

## HIGHLIGHT ARTICLE

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# Should Ageism Be a Stratification Factor in Patients with Pancreatic Cancer?

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### Summary

With ageism being a trend worldwide, and age being a known risk factor for pancreatic cancer, the optimal management of pancreatic cancer patients with advance age is becoming more and more of a pertinent discussion amongst GI oncologists, surgical oncologists and radiation oncologists that is being increasingly addressed in studies nowadays. In an attempt to answer the question of whether age should be a cultural bias in decision making in pancreatic cancer patients, we will review Abstracts #287, #310 and #332 that were presented in the 2014 ASCO Gastrointestinal Cancers Symposium. These abstracts explore whether neoadjuvant therapy should be offered to patients older than 75 years to increase the chances of bridging to surgical resectability (Abstract #287), if patients older than age 70 years would benefit from chemotherapy similar to younger patients (Abstract #310), also whether adjuvant radiation therapy and number of lymph nodes resected in patients older than 70 years correlates with overall survival (Abstract #332).

### Introduction

With approximately 43,000 people diagnosed with pancreatic cancer in 2010, and nearly 37,000 reported deaths from this malignancy, pancreatic cancer remains the fourth leading cause of cancer death in the United States [1]. It is well known that age is one of the risk factors for pancreatic cancer. In 2010, the National Cancer Institute statistics showed that the median age at diagnosis was 72.2 years [2], making pancreatic cancer a disease of older people with the majority of patients being older than 65 years at the time of diagnosis [3].

With the growing elderly population in the United States and increase in the average lifespan worldwide, optimally managing and treating this increasing number of elderly people with pancreatic cancer is becoming more of a challenge to clinicians. This decision making is made more difficult with the

under-representation of older adults in cancer registration trials [4], attributed to decline in functional reserve, increased comorbid conditions, concomitant medication use, lack of social/home support among other factors. Based on this, there has been increased focus on comparing different treatment options and their outcomes in elderly patients with pancreatic cancer compared to younger patients.

### What We Knew Before the 2014 ASCO Gastrointestinal Cancers Symposium

At our present time, older adults constitute a very important percentage of an adult oncologist everyday practice. This increasing demand is met by very scarce data and guidelines that address the evaluation and treatment of older patients. This includes patients diagnosed with pancreatic cancer that is well known to have the highest incidence in people older 65 years of age, with most of these patients presenting with metastatic disease at the time of diagnosis. Older patients require special attention when deciding on chemotherapy and other modalities of treatment including surgical options given the lower performance status in general, age-related organ function decline and associated medical comorbidities that affect their quality of life and treatment-related toxicities. All of these considerations should be thought of in the

**Key words** Aging; Geriatrics; Pancreatic Neoplasms; Risk Factors

**Abbreviations** CCI: Charlson comorbidity index; FOLFIRINOX: oxaliplatin, irinotecan, fluorouracil, and leucovorin

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context of estimated life expectancy keeping palliation as a mode therapy in elderly patients with metastatic pancreatic cancer.

### **What We Learned at the 2014 ASCO Gastrointestinal Cancers Symposium**

Surgical resection is the only potentially curative treatment for pancreatic cancer patients. Unfortunately, this is not an option that can be offered upfront for most patients because of the late presentation of the disease, with only about 20% of patients being candidates for surgery when they are diagnosed [1, 5]. Added to that challenge is the presence of comorbidities and suboptimal performance status that is present in older people who are diagnosed with resectable or borderline resectable pancreatic cancer.

Neoadjuvant therapies have been explored in patients with "locally advanced" pancreatic cancer for local tumor control and down-staging attempting to increase complete microscopic tumor resection rates [6]. A meta-analysis done in 2010, showed similar resection frequencies and survival after neoadjuvant therapy in patients with initially resectable tumors are comparable to patients with primarily resected tumors and adjuvant therapy [7]. They also showed that "approximately one-third of initially staged non-resectable tumor patients would be expected to have resectable tumors following neoadjuvant therapy, with comparable survival as initially resectable tumor patients". The conclusion from this study and other smaller studies would be to include patients with locally non-resectable tumors in neoadjuvant treatment protocols and then re-evaluate them for resectability.

