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Outpatient Palliative Care Referral System (PCRS) for patients with advanced cancer. An impact evaluation protocol.

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Complete List of Authors:	Brunelli, Cinzia; Fondazione IRCCS Istituto Nazionale Tumori Milan Zecca, Ernesto; Fondazione IRCCS Istituto Nazionale dei Tumori, Pigni, Alessandra; Fondazione IRCCS Istituto Nazionale dei Tumori Bracchi, Paola; Fondazione IRCCS Istituto Nazionale dei Tumori Caputo, Mariangela; Fondazione IRCCS Istituto Nazionale dei Tumori Lo Dico, Silvia; Fondazione IRCCS Istituto Nazionale dei Tumori Fusetti, Viviana; Fondazione IRCCS Istituto Nazionale dei Tumori Tallarita, Antonino; Fondazione IRCCS Istituto Nazionale dei Tumori, Bergamini, Cristiana; Fondazione IRCCS Istituto Nazionale dei Tumori, Medical Oncology Department Brambilla, Marta; Fondazione IRCCS Istituto Nazionale dei Tumori, Medical Oncology Department Raimondi, Alessandra; Fondazione IRCCS Istituto Nazionale dei Tumori, Medical Oncology Department Niger, Monica; Fondazione IRCCS Istituto Nazionale dei Tumori Provenzano, Salvatore; Fondazione IRCCS Istituto Nazionale dei Tumori, Medical Oncology Department Sepe, Pierangela; Fondazione IRCCS Istituto Nazionale dei Tumori, Medical Oncology Department Alfieri, Sara; Fondazione IRCCS Istituto Nazionale dei Tumori Tinè, Gabriele; Fondazione IRCCS Istituto Nazionale dei Tumori De Braud, Filippo; Fondazione IRCCS Istituto Nazionale dei Tumori, Medical Oncology Department; Università degli Studi di Milano Caraceni, A; Fondazione IRCCS Istituto Nazionale dei Tumori, Palliative Care, Pain Therapy and Rehabilitation; Università degli Studi di Milano
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Manuscripts

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3 **Outpatient Palliative Care Referral System (PCRS) for patients with advanced cancer. An**
4 **impact evaluation protocol.**
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8 Cinzia Brunelli^{1*}, Ernesto Zecca^{1*}, Alessandra Pigni¹, Paola Bracchi¹, Mariangela Caputo¹, Silvia
9 Lo Dico¹, Viviana Fusetti¹, Antonino Tallarita¹, Cristiana Bergamini², Marta Brambilla²,
10 Alessandra Raimondi², Monica Niger², Salvatore Provenzano², Pierangela Sepe², Sara Alfieri³,
11 Gabriele Tinè⁴, Filippo De Braud^{2,5} and Augusto Caraceni^{1,5}
12
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14
15

16 * Equally first Authors
17
18
19

20 ¹ Palliative care, Pain Therapy and Rehabilitation Unit, Fondazione IRCCS Istituto Nazionale dei Tumori,
21 Milan, Italy.

22 ² Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.

23 ³ Clinical Psychology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.

24 ⁴ Unit of Clinical Epidemiology and Trial Organisation, Fondazione IRCCS Istituto Nazionale dei Tumori,
25 Milan, Italy.

26 ⁵ Università degli Studi di Milano , Milan, Italy.
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32

33 **Corresponding author**

34 Ernesto Zecca, MD

35 Palliative care, Pain Therapy and Rehabilitation Unit,

36 Fondazione IRCCS Istituto Nazionale dei Tumori

37 via Venezian, 1- 20133 Milano, Italy

38 ernesto.zecca@istitutotumori.mi.it
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44 **Key words:**

45 early outpatient palliative care, advanced cancer, referral, oncology palliative care integration
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Abstract

Objectives

Early palliative care (EPC) in the clinical pathway of advanced cancer patients improves symptom control, quality of life and has a positive impact on overall quality of care. At present, standardized criteria for appropriate referral for EPC in oncology care are lacking. The aim of this project is to develop a set of standardized referral criteria and procedures to implement appropriate EPC for advanced cancer patients (the Palliative Care Referral System) and test its impact on user perception of quality of care received, on patient quality of life and on the use of healthcare resources.

Setting. Selected oncology clinics and the palliative care outpatient clinic will participate in the study.

Method. A scoping literature review and an expert consultation through a nominal group technique will be used to revise existing referral tools and to develop a new one. 25 patients will be enrolled in a pilot study to assess feasibility of the implementation of PCRS; 10 interviews with patients and health care professionals will be carried out to evaluate applicability.

Intervention. A pretest-posttest quasi-experimental study involving 150 patients before implementation of the PCRS and 150 patients after implementation will be used.

Outcome. Patient satisfaction with care received, quality life and use of resources; caregiver satisfaction with care will also be assessed to explore the impact of the intervention.

Conclusion. Our hypothesis is that the use of tools for standardized PC referral criteria can extend the benefits of improved care quality and efficient resources use to a wider population of frail patients. The timely identification of patients with terminal illness who can benefit from PC will likely promote “end-of-life” care approaches avoiding medical overtreatment, futile diagnostic examinations and access to acute care facilities.

Trial Registration. The pretest-posttest trial was registered on ClinicalTrials.gov database (NCT04936568).

Strengths and limitations of this study

- this project aims at developing and implementing a palliative care referral system (PCRS) developed on the basis of published evidence and consensus between oncology and palliative care professionals.
- the pre and post implementation study design will provide evidence on the feasibility of the PCRS and its impact on user experience of care, patient quality of life and use of health care resources.
- Ideally, a randomized trial would provide higher value evidence; however an individually randomized design may not be adequate due to the high risk of contamination typical of complex intervention studies. On the other hand a cluster randomized trial would limit contamination but should involve at least 6-8 first level units or hospitals for the results to be robust, and this was beyond the resources allocated to this preliminary phase research.

Introduction

Palliative care (PC) is aimed at reducing or preventing suffering and improving quality of life for patients affected by incurable advanced illnesses and their caregivers. Traditionally PC has been limited to the terminal phase of illness with an unclear impact on overall disease trajectory. In recent years the term “early palliative care” (EPC) has been coined to describe an anticipated approach to PC in the care pathway of advanced diseases. In the case of advanced cancer, this means that PC can already start along with treatments such as chemotherapy, radiotherapy and other disease modifying interventions, planned for the management of advanced disease [1].

According to the latest American Society of Clinical Oncology (ASCO) consensus on integration of PC into standard oncology care, PC is defined early when administered within eight weeks from the diagnosis of advanced cancer, a definition that is too generic to be operationally implemented [2]. As shown in systematic literature reviews [1] randomized controlled trials demonstrate that the introduction of outpatient PC from the time of diagnosis of advanced cancer is associated with benefit on several clinical and care dimensions [1].

On the other hand, EPC is associated with less aggressive cancer treatment at the end of life, such as reduced use of chemotherapy in the last weeks of life and reduced access to intensive care units and emergency rooms [3].

Despite the evidence on the benefit of EPC, there is no standard definition of how oncologists should decide to refer patients to the PC specialist once advanced or metastatic disease is diagnosed. To optimize the potential impact of EPC on the overall care pathway, it would be important to combine the capacity of PC teams to participate timely in the shared decision-making process (including patient, family and attending oncologist), and, at the same time, the capacity of the multidisciplinary oncology team to integrate the advice of the PC specialist [4].

Without a suitable patient selection process for palliative care referral, outpatient palliative care services may be overwhelmed by excessive and perhaps inappropriate requests or, alternatively, resources could be underutilised if referrals do not occur. At present the volume and timing of referral to outpatient PC for cancer patients vary widely among services. This can be in part explained by the lack of standardized referral criteria for outpatient PC, coupled with variable oncologists’ attitudes and beliefs about PC and differences in models and availability of PC services [4].

It would be desirable to provide a personalized care plan for each patient, taking into account different diseases trajectories and identifying the timing and the ways in which patients can be

referred to PC. Criteria establishing the right moment for the right patient for referral including are needed to personalize care pathways and optimize resource allocations to improve care outcomes.

This project has a twofold aim:

1. To develop and study the feasibility of a standardized palliative care referral system (PCRS) for outpatient PC in advanced cancer patients.
2. To evaluate the impact of routine application of the PCRS in a population of patients cared for in a comprehensive cancer centre. Study outcomes will be patient's satisfaction with care, quality of life, caregiver's satisfaction with care and use of health care resources.

Methods

The project has been organized into two main sequential phases and second level steps as reported in Figure 1. The study intervention will be applied within several selected oncology clinics covering both frequent and rare cancers (lung, gastrointestinal, genitourinary, head & neck and sarcoma) and the PC outpatient clinic. In our palliative care clinic patients regularly encounter palliative care specialists and are assessed by nurses for symptoms and psychosocial dimension with standardized validated patient reported outcome measurements. Psychological consult is also available as needed. For each oncology clinic one oncologist will participate directly in the study procedures.

