

Original Article

Impact of Body Mass Index on Survival of Pancreatic Cancer Patients in Japan

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The impact of body mass index (BMI) on postoperative survival in Japanese patients with pancreatic cancer is unclear. We examined the relationship between preoperative BMI and the prognosis of Japanese patients who underwent surgery for pancreatic cancer to determine whether BMI affects these patients' prognosis. Of the patients who underwent pancreatectomy between January 2004 and August 2015 at our institution, 246 were pathologically diagnosed with pancreatic tubular adenocarcinoma; the cancer was located in the pancreatic head (n = 161) and in the body and tail (n = 85). We classified the patients by BMI: underweight (n = 22), normal weight (n = 190), and overweight/obese (n = 34) groups. We retrospectively analyzed medical records for patient characteristics, lesion location, disease stage, postoperative complications, chemotherapy, and prognosis. Lesion location, disease stage, postoperative complications, and chemotherapy were not significantly different among the BMI groups. The median survival times were as follows (days): all patients, 686; underweight, 485; normal weight, 694; and overweight/obese, 839. In a multivariate analysis, after adjusting for competing risk factors, low BMI was associated with an increased risk of death (normal weight: HR 0.58, $p=0.038$; overweight/obese: HR 0.54, $p=0.059$). High BMI was not found to be a postoperative factor for poor prognosis in Japanese pancreatic cancer patients.

Key words: pancreatic cancer, BMI, prognosis, surgery, risk factor

The early diagnosis of pancreatic cancer is very difficult, and the prognosis of this cancer is poor. Advanced pancreatic cancer is the fifth leading cause of cancer-related death, carrying a devastating prognosis with a 5-year survival rate of 6% [1-3]. The length of a pancreatic cancer patient's survival is greatly influenced by the disease stage, but a few other markers of survival have been well characterized. A high baseline serum concentration of the tumor marker CA 19-9 has been

identified as a negative prognostic factor in patients with pancreatic cancer [4,5]. There is some evidence that men with this cancer have an increased risk of death compared to women [5], but this association was not confirmed by another group [6].

In recent years, it has become apparent that overweight and obesity, as defined by body mass index (BMI), is a risk factor for pancreatic cancer [7-10]. The mechanisms underlying this association are not fully elucidated, but hyperinsulinemia and insulin resistance

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are considered key factors [11-14]. The number of overweight individuals has increased dramatically worldwide; it is estimated that today there are approx. 1.6 billion individuals in the world who are overweight and 400 million who are obese [15,16]. High BMI—both overweight and obesity—is a well-recognized risk factor for several chronic degenerative diseases such as cardiovascular disease and diabetes and a number of types of cancer, including pancreatic cancer. According to the most recent 2014 Cancer Progress Report from the American Association for Cancer Research, a high BMI is responsible for nearly 25% of the relative contribution to cancer incidence, ranking second only to tobacco use [17, 18].

There are few reports regarding the effects of high BMI on the prognosis of pancreatic cancer patients, and a consensus has yet to be obtained. The numbers of overweight patients who are candidates for a pancreatectomy has increased, but the data concerning short-term and long-term outcomes for this procedure in overweight patients are lacking [16]. There is also little information about the relationship between BMI and the postoperative prognosis of Japanese patients with pancreatic cancer. In the present study, we examined the relationship between preoperative BMI and prognosis in Japanese patients who underwent surgery for pancreatic cancer at our hospital, to clarify whether high BMI affects the postoperative prognosis of Japanese individuals with pancreatic cancer.

Patients and Methods

Patients. Patients who underwent pancreatectomy at Okayama Saiseikai General Hospital between January 2004 and August 2015 were identified. We excluded cases with no follow-up records, cases with incomplete complication information, cases without records of postoperative therapies, and cases with incomplete BMI data. Patients whose tumors were identified as other than adenocarcinoma were excluded from study. A final total of 246 patients who were pathologically diagnosed with pancreatic tubular adenocarcinoma postoperatively were analyzed in this study. Among these, the cancer was located in the pancreatic head in 161 cases and in the body and tail in 85.

