER IN THE ELDERLY

Approximately one of each five patients with pancreatic adenocarcinoma is diagnosed at a resectable stage, which is the only option for cure. However, most of these patients will present local or metastatic relapse during the subsequent two years after resection.

Despite the benefits of adjuvant therapies in clinical trials, multimodal therapy clearly seems to be underutilized in the elderly. Parmar *et al*[13] identified only 1166 (11.1%) of 10505 patients older than 65 years (median age of 77 years) with locoregional pancreatic adenocarcinoma who received surgery and chemotherapy. Moreover, less than a half of the patients undergoing operative resection received chemotherapy. Nonetheless, other authors have reported an equivalent observation of only approximately 30% of elderly patients undergoing treatment with adjuvant therapies[40-42].

These findings could be explained by the perception of a limited life expectancy in patients with pancreatic cancer, the increased risk of an independent cancer cause of death and the longer post-surgical recovery of elderly patients. However, the role of adjuvant therapy has been demonstrated extensively, increasing the 5-year overall survival up to 25%. In addition, as described below, the prognosis and adjuvant therapy benefits in patients with pancreatic cancer are independent of age.

The adjuvant approach includes systemic chemotherapy to reduce the risk of distant metastases and chemoradiotherapy to reduce the risk of locoregional failure[43].

As discussed previously, the role of adjuvant chemotherapy has been well described in different prospective studies. In the CONKO-001 phase III trial, 368 patients were randomized to assess the effect of adjuvant chemotherapy with gemcitabine on the prognosis of resected pancreatic cancer. The median disease-free survival time was 13.4 mo *vs* 6.7 mo (HR = 0.55, *P* < 0.001) for the gemcitabine and observation groups, respectively. Treatment with the adjuvant gemcitabine also prolonged overall survival (HR = 0.76, *P* = 0.01). The median age of the patients was 62 years, and 219 patients (62%) were older than 65 years. No differences in progression-free survival were found in the multivariable analysis for age (*P* = 0.06)[44].

One thousand and eighty-eight patients were included in the ESPAC-3 trial, in which the superiority of fluorouracil *vs* gemcitabine as an adjuvant treatment after pancreatic cancer resection was assessed. No differences in the median overall survival were found (23 mo *vs* 23.6 mo for fluorouracil and gemcitabine, respectively; *P* = 0.039). As in other studies, age was not significantly associated with the prognosis[45].

As a consequence of the limited representation of elderly patients in clinical trials, several retrospective studies have been published to assess the use and efficacy of adjuvant chemotherapy in this population. In a multicenter series from 1990 to 2011, Nagrial *et al*[42] identified patients with resected pancreatic ductal adenocarcinoma, including 178 patients aged 70 years or older (median age of 75 years). Only 30% of the older patients received adjuvant chemotherapy. Not receiving adjuvant chemotherapy was a poor independent prognostic factor, with a median overall survival of 13.1 mo *vs* 21.8 mo for treated patients (HR = 1.89, *P* = 0.002)[42].

Davila *et al*[46] described the utilization and survival effects of adjuvant therapies among 1383 patients who were older than 65 years (41% older than 75 years). Forty-nine percent of the patients received adjuvant therapy. Patients younger than 75 years of age were significantly more likely to receive adjuvant chemotherapy or chemoradiotherapy. In contrast to other studies, the administration of adjuvant chemotherapy did not decrease the risk of mortality compared with surgery alone[46].

While the benefits of adjuvant chemotherapy are evident, the value of adjuvant chemoradiation therapy is controversial due to contradictory results between the European and United States clinical trials. The ESPAC-1 trial evaluated the role of chemotherapy and chemoradiotherapy using a two-by-two factorial design in 289 patients. This study showed a five-year survival rate benefit for chemotherapy compared with no chemotherapy (21% *vs* 8%; *P* = 0.009). However, chemoradiotherapy had a deleterious effect on survival compared with no chemoradiotherapy, with an estimated five-year survival of 10% *vs* 20%, respectively (*P* = 0.05). No significant differences in survival were found with respect to an age of 60 years or older compared with that younger than 60 years[47].

In contrast, the GITSG 9173 trial evaluated the benefit of adjuvant chemoradiation in 43 pancreatic cancer patients. The median survival was significantly longer for the treatment group (20 mo *vs* 11 mo)[48]. A similar study was performed by Klinkenbijl *et al*[49] in Europe. In that study, which included 218 patients up to 80 years old who were diagnosed with pancreatic head or periampullary adenocarcinoma, no significant differences in median survival were observed. The median duration of survival was 19.0 mo for the observation group and 24.5 mo for the treatment group (*P* = 0.208)[49].

