Sarcopenia represents a negative prognostic factor in pancreatic cancer patients undergoing EUS celiac plexus neurolysis

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ABSTRACT

Background and Objectives: Increasing evidence suggests a prognostic role of sarcopenia in pancreatic cancer patients. The aim of this study was to assess the influence of sarcopenia on treatment outcomes after EUS-guided celiac plexus neurolysis (CPN). **Materials and Methods:** Data regarding 215 patients treated with EUS CPN between 2004 and 2019 were reviewed. Determination of body composition was conducted on contrast-enhanced CT scan, and pain response was considered as the primary outcome. Univariate and multivariate logistic regression was performed to identify the independent predictors of pain response. **Results:** Treatment was successful in 187 patients (86.9%). The median age was 62 (range 39–84) years, and most patients were male (61.8%). Of the whole study population, 139 patients (64.6%) were defined as sarcopenic, of which 116 (83.4%) responded to the treatment and 5 (3.5%) experienced a complete response. Among 76 nonsarcopenic participants, 71 (93.4%) responded to the treatment and 22 (28.9%) obtained a complete response ($P = 0.03$ and <0.001, respectively). The median duration of pain relief was 8 (2–10) and 15 (8–16) weeks in sarcopenic and nonsarcopenic patients, respectively ($P = 0.01$). The median overall survival after neurolysis was 4 months (3–5) in sarcopenic participants and 7 months (6–8) in nonsarcopenic participants ($P = 0.05$). Tumoral stage, interval from the diagnosis to treatment, and sarcopenia resulted as significant prognostic factors for treatment response both in univariate and multivariate regression analyses. No severe treatment-related adverse events were reported in the whole study population, with no difference between the two groups. **Conclusions:** Sarcopenia represents a predictor of poorer response to EUS CPN.

Key words: celiac plexus neurolysis, EUS, pain, tumor

INTRODUCTION

Severe refractory abdominal pain arising from locally invasive pancreatic cancer (PC) has a considerable negative impact on the quality of life.[1] A considerable proportion of these patients require opioids but after the transient initial pain relief, usually experience systemic drug-related side effects and dependency,

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which often lead to therapy interruption and pain relapse.[2]

In order to overcome the limitations of systemic analgesic therapy, celiac plexus neurolysis (CPN) has been developed.[3] EUS-guided-CPN (EUS-CPN), consisting in the injection of a neurolytic agent directly into the celiac ganglion using a linear echoendoscope, was proven to be a relatively safe procedure able to significantly decrease the daily usage of narcotic analgesia and relieve pain in about 80% of treated patients.[4-6]

Unfortunately, the results of EUS-CPN are often suboptimal and transient, probably due to technical failure, disease extension outside of the celiac axis, or the concomitant presence of neuropathic pain. Repeat CPN is occasionally performed for refractory PC pain and might represent a valuable option in a subset of patients,[7] but this approach is not standardized and requires further validation.

Given the uncertain results of EUS-CPN is of fundamental importance to define the prognostic factors able to correlate with a better response and more positive outcomes, among the identified predictors of response, the timing of the treatment, evidence of tumor progression after neurolysis, and tumoral stage play a pivotal role in defining the efficacy of the procedure.[8,9]

Recently, body composition was evaluated in different oncologic patient cohorts, hereby, sarcopenia proved as a prognostic factor of morbidity, mortality, and survival in several malignancies.[10] In PC, sarcopenia was found to correlate with poorer outcomes both in resectable and in advanced stage,[11-14] mainly due to impaired wound healing, depressed immunity, and the imbalance in several proinflammatory cytokines such as interleukin 8 (IL-8) and tumor necrosis factor α (TNF-α).[15]

The aim of this study was to determine whether sarcopenia might influence treatment outcomes both in terms of pain relief and overall survival (OS), and therefore, can be considered a prognostic factor in PC patients undergoing EUS-CPN.