Methods. Each patient's BMI was calculated as weight in kilograms (kg) divided by height in meters squared (m^2), both of which were measured upon

admittance to our hospital for pancreatic cancer surgery. For the purpose of the analyses, we divided the patients into 3 groups based on their BMI values: underweight ($BMI < 18.5 \text{ kg}/m^2$), normal weight ($BMI \geq 18.5 \text{ kg}/m^2$ and $< 25 \text{ kg}/m^2$), and overweight/obese ($BMI \geq 25 \text{ kg}/m^2$) as described by the World Health Organization classification.

We retrospectively examined the patients' medical records to determine the patient characteristics, lesion location, disease stage, postoperative complications, chemotherapy, and prognosis in each group. We diagnosed the disease stage by the Union for International Cancer Control (UICC) classification system based on the postoperative pathological diagnosis. Regarding the surgical method, pylorus-preserving and subtotal stomach-preserving pancreaticoduodenectomies were treated as pancreatectomy. Postoperative complications were evaluated according to the number of postoperative mortalities occurring within 90 days of the surgery. Regarding the chemotherapy, we analyzed the cases of the patients who underwent preoperative or postoperative chemotherapy for >2 months. Generally, S1 or gemcitabine-based chemotherapy had been used. The patients' prognoses were evaluated based on the postoperative median survival time (MST).

Statistical methods. Statistical analyses were performed using STATA 13 software (StataCorp, College Station, TX, USA). Student's test was used to compare the means of the continuous variables, and Fisher's exact test was used to compare the frequencies of the categorical variables between groups. The Kaplan-Meier method and log-rank test were used to analyze the survival time (time from surgery until death, regardless of cause). After we performed a univariate analysis, we subjected the significant variables to a multivariate analysis using a Cox proportional hazards model. We accepted p -values < 0.05 as significant. This retrospective study was approved by the Institutional Review Board at Okayama Saiseikai General Hospital (no. 160306).

Results

The patients' background characteristics are presented in Table 1. Within the group of 246 patients, 9.0% ($n=22$) were underweight, 77.2% ($n=190$) were normal weight, and 13.8% ($n=34$) were overweight/obese. Regarding the sex ratio (numbers of males/

Table 1 Baseline characteristics of the study population of Japanese patients with pancreatic cancer

	No. (%)				P-value
	All patients	Underweight	Normal weight	Overweight/Obese	
No. of patients	246	22	190	34	
Population Characteristics					
Sex (male)	127 (51.6)	8 (36.4)	100 (52.6)	19 (55.9)	0.32
Age (median, year)	70 (33–88)	71 (47–84)	69 (33–88)	70 (46–87)	0.44
Lesion location (head/body and tail)	161/85	17/5	125/65	19/15	0.28
Underlying disease					
hypertension	90 (36.6)	5 (22.7)	67 (35.3)	18 (52.9)	0.05
hyperlipidemia	22 (8.9)	1 (4.5)	20 (10.5)	1 (2.9)	0.23
coronary artery disease	13 (5.3)	1 (4.5)	8 (4.2)	4 (11.8)	0.19
cerebrovascular disease	14 (5.7)	1 (4.5)	11 (5.8)	2 (5.9)	0.97
chronic hepatitis	17 (6.9)	2 (9.1)	14 (7.4)	1 (2.9)	0.59
chronic lung disease	2 (0.8)	0 (0)	2 (1.1)	0 (0)	0.74
previous history of cancer	117 (47.6)	12 (54.5)	92 (48.4)	13 (38.2)	0.43
HbA1c \geq 6.5	90/192 (46.9)	8/18 (44.4)	69/145 (47.6)	13/29 (44.8)	0.94
pStage (UICC)					0.49
pStage I – II	115 (46.7)	13 (59.1)	87 (45.8)	15 (44.1)	
pStage III – IV	131 (53.3)	9 (40.9)	103 (54.2)	19 (55.9)	
Mortality					
mortality within postoperative 90 days	8 (3.3)	2 (9.1)	4 (2.1)	2 (5.9)	0.07
Chemotherapy					0.73
Existence	203 (82.5)	17 (77.3)	157 (82.6)	29 (85.3)	
non-existence	43 (17.5)	5 (22.7)	33 (17.4)	5 (14.7)	

