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An onco-geriatric approach to select older patients for optimal treatments of pancreatic adenocarcinoma

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ABSTRACT

Introduction: Pancreatic adenocarcinoma affects mainly older patients. Surgery is indicated for localized tumors while chemotherapy alone is proposed in advanced or metastatic tumors.
Objective: To evaluate the feasibility of standard of care oncologic treatments in this population, the accuracy of the geriatric evaluation to predict the ability of patients to tolerate the recommended treatments and to identify specific geriatric prognosis factors.
Methods: We included, between 2007 and 2014, all consecutive patients over 70 years of age with a pathologically diagnosed pancreatic cancer. The patients underwent a comprehensive geriatric assessment before therapeutic decision in a multidisciplinary team meeting. We analyzed factors independently associated with all-cause mortality with Cox survival analysis.
Results: Seventy-three patients (median age = 77.9 years) were prospectively included. Among them, 42 patients underwent surgery whereas the 31 other patients not eligible for surgical treatment received chemotherapy (n = 22) or best supportive care alone (n = 9). Almost 62% of operated patients received adjuvant chemotherapy. In the non-surgical group, a mean of 9 cycles of palliative chemotherapy per patients were administrated. Median overall survival was 21.3 months in the surgical group and 6.1 months in the palliative group (p = 0.0001). Most of oncologic parameters were found to be independent survival predictors. Age was not associated with the survival, but a significant impact of *Lawton's Instrumental Activities of Daily Living* (IADL) impairment (IADL<4) (HR = 5.0, p = 0.047), Cumulative Index Rating Scale-Geriatric (CIRS-G) ≥2 (HR = 19, p = 0.035) and weight loss >10% (HR = 4.6, p = 0.03) on survival was detected. Surgery was the only factor independently predictive of survival in multivariate analysis (p < 0.001).
Conclusion: Almost 90% of selected older pancreatic patients with cancer (64 out of 73 patients) may benefit from the same standard treatments as younger patients. IADL impairment of patients, CIRS-G ≥2, and weight loss >10% constitute survival prognostic factors which should be added to the oncological criteria in the therapeutic decision-making process.

1. Introduction

The incidence of pancreatic adenocarcinoma varies between 7 and 11/100,000 persons in developed countries and has risen continuously over the past 40 years [1]. The prognosis of pancreatic cancer is very poor, being the 4th leading cause of cancer deaths in Europe with the mortality rate is quite similar to the incidence rate [2]. Ninety percent of pancreatic cancer are exocrine ductal adenocarcinoma and the median age at diagnosis is 72 years old [3]. Risk factors for pancreatic cancer are not well established, except tobacco, diabetes or other factors related to dietary habits, but none of them are specific to the older adult population [4]. Although familial pancreatic cancer is involved in 5 to 10% of cases, the impact of genetic predisposition appears restricted to younger patients [5]. The diagnosis of pancreatic cancer is mostly established at an advanced stage because of a late clinical expression of the disease and lack of screening tests for pancreatic cancer. Thus, about 90% of patients have an advanced pancreatic cancer at the time of diagnosis and

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only 20% of the patients are diagnosed at a stage where the tumor is resectable [6]. Despite recent advances in chemotherapy, pancreatic resection followed by 6 months of gemcitabine or 5-fluorouracil adjuvant chemotherapy remains the only potential curative option for patients with pancreatic cancer [7,8]. The 5-year survival rate at any stage of the disease is about 5% and in case of surgery with adjuvant chemotherapy, it is about 15–20%. Since 1997, gemcitabine monotherapy was established as the standard of care in advanced or metastatic disease [9] but recently, 2 randomized controlled studies introduced new standard treatments in this context. The first study published in 2011, compared gemcitabine *vs* a combination of 5 Fluoruracile, Oxaliplatine and Irinotecan, FOLFIRINOX [10]. Because only patients under 75 years were included in the study and given the toxicity of this combined schedule of chemotherapies, most oncological teams continue to reserve this treatment for young patients in good general condition (under 70–75 years of age with performance status 0 or 1). In 2013, Von Hoff et al. showed a significant improvement of the overall survival in patients treated by gemcitabine + nab-paclitaxel compared to those who received gemcitabine alone [11]. In this study, there was no age limit for patient inclusion but the median age was ultimately young (around 63 years old). Therefore, there remains a lack of data in older patients with pancreatic cancer with gemcitabine + nab-paclitaxel or FOLFIRINOX chemotherapy regimens.

