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Survival analysis of the metastatic cohort of Italian Association of Medical Oncology (AIOM) GARIBALDI survey

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ABSTRACT

This analysis from the GARIBALDI study was aimed to address the role of center self-declared expertise, type and commitment on the overall survival (OS) of patients with metastatic Pancreatic Ductal Adenocarcinoma (mPDAC).

Treatment-naïve patients ≥18-year with pathological diagnosis of mPDAC were enrolled. OS was defined as the time from chemotherapy start to death from any cause. The impact of clinical-demographic and centers characteristics on OS was evaluated using Cox models.

Between July 2017 and October 2019, 473 patients enrolled in 43 centers were eligible for this analysis. Median age was 69.3 (first-third quartile 61.2–74.5); 46.1 % females; 90.8 % ECOG PS 0–1; 67.4 % had liver metastases; median CA19.9700.5 UI/mL (first-third quartile 77.5-6629.5). For 37.1 % of patients chemotherapy started <4 weeks from diagnosis; 69.9 % of patients received nab-paclitaxel + gemcitabine; 16.9 % gemcitabine alone; 7.6 % FOLFIRINOX. The median follow-up was 51.8 months and 428 patients died. No statistically significant role of the type of institution was observed. Additionally, no statistically significant role of neither the self-declared expertise nor the accrual rate was observed.

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The GARIBALDI study suggests that the self-declared center expertise and the academic brand are not associated to OS in patients with mPDAC, while center commitment warrants further exploration.
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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a rare disease accounting for only 2.6 % of new cases of cancer. It is characterized by a poor prognosis with a 5-year overall survival (OS) rate of 11 % for all stages combined [1], dropping to 2–3% for metastatic disease, this latter setting representing >50 % of cases at diagnosis [1]. The diagnostic work-up and the therapeutic management of rare diseases is particularly complex because of limited expertise of most centers. The relationship of centralized surgical management with improved patient outcomes has consistently been shown e.g. in sarcomas [2]. Similarly, the relationship between surgical center, pancreaticoduodenectomy volume and operative mortality of patients with PDAC is well known [3] and, accordingly, different centralization models were proposed in Europe, using a minimum surgical volume requirement eventually in combination with a mortality rate threshold adjusted for co-variables [4,5]. However, the vast majority of patients affected by PDAC are diagnosed with a late stage disease and do not have any surgical indication. Keeping also in mind the palliative context, metastatic PDAC is particularly challenging to handle due to a number of reasons including frequent tumor- and treatment-related serious complications requiring a complex multidisciplinary approach. Limited information is available on the impact of hospital expertise on the outcome of oncological treatment in metastatic PDAC.

The GARIBALDI (Guideline Application in Real world: multi-Institutional Based survey of Adjuvant and first-Line pancreatic Ductal adenocarcinoma treatment in Italy) national, multicenter, prospective survey collected data on the therapeutic management of treatment-naïve patients with PDAC in a real world context to evaluate the agreement with national recommendations included in Italian Association of Medical Oncology (AIOM) guidelines. The aim of this analysis was to explore the impact of oncology center volume, type and commitment on the OS of chemo-naïve patients with metastatic PDAC.

2. Material and methods

The process of center selection for the GARIBALDI trial has been previously described [6]. Briefly, 46 centers representative of different geographical and expertise areas were involved in the survey.

According to patients' inclusion criteria, all chemotherapy and radiotherapy-naive patients aged ≥18 years with a pathological diagnosis of PDAC, candidate to receive active follow-up or treatment in the participating institutions, irrespective of stage, therapeutic management, and performance status, were eligible for this survey. Patients with prior surgery or other previous or concomitant malignancies were considered eligible.

The GARIBALDI study complied with the Declaration of Helsinki, was conducted per Good Clinical Practice (GCP) guidelines, and was approved by the Ethics Committees of all study sites. All patients provided written informed consent before enrolment.

After obtaining the informed consent to study participation and data processing, eligible patients were centrally registered by a web system, accessible 24 h a day at this address: http://GARIBALDI.aiom.it. All registered patients received a unique identification number before any study specific procedures was performed.

