

ORIGINAL ARTICLE

Pancreatic cancer patients who cannot undergo curative surgery live as much as patients over 70 years old

Yildirim Serkan¹, Erdogan Atike Pinar², Yilmaz Cengiz³, Ozveren Ahmet⁴, Ekinci Ferhat², Bulut Gulcan⁵

¹Bitlis Tatvan Public Hospital, ²Celal Bayar University Medical School, ³Izmir Bozyaka Training and Research Hospital, ⁴Izmir Kent Hospital, ⁵Hatay Defne Hospital.

Summary

Purpose: Patients over the age of 65 constitute approximately 54% of newly diagnosed cancers and approximately 70% of cancer-related deaths. These patients aged ≥ 65 years, who form the majority of clinical practice, are represented less in clinical studies than in real life. We designed this retrospective study to examine the treatment and response of patients to pancreatic cancer in patients over 70 years of age.

Methods: Our study is a retrospective study that included patients from 5 centers in Turkey. Inclusion criteria were being over the age of 18 years, diagnosed with pancreatic cancer, and with ECOG performance score between 0-2. These patients were divided into two groups according to their age. The classification was made as patients over 70 years of age in the first group (geriatric group) and patients under 70 years of age (<70 age group) in the second group.

Results: Overall survival of the <70 age group was statisti-

cally significantly longer (median 10 months vs 9.1 months $p=0.027$). When the patients who underwent only curative surgery were examined, the survival was statistically significant in favor of the <70 age group (median 20.96 months vs 14.5 months $p=0.011$). No statistically significant difference was found between the two groups in terms of the overall survival of patients with metastatic diagnosis (median 8.1 months vs 8.4 months $p=0.182$).

Conclusion: The survival of patients with pancreatic cancer aged 70 and over was shorter than other age groups. While this difference was significant in patients who could undergo surgery at an early stage, it was not found in the metastatic patient group. Prospective larger-scale studies are needed to evaluate the treatment of geriatric patients better.

Key words: pancreatic cancer, curative surgery, old patients, survival

Introduction

Pancreatic cancer is a fatal disease due to its aggressive nature and the advanced stages of patients when diagnosed. Annually, approximately 60.000 people are diagnosed with pancreatic cancer in the USA [1]. The majority of these patients die due to pancreatic cancer. Five-year survival is approximately 7-8% [2,3]. The only curative treatment is surgery. Survival is poor even in patients who can undergo surgery with curative-intent [4,5]. In metastatic disease, there are not many treatment options other than chemotherapy. Survival in

locally advanced and metastatic disease does not exceed 12 months even with modern treatments. Although FOLFIRINOX is the chemotherapy regimen that offers the highest survival, it reached a mean value of 11.3 months [6]. This regimen provides the best survival results, but it is very toxic. Not all patients can receive this treatment due to the side effects.

Patients over the age of 65 (≥ 65) constitute approximately 54% of newly diagnosed cancers and approximately 70% of cancer-related deaths

[7,8]. These patients aged ≥ 65 years, who form the majority of clinical practice, are represented less in clinical studies than in real life [9-13]. Therefore, there are fewer studies and data in this patient group. Also, elderly individuals are less likely to receive standard treatment than younger patients [14-18]. Toxicity, many comorbid diseases, clinicians and patient preferences affect the treatment of the elderly.

It is difficult to treat pancreatic cancer both in the early period in which surgery can be performed and in the metastatic period. This difficulty increases a little more with age which changes treatment and response to treatment with advanced age and constitutes an important research area. However, although there are many studies in elderly cancer patients, such as breast cancer and colon cancer, the number of studies on pancreatic cancer is very low. Therefore, we designed this retrospective study to examine the treatment and response of patients to pancreatic cancer in patients aged over 70 years.

Methods

This was a retrospective study that included patients from 5 centers in Turkey. Patients admitted to these centers between 2012 and 2017 and diagnosed with pancreatic cancer were included. The files of the patients were retrospectively reviewed. Inclusion criteria were being over 18 years, diagnosed with pancreatic cancer, and with ECOG performance score between 0-2. These patients were divided into two groups according to their age. The classification was made as patients over 70 years of age in the first group (geriatric group) and patients under 70 years of age (<70 age group) in the second group.

The primary endpoint of the study was overall survival. Overall survival was defined as the period from diagnosis to death or the last follow-up. Also, some factors affecting survival between the two groups were investigated. These were gender, ECOG performance score, primary tumor location, rates of pancreatic surgery performed with curative intent, and first-line treatment regimens in metastatic patients. While examining these factors, ECOG performance score and primary tumor locations were divided into two groups (ECOG 0-1 vs 2, and head vs tail-body). Our study was conducted as per the Declaration of Helsinki and performed with the approval of the Local Ethics Committee (Decision number: Manisa Celal Bayar University, 142/22.03.2021).