females), the underweight group was 8/14 cases, the normal weight group 100/90 cases, and the overweight/obese group was 19/15 cases ($p=0.32$). The median age of the patients was 71 (47–84) years in the underweight group, 69 (33–88) years in the normal weight group, and 70 (46–87) years in the overweight/obese group ($p=0.44$). The lesion was located in the pancreatic head/body and tail in 17/5 cases in the underweight group, 125/65 cases in the normal weight group, and in 19/15 cases in the overweight/obese group ($p=0.28$).

No significant differences in underlying disease such as hypertension, hyperlipidemia, coronary artery disease, cerebrovascular disease, chronic hepatitis, chronic lung disease, or previous history of cancer were observed among the 3 groups. A preoperative HbA1c level (National Glycohemoglobin Standardization Program units [NGSP]) of $\geq 6.5\%$ was observed in 8 of the 18 patients in the underweight group, 69 of the 145 patients in the normal weight group, and 13 of the 29 patients in the overweight/obese group ($p=0.90$). However, the preoperative HbA1c level was not measured in 34 pancreatic head cancer cases or in 20 pancreatic body and tail cancer cases. The disease stage of the pancreatic cancer cases was I, II/III, or IV in 13/9

patients in the underweight group, 87/103 patients in the normal weight group, and 15/19 patients in the overweight/obese group ($p=0.49$).

The surgical method was pancreatoduodenectomy in 167 cases, body and tail pancreatectomy in 76 cases, pancreatic partial resection in 2 cases, and pancreatic total resection in 1 case. Mortality within 90 days occurred in 8 of the 246 patients (3.3%). All 8 of these patients (6 pancreatic head patients and 2 body and tail cancer patients) underwent a pancreatoduodenectomy. There were no significant differences in mortality among the three BMI groups.

With regard to chemotherapy, preoperative or postoperative chemotherapy was performed in 203 of the 246 patients (82.5%), was 17 of the 22 underweight patients, 157 of the 190 normal-weight patients, and 29 of the 34 overweight/obese patients ($p=0.73$).

With regard to long-term outcomes, the 1-, 3-, and 5-year overall survival rates of the total series of patients following pancreatectomy were 72%, 34%, and 24%, respectively, with a median survival of 686 days. The MST of the patients was 485 days in the underweight group, 694 days in the normal weight group, and 839 days in the overweight/obese group (Fig. 1). Log-rank

tests showed a tendency of poor prognosis in the underweight patients ($p=0.07$) (Table 2).

The univariate analysis for survival rates identified the following 4 parameters as significant predictors: lesion location (head/body and tail) (hazard ratio [HR] 0.57, 95% confidence interval [CI] 0.41-0.80, $p=0.001$), disease stage (I, II/III, IV) (HR 1.3, 95%CI 0.96-1.76, $p=0.085$), chemotherapy (existence/non-existence) (HR 2.21, 95%CI 1.55-3.15, $p<0.001$), and BMI (underweight/normal weight/overweight, obese) (HR 0.6/0.5, 95%CI 0.37-0.99/0.27-0.94, $p=0.044/0.029$). The multivariate analysis indicated that the same 4 following factors were significantly associated with the patients' prognoses: lesion location (head/body and tail) (HR 0.59, 95%CI 0.42-0.83, $p=0.002$), disease stage (I, II/III, IV) (HR 1.63, 95%CI 1.18-2.25, $p=0.003$), chemotherapy (existence/non-existence) (HR 2.85, 95%CI 1.85-4.40, $p<0.001$), BMI (underweight/normal weight/overweight, obese) (HR 0.58/0.54, 95%CI 0.35-0.97/0.28-1.02, $p=0.038/0.059$)