Data collected were pseudonymized in order to guarantee the protection of privacy as for D. Lgs. 196/2003 and Del n. 52, July 24, 2008 and for the GDPR 679/16 - "European regulation on the protection of personal data". Data collection was electronically done throughout a remote data-entry, allowing integrity and transparency of data and maintaining memory of the changes done.

This survey was sponsored by AIOM that played the role of not-for-profit Sponsor. It was supported by Celgene Italia with an unrestricted economical support for costs related to data collection and management, generation of electronic Case Report Form (eCRF) for remote data-entry, data quality control, central and local monitoring, and statistical analysis. Celgene Italia had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility to submit for publication.

The survey was divided prospectively in two periods due to the change in the national recommendations' statements in the 2019. The first period includes patients enrolled until October 31, 2019 and referring to the AIOM guidelines of 2017 and 2018; the second period, in which the AIOM guidelines of 2019–2021 are considered, was closed on November 2022.

Patients enrolled in the GARIBALDI study during the first period with a metastatic disease and receiving a chemotherapy treatment were considered for this paper.

The patients were categorized based on specific characteristics of the institutions in which they were treated, i.e., A) self-declared expertise (high-volume with >50 patients with PDAC treated/year; medium-volume with 25–50 patients treated/year; low-volume with <25 patients treated/year); B) type (academic; general hospital); and C) commitment (high-accrual with >50 patients/year; medium-accrual with 10–50 patients/year; low-accrual with <10 patients/year). Each center was categorized in a commitment group based on the accrual rate, calculated as the ratio of the total number of enrolled patients, irrespective of study period, and the time extent of active status into the study of the institution.

No formal hypothesis testing was planned for this analysis also due to the lack of available benchmarks for the topic in the literature.

The median follow-up, calculated by means of the reverse Kaplan-Meier (KM) method, and the follow-up completeness, defined as the proportion between the observed and potential follow-up, are provided. The potential follow-up is defined as the time from the start of follow-up to death or data snapshot, whichever comes first.

OS was defined as the time from the date of the chemotherapy start to death from any cause. Subjects alive and lost to follow-up were censored at the last date on which they were known to be alive. Survival curves were estimated by the KM method and compared using the log-rank test.

The effect of the institutions' characteristics described above on the OS was evaluated using the univariable and multivariable Cox proportional hazard models. All the multivariable models included demographical (age and sex) and clinical (body mass index, ECOG performance status, baseline CA 19-9, liver metastases, time from metastatic disease diagnosis to chemotherapy) prognostic

characteristics. Results of the analysis were expressed as hazard ratios (HRs) and 95 % confidence intervals (95 % CIs).

Continuous variables were summarized by mean, standard deviation, first quartile (Q1), median, third quartile (Q3), ranges (minimum and maximum) and number of missing values. Categorical variables were summarized by frequency and proportion of each subject in each category. The chi-square test and the Fisher test, as appropriate, were carried out to compare the distributions of categorical variables. The Student's T test and the Kruskal-Wallis test, as appropriate, were carried out to compare the distributions of continuous variables.

All analyses were done with SAS software, version 9.4 (SAS Institute).

3. Results

The data snapshot was performed on March 01, 2024. Between July 2017 and October 2019, 907 eligible patients were enrolled in the GARIBALDI study. Overall, 492 (54.2 %) patients were diagnosed with a metastatic disease. Out of these, 19 were not treated. Therefore, 473 patients, enrolled by 43 out of 46 centers, were considered for this analysis. Of these, 19 were academy centers and 24 where community centers; 8 had a low self-declared expertise of patients, 14 had a middle expertise and 18 had a high expertise, while 3 did not declare their expertise. As for commitment 31 centers resulted as low committed, 11 as mid committed and only one as high committed center. Characteristics of patients, tumor, diagnostic process, and treatment in the whole population and according to type of institution, self-declared expertise, and commitment are reported in Tables 1, 2, and 3, respectively.

Overall, median age was 69.3 years (first-third quartile 61.2–74.5); 218 (46.1 %) patients were females, 420 (90.8 %) patients had an ECOG score 0–1, median CA19.9 value was 700.5 UI/ml (first-third quartile 77.5–6629.5), 319 (67.4 %) patients had liver metastases, 168 (36.5 %) patients were overweight/obese, 82 (17.4 %) patients had prior cancer history. The first consulted physician was an oncologist for 10 (2.1 %) patients and a surgeon in 68 (14.6 %). The chemotherapy started less than 4 weeks from pathologic diagnosis and from CT baseline scan in 168 (37.1 %) and in 165 (36.7 %) cases, respectively.