MATERIALS AND METHODS

Patients
From a prospectively collected database, data regarding 215 patients suffering from cancer-related abdominal pain secondary to unresectable pancreatic adenocarcinoma (confirmed by EUS-guided fine-needle aspiration and CT scan) treated with EUS-guided CPN at our institution between March 2004 and October 2019 were reviewed. All patients had undergone neoadjuvant gemcitabine-based chemotherapy ± radiotherapy and as they did not meet the resectability criteria when experienced pain-related symptoms, were offered EUS-guided pain therapy. Institutional Review Board approbation for this retrospective report was obtained.

The following exclusion criteria were used: the presence of an implanted pain-relieving device, direct invasion of PC to the stomach or other nearby organs, patients under antithrombotic therapy, or presence of diseases impairing normal blood clotting.

All procedures were performed by a board-certified gastroenterologist (NM) who had performed more than 60 EUS-CPNs before the study period.

Written informed consent was obtained from all patients before the procedure.

Technical procedure
Under sedation with propofol, EUS was conducted with a Pentax FG-36UA ultrasound endoscope (Pentax Europe, Ltd., Hamburg, Germany) using a curved-array transducer. Once into the stomach, the EUS probe was located in contact with the gastric wall, and the aorta was identified in an elongated cross section and such a finding was confirmed by color Doppler imagery. The scope was then slowly advanced to identify the celiac trunk. A 19 G needle (Echotip 19, Cook Medical, Winston-Salem, NC, USA) was introduced though the endoscope's working channel to inject the medication to the celiac region. Once the injection needle was targeted in the desired area, an aspiration syringe was used to confirm that a blood vessel was not punctured. If blood was not aspirated, 10 mL 2.0% lidocaine and 20 mL 95% ethanol were injected into the base of the celiac trunk at its origin from the aorta (central approach).[6,7,16]

Patients were continuously monitored during the procedure by a board-certified anesthesiologist with an automated noninvasive blood pressure device, electrocardiogram tracing, and pulse oximetry.

Anthropometric measures
The determination of body composition was conducted on contrast-enhanced CT scan and two consecutive

transverse CT images extending from the third lumbar vertebrae (L3) in the inferior direction were analyzed for total lean tissue, total lean muscle (psoas, erector spinae, quadratus lumborum, transverse abdominis, external and internal obliques, and rectus abdominis) and adipose tissue [subcutaneous, intramuscular, and visceral; Figure 1].[17] In addition, tissue cross-sectional areas (cm²) were computed automatically by summing tissue pixels and multiplying by pixel surface area. Areas were normalized for stature (cm²/m²).[17] Cutoffs for sarcopenia were based on the computed tomography-based sarcopenic obesity study of cancer patients conducted by Prado *et al.* (*i.e.*, L3 skeletal muscle index ≤38.5 cm²/m² for women and 52.4 cm²/m² for men).[18]

Follow–up and outcomes

All patients undergoing the procedures were hospitalized and were administered pre- and post-procedure questionnaires.

Pain intensity was measured according to the Visual Analog Scale (VAS), ranging from 0 (no pain) to 10 (maximal pain).[19] A successful procedure (pain response) was defined as a ≥50% pain relief persisting for ≥1 month after EUS-CPN without an increase in analgesic usage (primary outcome).[8] Complete pain response was defined as VAS score 0 without increase in pain medication dosage.[6] VAS score was recorded at baseline, at 24 h after the procedure (before hospital discharge), during the scheduled ambulatory visits at 7, 14 days, and monthly thereafter.

Adverse event (AE) rates were evaluated during the procedure, before discharge, at 7 and 14 days using ambulatory visits.
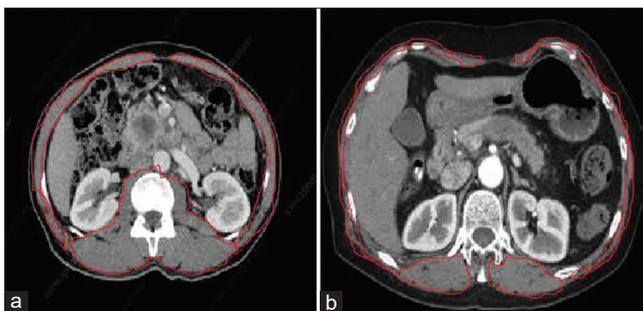