There are doubts concerning the benefits of adjuvant chemoradiotherapy in the elderly. As observed for the adjuvant chemotherapy trials, the previously described studies did not focus on this subgroup of the patient population.

Horowitz *et al*[41] prospectively collected the clinical and pathological data for patients undergoing treatment for pancreatic cancer. Among the 166 patients aged 75 years or older, the 2-year survival improved for the patients who received adjuvant chemoradiation compared with surgery alone (49.0% *vs* 31.6%, respectively, *P* = 0.013)[41]. Another study of 1383 patients who were older than 65 years showed a benefit of adjuvant chemoradiation with a 23% lower risk of mortality compared with surgery alone (HR = 0.77)[46]. Miyamoto *et al*[50] retrospectively reviewed patients aged 75 years or more who were treated with chemoradiation for pancreatic cancer (eighteen patients as adjuvant therapy after surgery). The median overall survival for the adjuvant group was 20.6 mo, although the patients suffered from significant toxicity[50].

In conclusion, despite the lack of specific adjuvant data for the elderly, age does not seem to be a determinant factor in decisions regarding the administration of adjuvant chemotherapy. In our opinion, similarly to younger patients, older patients with a good performance status and no significant comorbidities can be treated with adjuvant chemotherapy preferably based on gemcitabine.

LOCALLY ADVANCED PANCREATIC CANCER IN THE ELDERLY

Locally advanced pancreatic cancer is defined as a tumor that encases a vascular structure, such as the superior mesenteric artery, celiac axis or superior or mesenteric vein-portal confluence[51]. It represents approximately 20%-25% of all newly diagnosed pancreatic cancers. In the strictest sense, in locally advanced pancreatic carcinoma, resection is not an option. In cases of locally non-resectable disease, the results of previous randomized trials indicated that concurrent external beam radiation therapy (EBRT) and 5-fluorouracil (5-FU) therapy resulted in significantly improved survival compared with EBRT

alone or chemotherapy alone[52]. Thus, for locally advanced pancreatic cancer, chemoradiation is the standard of care[53,54].

In elderly patients with locally advanced pancreatic adenocarcinoma, oncologists are hesitant to indicate chemoradiotherapy because of the associated poor prognosis and high risk of severe toxicities. In fact, in a retrospective cohort study conducted by Kryzanowska, only 21% to 27 % of the elderly patients with locally advanced pancreatic adenocarcinoma received chemoradiation therapy in the United States[55].

In the elderly, the tolerability, efficacy and long-term outcomes associated with chemoradiotherapy remain unclear. Morizane *et al*[56] reported the efficacy and tolerability of chemoradiotherapy (fluorouracil infusion 200 mg/m^2 per day plus concurrent radiotherapy (50.4 Gy in 28 fractions over 5.5 wk) in elderly (> 70 years) *vs* younger patients (< 70 years) with locally advanced pancreatic cancer. The median survival time was longer in the elderly patients (11.3 mo *vs* 9.5 mo), and there were no significant differences in the frequency of severe toxicity[56].

Similarly, Miyamoto *et al*[50] analyzed a subset of elderly patient (median age of 78 years) receiving definitive chemoradiation therapy. The median overall survival was 8.6 mo, which is comparable to the survival of younger historic controls. The authors also concluded that chemoradiation therapy in selected elderly patients with locally advanced pancreatic cancer can be considered an appropriate treatment and that further research is needed to reduce the high toxicity associated with this treatment approach[50].

Stereotactic body radiation therapy (SBRT) has been an important recent advance in RT for pancreatic cancer. Pioneered in the locally advance setting, the majority of the literature has shown that SBRT is well tolerated and effective, providing excellent local control and minimal toxicity[57]. Therefore, SBRT is a promising alternative modality as a definitive treatment for elderly patients with unresectable tumors. Several small studies have evaluated the efficacy and tolerability of SBRT in locally advanced setting. Chang *et al*[58] evaluated 77 patients with unresectable pancreatic adenocarcinoma who received 25 Gy in 1 fraction. In their study, the local free progression rates at 6 and 12 mo were 91% and 84%, respectively, and the rate of grade > 2 toxicity was 9%[58]. Another interesting recently reported study investigated twenty-six patients aged 80 years or greater who were treated with SBRT (24 Gy in one fraction) alone or with chemotherapy[59]. The median OS from SBRT was 7.6 mo. More interestingly, there were no acute or late $\geqslant$ grade 3 toxicities, and the treatment was very effective for achieving symptom relief, particularly abdominal and back pain.

