



Original Research

# Systematic versus on-demand early palliative care: results from a multicentre, randomised clinical trial



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Received 10 May 2016; accepted 7 June 2016

## KEYWORDS

Early palliative care;  
Quality of life;  
Quality of care

**Abstract Background:** Early palliative care (EPC) in oncology has been shown to have a positive impact on clinical outcome, quality-of-care outcomes, and costs. However, the optimal way for activating EPC has yet to be defined.

**Methods:** This prospective, multicentre, randomised study was conducted on 207 outpatients with metastatic or locally advanced inoperable pancreatic cancer. Patients were randomised to receive 'standard cancer care plus on-demand EPC' (n = 100) or 'standard cancer care plus systematic EPC' (n = 107). Primary outcome was change in quality of life (QoL) evaluated through the Functional Assessment of Cancer Therapy – Hepatobiliary questionnaire between baseline (T0) and after 12 weeks (T1), in particular the integration of physical, functional, and Hepatic Cancer Subscale (HCS) combined in the Trial Outcome Index (TOI).

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Patient mood, survival, relatives' satisfaction with care, and indicators of aggressiveness of care were also evaluated.

**Findings:** The mean changes in TOI score and HCS score between T0 and T1 were  $-4.47$  and  $-0.63$ , with a difference between groups of  $3.83$  (95% confidence interval [CI]  $0.10-7.57$ ) ( $p = 0.041$ ), and  $-2.23$  and  $0.28$  (difference between groups of  $2.51$ , 95% CI  $0.40-4.61$ ,  $p = 0.013$ ), in favour of interventional group. QoL scores at T1 of TOI scale and HCS were  $84.4$  versus  $78.1$  ( $p = 0.022$ ) and  $52.0$  versus  $48.2$  ( $p = 0.008$ ), respectively, for interventional and standard arm. Until February 2016, 143 (76.9%) of the 186 evaluable patients had died. There was no difference in overall survival between treatment arms.

**Interpretations:** Systematic EPC in advanced pancreatic cancer patients significantly improved QoL with respect to on-demand EPC.

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## 1. Introduction

Over the years, the palliative care (PC) professional community has attempted to change how PC is conceived, offering an interpretation that is not limited to hospice or end-of-life care. Although there is, in fact, more than one 'definition' for PC [1], it is acknowledged that it can be subdivided in two major areas: 'early' palliative care (EPC) and 'end-of-life' palliative care (EoL PC). EPC is mainly delivered through PC clinics for outpatients or through PC consultations for patients in inpatient units. EoL PC is more often performed in inpatient hospice and PC units. Although some regard 'home care hospice programmes' as a form of EPC [1], this is open to debate. For the purposes of this study, the concept of home care hospice programmes is considered a part of EoL PC.

Different outcomes have been studied for EPC, e.g. improved quality of life (QoL), better healthcare, and lower costs [2]. Results from several original studies and systematic reviews showed evidence in favour of EPC together with best anticancer treatment compared to the latter alone, although data were not uniformly positive [1,3–6]. When this study began, the presence of EPC in the management of advanced cancer patients was generally accepted [7] and it would have been anachronistic to consider a 'best anticancer treatment only' arm as the standard arm.

In clinical practice, however, oncologists tend to request the intervention of EPC professionals only when they feel that a situation is too complex to manage alone. One could say that the standard arm in oncology for EPC has become the 'best anticancer treatment plus on-demand EPC'. We considered the interventional arm as the best anticancer treatment plus systematic EPC, defined as planned, systematic EPC together with standard cancer care starting from the diagnosis of metastatic disease. PC, although in different ways, is so performed in both arms, as it was in the previous studies from other authors [4,5]. Reasonably, the first on-demand PC intervention is almost never an isolated event, with EPC subsequently performed on a continuous basis

to manage the needs of the patient also in the 'on-demand' approach.

We chose to evaluate patients with a highly lethal tumour such as pancreatic cancer. The 2008 global cancer incidence estimates ranked pancreatic cancer as 13th of the 20 most commonly diagnosed cancers worldwide (2%, about 250,000) [8]. In 2014, pancreatic cancer had the lowest 5-year relative survival (6%) of 30 classified tumours in the United States of America [9]. In 2008, pancreatic cancer was the eighth cause of death worldwide, accounting for 4% of all cancer deaths (304,000) [10]. In Europe, pancreatic cancer is currently the fifth (5.4%) cause of death from cancer in males and the fourth (6.7%) in females [11].