Figure 1. Determination of body composition in patients with pancreatic ductal adenocarcinoma. Axial contrast-enhanced CT scan at the L3 level of (a) nonsarcopenic patient compared to (b) a sarcopenic patient with pancreatic adenocarcinoma. Marked red: psoas, paraspinal, transverse abdominal, external oblique, internal oblique, and rectus abdominis muscles

Statistical analysis

Categorical variables were described as frequencies and percentages and continuous variables as medians and ranges. Comparison of baseline parameters between sarcopenic (Group 1) and nonsarcopenic patients (Group 2) was performed using Kruskal–Wallis test in the case of continuous variables and Chi-square test in cases of categorical ones. Time to event data was estimated in terms of medians (95% confidence intervals [CI]) and compared using the log-rank test.

Univariate and multivariate logistic regression models were applied to identify the independent predictors of pain response after EUS-CPN, and the results were expressed as odds ratio (OR) and 95% CI. Statistically significant variables from the univariate analysis were considered for the multivariate model.

The analysis was performed using the R Statistical Software (Foundation for Statistical Computing, Vienna, Austria), and significance was established at the 0.05 level (two-sided).

RESULTS

Patients

Baseline characteristics of the whole study population of 215 patients who underwent EUS-guided CPN are reported in Table 1. Treatment was successful in 187 patients (86.9%), whereas 28 participants (13.1%) were classified as nonresponders.

No significant differences in terms of most baseline patient clinical characteristics were reported between responders and nonresponders. The median age was 62 (range 39–84) years, and most patients were male (61.8%) without differences between groups.

Preprocedural VAS score was 7 in both groups ($P = 0.8$), and the majority of patients had already been administered opioids (85.5% and 85.7% in responders and nonresponders, respectively; $P = 0.98$).

Nonresponders were significantly more frequently in Stage IV (presence of metastases; $P = 0.01$) and presented a longer interval between the diagnosis and EUS-CPN ($P = 0.03$).

Out of the whole study population, 139 patients (64.6%) were defined as sarcopenic, of which 116

responded to the treatment, whereas 23 were classified as nonresponders.

Treatment outcomes

Treatment outcomes after EUS-CPN are reported in Table 2.

After EUS-CPN, 187 (86.9%) patients achieved a condition of pain relief, of which 27 (12.5%) obtained a complete pain response. In particular, out of 139 patients defined as sarcopenic, 116 (83.4%) obtained a pain relief and only 5 (3.5%) a complete response while among 76 nonsarcopenic participants, 71 (93.4%) achieved a pain relief and 22 (28.9%) a complete response ($P = 0.03$ and <0.001, respectively).

Similarly, median duration of pain relief was 8 (2–10) and 15 (8–16) weeks in sarcopenic and nonsarcopenic patients, respectively ($P = 0.01$). Treated patients experienced a 31% decrease in VAS score in Group 1 (sarcopenia) and 73% in Group 2 (nonsarcopenia; $P = 0.02$).

After the procedure, reduction in opioid use was registered in 26 (18.7%) patients in Group 1 and in 38 (50%) patients in Group 2 ($P < 0.001$).

In the whole study population, median OS after EUS-CPN was 5 months (4–6), 4 months (3–5) in Group 1, and 7 months (6–8) in Group 2 [$P = 0.05$; Figure 2].

Predictors of response and safety data

All relevant clinical, tumoral, and demographical parameters were entered into a univariate logistic regression model, where tumoral stage (Stage IV *vs.* Stage III), interval from the diagnosis to EUS-CPN (>3 months *vs.* ≤3 months), and sarcopenia resulted as significant prognostic factors for treatment response [Table 3]. All of these features were confirmed as significant predictors of response to CPN in the multivariate analysis [Table 3].