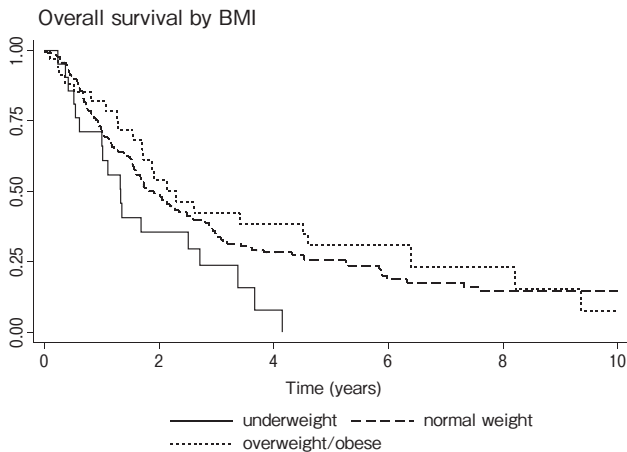


Fig. 1 The MSTs were 485, 694, and 839 days in the underweight, normal weight, and overweight/obese groups, respectively. Log-rank tests showed a tendency of poor prognosis in the underweight pancreatic cancer cases ($p=0.07$).

Table 2 Survival according to BMI (underweight, normal, and overweight/obese)

	No. of patients	1-year survival rate (95%CI)	5-year survival rate (95%CI)	MST, day (95%CI)
All patients	246	72 (66-78)	24 (18-30)	686 (583-839)
underweight	22	71 (47-86)	0	485 (224-989)
normal weight	190	71 (64-77)	26 (19-33)	694 (581-906)
overweight/obese	34	82 (64-91)	31 (15-48)	839 (581-906)

BMI, body mass index.

p -value = 0.07

(Table 3). Thus, the pancreatic head lesion location, an advanced disease stage, the non-use of chemotherapy, and underweight were associated with a poor prognosis. An overweight/obese body weight was not a factor for poor prognosis. In addition, age and sex were not poor-prognosis factors.

Discussion

The morbidity and mortality rates of pancreatic cancer have increased annually, and the prevalence of pancreatic cancer is expected to increase in the future [19]. It has been suggested that pancreatic cancer is related to lifestyle-related diseases such as obesity and diabetes, and it has been made clear that excess body weight is a risk factor for pancreatic cancer [7-10]. In individuals with excess body weight, the level of adiponectin (an anti-inflammatory cytokine) is decreased, whereas the level of leptin (an inflammatory cytokine) is increased, thereby promoting insulin resistance. Hyperinsulinism and high levels of blood-activated insulin-like growth factor 1 (IGF-1) result from insulin resistance and can contribute to tumor promotion through the resultant activation of cell proliferation, apoptosis and angiogenesis. Pancreatic cancer growth is subsequently promoted.

Despite these suggested theories [11-14], there have been few reports regarding the influence of excess body weight on the prognosis of pancreatic cancer, and the findings from these studies have been controversial [20, 21]. In addition, there are few reports from Japan about the relationship between BMI and the postoperative prognosis of pancreatic cancer.