The aim of the present study was to compare the impact of 'standard cancer care + systematic EPC' with that of 'standard cancer care + on-demand EPC' on patient-reported outcomes, use of health services and quality of end-of-life care in patients with advanced gastric or pancreatic cancer who were candidates for antitumour treatment. This paper presents the clinical results from the pancreatic study population.

## 2. Materials and methods

### 2.1. Study design

From October 2012 to February 2015, we randomly enrolled patients with newly diagnosed metastatic pancreatic cancer to a multicentre, randomised study to receive either 'standard cancer care plus on-demand EPC' (standard arm) or 'standard cancer care plus systematic EPC' (interventional arm). The study was approved by the Ethics Committee of the participating centres and all patients provided written informed consent ([ClinicalTrials.gov](http://ClinicalTrials.gov) NCT01996540).

### 2.2. Patient selection

Eligibility criteria were as follows: diagnosis of inoperable locally advanced and/or metastatic pancreatic

cancer for a maximum of 8 weeks prior to enrolment; age  $\geq 18$  years; Eastern Cooperative Oncology Group (ECOG) performance status 0–2; life expectancy  $> 2$  months; and candidate for antitumour treatment (chemotherapy or target therapy). All newly referred patients were considered for participation in the study. Patients who were already receiving PC, who had received prior chemotherapy for metastatic or advanced disease, or who had participated in a clinical trial were not eligible.

### 2.3. Randomisation

Eligible patients were randomised for a maximum of 8 weeks after diagnosis and before anticancer treatment to one of the two groups on a 1:1 allocation rate. Separate randomisation lists using a permuted block balanced procedure were generated for each participating centre. No masking was involved in this open-label trial.

### 2.4. Study treatment and procedures

Patients assigned to the interventional arm had an appointment scheduled with a PC specialist who had a predefined checklist of issues to be addressed during the consultation. The use of the checklist by the individual researcher was not monitored from the outside, but reported by the researcher himself. The checklist of topics to be discussed during the visit of PC is the same used by Temel [4] and is reported in the original protocol.

Patients met a member of the PC team within 2 weeks of enrolment and were seen thereafter every 2–4 weeks until death. In both arms, availability between appointments not scheduled in the protocol, but according to the clinical and organisational solutions, was present in every centre. Moreover, every researcher could have adjunctive routine tools of assessment, not considered in the present study.

PC appointments and interventions were oriented by general PC guidelines [12]. The full-time PC specialist who regularly saw interventional arm patients could prescribe drugs and request other interventions pertaining to physical, psychological, and spiritual needs. However, recommendations made by the PC expert on decision making processes had to be shared by the oncologist. Patients assigned to the standard arm were not scheduled to meet the PC team unless they, their families, or the attending oncologist requested an appointment. After the evaluation period ( $T_1 = 12 \pm 3$  weeks from  $T_0$ ), patients were followed by the PC team as needed.

After informed consent was obtained ( $T_0 =$  date of randomisation), patients completed the QoL and mood questionnaires. At  $T_1$  ( $12 \pm 3$  weeks from  $T_0$ ), information on ECOG performance status, QoL, mood and family satisfaction about care was recorded. After the patient's death ( $T_2$ ), information on the use of health

services and EoL care, including anticancer therapy, referral to hospice, hospital admissions, emergency department visits, and the date and location of death, was collected.

### 2.5. Measures

Health-related QoL and physical symptoms were measured using the Functional Assessment of Cancer Therapy – Hepatobiliary (FACT-Hep) scale [13].

The FACT-Hep scale assesses generic QoL concerns (physical, social, emotional and functional well-being) and disease-specific issues (Hepatobiliary Cancer Subscale [HCS]). FACT-Hep scores range from 0 to 180 and HCS scores range from 0 to 72 (higher score is better). The Trial Outcome Index (TOI) combines the scores of physical, functional and disease-specific subscales [14] (score range 0–128).