- Insert Figure 1 around here -

Phase I: Development and pilot testing of the PCRS

Criteria used for PC referral in advanced cancer patients will be identified through a scoping review of the literature on existing PC needs screening tools and methods (Table 1). The choice of the criteria that will constitute the PCRS will be based on their clinical relevance and prognostic value; existing criteria will be modified if needed. A first draft of the PCRS tool will be developed and its appropriateness and feasibility in routine clinical practice will be evaluated using Nominal group technique (NGT) [5] carried out with different health care providers (oncologists, PC specialists, nurses and psychologist) with extensive experience in oncology and palliative care. NGT is a qualitative research methodology aimed at verifying the possible convergence of a group of experts on an idea, judgment or proposal. NGT consists of six stages [6]: 1. Presentation of the nominal question; 2. Individual generation of ideas or voting; 3. Round-robin feedback from participants to record each idea/voting; 4. Group discussion of each idea/voting in turn for

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3 clarification and evaluation; 5. Individual voting on priority ideas with the group decision derived
4 through rank-ordering or rating; 6. Sharing of results, further discussion and re-voting. Based on the
5 NGT results, the PCRS will be adjusted/modified as needed and standard implementation
6 procedures will be developed.
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10 Then a pilot cross-sectional feasibility study on the application of the PCRS will be carried
11 out on 5 consecutive patients in each of the 5 outpatient clinics that will be involved in the Phase II
12 of the project. Feasibility assessment will include: time needed to screen the patient, number of
13 patients for which the screening was complete, number of missing data for each criterion.
14 Acceptability of PCRS by patients and by health care professionals (HCPs), as well as integration of
15 the assessment procedure with routine clinical practice will also be evaluated through debriefing
16 interviews with 5 patients and 5 HCPs. A final revision of the PCRS and of its implementation
17 procedure by the study group will follow the pilot testing.
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25 **Phase II: PCRS impact evaluation.**

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27 The potential impact of the PCRS will be explored using a quasi-experimental study design
28 measuring study endpoints before and after PCRS implementation (Figure1).
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30 Study design and patient population

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32 A longitudinal pretest-posttest design will be carried out. Two different cohorts of advanced
33 cancer patients will be enrolled before (pretest) and after (posttest) the introduction of the PCRS in
34 outpatient clinics. Patient inclusion criteria are: age >18 years; diagnosis of inoperable locally
35 advanced and/or metastatic cancer. Exclusion criteria: eligibility to anticancer treatment with
36 curative intent; patients already enrolled in a PC program; cognitive impairment.
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43 Study Outcomes and assessment methods

44 The following outcomes will be evaluated: patient's satisfaction with care (main outcome), patient's
45 quality of life, caregiver's satisfaction with care, use of health care resources, and end of life care
46 quality indicators.
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49 The FAMCARE-P13 will be used to assess patient satisfaction with care in the present
50 study. It is a 13 item self-report questionnaire, developed to be used with advanced cancer patients
51 [7]. Its items are rated from 1 (very dissatisfied) to 5 (very satisfied) producing a single satisfaction
52 score ranging from 13 to 65.
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56 The EORTC Quality of Life Questionnaire Core 15 for Palliative Care (QLQ-C15-PAL) [8]
57 will be used to evaluate patients' quality of life. QLQ-C15-PAL is an abbreviated 15-item version
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3 of EORTC-QLQC30 specifically developed for use in a palliative care setting. It includes two
4 multi-item functional scales (physical and emotional functioning), two multi-item symptom scales
5 (fatigue and pain), five single-item symptom scales (nausea/vomiting, dyspnoea, insomnia, appetite
6 loss and constipation) and a question regarding overall QoL (global health status). Items are rated
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8 on a Likert scale from 1 (not at all) to 4 (very much) with the exception of global health status,
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10 which is rated from 1 (very poor) to 7 (excellent).
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14 Family satisfaction with care will be assessed with the FAMCARE scale [9, 10]. It is a self-
15 assessment satisfaction composed of 20 items rated according to a 5-point Likert scale from 1 (very
16 satisfied) to 5 (very dissatisfied). The items are grouped into four subscales: Physical patient care
17 (PPC), Information giving (IG), Availability of care (AC) and Psychosocial care (PsC) subscale.
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19 The FAMCARE Scale can be administered to family members while a patient is receiving palliative
20 care or at some point after a patient's death.
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24 All tools applied are validated in Italian language but the FAMCARE P-13, which will be
25 culturally adapted from English using "forward-backward" translation method [11] as part of the
26 present project; basic psychometric properties will be assessed as well.
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30 Use of health care resources during study follow-up will be monthly assessed by a dedicated
31 research nurse with an ad-hoc developed form reporting: access to a PC service (regular outpatient
32 PC visits, home care, hospice admission), number of multidisciplinary team visits (oncology and
33 PC), number of hospitalization and of emergency department admission, with reason and duration.
34
35 End of life care quality indicators will be assessed by a dedicated research nurse from the medical
36 record only for those patients who will die during the follow-up period with an ad-hoc developed
37 form reporting: chemotherapy administration during the last month of life, place of death and
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39 activation of any PC service (home care or hospice) during the last month.
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49 For all data to be collected, Table 1 reports the assessment tools and the timing of various
50 assessments. Eligible patients will undergo FAMCARE P-13 and EORTC QLQC15-PAL
51 evaluation at baseline and then monthly for at least 6 months from enrollment or till death (T1, T2,
52 T3, T4, T5, T6). The choice of interviewing patients every month is suggested by the need to
53 minimize attrition due to potential patients drop and also to take into account the frequent possible
54 changes in clinical conditions in a fragile patient population. FAMCARE will be administered to
55 the main caregiver identified by the patient at T0, T3 and T6 or after patient's death in patients
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3 who will die during the follow-up. Patient and caregiver reported outcomes will be collected
4 through telephone interview. This method was chosen in order to avoid contamination between the
5 pre- and post- PCRS implementation groups; in fact the PCRS implementation in the posttest
6 group will be based also on patient reported symptom assessment which will be electronically
7 collected [12]. HCP reported data will be collected using REDCap electronic data capture tools
8 hosted at Fondazione IRCCS Istituto Nazionale dei Tumori of Milan
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DATA	REPORTED BY	TOOL	T0 Baseline	T1 30±3days	T2 60±3days	T3 90±3days	T4 120±3days	T5 150±3days	T6 180±3days	EOS (*)
Socio-Demographic	PATIENT	Ad hoc form (eCRF)	X							
Clinical	RN/MD	Ad hoc form (eCRF)	X	X	X	X	X	X	X	
Patient satisfaction with care	PATIENT	FAMCARE P13	X	X	X	X	X	X	X	
Quality of life	PATIENT	EORTC-C15 PAL	X	X	X	X	X	X	X	
Caregiver satisfaction with care	CAREGIVER	FAMCARE	X			X			X	(X)
Use of health care resources	RN	Ad hoc form (eCRF)		X	X	X	X	X	X	
End of life care quality indicator	RN	Ad hoc form (eCRF)								(X)

Table 1: Data collection during study period

Legenda: RN = research nurse; MD = medical doctor; eCRF = electronic case report forms; EOS = End of study;

* End of study assessments will be performed only for those patients who die within the study follow-up period.

Power considerations and statistical analysis

The main endpoint is the variation in patient's satisfaction between baseline and the average of repeated follow-up assessments. t-test for independent samples on this endpoint will be used to compare pre- and post-referral patient cohorts. Power calculations [13] indicate that 150 patients in each group will allow a two tailed t-test for independent samples, a power of 0.9 to detect an effect size of 0.32 with alpha error=0.05. The same analysis scheme will be applied for all continuous repeated measurement outcomes, while binary outcomes (i.e. activation of PC during follow-up or chemotherapy administration during the last month of life) will be analyzed using logistic regression models. Linear and logistic regression models will be used for covariate adjustment estimations.

Data sharing

De-identified data of participants in this project will be available from the project principal investigator (AC) upon request, provided that the data reuse is in agreement the European General Data Protection Regulation 2016/679 (GDPR)

Patient and public involvement

No patient nor other member of the public was involved in the development of this research project

Discussion

Early palliative care referral, that is while concurrent anti-neoplastic treatment is still possible and indicated, is considered to improve integration of palliative care in the clinical pathway of patients with advanced disease who cannot achieve cure with the available antineoplastic treatments [2]. This general statement is based on several clinical trials [1] showing advantages of early access to palliative care in improving patient's quality of life, psychological distress, use of health care resources at the end of life and caregivers' distress.

These trials were however based on different clinical models and settings. The model which was more consistently tested as an experimental intervention has been based on the access of patients to specialized palliative care outpatient clinic. In fact, the implementation of this model [14-21] has more consistently shown efficacy if compared with other interventions of care coordination without direct encounters between patients and palliative care professionals [22-25]. This has been also described as an "integrated care model" [26, 27].

Within the integrated model trials, the number and duration of encounters of patients with palliative care professionals varied from 1 every 1.3 weeks to 1 every 6 weeks with a total mean

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4 number of visits during the study period ranging from 2.4 to 8.9. Two of the three negative studies
5 on the integrated model [14, 20] resulted in very limited if any access to specialized palliative care
6 visits. The third one acknowledged significant in between trial arms contamination [21].
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9 Also qualitative type evidences from the same trials support subjective appreciation of
10 clinical value attributed by patients to integrated palliative care interventions. Patients and
11 caregivers considered specialized outpatient palliative care capable of providing personalized and
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3 prompt symptom management, holistic support to patients and caregivers, guidance in decision
4 making and preparation for the future [28]. Another study addressed specifically the clinical content
5 of early outpatient palliative care and showed that interventions based on psychological and cognitive
6 coping, disease understanding, decision making and care planning were associated with lower
7 psychological distress and better use of health care resources at the end of life [29]. Finally, the study
8 by Costantini et al. [30] shows that an early integration of specialized palliative care after the
9 diagnosis of advanced cancer is feasible and well accepted by patients, relatives and, to a lesser
10 extent, by oncologists.

11
12 Overall these data confirm the usefulness of making palliative care outpatient clinic, with
13 specialized clinical skills and multidimensional assessment, available for patients with advanced
14 cancer but the selection criteria used in the clinical trials are difficult to translate into clinical
15 practice. The trials aimed at demonstrating efficacy and detecting outcome changes at the group
16 level, while statistically accounting for patients heterogeneity. In clinical practice the decision to
17 refer a patient to palliative care outpatient clinic needs instead to be individualized. Therefore trials'
18 result cannot clarify how to guarantee timely access at the individual level and to optimize resource
19 allocation. Trials are also not enough to change clinical practice, without taking into account
20 practical and cultural barriers that impact on palliative care perception by oncologists and patients
21 [27, 31].

22
23 In conclusion the best ways to address earlier palliative care needs identification, timely
24 access to outpatient palliative care and also to overcome barriers to integration with oncology are
25 still unresolved issues, and yet late referral is considered to be a significant barrier in many cases
26 [27, 31-35].