In particular, a condition of sarcopenia determined an OR for treatment response of 0.35 (0.12–0.97;

Table 1. Baseline patients' characteristics of the study population

Variable	All patients (*n*=215)	Responders (*n*=187)	Nonresponders (*n*=28)	P
Age (years)	62 (39-84)	56 (39-82)	66 (41-84)	0.3
Gender male (%)	133 (61.8)	116 (62)	17 (60.7)	0.89
BMI	20.5 (17-27)	21 (17-27)	18 (17-26)	0.6
ASA score	2 (1-3)	2 (1-3)	2 (1-3)	0.9
VAS score	7 (5-10)	7 (6-10)	7 (5-10)	0.8
Concomitant opioid use (%)	184 (85.5)	160 (85.5)	24 (85.7)	0.98
Tumor max diameter (mm)	41 (24-61)	39 (25-60)	42 (23-59)	0.37
Pancreatic cancer location head (%)	119 (55.3)	107 (57.2)	12 (42.8)	0.15
Tumoral stage (%)				
Stage III	68 (31.6)	65 (34.7)	3 (10.7)	0.01
Stage IV	147 (68.4)	122 (65.3)	25 (89.3)	
CT±RT at the time of intervention (%)	193 (89.7)	167 (89.3)	25 (89.2)	0.99
Median duration of CT (months)*	7.4 (4.7-8.3)	7.7 (4.7-8.2)	7.2 (4.8-7.9)	0.12
Interval from diagnosis to neurolysis (months)*	5.8 (2.7-6.5)	3.9 (2.7-6.2)	5.9 (4.7-6.5)	0.03
Sarcopenia (%)	139 (64.6)	116 (62)	23 (82.1)	0.03

*Compared by means of log-rank test. Continuous variables are reported as median values and range. Comparisons were performed by Kruskal-Wallis test for continuous variables and Chi-square test for categorical ones. BMI: Body mass index; ASA: American Society of Anesthesiology; CT: Chemotherapy; RT: Radiotherapy; VAS: Visual Analog Scale.

Table 2. Pain control outcomes after EUS celiac plexus neurolysis

Variable	Overall (*n*=215)	Sarcopenia (*n*=139)	NonSarcopenia (*n*=76)	P
Pain relief	187 (86.9)	116 (83.4)	71 (93.4)	0.03
Onset of pain relief (days)	3 (2-6)	5 (2-6)	3 (2-5)	0.10
Duration of pain relief (weeks)	11 (8-16)	8 (2-10)	15 (8-16)	0.01
Complete pain response	27 (12.5)	5 (3.5)	22 (28.9)	<0.001
VAS score reduction (%)	64 (13-75)	31 (12-40)	73 (23-75)	0.02
Reduction in opioid use	64 (29.7)	26 (18.7)	38 (50)	<0.001
Reduction in opioid dosage (%)	33.1 (29.3-52.2)	28.2 (14.3-41.2)	43.4 (33-52.2)	0.02

Variables expressed as absolute *n* (%) and median (95% CI) when appropriate. Comparisons were performed through the Chi-square test in the case of categorical variables, Kruskall-Wallis test in the case of continuous variables and log-rank test in the case of time-to-event data. CI: Confidence interval; VAS: Visual analog scale.

P = 0.03) in the univariate analysis and 0.39 (0.21–0.98; *P* = 0.04) in the multivariate model.

No severe treatment-related AEs were reported in the whole study population, and no difference was observed between the two groups [Table 4]. Mild diarrhea was reported in 33 patients (23.7%) in Group 1 and 19 (25%) in Group 2 (*P* = 0.83), whereas 26 (18.7%) and 17 (22.3%) patients experienced Grade 1/2 fever in the two groups, respectively (*P* = 0.5). Postprocedural mild abdominal pain was recorded in 48 (34.5%)

patients in Group 1 and 23 (30%) patients in Group 2 (*P* = 0.47). None of the treated patients experienced any cases of severe pancreatitis, whereas mild pancreatitis (mild abdominal pain with a slight increase in pancreatic enzymes) was observed in 41 patients (29.4%) in Group 1 and 19 patients (25%) in Group 2 (*P* = 0.44).

