

# Effect of Radiologically Evaluated Sarcopenia on Survival in Advanced Pancreatic Cancer

Metastatik Pankreas Kanserinde Radyolojik Olarak Değerlendirilen Sarkopeninin Sağkalıma Etkisi

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## Abstract

**Objective:** Pancreatic cancer is one of the deadliest cancers. The 5-year survival rate in advanced pancreatic cancer is 2%. The presence of sarcopenia in advanced pancreatic cancer is associated with negative outcomes. Although there are many measurements for the diagnosis of sarcopenia, there is still no standard method. In our study, the effect of radiological measurement of sarcopenia on the results of pancreatic cancer was investigated.

**Methods:** Seventy-four patients were retrospectively evaluated. Demographic data and laboratory and imaging parameters of the patients were recorded and analyzed using the SPSS 25 program.

**Results:** The mean age was 64.4 years, and the mean body mass index (BMI) was 25.5 kg/m<sup>2</sup>. 58.1% of the patients were male. mOS was 9.3±2.4 months in patients with sarcopenia detected with Psoas muscle density (PMD) Hounsfield unit avarage calculation, and 16.1 16.1±1.5 months in those without (\*p=0.002). mOS was 5.6±1.6 months in patients with sarcopenia detected with PMI and 16.1 16.1±1.5 months in those without (\*p<0.0001). Age, gender, BMI, hemoglobin, CA19-9, and albumin levels did not affect overall survival.

**Conclusion:** Overall survival is significantly lower in patients with radiologically detected sarcopenia with PMD and PMI. The use of PMI and PMD is an effective method for radiological evaluation of sarcopenia.

Keywords: Sarcopenia, radiological measurements, pancreatic cancer

# Öz

**Amaç:** Pankreas kanseri en ölümcül kanserlerden biridir. Metastatik pankreas kanserinde 5 yıllık sağkalım %2'dir. Metastatik pankreas kanserinde sarkopeninin varlığı olumsuz sonuçlarla ilişkilidir. Sarkopeni tanısına yönelik birçok ölçüm olmasına rağmen halen standart bir yöntem bulunmamaktadır. Çalışmamızda sarkopeninin radyolojik ölçümünün pankreas kanseri sonuçlarına etkisi araştırıldı.

Yöntem: Yetmiş dört hasta retrospektif olarak değerlendirildi. Hastaların demografik verileri, laboratuvar ve görüntüleme parametreleri kayıt altına alınarak SPSS 25 programına analiz edildi.

**Bulgular:** Ortalama yaş 64,4, ortalama vücut kitle indeksi (BMI) 25,5 kg/m<sup>2</sup> idi. Hastaların %58,1'i erkekti. Psoas kas dansitesi (PMD) Hounsfield ünitesi ortalama hesaplaması ile tespit edilen sarkopeni hastalarında mOS 9,3±2,4 ay, olmayanlarda ise 16,1±1,5 ay idi (\*p=0,002). Psoas kas indeksi (PMI) ile sarkopenisi saptanan hastalarda mOS 5,6±1,6 ay, saptanmayanlarda ise 16,1±1,5 aydı (\*p<0,0001). Yaş, cinsiyet, BMI, hemoglobin, CA19-9 ve albümin düzeyleri genel sağkalımı etkilemedi.



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## Öz

**Sonuç:** PMD ve PMI ile radyolojik olarak sarkopenisi saptanan metastatik pankreas kanseri hastalarında genel sağkalım anlamlı olarak daha düşüktür. PMI ve PMD'nin kullanımı sarkopeninin radyolojik değerlendirmesinde etkili bir yöntemdir.