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28 The literature discussion about criteria to be used and the domains to be assessed, beyond the
29 stage of the disease, already considered in all trials, includes symptoms, psychosocial distress,
30 prognosis, trigger disease related events and critical care planning issues [4, 36-38]. A number of
31 palliative care need screening and assessment instruments have been developed and sometimes
32 tested [38-49] but only a few of them were specifically designed to improve appropriate selection of
33 cancer patients for referral to outpatient specialized palliative care [4, 50]. There are no studies nor
34 agreed guidelines upon criteria to guide timely referral [47, 51, 52] beyond disease stage [2, 4].

35
36 Hui et al. [26] published a Delphi study building a consensus on referral criteria among a
37 number of palliative care expert identifying major and minor criteria and suggesting that referral
38 should occur anytime one major criterion is met. The same Authors [53], in a retrospective
39 assessment of the characteristics of patients referred to their palliative care clinic, found that 85%
40 fulfilled one major criteria and that referral occurred as an average 14 months before death.

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3 Interestingly in the study by Singh et al [54] prognostic assessment alone using the Surprise
4 question had no effect on referral to palliative care including the outpatient setting.

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6 The only study looking at implementing an intervention to improve referral to ambulatory
7 palliative care was planned by a cancer center in Texas as a quality improvement intervention,
8 including, in a plan-do-study-act cycle, the adoption of a symptom assessment tool and a referral
9 pathway in oncology clinics. Their initial results show a 10 fold increase of referrals after
10 implementation, from 0.07% of all oncology clinic encounters to 0.8%. It is unclear how
11 satisfactory this result can be considered, given the modest number of referrals, in particular
12 because the relationship with high symptom score is not consistent with such a low referral rate.
13 The study is still under development [55].

14
15 The primary aim of our study is therefore to develop and implement a palliative care referral
16 system which takes into account the suggestions from the literature in combination with consensus
17 between oncology and palliative care specialists. It is anticipated that in an implementation study
18 with the aim of intervening on clinical practices evidence based concepts need to be combined with
19 professional interaction, knowledge of service availability, professional trust and resource allocation
20 that avoid extra workload burden and alert fatigue [56].

21
22 Our model of palliative care integration has been available at our center since 2001 [57] and
23 we recently described its operational characteristics on a consecutive lung cancer patients
24 population seen at a thoracic oncology clinic. In a two year period, 43% of patients were referred to
25 palliative care clinics, mainly for symptom control, usually pain and or dyspnoea, and poor
26 performance status. The mean duration of outpatient palliative care was 128 days [58].

27
28 The pre and post implementation study design in this protocol will give information on the
29 feasibility of the PCRS, its impact on user experience of care, patient quality of life and use of
30 health care resources. Ideally, a cluster randomized trial design would be preferable but at least
31 6-8 first level units (hospitals) should be involved for the results to be robust, and this is beyond
32 resources allocated to this research. An individually randomized design, instead, may not be
33 adequate for the evaluation of a complex intervention with a high contamination risk.
34 Furthermore the evidence of the potential efficacy of PC referral implementation are still to be
35 shown. Considering these limitations the aim of the study is not to provide a final estimate of the
36 effectiveness of PC needs screening but to provide a first estimate of feasibility and impact.
37 Study completion would also allow the subsequent integration of the PCRS, or of some of its
38 components [12], at the institutional level in order to steer a change in clinical practice to augment
39 palliative and oncology integration and improve patient care.

40
41 The study is part of a nationally funded program (Finalizzata di Rete NET-2018-12367032 - funded

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3 by the Italian Ministry of Health and by Regione Lombardia) to address the recognition and
4 response to palliative care needs in different patients populations and has the opportunity to raise
5 awareness at the national level about the importance of palliative care integration at the outpatient
6 level. The national program finalization could strengthen directions for the Ministry of Health to
7 allocate resources for recognizing the lack of specialized palliative care services at acute hospitals
8 and promoting their implementation
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3 **Ethics** Ethical approval for the study has been granted by the Institutional Review board of the
4 Fondazione IRCCS Istituto Nazionale Tumori, approval reference INT201/19. The protocol of the
5 pretest-posttest quasi-experimental design was registered on ClinicalTrials.gov database
6 (NCT04936568).
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9

10 11 **Funding**

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13 Lombardia (NET-2018-12367032)
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17 18 **Author Contributions**

19
20
21 Conceptualization: CB, EZ, AP, PB, MC, SLD, VF, AT, CBe, MB, AR, MN, PS, SP, SA, GT,
22 FDB, AC

23
24 Writing—original draft preparation: CB, EZ, AP, PB, MC, SLD, VF, CBe, MB, AR, MN, PS, SP,
25 SA, GT, FDB, AC

26
27 Writing—review and editing: CB, EZ, AP, PB, MC, SLD, VF, CBe, MB, AR, MN, PS, SP, SA,
28 GT, FDB, AC

29
30 Supervision: CB, EZ, AC

31
32 All authors have read and agreed to the published version of the manuscript.
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36 37 **Conflicts of Interest**

38
39 AC has received consultant honoraria from Mundipharma, Pfizer/Eli Lilly Italia Spa, Angelini,
40 Shionogi, Molteni and Kyowa Kirin. He has also received research grants from Molteni & C Soc
41 Esercizio Spa and Ipsen.
42

43
44 EZ has received consultant honoraria from Amgen.

45
46 MN has received travel expenses from Celgene, speaker honorarium from Accademia della
47 Medicina and consultant honoraria from EMD Serono, Basilea Pharmaceutica, Incyte and MSD
48 Italia.
49

50
51 FDB has received consultant honoraria from Roche, EMD Serono, NMS Nerviano Medical
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59 AP, PB, MC, SLD, VF, CBe, MB, PS, SP, SA, AR, GT and CB declare no conflicts of interest.
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Figure 1: Project scheme

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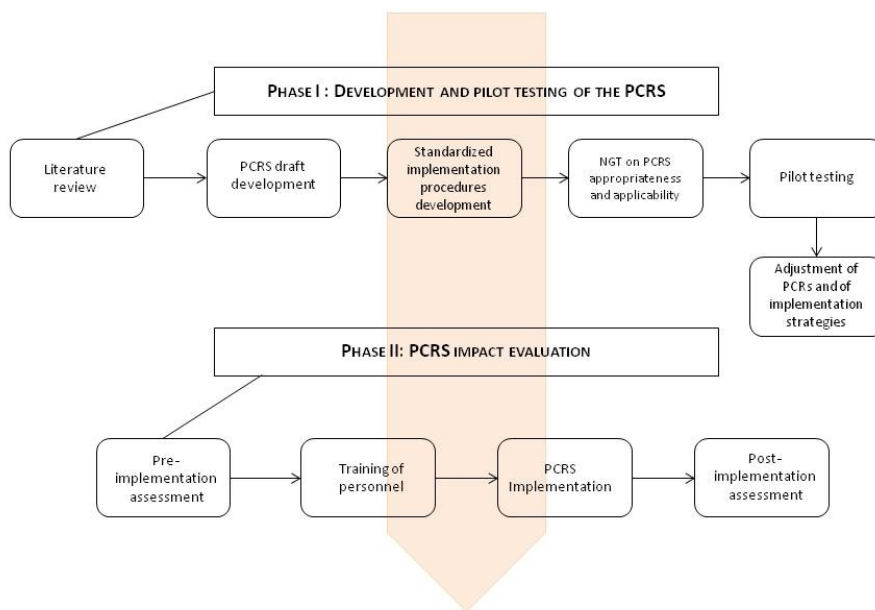


Figure 1: Project scheme

254x190mm (96 x 96 DPI)

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Outpatient Palliative Care Referral System (PCRS) for patients with advanced cancer. An impact evaluation protocol.

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3 **Outpatient Palliative Care Referral System (PCRS) for patients with advanced cancer. An**
4 **impact evaluation protocol.**
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9 Cinzia Brunelli^{1*}, Ernesto Zecca^{1*}, Alessandra Pigni¹, Paola Bracchi¹, Mariangela Caputo¹, Silvia
10 Lo Dico¹, Viviana Fusetti¹, Antonino Tallarita¹, Cristiana Bergamini², Marta Brambilla²,
11 Alessandra Raimondi², Monica Niger², Salvatore Provenzano², Pierangela Sepe², Sara Alfieri³,
12 Gabriele Tinè⁴, Filippo De Braud^{2,5} and Augusto Caraceni^{1,5}
13
14
15

16 * Equally first Authors
17
18

19 ¹ Palliative care, Pain Therapy and Rehabilitation Unit, Fondazione IRCCS Istituto Nazionale dei Tumori,
20 Milan, Italy.
21

22 ² Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.
23

24 ³ Clinical Psychology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.
25

26 ⁴ Unit of Clinical Epidemiology and Trial Organisation, Fondazione IRCCS Istituto Nazionale dei Tumori,
27 Milan, Italy.
28

29 ⁵ Università degli Studi di Milano , Milan, Italy.
30

31 **Corresponding author**

32 Ernesto Zecca, MD

33 Palliative care, Pain Therapy and Rehabilitation Unit,

34 Fondazione IRCCS Istituto Nazionale dei Tumori

35 via Venezian, 1- 20133 Milano, Italy

36 ernesto.zecca@istitutotumori.mi.it
37
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41 **Key words:**

42 early outpatient palliative care, advanced cancer, referral, oncology palliative care integration
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Abstract

Objectives. Early palliative care (PC) in the clinical pathway of advanced cancer patients improves symptom control, quality of life and positively impact on overall quality of care. Currently, standardized criteria for appropriate referral to early PC in oncology care are lacking. The project aims to develop a set of standardized referral criteria and procedures to implement appropriate early PC for advanced cancer patients (the Palliative Care Referral System, PCRS) and test its impact on user perception of quality of care received, on patient quality of life, and the use of healthcare resources.

Setting. Selected oncology clinics and PC outpatient clinics.

Method. A scoping literature review and an expert consultation through a nominal group technique will be used to revise existing referral tools and to develop a new one, the PCRS. Twenty-five patients will be enrolled in a pilot study to assess the feasibility of implementing PCRS; ten interviews with patients and health care professionals will be conducted to evaluate applicability.