Our present analyses revealed that excess body weight was not a factor for poor prognosis in Japanese patients with pancreatic cancer who underwent surgery. This result is similar to the findings of Gaujoux *et al.* and Tasi *et al.*, who reported that excess body weight was not a poor prognostic factor in patients who under-

Table 3 Factors related to the survival of Japanese patients with pancreatic cancer

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95%CI	p-value	Hazard ratio	95%CI	p-value
Sex						
male	1			1		
female	0.86	0.64–1.16	0.326	0.83	0.61–1.13	0.235
Age (year)						
< 80	1			1		
≥ 80	1.10	0.70–1.72	0.680	0.71	0.41–1.22	0.212
Lesion location						
head	1			1		
body and tail	0.57	0.41–0.80	0.001	0.59	0.42–0.83	0.002
pStage (UICC)						
pStage I – II	1			1		
pStage III – IV	1.30	0.96–1.76	0.085	1.63	1.18–2.25	0.003
Chemotherapy						
existence	1			1		
non-existence	2.21	1.55–3.15	< 0.001	2.85	1.85–4.40	< 0.001
BMI						
underweight	1			1		
normal weight	0.60	0.37–0.99	0.044	0.58	0.35–0.97	0.038
overweight/obese	0.50	0.27–0.94	0.029	0.54	0.28–1.02	0.059

went pancreatoduodenectomy for pancreatic cancer [22–24]. Most of the studies that have compared survival rates between obese and nonobese patients with pancreatic cancer have been limited to patients who underwent a pancreaticoduodenectomy, and there have been few reports involving cases with pancreatic body and tail cancer.

In the present investigation, there were no significant differences among the weight groups in terms of patient characteristics, disease stage, postoperative complications, or chemotherapy in both the subgroup of patients with pancreatic head lesions and those with body and tail lesions. Stage III/IV disease was present in 47.8% of the pancreatic head cancer group and 63.5% of the body and tail cancer group. Many of the patients had advanced-stage disease, because it is difficult to diagnose pancreatic cancer during the early stages. As far as postoperative complications, there were no significant differences in the number of mortalities occurring within 90 days among the three BMI groups. We did not examine perioperative stress parameters such as the operation time or the amount of blood loss; however, the 90-day mortality rate was 3.3%, which is low, and surgery had little influence on the prognosis.

Tasi *et al.* reported that of the perioperative compli-

cations evaluated, only pancreatic fluid leakage from a fistula differed significantly according to their patients' BMI values, and other complications generally did not show a significant difference according to BMI [22, 25]. It is also believed that the surgical skills for pancreatic cancer have improved in high-volume centers over recent years.

In this study, the MST was longer in the overweight/obese group, and the underweight patients had poorer prognoses. A more advanced disease stage was also associated with a poorer prognosis. The poor prognoses of our underweight pancreatic cancer patients may have been caused by poor nutrition. Because we could not examine the patients' nutrition conditions in detail in this study, this is an issue to be addressed in the future. It has been suggested that, in general, obesity is associated with the risk of postoperative complications in the short term [26, 27] but is not a poor prognostic factor in the long term. Our results showed no relationship between the prognosis of pancreatic cancer in Japanese individuals and excess body weight.

A limitation of this study is its retrospective design from a single institution. We did not examine metabolic syndrome, patient lifestyle factors (diet, smoking, alcohol intake, exercise, *etc.*), longitudinal changes in body weight (*e.g.*, history of obesity or underweight), or

concurrent medico-surgical illnesses. In addition, the numbers of cases in the underweight and overweight/obese groups were very small (n=22 and n=34, respectively). The obese population in Japan is small compared to those in Europe and the U.S. In Japan, the obesity rate is reported to be 28.7% in males and 21.3% in females, and the underweight rate is 4.5% in males and 10.4% in females [28]. In the present patient series, the percentage of overweight/obese patients was 13.8%, which is lower than that in a previous study. Because each patient's BMI was measured just before surgery in the present study, weight loss due to disease progression was also a possibility. Moreover, a greater number of cases is necessary for more precise results. Preoperative or postoperative chemotherapy was performed in approx. 80% of our patients, and the chemotherapy was shown to be an independent factor for overall survival.

In conclusion, our study revealed that excess body weight does not carry prognostic significance in Japanese patients with pancreatic cancer who undergo pancreatectomy. Additional studies are needed to further investigate the prognostic significance of other factors in such patients.

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