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Early palliative care for cancer patients

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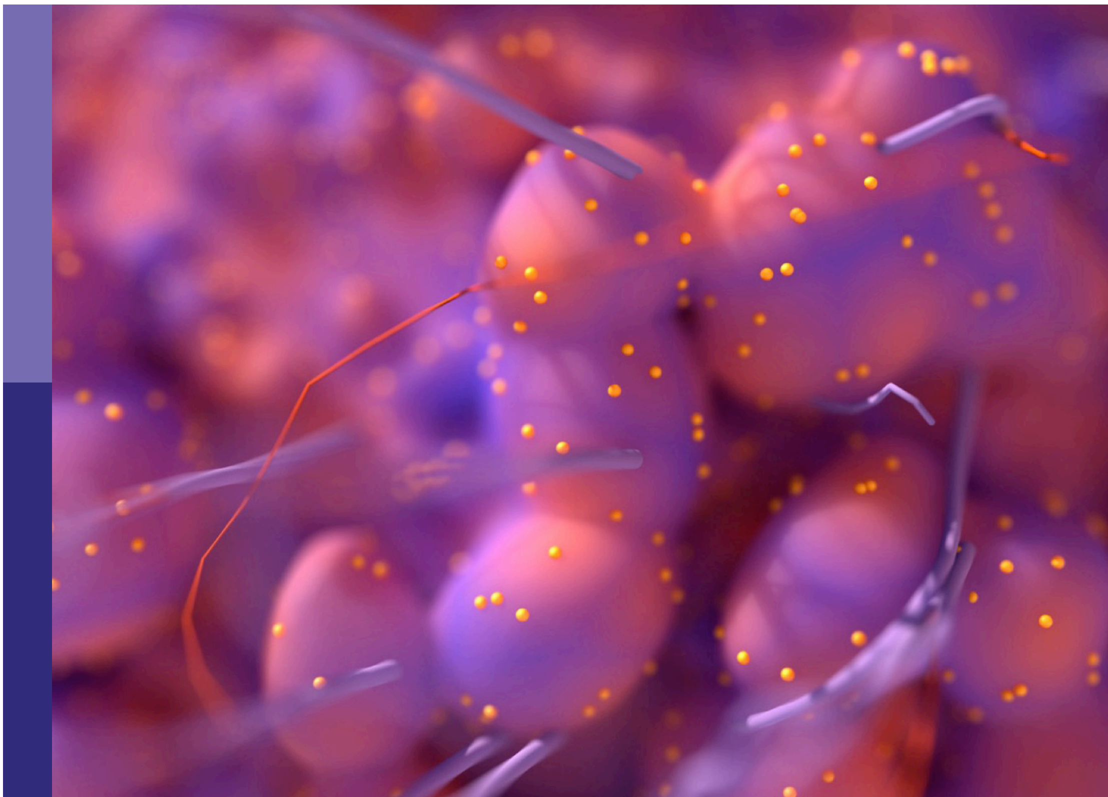

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Early palliative care for cancer patients

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Editorial: Early palliative care for cancer patients

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early palliative care, end of life care, multidisciplinary approach, advanced cancer patients, patients needs

Editorial on the Research Topic
Early palliative care for cancer patients

In the past, oncological palliative care (PC) had been identified as “end-of-life palliative care” (EoLPC), and EoLPC always began by carrying out a prognostic evaluation of life expectancy when antitumor therapies had been exhausted. In recent years, however, this approach has been modified, giving way to a process of PC based on needs, not only at the end of life, and not only after having withdrawn all antineoplastic treatments. This non-EoLPC process has been variously identified as early palliative care (EPC), simultaneous palliative care (SPC), or timely palliative care (TPC) (1–3). EPC is generally delivered together with anticancer therapies, while EoLPC represents the unique treatment delivered at that end of the disease trajectory.

From an organizational point of view, EPC is mainly provided in outpatient and consultant settings within acute hospitals, while EoLPC is mainly in home-care programs or hospice residential facilities (4). The best methods of activation of palliative care and referral to the palliative care team by oncologists are still the subject of studies and clinical research (5). Timely provision of seamless palliative care across all settings must be guaranteed without interruptions (6).

EPC has among its aims a favorable impact on the quality of life, on the quality of care, and finally on costs (7). In fact, in addition to objectives related to individual patient benefits, a personalization of treatment can allow a more appropriate use of health care services and an impact on indicators of therapeutic aggressiveness at the end of life: timelier referral to end-of-life palliative care and reduction of futility of treatments (8).

Clinical trials and systematic reviews have highlighted, among the outcomes on which efficacy has been demonstrated, quality of life, symptom burden, satisfaction, communication, caregivers outcomes, EoL care, and, with more controversial evidence, survival (9, 10).

In some cases, systematically activated EPC did not have a clinically or statistically favorable impact. Reasons for possible lack of effectiveness can be the model of EPC intervention (monoprofessional vs. multiprofessional; remote vs in-person specialized contact), risk of contamination and/or crossover with the conventional arm, study duration, timing of evaluation, timeliness of cohort inception (this will probably differ for different cancer types), level of symptom burden, and reduced QoL of recruited patients (11).

A topic under discussion is whether palliative care can be provided by professionals with two different levels of expertise: a basic one (for example, oncologists capable of ensuring a good palliative approach) and a specialized one (palliative care specialists who are dedicated full-time to palliative care delivery). These two levels are indeed both essential, and one of them alone cannot exhaustively perform the functions of both (12–14). The specification of hematological pathologies could lead to the identification of specific models of EPC intervention.

Finally, it is possible that different health systems, in low-income and high-income countries, recognize the need for different models of PC integration (6).

From what is described above, it follows that some aspects relating to EPC have been confirmed, while for others further research is necessary. The process of collating articles on these topics aimed to highlight issues still worthy of research that had not been completely clarified.

Some articles in this Special Issue have focused on the most appropriate way to activate EPC. The integration of clinical practice and education programs and clinical research can demonstrate the usefulness of PC programs in cancer research centers and promote program penetrance. (Alquati et al.) Moreover, a qualitative study reports how improved communication by treating oncologists can contribute to a timely and appropriate activation of EPC (Collins et al.).

The search for triggers to integrate standardized early palliative care (STEP care) has proved to be feasible for certain primary neoplasms (brain) but not for others, representing the need to activate EPC in a modulated way for individual pathologies and not in the same way for all tumors, binding to specific objectives, and identifiable and visible parameters (Collins et al.). A very early screening of palliative care needs can be performed in low-income countries with a simple and reproducible instrument such as the Distress Thermometer (Abu-Odah et al.). Even in developed countries, a structured low-threshold screening program for supportive and palliative can preserve several dimensions of quality of life as a comprehensive multidimensional assessment (Solar et al.).

Some outcomes of EPC were also evaluated. It has been reported that therapeutic appropriateness can occur in palliative radiotherapy using validated prognostic scores, including the Palliative Prognostic Score (PaP Score) already used in other end-of-life settings (Maltoni et al.). Another proved outcome is gratitude from patients and their families for the care received in the EPC program (Borelli et al.). Finally, particular attention should be paid to the outcomes of the EPCs relating to sub-populations that require particular attention and support: women and younger adults (Galiano et al.).

Finally, two papers focus on the specifics of early palliative care in hematological and neurological pathologies (Tanzi and Martucci, Armitage and Fonkem).

The paper on PC research in hematologic cancer patients provides an expert opinion about what works, and how and for whom, in facilitating enrollment in PC studies for patients with hematological malignancies. A qualitative review regarding contexts, mechanisms, and outcomes (CMOs) was performed, and the resulting theory was informed by narrative research, along with a structured interview of PC experts and a pilot study by the authors. The work identifies some crucial points to carry out PC research in hematology, concerning the mutual perceptions of the different actors and the relationships between PC specialists and hematologists (Tanzi and Martucci).

The article concerning neurodegenerative pathologies underlines the aggressiveness of some neurological tumors compared to other non-oncological neurodegenerative pathologies slowly progressing. Glioblastoma (WHO Grade IV) and Parkinson's disease are mentioned as archetypes of the two trends. As result of a qualitative review of the literature, summarized by expert opinions, in glioblastoma the timely referral to early palliative care is recommended to improve quality of life, ensure a dignified death, and alleviate and ease grief and burden for family members and other caregivers. Specific points that are discussed are diagnosis, progression, and prognostication; patient and family education; and caregiver burden (Armitage and Fonkem).

In conclusion, medical oncology and palliative care are mutually necessary, and early and progressive integration must be pursued, with the support of clinical and organizational, which must be systematically and continuously promoted and supported (15–17).

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Lesson Learned From Hospital Palliative Care Service in a Cancer Research Center in Italy: Results of 5 Years of Experience

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Background: International studies have documented that over a third of all hospital beds are occupied by patients with palliative care needs in their last year of life. Experiences of Palliative Care Services that take place prevalently or exclusively in hospital settings are very few in Italy.

Objective: Describe clinical, educational and research activities performed by a hospital PCS and discussing opportunities and critical issues encountered in an Italian Cancer Center.

Method: Retrospective data regarding adults with advanced stage diseases referred from January 2015 to December 2019.

Results: *Clinical activity* - The PCS performed 2422 initial consultations with an average of 484 initial consultations per year. A majority of patients had advanced cancer, from 85% to 72%, with an average of 2583 total consultations per year and an average of 4.63 consultations per patient. The penetrance has increased over time from 6.3% to 15.75%. *Educational and research activity* - Since 2015, PCS has provided training to health professionals (HPs) of different departments of our hospital. Most of the educational projects for HPs were part of research projects, for example the communication training program, management of pain and end-of-life symptoms and the training program for PC-based skills.

Conclusion: Our data suggests that a PCS able to provide palliative care to inpatients and outpatient and continuous training support to other hospital specialists can relatively quickly improve the level of its penetrance in hospital activities.

Keywords: palliative care service, hospital, education, retrospective analysis, quality improvement, cancer

INTRODUCTION

Around the world, the demographic, epidemiological and social situation is constantly evolving with a progressive increase of patients suffering from chronic degenerative diseases and palliative care (PC) needs. The prevalence of adult patients with PC needs has been estimated to correspond to 1-1.4% of the European population (1–5) while each year the incidence of adult patients with PC needs in their last period of life has been estimated between 69% and 84% of all deaths/year (6, 7), with forecasts of further growth of these percentages (8). In Italy, the prevalence of adult patients with PC needs can be estimated at 524,000-733,000, while the incidence of patients with PC needs in their last period of life can be estimated at 465,000-517,000 (1).

Many international studies have documented that over a third of all hospital beds are occupied by patients in their last year of life, with palliative care needs that significantly affect their quality of life (9, 10). A large percentage of patients die in the hospital or are admitted to the hospital at least once in the last 6 months of life (11).

The Italian National Institute of Statistics (ISTAT) announced that in 2015, 42.6% of deaths occurred in the hospital, 39.6% at home, 5.7% in a hospice, and 9.2% in nursing homes, with a significant difference in mortality at home between the Italian regions of the Center-North (30.7%) compared to those of the South and the Islands (58.6%) (12).

In Italy, a specific law (13) in 2010 established the right of every citizen to access PC and pain therapy and established that regional and local Palliative Care Networks should be able to provide care to all people with PC needs, regardless of their age, pathology, and care setting. It is a highly innovative law, approved by the Italian Parliament unanimously, and which has received the consensus of public opinion and Italian palliative care professionals.

Unlike in the United States and in Western European countries, where continual growth in the number of Palliative Care Services (PCS) in hospitals has been reported (14–16), PC in Italy has developed from its outset primarily as a home care service and then in dedicated beds in hospices. Currently more than 300 hospices (17) and over 300 home PCSs are operating in Italy, while experiences of PCS that take place prevalently or exclusively in hospital settings are very few (10, 18).

Hospitals' PCSs are to be considered specialized second-level services, with staff who performs this activity full-time (or in any case as a prevalent activity), and who has completed an advanced theoretical and experiential training approach in the field of palliative medicine. This staff can face complex needs, and can implement training and quality improvement programs in the context in which it operates (19, 20). Studies, mostly performed in the United States, have reported that involvement of hospitals' PCSs was found to reduce the length of hospital stay, to improve communication regarding care goals, and to effectively improve quality of care for cancer patients, which resulted in a reduction in diagnostic tests, a decreased use of intensive care and less aggressive treatments during the last week of life (21–23).

