



Retrospective study of testosterone deficiency and symptom burden in patients with pancreatic cancer

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Background: Pancreatic cancer patients have poor quality of life. Testosterone deficiency is associated with constitutional symptoms and sexual dysfunction which may contribute to poor quality of life. We investigated the prevalence of screening for and presence of testosterone deficiency in male pancreatic cancer patients.

Methods: To determine the frequency of screening for testosterone deficiency in pancreatic cancer patients, our institution's electronic medical record system was queried for male patients diagnosed with a pancreatic mass between 2006 and 2020 and an available testosterone level. In a separate analysis, total testosterone was measured in serum samples from a cohort of 89 male pancreatic ductal adenocarcinoma (PDAC) patients. Low serum testosterone was defined as <300 ng/dL.

Results: One thousand five hundred and sixty-six male patients were identified with a pancreatic mass, and 35 (2.2%) also had a testosterone level. In our analysis cohort, 44 of 89 patients (49.4%) were found to have low serum testosterone. Symptoms consistent with testosterone deficiency were documented for 70% of these patients, with fatigue being the most common. Testosterone level had no significant association with progression-free survival (PFS) (P=0.66) or overall survival (OS) (P=0.95).

Conclusions: Testosterone deficiency is common but rarely assessed in male patients with pancreatic cancer. Further studies are warranted to explore the possibility of testosterone supplementation to improve quality of life in this patient population.

Keywords: Pancreatic neoplasms; testosterone; hypogonadism

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a leading cause of cancer-related death in the United States with increasing incidence. Unfortunately, this cancer has a poor 5-year survival rate of 12% (1). Treatment for PDAC involves an intensive combination of surgery, chemotherapy, and/or radiation.

Constitutional symptoms are common in patients with PDAC, with many people reporting fatigue, weakness, cognitive dysfunction, and weight loss (2,3). These symptoms likely contribute to patients with PDAC reporting worse quality of life compared to patients with other cancers (2). Furthermore, a significant proportion of PDAC patients note a lack of sexual interest or enjoyment (2-5). In clinical practice, constitutional symptoms are often assumed to be manifestations of disease or treatment. However, they are also consistent with testosterone deficiency in males, which is characterized by fatigue, weakness, cognitive dysfunction, decreased lean muscle mass, and sexual dysfunction (6).

Symptomatic testosterone deficiency, defined as low serum testosterone combined with associated symptoms, affects between 10% and 40% of adult males and increases in prevalence with age (7). Testosterone is not a current guideline recommended laboratory test in the diagnosis or management of PDAC (8). To our knowledge, no data are currently available on the clinical patterns for testosterone

screening in this population and limited data exist regarding the prevalence of testosterone deficiency in male patients with PDAC. Therefore, we sought to investigate clinical practices regarding screening for testosterone deficiency, the prevalence of testosterone deficiency, and the relationship between testosterone status and oncologic outcomes in a cohort of male patients with PDAC. We present this article in accordance with the STROBE reporting checklist (available at <https://tau.amegroups.com/article/view/10.21037/tau-22-684/rc>).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Two cohorts of patients were developed for this study. Cohort A was developed for the purpose of addressing our question about the frequency of testosterone screening in clinical practice for patients with pancreatic cancer under two retrospective records review approvals from the Institutional Review Board of the University of Iowa (protocols No. #201102712 and No. #201903702), and individual consent for this retrospective analysis was waived.

Cohort B was developed using patients who had consented to participation in an institutional tissue repository also approved by the Institutional Review Board of the University of Iowa (protocol No. #201202743) to investigate the frequency of testosterone deficiency in this patient population and to associate oncologic outcomes to testosterone levels. Most patients, but not all, were sampled shortly after diagnosis and prior to treatment initiation. Individual consent was obtained for future research at the time of donation to the tissue repository.

For cohort A, existing patterns of testosterone testing in patients with primary tumors of the pancreas were analyzed by querying the electronic medical record at the University of Iowa Hospitals and Clinics, a National Cancer Institute-designated comprehensive cancer center delivering high-volume pancreatic cancer care. This query sought to identify all male patients with billing codes for masses of the pancreas (C.25X) and then identify those who also had an available testosterone laboratory level between 2006 and 2020. Non-primary pancreatic masses were eliminated from analysis. Testosterone levels, as well as demographics and clinicopathologic variables, were abstracted and assessed. Available testosterone levels were analyzed for testosterone deficiency.