A pretest-posttest quasi-experimental study involving 150 patients before and 150 patients after implementation will be carried out.

Intervention. Implementation of PCRS for the identification of advanced cancer patients in need of palliative care in routine outpatient cancer care.

Outcome. Patient satisfaction with care received, quality life, and use of resources; caregiver satisfaction with care to explore the impact of the intervention.

Conclusion. Our hypothesis is that using tools for standardized PC referral criteria can extend the benefits of improved care quality and efficient resource use to a broader population of frail patients. The timely identification of patients who can benefit from PC will likely promote “end-of-life” care approaches, avoiding medical overtreatment, futile diagnostic examinations, and access to acute care facilities.

Trial Registration. The pretest-posttest trial was registered on ClinicalTrials.gov database (NCT04936568).

Strengths and limitations of this study

- The development and implementation of a palliative care referral system (PCRS) that takes into account published evidence and consensus among oncology and palliative care professionals constitute a strength of this project.
- The pre and post implementation study design will provide evidence on the feasibility of the PCRS and its impact on user experience of care, patient quality of life and use of health care resources.
- Ideally, a randomized trial would provide higher value evidence; however an individually randomized design may not be adequate due to the high risk of contamination typical of complex intervention studies. On the other hand a cluster randomized trial would limit contamination but should involve at least 6-8 first level units or hospitals for the results to be robust, and this was beyond the resources allocated to this preliminary phase research.

Introduction

Palliative care (PC) is aimed at reducing or preventing suffering and improving quality of life for patients affected by incurable advanced illnesses and their caregivers. Traditionally PC has been limited to the terminal phase of illness with an unclear impact on overall disease trajectory. In recent years the term “early palliative care” has been coined to describe an anticipated approach to PC in the care pathway of advanced diseases. In the case of advanced cancer, this means that PC can already start along with treatments such as chemotherapy, radiotherapy and other disease modifying interventions, planned for the management of advanced disease [1].

According to the latest American Society of Clinical Oncology consensus on integration of PC into standard oncology care, PC is defined early when administered within eight weeks from the diagnosis of advanced cancer, a definition that is too generic to be operationally implemented [2]. As shown in systematic literature reviews [1] randomized controlled trials demonstrate that the introduction of outpatient PC from the time of diagnosis of advanced cancer is associated with benefit on several clinical and care dimensions [1].

On the other hand, early PC is associated with less aggressive cancer treatment at the end of life, such as reduced use of chemotherapy in the last weeks of life and reduced access to intensive care units and emergency rooms [3].

Despite the evidence on the benefit of early PC, there is no standard definition of how oncologists should decide to refer patients to the PC specialist once advanced or metastatic disease is diagnosed. To optimize the potential impact of EPC on the overall care pathway, it would be important to combine the capacity of PC teams to participate timely in the shared decision-making process (including patient, family and attending oncologist), and, at the same time, the capacity of the multidisciplinary oncology team to integrate the advice of the PC specialist [4].

Without a suitable patient selection process for palliative care referral, outpatient palliative care services may be overwhelmed by excessive and perhaps inappropriate requests or, alternatively, resources could be underutilised if referrals do not occur. At present the volume and timing of referral to outpatient PC for cancer patients vary widely among services. This can be in part explained by the lack of standardized referral criteria for outpatient PC, coupled with variable oncologists’ attitudes and beliefs about PC and differences in models and availability of PC services [4].

It would be desirable to provide a personalized care plan for each patient, taking into account different diseases trajectories and identifying the timing and the ways in which patients can be referred to PC. Criteria establishing the right moment for the right patient for referral including are

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3 needed to personalize care pathways and optimize resource allocations to improve care outcomes.

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5 This project has a twofold aim:

- 6
7 1. To develop and study the feasibility of a standardized palliative care referral system (PCRS)
8 for outpatient PC in advanced cancer patients.
- 9
10 2. To evaluate the impact of routine application of the PCRS in a population of patients cared
11 for in a comprehensive cancer centre.

12 13 14 15 **Methods**

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17 The project has been organized into two main sequential phases and second level steps as
18 reported in Figure 1. The study intervention will be applied within several selected oncology clinics
19 covering both frequent and rare cancers (lung, gastrointestinal, genitourinary, head & neck and
20 sarcoma) and the PC outpatient clinic. In our PC clinic patients regularly encounter PC specialists
21 and are assessed by nurses for symptoms and psychosocial dimension using validated self reported
22 questionnaires [5]. Psychological consult is also available as needed. For each oncology clinic one
23 oncologist will participate directly in the study procedures.

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34 **Phase I: Development and pilot testing of the PCRS**

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36 Criteria used for PC referral in advanced cancer patients will be identified through a scoping
37 review of the literature on existing PC needs screening tools and methods (Table 1). The choice of
38 the criteria that will constitute the PCRS will be based on their clinical relevance and prognostic
39 value; existing criteria will be modified if needed. A first draft of the PCRS tool will be developed
40 and its appropriateness and feasibility in routine clinical practice will be evaluated using Nominal
41 group technique (NGT) [6] carried out with different health care providers (oncologists, PC
42 specialists, nurses and psychologist) with extensive experience in oncology and palliative care.
43 NGT is a qualitative research methodology aimed at verifying the possible convergence of a group
44 of experts on an idea, judgment or proposal. NGT consists of six stages [7]: 1. Presentation of the
45 nominal question; 2. Individual generation of ideas or voting; 3. Round-robin feedback from
46 participants to record each idea/voting; 4. Group discussion of each idea/voting in turn for
47 clarification and evaluation; 5. Individual voting on priority ideas with the group decision derived
48 through rank-ordering or rating; 6. Sharing of results, further discussion and re-voting. Based on the
49 NGT results, the PCRS will be adjusted/modified as needed and standard implementation
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3 procedures will be developed.

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5 Then a pilot cross-sectional feasibility study on the application of the PCRS will be carried
6 out on 5 consecutive patients in each of the 5 outpatient clinics that will be involved in the Phase II
7 of the project. Feasibility assessment will include: time needed to screen the patient, number of
8 patients for which the screening was complete, number of missing data for each criterion.
9
10 Acceptability of PCRS by patients and by health care professionals, as well as integration of the
11 assessment procedure with routine clinical practice will also be evaluated through debriefing
12 interviews with 5 patients and 5 health care professionals. A final revision of the PCRS and of its
13 implementation procedure by the study group will follow the pilot testing.
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20 **Phase II: PCRS implementation and impact evaluation.**

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22 The potential impact of the PCRS will be explored using a quasi-experimental study design
23 measuring study endpoints before and after PCRS implementation (Figure 1).
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25 Study design and patient population

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27 A longitudinal pretest-posttest design will be carried out. Two different cohorts of advanced
28 cancer patients will be enrolled before (pretest) and after (posttest) the introduction of the PCRS in
29 outpatient clinics. Patient inclusion criteria are: age >18 years; diagnosis of inoperable locally
30 advanced and/or metastatic cancer. Exclusion criteria: eligibility to anticancer treatment with
31 advanced and/or metastatic cancer. Exclusion criteria: eligibility to anticancer treatment with
32 curative intent; patients already enrolled in a PC program; cognitive impairment.
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36 PCRS implementation

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38 For implementing the PCRS, patient clinical assessment will be performed initially by a
39 nurse, collecting self reported questionnaires and partially completing the PCRS. This evaluation
40 will be entered in the electronic medical records and then integrated and validated by the oncologist
41 during the visit. The oncologist will finally decide to refer or not the patient to PC using the PCRS
42 predefined criteria and his or her clinical judgment.
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46 Study Outcomes and assessment methods

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48 The following outcomes will be evaluated: patient's satisfaction with care (main outcome), patient's
49 quality of life, caregiver's satisfaction with care, use of health care resources, and end of life care
50 quality indicators.
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54 The FAMCARE-P13 will be used to assess patient satisfaction with care in the present
55 study. It is a 13 item self-report questionnaire, developed to be used with advanced cancer patients
56 [8]. Its items are rated from 1 (very dissatisfied) to 5 (very satisfied) producing a single satisfaction
57 score ranging from 13 to 65.
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3 The EORTC Quality of Life Questionnaire Core 15 for Palliative Care (QLQ-C15-PAL) [9]
4 will be used to evaluate patients' quality of life. QLQ-C15-PAL is an abbreviated 15-item version
5 of EORTC-QLQC30 specifically developed for use in a palliative care setting. It includes two
6 multi-item functional scales (physical and emotional functioning), two multi-item symptom scales
7 (fatigue and pain), five single-item symptom scales (nausea/vomiting, dyspnoea, insomnia, appetite
8 loss and constipation) and a question regarding overall QoL (global health status). Items are rated
9 on a Likert scale from 1 (not at all) to 4 (very much) with the exception of global health status,
10 which is rated from 1 (very poor) to 7 (excellent).
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17 Family satisfaction with care will be assessed with the FAMCARE scale [10, 11]. It is a self-
18 assessment satisfaction composed of 20 items rated according to a 5-point Likert scale from 1 (very
19 satisfied) to 5 (very dissatisfied). The items are grouped into four subscales: Physical patient care,
20 Information giving, Availability of care and Psychosocial care subscale.
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22 The FAMCARE Scale can be administered to family members while a patient is receiving palliative
23 care or at some point after a patient's death.
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28 All tools applied are validated in Italian language but the FAMCARE P-13, which will be
29 culturally adapted from English using "forward-backward" translation method [12] as part of the
30 present project; basic psychometric properties will be assessed as well.
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33 Use of health care resources during study follow-up will be monthly assessed by a dedicated
34 research nurse with an ad-hoc developed form reporting: access to a PC service (regular outpatient
35 PC visits, home care, hospice admission), number of multidisciplinary team visits (oncology and
36 PC), number of hospitalization and of emergency department admission, with reason and duration.
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38 End of life care quality indicators will be assessed by a dedicated research nurse from the medical
39 record only for those patients who will die during the follow-up period with an ad-hoc developed
40 form reporting: chemotherapy administration during the last month of life, place of death and
41 activation of any PC service (home care or hospice) during the last month.
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51 For all data to be collected, Table 1 reports the assessment tools and the timing of various
52 assessments. Eligible patients will undergo FAMCARE P-13 and EORTC QLQC15-PAL
53 evaluation at baseline and then monthly for at least 6 months from enrollment or till death (T1, T2,
54 T3, T4, T5, T6). The choice of interviewing patients every month is suggested by the need to
55 minimize attrition due to potential patients drop out and also to take into account the frequent
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3 possible changes in clinical conditions in a fragile patient population. FAMCARE will be
4 administered to the main caregiver identified by the patient at T0, T3 and T6 or after patient's
5 death in patients who will die during the follow-up. Patient and caregiver reported outcomes will
6 be collected through telephone interview. This method was chosen in order to avoid contamination
7 between the pre- and post- PCRS implementation groups; in fact the PCRS implementation in the
8 posttest group will be based also on patient reported symptom assessment which will be
9 electronically collected [13]. Health care professional reported data will be collected using
10 REDCap electronic data capture tools hosted at Fondazione IRCCS Istituto Nazionale dei Tumori
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DATA	REPORTED BY	TOOL	T0 Baseline	T1 30±3days	T2 60±3days	T3 90±3days	T4 120±3days	T5 150±3days	T6 180±3days	EOS (*)
Socio-Demographic	PATIENT	Ad hoc form (eCRF)	X							
Clinical	RN/MD	Ad hoc form (eCRF)	X	X	X	X	X	X	X	
Patient satisfaction with care	PATIENT	FAMCARE P13	X	X	X	X	X	X	X	
Quality of life	PATIENT	EORTC-C15 PAL	X	X	X	X	X	X	X	
Caregiver satisfaction with care	CAREGIVER	FAMCARE	X			X			X	(X)
Use of health care resources	RN	Ad hoc form (eCRF)		X	X	X	X	X	X	
End of life care quality indicator	RN	Ad hoc form (eCRF)								(X)