The aim of this article is to describe clinical, educational and research activities performed by a hospital PCS in Italy and to discuss opportunities and critical issues encountered during PCS experience in an Italian Cancer Research Center.

PCS HISTORY

Our PCS is a specialized hospital-based unit with no dedicated beds in a Reggio Emilia hospital, a 900-bed cancer research hospital. The PCS was established in April 2013 as a part of a research project on implementation of early PC intervention in hospital for advanced cancer patients (24). At present, the PCS staff includes three senior physicians and two advance practice nurses, dedicated full-time to hospital palliative care (25), an advance practice nurse expert in training and a data manager dedicated to the collection and analysis of research project data.

The PCS assists outpatients and inpatients with advance oncological disease or chronic progressive illnesses. A psychologist is also involved in bi-weekly team meetings and in the care of patients and relatives with severe psychological suffering. PCS is very often involved in clinical situations and treatment pathways concerning end of life care that require ethical clarification (26). In these cases, the hospital's bioethicist is also called to attend team meetings to consult and discuss the best management of a specific case.

The vision of the PCS takes as reference the definition of palliative care proposed by the WHO in 2002 (27), with particular reference to the following points:

1. Awareness that palliative care needs are common to many different diagnoses, not one specific pathology;
2. Requirement of early identification, to ensure a gradual and appropriate response to palliative care needs also in association with interventions aimed at prolonging life;
3. Importance of extending palliative care basic skills to the entire hospital setting.

The mission of PCS is three-pronged:

1. patient assistance by performing inpatient and outpatient consultations
2. research activities in PC
3. specialized training to improve PC core skills in health care professionals.

The PCSs have acquired advanced skills that they can transmit to other hospital professionals, according to the model from the 2nd level (specialist) to the 1st level (non-specialist) professional (28). Educational activities are offered to hospital healthcare professionals and students with the aim to improve both the quality of patient care in their specific ward and the medical education that novice professionals receive.

The educational programs proposed to professionals (29–31) belong to research projects that evaluate qualitative and/or quantitative aspects and effects on the professionals themselves. Currently, the main three lines of research of our PCS concern studies on the outcomes of palliative care education, new integrated models of assistance and evaluation of palliative care needs in patients with chronic progressive illnesses.

DATA COLLECTION

Retrospective data regarding adults with advanced stage diseases (at least 18 years old at time of initial consultation) refers to the hospital PCS of Reggio Emilia from January 2015 to December 2019.

Data for the study has been extracted from the Local Health Service Clinical Data Repository (CDR) by the Clinical ICT Data Management unit. The CDR system gathers structured data from all clinical systems in use in the Reggio Emilia Local Health Authority in real time. The following data was extracted and processed for the study: date of death, date of admission, discharge and transfer (ADT), discharge information based on International Classification of Diseases Ninth Revision (ICD-9), E-Prescriptions and Administration information.

The data of prescription volumes of specific drugs were processed from database of the Computerized Prescription and Administration Program. All data are matched by means of a common patient identification code and a common patient contact identification code. For data protection regulatory purposes, all data extractions have been authorized and regularly traced and logged.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Ethic Committee AVEN (Protocol UCP ITA 2017 n. 81/2017).

RESULTS

Clinical Activity

In analyzing data of the clinical activity carried out for patients with palliative care needs, from January 2015 to December 2019, the PCS performed 2422 initial consultations, as shown in **Table 1**, with an average of 484 initial consultations per year.

A majority of patients had advanced cancer as primary diagnosis and were cared for at the Azienda USL-IRCCS Hospital in Reggio Emilia. However, as shown in **Table 1**, consultations were also given to patients with advanced non-oncological diseases, for example chronic renal disease or sclerosis lateral amyotrophic, showing a decrease in percentage of oncologic consultation from 85% to 72% of total consultations. From January 2015 to December 2019, the total consultations carried out by the PCS - in particular initial consultation, control visits and family conferences - were 12,917, with an average of 2583 consultations per year and an average of 4.63 consultations per patient. An important activity of the PCS is the family conference and 1373 of them were carried out from January 2015 to December 2019. Family conferences between the patient, their family and HPs are undertaken for multiple purposes, including the sharing of information and concerns, clarifying the goals of care, discussing diagnosis, treatment, prognosis and developing a plan of care for the patient and family carers (32).

Table 2 analyzes the number of days that patients remained in charge at the PCS from January 2015 to December 2019. During the years of activity of PCS, outpatient and inpatients remained in charge of the PCS for several days over time with an increasing trend in the days of care.

In the four years of activity analyzed, from 59% to 65% of cancer patients who were examined at least once by the PCS underwent CT or RT treatments at the time of the initial consultation.

The hospital was the place of death for 37 to 41% of patients who received at least one consultation from the PCS. The average number of days from admission to first consultation of the Palliative Care Service is 12 and the average number of days from first consultation or family conference to discharge is 10.

The penetrance, that is the percentage of cancer patients assessed by the PCS out of the total number of cancer patients hospitalized per year, has increased over time from 6.3% to 15.75% (**Figure 1**).

We also evaluated the impact of the specialist palliative care service on the use of some drugs for pain management in patients with palliative care needs.

In particular, we evaluated the prescription volumes of specific opioid drugs: morphine hydrochloride, methadone and specific drugs that are used in controlling end-of-life symptoms: haloperidol and subcutaneous or hypodermic midazolam in continuous infusion within the last 72 hours of life (**Figure 2**).

Moreover, we analyzed the prescription volume of therapies administered hypodermically and in infusion through elastomeric pump (**Figure 3**).

Educational and Research Activity

Since 2015, PCS has provided training to health professionals (HPs) of different departments of our hospital. Most of the educational projects for HPs were part of research projects, for example the communication training program performed for the Medical Oncology and Hematology Departments (33), projects carried out to improve the management of pain and end-of-life symptoms (31), and the training program, for PC-based skills for HPs from the Radiotherapy, Geriatrics and Nephrology/Dialysis wards (29).

Other projects have been implemented with the aim of training HPs to better recognize PC needs and to improve the appropriateness of requests for advice from PCS (30, 34).

PCS carries out, according to the needs of the ward, specific training on HPs (physicians and/or nurses) shared with the Bioethics Unit on palliative sedation or weekly meetings regarding the management of complex cases (35). The Bioethics Unit has also developed specific training on PCS professionals to advance first level ethical skills for consultancy (36).

We have been implemented research projects of early PC intervention in hospital for advanced cancer patients (24, 37) in which we used quality of life questionnaires and collected qualitative data.

We are currently developing a database of PSC activity that not only highlights the quantitative data, but that includes clinical data useful to better evaluate the outcome of our interventions, using some the Italian version of tools included in the Outcome Assessment and Complexity Collaborative Suite of Measure (OACC) (38).

TABLE 1 | Initial consultation from January 2015 to December 2019 and comparison between initial consultation of patients with oncological disease and patients with non-oncological disease.

YEAR OF ACTIVITY	TOTAL INITIAL CONSULTATIONS	INITIAL CONSULTATIONS OF PATIENTS WITH ONCOLOGICAL DISEASE	PERCENTAGE OF PATIENTS WITH ONCOLOGICICAL DISEASE
2015	441	375	85.03%
2016	495	431	87.07%
2017	505	420	83.16%
2018	443	363	81.94%
2019	538	388	72.11%
Total from 2015 to 2019	**2422**	**1977**	81.62%

DISCUSSION

In Italy, there are very few specialist PCSs dedicated full time to the care of hospitalized patients in public hospitals. To our knowledge, this study is the first to describe the activities and impact of this kind of specialist PCS in Italy. Even if administrative data is not amendable to fully describe the involvement of PCSs (39), it emerges that the performance of our PCS has grown over the years.

By evaluating the penetrance data with particular reference to the data of the American National Palliative Care Registry (40), our study shows how penetrance has significantly grown over time, with a penetrance quite superior to that of US hospitals with more than 500 beds. This data is in accordance with the vision of our PCS, the hospital's health policy and the changes in palliative care needs of the population worldwide (2). These results also highlight hospital need for PC specialist not only as an organizational tool for protected discharge but also to ensure outpatient activities and clinical support at the patient's bed in synergy with hospital wards.

We also believe that penetrance results obtained are partly due to the collaboration between PCS and hospital specialist teams. Although further studies are needed to validate PC penetration rates, a recent study by Gruhler 2017 (41) suggests that PC penetration rates could range from 17.6 to 26.4% in the total inpatient population. In our opinion, these positive results are linked to the continuous work of consultancy and sharing palliative care issues with other professionals, and also to specific programs of basic training on palliative care performed by the PCS in each department of our hospital (29–31).

Several strategies to manage and improve the penetration rate are already established by our service and we plan to proceed to implement these programs: we are carrying out research projects on the training of other professionals in diagnostic, therapeutic and assistance palliative care pathways and on better stratifying palliative care needs in different degrees of complexity. The aim of these projects is to improve the appropriateness of referrals to our specialized PCS. Some authors underline the importance of activating training courses to improve 1st-level skills among non-specialized PC professionals on basic principles of palliative care and to implement cooperation between the 1st and 2nd levels (28, 42, 43).

Hospital HPs recognize the expertise of PCS and the required specific training on specialized PC skills such as advance communication, treatment of pain, and palliative sedation. As in other published experiences (44), team-based learning supports the transferability of knowledge to clinical practice and the need for continuing PC training. The experience gained in recent years and the collaboration between PCS and the department has stimulated a rapid collaboration during the COVID-19 pandemic with the department at the forefront against the pandemic (30).

Over the five years analyzed, there was an increase of days in charge by PCS and number of first examinations of patients who were receiving active anticancer treatment. The greater knowledge of PCS by HPs, the educational and research project carried out and the consultations in simultaneous care have contributed to greater development of early palliative care.

Outpatient days in charge from 2015 to 2019 show an increasing rate with an average of patients in charge of more than 2 months. These results, in our opinion, could be related to a better knowledge of the PC Service by other professionals and a positive secondary outcome of the development of specific research projects (24, 29, 33).

Since the beginning of activity of the PCS, the volume of prescriptions of some drugs, such as opioids, haloperidol and midazolam, have increased in our hospital, and we also observed an increase in use of subcutaneous route for the administration of these drugs. The PCS educated hospital professionals on how to treat patients with pain and delirium and, when indicated, to manage palliative sedation with our support. Opioid analgesia is

TABLE 2 | Analysis of days in charge of the PCS.

Outpatients	2015	2016	2017	2018	2019
Average days in charge	13	12	38	53	77
Minimum and maximum number of days in charge	1-1904	1-1456	1-1232	1-876	1-565
Inpatients	**2015**	**2016**	**2017**	**2018**	**2019**
Average days in charge	8	8.5	12	18	20
Minimum and maximum number of days in charge	1-46	1-760	1-639	1-632	1-321

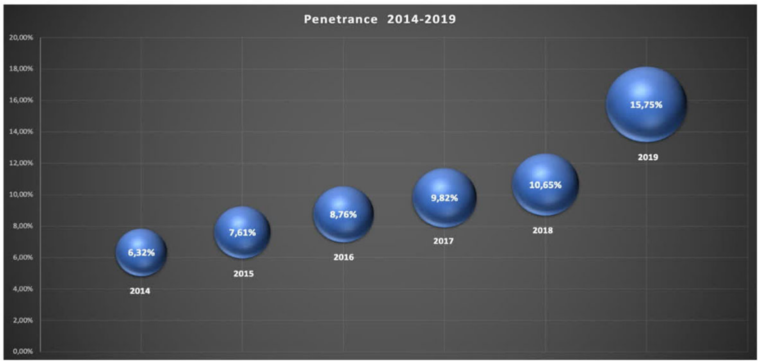

FIGURE 1 | Penetrance: the percentage of patients assessed by the PCS out of the total number of cancer patients hospitalized per year.

the recommended treatment for moderate to severe pain, the prevalence of which is estimated to be between 62% and 86% in advanced cancer patients (45).

Guidelines on cancer pain treatment suggest morphine as the drug of choice for the opioid analgesia (45); our data show an increase in the use of morphine.

The data collected seem to suggest that both intense training on pain management (31) and discussion on complex clinical cases concerning the use of palliative sedation contributed to the increased use of these drugs.