For cohort B, serum samples were obtained from male

Highlight box

Key findings

- Our retrospective study suggests one in two pancreatic cancer patients have laboratory evidence of testosterone deficiency, but symptoms associated with testosterone deficiency are not more common in patients with low testosterone.

What is known and what is new?

- Male patients with pancreatic tumors report symptoms associated with testosterone deficiency including fatigue and weakness.
- Male patients with pancreatic tumors are rarely screened for testosterone deficiency, even when reporting symptoms associated with testosterone deficiency. Many male PDAC patients meet guideline recommendations for additional screening for testosterone deficiency and supplementation.

What is the implication, and what should change now?

- Further prospective studies are warranted to explore the role of testosterone supplementation in improving men's health and overall well-being during pancreatic cancer treatment.

PDAC patients enrolled in an institutional prospective biospecimen repository at a National Cancer Institute-designated comprehensive cancer center from 2012–2020. Total testosterone (ng/dL) of each sample was measured using serum testosterone ELISA kits (11-TESTU-E01, Alpco, Salem, NH, USA). Demographic, clinicopathologic, treatment, and outcome data were abstracted from the electronic medical record. For both surgically- and medically-treated patients, clinical staging based on AJCC 7th edition was used for consistency in analysis (9).

For both cohorts, low serum testosterone was defined as a level <300 ng/dL per the American Urological Association guideline (6) and obesity was defined as body mass index (BMI) >30 kg/m².

Statistical analysis

Chi-squared or Fisher's exact tests were used to compare categorical variables, and Wilcoxon rank sum tests were used to compare continuous variables between low and normal testosterone groups. Survival probabilities were estimated and plotted using the Kaplan-Meier method. Cox regression models were used to assess the association of patient and disease characteristics on progression-free survival (PFS) and overall survival (OS). Survival time was calculated from date of diagnosis to progression or death due to any cause for PFS and to death due to any cause for OS. Patients (n=1) for whom the date of progression is unknown were excluded from the PFS analysis. All tests were two-sided and assessed for significance at the 5% level using SAS v9.4 (SAS Institute, Cary, NC, USA).

Results

In cohort A, 1,566 male patients were identified with a pancreatic mass billing code. Of these, 35 (2.2%) had both a primary pancreatic mass and a testosterone level in their electronic medical records. *Table 1* contains demographic and clinical data of interest.

The most common documented reason prompting a provider to check a testosterone level in these 35 cancer patients were complaints of fatigue (n=14, 40%), followed by low libido and/or erectile dysfunction (n=8, 23%), or monitoring ongoing testosterone therapy (n=4, 11%).

In cohort A, 16 patients (46%) had a low testosterone level while an additional 4 (11%) patients had a normal testosterone level, but were on testosterone therapy at the

time of the blood draw and therefore included within the low testosterone group. Therefore, 20/35 (57%) of cohort A were considered to have low testosterone. When limiting our analysis to patients for whom testosterone levels were measured within one year before or after cancer diagnosis, 4/12 (33%) had measured low testosterone. An additional 3 patients were already on testosterone therapy at time of the lab draw, which represents a low testosterone proportion of 7/12 (58%).

In cohort B, the majority of patients (62/89, 69.7%) had documented symptoms associated with testosterone deficiency in the medical record prior to sample collection. Fatigue was the most-commonly reported symptom consistent with testosterone deficiency.

Upon analysis, nearly half (44/89, 49.4%) were found to have a low serum testosterone level (median: 301 ng/dL; range, 123–2,378 ng/dL). Only 2/89 (2.2%) patients had a prior testosterone level measured; none had received testosterone therapy per review of electronic medical records.

Low and normal testosterone subgroups of cohort B are compared in *Table 2*. Patients with low serum testosterone were of similar age and were no more likely to be obese, have diabetes, or have heart disease. For the 49 patients with an Eastern Cooperative Oncology Group (ECOG) score, there was no difference between groups. Patients with low serum testosterone were not more likely to report any symptom of testosterone deficiency (low: 77.3%, normal: 62.2%, P=0.12) or more likely to have documented fatigue or weakness. There was no significant difference between groups in receipt of surgery, chemotherapy, or radiation. Furthermore, patients with low testosterone were not more likely to have more advanced disease.