Nab-paclitaxel + gemcitabine was the regimen most often administered (330 patients; 69.9 %), followed by single agent gemcitabine (80 patients; 16.9 %), and FOLFIRINOX (36 patients; 7.6 %). Among patients treated with gemcitabine alone, 62 (77.5 %) were 75 years or older or/and had a ECOG PS equal to 2 or higher (data not shown). Considering the characteristics of the institutions, 242 (51.2 %) and 231 (48.8 %) patients were treated in an academic institution and in a general hospital, respectively; 259 (57.8 %), 126 (28.1 %) and 63 (14.1 %) patients were treated in a self-declared high-, medium- and low-volume centers, respectively; 61 (12.9 %), 200 (42.3 %) and 212 (44.8 %) patients were treated in high-, medium- and low-accrual centers, respectively. Notably, only one center reached the threshold to be defined as a high-accrual center. As reported in Tables 1–3, no statistically significance differences were found between the analyzed groups in terms of baseline characteristics of patient and tumor, and of diagnostic process duration, with a few exceptions for age, sex, ECOG PS, interval between pathologic diagnosis and treatment start and type of chemotherapy regimen chosen. With regard to chemotherapy regimen, nab-paclitaxel + gemcitabine was universally the preferred treatment followed by gemcitabine, while FOLFIRINOX was overall rarely recommended. Namely, the single high-accrual center, never recommended FOLFIRINOX use.

A median follow-up of 51.8 months was observed with a follow-up completeness of 74.0 %. Overall, 428 (90.5 %) patients died.

Table 1
Patients characteristics by type of institution.

	Academy N = 242	Community N = 231	P-value
Age (years)			0.0401[a]
Mean (SD)	66.8 (9.4)	68.6 (9.5)	
Median (Q1 - Q3)	68.5 (60.4 −73.1)	69.9 (62.2 −75.4)	
Min - Max	41.7–89.1	35.9–86.3	
Gender – n (%)			0.9316[c]
Male	130 (53.7)	125 (54.1)	
Female	112 (46.3)	106 (45.9)	
BMI (Kg/m2)			0.0328[a]
Mean (SD)	24.3 (3.9)	23.6 (3.8)	
Median (Q1 - Q3)	23.9 (21.6 −27.0)	23.5 (20.8 −26.1)	
Min - Max	14.9–35.5	13.8–34.8	
Missing	4	9	
ECOG PS – n (%)			0.6113[b]
0	122 (50.4)	107 (48.4)	
1	99 (40.9)	92 (41.6)	
2+	21 (8.7)	22 (10.0)	
Missing	0	10	
Baseline CA 19-9 – n (%)			0.0602[b]
CA 19-9 ≤ 200 UI/mL	84 (36.7)	61 (30.0)	
200 UI/mL < CA 19-9 < 3150 UI/mL	78 (34.1)	66 (32.5)	
CA 19-9 ≥ 3150 UI/mL	67 (29.3)	76 (37.4)	
Missing	13	28	
Liver metastasis - n (%)			0.6645[c]
No	81 (33.5)	73 (31.6)	
Yes	161 (66.5)	158 (68.4)	
Chemotherapy regimen administered – n (%)			0.1059[c]
Nab-paclitaxel + Gemcitabine	174 (71.9)	156 (67.8)	
Gemcitabine	38 (15.7)	42 (18.3)	
FOLFIRINOX	13 (5.4)	23 (10.0)	
Other	17 (7.0)	9 (3.9)	
Missing	0	1	
Weeks from diagnosis to chemotherapy start			0.1194[c]
Less than four weeks	78 (32.9)	90 (41.7)	
Between four and six weeks	70 (29.5)	61 (28.2)	
More than six weeks	89 (37.6)	65 (30.1)	
Missing	5	15	

Legend: N: number of patients; SD: standard deviation; Q1 - Q3: First – third quartile; Min - Max: minimum – maximum values; BMI: body mass index; ECOG PS: Eastern cooperative oncology group performance status.
[a] Student's T test.
[b] Kruskal-Wallis' test.
[c] Chi squared test.