Published guidelines from the European Association for Palliative Care (EAPC) (46) on the use of opioid analgesics for the treatment of cancer pain recommend limiting the use of methadone to highly experienced teams because of its long, unpredictable half-life and substantial inter-individual variability of its metabolism in the liver. For this reason, since 2016 we have been carrying out specific training to all the healthcare staff of the oncology department regarding the administration of methadone and the management of its side effects, stressing the importance of supervision by the PCS.

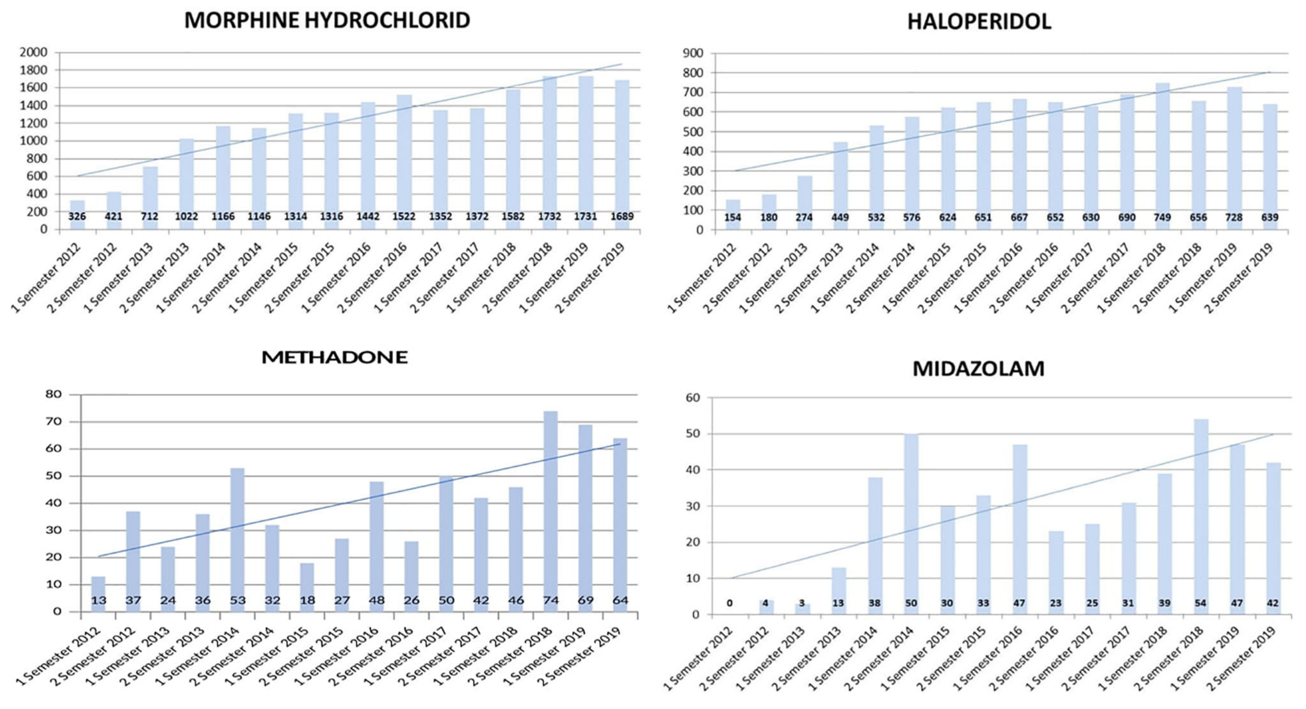

FIGURE 2 | Prescription volumes of morphine, haloperidol, methadone and midazolam.

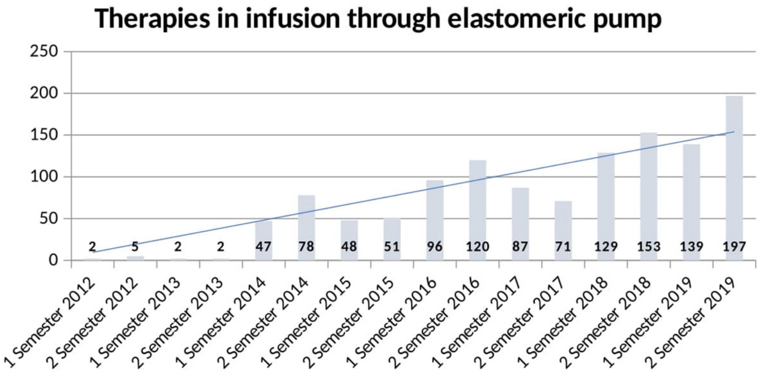

FIGURE 3 | Volume of therapies administered in infusion through elastomeric pump.

In analyzing our data, several critical issues have emerged: the time taken to involve PCS from the beginning of hospitalization is still too long (12 days average). The data regarding the time taken to involve PCS is higher compared to that reported in the National Palliative Care Registry in the USA (40) and in a Canadian document regarding hospitals with more than 500 beds (47). A recent Danish study investigated the association between palliative care team consultation and the content and costs of hospital care in patients with advanced cancer, and the average time between hospital admission and palliative care consultation was 4 days (19).

Other critical issues are the high percentage (38%) of patients with palliative care needs who died in the hospital and a time lapse between consultancy and discharge of 10 days.

This critical issue, which in US hospitals is associated with the staffing level of PCS (22, 48), in our local reality could be due to a still insufficient early recognition of PC needs in some wards, which leads to a late consultation of the specialist team on fragile patients with poor prognosis.

Italian data shows the percentage of hospital deaths related to all chronic pathologies to settle at about 40%, while lately there has been a small decrease in cancer-related hospital deaths to approximately 35% (49). Our data confirms that the hospital is a very common place of death for cancer patients, and the importance of ensuring the delivery of quality palliative care to hospitalized patients within the activity of palliative care networks in Italy.

Data relating to the high mortality of cancer patients in our hospital suggest also that an effective collaboration with home care services within the local palliative care network is still lacking; we are working to strengthen this collaboration and we are confident in future meaningful improvements. On the other hand, a recent report suggests that an early identification of PC needs could bring to a higher acute care services utilization and hospitalization (50).

Despite this high number of cancer patients who die in the hospital in Italy, unfortunately there are still difficulties in giving specific importance to hospital PCS. Until recently, at the national level and in many regions, there was no specific code to detect the activities of the PCS, which therefore did not obtain dedicated monitoring and consequent economic enhancement. This poor visibility and enhancement continue even in the region where PC development is widespread.

In our experience, it was difficult to introduce the activities of the PCS into a PC network that did not contemplate a specialized presence of PC inside the hospital. Data relating to high mortality of cancer patients in our hospital and hospital discharge times suggests the importance of improving effective collaboration with home care services, so we are working to strengthen this collaboration and we are confident in future meaningful improvements.

CONCLUSION

Demonstrating the value of a PCS in public hospitals is important to guarantee the sustainability of these services within the activities of palliative care networks in Italy. Our data suggests that a specialized hospital PCS, able to provide early palliative care to patients admitted to hospitalization and outpatient departments, and continuous training support to other hospital specialists, can relatively quickly improve the level of its penetrance in hospital activities mainly if referred to cancer patients.

The expected increase in palliative care needs will force a higher level of attention given to the appropriateness of specialist palliative care interventions. Hospitals will have to face a growing number of patients with palliative care needs, and we should implement new organizational and training models to ensure that all these patients are taken care of in accordance with the level of complexity of the needs they express.

For this aim, there is a need to promote specific research programs to evaluate the efficacy of these educational interventions and to develop dedicated and specific data systems to better document the results of the activities of Hospital PCS.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/ supplementary material.

AUTHOR CONTRIBUTIONS

SA, ST and CP: contributed to the concept and design of work; CT contributed to the analysis of the data of the prescription volume of specific drug. SA, CP and ST analyzed the data and drafted the article. All authors read and approved the final manuscript.

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Prognostication in palliative radiotherapy—ProPaRT: Accuracy of prognostic scores

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Background: Prognostication can be used within a tailored decision-making process to achieve a more personalized approach to the care of patients with cancer. This prospective observational study evaluated the accuracy of the Palliative Prognostic score (PaP score) to predict survival in patients identified by oncologists as candidates for palliative radiotherapy (PRT). We also studied interrater variability for the clinical prediction of survival and PaP scores and assessed the accuracy of the Survival Prediction Score (SPS) and TEACHH score.

Materials and methods: Consecutive patients were enrolled at first access to our Radiotherapy and Palliative Care Outpatient Clinic. The discriminating ability of the prognostic models was assessed using Harrell's C index, and the corresponding 95% confidence intervals (95% CI) were obtained by bootstrapping.

Results: In total, 255 patients with metastatic cancer were evaluated, and 123 (48.2%) were selected for PRT, all of whom completed treatment without interruption. Then, 10.6% of the irradiated patients who died underwent treatment within the last 30 days of life. The PaP score showed an accuracy of 74.8 (95% CI, 69.5–80.1) for radiation oncologist (RO) and 80.7 (95% CI, 75.9–85.5) for palliative care physician (PCP) in predicting 30-day survival. The accuracy of TEACHH was 76.1 (95% CI, 70.9–81.3) and 64.7 (95% CI, 58.8–70.6) for RO and PCP, respectively, and the accuracy of SPS was 70 (95% CI, 64.4–75.6) and 72.8 (95% CI, 67.3–78.3).

Conclusion: Accurate prognostication can identify candidates for low-fraction PRT during the last days of life who are more likely to complete the planned treatment without interruption.All the scores showed good discriminating capacity; the PaP had the higher accuracy, especially when used in a multidisciplinary way.

KEYWORDS

outpatient palliative care, palliative radiotherapy, prognostication, aggressiveness of care, personalized palliative care

Introduction

Prognostic evaluation is part of the overall assessment of cancer patients. Information on prognosis helps in clinical and therapeutic decision-making, patient and family counselling, and clinical research, facilitates the timely referral for palliative care (PC), and impacts the quality and costs of healthcare (1). A new approach to PC that takes into account the patients' needs more than prognosis was recently proposed (2). However, the needs and prognostic factors in PC are not exclusive to each other but rather complementary and integrated in this care setting (3).

Within the areas of medical oncology and palliative care, it has been seen that an integrated, multiprofessional evaluation allows for a more complete assessment that takes into account different points of view, skills, and expertise (4, 5). Prognostic factors have further been combined to build prognostic scores or prognostic tools that can be used in the advanced phases of the disease (6–9). Issues such as needs assessment, prognostic evaluation, and multidisciplinary approaches have been proven useful for decision-making in the medical oncology/palliative care interface and have also been assessed by our group in a palliative radiotherapy (PRT) setting (10).

Around 50% of radiotherapy (RT) activities can be defined as PRT with a symptomatic or palliative aim. The decision-making process is complex and involves several issues, *i.e.*, whether or not to perform RT, the choice of appropriate fractionation, the correct timing of RT to guarantee the relief or prevention of symptoms, and the best technique to use (11). Over the past few years, several prognostic factors have been developed for PRT. In particular, Chow et al. developed the SPS on 395 patients undergoing RT using six items weighted for their prognostic importance [primary cancer site, site of metastasis, Karnofsky performance status (KPS), fatigue, appetite, and shortness of breath]. The presence or absence of a number of these risk factors (NRF) was equally predictive and easier to manage. The median overall survival (OS) of the three groups evaluated with the NRF method was 62, 24, and 11 weeks (12). Thereafter, a simplified score (NRF) was built with only three factors: primary cancer site, site of metastasis and KPS. Three groups again were identified with a distinct survival of 15.0 *vs.* 6.5 *vs.* 2.3 months and a median OS of 4.9 months (13–15).

Krishnan et al. (16) developed another model (TEACHH model) to identify patients with short-term (<3 months) or long-term (>12 months) life expectancy within a population receiving PRT. The median survival of the entire group was 5.6 months. The score was built on factors that remained statistically significant at multivariate analysis: cancer type, ECOG PS, older age, number of prior palliative chemotherapy courses, hepatic metastases, and number of hospitalizations ≤3 months before PRT. The population was subdivided into three groups with different median survival. SPS NRF and TEACHH scores have been shown to be most effective for predicting survival at 3, 6, or 12 months and would appear to be less useful for predictions of short-term survival in an end-of-life setting (17).

The Palliative Prognostic Score (PaP score) was built and validated by our group (18, 19) and has been validated by independent groups (20–22) in a number of advanced cancer populations. PaP score consists of a "weighted" scoring system obtained with factors that remained statistically significant at multivariate analysis. The total scores ranged from 0 to 17.5 and assigned the patients to three different risk groups with a median survival of 10, 30, and 60 days (18, 19), showing a high accuracy at 88% (8).