Mood was assessed using the Hospital Anxiety and Depression Scale (HADS), a 14-item instrument composed of 2 subscales that screens for symptoms of anxiety and depression (score range 0–21, higher score indicates greater anxiety or depression; score  $> 7$  indicates borderline or clinical anxiety or depression) [15].

The impact of family satisfaction about care was evaluated by Italian version of the Family Satisfaction with the End-of-Life Care (FAMCARE) questionnaire. The FAMCARE is a 20-item scale and includes 4 subscales: information giving, physical patient care, psychosocial care and availability of care. Scores range from 20 to 100: the lower the score, the higher the family satisfaction [16]. The caregivers were considered 'the individual identified by the patient as the person most involved in the care of the patient. The relationship with the patient could be biological, legal, or functional' [17].

Licenses to use the Italian versions of the FACT-Hep and HADS questionnaires were obtained.

### 2.6. Statistical analysis

The primary objective of the study was to assess the effects of systematic EPC versus on-demand EPC consultation during standard cancer care on QoL and clinical symptoms. The TOI score evaluation was the primary end-point. Secondary objectives were symptom burden relief and mood, family satisfaction about care, use of health-care services location of death and overall survival (OS). End-points were the percentage of patients with anxiety and/or depression, the impact of family satisfaction about care, the use of healthcare services and OS.

The study was designed to enroll 240 patients with advanced gastric or pancreatic cancer who were candidates for antitumour treatment. This report presents the clinical results from the only pancreatic study population.

We estimated that, with 120 patients, the study would have 80% power to detect a significant between-group difference in the change in the TOI score between  $T_0$

and T1, with a medium effect size of 0.5 standard deviation (SD). We computed effect sizes as standardised mean differences (Cohen's *d*); effect size of at least 0.3 was considered clinically relevant.

Differences in clinical outcomes between study groups were assessed with the chi-square test for categorical variables and the Student's *t*-test or non-parametric ranking statistics (median test) for continuous variables.

OS was defined as the time from the date of randomisation to the date of death due to any cause. Patients who were still alive at the time of analysis (February 2016) were censored at their last date of follow-up. OS and 95% confidence intervals (95% confidence interval [CI]) were estimated with the Kaplan–Meier product-limit method.

The statistical analysis on the primary outcome (the change in the TOI score between T0 and T1) was performed by applying the multiple imputation method in order to handle missing data to achieve valid statistical inference [18].

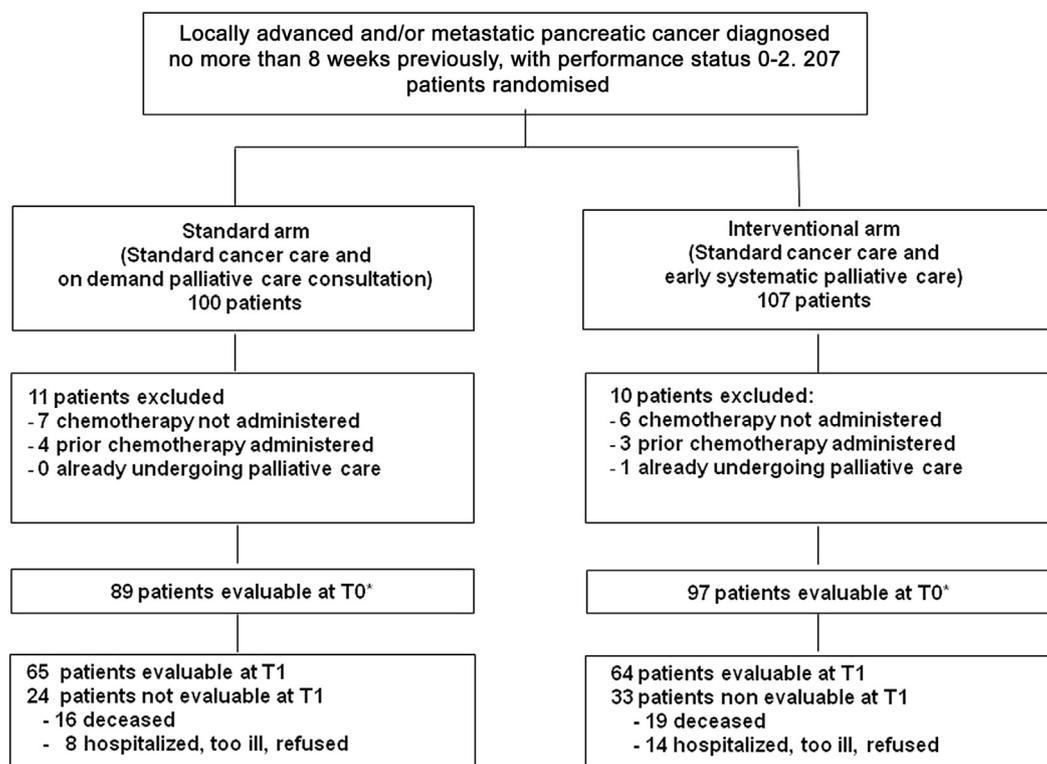
All analyses were performed on an intention-to-treat population meeting eligibility criteria, adjusted for baseline values. All tests were two sided at a significance level of 0.05. No interim analysis was planned and no multiplicity test correction was performed. All statistical analyses were performed using SAS Statistical Software version 9.4 (SAS Institute, Cary, NC, USA).