Univariate and multivariable analysis of the serum sample cohort is presented in *Tables 3,4*, respectively. Stage III or IV disease and presence of metastatic disease at diagnosis were significantly associated with decreased PFS and OS in univariate analysis. Receiving surgery was significantly associated with increased PFS and OS, with receipt of radiation therapy also associated with increased OS on univariate analysis. A statistically significant difference in PFS and OS by testosterone level was not evidenced on univariate analysis (*Figures 1,2*). Only the presence of metastatic disease and receiving surgery remained associated with both PFS and OS on multivariable analysis. After adjusting for metastatic disease at the time of diagnosis and treatment, testosterone level had no statistically significant association with PFS (P=0.66) or OS (P=0.95).

Table 1 Demographics of male patients with pancreatic cancer from chart review and serum sample cohorts

Covariate	Level	Chart review cohort (cohort A) (n=35)	Serum sample cohort (cohort B) (n=89)
Age at diagnosis (years)	Median (range)	61.9 (22.7–87.5)	66.0 (44.0–87.0)
Race	African American	0 (0.0)	3 (3.4)
	White	35 (100.0)	85 (95.5)
	Unknown	0 (0.0)	1 (1.1)
BMI at diagnosis (kg/m ²)	Median (range)	31.3 (13.7–59.7)	27.8 (17.2–52.2)
Obese (BMI >30 kg/m ²)	Yes	20 (57.1)	34 (38.2)
	No	15 (42.9)	55 (61.8)
Diabetes	Yes	16 (45.7)	38 (42.7)
	No	19 (54.3)	51 (57.3)
Heart disease	Yes	18 (51.4)	63 (70.8)
	No	17 (48.6)	26 (29.2)
Hypo/hyperthyroidism	Yes	6 (17.1)	10 (11.2)
	No	29 (82.9)	79 (88.8)
Obstructive sleep apnea	Yes	4 (11.4)	12 (13.5)
	No	31 (88.6)	77 (86.5)
HIV/AIDS	Yes	0 (0.0)	0 (0.0)
	No	35 (100.0)	89 (100.0)
Chronic kidney disease	Yes	2 (5.7)	3 (3.4)
	No	33 (94.3)	86 (96.6)
Sarcoidosis	Yes	0 (0.0)	0 (0.0)
	No	35 (100.0)	89 (100.0)
Corticosteroid use	Yes	2 (5.7)	5 (5.6)
	No	33 (94.3)	84 (94.4)
Opioid use	Yes	5 (14.3)	25 (28.1)
	No	30 (85.7)	64 (71.9)
Pre-existing autoimmune disease	Yes	1 (2.9)	3 (3.4)
	No	34 (97.1)	86 (96.6)
Previous cancer diagnosis	Yes	7 (20.0)	22 (24.7)
	No	28 (80.0)	67 (75.3)
Clinical stage	I	8 (22.9)	17 (19.1)
	II	7 (20.0)	38 (42.7)
	III	2 (5.7)	13 (14.6)
	IV	17 (48.6)	21 (23.6)
	Not staged	1 (2.9)	0 (0.0)

Table 1 (continued)

Table 1 (continued)

Covariate	Level	Chart review cohort (cohort A) (n=35)	Serum sample cohort (cohort B) (n=89)
Histology	Adenocarcinoma	18 (51.4)	89 (100.0)
	Neuroendocrine tumor	17 (48.6)	0 (0.0)
Testosterone level (ng/dL)	Median (range)	365 (5–1,497)	301 (123–2,378)
Low testosterone (<300 ng/dL)	Yes	20 (57.1)	44 (49.4)
	No	15 (42.9)	45 (50.6)
Prior testosterone assessment	Yes	–	2 (2.2)
	No	–	87 (97.8)
Symptoms of low testosterone	Yes	–	62 (69.7)
	No	–	27 (30.3)

Except where otherwise noted, data are presented as n (%). BMI, body mass index; HIV/AIDS, human immunodeficiency virus or acquired immunodeficiency syndrome.