DISCUSSION

Given the suboptimal results either in terms of pain control and duration of pain relief of EUS-CPN, several clinical and tumoral features able to influence treatment outcomes have been studied. Among them, tumoral characteristics or technical variables related to the procedure were found to be reliable prognostic factors in this setting;[20,21] lower quality of evidence seems to suggest a role of clinical or anthropometric parameters in this regard.

Sarcopenia and cachexia represent well-known predictors of poorer outcomes in several malignancies. In fact, the occurrence of these conditions in cancer patients depends on the host response to tumor progression, including activation of the inflammatory response and energetic inefficiency involving the mitochondria.[22] Evidence has revealed that sarcopenia results from the spill-over effects of cytokine production by tumors on individual organs, leading to anorexia, muscle
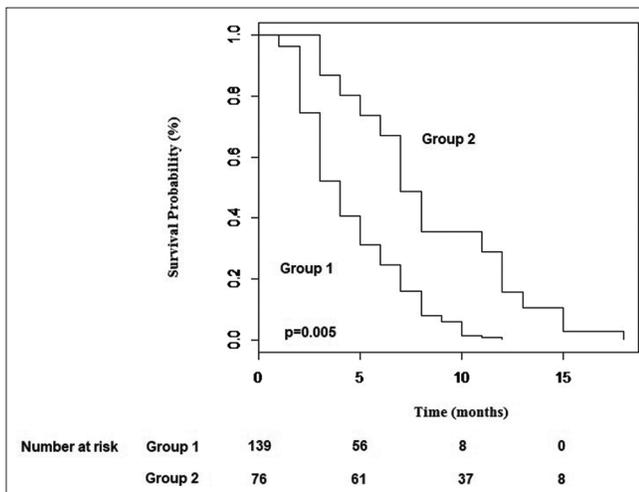

Figure 2. Kaplan–Meier curves of overall survival stratified by the study group. Median overall survival after celiac plexus neurolysis was 4 months (3–5) in sarcopenic patients (Group 1) and 7 months (6–8) in nonsarcopenic patients (Group 2; *P* = 0.05)

Table 3. Logistic regression analysis of predictors for pain relief

Variables	Univariate analysis, OR (CI 95%)	*P*	Multivariate analysis, OR (CI 95%)	*P*
Age (reference≤60 years)	1.05 (0.95-1.09)	0.32		
Gender (reference male)	1.02 (0.63-1.83)	0.92		
BMI (reference≤20)	1.12 (0.87-1.32)	0.23		
ASA (reference 1)	1.09 (0.75-1.55)	0.49		
VAS score (reference≤7)	0.89 (0.67-1.14)	0.35		
Opioid use (reference no)	0.88 (0.59-1.26)	0.39		
Tumor diameter (reference≤40 mm)	0.87 (0.68-1.23)	0.54		
Cancer location (reference head)	0.84 (0.69-1.17)	0.32		
Tumoral stage (reference III)	0.22 (0.06-0.77)	0.01	0.23 (0.11-0.85)	0.01
Interval from the diagnosis to neurolysis (reference ≤3 months)	0.27 (0.11-0.85)	0.03	0.32 (0.15-0.89)	0.04
Sarcopenia (reference no)	0.35 (0.12-0.97)	0.03	0.39 (0.21-0.98)	0.04

CI 95%: Confidence interval 95%; BMI: Body mass index; ASA: American Society of Anesthesiology; VAS: Visual analog scale; OR: Odds ratio.

