Jikeikai Med J 2016 ; 63 : 55-61

Clinical Outcomes of Super-elderly Pancreatic Cancer Patients Who Are Not Considered to Be Suitable for Surgical Resection

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ABSTRACT

Background : To investigate the clinical features and prognosis of super-elderly patients who do not undergo surgical resection for pancreatic cancer, we performed a retrospective study evaluating the characteristics and outcomes of patients 80 years or older and younger patients.

Methods : The subjects evaluated were 67 patients who did not undergo surgical resection of a newly diagnosed pancreatic cancer. Of these patients 19 were super-elderly (age ≥ 80 years) and 48 were younger (age < 80 years). The differences in the overall survival (OS) rates between the groups were compared, and the prognostic factors were also evaluated.

Results : The OS rates did not differ significantly between the patient groups. Multivariate analysis revealed that independent prognostic factors for the OS rate were the serum lactate dehydrogenase level (hazard ratio [HR], 1.004 ; $P = 0.002$), serum albumin level (HR, 0.469 ; $P = 0.011$), chemotherapy (HR, 1.727 ; $P = 0.001$), tumor site (HR, 1.474 ; $P = 0.048$) and tumor metastasis (HR, 0.554 ; $P = 0.001$).

Conclusions : The lack of a significant difference in the OS rates between super-elderly patients and younger patients with pancreatic cancer who did not undergo surgical resection suggests that a super-elderly age alone should not restrict the therapeutic options.

(Jikeikai Med J 2016 ; 63 : 55-61)

Key words : pancreatic cancer, elderly patients, clinical characteristics, prognosis, nonsurgical treatment

INTRODUCTION

Pancreatic cancer is the fourth most common cause of cancer-related mortality in the Western world. Unlike other cancers, pancreatic cancer has a mortality rate that has not decreased. In 2014, the number of deaths pancreatic cancer was related to was 39,590 in the United States, 73,439 in the European Union, and 31,716 in Japan in 2014, which indicate that this disease has a poor outcome[1-3].

The average human lifespan during the 20th century has increased worldwide. Therefore, for elderly persons the treatment of cancer, including those with pancreatic cancer, has become a global problem. Several studies have shown that for treating pancreatic cancer in patients 80 years or older surgical resection is safe and achieves satisfactory outcomes[4,5].

However, because pancreatic cancer is often diagnosed at an advanced phase, many patients are not candidates for surgery. Moreover, elderly patients have comorbid diseases more often than do younger patients. To date, few studies

Received for publication, March 23, 2016

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have investigated the clinical features and prognosis of patients 80 years or older with pancreatic cancer who are not candidates for surgical resection[6].

Therefore, to investigate the clinical features and prognosis of such patients, in the present retrospective study we examined the characteristics and outcomes of super-elderly patients and younger patients who did not undergo surgical resection of pancreatic cancer.

METHODS

Enrolled subjects of this study were 96 patients who had received new diagnoses of pancreatic cancer and had been treated in our hospital from January 2011 through March 2015. The patients' medical records were reviewed and analyzed. Of these patients, 18 patients were lost to follow-up and 11 who were treated surgically patients were excluded. Therefore, the remaining 67 patients were evaluated and divided into 2 groups according to their age at inclusion : 19 patients who were super-elderly (age ≥ 80 years) and 48 patients who were younger (age < 80 years). The diagnosis of pancreatic cancer had been confirmed with computed tomography or magnetic resonance imaging. The characteristics of the cancer, such as the site of primary tumor in the pancreas (head, body, or tail) and the level of progression (locally advanced or metastatic), had also been assessed with imaging techniques.

The study was performed in accordance with the standards of the Declaration of Helsinki and was approved by our hospital's institutional ethics board (28-107[8,350]). The need for written informed consent for participation in this study was waived because this study was not a clinical trial and because the data was retrospectively collected and anonymously analyzed.

Blood samples had been obtained before the start of treatment to assess the levels of aspartate aminotransferase, alanine aminotransferase, total bilirubin, lactate dehydrogenase, albumin, C-reactive protein, white blood cells, platelets, hemoglobin, carcinoembryonic antigen, and carbohydrate antigen 19-9.