Statistics

All analyses were performed using the SPSS statistical software program package (SPSS version 20.0 for windows). The chi-square test analyzed the differences in the clinical characteristics between the two groups. OS was calculated with the log-rank test. The Kaplan-Meier method was used to draw survival curves. The Cox proportional hazards regression model was used to determine statistically significant variables related to OS. Differences were assumed to be significant when the p value of less than 0.05.

Results

A total of 363 patients were included in the study. Of these patients, 78 were over 70 years old (geriatric group), and the remaining 285 were under 70 years old (<70 age group). There were 48 female and 30 male patients in the geriatric group. In the <70 age group, there were 171 female patients vs 114 male patients. When the gender distributions were compared between the

Table 1. General patient characteristics

Characteristics	≥ 70 age group (n=78)	<70 age group (n=285)	Overall (n=363)	p value
Sex				0.45
Female	48	171	219	
Male	30	114	144	
ECOG				0.004
0-1	56	245	301	
2	22	40	62	
Primary tumor side				0.116
Head	54	174	228	
Body-Tail	24	111	135	
Curative-intent surgery	15	45	60	0.539
Metastatic first line therapy	48	212	260	<0.000
Gemcitabine	30	71		
Gemcitabine-Cisplatin	16	99		
FOLFIRINOX	2	32		

two groups, no significant difference was found ($p=0.45$).

When the distribution of the ECOG performance score in the two groups was examined, the number of patients with ECOG score 0-1 in the geriatric group was 56, and the number of patients with ECOG score 2 was 22. In the <70 age group, the number of patients with ECOG score 0-1 was 245, and ECOG score 2 was 40. When the two groups were compared, the ratio of patients with an ECOG performance score 2 was statistically significantly higher in the geriatric group ($p=0.004$).

When the distribution of the primary tumor location in the two groups was examined, the number of patients with pancreatic tumor originating from the head was 54 in the geriatric group, and the body-tail part was 24. In the <70 age group, the number of patients with pancreatic tumor originating from the head was 174, and in the body-tail part was 111. No statistically significant difference was found between the two groups in terms of primary tumor location ($p=0.116$).

When the rate of performing pancreatic surgery with curative intent in the two patient groups was considered, the number of patients who underwent curative surgery in the geriatric group was 15 and for those who did not undergo was 63. In the <70 age group, the number of patients who underwent curative surgery was 45, and those who did not undergo was 229. No statistical difference was observed between the two groups in terms of the rate of performing pancreatic surgery for curative intent ($p=0.539$).

There were 292 patients diagnosed with metastatic disease. The number of patients who received first-line chemotherapy was 260. Forty-eight patients had received metastatic first-line therapy

in the geriatric group. Thirty of these patients received single-agent gemcitabine treatment, while 18 patients were able to receive other regimens. Other regimens were cisplatin-gemcitabine for 16 patients and FOLFIRINOX for two patients. While 71 of 212 patients who received first-line chemotherapy in the <70 years age group received gemcitabine as a single agent, 141 patients received other regimens. Other regimens were cisplatin-gemcitabine for 99 patients, FOLFIRINOX for 32 patients, FOLFOX for 4 patients, Xelox for 3 patients, and Capecitabine for 3 patients. When the two groups were compared, the rate of patients receiving gemcitabine alone was statistically significantly higher in the geriatric group ($p<0.000$). The characteristics of the patients are presented in Table 1.

When the overall survival, which was the primary endpoint of our study, was examined, the overall survival of the <70 age group was statisti-

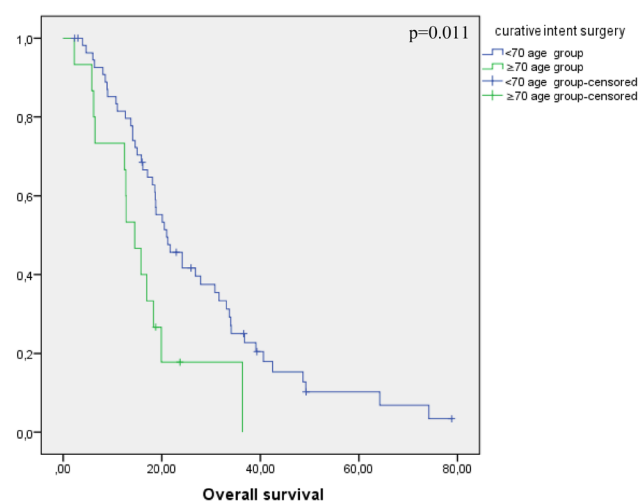


Figure 2. Overall survival of all patients who underwent curative-intent surgery.