In a study by Tayjasanant et al., the terms *advanced*, *end-of-life*, *terminal*, *end-stage*, and *dying* in cancer literature

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Abbreviations: TEACHH, Type of cancer, ECOG PS, age, prior palliative chemotherapy, prior hospitalizations and hepatic metastases; CPS, clinical prediction of survival; KPS, Karnofsky performance status; NRF, number of risk factors; OS, overall survival; PaP score, palliative prognostic score; PC, palliative care; PCP, palliative care physician; PRT, palliative radiotherapy; PSM, partial score method; RO, radiation oncologist; RT, radiotherapy; SPS, survival prediction score; WBC, white blood count.

corresponded to a median survival of 114, 63, 42, 25, and 4 days, respectively (9). It has been reported that some scores are more useful in the advanced phase and others in the terminal phase of illness (6).

A recent study by Mojica-Marquez et al. (17) reported that, although both of these models provided accurate prognostication, they were more accurate in patients with a median survival of ≥3 months. In fact, in 505 patients with a median OS of 2.1 months, the TEACHH score correctly predicted life expectancy in 21.4% of cases, while the Chow model was accurate in 29.1%. The TEACHH method has also been used to select appropriate treatment to reduce the risk of 30-day mortality after PRT. In a study by Kain et al. (23), the 30-day mortality was 10% and was higher in patients in the TEACHH subgroups B/C (21% in C, 11% in B, and 2% in group A).

The study reported in the present paper, "Prognostication in palliative radiotherapy—ProPaRT" had the primary aim of evaluating the accuracy of the PaP score in a group of patients selected for PRT by oncologists. Working together with specialists from our Radiotherapy and Palliative Care Outpatient Clinic, this multidisciplinary team evaluated the 30-day prognostic accuracy to identify suitable candidates for PRT. The secondary endpoints of the study were as follows (1): to evaluate the interrater agreement between the clinical prediction of survival (CPS) and PaP score according to different professionals (radiation oncologists—RO and palliative care physicians—PCP) and (2) to assess and compare the accuracy of the SPS (PSM and NRF methods) and TEACHH (PSM and NRF methods) scores.

Materials and methods

The organization of the integrated activities of the Radiotherapy and Palliative Care Outpatient Clinic has been described in detail elsewhere (10). The eligibility criteria for the present study were as follows: outpatients with advanced cancer (solid or hematologic tumors), ≥18 years old, and written informed consent. The patients were enrolled at their first access to the clinic, and the RO and PCP calculated all the prognostic scores simultaneously during the visit. A second appointment was scheduled for 1 month after the end of RT or 1 month after the first appointment for patients who were not amenable to RT. The patients were thereafter followed up for survival. All decisions regarding drug administration were taken by physicians and based on clinical judgment within the context of routine clinical practice, independently of the decision to include the patient in this study or not. Complete blood count data for this analysis were collected in the general laboratory of our hospital at a maximum of 7 days before or after the visit.

All the information needed to build the three prognostic scores (PaP, SPS, and TEACHH) were collected: age, KPS, CPS, dyspnea, anorexia, primary tumor site and type, location of all metastases, Eastern Cooperative Oncology Group Performance Status (ECOG PS), hospitalizations ≤3 months before the radiation consultation, and number of prior palliative chemotherapy and RT courses.

The PaP score was obtained from a Weibull multivariate regression model including six variables (KPS, CPS, anorexia, dyspnea, total white blood count, and lymphocyte percentage) chosen after a backward selection procedure from a set of 34 biological and clinical factors (18, 19). Each variable was allotted a "partial score" related to the size of the regression coefficient. The sum of the partial scores produced the PaP score. The total scores range between 0 and 17.5 and assigned the patients to one of three different risk groups according to a 30-day survival probability: group A, >70%; group B, 30–70%; and group C, <30% (Supplementary Table S1).

The SPS (12–15) was obtained in two ways. The first method (PSM) consisted in assigning a partial score on the basis of the prognostic "weight" of a single factor to each of the factors included (primary cancer site, site of metastases, and KPS) and then adding them together. The second method (NRF) consisted in grouping patients according to the total number of risk factors that they possessed. The three risk factors were non-breast cancer, sites of metastasis other than bone, and KPS ≤60 (Supplementary Table S2) (13).

The TEACHH model (16) divided the patients receiving PRT into three distinct life expectancy groups based on both the PSM and the NRF methods. For the PSM method, the partial scores for each variable were summed up to calculate a total PSM score for each patient. Each patient's NRF score was based on the sum of those predictors present. The PSM and NRF methods' scores were then used to classify the patients into three groups aimed at identifying those with the poorest (≤3 months) and best (>1 year) life expectancy (Supplementary Table S3).

The study was approved by the Area Vasta Romagna Ethics Committee (code L2P1517 of May 17, 2017) and performed with the 1964 Helsinki Declaration and its later amendments and with Good Clinical Practice guidelines. Written informed consent was obtained from all individual participants included in the study. No identifiable human data were included in the manuscript.

Statistical analysis

Continuous variables were summarized by descriptive statistics (number of cases, mean, standard deviation, median, minimum, and maximum) and categorical variables using counts of patients and percentages. Overall survival was defined as the time from the date of enrollment in the study to the date of death from any cause or the date of the last available information. Survival curves were estimated using the product-limit method of Kaplan–Meier and compared by log-rank test. The discriminating ability of the prognostic models was assessed using Harrell's C index, and the corresponding 95% confidence intervals (95% CI) were obtained by bootstrapping. Overall accuracy, sensitivity, specificity, positive predictive value, negative predictive value, and relative 95% CI were calculated at the 30th day of follow-up. The inter-rater agreement of the CPS and the PaP scores between the RO and PCP was measured with the Kappa statistic: kappas over 0.75—excellent, 0.40 to 0.75—fair to good, and below 0.40—poor (24). Assuming an accuracy level of 88% and a precision level of 4%, with an estimated type I error of 5% type, and using two-tailed test, a total recruitment of 254 patients was needed for the study. Statistical analyses were performed using SAS software, version 9.4 (SAS Inst., Cary, NC, USA).

TABLE 1 Main clinical–biological charactestistics of 255 patients.

Variables	Number	%
Median age, years (range; IQR)	70 (38–99; 60–77)	
≤60	67	26.3
>60	188	73.7
Gender		
Male	141	55.3
Female	114	44.7
Primary tumor site		
Lung	79	30.9
Breast	57	22.3
Prostate	27	10.6
Urogenitary tract (not prostate)	35	13.7
Gastrointestinal tract	27	10.6
Others	34	13.3
Metastatic sites		
Bone	186	72.9
Lymph nodes	113	44.3
Lung	76	29.8
CNS	55	21.6
Liver	42	16.5
Soft tissue	13	5.1
Locally advanced disease	36	14.1
Other	46	18.0
Number of metastatic sites		
1	66	25.9
2	95	37.3
3	71	27.8
4	17	6.7
5	6	2.3

IQR, interquartile range; CNS, central nervous system.

Results

This prospective, observational study enrolled 255 patients with metastatic cancer referred from medical oncologists at the Radiotherapy and Palliative Care Outpatient Clinic from August 2017 to April 2020. The patients were evaluated jointly by a RO and PCP. The patients' characteristics are reported in Table 1. Median age was 70 years (interquartile range, 60–77), and 141 (55.3%) were male patients. Lung cancer was the most frequent primary tumor (30.9%), followed by breast (22.3%) and tumors of the urogenitary tract (13.7%). Bone metastases were present in 72.9%, and there was lymph node involvement in 44.3%. Sixty-six (25.9%) patients had one site of metastatic disease at the first RaP visit, 95 (37.3%) had two sites, and 94 (36.8%) had three or more. PRT was indicated in 123 patients (48.2%) of the 255 patients at the first visit.

Seventy-six (61.8%) patients selected for PRT underwent a single fraction schedule, 43 (35.0%) had two to five fractions, one (0.8%) had 10 fractions, and 3 (2.4%) had >10 fractions (Table 2). All irradiated patients completed the treatment as planned. There was an average interval of 40.6 (standard deviation 194.5) days between the last dose of chemotherapy and the visit in the Radiotherapy and Palliative Care Outpatient Clinic (median, 9 days; range, 0–2,624; interquartile range, 5–22). At the time of analysis, 83 (67.5%) irradiated patients had died: 26 (31.3%) underwent RT in the last 60 days of life, of whom 13 (15.6%) had it in the last 30 days. None of the patients had RT in the last 10 days of life. Eighteen patients died within 30 days of the first RaP visit, but only three were treated with PRT, indicating a 30-day survival from the first visit to death of 2.4%. In treated patients, 13 died within 30 days, representing a 30-day mortality rate of 10.6%. With regard the OS of the entire group, median follow-up was 484 days (range, 9–1,064), and median OS was 250 days (95% CI, 200–342). The median OS

TABLE 2 Characteristics of palliative radiotherapy in 123 patients.

Variables	Number	%
Irradiated sites		
Bone	88	71.6
CNS	18	14.6
Visceral	6	4.9
Lymph nodes	5	4.1
Soft tissue	4	3.2
Other	2	1.6
Number of fractions		
1	76	61.8
2–5	43	35.0
10	1	0.8
>10	3	2.4

CNS, central nervous system.

TABLE 3 Univariate analysis of overall survival (OS) according to scores and different professionals.

Risk groups	RO				PCP			
	Number of patients	Number of events	Median OS (days) (95% CI)	30-day OS, % (95% CI)	Number of patients	Number of events	Median OS (days) (95% CI)	30-day OS, % (95% CI)
PaP score (PSM)								
A (0–5.5)	222	133	334 (249–431)	96 (93–99)	203	116	385 (263–468)	97 (94–99)
B (5.6–11.0)	33	32	65 (48–93)	73 (58–88)	51	48	95 (63–148)	76 (64–88)
C (11.1–17.5)	0	–	–	–	1	1	48 (-)	100
p-value			<0.0001				<0.0001	
C-index (95% CI)			0.81 (0.69–0.93)				0.82 (0.72–0.92)	
SPS (PSM)								
A (0–4)	68	29	516 (311-nr)	100	64	27	516 (311-nr)	100
B (5)	131	88	263 (185–382)	94 (90–98)	124	81	259 (168–389)	94 (89–98)
C (6–8)	56	48	101 (65–185)	82 (72–92)	67	57	134 (85–209)	85 (77–94)
p-value			<0.0001				<0.0001	
C-index (95% CI)			0.73 (0.64–0.82)				0.70 (0.60–0.80)	
TEACHH (PSM)								
A (0–4)	72	29	nr	100	58	21	nr	100
B (5–15)	181	134	186 (147–240)	91 (86–95)	194	142	190 (150–249)	91 (87–95)
C (16–22)	2	2	34 (15-nr)	50 (0–100)	3	2	53 (15-nr)	67 (13–100)
p-value			<0.0001				<0.0001	
C-index (95% CI)			0.81 (0.74–0.88)				0.76 (0.67–0.84)	
SPS (NRF)								
I (0–1)	61	27	516 (311-nr)	100	58	26	516 (294-nr)	100
II (2)	142	94	263 (185–389)	93 (89–97)	135	86	263 (170–409)	93 (88–97)
III (3)	52	44	107 (65–197)	85 (75–94)	62	53	141 (85–209)	87 (79–95)
p-value			<0.0001				<0.0001	
C-index (95% CI)			0.69 (0.59–0.78)				0.66 (0.56–0.76)	
TEACHH (NRF)								
A (0–1)	59	22	575 (411-nr)	100	52	19	nr	100
B (2–4)	194	141	190 (149–240)	91 (87–95)	201	144	196 (156–249)	91 (87–95)
C (5–6)	2	2	96 (68-nr)	100	2	2	96 (68-nr)	100
p-value			<0.0001				<0.0001	
C-index (95% CI)			0.80 (0.72–0.89)				0.77 (0.67–0.86)	

nr, not reached; RO, radiation oncologist; PCP, palliative care physician; PSM, partial score method; NRF, number of risk factors; CI, confidence interval.

in the 123 patients undergoing RT was 274 (95% CI, 190–416) days, and it was 234 (95% CI, 186–376) days in those (n = 132) who did not receive RT (p = 0.702).