#### *Is Neoadjuvant Therapy Feasible in Elderly Patients? (Abstract #287) [8].*

The question that comes up at this point is whether this data can be extrapolated to include older patients with pancreatic cancer. This question was addressed by Miura *et al.* at the 2014 ASCO Gastrointestinal Cancers Symposium who looked at outcomes in older patients with resectable (42.5%) or borderline resectable (57.5%) pancreatic cancer receiving neoadjuvant therapy from 2008-2012 [8]. They divided their study population into patients aged 75 years or more (Old group; 16% of the 180 patients studied) and those aged less than 75 years (Young group) and defined completion of all therapy as receiving neoadjuvant therapy and surgical resection. They showed that patients in the Old group had a higher Charlson comorbidity index (CCI) (median CCI 4 vs. 2;  $P<0.01$ ) and more hospitalizations during neoadjuvant therapy (50% vs. 28%,  $P=0.04$ ) and they were also less likely to complete all therapy compared to patients of the

Young group (72.4% vs. 89.5%;  $P<0.01$ ). Based on their data, the most common reason for failure to complete therapy was a poor performance (17.2% vs. 0.7%;  $P<0.01$ ), higher CCI (OR=0.25; 95% confidence interval (95% CI): 0.08-0.74;  $P=0.01$ ) and higher clinical stage (OR=0.17; 95% CI: 0.06-0.48,  $P<0.01$ ). What was interesting is that out of the 138 patients that completed all therapy, there was no significant differences observed in complication rates (15.0% vs. 15.3%;  $P=0.33$ ), median length of hospital stay (10 vs. 9 days;  $P=0.29$ ), 30-day readmission rates (10.0% vs. 11.9%;  $P=0.81$ ), or median overall survival (24.3 vs. 36.7 months;  $P=0.20$ ) between the two age groups. The main reason for the Old group patients to not undergo surgical resection was a decline in performance status after chemotherapy (25% in their study). This poses the question of whether neoadjuvant therapy acts as a selection process for older patients who are not surgical candidates to start with, or rather decreases the chances of resection that might have been successful if not preceded by chemotherapy.

#### *Is Chemotherapy an Acceptable Option for Elderly Patients? (Abstract #310) [9].*

This dilemma of the benefit of chemotherapy in elderly patients with pancreatic cancer was addressed by Teo *et al.* by a population based trial that identified 4,509 patients from the National Cancer Registry of Ireland database who were diagnosed between 1998 and 2010 inclusive who did not receive radical resection [9]. To study the effect of age, if any, the patients were divided based on their age (70 years or more vs. less than 70 years) and metastatic status (M0 vs. M1). Sixty-four percent of their patients were 70 years or older, 16% were staged M0, 42% were staged M1 and 42% did not have documented staging (Mx). The patients were divided as follows: 16% received chemotherapy, 5% chemoradiotherapy and 79% no cancer directed therapies. Their results showed that more patients with age 70 years or more were Mx compared to patients less than 70 years (48% vs. 30%,  $P<0.01$ ) and patients with age 70 years or more were also less likely to receive any treatment ( $P<0.01$ ). In addition, comparing the 70 years or more vs. less than 70 years groups, median overall survival for M0 who received chemotherapy was 6.0 vs. 7.3 months (HR=1.28; 95% CI: 0.85-1.89;  $P=0.24$ ), for those who received chemoradiotherapy was 7.0 vs. 9.7 months (HR=0.95; 95% CI: 0.42-1.88;  $P=0.89$ ) and for those who received no treatment was 3.0 vs. 3.5 months (HR=1.03; 95% CI: 0.84-1.29);  $P=0.75$ ); median overall survival for M1 who received chemotherapy was 2.4 vs. 3.4 months (HR=1.21; 95% CI: 0.97-1.49;  $P=0.09$ ), for those who received chemoradiotherapy was 4.3 vs. 6.0 months (HR=1.69; 95% CI: 0.89-3.03;  $P=0.11$ ) and

for those who received no treatment was 1.2 vs. 1.4 months (HR=1.11; 95% CI: 1.00-1.24; P=0.06). They concluded that chemotherapy and chemoradiotherapy improved the medical overall survival regardless of the M stage or the age group and those patients older than 70 years would have similar benefits to treatment as younger patients.