Discussion

Patients with PDAC are not only afflicted by a poor prognosis, but also experience a poor quality of life, particularly in comparison to patients with other cancers. We found that while pancreas cancer patients are rarely assessed for testosterone deficiency, nearly 70% of patients in our samples have symptoms consistent with low testosterone. Further, nearly 50% of our sampled cohort had low levels of testosterone in their serum.

The primary therapy for testosterone deficiency is testosterone supplementation. Large trials suggest that testosterone therapy increases activity, sexual desire, erectile function, both perceived ability and objective distance of walking, vitality, mood, depressive symptoms, anemia, bone mineral density and bone strength (10). Additional reported benefits include stabilizing metabolic syndromes in hypogonadal patients (11). Testosterone therapy is generally considered safe, with the only significant adverse event associated with supplementation being erythrocytosis, which may become a potential benefit for those with chemotherapy-induced anemia (10). Although preclinical studies suggested that pancreatic cancer tissue may overexpress the androgen receptor (AR) (12,13), later studies have failed to replicate this finding or find an association between survival and AR expression (14,15). AR has been explored as a therapeutic target for PDAC but has not shown significant benefit (16–18). Low testosterone was not associated with a survival advantage in our data, consistent with a likely limited role for AR signaling in

PDAC progression.

Androgen deficiency has previously been identified in patients with advanced cancer and is considered a potential contributor to systemic inflammation, fatigue, depression, decreased sexual desire, anorexia, and weight loss, consistent with the anorexia-cachexia syndrome (19–21). In our study, patients with low serum testosterone did not significantly differ from patients with normal serum testosterone in fatigue, weakness, obesity, diabetes, or heart disease, nor were they more likely to report symptoms of testosterone deficiency or have different ECOG scores. Our modest sample size may have contributed to this finding.

Decreased circulating testosterone has been associated with decreased OS in male cancer patients (19). In contrast to our study, an association between low testosterone and reduced survival has also been found in patients with pancreatic cancer (21). Although using a similar sample size, only advanced PDAC patients were included in this study, and more than 70% of patients were considered hypogonadal, which may account for the differences in our findings.

Higher circulating levels of testosterone have been associated with improved performance on a stair climb test in cancer patients (22), suggesting that testosterone likely impacts physical performance and that testosterone supplementation may benefit patients with cancer. Two small trials of testosterone supplementation have been conducted. In a double-blind, placebo-controlled trial of testosterone therapy for 10 weeks in patients with advanced cancer, treated patients demonstrated a decrease in fatigue,

Table 2 Demographics and treatment variables for the serum sample cohort (continues onto subsequent page)

Covariate	Level	Total (n=89)	Testosterone low (<300 ng/dL)		P value
			No (n=45)	Yes (n=44)	
Age at diagnosis (years)	Median (range)	66.0 (44.0–87.0)	65.0 (44.0–87.0)	66.0 (45.0–82.0)	0.67
BMI (kg/m ²)	Median (range)	27.8 (17.2–52.2)	27.3 (19.3–52.2)	28.6 (17.2–39.1)	0.37
Obesity (BMI >30 kg/m ²)	Yes	34 (38.2)	15 (33.3)	19 (43.2)	0.34
	No	55 (61.8)	30 (66.7)	25 (56.8)	
Diabetes	Yes	38 (42.7)	17 (37.8)	21 (47.7)	0.34
	No	51 (57.3)	28 (62.2)	23 (52.3)	
Heart disease	Yes	63 (70.8)	35 (77.8)	28 (63.6)	0.14
	No	26 (29.2)	10 (22.2)	16 (36.4)	
Hypothyroidism	Yes	8 (9.0)	4 (8.9)	4 (9.1)	1.00
	No	81 (91.0)	41 (91.1)	40 (90.9)	
Hyperthyroidism	Yes	2 (2.2)	2 (4.4)	0 (0.0)	0.49
	No	87 (97.8)	43 (95.6)	44 (100.0)	
Obstructive sleep apnea	Yes	12 (13.5)	4 (8.9)	8 (18.2)	0.20
	No	77 (86.5)	41 (91.1)	36 (81.8)	
Chronic kidney disease	Yes	3 (3.4)	1 (2.2)	2 (4.5)	0.62
	No	86 (96.6)	44 (97.8)	42 (95.5)	
Corticosteroid use	Yes	5 (5.6)	4 (8.9)	1 (2.3)	0.36
	No	84 (94.4)	41 (91.1)	43 (97.7)	
Opioid medications	Yes	25 (28.1)	12 (26.7)	13 (29.5)	0.76
	No	64 (71.9)	33 (73.3)	31 (70.5)	
Pre-existing autoimmune disease	Yes	3 (3.4)	2 (4.4)	1 (2.3)	>0.99
	No	86 (96.6)	43 (95.6)	43 (97.7)	
Other cancer diagnoses	Yes	22 (24.7)	12 (26.7)	10 (22.7)	0.67
	No	67 (75.3)	33 (73.3)	34 (77.3)	
Clinical stage	IA	4 (4.5)	2 (4.4)	2 (4.5)	0.77
	IB	13 (14.6)	6 (13.3)	7 (15.9)	
	IIA	10 (11.2)	5 (11.1)	5 (11.4)	
	IIB	28 (31.5)	16 (35.6)	12 (27.3)	
	III	13 (14.6)	8 (17.8)	5 (11.4)	
	IV	21 (23.6)	8 (17.8)	13 (29.5)	
Metastatic disease at diagnosis	Yes	21 (23.6)	8 (17.8)	13 (29.5)	0.19
	No	68 (76.4)	37 (82.2)	31 (70.5)	