Characteristics excluded from analysis were pretreatment comorbid diseases, including hypertension, diabetes mellitus, cardiovascular disease, cerebrovascular disease, renal failure and, other malignant neoplasms.

The decision for a patient to undergo nonsurgical treatment had been made according to factors associated with the patient (having a poor medical condition, being unable to undergo a major operation, or refusing to undergo surgical resection) and factors associated with the tumor (presence of remote metastasis or major vascular invasion [main portal vein, hepatic artery, celiac artery, or superior mesenteric artery]).

The patients had been treated with best supportive care or palliative chemotherapy (gemcitabine or S-1 [tegaful, gimeracil, and oteracil potassium] or both in combination). The patients had been considered eligible for palliative chemotherapy[7] if they were 20 years or older and had adequate bone marrow and liver and kidney function (white blood cell count ≥3,000/μL, platelet count ≥10^4/μL, hemoglobin ≥8.0 g/dL, total bilirubin ≤2.0 mg/dL, aspartate aminotransferase and alanine aminotransferase ≤100 IU/L, and serum creatinine ≤2.0 mg/dL). Before palliative chemotherapy was started, percutaneous transhepatic or endoscopic retrograde biliary drainage had been performed for patients with obstructive jaundice.

After the first treatment, the patients were carefully monitored, including with imaging techniques and tumor markers. For the patients who showed tumor progression, palliative chemotherapy or best supportive care was provided. The start date of follow-up was when pancreatic cancer was diagnosed, and the end date of follow-up was the final follow-up examination in March 2015 or earlier in case of death.

Differences between the groups were analyzed with the Mann-Whitney U-test for continuous and ordinal variables and the Chi-square test or Kruskal-Wallis test for categorical variables. The overall survival (OS) rates were calculated with the Kaplan-Meier method and compared by means of the log-rank test. To evaluate prognostic factors, both univariate and multivariate analyses were performed with the Cox proportional hazard model. Variables found to be significant with univariate analysis were subsequently entered into a multivariate Cox proportional hazard model.

We performed subclass analysis to exclude the potential effects of the treatment and remote metastasis on the OS rate. The OS rates of the two groups were compared according to the type of treatment (chemotherapy [n = 43, 64.2%], best supportive care [n = 24, 35.8%]). The OS rates of the two groups were compared according to the remote metastasis (absent [n = 21, 31.3%], present [n = 46,

68.7%]).

Statistical significance was indicated by P values < 0.05. All statistical analyses were performed with the IBM SPSS Statistics software program, version 19.0 (IBM Corp., Armonk, NY, USA).

Results

At first admission both of the serum hemoglobin level ($P = 0.046$) and the percentage of patients undergoing chemotherapy ($P = 0.018$) were significantly lower for super-elderly patients than for younger patients (Table 1). However, no significant difference between the groups was observed re-