Anahtar Kelimeler: Sarkopeni, radyolojik ölçümler, pankreas kanseri

## Introduction

Pancreatic cancer is one of the most common cancers, with a 5-year survival rate of less than 5%<sup>(1)</sup>. Most patients are unresectable, and the results are worse in this patient group. The stage of the disease, area of involvement, presence of additional diseases, and performance status determine the probability of resectability<sup>(2)</sup>. Sarcopenia is defined as a decrease in muscle mass and consequent decrease in measurable muscle strength. According to ESPEN, values below -2 standard deviations as measured by healthy young adults are defined as cachexia<sup>(3)</sup>. Decreased muscle density and muscle area are associated with decreased overall survival in many cancers. The relationship between sarcopenia and pancreatic cancer has been known for a longtime. In recent years, the number of studies on the negative effects of sarcopenia on survival outcomes in pancreatic cancer has been increasing<sup>(4)</sup>. In various studies, sarcopenia in pancreatic cancer has been shown to be between 20% and  $65\%^{(5-7)}$ . This wide range may be due to the heterogeneity of the patient group and the differences in sarcopenia measurement techniques. Malnutrition and sarcopenia are common in pancreatic cancer due to localization of the disease, obstruction, inadequate oral intake, failure to meet the increased metabolic rate due to malignancy, and malabsorption due to exocrine hormonal failure<sup>(8)</sup>. Decreased performance due to sarcopenia adversely affects both post-surgical complications and chemotherapy-related outcomes<sup>(9)</sup>. Due to the differences in defining sarcopenia, there were also differences in measurement techniques<sup>(10,11)</sup>. Various measurements can be made with anthropometry, bioelectrical impedance, dual X-ray absorptiometry (DEXA), computed tomography (CT), and magnetic resonance imaging (MRI) in the evaluation of sarcopenia. To eliminate the subjectivity of measurement techniques, it is becoming increasingly common to evaluate using imaging methods<sup>(12)</sup>. There are many studies evaluating sarcopenia by measuring muscle with conventional imaging methods used in the diagnosis, staging, and follow-up of pancreatic cancer<sup>(13)</sup>. Sarcopenia assessments with CT and MRI are more sensitive than DEXA<sup>(14)</sup>. It has been shown that muscle measurement from L3 vertebrae correlates much better with whole body muscle mass, and measurements from L4-5 vertebrae can be an alternative to L3 measurement<sup>(15)</sup>. Besides which technique is used for measurement, it should also be considered whether it is evaluated according to height, weight, and body mass index.

In our study, the data of patients with advanced pancreatic cancer diagnosed in our clinic in the last five years were retrospectively analyzed. In addition to descriptive data such as age, gender, and performance status at the time of diagnosis, the effects of laboratory parameters and muscle measurements determined by CT imaging on progressionfree survival (PFS) and overall survival (OS) were examined.

## **Materials and Methods**

#### Measurements

Muscle measurements were calculated as follows: Psoas muscle index (PMI) and Psoas muscle density (PMD) hounsfield unit average calculation (HUAC) was used to evaluate cachexia. PMI: (Right psoas muscle area + left psoas muscle area)/height height. Right hounsfield unit (RHUC): (RHUC x right psoas muscle area)/total psoas muscle area. LHUC: (left hounsfield unit x left psoas muscle area)/ total psoas muscle area. PMD HUAC: RHUC +LHUC/2. Low skeletal muscle mass was defined as the lowest quartile in male and female patients separately in categorical analyses. The PMI cutoffs to define low skeletal muscle mass were 2,4 cm<sup>2</sup>/m<sup>2</sup> in females and 3.3 cm<sup>2</sup>/m<sup>2</sup> in males, and for Psoas Muscle Dansity, HUAC was 21.53 HU in females and 27,08 HU in males.

Manisa Celal Bayar University Ethics Committee date: 21.03.2022, decision no: 251 approval was received. The procedures followed were in accordance with the ethical standards of the Manisa Celal Bayar University Ethics Committee and with the Helsinki Declaration of 1975, as revised in 2013.

#### **Statistical Analysis**

Overall survival (OS) and progression-free survival (PFS) analyzes were calculated using the Kaplan-Meier method,

and differences between curves were estimated using Log-Rank tests. The effect of low skeletal muscle mass on PFS and OS was evaluated using univariate and multivariate logistic regression analyses. Quantitative variables are expressed as medians. Variables are compared using the two-tailed Student's t-test or the Kruskal-Wallis test, whichever is appropriate. Categorical data were expressed as percentages (numbers) and compared using the  $\chi^2$  test or Fisher's Exact test, as appropriate. P-values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS 25 software.

# Results

In our study, 87 patients diagnosed with advanced pancreatic cancer in our hospital between 2016 and 2021 were included in the study. Seventy-four patients whose data were fully accessible were included in the study. Thirteen patients were excluded from the study because of reasons such as change of institution for treatment, inability to access chemotherapy regimens, and undetectable PFS and OS data.