Table 2 (continued)

Table 2 (continued)

Covariate	Level	Total (n=89)	Testosterone low (<300 ng/dL)		P value
			No (n=45)	Yes (n=44)	
Grade of tumor	High grade	15 (16.9)	6 (13.4)	9 (20.4)	0.75
	Intermediate grade	26 (29.2)	14 (31.1)	12 (27.3)	
	Low grade	2 (2.2)	1 (2.2)	1 (2.3)	
	Missing	46 (51.7)	24 (53.3)	22 (50.0)	
ECOG status	0	21 (23.6)	10 (22.2)	11 (25.0)	0.57
	1	31 (34.8)	19 (42.2)	12 (27.3)	
	2	6 (6.8)	3 (6.7)	3 (6.8)	
	3	1 (1.1)	0 (0.0)	1 (2.3)	
	Missing	30 (33.7)	13 (28.9)	17 (38.6)	
Testosterone level (ng/dL)	Median (range)	301 (123–2,378)	529 (301–2,378)	202.5 (123–294)	
Symptoms of low testosterone present prior to sample collection	Yes	62 (69.7)	28 (62.2)	34 (77.3)	0.12
	No	27 (30.3)	17 (37.8)	10 (22.7)	
Fatigue or weakness reported	Yes	55 (61.8)	26 (57.8)	29 (65.9)	0.43
	No	34 (38.2)	19 (42.2)	15 (34.1)	
Pituitary aberrancies	No	0 (0.0)	–	–	
Adrenal aberrancies	Yes	3 (3.4)	1 (2.2)	2 (4.5)	0.62
	No	86 (96.6)	44 (97.8)	42 (95.5)	
Thyroid aberrancies	Yes	7 (7.9)	4 (8.9)	3 (6.8)	>0.99
	No	82 (92.1)	41 (91.1)	41 (93.2)	
Received surgery	Yes	43 (48.3)	22 (48.9)	21 (47.7)	0.91
	No	46 (51.7)	23 (51.1)	23 (52.3)	
Received radiation therapy	Yes	32 (36.0)	19 (42.2)	13 (29.5)	0.21
	No	57 (64.0)	26 (57.8)	31 (70.5)	
Received chemotherapy	Yes	74 (83.1)	38 (84.4)	36 (81.8)	0.74
	No	15 (16.9)	7 (15.6)	8 (18.2)	
Received any cancer treatment before serum draw	Yes	8 (9.0)	5 (11.1)	3 (6.8)	0.71
	No	81 (91.0)	40 (88.9)	41 (93.2)	

Except where otherwise noted, data are presented as n (%). BMI, body mass index; ECOG, Eastern Cooperative Oncology Group.

an increase in performance status, and an increase in sexual desire (23). A randomized trial of testosterone as an adjuvant supplement in patients with head and neck cancer undergoing therapy found that the testosterone cohort experienced improved lean body mass, quality of life, and physical activity compared to placebo (24). Additional larger

trials are ongoing in cancer patients and cancer survivors, including NCT05367284, NCT04492553, NCT04301765, and NCT04049331, although patients with active PDAC are not eligible for any of these trials.