Supplementary Table 1 shows the results of univariable analysis. The multivariable analyses are provided in Table 4.

Median OS was 10.2 (95%CI 9.3–11.4) months in academic institutions and 8.1 (95%CI 6.9–9.8) months in general hospital (HR 1.10, 95%CI 0.91–1.33; p-value 0.33). These results were confirmed by the multivariable analysis (HR 1.04, 95%CI 0.83–1.30; p-value 0.76).

KM survival curves of overall survival according to the type of institution are depicted in Fig. 1, panel A.

Similarly, no statistically significant difference was observed between high-volume centers (median OS 10.3 months, 95%CI 9.6–11.5) and medium-volume centers (median OS 8.1 months, 95% CI 6.4–10.5; HR 1.11, 95%CI 0.88–1.39; p-value 0.37) or low-volume institutions (median OS 7.4 months, 95%CI 6.4–9.6; HR 1.28, 95%CI 0.96–1.71; p-value 0.09). The multivariable analysis confirmed the lack of statistically significant difference among groups (medium-volume vs high-volume: HR 0.95; 95%CI 0.72–1.25; p-value 0.73; low-volume vs high-volume: HR 1.14; 95%CI 0.83–1.57; p-value 0.45).

Table 2
Patients characteristics by self-declared expertise.

	<25 pancreatic pts/year N = 63	25-50 pancreatic pts/year N = 126	>50 pancreatic pts/year N = 259	P-value
Age (years)				0.0552[a]
Mean (SD)	70.3 (8.3)	68.1 (9.3)	67.2 (9.5)	
Median (Q1 - Q3)	71.6 (65.5 −76.9)	69.5 (60.9 −74.0)	68.5 (60.6 −74.0)	
Min - Max	49.2–85.7	45.1–86.3	41.7–89.1	
Gender – n (%)				0.6232[b]
Male	36 (57.1)	72 (57.1)	136 (52.5)	
Female	27 (42.9)	54 (42.9)	123 (47.5)	
BMI (Kg/m2)				0.4656[a]
Mean (SD)	23.7 (4.0)	23.8 (3.6)	24.2 (3.9)	
Median (Q1 - Q3)	22.8 (20.8 −26.2)	23.9 (20.9 −26.4)	23.8 (21.5 −26.7)	
Min - Max	17.6–34.8	17.2–32.6	13.8–35.5	
Missing	0	2	11	
ECOG PS – n (%)				0.0197[a]
0	20 (31.7)	66 (56.4)	131 (50.8)	
1	37 (58.7)	39 (33.3)	105 (40.7)	
2+	6 (9.5)	12 (10.3)	22 (8.5)	
Missing	0	9	1	
Baseline CA 19-9 – n (%)				0.1192[a]
CA 19-9 ≤ 200 UI/mL	16 (26.2)	33 (28.4)	87 (37.5)	
200 UI/mL < CA 19-9 < 3150 UI/mL	21 (34.4)	41 (35.3)	74 (31.9)	
CA 19-9 ≥ 3150 UI/mL	24 (39.3)	42 (36.2)	71 (30.6)	
Missing	2	10	27	
Liver metastasis - n (%)				0.9691[b]
No	21 (33.3)	40 (31.7)	85 (32.8)	
Yes	42 (66.7)	86 (68.3)	174 (67.2)	
Chemotherapy regimen administered – n (%)				0.0368[b]
Nab-paclitaxel + Gemcitabine	40 (63.5)	92 (73.0)	181 (70.2)	
Gemcitabine	17 (27.0)	22 (17.5)	38 (14.7)	
FOLFIRINOX	1 (1.6)	10 (7.9)	20 (7.8)	
Other	5 (7.9)	2 (1.6)	19 (7.4)	
Missing	0	0	1	
Weeks from diagnosis to chemotherapy start				0.0131[a]
Less than four weeks	14 (24.6)	58 (47.9)	87 (34.8)	
Between four and six weeks	22 (38.6)	31 (25.6)	71 (28.4)	
More than six weeks	21 (36.8)	32 (26.4)	92 (36.8)	
Missing	6	5	9	

Legend: N: number of patients; SD: standard deviation; Q1 - Q3: First – third quartile; Min - Max: minimum – maximum values; BMI: body mass index; ECOG PS: Eastern cooperative oncology group performance status.
Note: The table includes 448 patients from centers with known hospital expertise.
[a] Kruskal-Wallis test.
[b] Chi squared test.