Table 1. Baseline characteristics of patients

Characteristic	Super-elderly patients (n=19) n or median (range or percentage)	Younger patients (n=48) n or median (range or percentage)	P
Age (years)	83 (80-88)	72 (35-79)	<0.0001
Male sex (%)	8 (42.1%)	27 (56.3%)	0.296
White blood cell count (/μL)	7,100 (4,200-26,300)	6,600 (3,400-22,700)	0.884
Hemoglobin (g/dL)	11.7 (8.6-14.8)	12.7 (8.7-16.9)	0.046
Platelet (10^4/μL)	21.2 (16-173)	22.7 (8.9-52.9)	0.482
Lactate dehydrogenase (U/L)	229 (154-823)	213 (127-1,969)	0.607
Alkaline phosphatase (U/L)	1,222 (158-3,041)	688 (173-5,699)	0.424
Albumin (g/dL)	3.5 (2.1-4.6)	3.8 (2.3-4.6)	0.079
C-reactive protein (mg/dL)	2.1 (0.1-13.3)	1.2 (0.1-24)	0.254
Carcinoembryonic antigen (ng/mL)	7.1 (3-135)	9.8 (1.6-2,224.9)	0.313
Carbohydrate antigen 19-9 (U/mL)	749 (1-53,609)	1,275 (1-566,900)	0.769
Chemotherapy (%)	8 (42.1%)	35 (72.9%)	0.018
Regimen of chemotherapy (%)			
Gemcitabine	7 (87.5%)	20 (57.1%)	
S-1	1 (12.5%)	3 (8.6%)	
Gemcitabin+S-1	0 (0)	12 (34.3%)	
Tumor site			0.28
Head	12 (63.2%)	25 (52.1%)	
Body	2 (10.5%)	10 (20.8%)	
Tail	4 (21.1%)	13 (27.1%)	
Unkown	1 (5.3%)		
Tumor size (mm)	38 (20-80)	37 (15-85)	0.889
Metastasis (%)	11 (57.9%)	35 (72.9%)	0.232
Reasons for nonsurgical treatment			0.15
Remote metastasis	11	35	
Major vascular invasion	3	9	
Others (poor medical condition or patient refusal)	5	4	
Comorbidities present (%) (someoverlap)	13 (68.4%)	26 (54.2%)	0.286
Hypertension	9 (47.4%)	20 (41.7%)	0.671
Diabetes mellitus	4 (21.1%)	15 (31.3%)	0.404
Other malignant disease	7 (36.8%)	5 (10.4%)	0.11
Cardiovascular disease	0 (0%)	3 (6.3%)	0.265
Cerebrovascular disease	1 (5.3%)	3 (6.3%)	0.878
Renal failure	0 (0%)	2 (4.2%)	0.366
Patient outcome dead (%)	17 (89.5%)	42 (87.5%)	0.594
Cause of death (%)			1
Pancreatic cancer	17 (100%)	42 (100%)	
Other cause of death	0 (0%)	0 (0%)	

n : number ; S-1 : tegafur, gimeracil, and oteracil potassium.

garding the white blood cell or platelet count ; concentration of lactate dehydrogenase, alanine aminotransferase, albumin, C-reactive protein, carcinoembryonic antigen, or carbohydrate antigen 19-9 levels ; the percentage of men ; the site or size of tumors ; or the presence of metastasis or comorbidities.

The median follow-up time was 5.33 months (range, 0.85-27.4 months). During the follow-up period, 17 (89.5%) super-elderly patients and 42 younger patients (87.5%) had died, and all patients died of pancreatic cancer (Table 1).

The OS rates at 1 and 2 years did not differ between super-elderly patients (26.3% and 21.1%) and younger patients (17.8% and 9.5%, $P = 0.696$) (Fig. 1).

No significant difference in the OS rates was observed between the groups according to the treatment (chemotherapy, $P = 0.845$, Fig. 2a ; best supportive care, $P = 0.906$, Fig. 2b) or to the presence of remote metastasis (absent, $P = 0.790$, Fig. 3a ; present, $P = 0.099$, Fig. 3b).

Multivariate analysis showed that the following factors were independent factors for the OS rates : lactate dehydrogenase level (hazard ratio [HR], 1.004 ; 95% confidence interval [CI], 1.001-1.007 ; $P = 0.002$), serum albumin level (HR, 0.469 ; 95% CI, 0.267-0.825 ; $P = 0.011$), performance of chemotherapy (HR, 1.727 ; 95% CI, 1.261-2.365 ; $P = 0.001$), tumor site (HR, 1.474 ; 95% CI, 1.008-2.156 ; $P = 0.048$), and metastasis (HR, 0.554 ; 95% CI, 0.3830-0.801 ; $P = 0.001$) (Table 2). With both univariate and multivariate analysis neither a super-elderly age nor the presence of co-