### 3. Results

Between October 2012 and February 2015, 207 patients with advanced and/or metastatic pancreatic cancer were recruited in 21 Italian centres. Twenty-one (10%) patients were not considered for analysis at T0 for various reasons (Fig. 1), leaving 186 eligible patients (89 in the standard arm and 97 in the interventional arm). The most frequent reasons for not administering chemotherapy, after informed consent was obtained, were patient refusal or a rapid worsening of clinical conditions. Baseline characteristics of patients enrolled in the two arms were superimposable (Table 1). From the date of the first randomised patient until February 2016, all patients received at least one PC consultation, those in the interventional arm seeing the PC specialist more often than standard arm patients (mean 8.9 consultations (SD 4.2, range 1–16) versus 3.9 (SD 3.3, range 1–10), respectively). Data referring to the period T0–T1 are as follows: mean value for interventional arm 5.1 (SD 1.6, range 1–11) and for standard arm 0.8 (SD 1.5, range 0–8).

Fifty-seven of the 186 evaluable patients at T0 did not complete QoL and mood questionnaires at T1 because they were too ill or had died (24 patients in standard arm and 33 in the interventional arm).

The mean change in TOI scores from baseline to 3 months was  $-4.47$  (SD 14.12) for standard arm patients



T0\*: baseline T1: 12±3 weeks

Fig. 1. Flow chart of the study (CONsolidated Standards of Reporting Trials [CONSORT] diagram).

Table 1  
Baseline characteristics of the study participants (n = 186).

	Standard arm (n = 89)	Interventional arm (n = 97)
	n (%)	n (%)
Median age, years (range)	66 (31–84)	67 (43–85)
Gender		
Male	47 (52.8)	59 (61.5)
Female	42 (47.2)	37 (38.5)
Marital status		
Married	59 (78.6)	70 (76.9)
Single	5 (6.7)	8 (8.8)
Divorced or separated	5 (6.7)	4 (4.4)
Widowed	6 (8.0)	9 (9.9)
Unknown/missing	14	6
ECOG performance status		
0	50 (56.2)	55 (56.7)
1	35 (39.3)	36 (37.1)
2	4 (4.5)	6 (6.2)
Assessment of mood symptoms		
HADS anxiety subscale		
Normal ( $\leq 7$ )	45 (53.6)	54 (58.7)
Abnormal ( $> 7$ )	39 (46.4)	38 (41.3)
HADS depression subscale		
Normal ( $\leq 7$ )	50 (59.5)	69 (75.0)
Abnormal ( $> 7$ )	34 (40.5)	23 (25.0)
<b>Scores on QoL measures</b>	<b>Mean value (SD)</b>	<b>Mean value (SD)</b>
FACT-Hep	117.5 (22.9)	120.6 (20.8)
HCS	50.5 (9.2)	51.8 (8.8)
TOI	82.6 (18.1)	85.1 (16.8)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; FACT-Hep = Functional Assessment of Cancer Therapy – Hepatobiliary; HADS = Hospital Anxiety and Depression Scale; QoL = quality of life; HCS = Hepatobiliary Cancer Subscale; SD = standard deviation; TOI = Trial Outcome Index.

and  $-0.63$  (10.95) for those in the interventional arm, with a difference between groups of 3.83 (95% CI 0.10–7.57) ( $p = 0.041$ ) (Table 2).