Each prognostic score was calculated separately by both the RO and PCP. The univariate analysis of OS according to prognostic scores and evaluations of RO/PCP is reported in Table 3. According to the scores calculated by RO, 222 (87%) patients were classified in PaP score class A, 33 (13%) in class B, and 0 in class C, with a median OS of 334 days for class A and 65 days for class B. The TEACHH score (PSM) also subdivided the population into two groups, with 28.2% of patients in class A (median OS not reached), 71% in class B (median OS, 186 days), and only 0.8% in class C (median OS, 34 days). The SPS score (PSM) showed 26.6% of patients in class A (median OS, 516 days), 51.4% in class B (median OS, 263 days), and 22% in class C (median OS, 101 days). Similar results were obtained for the scores calculated by NRF or by the PCP. All prognostic scores identified groups with different prognoses (p < 0.0001) (Figures 1A–E).

The PaP score proved to be the best at discriminating patient prognosis as the median OS and 30-day survival probability were more in line with those of the risk group in which the patients were categorized. The SPS score showed a poorer performance in discriminating patients with better or worse prognosis. The TEACHH score (evaluated with PSM) had results similar to those of the PaP score.

The PaP score showed an accuracy of 74.8 (95% CI, 69.5–80.1) for RO and 80.7 (95% CI, 75.9–85.5) for PCP in predicting 30-day survival. The other scores, calculated after selecting the best cutoff, are detailed in Table 4.

The C index of the PaP score was 0.81 (95% CI, 0.69–0.93) and 0.82 (95% CI, 0.72–0.92) for RO and PCP, respectively, while that of the CPS was 0.711 (95% CI, 0.57–0.85) and 0.79 (95% CI, 0.64–0.88), respectively. Considering only irradiated patients (the TEACHH score was originally built only on the group of patients undergoing RT), the accuracy was as follows: PaP score: 70.7 (95% CI, 65.1–76.3) and 80.5 (95% CI, 75.6–85.4), SPS-PSM: 74.0 (95% CI, 68.6–79.4) and 78.9 (95% CI, 73.9–83-9), SPS-NRF method: 26.8 (95% CI, 21.4–32.2) and 25.2 (95% CI, 19.9–30.5), TEACHH-SPM: 69.1 (95% CI, 63.4–74.8) and 59.3 (95% CI, 53.3–65.3), and TEACHH-NRF: 49.6 (95% CI, 43.7–55.7) and 46.3 (95% CI, 40.2–52.4).

The interrater agreement between RO and PCP was 0.51 (95% CI, 0.42–0.59) for CPS and 0.75 (95% CI, 0.70–0.79) for the PaP score. The interrater agreement of the scores between RO and PCP using SPS-PSM was 0.87 (95% CI, 0.82–0.92); this was 0.88 (95% CI, 0.83–0.93) for SPS-NRF, 0.86 (95% CI, 0.82–0.90) for TEACCHH-PSM, and 0.90 (95% CI, 0.87–0.94) for the TEACHH-NRF scores. These agreements were higher than that of the PaP score because of the presence of a larger number of objective factors.

Both SPS and TEACHH predictive capacity, calculated using the PSM and NRF methods, did not differ (data not shown). It follows that, given the same accuracy, the simplest method (NRF) is the best one to use.

PaP score accuracy was also compared with that of CPS alone. The C index of PaP score was 0.81 (95% CI, 0.69–0.93) for RO and 0.82 (95% CI, 0.72–0.92) for PCP. The PaP score had a higher C index than that of CPS alone (0.71, 95% CI: 0.57–0.85 for RO and 0.76, 95% CI: 0.64–0.88 for PCP) and than that of the PaP score without CPS (0.78, 95% CI: 0.67–0.89 for RO and 0.78, 95% CI: 0.67–0.89 for PCP).

Discussion

Prognosis in PRT should be systematically evaluated to decide whether or not to pursue the recommended treatment (and if so, with which schedule). We chose to focus on a 30-day survival prediction because this cutoff seemed the most suitable to manage patients assigned to PRT at the end of life. A too-optimistic prediction of survival can have negative iatrogenic effects and an unfavorable impact on the indicators of poor quality of care such as an increase in the request for futile aggressive treatments, late referral to palliative care settings, and a higher percentage of deaths in hospital (sometimes in the intensive care unit) (25–27).

Efforts have been made using different methods to improve CPS performance, *e.g.*, in a temporal way, in a probabilistic way, and using the surprise question (28–31). Nonetheless, CPS alone continues to show limited accuracy, often overestimating the survival lifespan. CPS has also been tested in the PRT setting and shown insufficient prognostic accuracy. Chow et al. reported on 739 patients (median survival, 15.9 weeks) for whom six ROs calculated estimates of survival. The mean difference between actual survival and CPS was 12.3 weeks, indicating an inaccurate prediction of survival in an optimistic sense (32). Benson reported that, out of 877 predictions by 22 ROs, only 39.7% were accurate, with 26.5 underestimations and 33.9% overestimations. The estimates were considered accurate when the actual OS was within the prediction category (0–6 months, >6–12 months, >12–24 months, and >24 months). Using this definition of accuracy, there was an overall 60.3% of inaccurate predictions, albeit with a less systematic overprediction than that usually reported in the literature. Predictions were most accurate for lower KPS (33).

In a study by Razvi et al. (34), CPS used alone did not perform better, with an overestimation in 78.5% of cases and a survival overestimation of 19.0 weeks on average. The inaccuracy was even greater than that of a similar but older study (32) in which the difference between predicted and actual survival was 12.3 weeks. Sborov et al. reported that 22% of clinical predictions of survival by ROs were incorrect in an

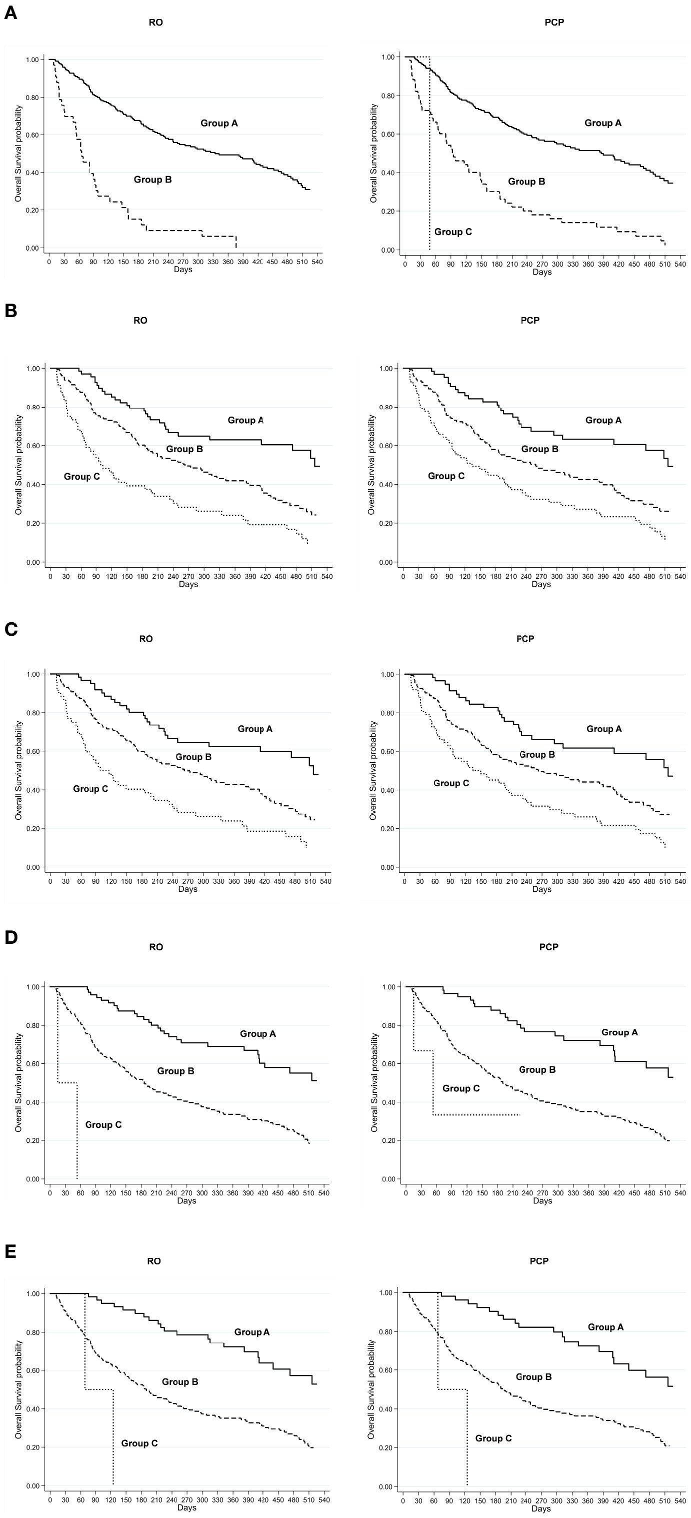

FIGURE 1
RO, radiation oncologist; PCP, palliative care physician; Kaplan–Meier overall survival curve for low-risk (group A), intermediate-risk (group B), and high-risk (group C) groups defined by **(A)** PaP score, **(B)** SPS score (PSM), **(C)** SPS score (NRF), **(D)** TEACHH score (PSM), and **(E)** TEACHH score (NRF).

TABLE 4 Accuracy of scores.

Score	Cutoff[a]	% sensitivity (95% CI)	% specificity (95% CI)	% PPV (95% CI)	% NPV (95% CI)	% accuracy (95% CI)
RO						
PaP score	5	70.6 (48.9–92.3)	74.7 (69.2–80.2)	25.6 (14.3–36.9)	97.2 (94.9–99.5)	74.8 (69.5–80.1)
SPS score (PSM)	7	41.2 (17.8–64.6)	76.8 (71.4–82.2)	14.9 (4.7–25.1)	95.2 (94.3–96.1)	70.0 (64.4–75.6)
SPS score (NRF)	2	41.2 (17.8–64.6)	81.1 (76.0–86.0)	13.5 (4.2–18.5)	95.1 (92.3–97.9)	68.7 (63.0–74.4)
TEACHH score (PSM)	10	82.4 (64.3–100)	75.8 (70.4–81.2)	19.4 (10.3–28.5)	98.4 (96.6–100)	76.1 (70.9–81.3)
TEACHH score (NRF)	3	88.9 (82.9–94.9)	59.7 (53.5–65.9)	25.8 (10.4–41.2)	96.0 (94.1–97.4)	61.8 (55.8–67.8)
PCP						
PaP score	5	76.5 (56.3–96.7)	81.4 (76.6–86.4)	21.0 (1.6–40.4)	97.9 (96.1–99.7)	80.7 (75.9–85.5)
SPS score (PSM)	7	41.2 (17.8–64.6)	81.0 (76.0–86.0)	12.5 (3.8–21.2)	95.0 (92.2–97.8)	72.8 (67.3–78.3)
SPS score (NRF)	2	41.2 (17.8–64.6)	76.9 (71.6–82.3)	11.3 (3.4–19.2)	94.8 (91.7–97.9)	66.2 (60.4–72.0)
TEACHH score (PSM)	10	76.5 (56.3–96.7)	63.9 (57.8–70.0)	13.1 (4.0–22.2)	97.4 (95.2–99.6)	64.7 (58.8–70.6)
TEACHH score (NRF)	3	88.9 (82.9–94.9)	53.8 (47.5–60.1)	20.6 (7.0–34.2)	95.5 (93.1–97.0)	56.3 (50.3–62.5)

RO, radiation oncologist; PCP, palliative care physician; PSM, partial score method; NRF, number of risk factors; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval.

[a]We chose to show the best performance cutoff for each score.

optimistic sense. The optimistic prediction was related to aggressive end-of-life in the last 30 days of life as an additional operational metric (35).

Other authors have described futile behavior in end-of-life care. In a SEER study by Guadagnolo et al., 15,287 patients received RT in the last month of life. Of these, 2,721 (17.8%) received more than 10 days of treatment. Almost one in five patients who underwent RT in their final 30 days of life spent more than 10 of those days receiving treatment (36). From 2000 to 2009, there was also an increase in the number of patients treated in the last 30 days of life with three-dimensional RT with respect to two-dimensional RT (from 27.2 to 58.5%) and with intensity-modulated RT (from 0 to 6%). There was no evidence of improved quality of life or OS from this increase in treatment intensity (37).

