Journal of Geriatric Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

Age as a prognostic indicator for adjuvant therapy in patients who underwent pancreatic resections for cancer☆

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ARTICLE INFO

Article history:
Received 28 September 2017
Received in revised form 31 October 2017
Accepted 28 December 2017
Available online xxxx

Keywords:
Pancreas cancer
Chemotherapy
Adjuvant
Pancreas surgery
Pancreaticoduodenectomy
Whipple
Older

ABSTRACT

Purpose: In pancreatic cancer, the greatest increase in survival is attained by surgical resection followed by adjuvant chemotherapy. Although surgical complications and functional status are recognized as independent factors for halting adjuvant therapy in patients that undergo pancreatic resections, other elements may play a role in deciding which patients get treated postoperatively. Here we determined demographic and clinical characteristics of patients receiving adjuvant chemotherapy, with the primary intent to investigate if age alone affects rates of adjuvant therapy.
Methods/Materials: National Cancer Database (NCDB) was queried for patients that underwent surgery for pancreatic cancer. Groups were divided into: adjuvant chemotherapy (n = 17,924) and no adjuvant chemotherapy (n = 12,947). Basic demographics and treatment characteristics were analyzed. Age was compared with an independent means test; other comparisons used Chi-square test of independence.
Results: There was a statistical difference in age (adjuvant therapy 64.86 ± 9.89 vs. no therapy 67.78 ± 11.22, $p < 0.001$), insurance type, facility type, and cancer stage for patients that received adjuvant therapy and those that did not. Average age of patients not receiving chemotherapy was significantly older at each pathologic stage. Subset analysis of patients treated with chemotherapy showed that the majority of patients received single agent regimens (62%), at an average of 59 days following surgery, and at academic cancer programs (52%).
Conclusions: Regardless of postoperative complications and functional status, age alone appears to affect rates of adjuvant therapy in patients with resected pancreatic cancer. Older patients should be offered tailored regimens that would allow them to complete the intended extent of treatment.

1. Introduction

Pancreatic cancer continues to be on the rise, with an estimated 53,070 new cases in 2016 [1]. Even though only 15–20% of pancreatic cancers are resectable at the time of diagnosis [2], it has been well established that the only chance for cure comprises a combined approach of surgical resection and systemic therapy [3]. Debate on whether neoadjuvant systemic strategies for those with resectable neoplasms improve overall survival is ongoing [4,5], but the benefits of adjuvant therapy for those individuals that are able to undergo a curative intent resection have been well established in several randomized trials [2,6–12]. Indeed, Level 1 evidence from the ESPAC 3 [8] and CONKO-001 [9] clinical trials have shown that there is a statistically significant increase in survival with the addition of adjuvant chemotherapy to surgical treatment of pancreatic adenocarcinoma. While adjuvant chemotherapy provides a clear survival benefit, reports are mixed as to whether the addition of radiation therapy increases overall survival in patients with pancreatic cancer [7,10,13].

Data from small retrospective studies have shown that the number of patients who are candidates for adjuvant chemotherapy following resection varies from 16% to 31% [6,13–15]. The reasons behind these diverse rates are multifactorial, but two of the most recognized elements influencing rates of adjuvant chemotherapy include postoperative morbidity, typically associated with pancreatic resections [16,17] and preoperative performance status [14]. When the performance of the patient is suboptimal preoperatively, the number of patients that will not receive adjuvant systemic therapy has been reported to be as high as 77% [14]. Our group and others have demonstrated that older patients tend to experience higher incidences of complications postoperatively [17–19], which may influence rates of postoperative chemotherapy in this population, but to date no study has examined the impact of age alone on rates of adjuvant chemotherapy.

With this background, the present study was designed to investigate patterns of adjuvant chemotherapy administrations for patients that underwent pancreatic resections with a curative intent using a

☆ **Funding**: None.
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https://doi.org/10.1016/j.jgo.2017.12.004
1879-4068/

validated national database. We specifically intended to research the hypothesis that age alone affected the rates of adjuvant therapy in pancreatic cancer. As a secondary objective, we also determined national patterns of adjuvant systemic therapy for patients with pancreatic cancer.

2. Experimental/Materials and Methods

2.1. Data Source and Subject Selection

This study was conducted using de-identified patient data from the National Cancer Database, a nationwide oncology outcomes database managed by the American College of Surgeons, Commission on Cancer, and American Cancer Society that contains approximately 34 million patient records from Commission-accredited cancer centers across the United States [20]. Our team was granted use of the Participant User File of patients with pancreatic cancer, which includes records for cases diagnosed from 2004 to 2014. From the original database file of patients with pancreatic cancer (N = 276,604), a subset was selected to include only patients who had undergone pancreatic resection followed by systemic chemotherapy, chemoradiation, or radiation therapy (N = 25,435). From this subset, subjects were excluded if records were missing data on any of the variables of interest. Additionally, if chemotherapy was initiated prior to surgery, subjects were eliminated from the dataset. The final data set for this subgroup (referred to as the "Surgery plus Chemotherapy" subgroup) contained 17,924 subjects. A comparison group of subjects that did not receive adjuvant systemic therapy following surgery ("Surgery only") was selected from the original dataset, and after excluding incomplete records, the comparison group contained 12,947 records. This study was declared exempt from institutional review by the Florida Hospital Institutional Orlando Review Board because all patient information was de-identified.