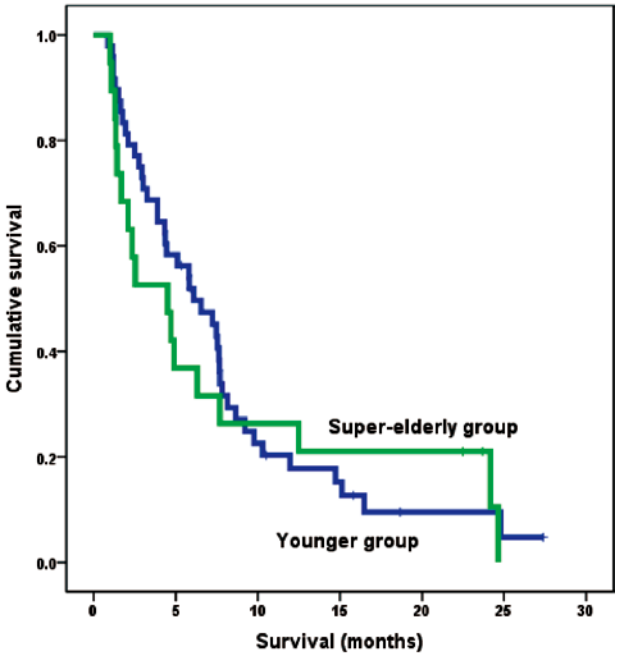

Fig. 1. Survival curves according to patient age.

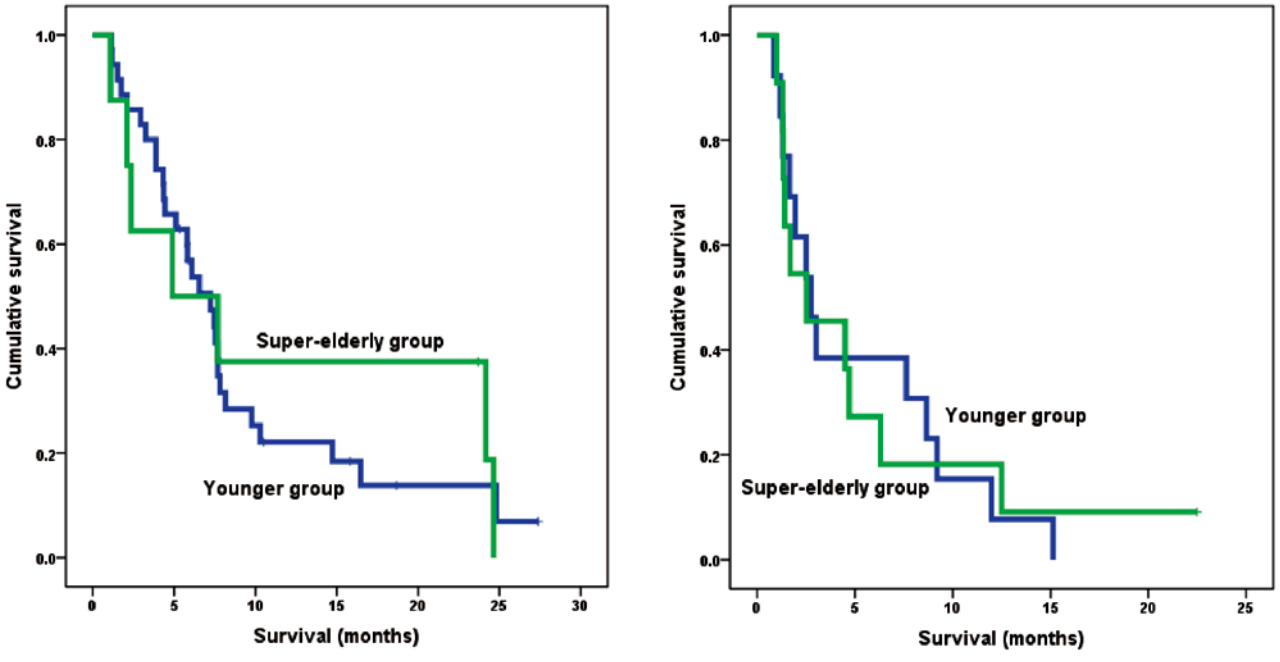

Fig. 2. Survival curves according to treatment. (a) Chemotherapy, (b) best supportive care.