Mean age at diagnosis was 64.4 (31-82), mean weight was 70 kg (45-110), and mean BMI was 25.5 (15.6-40.4). 58.1% (n=43) of the patients were male. Pancreatic head tumor was the primary focus in 74.3% (55) of the patients, whereas 25.7% (19) had pancreatic body or tail tumor. Twenty-three percent (15) of the patients were ECOG-0, 62.2% (46) ECOG-1, 17.5% (13) ECOG-2. There were no ECOG-3 and ECOG-4 patients. 75.7% (56) of the patients were receiving oral nutritional support (ONS). While 36.5% (27) of the patients were using the first or even FOLFIRINOX regimen, 27% (20) had a single agent gemcitabine and 36.5% (27) had a second chemotherapy agent (cisplatin, carboplatin, nab-paclitaxel) together with gemcitabine. While all of the patients included in the study received first-line chemotherapy, 47.3% (35) of the patients who received the second-line chemotherapy were 25.7% (19) who could receive the third-line treatment. Descriptive statistics are presented in Table 1.

When all patients were evaluated, mPFS was  $4.8\pm0.8$  months and mOS was  $14.3\pm1.2$  months. PFS was not affected by gender (p=0.96) and being over or under 65 years old (p=0.14). OS was not affected by gender (p=0.50) and being over or under 65 years old (p=0.86).

While mPFS was 5.3 months in those who received ONS, mPFS was 2.4 months in those who did not (\*p=0.004). There was no significant difference in mOS between those who received and those who did not receive ONS (p=0.66).

When laboratory data were examined, there was no significant difference in terms of PFS or OS between patients with hemoglobin ( $\leq$ 12 vs. >12) and CA19-9 ( $\leq$ 100 vs. >100). However, PFS and OS were significantly lower in those with albumin levels  $\leq$ 3.5 g/dL.

While mPFS was  $8\pm3.9$  months in patients with BMI <18.5, mPFS was  $4.8\pm0.8$  months in patients with BMI ≥18.5 (p=0.54). OS was  $13.6\pm6.4$  months in patients with BMI <18.5, and  $14.7\pm1.3$  months in patients with BMI ≥18.5 (p=0.31). While mPFS was  $2.6\pm0.4$  months in those with PMD HUAC and sarcopenia, it was  $5.8\pm0.5$  months in those without (\*p=0.009). While the mOS was  $9.3\pm2.4$  months in those

Table 1. Descriptives of advanced pancreatic cancer patients							
	n	%		n	%		
Sex			ONS				
Female	31	41.9	No	18	24.3		
Male	43	58.1	Yes	56	75.7		
Total	74	100.0	Total	74	100.0		
Age			Second line				
<65	29	39.2	No	39	52.7		
>65	45	60.8	Yes	35	47.3		
Total	74	100.0	Total	74	100.0		
ECOG			BMI				
0	15	20.3	<18	5	6.8		
1	46	62.2	>18	69	93.2		
2	13	17.5					
Total	74	100.0	Total	74	100.0		
Т			PMI				
2	40	54.1	Low	18	24.3		
3	31	41.9	High	56	75.7		
4	3	4.1	Total	74	100.0		
Total	74	100.0					
n			PMD HUAC				
0	12	16.2	Low	19	25.7		
1	27	36.5	High	55	74.3		
2	35	47.3	Total	74	100.0		
Total	74	100.0					
Localization			1 <sup>st</sup> -line regimen				
Head	55	74.3	Gemcitabine	20	27.0		
Tail	19	25.7	Gem-others	27	36.5		
Total	74	100.0	Folfirinox	27	36.5		
			Total	74	100.0		
ONS: Oral nutrition	ial suppor	t, BMI: Bo	dy mass index, PMI: Pso	as mus	cle index		

with sarcopenia with PMD HUAC, it was  $16.1\pm1.5$  months in those without (\*p=0.002). While mPFS was  $2.6\pm0.4$  months in those with PMI and sarcopenia, it was  $5.5\pm0.4$  months in those without (\*p=0.006). While mOS was  $5.6\pm1.6$  months in those with PMI and sarcopenia, it was  $16.1\pm1.5$  months in those without (\*p<0.0001). While mPFS was  $5.8\pm0.4$  months in patients who received FOLFIRINOX as first-line therapy, mPFS was  $4.0\pm0.8$  months in patients who received FOLFIRINOX as first-line therapy was  $16.1\pm10$  months, mOS was  $13.9\pm3.5$  months (p=0.61) in those who did not receive FOLFIRINOX. The PFS and OS data determined depending on the variables are presented in Table 2.