The implementation of a comprehensive geriatric assessment (CGA) is now recommended during the care of older adult patients with cancer by the SIOG (International Society of Geriatric Oncology) [12]. Indeed, the benefit of an onco-geriatric approach is demonstrated to improve quality of life and to optimize specific treatments (surgery, chemotherapy, *etc.*) [13]. Regarding pancreatic cancer, many authors studied the outcome of older patients who underwent surgery [14] or who received chemotherapies. Most of them concluded that standard of care oncologic treatments can be proposed to geriatric population but subject to a precise check-up, to detect specific frailties [15–18]. The data concerning the specific impact of geriatric criteria in term of treatment tolerance and overall survival remain scarce.

Here, we report a single-center experience of a systematic onco-geriatric evaluation and its integration in the entire process of treatment decision for older patients affected by a local, advanced, or metastatic pancreatic cancer. We evaluated i) the feasibility of standard of care oncologic treatments in this population, ii) the adequacy between the proposed treatments after the multidisciplinary onco-geriatric evaluation and those truly realized and iii) the respective weight of prognosis factors, whether oncological, general, or geriatric.

2. Patients & Methods

2.1. Patients

From March 2007 to September 2014, all consecutive patients from our single tertiary center older than 70 years, with histological diagnosis of pancreatic adenocarcinoma were enrolled in a prospective cohort. All patients underwent a geriatric assessment. At baseline, a complete medical history including co-morbidities, circumstances of diagnosis, and an evaluation of performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) scale was obtained. In addition to a physical examination, blood samples were also collected for measurement of routine laboratory parameters including serum chemistry analysis, serum albumin level, liver function tests, full blood cell count, specific tumor marker (Ca19-9), lactate-déshydrogenase (LDH), alkaline phosphatase (PAL), and neutrophil/lymphocyte ratio. The extension of the pancreatic disease was assessed for each patient with a thoraco-abdominal computed tomography (CT), a liver ultrasonography, and if necessary a pancreatic magnetic resonance imaging (MRI), and/or a pancreatic endoscopic ultrasonography. Histological diagnosis was performed after examination of operative specimens in case of surgery or biopsies in case of metastatic or advanced pancreatic cancer. Pathology reports described the tumor differentiation, the tumor size and localization, lymph nodes and margin status (R0 = complete resection, R1 = microscopic residual tumor, R2 = macroscopic residual tumor). Finally, the tumor stage (TNM) was defined according to the American Joint Cancer Committee (AJCC) criteria [19]. For each patient, a personal plan of care was developed in a multidisciplinary onco-geriatric meeting composed of oncologists, geriatricians, surgeons, radiotherapists, and nurses, following the French guidelines for pancreatic cancer treatment [20]. All patients gave written informed consent for participation to the study which was previously approved by the local Ethics Committee of the University of Lyon.

Table 1
Content of the comprehensive geriatric assessment and scoring rules.

Geriatric conditions	Tools and/or scales
- Autonomy and functional status	- Katz Activities of Daily Living (ADLs) [21] → ADL disability if score ≥ 1 - Lawton's Instrumental Activities of Daily Living (IADLs) [22] → ADL disability if score ≥ 4 - Walking without help
- Nutrition	- Loss of weight → Significant if ≥10% of body weight loss - Mini Nutritional Assessment (MNA) [23] → Denutrition = score < 17.0 → Risk of denutrition = score between 17.0 and 23.5 → Correct nutritional status = score > 23.5 - Serum albumin level
- Comorbidities	- Cumulative Index Rating Scale-Geriatric (CIRS-G) (14 items) [24] Each item is scored from 0 to 4 as follows: → 0 = no problem → 1 = minor problem; → 2 = morbidity or moderate discomfort, requiring treatment → 3 = severe problem difficult to control → 4 = extremely severe problem, requiring immediate treatment or severe functional impairment.
- Cognitive and psychological status	- Mini-Mental State Examination (MMSE) [25] → Alteration of cognitive function if score < 24/30 - Geriatric Depression Scale (GDS) [26] → Depression if score > 5
- Polypharmacy	- Number of different medicines → Significant if number of medicines ≥5 [27]
- Social conditions	- Social environment questionnaire

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