Table 3
Patients characteristics by commitment.

	<10 pancreatic pts/year N = 212	10-50 pancreatic pts/year N = 200	>50 pancreatic pts/year N = 61	P-value
Age (years)				0.2194[a]
Mean (SD)	67.5 (9.7)	68.4 (9.2)	66.0 (9.8)	
Median (Q1 - Q3)	69.3 (60.9 −74.2)	69.5 (62.8 −75.2)	68.5 (58.2 −72.5)	
Min - Max	41.7–87.0	35.9–89.1	44.8–87.6	
Gender – n (%)				0.0076[b]
Male	107 (50.5)	123 (61.5)	25 (41.0)	
Female	105 (49.5)	77 (38.5)	36 (59.0)	
BMI (Kg/m2)				0.5711[a]
Mean (SD)	23.8 (4.0)	24.1 (3.7)	24.3 (3.7)	
Median (Q1 - Q3)	23.7 (20.8 −26.4)	23.8 (21.6 −26.3)	23.7 (21.4 −27.5)	
Min - Max	14.9–34.8	13.8–35.5	18.3–33.3	
Missing	4	7	2	
ECOG PS – n (%)				0.0283[a]
0	91 (44.4)	112 (56.9)	26 (42.6)	
1	96 (46.8)	69 (35.0)	26 (42.6)	
2+	18 (8.8)	16 (8.1)	9 (14.8)	
Missing	7	3	0	
Baseline CA 19-9 – n (%)				0.5125[a]
CA 19-9 ≤ 200 UI/mL	63 (32.6)	59 (33.0)	23 (38.3)	
200 UI/mL < CA 19-9 < 3150 UI/mL	60 (31.1)	64 (35.8)	20 (33.3)	
CA 19-9 ≥ 3150 UI/mL	70 (36.3)	56 (31.3)	17 (28.3)	
Missing	19	21	1	
Liver metastasis - n (%)				0.0963[b]
No	68 (32.1)	59 (29.5)	27 (44.3)	
Yes	144 (67.9)	141 (70.5)	34 (55.7)	
Chemotherapy regimen administered – n (%)				0.0578[b]
Nab-paclitaxel + Gemcitabine	145 (68.4)	135 (67.8)	50 (82.0)	
Gemcitabine	37 (17.5)	36 (18.1)	7 (11.5)	
FOLFIRINOX	15 (7.1)	21 (10.6)	0 (0.0)	
Other	15 (7.1)	7 (3.5)	4 (6.6)	
Missing	0	1	0	
Weeks from diagnosis to chemotherapy start				0.4237[a]
Less than four weeks	72 (36.4)	71 (36.6)	25 (41.0)	
Between four and six weeks	56 (28.3)	54 (27.8)	21 (34.4)	
More than six weeks	70 (35.4)	69 (35.6)	15 (24.6)	
Missing	14	6	0	

Legend: N: number of patients; SD: standard deviation; Q1 - Q3: First – third quartile; Min - Max: minimum – maximum values; BMI: body mass index; ECOG PS: Eastern cooperative oncology group performance status; CT: computerized tomography; NE: not evaluable.
[a] Kruskal-Wallis test.
[b] Chi squared test.

KM survival curves of overall survival according to the pancreatic self-declared expertise of the hospital are provided in Fig. 1, panel B.

No statistically significant difference was also observed between the single high-accrual institution (median OS 12.3 months, 95%CI 10.2–15.5) and the medium-accrual (median OS 9.6 months, 95%CI 8.3–10.9; HR 1.25, 95%CI 0.93–1.67; p-value 0.14) or the low-accrual centers (median OS 8.1 months, 95%CI 6.9–9.8; HR 1.19, 95%CI 0.88–1.60; p-value 0.25). Albeit the increase of hazard for death higher than 20 % is clinically relevant, the multivariable analysis confirmed the lack of statistically significant OS differences among the three groups (medium-accrual vs high-accrual HR 1.16; 95%CI 0.84–1.61; p-value 0.36; low-accrual vs high-accrual HR 1.28; 95%CI 0.92–1.77; p-value 0.14).