Affecting OS because of univariate analysis: ECOG status, second- line chemotherapy, PMD HUAC, PMI, NLR and albumin values were evaluated by multivariate analysis and the results are presented in Table 3.

## Discussion

In our study, it was shown that the overall survival results were worse in patients with advanced stage pancreatic cancer who were found to have cachexia because of CT evaluation at the time of diagnosis. Other factors affecting mOS in the multivariate analysis were ECOG performance and the patient's ability to receive second-line therapy.

It should also be considered that the optimal treatment of sarcopenia is still unknown. Follow-up of patients with appropriate ONS before their condition worsens may affect survival outcomes. There is an increased catabolic process and fragility in sarcopenic patients<sup>(16)</sup>. In our study, it was seen that mPFS was detected better in ONS patients. It can be recommended to evaluate cachexia and sarcopenia in terms of diagnosis and to start ONS as early as possible in those who need it. While some studies have shown that the presence of sarcopenia is associated with worse overall survival, there are studies that do not support this data<sup>(7,17-20)</sup>.

Many anti-inflammatory and proanabolic products have been tried to reverse sarcopenia, but many of them have not been shown to have a positive effect on the results. Although the results are contradictory, the use of polyunsaturated fatty acids has positive effects in patients receiving chemotherapy<sup>(21)</sup>. In addition, some studies have supported the role of megestrol acetate and medroxyprogesterone acetate in preventing the progression of sarcopenia<sup>(22,23)</sup>. However, because of the increased frequency of thromboembolic

Table 2. PFS and	d OS data	depend	ing on the	variabl	.es			
Variables	n/%	mPFS	p-value	mOS	p-value			
ECOG								
0	15/20.3	5.9		26.5	0.009			
1	46/62.2	5.5	0.004	13.6				
2	13/17.5	2.4		3.9				
Age								
<65	29/39.2	6.5	0.14	15.1	0.06			
≥65	45/60.8	3.6		13.9	0.00			
Sex								
Female	31/41.9	1.9 5.1		13.9	0.50			
Male	43/58.1	4.8	0.90	15.1	0.50			
Localisation								
Head	55/74.3	4.8	0.88	14.3	0.56			
Tail	19/25.7	5.3	0.00	13.9	0.00			
ONS								
No	18/24.3	2.4	0.004	15.1	0.66			
Yes	56/75.7	5.3	0.004	14.3	0.00			
2 <sup>nd</sup> line								
No	39/51.4			7.2	0.007			
Yes	35/48.6			16.1	0.007			
BMI								
<18	5/6.8	8	0.54	13.6	0.21			
≥18	69/93.2	4.8	0.54	14.7	0.31			
PMI								
Low	18/24.3	2.6	0.006	5.6	<0.001			
High	56/75.7	5.4	0.000	16.1	~0.001			
PMD HUAC								
Low	19/25.7	2.6	0.000	9.3	0.002			
High	55/74.3	5.8	0.009	16.1	0.002			
Folfirinox		i						
No	47/63.5	4.0	0.85	13.9	0.61			
Yes	27/36.5	5.8	0.05	15.1	0.01			
HGB								
≤12	27/36.5	4.0	0.16	12.8	0.41			
>12	47/63.5	5.5	0.10	15.4	0.41			
CA19-9								
≤100	32/43.2	5.8	0.76	15.4	0.22			
>100	42/56.8	3.3	0.70	14	0.22			
Albumin								
≤3.5	9/12.2	2.3	0.027	9.0	0.026			
>3.5	65/87.8	5.5	0.027	15.1	0.020			
NLR								
≤3	44/59.5	5.8	0.08	16.1	0.010			
>3	30/40.5	2.9	0.90	9.0	0.019			
ONS: Oral nutritional support, BMI: Body mass index, OS: Overall survival, PMI: Psoas muscle index								