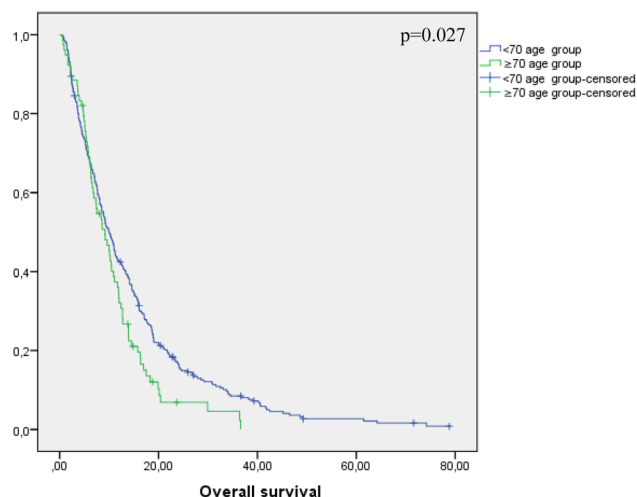


Figure 1. Overall survival of all patients.

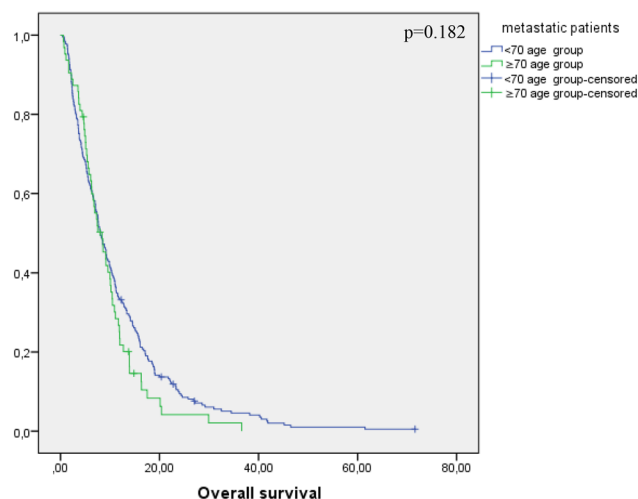


Figure 3. Overall survival of metastatic patients.

cally significantly longer (median 10 months vs 9.1 months, $p=0.027$) (Figure 1). When the patients who underwent only curative surgery were examined, the survival was statistically significant in favor of the <70 age group (median 20.96 months vs 14.5 months, $p=0.011$) (Figure 2). No statistically significant difference was found between the two groups in terms of overall survival of patients with metastatic diagnosis (median 8.1 months vs 8.4 months, $p=0.182$) (Figure 3).

Discussion

FOLFIRINOX and gemcitabine/nab-paclitaxel took their place in metastatic pancreatic cancer after using only gemcitabine for many years. Two large randomized controlled studies have been conducted in which the contribution of these regimens to survival has been demonstrated. In the first study, the FOLFIRINOX regimen was compared with single-agent gemcitabine. In this study, subgroup analysis was performed by dividing the patients into two groups (<65 years vs >65 years) [6]. As per this analysis, overall survival was prolonged with FOLFIRINOX treatment in both age groups, but patients under 65 years of age benefited more (hazard ratio 0.61 vs 0.41). The fact that its effectiveness as neoadjuvant [19] has also been demonstrated shows how effective the FOLFIRINOX treatment is. In the second study, the gemcitabine/nab-paclitaxel combination was compared with gemcitabine. Patients were also divided into two groups (<65 years vs >65 years) in this study. Overall survival of all age groups was prolonged with the combination therapy. However, the group under 65 years of age benefited more (hazard ratio 0.65 vs 0.81) [20]. Although the platinum-gemcitabine combination was effective in some studies [21], it did not create a difference in overall survival in phase 3 studies.