Table 1: Data collection during study period

Legenda: RN = research nurse; MD = medical doctor; eCRF = electronic case report forms; EOS = End of study;

* End of study assessments will be performed only for those patients who die within the study follow-up period.

Power considerations and statistical analysis

The main endpoint is the variation in patient's satisfaction between baseline and the average of repeated follow-up assessments. t-test for independent samples on this endpoint will be used to compare pre- and post- referral patient cohorts. Power calculations [14] indicate that 150 patients in each group will allow a two tailed t-test for independent samples, a power of 0.9 to detect an effect size of 0.375 with alpha error=0.05. In case of a 15% attrition rate the study power reduces at 85%, all else unchanged. The same analysis scheme will be applied for all continuous repeated measurement outcomes, while binary outcomes (i.e. activation of PC during follow-up or chemotherapy administration during the last month of life) will be analyzed using logistic regression models. Linear and logistic regression models will be used for covariate adjustment estimations.

Data sharing

De-identified data of participants in this project will be available from the project principal investigator (AC) upon request, provided that the data reuse is in agreement the European General Data Protection Regulation 2016/679 (GDPR).

Patient and public involvement

No patient nor other member of the public was involved in the development of this research project.

Discussion

Early palliative care referral, while concurrent anti-neoplastic treatment is still possible and indicated, is considered to improve integration of palliative care in the clinical pathway of patients with advanced disease who cannot achieve cure with the available antineoplastic treatments [2]. This general statement is based on several clinical trials [1] showing advantages of early access to palliative care in improving patient's quality of life, psychological distress, use of health care resources at the end of life and caregivers' distress.

Different early palliative care models

These trials were however based on different clinical models and settings. The model which was more consistently tested as an experimental intervention has been based on the access of patients to specialized palliative care outpatient clinic. In fact, the implementation of this model [15-22] has more consistently shown efficacy if compared with other interventions of care coordination without direct encounters between patients and palliative care professionals [23-26]. This has been also described as an "integrated care model" [27, 28].

Within the integrated model trials, the number and duration of encounters of patients with

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3 palliative care professionals varied from 1 every 1.3 weeks to 1 every 6 weeks with a total mean
4 number of visits during the study period ranging from 2.4 to 8.9. Two of the three negative studies
5 on the integrated model [15, 21] resulted in very limited if any access to specialized palliative care
6 visits. The third one acknowledged significant in between trial arms contamination [22].
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10 Also qualitative type evidences from the same trials support subjective appreciation of
11 clinical value attributed by patients to integrated palliative care interventions. Patients and
12 caregivers considered specialized outpatient palliative care capable of providing personalized and
13 prompt symptom management, holistic support to patients and caregivers, guidance in decision
14 making and preparation for the future [29]. Another study addressed specifically the clinical content
15 of early outpatient palliative care and showed that interventions based on psychological and cognitive
16 coping, disease understanding, decision making and care planning were associated with lower
17 psychological distress and better use of health care resources at the end of life [30]. Finally, the study
18 by Costantini et al. [31] shows that an early integration of specialized palliative care after the
19 diagnosis of advanced cancer is feasible and well accepted by patients, relatives and, to a lesser
20 extent, by oncologists.
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23 Palliative care needs selection criteria

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25 Overall these data confirm the usefulness of the palliative care outpatient clinic approach,
26 with specialized clinical skills and multidimensional assessment, for patients with advanced cancer
27 but the selection criteria used in the clinical trials are difficult to translate into clinical practice. The
28 trials aimed at demonstrating efficacy and detecting outcome changes at the group level, while
29 statistically accounting for patients heterogeneity. In clinical practice the decision to refer a patient
30 to palliative care outpatient clinic needs instead to be individualized. Therefore trials' result cannot
31 clarify how to guarantee timely access at the individual level and to optimize resource allocation.
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33 Trials are also not enough to change clinical practice, without taking into account practical and
34 cultural barriers that impact on palliative care perception by oncologists and patients [28, 32].
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38 In summary the best ways to address earlier palliative care needs identification, timely
39 access to outpatient palliative care and also to overcome barriers to integration with oncology are
40 still unresolved issues, and yet late referral is considered to be a significant barrier in many cases
41 [28, 32-36].
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45 The literature discussion about criteria to be used and the domains to be assessed, beyond the
46 stage of the disease, already considered in all trials, includes symptoms, psychosocial distress,
47 prognosis, trigger disease related events and critical care planning issues [4, 37-39]. A number of
48 palliative care need screening and assessment instruments have been developed and sometimes
49 tested [39-50] but only a few of them were specifically designed to improve appropriate selection of
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3 cancer patients for referral to outpatient specialized palliative care [4, 51] . There are no studies nor
4 agreed guidelines upon criteria to guide timely referral [48, 52, 53] beyond disease stage [2, 4].

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6 Hui et al. [27] published a Delphi study building a consensus on referral criteria among a
7 number of palliative care expert identifying major and minor criteria and suggesting that referral
8 should occur anytime one major criterion is met. The same Authors [54], in a retrospective
9 assessment of the characteristics of patients referred to their palliative care clinic, found that 85%
10 fulfilled one major criteria and that referral occurred as an average 14 months before death.
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15 Interestingly in the study by Singh et al [55] prognostic assessment alone using the
16 Surprise question had no effect on referral to palliative care including the outpatient setting.
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19 The only study looking at implementing an intervention to improve referral to ambulatory
20 palliative care was planned by a cancer center in Texas as a quality improvement intervention,
21 including, in a plan-do-study-act cycle, the adoption of a symptom assessment tool and a referral
22 pathway in oncology clinics. Their initial results show a 10 fold increase of referrals after
23 implementation, from 0.07% of all oncology clinic encounters to 0.8%. It is unclear how
24 satisfactory this result can be considered, given the modest number of referrals, in particular
25 because the relationship with high symptom score is not consistent with such a low referral rate.
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27 The study is still under development [56].
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32 The PCRS project

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34 The primary aim of our study is therefore to develop and implement a palliative care referral
35 system which takes into account the suggestions from the literature in combination with consensus
36 between oncology and palliative care specialists. It is anticipated that in an implementation study
37 with the aim of intervening on clinical practices, evidence based concepts need to be combined with
38 professional interaction, knowledge of service availability, professional trust and resource allocation
39 that avoid extra workload burden and alert fatigue [57].
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45 Palliative care integration has been available at our center since 2001 [58] and we recently
46 described its operational characteristics on a consecutive lung cancer patients population seen at a
47 thoracic oncology clinic. In a two year period, 43% of patients were referred to palliative care
48 clinics, mainly for symptom control, usually pain and or dyspnoea, and poor performance status.
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50 The mean duration of outpatient palliative care was 128 days [59].
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54 The pre and post implementation study design in this protocol will give information on the
55 feasibility of the PCRS, its impact on user experience of care, patient quality of life and use of
56 health care resources. Ideally, a cluster randomized trial design would be preferable but at least
57 6-8 first level units (hospitals) should be involved for the results to be robust, and this is beyond
58 resources allocated to this research. An individually randomized design, instead, may not be
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adequate for the evaluation of a complex intervention with a high contamination risk. Furthermore the evidence of the potential efficacy of PC referral implementation are still to be shown. Considering these limitations the aim of the study is not to provide a final estimate of the effectiveness of PC needs screening but to provide a first estimate of feasibility and impact. Study completion would also allow the subsequent integration of the PCRS, or of some of its components [13], at the institutional level in order to steer a change in clinical practice to augment palliative and oncology integration and improve patient care.

The study is part of a nationally funded program (Finalizzata di Rete NET-2018-12367032 - funded by the Italian Ministry of Health and by Regione Lombardia) to address the recognition and response to palliative care needs in different patients populations and has the opportunity to raise awareness at the national level about the importance of palliative care integration at the outpatient level. The national program finalization could strengthen directions for the Ministry of Health to allocate resources for recognizing the lack of specialized palliative care services at acute hospitals and promoting their implementation.