Table 3. Univariate-multivariate analyses of overall survival							
	Univariate analysis			Multivariate analysis			
Variables	HR	(95% CI)	p-value	HR	(95% CI)	p-value	
ECOG	1.95	(1.26-3.0)	0.009	2.69	(1.58-4.56)	<0.001	
2 <sup>nd</sup> line	0.47	(0.27-0.82)	0.008	0.32	(0.17-0.62)	0.001	
PMI	0.33	(0.18-0.61)	0.026	0.48	(0.25-0.95)	0.034	
PMD HUAC	0.40	(0.21-0.73)	0.003	0.40	(0.19-0.70)	0.008	
Alb ≤3.5/>3.5	0.42	(0.20-0.90)	0.026	0.90	(0.38-2.12)	0.81	
NLR ≤3/>3	1.95	(1.11-3.40)	0.019	1.46	(0.78-2.74)	0.24	
CI: Confidence interval, PMI: Psoas muscle index, HR: Hazard ratio, Alb: Albumin							

events in pancreatic cancer, these molecules can be used by considering the potential benefit-harm balance.

The presence of sarcopenia also affects the performance status of the patient. In patients with low performance scores, the preferred chemotherapy regimen may change. In addition, chemotherapy is more toxic in sarcopenic patients, which negatively affects survival outcomes<sup>(24)</sup>.

There are studies showing that there are more serious complications with chemotherapy in patients with sarcopenia<sup>(24,25)</sup>. In our study, there was no difference in terms of mPFS or mOS between patients with BMI <18.5 and patients with >18.5 because of BMI evaluation. Cachexia can also be seen in patients who are in the obesity or normal group according to BMI. Therefore, BMI is considered insufficient in the evaluation of sarcopenia<sup>(26,27)</sup>. CT, PET-CT, and MRI can be used in the diagnosis and follow-up of cancer. While manual measurements may lead to subjective results in the evaluation of cachexia and sarcopenia, more objective results can be determined by CT. However, in CT measurements, the problem is that the standard values differ between nationalities. For this reason, it is recommended that countries determine their own sarcopenia values and studies are conduct studies in this direction<sup>(12,28,29)</sup>. It should be considered that both chemotherapy response and overall survival will be worse in patients with sarcopenia detected at the time of diagnosis. Disease management should be shaped according to this situation.

When the literature is evaluated, it is seen that there is more than one method in the evaluation of sarcopenia with imaging methods. PMD, HUAC, and PMI are two of these methods. Sarcopenia detected with PMD, HUAC, and PMI is an independent poor prognostic factor in pancreatic cancer. Other prognostic factors affecting mOS in our study were the patient's ECOG performance and ability to receive second-line chemotherapy. Having received second-line chemotherapy is also an indirect indicator of good performance status. There is no standard consensus regarding the assessment of sarcopenia. It is suggested that each nation determines an index according to their own data. The reason why we preferred PMD HUAC and PMI in our study is the effort to identify patients who are in the lowest quartile compared with our population, instead of using a standard value.

## **Study Limitations**

The limitations of our study are the small number of patients and the retrospective nature of our study. The results may have been affected by individual differences in chemotherapy preference and difficulties in accessing nabpaclitaxel in our country. The fact that chemotherapy complications were not evaluated in our study is one of the limitations of our study. Complications were excluded from the evaluation because there were insufficient complication data in the file information.

## Conclusion

The evaluation of sarcopenia in the imaging control performed during the staging of metastatic pancreatic cancer provides information both in terms of prognosis and gives an idea about the intensity of the treatment modality to be applied and the complications that may occur. In addition, in patients with sarcopenia at the time of diagnosis, ONS can be initiated at an early stage and contribute to the improvement of the results.

## Ethics

**Ethics Committee Approval:** Manisa Celal Bayar University Ethics Committee date: 21.03.2022, decision no: 251 approval was received. The procedures followed were in accordance with the ethical standards of the Manisa Celal Bayar University Ethics Committee and with the Helsinki Declaration of 1975, as revised in 2013. **Informed Consent:** In our study, which was conducted as a retrospective patient file scan, a patient consent form was obtained.

#### **Authorship Contributions**

Surgical and Medical Practices: A.Ö., S.A., Concept: A.Ö., Design: A.Ö., S.A., Data Collection or Processing: A.Ö., S.A., Analysis or Interpretation: A.Ö., Literature Search: A.Ö., S.A., Writing: A.Ö.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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