In both large randomized studies, efficacy was less in patients over 65 years of age. Although 70-year of age was determined as the limit in our study, despite there was a difference in overall survival when all patients were considered, this difference disappeared when only metastatic patients were evaluated. Even numerically, the overall survival was higher in patients over 70 years old (median 8.1 months vs 8.4 months $p=0.182$). These results were despite the disadvantage of patient selection between groups. The proportion of patients with ECOG performance score 2 was higher in patients over 70 years of age. A second data supporting this is that patients who had

gemcitabine alone were also more likely to be in the group over 70 years of age, because single-agent gemcitabine was mostly given to patients with low clinical performance scores. As a result, patients with low performance overall survival based on these two data were more in the group with patients over 70 years old. Despite this disadvantage, the reason that the overall survival was not statistically different between the two groups may be that patients had less access to effective treatments since in our study, metastatic patients did not receive gemcitabine/nab-paclitaxel treatment in the first-line treatment. Also, the number of patients who had FOLFIRINOX was low. When first-line treatments were evaluated, patients mostly took the combination of cisplatin-gemcitabine, whose survival benefit could not be demonstrated in prospective studies [22].

As a result, it was observed in our study that the survival of patients over 70 years old was lower than other patients. However, this difference was due to the patients who had surgery for curative intent ($p=0.027$). No survival difference was found among metastatic patients. Therefore, it can be stated that the main difference between these two age groups was surgery. Earlier diagnosis and more widespread use of curative treatments are what needs to be done to offer patients longer survival rates. As can be seen in our study, as long as the patients are in the metastatic stage, age and the treatments given cannot make a significant difference.

Conclusion

The survival of patients with a diagnosis of pancreatic cancer aged 70 and over was shorter than other age groups. While this difference was significant in patients who could undergo surgery at an early stage, it was not found in the metastatic patient group. Prospective larger-scale studies are needed to better evaluate the treatment of geriatric patients.

Conflict of interests

The authors agree with the content of this manuscript. They also declare that they have no conflict of interest. The study with accompanying material is an original work, neither published, accepted, or submitted for publication elsewhere. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020;70:7.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015;65:5-29.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016;66:7-30.
4. 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.
5. Oettle H, Post S, Neuhaus P et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA* 2007;297:267-77.
6. Conroy T, Desseigne F, Ychou M et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817.
7. Ries EM, Kosary CL, Hankey BF et al. SEER Cancer Statistics Review: 1975-2000. National Cancer Institute, Bethesda, MD.
8. Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review, 1975-2015. http://seer.cancer.gov/archive/csr/1975_2015/ (Accessed on July 31, 2019).
9. Hutchins LF, Unger JM, Crowley JJ et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med* 1999;341:2061.
10. Yee KW, Pater JL, Pho L et al. Enrollment of older patients in cancer treatment trials in Canada: why is age a barrier? *J Clin Oncol* 2003;21:1618.
11. Trimble EL, Carter CL, Cain D et al. Representation of older patients in cancer treatment trials. *Cancer* 1994;74:2208.
12. Freedman RA, Foster JC, Seisler DK et al. Accrual of Older Patients With Breast Cancer to alliance Systemic Therapy Trials Over Time: Protocol A151527. *J Clin Oncol* 2017;35:421.
13. Pang HH, Wang X, Stinchcombe TE et al. Enrollment Trends and Disparity Among Patients With Lung Cancer in National Clinical Trials, 1990 to 2012. *J Clin Oncol* 2016;34:3992.
14. Hurria A, Leung D, Trainor K et al. Factors influencing treatment patterns of breast cancer patients age 75 and older. *Crit Rev Oncol Hematol* 2003;46:121.
15. Mandelblatt JS, Hadley J, Kerner JF et al. Patterns of breast carcinoma treatment in older women: patient preference and clinical and physical influences. *Cancer* 2000;89:561.
16. Newcomb PA, Carbone PP. Cancer treatment and age: patient perspectives. *J Natl Cancer Inst* 1993;85:1580.
17. Merchant TE, McCormick B, Yahalom J, Borgen P. The influence of older age on breast cancer treatment decisions and outcome. *Int J Radiat Oncol Biol Phys* 1996;34:565.
18. Bergman L, Dekker G, van Leeuwen FE et al. The effect of age on treatment choice and survival in elderly breast cancer patients. *Cancer* 1991;67:2227.
19. Karahaliou GS, Lazarou V, Giannis D et al. Initial experience with neoadjuvant FOLFIRINOX as first-line therapy for locally advanced pancreatic cancer. *JBUON* 2020;25:2525-27.
20. 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.
21. Ergun Y, Ozdemir NY, Guner EK et al. Combination of gemcitabine monotherapy with gemcitabine and cisplatin combination in metastatic pancreatic cancer: a retrospective analysis. *JBUON* 2018;23:116-21.
22. Heinemann V, Quietzsch D, Gieseler F et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol* 2006;24:3946-52.