2.2. Demographic and Clinical Characteristics

Data on multiple demographic and clinical variables were collected to characterize the patient samples. Demographic variables queried included facility type, facility location, age at diagnosis, sex, race, insurance status, urban/rural location, and income quartile. Clinical characteristics included Charlson/Deyo score (a measure of comorbid conditions) [21], year of diagnosis, primary tumor site, grade, number of regional lymph nodes positive for malignancy, number of regional nodes examined, number of days between diagnosis and staging procedure, tumor pathologic characteristics, tumor size, surgical margins, number of days between diagnosis and initiation of treatment, type of systemic treatment, number of days between diagnosis and first surgery, number of days between diagnosis and initiation of radiation therapy, type of radiation therapy, location of radiation therapy, details of radiation of therapy, reason for no radiation, type and timing of chemotherapy, type and timing of hormonal therapy, type and timing of immunotherapy, and type and timing of other systemic therapies.

2.3. Outcomes Variables

Variables collected included 30-day mortality, 60-day mortality, palliative care, number of months between diagnosis and death or last contact, and vital status (dead/alive) at date of last contact.

3. Statistical Analysis

The objective of this study was to determine if age alone, regardless of comorbidities affects the rate of adjuvant therapy in patients undergoing surgery for pancreatic cancer. The Charlson/Deyo score, a measure of significant comorbidities, was used in this case to determine whether the presence of comorbid conditions prevented patients from receiving chemotherapy. Accurate data on pre and postoperative functional status is not available from the database. Logistic regression modeling of age and Charlson/Deyo scores association with having chemotherapy or not was done with a random sample of approximately 500 subjects from each AJCC (American Joint Committee on Cancer) pathologic state. Age was treated as a continuous variable and Charlson/Deyo score was categorical.

After determining the Charlson/Deyo score was not a significant factor in determining rates of adjuvant therapy, it was removed from analysis in order to simplify results. Using Analysis of Variance (ANOVA), the association of age with treatment was analyzed by comparing the mean age at treatment in the subset of patients that received adjuvant therapy with the mean age of patients who had surgery without adjuvant therapy. Subjects were divided by JCAA pathologic stage because of the association of therapy related to tumor stage. Rates of adjuvant chemotherapy/radiation were analyzed and compared between groups using a Chi-square test of independence.

When appropriate, a 10% sample was selected because of the large sample sizes and the effect on p-values [22].

Analysis of Variance (ANOVA), log transformed, was computed to understand the timing of chemotherapy initiation. Year of diagnosis, age, sex, type of insurance, income, education, residence status (urban or rural), and location of treatment center were investigated.

All statistical analyses were performed with SPSS Version 21 (IBM, Armonk, NY).

4. Results

A total of 30,871 patients who underwent pancreatic resection for cancer were included in this analysis. Of these patients, 12,947 (41.9%) underwent surgery alone, while 17,924 (58.1%) underwent surgery followed by adjuvant therapy. Demographic data for these patient cohorts are shown in Table 1. Patients receiving adjuvant chemotherapy were younger than those in the surgery alone group ($p < 0.001$). There was a statistically significant difference in distribution of patients by facility type and insurance type, with more patients in the "surgery alone" group enrolled in government insurance. There was also a significant difference in the distribution of patients among AJCC pathologic stage groups ($p < 0.001$), with a majority of patients receiving adjuvant chemotherapy with stage 2B disease. Subset analysis of patients treated with chemotherapy showed that the majority of patients received single agent regimens (62%), at a median of 54 days following surgery, and at academic cancer programs (52%).

4.1. Factors Impacting Adjuvant Chemotherapy Rates

Comparison of the mean age of patients between groups by tumor stage is shown in Table 2 and Fig. 1. The average age of a patient receiving chemotherapy was younger than patients not receiving adjuvant therapy for each stage, with a statistically significant difference in all stages except for stage 1B. Logistic regression modeling of Charlson/Deyo scores and the receipt of chemotherapy showed no significant correlation between number of comorbid conditions and whether a patient received chemotherapy at all pathologic stages. Additional testing determined that the percentage of older patients (80–90) within each stage had a lower percentage receiving adjuvant chemotherapy (Table 3). There is a statistical difference in the rates of adjuvant therapy of older patients by stage (Fig. 2); the p-values may be inflated due to the large sample size, but there is a clinical difference that is more important. The rate of adjuvant therapy in older patients (all stages) was much lower (1094/3150 or 35%) than for all age groups (17,924/30,871 or 58%).

Among patients who did not receive chemotherapy there were two statistical pairwise differences ($p = 0.023$) when patients were grouped by recommendations for chemotherapy. The group that had chemotherapy recommended but did not receive it was younger (mean age = 68) than the group that had chemotherapy recommended

Please cite this article as: Eubanks A, et al, Age as a prognostic indicator for adjuvant therapy in patients who underwent pancreatic resections for cancer, J Geriatr Oncol (2018), https://doi.org/10.1016/j.jgo.2017.12.004