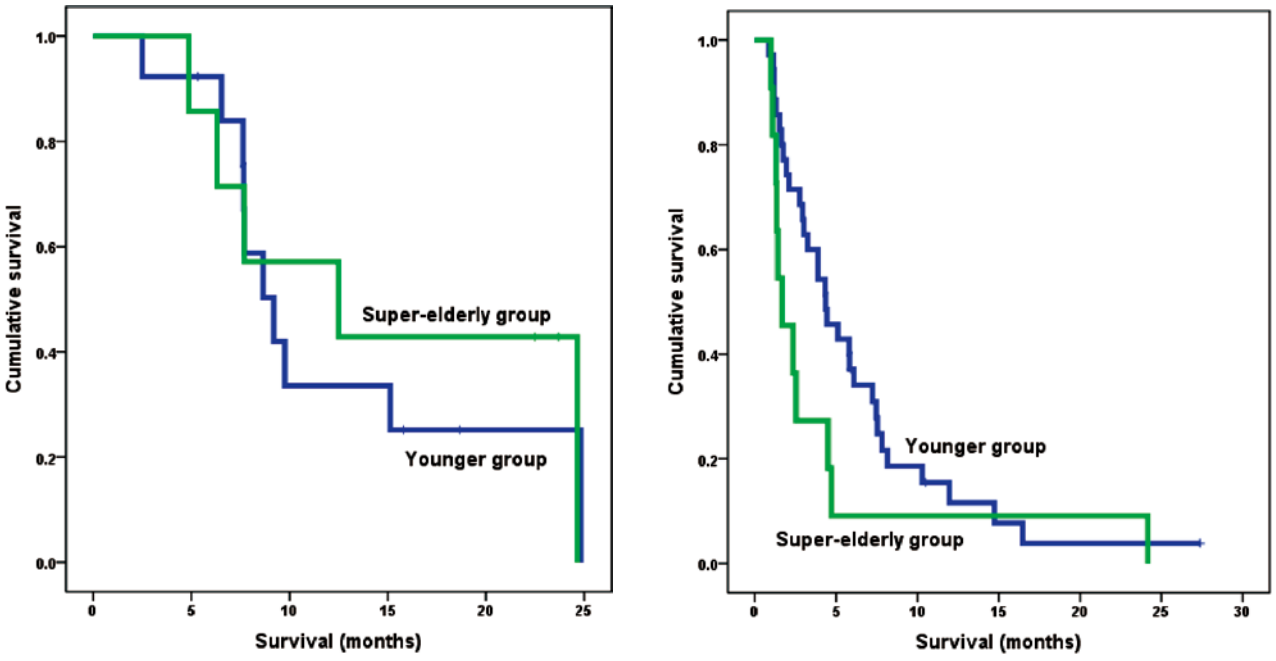

Fig. 3. Survival curves according to remote metastasis. (a) Absent (b) present.

Table 2. Univariate and multivariate analyses of factors associated with overall survival

Factor	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% confidence interval)	*P*	Hazard ratio (95% confidence interval)	*P*
Age	1.120 (0.633-1.983)	0.696		
Sex	0.950 (0.735-1.228)	0.696		
White blood cell	1.000 (1.000-1.000)	<0.0001		
Hemoglobin	0.873 (0.730-1.044)	0.136		
Platelet	0.993 (0.979-1.007)	0.305		
Lactate dehydrogenase	1.004 (1.002-1.007)	<0.0001	1.004 (1.001-1.007)	0.002
Alkaline phoshatase	1.000 (1.000-1.000)	0.331		
Albumin	0.521 (0.321-0.845)	0.08	0.469 (0.267-0.825)	0.011
C-ractive protein	1.035 (0.991-1.081)	0.113		
Carcinoembryonic antigen	1.001 (0.998-1.003)	0.609		
Carbohydrate antigen 19-9	1.000 (1.000-1.000)	<0.0001		
Chemotherapy	1.361 (1.041-1.779)	0.022	1.727 (1.261-2.365)	0.001
Tumor site	1.322 (0.954-1.831)	0.093	1.474 (1.008-2.156)	0.048
Tumor size	1.006 (0.992-1.021)	0.403		
Metastasis	0.617 (0.460-0.826)	0.001	0.554 (0.383-0.801)	0.001
Comorbidities present	1.026 (0.791-1.332)	0.846		

morbid disease was correlated with the OS rate.