Table 2  
Mean change in QoL scores between T0 and T1.

	Mean change between T0 and T1		Difference between interventional and standard arm (95% CI)	p Value
	Standard arm, mean value (SD)	Interventional arm, mean value (SD)		
FACT-Hep score	$-4.49$ (17.68)	$-0.92$ (13.01)	3.57 ( $-1.02$ to 8.15)	0.176
HCS score	$-2.23$ (7.70)	0.28 (6.47)	2.51 (0.40 to 4.61)	0.013
TOI score	$-4.47$ (14.12)	$-0.63$ (10.95)	3.83 (0.10 to 7.57)	0.041

Abbreviations: QoL = quality of life; CI = confidence interval; FACT-Hep = Functional Assessment of Cancer Therapy – Hepatobiliary; HCS = Hepatobiliary Cancer Subscale; SD = standard deviation; TOI = Trial Outcome Index.

Table 3  
QoL outcomes at T1 ( $12 \pm 3$  weeks).

	Standard arm	Interventional arm	Difference between interventional and standard arms (95% CI)	p Value <sup>a</sup>	Effect size
		Mean value (SD)			
FACT-Hep score	113.0 (26.7)	119.6 (21.1)	6.63 ( $-0.47$ to 13.73)	0.080	0.30
HCS score	48.2 (11.2)	52.0 (8.4)	3.78 (0.86 to 6.71)	0.008	0.42
TOI score	78.1 (21.3)	84.4 (16.3)	6.35 (0.75 to 11.95)	0.022	0.36

Abbreviations: QoL = quality of life; CI = confidence interval; FACT-Hep = Functional Assessment of Cancer Therapy – Hepatobiliary; HCS = Hepatobiliary Cancer Subscale; SD = standard deviation; TOI = Trial Outcome Index.

<sup>a</sup> Adjusted for baseline scores.

Also, the mean change in HCS scores from baseline to 3 months was  $-2.23$  (SD 7.70) for standard arm patients and 0.28 (6.47) for those in the interventional arm (difference between groups of 2.51, 95% CI 0.40–4.61,  $p = 0.013$ ) (Table 2).

Mean values of FACT-Hep, HCS and TOI scale at T1 were significantly better for patients enrolled in the interventional arm (Table 3), especially in the latter two scores (adjusted for baseline QoL values,  $p = 0.008$  and  $p = 0.022$ , respectively).

With regard to mood, HADS anxiety subscale showed 64.1% of normal value for interventional arm versus 47.7% of normal value for control arm. Depression subscale showed 65.7% of normal values for interventional arm and 55.4% of normal value for control arm. However, none of those differences got a statistically significant p value (0.062 for anxiety and 0.281 for depression, respectively) (Table 4), also after adjusting for baseline mood values ( $p = 0.108$  for anxiety and  $p = 0.164$  for depression).

For anxiety symptoms, the percentage of patients at T1 that moved from a normal to abnormal values was 18.5% for the interventional arm and 16.3% for the standard arm, respectively; on the contrary, the percentage of patients that moved from abnormal to normal group was 34.2% in the interventional arm and 13.5% in the standard arm.

For depression, changes in the category were superimposable between the two arms. Also in relation to family satisfaction with care received, there were no differences in values (data not shown).

When the results of the study were evaluated (February 2016), 143 (76.9%) of the 186 evaluable patients had already died. Overall survival probability at

Table 4  
Mood symptoms at T1 (12 ± 3 weeks).

	Standard arm	Interventional arm	P Value
	n (%)	n (%)	
Assessment of mood symptoms			
HADS anxiety subscale			
Normal (≤7)	31 (47.7)	41 (64.1)	0.062
Abnormal (>7)	34 (52.3)	23 (35.9)	
HADS depression subscale			
Normal (≤7)	36 (55.4)	42 (65.7)	0.281
Abnormal (>7)	29 (44.6)	22 (34.3)	

Abbreviation: HADS = Hospital Anxiety and Depression Scale.