A systematic review by Park et al. showed that PRT was performed in the last 30 days of life in 5–10% of patients who died of cancer and in 9.0–15.3% of those who underwent PRT. Single fractions were used in 0 to 59% of patients, while the majority received 30 Gy in 10 fractions (36 to 100%), with a high rate of incomplete treatments (53–83%). This suggests that shorter or single-fraction regimens are more appropriate, especially in patients with poor performance status (38). A study by Gripp et al. reported on 33 patients who died within 30 days from RT. Only 16% of the survival estimates made by ROs were correct, suggesting that RT was not adequately tailored in this population. Only 58% of patients completed RT, indicating that just under half spent 60% or more of their remaining life undergoing treatment (39).

In medical oncology, many tools have been tested, but only a few have been validated by independent researchers (40, 41)

In the present study, which is focused on 30-day survival prediction, the PaP score calculated by both the RO and PCP showed good accuracy and performed a little better than the other scores. The integrated RO and PCP Outpatient Clinic obtained a 30-day mortality rate after PRT of 8.9%, which was lower than the rates reported in other studies (42–44) and lower than the 20% recommended by the Royal College of Radiologists. Moreover, there were no interruptions in PRT (single fraction in 61.8% and five fractions in 35%), and 51.8% of patients were spared from futile RT, with an overall 30-day mortality from the time of first access to the outpatient clinic of 2.4%. Of the 123 treated patients, 13 (10.6%) were treated in the last 30 days, and none died in the last 10 days of life The PSM- and NRF-based SPS and the SPS- and NRF-based TEACHH had a higher interrater concordance than the PaP score as they are built on more objective factors, but with a lower level of accuracy. However, the interrater concordance of PaP was higher than that of CPS alone as it is corrected by objective factors.

Our study had a number of limitations. Given that it was a monocenter study, the results were limited to a single population. Moreover, it was performed in an outpatient clinic in which ROs, PCPs, and nursing staff worked as a team. Finally, as the PaP score is more accurate in the final trajectory of the disease, the overall population was not divided into three balanced groups.

Conclusions

Our prospective, observational study had a sharply focused aim and a patient sample coherent with the needs of the study, *i.e.*, to understand whether the PaP score maintains its predictive capacity in terminally ill cancer patients undergoing PRT. This capacity was confirmed by our results. The interrater variability of the score was good but slightly less than that of the other scores that had more objective items. Although all the scores showed good discriminating capacity, the PaP had the higher accuracy, especially when used in a multidisciplinary way.

Data availability statement

The original contributions presented in the study are included in the artile/Supplementary Material (Table S4).

Ethics statement

This study was reviewed and approved by Area Vasta Romagna Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conception and design: MM, RR, and ES. Collection and assembly of data: MDA and RR. Data analysis and interpretation: MM, ES, and RR. Manuscript writing: all authors. Final approval of the manuscript: all authors. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.918414/full#supplementary-material

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The feasibility of triggers for the integration of Standardised, Early Palliative (STEP) Care in advanced cancer: A phase II trial

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Background: While multiple clinical trials have demonstrated benefits of early palliative care for people with cancer, access to these services is frequently very late if at all. Establishing evidence-based, disease-specific 'triggers' or times for the routine integration of early palliative care may address this evidence-practice gap.

Aim: To test the feasibility of using defined triggers for the integration of standardised, early palliative (STEP) care across three advanced cancers.

Method: Phase II, multi-site, open-label, parallel-arm, randomised trial of usual best practice cancer care +/- STEP Care conducted in four metropolitan tertiary cancer services in Melbourne, Australia in patients with advanced breast, prostate and brain cancer. The primary outcome was the feasibility of using triggers for times of integration of STEP Care, defined as enrolment of at least 30 patients per cancer in 24 months. Triggers were based on hospital admission with metastatic disease (for breast and prostate cancer), or development of disease recurrence (for brain tumour cohort). A mixed method study design was employed to understand issues of feasibility and acceptability underpinning trigger points.

Results: The triggers underpinning times for the integration of STEP care were shown to be feasible for brain but not breast or prostate cancers, with enrolment of 49, 6 and 10 patients across the three disease groups respectively. The varied feasibility across these cancer groups suggested some important characteristics of triggers which may aid their utility in future work.

Conclusions: Achieving the implementation of early palliative care as a standardized component of quality care for all oncology patients will require further attention to defining triggers. Triggers which are 1) linked to objective points within the illness course (not dependent on recognition by individual clinicians), 2) Identifiable and visible (heralded through established service-level activities) and 3) Not reliant upon additional screening measures may enhance their feasibility.

KEYWORDS

early palliative care, outpatient palliative care, cancer, personalized palliative care, clinical trial, phase II

Introduction

Patients with advanced cancer suffer numerous distressing physical symptoms, psychological morbidity and unmet information and psychosocial needs (1–4). Despite assigning high priority to symptom relief, open communication and collaborative decision making (5), such needs are frequently not recognised nor managed in routine oncology care (6, 7).. Addressing these needs are core tasks of palliative care, and increasingly meta-analyses demonstrate the benefits of early palliative care for patients, including improved symptom management, quality-of-life and care satisfaction; reduced rates of hospitalization and emergency department presentations, and for family carers, improved quality-of-life and care satisfaction (8–13).

Despite benefits and recommendations from peak professional bodies (ASCO, ESMO) (14–16), in practice 'early' palliative care referrals are not routine and access to palliative care frequently occurs very late in the illness course (17). Our earlier work demonstrated only 59% of decedents with metastatic non-small cell lung, small cell lung, prostate and breast cancers in Victoria, Australia received a palliative approach to care, a median of 27 days prior to death (17). A repeat of these analyses (almost 10 years on) for decedents from cancer in 2018 revealed 67% had a palliative care referral, but at a later time, median 20 days before death (18). Equivalent data on cancer decedents from the United Kingdom (19) and other international jurisdictions demonstrated palliative care referral 53 days and 18.9 days prior to death respectively (20). As such, there remains a significant evidence-practice gap associated with the implementation of early palliative care in routine cancer care.

Barriers to palliative care referral have been identified, including: concerns about difficulty of referral, fear of destroying patient hope associated with perceptions of palliative care (21) and uncertainty over the 'best time' to refer (22). The literature has variably defined 'early', including to mean at least 3-4 months prior to death to confer benefits (8), within 3 months of advanced cancer diagnosis for patients with a life expectancy of 1 year or less (23), and ideally engagement with palliative care spanning 6-18 months before death (24).

An approach which seeks to standardise the timing of 'early' palliative care referral would do much to overcome such barriers, including through increasing patient acceptance of referrals, as it represents a 'routine' care pathway (25). Similarly, standardisation would reduce variations and inequities in access to care. Such a standardised time of introduction should be based on evidence and be tailored to the disease characteristics and likely history, allowing for consideration of balancing the potential for maximal outcome benefit versus managing the volume of early consultations and resourcing implications (23, 24). Yet to date, few studies have explored the role of systematic triggers for timely palliative care referral (26–29).

We previously examined population level hospital admission datasets to map health care use by patients with high grade glioma (HGG) and metastatic breast, prostate as well as lung cancers (17, 30–32). This work demonstrated potential disease-specific transition points in the illness course which heralded subsequent poor prognosis (defined as less than 6 months) and subsequent increased health service utilisation (17). These 'transition points' or 'triggers' represented times for the integration of early palliative care as part routine clinical practice when we recommended that palliative care should be routinely introduced, if not already in place, to maximise patient and carer benefit (33). These triggers for palliative care are linked with electronic health records or usual systems of clinical care, may prompt clinicians and in this way, serve to augment clinician-based decision making (24). However, there is a clear need for the testing of such cancer specific time points as triggers for referral to palliative care occurring as 'standard quality care' (17).

Responding to this gap, we undertook a randomised, phase 2 feasibility trial of a standardised outpatient model of 'early' palliative care [Standardised Early Palliative Care: STEP Care] for advanced cancer patients and their family carers, with referrals occurring at the defined disease-specific, evidence-based trigger points. The trial sought to test the feasibility and preliminary efficacy of using defined triggers for the the integration of standardised, early palliative (STEP) care across three advanced cancers. This paper reports on the feasibility of triggers.

Methods

Study setting

The trial was undertaken at four metropolitan tertiary cancer services in Melbourne, Victoria, each with active inpatient and outpatient palliative care consultation services. Central multi-site ethical approval was provided by the Human Research Ethics Committee at St Vincent's Hospital Melbourne [HREC 179/16], and the trial registered with the Australian and New Zealand Clinical Trial Registry [ACTRN12617000534381]. Funding was provided by the Victorian Cancer Agency [Grant number: HSR15022] and the St Vincent's Hospital Foundation (private philanthropic donation).

Patient and public involvement

The trial had patient and public involvement embedded within the research team (SH), and additionally through the guidance of an advisory group comprising community contributors who met regularly with the research team (quarterly meetings) across the life of the trial. This group had a significant role in shaping the following areas: grant application, review of patient consent forms and plain language summary, review of language to introduce the study, input into selection of research outcomes and qualitative question guides, trouble-shooting recruitment, and grounding interpretation of study results.

Primary endpoint

The primary outcome was the feasibility of using triggers for times of integration of STEP Care, with a view to proceeding to a definitive Phase 3 randomised trial, which would evaluate effectiveness of STEP Care (compared to usual best practice cancer care) for patients with advanced breast or prostate cancer or high grade glioma (HGG). The specific feasibility endpoint was defined as enrolment of at least 30 patients in each disease cohort (total n=90) in 24 months, at which time those cancers not meeting feasibility cut off were ceased. Secondary aims to examine the preliminary efficacy of STEP Care on patient- and carer- reported outcomes, including quality of life, mood, symptoms, illness understanding, and overall survival will be reported elsewhere. Consistent with the exploratory study aims, the feasibility endpoint was determined by the authors primarily balancing pragmatic considerations around the available study timeframe. It was consistent with other phase II studies of this nature (34) and also considered the minimum sample required to determine a preliminary estimate of effect size for secondary patient-reported outcomes which would be the subject of a future phase III definitive trial.

Design

We conducted a phase 2, multi-site, open-label, parallel-arm, Randomized Controlled Trial (RCT) of usual Best Practice Cancer Care +/- STEP Care according. This RCT development aligned with the Medical Research Council (MRC) Framework for the development and testing of Complex Interventions (35, 36) which prioritises phased, sequential, intervention development leading towards implementation (35, 36). The nature and timing of the triggered early palliative care was thus underpinned by our exploratory data resulting from Phase 1 qualitative (22, 37–39) and health service use studies (17, 30, 31, 40) which defined transition points or triggers for the integration of early palliative care.

Triggers for standardised early palliative (STEP) care

The triggers for STEP Care as defined for this feasibility trial included (Table 1): for prostate- first multiday admission where patient had any metastatic disease; for breast- first multiday admission where patient had metastatic disease including at least

TABLE 1 Trigger definitions.

Characteristics and identification of cases meeting the trigger		
Prostate cancer	Presence of metastatic disease AND Multi-day hospital admission.	Presence of advanced disease ANDChange in care requirementANDHeralded *via* electronic health record
Breast cancer	Presence of visceral metastatic disease (metastases involving organs other than bone only) ANDMulti-day hospital admission.	Presence of advanced diseaseAND Change in care requirement ANDHeralded *via* electronic health record
High grade glioma	First recurrence of primary HGG where pathological or clinical diagnosis is Glioblastoma/ WHO grade IV disease; ORFirst diagnosis of primary HGG and no cancer specific treatment being prescribed. ANDHospital presentation (inpatient or outpatient)	Illness based (e.g. new point in illness course*)ANDHeralded in usual systems of clinical care (illness point anchored to key treatment decision discussed at multidisciplinary cancer meetings)

*time of new complication or disease progression determined by radiological and surgical evidence.

one visceral site; for brain- any hospital presentation with first recurrence of HGG (determined by radiological or surgical evidence). Given our earlier state-wide population cohort studies of cancer decedents found first palliative care occurred a median of <30 days prior to death (17, 18), these triggers were selected to offer an objective time for systematic identification of a cohort likely to benefit from palliative care earlier in the disease trajectory.