Our study has several limitations including a relatively small sample size and a single-institution setting. To

Table 3 Univariate analysis of factors associated with PFS and OS in the serum sample cohort

Covariate	Level	PFS			OS		
		HR	95% CI	P	HR	95% CI	P
Diabetes	Yes	0.82	0.50–1.35	0.44	1.38	0.83–2.30	0.21
	No	Reference	–		Reference	–	
Obesity	Yes	1.34	0.83–2.17	0.23	0.69	0.40–1.18	0.18
	No	Reference	–		Reference	–	
Opioid medications	Yes	1.49	0.90–2.48	0.12	1.27	0.73–2.20	0.40
	No	Reference	–		Reference	–	
Other cancer diagnoses	Yes	0.80	0.45–1.41	0.43	0.73	0.40–1.36	0.33
	No	Reference	–		Reference	–	
Received surgery	Yes	0.30	0.18–0.50	<0.01	0.28	0.16–0.49	<0.01
	No	Reference	–		Reference	–	
Received chemotherapy	Yes	1.04	0.56–1.94	0.90	0.80	0.43–1.52	0.50
	No	Reference	–		Reference	–	
Received radiation therapy	Yes	0.68	0.42–1.12	0.13	0.80	0.43–1.52	0.03
	No	Reference	–		Reference	–	
Stage at diagnosis	I	Reference	–	<0.01	Reference	–	<0.01
	II	1.71	0.85–3.43		1.58	0.75–3.33	
	III	2.36	1.00–5.56		3.28	1.32–8.15	
	IV	6.52	2.76–15.42		8.04	3.27–19.72	
Metastatic disease at diagnosis	Yes	3.89	2.06–7.34	<0.01	4.64	2.41–8.92	<0.01
	No	Reference	–		Reference	–	
Low testosterone (<300 ng/dL)	Yes	0.87	0.54–1.41	0.56	1.06	0.64–1.76	0.81
	No	Reference	–		Reference	–	
Age at diagnosis (years)	Units =1	1.00	0.98–1.02	0.94	1.00	0.97–1.03	0.99
Measured total serum level (ng/dL)	Units =1	1.00	1.00–1.00	0.93	1.00	1.00–0.51	>0.99

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

diagnose testosterone deficiency, two morning testosterone measurements should be made at separate visits, and our study only was able to make one measurement. We were also unable to control for time of day that serum samples were drawn in our analysis cohort, and therefore our data may overestimate proportion of patients with testosterone deficiency due to late-day sampling. Circadian variation in serum testosterone becomes blunted in older men, however, and our study population median ages at diagnosis were in

the 60's, so morning samples are likely less important in our particular populations (25). Our study is also limited by its retrospective nature and a primarily Caucasian population, a byproduct of the patient population seen at our institution. Further, our method for developing cohort A was unable to limit this group to only patients with pancreatic adenocarcinoma. Therefore, patients with endocrine neoplasms are also included, limiting the precision of our estimation of testosterone assessment

Table 4 Multivariable analysis of factors associated with PFS and OS in the serum sample cohort

Covariate	Level	PFS			OS		
		HR	95% CI	P	HR	95% CI	P
Metastatic disease at diagnosis	Yes	2.30	1.14–4.67	0.02	2.53	1.20–5.30	0.01
	No	Reference	–		Reference	–	
Low testosterone (<300 ng/dL)	Yes	0.89	0.54–1.48	0.66	0.98	0.58–1.67	0.95
	No	Reference	–		Reference	–	
Received surgery	Yes	0.36	0.20–0.66	<0.01	0.40	0.21–0.78	<0.01
	No	Reference	–		Reference	–	
Received chemotherapy	Yes	1.53	0.79–2.95	0.21	1.01	0.52–1.95	0.98
	No	Reference	–		Reference	–	
Received radiation therapy	Yes	0.70	0.42–1.18	0.18	0.62	0.35–1.10	0.10
	No	Reference	–		Reference	–	