Ethics Ethical approval for the study has been granted by the Institutional Review board of the Fondazione IRCCS Istituto Nazionale Tumori, approval reference INT201/19. The protocol of the pretest-posttest quasi-experimental design was registered on ClinicalTrials.gov database (NCT04936568).

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Author Contributions

Conceptualization: CB, EZ, AP, PB, MC, SLD, VF, AT, CBe, MB, AR, MN, PS, SP, SA, GT, FDB, AC

Writing—original draft preparation: CB, EZ, AP, PB, MC, SLD, VF, CBe, MB, AR, MN, PS, SP, SA, GT, FDB, AC

Writing—review and editing: CB, EZ, AP, PB, MC, SLD, VF, CBe, MB, AR, MN, PS, SP, SA, GT, FDB, AC

Supervision: CB, EZ, AC

All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

AC has received consultant honoraria from Mundipharma, Pfizer/Eli Lilly Italia Spa, Angelini, Shionogi, Molteni and Kyowa Kirin. He has also received research grants from Molteni & C Soc Esercizio Spa and Ipsen.

EZ has received consultant honoraria from Amgen.

MN has received travel expenses from Celgene, speaker honorarium from Accademia della Medicina and consultant honoraria from EMD Serono, Basilea Pharmaceutica, Incyte and MSD Italia.

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AP, PB, MC, SLD, VF, CBe, MB, PS, SP, SA, AR, GT and CB declare no conflicts of interest.

Figure 1: Project scheme

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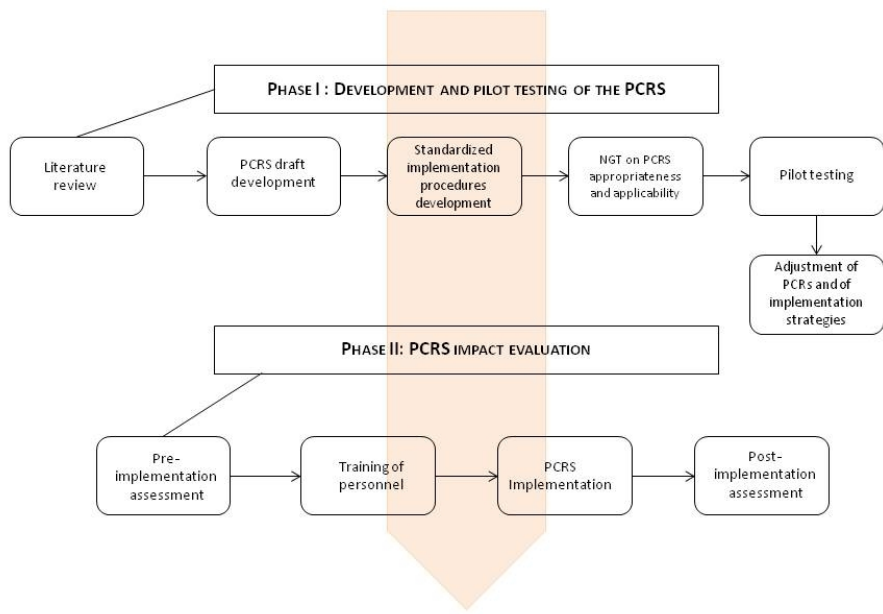


Figure 1: Project scheme
254x190mm (96 x 96 DPI)

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Outpatient Palliative Care Referral System (PCRS) for patients with advanced cancer. An impact evaluation protocol.

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3 **Outpatient Palliative Care Referral System (PCRS) for patients with advanced cancer. An**
4 **impact evaluation protocol.**
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9 Cinzia Brunelli^{1*}, Ernesto Zecca^{1*}, Alessandra Pigni¹, Paola Bracchi¹, Mariangela Caputo¹, Silvia
10 Lo Dico¹, Viviana Fusetti¹, Antonino Tallarita¹, Cristiana Bergamini², Marta Brambilla²,
11 Alessandra Raimondi², Monica Niger², Salvatore Provenzano², Pierangela Sepe², Sara Alfieri³,
12 Gabriele Tinè⁴, Filippo De Braud^{2,5} and Augusto Caraceni^{1,5}
13
14
15

16 * Equally first Authors
17
18

19 ¹ Palliative care, Pain Therapy and Rehabilitation Unit, Fondazione IRCCS Istituto Nazionale dei Tumori,
20 Milan, Italy.
21

22 ² Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.
23

24 ³ Clinical Psychology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.
25

26 ⁴ Unit of Clinical Epidemiology and Trial Organisation, Fondazione IRCCS Istituto Nazionale dei Tumori,
27 Milan, Italy.
28

29 ⁵ Università degli Studi di Milano , Milan, Italy.
30

31 **Corresponding author**

32 Ernesto Zecca, MD

33 Palliative care, Pain Therapy and Rehabilitation Unit,

34 Fondazione IRCCS Istituto Nazionale dei Tumori

35 via Venezian, 1- 20133 Milano, Italy

36 ernesto.zecca@istitutotumori.mi.it
37
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41 **Key words:**

42 early outpatient palliative care, advanced cancer, referral, oncology palliative care integration
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Abstract

Introduction. Early palliative care (PC) in the clinical pathway of advanced cancer patients improves symptom control, quality of life and has a positive impact on overall quality of care. At present, standardized criteria for appropriate referral for early PC in oncology care are lacking. The aim of this project is to develop a set of standardized referral criteria and procedures to implement appropriate early PC for advanced cancer patients (the Palliative Care Referral System, PCRS) and test its impact on user perception of quality of care received, on patient quality of life and on the use of healthcare resources.

Setting. Selected oncology clinics and palliative care outpatient clinic.

Methods and analysis. A scoping literature review and an expert consultation through a nominal group technique will be used to revise existing referral tools and to develop a new one, the PCRS. 25 patients will be enrolled in a pilot study to assess feasibility of the implementation of PCRS; 10 interviews with patients and health care professionals will be carried out to evaluate applicability. A pretest-posttest quasi-experimental study involving 150 patients before implementation of the PCRS and 150 patients after implementation will be carried out.

Patient satisfaction with care received, quality of life and use of resources, and caregiver satisfaction with care will also be assessed to explore the impact of the intervention.

Ethics and dissemination. Ethical approval for the study has been granted by the Institutional Review board of the Fondazione IRCCS Istituto Nazionale Tumori; approval reference INT201/19. Results will be disseminated through open access publications and through scientific communication presented at national and international conferences.

Trial Registration. The pretest-posttest trial was registered on ClinicalTrials.gov database (NCT04936568).

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Strengths and limitations of this study
<ul style="list-style-type: none">➤ The development of the palliative care referral system (PCRS) is based on published evidence and consensus among oncology and palliative care professionals.➤ Nominal group technique is particularly adequate to reach clinical practice consensus for subsequent implementation.➤ The pre and post-implementation study can provide evidence on the feasibility of the PCRS and its clinical impact.➤ Limitations include the single-centre and non-randomized study design.

- For peer review only

Introduction

Palliative care (PC) is aimed at reducing or preventing suffering and improving quality of life for patients affected by incurable advanced illnesses and their caregivers. Traditionally PC has been limited to the terminal phase of illness with an unclear impact on overall disease trajectory. In recent years the term “early palliative care” has been coined to describe an anticipated approach to PC in the care pathway of advanced diseases. In the case of advanced cancer, this means that PC can already start along with treatments such as chemotherapy, radiotherapy and other disease modifying interventions, planned for the management of advanced disease [1].

According to the latest American Society of Clinical Oncology consensus on integration of PC into standard oncology care, PC is defined early when administered within eight weeks from the diagnosis of advanced cancer, a definition that is too generic to be operationally implemented [2]. As shown in systematic literature reviews [1] randomized controlled trials demonstrate that the introduction of outpatient PC from the time of diagnosis of advanced cancer is associated with benefit on several clinical and care dimensions [1].

On the other hand, early PC is associated with less aggressive cancer treatment at the end of life, such as reduced use of chemotherapy in the last weeks of life and reduced access to intensive care units and emergency rooms [3].

Despite the evidence on the benefit of early PC, there is no standard definition of how oncologists should decide to refer patients to the PC specialist once advanced or metastatic disease is diagnosed. To optimize the potential impact of EPC on the overall care pathway, it would be important to combine the capacity of PC teams to participate timely in the shared decision-making process (including patient, family and attending oncologist), and, at the same time, the capacity of the multidisciplinary oncology team to integrate the advice of the PC specialist [4].

Without a suitable patient selection process for palliative care referral, outpatient palliative care services may be overwhelmed by excessive and perhaps inappropriate requests or, alternatively, resources could be underutilized if referrals do not occur. At present the volume and timing of referral to outpatient PC for cancer patients vary widely among services. This can be in part explained by the lack of standardized referral criteria for outpatient PC, coupled with variable oncologists’ attitudes and beliefs about PC and differences in models and availability of PC services [4].

It would be desirable to provide a personalized care plan for each patient, taking into account different diseases trajectories and identifying the timing and the ways in which patients can be referred to PC. Criteria establishing the right moment for the right patient for referral including are

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3 needed to personalize care pathways and optimize resource allocations to improve care outcomes.

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5 This project has a twofold aim:

- 6
7 1. To develop and study the feasibility of a standardized palliative care referral system (PCRS)
8 for outpatient PC in advanced cancer patients.
- 9
10 2. To evaluate the impact of routine application of the PCRS in a population of patients cared
11 for in a comprehensive cancer centre.

12 13 14 15 **Methods and analysis**

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17 The project has been organized into two main sequential phases and second level steps as
18 reported in Figure 1. The study intervention will be applied within several selected oncology clinics
19 covering both frequent and rare cancers (lung, gastrointestinal, genitourinary, head & neck and
20 sarcoma) and the PC outpatient clinic. In our PC clinic patients regularly encounter PC specialists
21 and are assessed by nurses for symptoms and psychosocial dimension using validated self reported
22 questionnaires [5]. Psychological consult is also available as needed. For each oncology clinic one
23 oncologist will participate directly in the study procedures.