12 months was 38% (95% CI 28–48) for patients in the interventional arm and 32% (95% CI 22–41) for the standard arm population. The difference was not statistically significant.

In patients who died, we evaluated end-of-life care aggressiveness as indirect indicator of the impact of EPC on decision making during the final stage of the disease. In a preliminary analysis, according to data available up to now, standard arm versus interventional arm major data were as follows: chemotherapy in the last 30 days of life 27.8% versus 18.7% ( $p = 0.192$ ); median duration of hospice admission 14 d versus 20 d ( $p = 0.237$ ); and death at home or in hospice 66.7% versus 77.8% ( $p = 0.138$ ). However, definitive results will be object of a specific paper.

#### 4. Discussion

The primary aim of our study was to compare the effect of systematic EPC and on-demand EPC consultation on QoL during standard cancer care in patients with advanced pancreas cancer. All the studies performed on this topic had a control arm in which PC was performed on demand, compared with an interventional arm in which PC was given systematically. Of three major randomised trials that demonstrated the efficacy of systematic EPC [3–5], ours most closely resembles the study of Temel *et al.* [4] which focused on EPC in metastatic lung cancer which, like pancreas cancer, is a disease with a survival expectancy of less than 12 months and an immediately high symptomatic burden [4,19]. When we began the study, the results available on EPC performed simultaneously with the best standard cancer care, albeit scanty, suggested the usefulness of the combination [1,5].

It is now a routine practice for oncologists to call in a PC expert when they do not feel equipped to deal alone with a situation, e.g. when patients and/or family members ask for support for a physical, psychological, relational or spiritual issue [7,20–22]. A control arm in which on-demand PC consultations are often followed by direct intervention from the PC group could be considered as poorly differentiated from the

interventional arm. However, our study showed positive results in terms of its primary aim, i.e. QoL, mainly with regard to physical aspects. This is understandable as advanced pancreatic cancer has an immediate heavy physical burden on patients. EPC would probably have a greater impact on psychological rather than physical symptoms in tumours with a longer advanced phase.

A study by Zimmermann *et al.* [5] conducted on 461 patients with different solid tumours compared standard care (conventional arm) with standard care + EPC (interventional arm) consisting of monthly PC consultations and the possibility of contacting PC specialists by phone. The primary aim of Zimmerman's study, QoL evaluation after 3 months, showed a trend towards improved QoL in the interventional arm that became statistically significant after 4 months. Overall, the interventional arm resulted in a reduced symptom burden at 4 months, greater satisfaction with some areas of care at different time points, and a better use of healthcare services. In our study, QoL was impacted by intervention, although mainly in its physical components.

The first two studies by Bakitas *et al.* [3,23] compared standard care alone with standard care + EPC in 322 patients with advanced cancer in a rural setting. EPC consisted in a structured multicomponent nurse-led intervention. The studies showed changes in favour of the interventional arm in QoL and depression, a positive trend for symptom burden, but no differences in the use of healthcare services. In our experience, impact of systematic EPC on mood was detectable, but not significant.

A subsequent study by Bakitas *et al.* [24] focused on early versus delayed activation of EPC. Although the majority of outcomes evaluated did not show significant differences, 1-year survival was better in the early activation arm. Moreover, a statistical advantage was seen in depression experienced by family caregivers [25].

There has been much discussion about the reason for the positive impact of EPC on overall survival. Some correlate it with the benefit of EPC on QoL and depression as both characteristics have been shown to be correlated with overall survival [4,26]. An EPC strategy may also facilitate a more appropriate decision-making process.

The studies by Temel *et al.* [4,26] showed an advantage in the interventional arm with regard to QoL, depression and survival. Moreover, although not powered to assess specific differences in aggressiveness of end-of-life care, other works by the same authors reported a reduction in intravenous chemotherapy administered in the 14 d before death [27], a longer hospice stay [4] and improved prognosis awareness [19].