Chemotherapy alone without radiotherapy remains an option in the elderly subgroup of patients. Recent phase Ⅲ studies comparing chemoradiotherapy with chemotherapy alone in patients with locally advanced

non-resectable pancreatic cancer have shown that chemotherapy alone is more beneficial in terms of survival outcomes and is more tolerable than combined chemoradiation therapy[60,61].

With the development of more sophisticated imaging tools, a greater number of patients have been included in a new subgroup: borderline resectable pancreatic cancer[62]. Several criteria have been proposed to define this group. MDACC criteria defines borderline resectable pancreatic cancer following possible tumor-vessel relationships as follows: a tumor abutment of the superior mesenteric artery or celiac axis measuring ⩽ 180 degrees; or encasement of the hepatic artery amenable to resection and reconstruction; or short - segment reconstructable occlusion of the superior mesenteric vein, portal vein, or superior mesenteric-portal vein confluence[63].

In this scenario, neoadjuvant therapies have been proposed as an alternative option with the aim of downstaging tumor in order to improve microscopic resection rates[64]. This approach could be interesting for elderly patients with borderline or resectable pancreatic cancer in which the initiation of adjuvant chemotherapy is frequently delayed due to surgical complications or comorbidities, or is even discarded. Preoperative therapies also provide a time window in which patients who progress or develop distant metastases during treatment, or those with a significant functional impairment, can be identified to avoid unnecessary surgery[65]. Few studies have explored the role of neoadjuvant therapy in elderly patients. At the 2014 ASCO Gastrointestinal Cancer Symposium, Miura *et al*[66] reported the outcomes associated with neoadjuvant therapy (chemotherapy or chemoradiotherapy) in older patients with resectable or borderline resectable pancreatic cancer. They showed that the elderly group (aged 75 years or older) compared with the young group (aged younger than 75 years) had more hospitalizations during neoadjuvant therapy (50% *vs* 28%, respectively) and were also less likely to complete the therapy (72.4% *vs* 89.5%, respectively). Among the patients who completed the therapy, there were no significant differences in complication rates or median overall survival between the two groups. In conclusion, the neoadjuvant approach is an effective treatment option in elderly patients with borderline resectable pancreatic cancer and could be included in the treatment selection process for older patients who are not candidates for surgery.
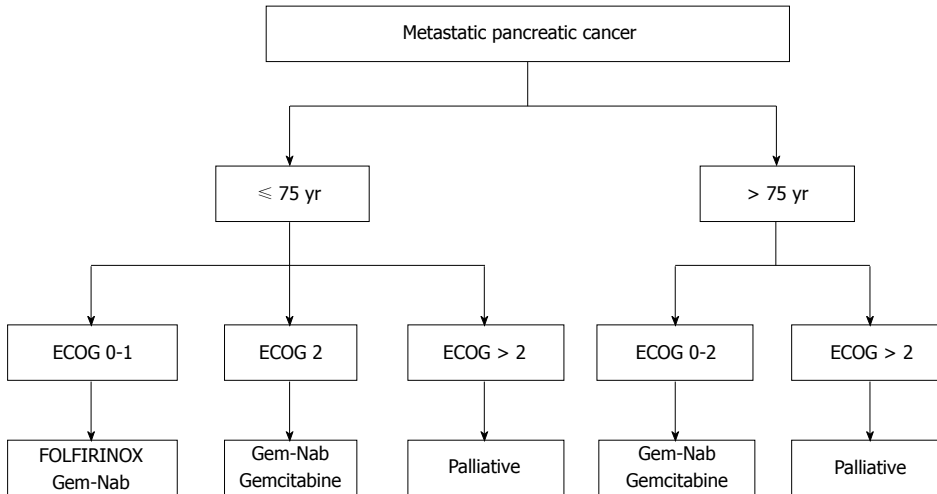
METASTATIC PANCREATIC CANCER IN THE ELDERLY