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

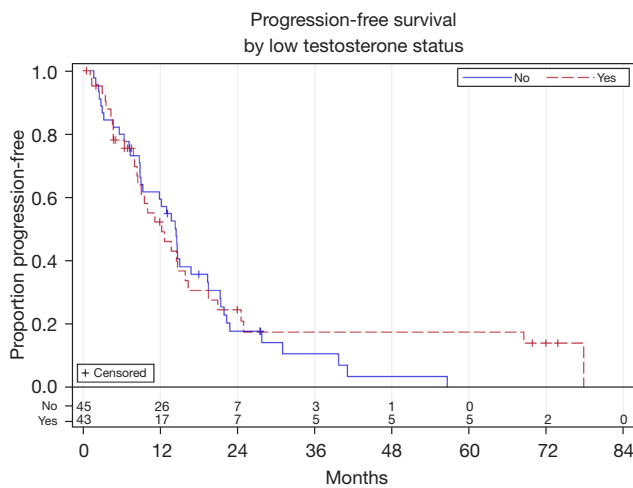


Figure 1 Univariate analysis of PFS by low testosterone status for the serum sample cohort. PFS was not significantly different between patients with low or normal testosterone levels (P=0.56). PFS, progression-free survival.

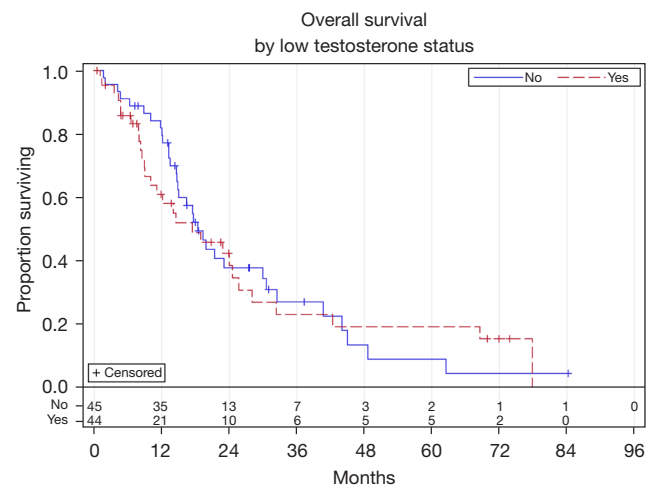


Figure 2 Univariate analysis of OS by low testosterone status for the serum sample cohort. OS was not significantly different between patients with low or normal testosterone levels (P=0.81). OS, overall survival.

in this population. Finally, our sample is biased towards individuals who consented to participate in research and by a high percentage of surgery-eligible patients because of our status as a tertiary referral center.

Conclusions

Male patients with tumors of the pancreas commonly

report symptoms associated with testosterone deficiency and meet guideline recommendations for screening for testosterone deficiency. However, at our center, these patients are rarely screened. One in two patients were found to have laboratory evidence of testosterone deficiency, and symptoms associated with testosterone deficiency were not statistically more common in patients with low testosterone. Further prospective studies are warranted to explore the

role of testosterone supplementation in improving men's health and overall well-being during PDAC treatment.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Cohort A received approvals from the Institutional Review Board of the University of Iowa (protocols No. #201102712 and No. #201903702) and individual consent for this retrospective analysis was waived. Cohort B was approved by the Institutional Review Board of the University of Iowa (No. #201202743) and individual consent was obtained for future research at the time of donation to the tissue repository.

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References

1. Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023. *CA Cancer J Clin* 2023;73:17-48.
2. Bauer MR, Bright EE, MacDonald JJ, et al. Quality of Life in Patients With Pancreatic Cancer and Their Caregivers: A Systematic Review. *Pancreas* 2018;47:368-75.
3. Frick MA, Vachani CC, Hampshire MK, et al. Survivorship after treatment of pancreatic cancer: insights via an Internet-based survivorship care plan tool. *J Gastrointest Oncol* 2017;8:890-6.