KM survival curves of overall survival according to the centers commitment are provided in Fig. 1, panel C.

In multivariable analyses, older age, worse ECOG PS, the presence of liver metastases, a higher baseline CA19.9 value, the treatment with gemcitabine alone and a shorter time interval between pathologic diagnosis and chemotherapy start, were significantly correlated to a worse OS, while no association was found for sex and BMI class, as shown in Table 4.

4. Discussion

The present analysis of the role of center characteristics on OS in the cohort of treated patients with metastatic PDAC enrolled in the GARIBALDI study does not show statistically significant differences in OS between patients treated in academic versus general hospitals, in low-versus medium- and versus high self-declared volume, and in low-versus medium-versus high-accrual institutions.

Our findings are in line with previous reports addressing the

Table 4
Impact of recruiting centers' charachteristics and demographic and clinicopathologic characteristics on overall survival. Multivariable Cox proportional hazard models.

	Type of institution (N = 398)		Hospital self-declared expertise (N = 375)		Overall commitment (N = 398)	
	HR (95 % CI)	P-value	HR (95 % CI)	P-value	HR (95 % CI)	P-value
General hospital vs academy	1.04 (0.83–1.30)	0.7562				
Hospital self-declared expertise (ref. >50 pancreatic pts/year)				0.6405		
<25 pancreatic pts/year			1.14 (0.83–1.57)	0.4473		
25-50 pancreatic pts/year			0.95 (0.72–1.25)	0.7260		
Overall commitment (ref. >50 pancreatic pts/year)						0.3210
<10 pancreatic pts/year					1.28 (0.92–1.77)	0.1383
10-50 pancreatic pts/year					1.16 (0.84–1.61)	0.3633
Age (one year increase)	1.02 (1.00–1.03)	0.0295	1.02 (1.00–1.03)	0.0113	1.01 (1.00–1.03)	0.0367
Male vs female sex	0.94 (0.76–1.17)	0.5868	0.91 (0.73–1.15)	0.4426	0.94 (0.75–1.17)	0.5857
BMI class (ref. Normal weight)		0.7988		0.5911		0.7895
Underweight	0.93 (0.61–1.42)	0.7505	0.88 (0.55–1.40)	0.5910	0.92 (0.61–1.40)	0.7079
Overweight	0.93 (0.73–1.19)	0.5488	0.89 (0.69–1.15)	0.3787	0.93 (0.73–1.19)	0.5708
Obese	0.83 (0.55–1.25)	0.3643	0.78 (0.51–1.18)	0.2355	0.82 (0.55–1.24)	0.3511
ECOG PS (ref. 0)		0.0278		0.1172		0.0173
1	1.26 (1.00–1.59)	0.0487	1.19 (0.93–1.51)	0.1660	1.27 (1.01–1.60)	0.0451
2+	1.60 (1.08–2.37)	0.0178	1.49 (0.99–2.23)	0.0565	1.68 (1.13–2.50)	0.0098
Baseline CA 19-9 (UI/mL) (ref. Up to 200)		0.0040		0.0023		0.0056
Higher than 200, lower than 3150	1.25 (0.96–1.62)	0.0921	1.27 (0.97–1.67)	0.0781	1.25 (0.96–1.62)	0.0985
3150 or higher	1.59 (1.21–2.08)	0.0009	1.65 (1.24–2.19)	0.0005	1.56 (1.19–2.05)	0.0013
Liver metastasis	1.48 (1.16–1.88)	0.0015	1.53 (1.19–1.98)	0.0011	1.46 (1.15–1.87)	0.0023
Chemotherapy regimen administered (ref. Nab-paclitaxel + Gemcitabine)		0.0022		0.0043		0.0020
Gemcitabine	1.84 (1.33–2.55)	0.0002	1.83 (1.31–2.56)	0.0004	1.85 (1.34–2.55)	0.0002
FOLFIRINOX	0.97 (0.61–1.55)	0.9006	1.06 (0.64–1.74)	0.8227	0.94 (0.59–1.49)	0.7865
Other	0.88 (0.53–1.47)	0.6206	0.91 (0.54–1.53)	0.7230	0.85 (0.51–1.42)	0.5287
Time from metastatic disease diagnosis to chemotherapy start (ref. More than six weeks)		0.0375		0.0406		0.0352
Less then four weeks	1.35 (1.04–1.77)	0.0265	1.39 (1.05–1.83)	0.0226	1.36 (1.05–1.77)	0.0219
Between four and six weeks	1.01 (0.77–1.32)	0.9540	1.04 (0.78–1.38)	0.8022	1.02 (0.78–1.34)	0.8923