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34 **Phase I: Development and pilot testing of the PCRS**

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36 Criteria used for PC referral in advanced cancer patients will be identified through a scoping
37 review of the literature on existing PC needs screening tools and methods (Table 1). The choice of
38 the criteria that will constitute the PCRS will be based on their clinical relevance and prognostic
39 value; existing criteria will be modified if needed. A first draft of the PCRS tool will be developed
40 and its appropriateness and feasibility in routine clinical practice will be evaluated using Nominal
41 group technique (NGT) [6] carried out with different health care providers (oncologists, PC
42 specialists, nurses and psychologist) with extensive experience in oncology and palliative care.
43 NGT is a qualitative research methodology aimed at verifying the possible convergence of a group
44 of experts on an idea, judgment or proposal. NGT consists of six stages [7]: 1. Presentation of the
45 nominal question; 2. Individual generation of ideas or voting; 3. Round-robin feedback from
46 participants to record each idea/voting; 4. Group discussion of each idea/voting in turn for
47 clarification and evaluation; 5. Individual voting on priority ideas with the group decision derived
48 through rank-ordering or rating; 6. Sharing of results, further discussion and re-voting. Based on the
49 NGT results, the PCRSs will be adjusted/modified as needed and standard implementation
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3 procedures will be developed.

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5 Then a pilot cross-sectional feasibility study on the application of the PCRS will be carried
6 out on 5 consecutive patients in each of the 5 outpatient clinics that will be involved in the Phase II
7 of the project. Feasibility assessment will include: time needed to screen the patient, number of
8 patients for which the screening was complete, number of missing data for each criterion.
9
10 Acceptability of PCRS by patients and by health care professionals, as well as integration of the
11 assessment procedure with routine clinical practice will also be evaluated through debriefing
12 interviews with 5 patients and 5 health care professionals. A final revision of the PCRS and of its
13 implementation procedure by the study group will follow the pilot testing.
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20 **Phase II: PCRS implementation and impact evaluation.**

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22 The potential impact of the PCRS will be explored using a quasi-experimental study design
23 measuring study endpoints before and after PCRS implementation (Figure 1).
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25 Study design and patient population

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27 A longitudinal pretest-posttest design will be carried out. Two different cohorts of advanced
28 cancer patients will be enrolled before (pretest) and after (posttest) the introduction of the PCRS in
29 outpatient clinics. Patient inclusion criteria are: age >18 years; diagnosis of inoperable locally
30 advanced and/or metastatic cancer. Exclusion criteria: eligibility to anticancer treatment with
31 advanced and/or metastatic cancer. Exclusion criteria: eligibility to anticancer treatment with
32 curative intent; patients already enrolled in a PC program; cognitive impairment.
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36 PCRS implementation

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38 For implementing the PCRS, patient clinical assessment will be performed initially by a
39 nurse, collecting self reported questionnaires and partially completing the PCRS. This evaluation
40 will be entered in the electronic medical records and then integrated and validated by the oncologist
41 during the visit. The oncologist will finally decide to refer or not the patient to PC using the PCRS
42 predefined criteria and his or her clinical judgment.
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46 Study Outcomes and assessment methods

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48 The following outcomes will be evaluated: patient's satisfaction with care (main outcome), patient's
49 quality of life, caregiver's satisfaction with care, use of health care resources, and end of life care
50 quality indicators.
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54 The FAMCARE-P13 will be used to assess patient satisfaction with care in the present
55 study. It is a 13 item self-report questionnaire, developed to be used with advanced cancer patients
56 [8]. Its items are rated from 1 (very dissatisfied) to 5 (very satisfied) producing a single satisfaction
57 score ranging from 13 to 65.
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3 The EORTC Quality of Life Questionnaire Core 15 for Palliative Care (QLQ-C15-PAL) [9]
4 will be used to evaluate patients' quality of life. QLQ-C15-PAL is an abbreviated 15-item version
5 of EORTC-QLQC30 specifically developed for use in a palliative care setting. It includes two
6 multi-item functional scales (physical and emotional functioning), two multi-item symptom scales
7 (fatigue and pain), five single-item symptom scales (nausea/vomiting, dyspnoea, insomnia, appetite
8 loss and constipation) and a question regarding overall QoL (global health status). Items are rated
9 on a Likert scale from 1 (not at all) to 4 (very much) with the exception of global health status,
10 which is rated from 1 (very poor) to 7 (excellent).
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17 Family satisfaction with care will be assessed with the FAMCARE scale [10, 11]. It is a self-
18 assessment satisfaction composed of 20 items rated according to a 5-point Likert scale from 1 (very
19 satisfied) to 5 (very dissatisfied). The items are grouped into four subscales: Physical patient care,
20 Information giving, Availability of care and Psychosocial care subscale.
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22 The FAMCARE Scale can be administered to family members while a patient is receiving palliative
23 care or at some point after a patient's death.
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28 All tools applied are validated in Italian language but the FAMCARE P-13, which will be
29 culturally adapted from English using "forward-backward" translation method [12] as part of the
30 present project; basic psychometric properties will be assessed as well.
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33 Use of health care resources during study follow-up will be monthly assessed by a dedicated
34 research nurse with an ad-hoc developed form reporting: access to a PC service (regular outpatient
35 PC visits, home care, hospice admission), number of multidisciplinary team visits (oncology and
36 PC), number of hospitalization and of emergency department admission, with reason and duration..
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39 For those patients who will die during the follow-up period, a dedicated research nurse will
40 collect the following data relative to the last 30 days of life: active oncological treatments
41 administration (chemotherapy, radiotherapy, immunotherapy, etc.) and date of last administration,
42 number of ER visits, hospitalization (number and length in days), activation of any PC service
43 (home care or hospice) and place of death. The above information will allow us to calculate end-of-
44 life care quality indicators, like the proportions of patients with chemotherapy in the last 14 days of
45 life [3].
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55 For all data to be collected, Table 1 reports the assessment tools and the timing of various
56 assessments. Eligible patients will undergo FAMCARE P-13 and EORTC QLQC15-PAL
57 evaluation at baseline and then monthly for at least 6 months from enrollment or till death (T1, T2,
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3 T3, T4, T5, T6). The choice of interviewing patients every month is suggested by the need to
4 minimize attrition due to potential patients drop out and also to take into account the frequent
5 possible changes in clinical conditions in a fragile patient population. FAMCARE will be
6 administered to the main caregiver identified by the patient at T0, T3 and T6 or after patient's
7 death in patients who will die during the follow-up. Patient and caregiver reported outcomes will
8 be collected through telephone interview. This method was chosen in order to avoid contamination
9 between the pre- and post- PCRS implementation groups; in fact the PCRS implementation in the
10 posttest group will be based also on patient reported symptom assessment which will be
11 electronically collected [13]. Health care professional reported data will be collected using
12 REDCap electronic data capture tools hosted at Fondazione IRCCS Istituto Nazionale dei Tumori
13 of Milan

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21 The planned duration of the entire project, considering phase 1 and phase 2, is 4 years (15
22 September 2020-14 September 2024)
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DATA	REPORTED BY	TOOL	T0 Baseline	T1 30±3days	T2 60±3days	T3 90±3days	T4 120±3days	T5 150±3days	T6 180±3days	EOS (*)
Socio-Demographic	PATIENT	Ad hoc form (eCRF)	X							
Clinical	RN/MD	Ad hoc form (eCRF)	X	X	X	X	X	X	X	
Patient satisfaction with care	PATIENT	FAMCARE P13	X	X	X	X	X	X	X	
Quality of life	PATIENT	EORTC-C15 PAL	X	X	X	X	X	X	X	
Caregiver satisfaction with care	CAREGIVER	FAMCARE	X			X			X	(X)
Use of health care resources	RN	Ad hoc form (eCRF)		X	X	X	X	X	X	
End of life care quality indicator	RN	Ad hoc form (eCRF)								(X)

Table 1: Data collection during study period

Legenda: RN = research nurse; MD = medical doctor; eCRF = electronic case report forms; EOS = End of study;

* End of study assessments will be performed only for those patients who die within the study follow-up period.

Power considerations and statistical analysis

The main endpoint is the variation in patient's satisfaction between baseline and the average of repeated follow-up assessments. t-test for independent samples on this endpoint will be used to compare pre- and post- referral patient cohorts. Power calculations [14] indicate that 150 patients in each group will allow a two tailed t-test for independent samples, a power of 0.9 to detect an effect size of 0.375 with alpha error=0.05. In case of a 15% attrition rate the study power reduces at 85%, all else unchanged. The same analysis scheme will be applied for all continuous repeated measurement outcomes, while binary outcomes (i.e. activation of PC during follow-up or chemotherapy administration during the last month of life) will be analyzed using logistic regression models. Linear and logistic regression models will be used for covariate adjustment estimations.

Data sharing

De-identified data of participants in this project will be available from the project principal investigator (AC) upon request, provided that the data reuse is in agreement the European General Data Protection Regulation 2016/679 (GDPR).

Patient and public involvement

No patient nor other member of the public was involved in the development of this research project.

Discussion

Early palliative care referral, while concurrent anti-neoplastic treatment is still possible and indicated, is considered to improve integration of palliative care in the clinical pathway of patients with advanced disease who cannot achieve cure with the available antineoplastic treatments [2]. This general statement is based on several clinical trials [1] showing advantages of early access to palliative care in improving patient's quality of life, psychological distress, use of health care resources at the end of life and caregivers' distress.

Different early palliative care models

These trials were however based on different clinical models and settings. The model which was more consistently tested as an experimental intervention has been based on the access of patients to specialized palliative care outpatient clinic. In fact, the implementation of this model [15-22] has more consistently shown efficacy if compared with other interventions of care coordination without direct encounters between patients and palliative care professionals [23-26]. This has been also described as an "integrated care model" [27, 28].