Discussion

In the present study, we found no significant difference between super-elderly patients (≥ 80 years) and younger patients (< 80 years) who did not undergo surgical resection for pancreatic cancer. We also found that a super-elderly age was not correlated with the OS rate.

Pancreatic cancer is diagnosed in the United States at a

median age of 72 years of age and at an age of 75 years or more in 42.4% of patients[8]. Because of Japan's aging society, the treatment of older patients with cancer has becoming more challenging. Unfortunately, older patients are often under-represented in clinical trials, being only 25% to 30% of study participants, and less than 1% of subjects aged 75 to 79 years are enrolled[9]. Thus, oncologists would find it difficult to determine whether a treatment with a benefit observed in younger patients can be applied to elderly patients with the same cancer.

In the present study, we found no significant differences in the OS rate between super-elderly patients and younger patients. Moreover, multivariate analysis showed no correlation of the OS rate and a super-elderly age. Several studies have demonstrated that pancreatectomy can be safely performed and yield similar survival benefits in patients 80 years and older compared with younger patients[4,5,10-18]. However, a recent study has found that the rate of elderly patients (≥ 66 years old) with early-stage pancreatic cancer undergoing surgical resection did not significantly increase from 2001 to 2009[19].

In contrast to surgical treatments, chemotherapy has rarely been studied regarding its efficacy in elderly patients with pancreatic cancer. However, a recent study has found that chemotherapy improves prognoses to a similar extent in patients 70 years or older and in younger patients[20].

Inconsistent with our study, most of these previous studies of outcome of chemotherapy defined "elderly patients" as those aged 70 years or older. Taking into consideration the current mean life expectancies in Japan of 80-year-old men (8.61 years) and women (11.52 years)[21], investigating the therapeutic safety and long-term outcomes in cancer patients 80 years or older has become more important. A previous study of 440 patients 80 years or older with metastatic pancreatic cancer[6] found that 83% received no therapy. The study also found that in patients receiving chemotherapy the risk of death was reduced by 59%[6]. However, the study did not compare the efficacy of chemotherapy between patients 80 years or older and younger patients. Therefore, we believe that our finding that the OS rate in case of pancreatic cancer not treated with surgical resection was equal in super-elderly patients and younger patients is significant for the aging society.

In the present study, all patients in both age groups died of pancreatic cancer. Furthermore, multivariate analysis revealed that chemotherapy was independently correlated with the OS rate. These findings suggest that chemotherapy might improve the prognosis of patients who have pancreatic cancer and should be considered even for patients 80 years or older.

When considering the treatment and prognosis of elderly patients with cancer, we should understand the following points. First, the selection process may have an unintentional bias, because aggressive treatments, such as surgical resection and chemotherapy, tend to be selected for elderly patients if they have a good performance status[22], which may favor a prognosis similar to that seen in younger patients. On the other hand, palliative treatment tend to be selected for elderly patients and may lead to their outcomes being poorer than those of younger patients[23].

The present study had several limitations. First, the study was retrospective and performed at a single institution with a small number of subjects. Therefore, our results could have been affected by an unintentional bias in the selection of patients. Second, the diagnosis of pancreatic cancer was not confirmed with pathological examination. Third, because medical records were reviewed, the TMN classification and the performance status of each patient was not be precisely evaluated. Fourth, because this study began in 2011, neither FOLFIRINOX (folinic acid, fluorouracil, irinotecan, and oxaliplatin)[24] nor nab-paclitaxel plus gemcitabine[25] therapy was administered to the subjects. Therefore, a large-scale prospective study is necessary to confirm our findings.

In conclusion, we observed no significant differences in the OS rates among super-elderly patients and younger pancreatic cancer patients with pancreatic cancer who did not undergo surgical resection. We also observed that a super-elderly age (≥ 80 years) was not correlated with the OS rate. The results of this study suggest that super-elderly age alone does not limit the treatment options in patients with pancreatic cancer, even for those who do not undergo surgical resection.

Authors have no conflicts of interest.

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