Legend: N: number of patients; HR: hazard ratio; BMI: body mass index; ECOG PS: Eastern cooperative oncology group performance status.

role of type of institution (academic/community) in other diseases [7–9]. Indeed, the statistically significant differences in OS that were observed in these studies were of negligible clinical significance (HR ranged from 0.88 to 0.90) [7–9] and were not confirmed in multivariable analyses [9]. Overall, data suggest that the academic context does not necessarily warrant a better outcome.

Another variable that could potentially influence therapeutic management results is the center volume. Some previous analyses on the relationship between the institution's volume and survival in patients affected by various types of cancer have been reported [7,10–14]. These analyses, mainly addressing technically demanding procedures such as surgery or radiotherapy that require specific skills and competences that are available in a limited number of centers, reported conflicting results in different cancers [3–5,7,10–14]. When the overall therapeutic management was taken into account in other rare diseases, a statistically significant but negligible reduction (HR ranged from 0.85 to 0.92) or no difference in the risk of death between medium and high-volume centers, respectively, was mainly reported [15–17], albeit a statistically significant OS benefit was reported in other cases [18,19]. Globally, these results are likely related to the general organization of the multidisciplinary approach, to the interaction between different specialists within a center, and to the therapeutic strategy and sequence that the local team identified among different available options. Consistently, a difference in OS was observed even among high volume hospitals based on a wide variation in the utilization of neoadjuvant chemotherapy to treat epithelial ovarian cancer [20]. Furthermore, all the above-mentioned studies were based on National Cancer Databases that collected data during a protracted extent of time (4–16 years) during which therapeutic guidelines and treatment approach possibly changed, thus hampering the chance of identifying the independent role of center volume in determining the patients' outcome due to the large number of confounding factors, including private insurance, annual income, and education [7–20]. Conversely, our study had the different perspective to focus on a more selected oncological setting of palliative chemotherapy for a disease with a very limited number of therapeutic options, in the context of a Country without census or insurance disparities in the access to the cure, and by means of a prospectively collected dataset in a sharply framed time-period of 2 years during which guidelines remained unmodified. Accordingly, the GARIBALDI study had the strength to address more specifically the physician's skill and expertise in managing the same few therapeutic instruments in the context of centers with different volume. The lack of a relationship between volume and OS was also previously reported by another larger study that was performed based on the Danish Pancreatic Cancer Database on PDAC patients treated between 2012 and 2018 in which the outcome difference was related to more use of combination chemotherapy (66 % versus 41 %) rather than to center volume [21]. Albeit an excess risk of death for patients treated at secondary facilities was observed (HR1.16, 95%CI 1.07–1.27; median OS 7.7 months in tertiary and 6.1 months in secondary facilities), the outcome difference was more related to the use of a combination chemotherapy strategy (66 % versus 41 %) rather than to center volume [21].

While the absence of any impact on OS of center volume or of type of institution seems reassuring for the patients' choice of the site in which receiving therapy, it should be reminded that the GARIBALDI study, in the absence of an Italian National Cancer Database, was planned to verify the AIOM guidelines application and a possible limitation was the selection of centers that may not