The point of hospitalisation with the disease characteristics outlined was selected because it was: not reliant upon individual clinician judgement of prognosis or of the person's needs; common to most patients with these cancer illnesses; and could be identified within the electronic health record. An anticipated life expectancy of between 6 and 24 months has been advocated as appropriate for patient inclusion in early palliative care (24, 41). These points of hospitalization were previously found in our population studies to have a median survival of approximately 6 months (42), thus balancing the imperatives for early palliative care input against common service concerns about capacity to respond (41) and relevant to the variable and not infrequently long metastatic illness course experienced particularly by the breast and prostate cohorts.

Participants

Participants included adult patients with advanced breast, prostate and brain cancers as identified by the defined triggers (Table 1), and in attendance at the included hospital sites at this time. Further eligibility requirements included the ability to provide informed consent, to comply with study procedures, and an ability to understand written and spoken English. Exclusion criteria for patients included those less than 18 years, those previously seen by hospital consultancy palliative care services within the previous 12 months or presenting with needs required urgent palliative care review, or those who were more than 30 days following the identified cancer-specific trigger. Patients meeting the eligibility criteria who were identified by a mechanism other than the route specified (Table 1) could be included in the study, however none were referred in this way.

Study Procedures

Recruitment and consent

Consecutive eligible inpatients and outpatients from participating cancer treatment centres were approached for potential study inclusion by research staff. At patient identification, clinical teams were asked to confirm eligibility, permission was sought from the patient to provide information about the study, with those willing to proceed completing a study consent form. Information on eligibility along with reasons for refusal to participate were recorded.

Randomisation

Patient-level randomisation was centralised and coordinated by an independent Trial Coordinator. The randomisation schedule involved 1:1 allocation and used the minimisation method to ensure a balanced distribution between groups with respect to the patient's tumour type and hospital site.

Usual care: Standard Best Practice Cancer Care

All patients received usual oncological care through their health care providers, including systemic therapy, radiotherapy, surgery or other treatments deemed appropriate. In addition, those patients randomised to usual care were able to be referred to palliative care services at any time at the treating clinician's discretion.

Intervention: STEP Care plus Standard Best Practice Cancer Care

Those patients randomised to the intervention arm received STEP Care in addition to Standard Best Practice Cancer Care. STEP Care consisted of, at minimum, monthly Palliative Care consultations for at least 3 months. These consultations were primarily delivered in the outpatient setting. All STEP Care consultations were conducted by a Palliative Care Physician or Specialist Nurse and involved a series of activities (Table 2) which were documented according to a framework adapted from the PC-NAT-PD (43).

Data collection

Demographic, clinical, and treatment data were collected from patient medical records. Mixed method study data were collected to assess the feasibility and acceptability of the triggers as prompting referral to the standardized early palliative care intervention. Measures of feasibility were assessed according to the number of eligible participants identified, consented and completing the study. Acceptability of the STEP Care intervention was assessed according to the number of withdrawals from the study, the completeness of delivery and timing of STEP care consultations for those assigned to the intervention arm, and the development of any adverse events. In addition, semi structured qualitative data with providing perspectives of purposively sampled participating oncology and palliative care clinicians, was supplemented to explore issues of feasibility and acceptability associated with using triggers for the integration of early palliative care.

TABLE 2 Key components of STEP Care intervention.

1. Identification of patients for eligibility at defined trigger in the illness course.
2. Initial hospital based palliative care consultation, addressing:
   a. Review of underlying disease management
   b. Screening for symptom distress
   c. Screening for psychological distress
   d. Review of informal social supports
   e. Review of formal community supports, including local community palliative care
   f. Providing information
   g. Advance care planning discussions
   h. Involvement of family carer, including enquiry of concerns, needs for information
3. Regular follow up, at minimum monthly for minimum of 3 months.
4. Case conference with the general practitioner within 28 days, addressing
   a. Current and anticipated problems.
   b. Recommended management and therapies
   c. Designation of responsibility for different aspects of care.

Analyses

Feasibility outcomes were summarised using descriptive statistics, including frequency counts and percentages (categorical variables), and mean/standard deviation or median/interquartile range (continuous variables) as appropriate. Qualitative data aligned to the primary outcome of feasibility and acceptability was subjected to a thematic analysis (44) to supplement the basic descriptive analyses consistent with the study aims.

Results

Participant characteristics

Patients

Of 513 patients identified as meeting the cancer-specific trigger point (141 brain, 118 prostate, 254 breast), 406 were not eligible to approach for study participation (58 brain, 106 prostate, 242 breast), most commonly owing to already being linked into palliative care (n=183, 45%), or presenting with needs requiring immediate referral to palliative care (n=71, 18%), or cognitive impairment (n=42, 10%) (Table 3). Of the 107 patients identified as eligible, 42 (39%) declined study participation, mostly citing they were not interested at this time (23, 55%) as opposed to high levels of distress (n=3, 7%), or the time commitment involved (n=2, 5%). The remaining 65 (61%) participants were consented for study participation and underwent random assignment.

Participating clinicians

Interview and focus group data was obtained from oncology and palliative care clinicians (n=19) who were directly or peripherally involved in the STEP care trial as a member of the treating teams involved in the care of included breast, prostate or brain cancer patients. This included perspectives from palliative care nurses (n=3) and consultants (n=6), and oncology nurses (n=3) and consultants (n=7).

Feasibility of triggers

The triggers underpinning times for the integration of standardised, early palliative care (STEP care) were shown to be feasible for brain, but not breast or prostate cancers, with total enrolment of 49, 6 and 10 patients across the three disease groups respectively. The breast and prostate groups were determined not feasible and ceased at the pre-specified 24 month timeframe, with recruitment for the brain cohort (then n=38) continuing through to 36 months.

Timing of identified triggers

The cancer specific triggers used in this trial appeared to be '*too late*' for the breast and prostate groups, with high rates of these participants identified already having a previous palliative care referral (breast: 101/254, 40%; prostate: 55/118, 47%) as compared to the brain group (27/141, 20%), and additional breast (32/254, 13%) and prostate (15/118, 13%) cancer patients identified as having urgent palliative care needs. These data suggest earlier involvement may have been helpful.

> "If there's been an admission in the setting of metastatic disease that can often mean that there are symptoms and they're not doing so well at home and (we) get the palliative care team involved" (Oncology consultant)
> "Many of the patients (breast, prostate) have been seen by palliative care already" (Palliative care nurse)

On the other hand, the median overall survival of the cohort from the identified trigger until death or censored at study completion was 9 months (Figure 1). The median follow-up time from the trigger was: for brain 7.1 (4.1, 14.1) months, for breast 32.15 (8.4, 32.4) months, and for prostate 33.65 (10.3, 39.4) months. This suggests the triggers were aligned with a period where a person is likely to benefit from palliative care, and highlights the resourcing challenge in groups such as breast and prostate where a person may experience palliative care needs over a long metastatic illness course.

Characteristics of a feasible trigger

The feasible trigger associated with care of the brain cancer cohort was illness based (e.g. at time of new progressive disease or a new complication of the illness) and heralded in usual clinical systems of care (anchored to key treatment decision discussed at multidisciplinary cancer meetings). The 'not feasible' triggers of breast and prostate cancer care were at a

TABLE 3 Feasibility and acceptability data.

Domain	Measure	HGG	Prostate	Breast	Total
Feasibility data	**Identified as ineligible**	141	118	254	513
	Reason for ineligibility				
	Cognitive impairment	21	7	14	42
	More than 30 days since trigger	6	0	2	8
	Already receiving palliative care	27	55	101	183
	Needs imminent palliative care	24	15	32	71
	Language other than English	7	11	13	31
	Receiving treatment elsewhere/ regional	23	–	–	23
	Other (eg. on another clinical trial, advice of treating clinician)	33	30	92	155
	Identified as eligible	N=83	N=12	N=12	107
	Declined participation	34	2	6	42
	Reason for declining				
	too distressed	2	0	1	3
	not interested	19	1	3	23
	time commitment	2	0	0	2
	other	11	1	2	14
	Consented to participation	49 (58%)	10 83%)	6 (50%)	65
	(61%)				
Median (IQR) time from trigger to death or study completion (months)	7.1 (4, 14)	33.7 (10, 39)	32.2 (8, 32)		
Acceptability of STEP Care to patients and carers	Assigned to STEP Care study arm	24	5	5	34
	Completion of first STEP Care consultation within 14 days of consent	19 (86%)	4 (80%)	4 (80%)	27
	(79%)				
	Days from consent to first STEP interaction	10 (0, 12)	2 (1, 4)	2 (0, 4)	5
	(0,12)				
	Number of consultations per patient	3 (2, 4)	4 (2, 4)	1 (1, 2)	3 (2, 4)
	Received at least 3 STEP Care consultations	18 (75%)	3 (60%)	1 (20%)	22
	(65%)				
Number of consultations per patient within first 3 months	3 (2, 3)	3 (2, 3)	1 (1, 2)	2.5 (2, 3)	
Number of withdrawals from Trial (STEP Care) intervention	2 (8%)	0	1 (20%)	3 (8.8%)	
Number of adverse events arising from Trial (STEP Care intervention)	0	0	0	0	

time of advanced illness (though not necessarily a new development of progressive disease or complication), when care requirements changed and required screening of the electronic health medical records to identify patients.

Qualitative data from clinicians revealed that electronic medical records within the included hospital settings were not yet established for *real time* prompting of eligible patients. This was largely because relevant data such as the cancer diagnosis that may be uncovered within the admission and recorded in the patient's electronic health record was only 'coded' by hospital administrative teams following the patient discharge. This meant that administrative teams could not generate an automatic list of 'eligible' patients meeting the identified trigger in real time, which reduced the feasibility for breast and prostate triggers since it therefore required usual care teams to additionally screen inpatients for eligibility. This was compared to the brain patient cohort, where the trigger was anchored to a new illness development which prompted discussion in usual clinical care systems – specifically the multidisciplinary cancer team meeting. For brain patients, no additional surveillance over and above usual care processes was required to identify people meeting eligibility.

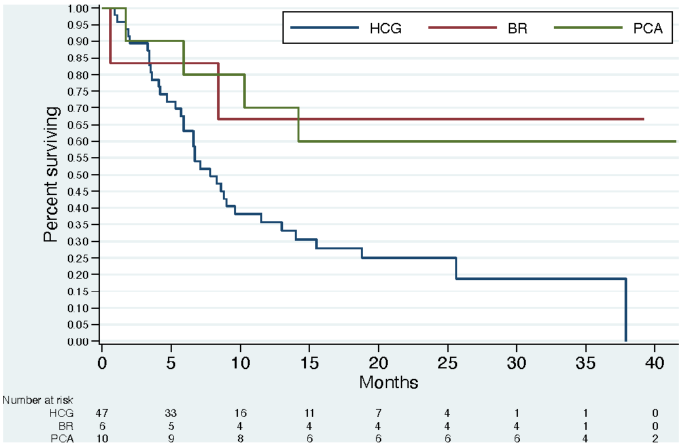

FIGURE 1
Overall Survival by Cancer Type.

> "Having an easy mechanism of referral is really important … I think there's particular patients when we've got some big life decisions to discuss at our M.D.M, that would be a good time to bring in palliative care" (Surgical Oncology – Urology)
>
> "I think it provides a standardised pathway that you can offer to patients, and an easy access pathway … and it keeps it at the front of your mind." (Oncology nurse)

Acceptability of a trigger to STEP Care Intervention

Of the 65 participants, 34 were assigned to receive the STEP Care Intervention (24 brain, 5 breast, 5 prostate). Of these, 27 (79%) completed the first consultation within 14 days as per protocol, a median (IQR) of 5 days (0, 12) following identification and consent (Table 3), suggesting the responsiveness of the palliative care teams who were able to facilitate an initial review within the planned timeframe. Most patients (22, 65%) received a 'minimum dose' of 3 (monthly) consultations as prescribed, with a median (IQR) of 3 (2, 4) consultations per patient across the study period. These data suggest that the timing of the trigger was broadly acceptable to patients who continued to attend appointments. Of note, there were 3 patients (9%) who withdrew from the STEP Care intervention due to increasing illness burden, and no adverse events recorded.

Standardisation of practices

The triggers also appeared to be acceptable to clinicians who described standardization of practices around referral to palliative care referral as reassuring to both themselves and the patients.