Within the integrated model trials, the number and duration of encounters of patients with

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3 palliative care professionals varied from 1 every 1.3 weeks to 1 every 6 weeks with a total mean
4 number of visits during the study period ranging from 2.4 to 8.9. Two of the three negative studies
5 on the integrated model [15, 21] resulted in very limited if any access to specialized palliative care
6 visits. The third one acknowledged significant in between trial arms contamination [22].
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10 Also qualitative type evidences from the same trials support subjective appreciation of
11 clinical value attributed by patients to integrated palliative care interventions. Patients and
12 caregivers considered specialized outpatient palliative care capable of providing personalized and
13 prompt symptom management, holistic support to patients and caregivers, guidance in decision
14 making and preparation for the future [29]. Another study addressed specifically the clinical content
15 of early outpatient palliative care and showed that interventions based on psychological and cognitive
16 coping, disease understanding, decision making and care planning were associated with lower
17 psychological distress and better use of health care resources at the end of life [30]. Finally, the study
18 by Costantini et al. [31] shows that an early integration of specialized palliative care after the
19 diagnosis of advanced cancer is feasible and well accepted by patients, relatives and, to a lesser
20 extent, by oncologists.
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23 Palliative care needs selection criteria

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25 Overall these data confirm the usefulness of the palliative care outpatient clinic approach,
26 with specialized clinical skills and multidimensional assessment, for patients with advanced cancer
27 but the selection criteria used in the clinical trials are difficult to translate into clinical practice. The
28 trials aimed at demonstrating efficacy and detecting outcome changes at the group level, while
29 statistically accounting for patients heterogeneity. In clinical practice the decision to refer a patient
30 to palliative care outpatient clinic needs instead to be individualized. Therefore trials' result cannot
31 clarify how to guarantee timely access at the individual level and to optimize resource allocation.
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33 Trials are also not enough to change clinical practice, without taking into account practical and
34 cultural barriers that impact on palliative care perception by oncologists and patients [28, 32].
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38 In summary the best ways to address earlier palliative care needs identification, timely
39 access to outpatient palliative care and also to overcome barriers to integration with oncology are
40 still unresolved issues, and yet late referral is considered to be a significant barrier in many cases
41 [28, 32-36].
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45 The literature discussion about criteria to be used and the domains to be assessed, beyond the
46 stage of the disease, already considered in all trials, includes symptoms, psychosocial distress,
47 prognosis, trigger disease related events and critical care planning issues [4, 37-39]. A number of
48 palliative care need screening and assessment instruments have been developed and sometimes
49 tested [39-50] but only a few of them were specifically designed to improve appropriate selection of
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3 cancer patients for referral to outpatient specialized palliative care [4, 51]. In the study by Paiva et
4 al., the use of the PC referral tool would have increased referral rate by 3.2 fold [51]. There are no
5 studies nor agreed guidelines upon criteria to guide timely referral [48, 52, 53] beyond disease stage
6 [2, 4].
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10 Hui et al. [27] published a Delphi study building a consensus on referral criteria among a
11 number of palliative care expert identifying major and minor criteria and suggesting that referral
12 should occur anytime one major criterion is met. The same Authors [54], in a retrospective
13 assessment of the characteristics of patients referred to their palliative care clinic, found that 85%
14 fulfilled one major criteria and that referral occurred as an average 14 months before death.
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18 Interestingly in the study by Singh et al [55] prognostic assessment alone using the
19 Surprise question had no effect on referral to palliative care including the outpatient setting.
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22 The only study looking at implementing an intervention to improve referral to ambulatory
23 palliative care was planned by a cancer center in Texas as a quality improvement intervention,
24 including, in a plan-do-study-act cycle, the adoption of a symptom assessment tool and a referral
25 pathway in oncology clinics. Their initial results show a 10 fold increase of referrals after
26 implementation, from 0.07% of all oncology clinic encounters to 0.8%. It is unclear how
27 satisfactory this result can be considered, given the modest number of referrals, in particular
28 because the relationship with high symptom score is not consistent with such a low referral rate.
29 The study is still under development [56].
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32 The PCRS project

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34 The primary aim of our study is therefore to develop and implement a palliative care referral
35 system which takes into account the suggestions from the literature in combination with consensus
36 between oncology and palliative care specialists. It is anticipated that in an implementation study
37 with the aim of intervening on clinical practices, evidence based concepts need to be combined with
38 professional interaction, knowledge of service availability, professional trust and resource allocation
39 that avoid extra workload burden and alert fatigue [57].
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43 Palliative care integration has been available at our center since 2001 [58] and we recently
44 described its operational characteristics on a consecutive lung cancer patients population seen at a
45 thoracic oncology clinic. In a two year period, 43% of patients were referred to palliative care
46 clinics, mainly for symptom control, usually pain and or dyspnoea, and poor performance status.
47 The mean duration of outpatient palliative care was 128 days [59].
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51 The pre and post implementation study design in this protocol will give information on the
52 feasibility of the PCRS, its impact on user experience of care, patient quality of life and use of
53 health care resources. Ideally, a cluster randomized trial design would be preferable but at least
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3 6-8 first level units (hospitals) should be involved for the results to be robust, and this is beyond
4 resources allocated to this research. An individually randomized design, instead, may not be
5 adequate for the evaluation of a complex intervention with a high contamination risk.
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8 Furthermore the evidence of the potential efficacy of PC referral implementation are still to be
9 shown. Considering these limitations the aim of the study is not to provide a final estimate of the
10 effectiveness of PC needs screening but to provide a first estimate of feasibility and impact.
11
12 Study completion would also allow the subsequent integration of the PCRS, or of some of its
13 components [13], at the institutional level in order to steer a change in clinical practice to augment
14 palliative and oncology integration and improve patient care.
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17
18 The study is part of a nationally funded program (Finalizzata di Rete – project ID NET-2018-
19 12367032 to AC – funded by the Italian Ministry of Health and by Regione Lombardia) to address
20 the recognition and response to palliative care needs in different patients populations and has the
21 opportunity to raise awareness at the national level about the importance of palliative care
22 integration at the outpatient level. The national program finalization could strengthen directions for
23 the Ministry of Health to allocate resources for recognizing the lack of specialized palliative care
24 services at acute hospitals and promoting their implementation.
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32 **Ethics and Dissemination** Ethical approval for the study has been granted by the Institutional
33 Review board of the Fondazione IRCCS Istituto Nazionale Tumori, approval reference
34 INT201/19.
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37 The protocol of the pretest-posttest quasi-experimental design was registered on
38 ClinicalTrials.gov database (NCT04936568).
39
40

41 Patients and caregivers will be enrolled in the pre-test and post-test after obtaining informed
42 consent.
43
44

45 Dissemination of the study results will occur through publications in peer-reviewed open-access
46 scientific journals and the presentation of data at national and international conferences.
47
48
49

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53
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55

56 **Author Contributions**

57
58 Conceptualization: CB, EZ, AP, PB, MC, SLD, VF, AT, CBe, MB, AR, MN, PS, SP, SA, GT,
59 FDB, AC
60

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2
3 Writing—original draft preparation: CB, EZ, AP, PB, MC, SLD, VF, CBe, MB, AR, MN, PS, SP,
4 SA, GT, FDB, AC

5
6 Writing—review and editing: CB, EZ, AP, PB, MC, SLD, VF, CBe, MB, AR, MN, PS, SP, SA,
7 GT, FDB, AC

8
9 Supervision: CB, EZ, AC

10
11 All authors have read and agreed to the published version of the manuscript.
12
13

14 15 **Conflicts of Interest**

16
17 AC has received consultant honoraria from Mundipharma, Pfizer/Eli Lilly Italia Spa, Angelini,
18 Shionogi, Molteni and Kyowa Kirin. He has also received research grants from Molteni & C Soc
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21
22 EZ has received consultant honoraria from Amgen.
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24 MN has received travel expenses from Celgene, speaker honorarium from Accademia della
25 Medicina and consultant honoraria from EMD Serono, Basilea Pharmaceutica, Incyte and MSD
26 Italia.
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29 FDB has received consultant honoraria from Roche, EMD Serono, NMS Nerviano Medical
30 Science, Sanofi, MSD, Novartis and Incyte. He has received speaker honoraria from BMS,
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37 AP, PB, MC, SLD, VF, CBe, MB, PS, SP, SA, AR, GT and CB declare no conflicts of interest.
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41 Figure 1: Project scheme
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45 Word Count: 3672
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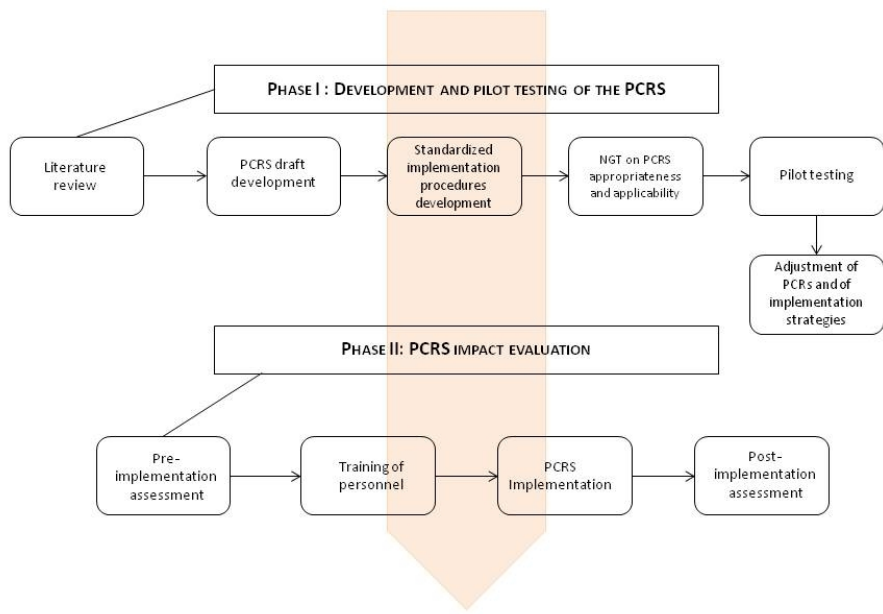


Figure 1: Project scheme

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