Table 4. Adverse events observed after EUS celiac plexus neurolysis

Event	Overall (*n*=215)	Sarcopenia (*n*=139)	Nonsarcopenia (*n*=76)	*P*
Mild diarrhea (%)	52 (24.1)	33 (23.7)	19 (25)	0.83
Mild fever (%)	43 (20)	26 (18.7)	17 (22.3)	0.5
Mild abdominal pain (%)	71 (33)	48 (34.5)	23 (30)	0.47
Mild pancreatitis (%)	60 (27.9)	41 (29.4)	19 (25)	0.44

Variables expressed as absolute *n* (%) and comparisons were performed through the Chi-square test

wasting, fatigue, loss of adipose tissue, and increased lipolysis involving several signaling pathways and metabolites.[23] All these metabolic alterations, in addition to the increased levels of several proinflammatory cytokines such as IL-6, IL-8, and TNF-α,[15] represent an unfavorable condition which contributes to the dismal prognosis of advanced-stage cancer patients.

In our study, we used pretreatment planning CTs to evaluate the association between skeletal muscle radiographic features and treatment outcomes in PC patients undergoing EUS-CPN.

Although the prognostic role of sarcopenia in PC has already been described,[11-14] to the best of our knowledge, this is the first report on the correlation between sarcopenia and treatment outcomes of palliative therapy, such as EUS-guided CPN.

We retrospectively reviewed our cohort of 215 patients treated with EUS-CPN with baseline anthropometric measures, of which 139 patients (64.6%) were defined as sarcopenic.

Pain relief, defined according to commonly accepted criteria,[8] was registered overall in 187 (86.9%) patients, of which only 27 (12.5%) obtained a complete pain response. After stratification of the study population, according to CT scan determination of body composition, 83.4% of sarcopenic patients *versus* 93.4% of nonsarcopenic subjects experienced the pain response ($P = 0.03$). Similarly, the rate of complete pain response and the duration of the pain relief were statistically significantly more favorable in the absence of sarcopenia (28.9% *vs.* 3.5% and 15 weeks *vs.* 8, respectively; $P < 0.001$ and $P = 0.01$). As a consequence, also the reduction in opioid use, one of the main advantages of EUS-CPN, was more frequent in nonsarcopenic patients (50% *vs.* 18.7%).

As already observed in other series,[11-14] sarcopenia also showed an impact on OS, which resulted significantly prolonged in nonsarcopenic patients (7 months as compared to 4; $P = 0.05$).

Sarcopenia, in addition to other expected oncological parameters (tumoral stage and interval between diagnosis and treatment), resulted in a significant predictor of poorer outcomes both in univariate and multivariate analyses (OR 0.35; $P = 0.03$). The independent prognostic role of sarcopenia was confirmed in the multivariate analysis, thus confirming its predictive value regardless of other tumoral or clinical features.

In this study, more than half of patients were defined as sarcopenic. Malnutrition, pain, infection, and decrease in physical activity were the important factors of sarcopenia. In PC, the nutritional impairment due to the insufficiency of pancreatic exocrine and endocrine function, other metabolic factors, pain and infections may promote the development of sarcopenia. Therefore, it is important to treat such nutritional problems, pain, and infection to prevent the sarcopenia-related complications in such malignancy.

On the other hand, as already described in other reports,[11-14] sarcopenia does not seem to correlate with increased rates of complications after the treatment, and our data support the excellent safety profile of EUS-CPN as no severe treatment-related AEs nor deaths were observed throughout the follow-up.

The current manuscript has some limitations. First, the retrospective nature of the study which could have led to selection or outcome report biases. Second, the heterogeneity in the definition of sarcopenia as there are various methods for measuring muscle mass using CT and an unequivocal method have not been established yet. In particular, the thresholds adopted in our study could not been applicable to Asian patients, as demonstrated in the several Eastern reports.[13] Third, this series reported no objective documentation of functional improvement or quality of life. Fourth, the single-center nature of the study did not allow us to externally validate our results.

CONCLUSIONS

Despite the aforementioned limitations of our report, the results of this study show that pain response following EUS-CPN is generally less pronounced and more transient in the presence of sarcopenia. Our results might help the clinician to identify the best candidates to EUS-CPN, thus decreasing the risk to offer the treatment to patients very unlikely to benefit both in terms of pain relief and survival. Prospective studies are necessary to confirm our results and to identify the best candidates for EUS-CPN.

Conflicts of interest

There are no conflicts of interest

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