In the United States, as many as 53% of pancreatic cancer patients are diagnosed during the metastatic stage of the disease. The prognosis of patients with metastatic stage pancreatic cancer is poor, with a 5-year survival rate of 2%[67]. It is not clear that age is a prognostic factor for survival in patients with metastatic pancreatic cancer. Some studies suggest that age is a major contributing factor to a poor prognosis, while other studies reported no survival differences according to age[68,69]. Some of these studies are retrospective and small, and thus, their findings may be questionable. As described below, in the prospective PRODIGE clinical trial, age was an adverse prognostic factor[70]. However, the data obtained in retrospective studies and some large clinical trials show that the use of systemic therapy could provide a survival benefit in selected elderly and very elderly patients with metastatic pancreatic cancer[69-73]. Unfortunately, as mentioned above, the underrepresentation of elderly patients in clinical trials has resulted in treatment decisions in this patient population that are extrapolated from studies performed in younger patients. However, a change is currently underway with the development of clinical trials in elderly metastatic patients to explore the safety and efficacy of new combinations of chemotherapy.

From the end of the 1990s to 2011, gemcitabine has been considered the standard of care for patients with metastatic pancreatic cancer according to pivotal phase Ⅲ clinical trial results. Burris *et al*[74] showed a significant survival advantage with gemcitabine compared with 5FU as well as an improvement in clinical benefits. The inclusion of older patients was permitted, but the median age was only 62 years old, and the data were not separately analyzed for the elderly subgroup[74]. Maréchal *et al*[69] retrospectively analyzed the efficacy and tolerability of gemcitabine-based first-line chemotherapy in patients aged 70 years or older who were included in phase 2 and phase 3 trials. The results revealed a similar efficacy and toxicity compared with patients who were younger than 70 years old[69].

In the last 5 years, great advances have been achieved in the treatment of metastatic disease. The ACCORD-11 phase Ⅲ trial compared the efficacy and safety of FOLFIRINOX or gemcitabine as first-line therapy for metastatic pancreatic cancer[70]. In that study, the primary endpoint of overall survival was achieved (11.1 mo *vs* 6.8 mo for FOLFIRINOX and gemcitabine, respectively; HR = 0.57, *P* < 0.001). These robust efficacy results were achieved at the expense of a greater number of adverse events in the FOLFIRINOX group. It is relevant to consider that a performance status score > 1 and an age older than 75 years were exclusion criteria in this study. Only 98 of 342 patients (29%) were older than 65 years. Although an age of 65 years or older was identified as an independent prognostic factor for poor overall survival, this subgroup of patients also demonstrated a benefit in overall survival with FOLFIRINOX (HR = 0.48). The limited safety data for this regimen in older patients has prompted some authors to conduct small retrospective studies of advanced pancreatic cancer using modified

Figure 1 Choices of chemotherapy regimens for metastatic pancreatic cancer according to age and performance status. ECOG: Eastern cooperative oncology group; Gem-Nab: Gemcitabine-nab-paclitaxel.

Table 3 Baseline characteristics of the Patients in the ACCORD-11 and MPACT trials		
Variable	ACCORD-11 (FOLFIRINOX)	MPACT (Gemcitabine-Nab-paclitaxel)
Age		
Median year (min, max)	61 (25, 76)	63 (27, 88)
⩾ 65-yr-old	29.0%	42%
⩾ 75-yr-old	-	10%
Performance status (ECOG)		
0	37.4%	16%
1	61.9%	44%
2		32%
3		7%

FOLFIRINOX, and the results suggest an improved toxicity profile with an apparently similar efficacy[75].

Moreover, new clinical trials are being developed to examine the efficacy and tolerability of dose-adjusted FOLFIRINOX in patients with metastatic pancreatic cancer who are aged 70 years or older[76].

In the MPACT phase Ⅲ clinical trial, the combination of gemcitabine and nab-paclitaxel also demonstrated superiority in terms of efficacy for metastatic pancreatic cancer compared with gemcitabine monotherapy[71]. In contrast to the PRODIGE trial, in this study, an age older than 75 years and a Karnofsky performance status of 70 (corresponding to an ECOG performance status of 2) were not exclusion criteria. The median age of the patients was higher than that in PRODIGE; in fact, 365 patients (42%) were at least 65 years of age, and 10% of the patients were 75 years or older (Table 3). The apparently better tolerance of this schedule despite the inclusion of patients who were older and had a worse ECOG performance status support nab-paclitaxel-gemcitabine as an interesting option for this group of patients.