A potential weakness of our study stems from the fact that the majority of the cancer centres involved were members of the 'Italian Association of Medical Oncology – Palliative Care Working Group' [21] and accredited as 'Designated Centres of Integrative Oncology and Palliative Care' by the European Society of Medical Oncology

[22]. These cancer centres have oncologists skilled in symptom management and PC. Thus, the centre profiles may have reduced the impact of the interventional arm. Our EPC intervention also involved a single physician expert in PC rather than a full multidisciplinary PC team [28]. Recommendations made by the PC expert concerning decision-making processes had to be accepted by the oncologist, possibly reducing the effectiveness of the intervention [4,29]. A further weakness is that, although we advised all centres to complete a predefined checklist on issues to be addressed during the PC consultation, we did not check to ensure that this had been done. Finally, our study was randomised but not blinded. Although patient blinding is not possible, blinding of the assessor could be used in future studies.

Our study also has some strengths. Whilst some authors chose a cluster study design due to the difficulty of randomising single patients in this clinical setting [5], we performed individual randomisation. Furthermore, the majority of previous studies were mono-institutional and carried out in large, research-oriented centres, whereas ours was a multicentric study involving both large cancer centres and small community-based centres. As far as we know, this was also the first study dedicated solely to the evaluation of EPC in advanced pancreatic cancer patients.

It has been reported that different referral modalities for EPC have been assessed, as some ways of addressing a patient to PC services can be identified: on spontaneously referred symptom on request activation, from patient and/or the attending physician (the conventional one), on symptom request actively searched by a screening tool [30] and automatically in all patients in a definite situation (i.e. metastatic solid tumour disease).

Our study assessed the comparison between a systematic activation of EPC in a single cancer population versus spontaneously presented on-demand need and showed an impact of the former on QoL, mainly in the physical aspects. Larger comparisons in different tumours including the other modalities can represent further steps of research in his field, also including impact on EoL PC items, and costs.

## 5. Panel: research in context

### 5.1. Evidence before this study

EPC together with standard oncological care has been assessed with respect with different outcomes: QoL, quality of care, and costs. While QoL assessment mainly reflects the impact of EPC on patient outcomes at the moment when EPC delivered, evaluation of quality of care and costs imply that EPC can have, through a shared (patient/family – oncologist – PC physician) decision-making process, an impact on aggressiveness in end-of-life care. Even though evidence of impact of EPC

on such outcomes has been studied with clinical studies by a variety of methodologies, the number of randomised clinical trials has so far still limited, and the evidence of impact of EPC is still uneven. We searched the relevant literature on PubMed until February 2016 using ‘early palliative care’ and ‘oncology’ and ‘randomised clinical trial’ and completed our investigation with hand search on the basis of the paper we found. We found all the relevant literature, both for original papers and systematic review, up to the most recently published.

As mentioned above, the evidence of efficacy of EPC is sparse. Most papers assessing different outcomes showed positive results for certain outcomes and negative for others (sometimes the positive result did not regard the primary outcome of the study, but secondary ones). However, globally, the evidence has been evaluated enough from different agencies (American Society for Clinical Oncology and European Society for Medical Oncology) to suggest the inclusion of the EPC in standard cancer care, with the recommendation to implement and increase the overall body of evidence.

### 5.2. Added value of this study

Our study is aimed to suggest change in oncological clinical practice concerning care of pancreas cancer patients. The study was conducted in a definite population of patients with cancer of pancreas, in metastatic or locally advanced unresectable phase, about to set up for a first-line chemotherapy. Our data show that systematic EPC approach added to standard cancer care, when compared with on-demand EPC added to standard cancer care, shows advantages in term of QoL, mainly in the physical subscale. In literature, there was not a specific study on pancreas cancer, but only in other specific populations (lung), or in mixed cancer patient populations.

### 5.3. Implications of the available evidence

Systematic EPC in pancreas cancer patients is justified to be proposed to patients and health services for its advantage in QoL and physical symptoms.

#### *Role of the funding source*

The study sponsor was not involved neither in the study design nor in the collection, analysis, and interpretation of data. The study sponsor did not provide writing support for the report. All authors had full access to all the data in the study. The corresponding author had the final responsibility to submit for publication.

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### Conflict of interest statement

None declared.

### Acknowledgements

This trial was partially supported by research grant no. RF-2011-02350971 from the Italian Ministry of Health. This study is registered on [ClinicalTrials.gov](http://ClinicalTrials.gov) (NCT01996540). The authors thank Ursula Elbling for editing the manuscript.

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