Is Radiotherapy Feasible in Elderly Patients? (Abstract #332) [10].

How about the impact of postoperative radiation therapy and lymph node resection on survival in patients ageing 70 years or more treated with surgery and chemotherapy? This was addressed by Freilich *et al.* at the 2014 ASCO Gastrointestinal Cancers Symposium by analyzing 961 patients from the Surveillance, Epidemiology, and End Results (SEER) database from 2004-2008 who underwent a surgical resection and received chemotherapy [10]. Age was the only significant difference between postoperative radiation therapy patients and no postoperative radiation therapy patients. Their results showed that overall survival in postoperative radiation therapy *versus* no postoperative radiation therapy patients was not statistically different in the whole cohort (P=0.064), as well as in N0 patients (P=0.803) while it was near the significant level in N1 patients (P=0.0501). They observed no overall survival difference based on gender, location, postoperative radiation therapy, number of lymph nodes removed in all patients (P=0.74), in N0 patients (P=0.59), and in N1 patients (P=0.07). Multivariate analysis showed that higher T stage, N1, and high grade were prognostic for worse mortality, while postoperative radiation therapy patients had decreased mortality, even if not reaching the significant level (P=0.052). They concluded that neither gender, age, nor tumor location seem to be prognostic for survival and that in patients older than 70 years with surgically resected pancreatic cancer treated with chemotherapy, adjuvant radiation therapy and number of lymph nodes removed does not translate into increased overall survival.

## Discussion

A review of the literature reflects the less aggressive treatment of elderly patients with pancreatic cancer, who are less likely to receive any chemotherapy compared to younger patients and are less likely to receive more than one drug. Gemcitabine, which was approved for advanced pancreatic cancer in 1996, is currently the most commonly used single agent for the treatment of elderly with advanced pancreatic cancer [11]. In 2011, a hallmark study compared combined oxaliplatin, irinotecan, fluorouracil, and leucovorin therapy (FOLFIRINOX) and gemcitabine for the treatment of metastatic pancreatic cancer [12]. Out

of the 342 patients in this study, only 76 patients were 65 years or older, and in these patients using FOLFIRINOX was associated with improvement in overall survival (HR=0.48; 95% CI: 0.30-0.77) despite the higher level of toxicity. Results from the Partenariat de Recherche en Oncologie Digestive 4/Action to Control Cardiovascular Risk in Diabetes11 (PRODIGE 4/ACCORD 11) randomized trial were also encouraging, with patients in the FOLFIRINOX arm experiencing less and slower decline in their quality of life compared to patients in gemcitabine arm [13]. Over the last two years, there has been an increasing move towards the use of FOLFIRINOX with a significant proportion of these patients being more than 65-year-old [14] in addition to studies looking into gemcitabine in combination with other agents [15]. In a prospective phase III randomized controlled trial published in 2013 comparing nab-paclitaxel plus gemcitabine *vs.* gemcitabine alone for the treatment of patients with metastatic pancreatic adenocarcinoma, overall survival, progression-free survival, and response rate were significantly improved in the arm receiving nab-paclitaxel [16]. Can we extrapolate these findings to older patients with pancreatic cancer?

To help address this question and predict chemotherapy toxicity in elderly patients, there has been emerging evidence on the role of comprehensive geriatric assessment looking into all the factors that can affect the outcome of therapy that can help guide oncologists [17], as well as stressing on the importance of symptom control, palliative care and quality of life in patients with advanced cancer who are more likely to belong to the older age group. It remains key to emphasize that the patient's age should not be the sole determinant in decision making and choice of therapy since chronologic age by itself does not provide information regarding the patients' tolerance to treatment. The highlights from the ASCO Gastrointestinal Cancers Symposium this year are a very positive move reflecting the general inclination of the clinicians and the scientific community to include older adults in cancer registration and population based studies and to design studies that compared the effect of the same treatment modality in different age groups. The aim from these studies is to help guide treatment in older patients with pancreatic cancer, as well as other cancers, with people older than 65 years bearing the greater burden of cancer in the United States and the industrial countries nowadays [18].

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