Many other randomized trials based on other combinations of gemcitabine such as gemcitabine plus oxaliplatin (GEMOX) or capecitabine-gemcitabine have been conducted without positive results[77-80]. Moreover, to our knowledge, the data collected in these studies have not been independently analyzed for the older subpopulation, and therefore, it is not yet possible to draw conclusions.

Moore *et al*[81] conducted a clinical trial evaluating the addition of erlotinib to gemcitabine. In their study, the primary end-point was met, with an overall survival that was significantly longer in the erlotinib group (5.91 mo *vs* 6.24 mo, HR = 0.82, *P* = 0.038). However, it remains questionable whether this difference is clinically relevant. Moreover, there were no differences in overall survival in the 268 patients (47%) who were older than 65 years (HR = 0.96).

The special characteristics of older patients and the observation that chemotherapy is not curative in this setting indicate that the risks and benefits of palliative chemotherapy should be carefully evaluated in terms of overall survival, tolerance and quality of life according to physiological rather than chronological age.

Considering the results and inclusion criteria obtained for large clinical trials of patients with metastatic pancreatic cancer, it is our opinion that FOLFIRINOX should be reserved for patients up to 75 years of age with an ECOG performance status of 0-1. This subgroup of patients could also be treated with the gemcitabine-nab-paclitaxel schedule. Patients with an ECOG performance status of 2 or who are older than 75 years with an ECOG performance status of 0-1 could be treated with nab-paclitaxel-gemcitabine. The most fragile patients would benefit from treatment with gemcitabine monotherapy (Figure 1).

PALLIATIVE CARE FOR PANCREATIC CANCER IN THE ELDERLY

Pancreatic cancer is characterized by a high symptom burden at the time of diagnosis and a short survival expectancy because most patients present with incu-

rable locally advanced or metastatic disease. Hence, palliative care plays a key role in the management of these patients.

The most common complications associated with pancreatic cancer are due to tumor growth and infiltration of adjacent structures (biliary obstruction, duodenal obstruction, pancreatic insufficiency, pain) and systemic phenomena (cachexia, thromboembolic events).

More than 75% of patients with pancreatic cancer experience pain due to pancreatic and celiac plexus infiltration[82]. In general, elderly patients with cancer pain are undertreated, and many of them underreport their pain[83]. Adequate treatment for pain is essential to avoid a decrease in quality of life, depression and deterioration of performance status[84]. Pain should be treated according to the WHO analgesic recommendations. Major opioids are effective in the elderly, but some precautions must be considered because these patients often receive multiple medications[85]. Another treatment option that is available for control pain is a celiac plexus block[86]. This invasive technique achieves adequate pain control in 70%-90% of cases and significantly reduces the consumption of narcotics[87]. However, the duration of the analgesic effect does not exceed 2-3 mo.

Biliary obstruction is observed in up to 70% of pancreatic cancer patients. Most of these patients are treated successfully with an endoscopically placed stent, with resolution of the obstruction in 90% of cases[88]. Older age was found to be an unfavorable prognostic factor for stent patency when a plastic stent was used[89]. Surgical biliary bypass is usually the last option for patients in whom stent placement is ineffective. Duodenal obstruction occurs in approximately 20% of patients, and metal stents and palliative surgery are feasible therapeutic approaches[90]. Therefore, elderly patients with a reasonable life expectancy should be offered these palliative procedures which may improve patient's quality of life, essential in this group of patients.

Cachexia is closely related to pancreatic cancer. It is a multifactorial syndrome that is defined by an ongoing loss of skeletal muscle mass (with or without a loss of fat mass) that cannot be fully reversed *via* conventional nutritional support and leads to progressive functional impairments. Its physiopathology is characterized by a negative protein and energy balance that is driven by a variable combination of reduced food intake and abnormal metabolism[91]. There is currently no single or combined treatment strategy that has been shown to be successful in all patients[92]. Glucocorticoids and megestrol acetate are effective for improvement of cachexia in 30%-50% of cases. Thus, the improved management of cancer cachexia may require a multimodal approach by a multi-disciplinary team[93].

In summary, the increasing incidence of pancreatic cancer in the elderly, the special features of this patient population, and the poor information available from clinical trials regarding the management of older patients has resulted in challenges in the treatment of these patients. However, age should not be the determining factor in decisions regarding the best approach. An integral evaluation of the patient in accordance with appropriate tools should be conducted. Some clinical trials targeting the elderly population are currently underway to gain a better understanding of this disease in the elderly.

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