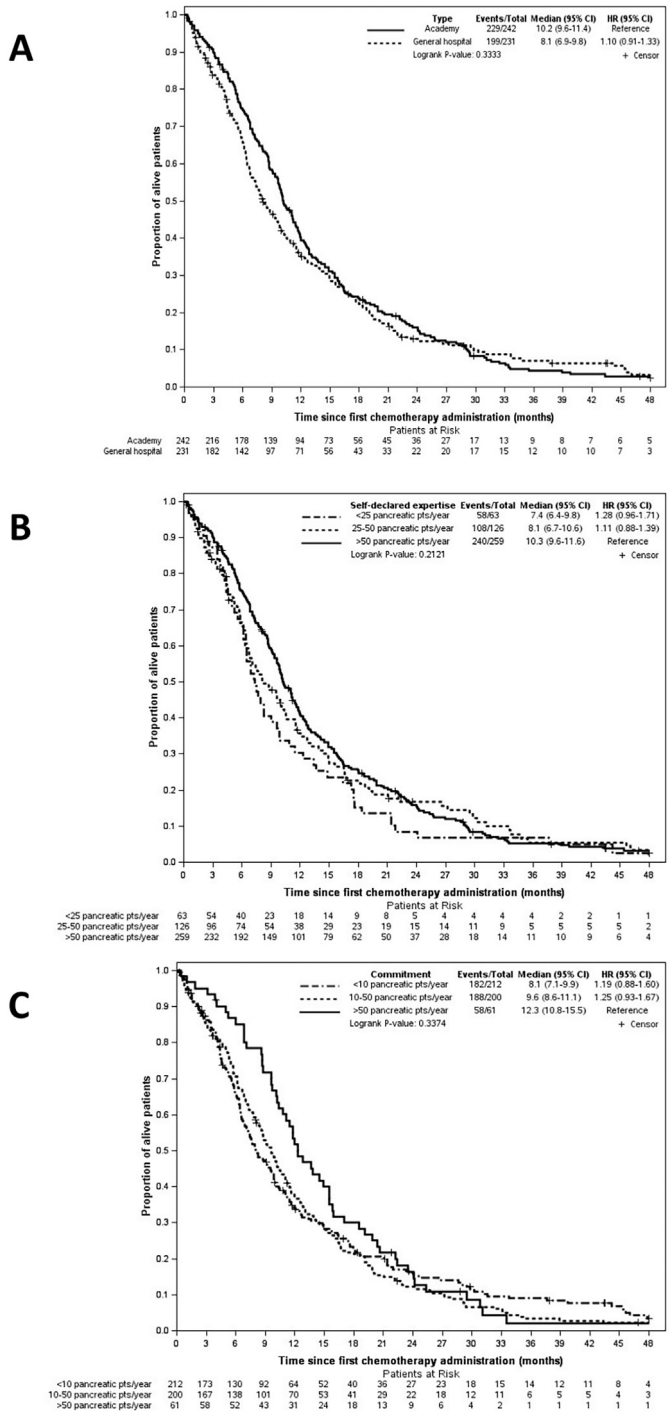

Fig. 1. (A) Kaplan-Meier curve of overall survival according to the type of institution; (B) Kaplan-Meier curve of overall survival according to the pancreatic self-declared expertise of the hospital; (C) Kaplan-Meier curve of overall survival according to the centers commitment.

be representative of the whole National scenario where knowledge and compliance with evidence-based medicine is not necessarily homogeneous. On the other hand, academic brand and numbers cannot be considered synonymous of a better treatment quality. Along the lines of this idea, we explored the role of the accrual rate, rather than the self-declared volume, as a proxy of center commitment to the disease. Actually, a clinically relevant numeric difference in median OS and hazard for death was observed in the high-accrual institution (median OS 12.3 months) compared to both medium- (+2.7 months; HR 1.25) and low-accrual centers (+4.2 months; HR 1.19). Albeit lacking a statistically significance, these figures warrant further analyses also because, in line with them, a worse survival in centers enrolling <10 patients was previously reported in an adjuvant PDAC trial [22]. The planned final analysis of the GARIBALDI study may provide further information to assess whether the center volume must be considered. In the case this hypothesis will be confirmed, the subsequent identification and validation of quality indicators, such as nutritional counselling, pancreatic exocrine insufficiency evaluation, chemotherapy dose-intensity, germ-line mutation screening etc., allowing the selection of hub referral centers for PDAC patients' management will became mandatory in view of providing them with the best possible care. Furthermore, quality indicators may allow planning focused educational interventions aimed at improving the global outcome of the disease.

In conclusion, the GARIBALDI study suggests that center volume and academic brand are not related to OS in patients with metastatic PDAC while center commitment warrants further exploration. The implementation of an Italian National PDAC database is eagerly expected. In the meanwhile, we are planning a prospective study for the **AN**alysis of quality **I**ndicators and their impact on the outcome of the oncologic **T**reatment for pancreatic **A**denocarcinoma (ANITA trial).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2024.10.002.

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