4. Moningi S, Walker AJ, Hsu CC, et al. Correlation of clinical stage and performance status with quality of life in patients seen in a pancreas multidisciplinary clinic. *J Oncol Pract* 2015;11:e216-21.
5. Beesley VL, Wockner LF, O'Rourke P, et al. Risk factors for current and future unmet supportive care needs of people with pancreatic cancer. A longitudinal study. *Support Care Cancer* 2016;24:3589-99.
6. Mulhall JP, Trost LW, Brannigan RE, et al. Evaluation and Management of Testosterone Deficiency: AUA Guideline. *J Urol* 2018;200:423-32.
7. Anaissie J, DeLay KJ, Wang W, et al. Testosterone deficiency in adults and corresponding treatment patterns across the globe. *Transl Androl Urol* 2017;6:183-91.
8. Pancreatic adenocarcinoma (1.2022): National Comprehensive Cancer Network. Available online: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf
9. Edge SB, Byrd DR, Compton CC, et al. editors. *AJCC Cancer Staging Manual*. 7th edition. New York, NY, USA: Springer; 2010.
10. Snyder PJ, Bhasin S, Cunningham GR, et al. Lessons From the Testosterone Trials. *Endocr Rev* 2018;39:369-86.
11. Salam R, Kshetrimayum AS, Keisam R. Testosterone and metabolic syndrome: The link. *Indian J Endocrinol Metab* 2012;16 Suppl 1:S12-9.
12. Corbishley TP, Iqbal MJ, Wilkinson ML, et al. Androgen receptor in human normal and malignant pancreatic tissue and cell lines. *Cancer* 1986;57:1992-5.
13. Okitsu K, Kanda T, Imazeki F, et al. Involvement of interleukin-6 and androgen receptor signaling in pancreatic cancer. *Genes Cancer* 2010;1:859-67.
14. Georgiadou D, Sergentanis TN, Sakellariou S, et al. Prognostic role of sex steroid receptors in pancreatic adenocarcinoma. *Pathol Res Pract* 2016;212:38-43.
15. Targarona EM, Pons MD, Gonzalez G, et al. Is exocrine pancreatic cancer a hormone-dependent tumor? A study of the existence of sex hormone receptors in normal and neoplastic pancreas. *Hepatogastroenterology* 1991;38:165-9.
16. Keating JJ, Johnson PJ, Cochrane AM, et al. A prospective randomised controlled trial of tamoxifen and cyproterone acetate in pancreatic carcinoma. *Br J Cancer* 1989;60:789-92.
17. Negi SS, Agarwal A, Chaudhary A. Flutamide in unresectable pancreatic adenocarcinoma: a randomized, double-blind, placebo-controlled trial. *Invest New Drugs* 2006;24:189-94.
18. Konduri S, Schwarz MA, Cafasso D, et al. Androgen receptor blockade in experimental combination therapy of pancreatic cancer. *J Surg Res* 2007;142:378-86.
19. Dev R, Hui D, Del Fabbro E, et al. Association between hypogonadism, symptom burden, and survival in male patients with advanced cancer. *Cancer* 2014;120:1586-93.
20. Burney BO, Hayes TG, Smiechowaska J, et al. Low testosterone levels and increased inflammatory markers in patients with cancer and relationship with cachexia. *J Clin Endocrinol Metab* 2012;97:E700-9.
21. Skipworth RJ, Moses AG, Sangster K, et al. Interaction of gonadal status with systemic inflammation and opioid use in determining nutritional status and prognosis in advanced pancreatic cancer. *Support Care Cancer* 2011;19:391-401.
22. Anderson LJ, Lee J, Mallen MC, et al. Evaluation of physical function and its association with body composition, quality of life and biomarkers in cancer cachexia patients. *Clin Nutr* 2021;40:978-86.
23. Del Fabbro E, Garcia JM, Dev R, et al. Testosterone replacement for fatigue in hypogonadal ambulatory males with advanced cancer: a preliminary double-blind placebo-controlled trial. *Support Care Cancer* 2013;21:2599-607.
24. Wright TJ, Dillon EL, Durham WJ, et al. A randomized trial of adjunct testosterone for cancer-related muscle loss in men and women. *J Cachexia Sarcopenia Muscle* 2018;9:482-96.
25. Plymate SR, Tenover JS, Bremner WJ. Circadian variation in testosterone, sex hormone-binding globulin, and calculated non-sex hormone-binding globulin bound testosterone in healthy young and elderly men. *J Androl* 1989;10:366-71.

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