> "It (the trigger) gives permission to refer people and it is normalised under the medical pathway … I think. the formality … gives it a much more medical procedural thing rather than an esoteric, nebulous sort of thing … by having the defined (trigger) points" (Oncology consultant)
>
> "Before. it was difficult because … I felt I needed … some problem to be able to put in that referral. Whereas having a trigger allows us to be able to much more fluidly, you know, send through that referral." (Oncology nurse)
>
> "The key you know, (having) flags that teams can recognise as a point for a referral as opposed to … where it could be a bit more subjective. These clear kind of delineated flags for a referral … certainly gets our foot in the door with a lot of patients earlier" (Palliative care consultant)

Triggers as reducing communication barriers

Having a trigger also meant that conversations around referral to palliative care were easier.

> "I think something like this for a junior clinician nurse, it gives them something tangible that they can open the discussion with" (Oncology consultant)

> "There's none of that having to break through the barrier of, you know, referring to pall care. It's just an automatic thing so there's no barrier to break because it happens all the time anyway." (Oncology nurse)

Trigger and intervention set the scene for longer term care

For most patients, clinicians perceived the 3 consultations delivered at time of the trigger was adequate to introduce the role of early pc, put some key plans in place, help with family discussions, and facilitate relationships so that subsequent contact could be initiated by the patient or their carer if and when the need arises.

> "…It's really good to have that concurrent pathway where we can link patients in from an early point,…As things progress it makes things much easier when you get further down the line as well, in terms of having them already linked in, knowing what services are available and making that transition." (Oncology Consultant)
>
> "some (patients) at those earlier stages … may have a significant survival trajectory still but have other potential symptoms or things that could be managed in the interim period of time … so they're not getting to the end stage before being referred" (Palliative Care Consultant)

Similarly for palliative care clinicians, having triggers was perceived as a means to build relationships between palliative care and referring teams that enabled the longer term care of patients to be met. In this way, the triggers were seen as providing patients with a universal opportunity to be linked with palliative care.

> "Although there's lots of rhetoric about taking a population-based approach to palliative care, when you are constrained by resources, you retreat and do what you just have to do to manage, don't you. So, I think this has been really positive in helping us look at these specific groups, and it's increased out dialogue with our referrers."(Palliative Care Consultant)

Limitations of triggers

As noted, the defined triggers for prostate or breast cancer patients were not useful since many patients were already linked to palliative care services, or already had high supportive care needs identified which had prompted earlier referral.

> "I think just maybe having a look at the (trigger) points and just seeing umm how, if there's certain groups that are coming in … too late. And then just revising those." (Palliative Care Consultant)

Other staff highlighted that while having a trigger was useful for some patients, the circumstances of other patients necessitated the need for flexibility around timing of palliative care referral.

> "I tend to tailor it per patient rather than having an automatic criteria for which I would refer someone because I just think everyone's very individual." (Surgical oncology)

Similarly, triggers were sometimes seen as interfering with practices of a staged approach to the introduction of palliative care or the providers 'clinical intuition' regarding the right time.

> "I don't think right now is the best time for me to … refer to palliative care. But, you know, as weeks go on and they settle in, you develop—we develop, as nurses and clinicians there, the best way of knowing what is the right time to introduce it." (Cancer nurse)

Discussion

Identifying the cohort of people who will benefit from palliative care and enacting this access in a timely manner requires new approaches in service delivery. This trial tested the feasibility of novel, evidence-based, cancer-specific, illness-based triggers for the integration of standardized early palliative care across three advanced cancer groups. The triggers as defined were shown feasible by our endpoint for the brain but not prostate or breast cancer groups. Achieving the implementation of early palliative care as a standardized component of quality care for all oncology patients will require attention to further defining triggers which can help reduce variation and enhance the equity of care. In this trial the successful trigger was characterized by being 1) linked to objective points within the illness course at a new development in the illness (thus, not dependent on recognition by individual clinicians), 2) Identifiable and visible (heralded through established systems of clinical care or service-level activities) and 3) Not reliant upon additional screening measures. While these are early data in the field, these characteristics are likely to be important to inform the development of feasible triggers going forward.

In this study, and others (45) we have sought through exploring triggers to test a universal approach to identifying the group of people who may benefit from palliative care. A handful of other single-centre studies have similarly examined models of 'triggered palliative care consultation', often also initiated on criteria involving hospitalisation, and these have reported variable outcomes (26, 27, 29). Adelson and colleagues used a hybrid of automatic criteria relating to health service use (prior hospital within 30 days; or > 7 bed days) and active symptoms for prompting palliative care referral, resulting in a two-fold increase in rates of consultation and a significant reduction of hospital re-admission (26). Rocque and colleagues demonstrated improved illness understanding following implementation of triggered palliative care for all hospitalised cancer patients with metastases, but this resulted in a minimal impact upon patient-reported symptoms, hospice utilisation, and cost of care (29). DiMartino and colleagues reported triggered palliative care for hospitalized solid tumour and gynecologic patients increased uptake, but this did not result in earlier timing of consultations (27).

Our approach to standardizing early palliative care differed in that it sought to test the feasibility of cancer specific triggers to initiate a prescribed palliative care intervention, which was then delivered in outpatient settings. The triggers, defined upon pre-identified health service parameters, differed for different cancers, and thus meant our results also reflected some nuance in the understanding of different cancer types and the feasibility of the respective triggers. In this way we have begun to define those characteristics of a successful trigger and also of those not likely to be successful. In this trial, a successful trigger was linked to a clear, new development in the illness, was identifiable and heralded in usual service systems, and did not rely on additional screening. Since the characteristics of services differ, local factors will necessarily inform the implementation of such a trigger into routine practice. The views of the referrers as to the acceptability of the trigger as point of referral to palliative care will be essential, with a successful trigger one that reflects and is adapted to local service conditions and agreed upon by referrers.

In the context of this clinical trial, with necessarily tight eligibility parameters, the triggers enacted for prostate and breast cancer were shown to be not feasible, or 'too late'. This was largely reflecting the high number of people already receiving, or needing imminent palliative care at the identified trigger, thus rendering them ineligible in the clinical trial context. Despite this, it was interesting that our survival data on the participants in these cohorts, albeit small numbers, was broadly consistent with the literature recommending palliative care input for those with a life expectancy of 6-24 months (24, 41). Going forward in clinical practice and outside of a trial setting, this may suggest that these trigger points as outlined are not unreasonable as a 'minimum standard' to prompt the initiation of palliative care if not already in place. Alternatively, these triggers could be adapted to earlier in the disease course, such as at the time of second line treatment. In this case, these triggers could be linked to identification *via* the systems whereby care is reviewed such as in the multi-disciplinary cancer meeting. Preliminary pilot testing, as undertaken here, would first be required to establish feasibility.

An alternative approach to using triggers, is to instead focus palliative care referral prompted by needs, with those identified as having greater or complex needs receiving specialist palliative care (46, 47). Such an approach seeks to target the limited resources of palliative care upon those who may benefit most, and is based in a population-centred model. The concept of 'complexity' at the centre of this approach however is not well defined (48). Furthermore, in order for referral of those with complex needs to occur, an assessment of needs by referring clinicians must take place. Such an assessment is frequently not part of their usual consultation, is not built into usual workflows and would constitute an additional task in an already busy consultation. As such it may be overlooked. Even when such needs are assessed, acting upon these does not occur routinely for many patients (7, 49).

Hui et al. (24) have attempted to bring this discussion of triggers and needs together in a service innovation which seeks to apply routine systematic screening, an established defined set of referral criteria which, if reached, triggers a referral to palliative care for appropriate patients. In addition an adequately staffed outpatient specialist palliative care service is available to respond to these referrals (24). In this way standardisation of practice is achieved with attendant equity of access for patients, but focused on those with greatest needs who may most benefit. The resources required for the systematic screening and implementation in this model will not however, be available in a number of centres.

Our focus on using triggers which may be built into usual care systems offers an approach which also will standardise the time of referral and address issues of equity of access. The opportunity to automate these triggers based in electronic systems associated with electronic medical records means fewer resources are required to standardise identification of the patient cohort. An electronic prompt to clinicians could serve as a reminder, reducing clinical uncertainty and reinforcing the service expectations (24). Clinicians, so prompted, could consider their response which may include consideration of activities of palliative care such as review of symptom burden, or discussion of goals and preferences, or it may include a referral to specialist palliative care. A system using electronic prompts needs to be as accompanied by clearly communicated but not overly prescriptive guidance, thus reducing uncertainty whilst not reducing physician agency (50). An effective trigger-prompt system would be one where clinicians are reminded of palliative care benefits and retain the decision making about how and when those are best enacted.

There are limitations to this trial that require mention, including a focus on those patients who were cared for in large cancer centres (where neuro-oncology units exist) and who may not be representative of all cancer patients. Similarly those people who did not speak English were excluded - a group which constitutes up to 21% of the Australian population (51). Furthermore our study was around the feasibility of using triggers for a trial of early palliative care, not simply referral to palliative care for all comers. As such, the eligibility criteria to enter the trial were likely to rule out some patients that may otherwise have welcomed (or benefited from) palliative care referral. This includes some participants excluded based on other clinical trial participation. Given the increasing potential for many patients to be accessing clinical trials of novel systemic therapies moving forward, future early palliative care trials may need to carefully consider this parameter, which will likely substantially reduce the available sample who may otherwise benefit from early palliative care. Nonetheless, by structuring the feasibility of triggers as time for referral within a trial, we were able to measure outcomes in a standardized formal manner including delivery and acceptability. We recognise that there are many parameters which impact upon feasibility and acceptability outcomes and our trial necessarily chooses selected measures likely not capturing all of these attendant influences.

We contend that key to the implementation of early, timely palliative care into clinical care is the development of novel ways of identifying the cohort of people who will benefit. The use of triggers offers an approach which provides standardization of the cohort identification and therefore will reduce variation and enhance equity of access to early palliative care. Characteristics of a successful trigger are that it is linked to a clear, new development in the illness, is identifiable and heralded in usual service systems and does not rely on additional screening. Future research focused upon linking these triggers to electronic clinical prompt systems offers interesting ways forward. The need to tailor the triggers and attendant responses to local conditions will be core to successful implementation endeavours.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The trial involving human participants was reviewed and approved by St. Vincent's Hospital Melbourne HREC. All participants provided their written informed consent to participate in this study.

Author contributions

JP was the lead investigator and obtained the study funding. JP & AC were responsible for the study conduct, had access to the data, and co-authored the first draft. All authors contributed to the study protocol, interpretation and, contributed to the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Simultaneous care in oncology: Assessment of benefit in relation to symptoms, sex, and age in 753 patients

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Background: Early activation of palliative care for patients with advanced cancer is central in the treatment trajectory. At the Veneto Institute of Oncology, a simultaneous-care outpatient clinic (SCOC) has been active since 2014, where patients are evaluated by an oncologist together with a palliative care team. Recently, we reported on consecutive patients admitted at SCOC from 2018 to 2021 in terms of appropriateness, process, and outcome indicators. Here, we report further analysis in the same group of 753 patients, evaluating other parameters and the correlation between symptom intensity, gender, age, and survival.

Methods: SCOC data were retrieved from a prospectively maintained database.

Results: Among the patients, 42.2% were women, and the median age was 68 years, with 46.7% of patients aged ≥70 years. The most prevalent disease type was gastrointestinal cancer (75.2%), and 90.9% of the patients had metastatic disease. The median score for the distress thermometer was 4; the vast majority of the patients (98.6%) reported physical problems, and 69.4% presented emotional issues. Younger women demonstrated a significantly greater median distress than other patients (p=0.0018). Almost all symptoms had a higher prevalence on the 0–3 Edmonton Symptom Assessment Scale (ESAS) score, except for fatigue. About 43.8% of the patients received systemic anticancer treatment (SAT) in the last 60 days of life, 15.0% of whom received SAT in the last month and 3.1% in the last 2 weeks. For some symptoms, women frequently had more ESAS >3. Pain and nausea were significantly less reported by older patients compared with younger adults. Men had a lower risk of having MUST score $\geq$ 2 (p=0.0311). Men and older patients showed a lower prognosis awareness (p=0.0011 and p=0.0049, respectively). Older patients received less SAT within the last 30 days of life (p=0.0006) and had death risk decreased by 20.0%.

Conclusion: Our study identified two subgroups of patients with advanced cancer who require special attention and support due to important symptoms' burden detected by Patient Reported Outcome Measures tests: women and younger adults. These categories of patients require special attention and should be provided early access at SCOC. The role of an oncologist remains crucial to intercept all patients in need of early palliative care and balancing trade-offs of anticancer treatment in advanced metastatic disease.

KEYWORDS

simultaneous care, early palliative care (EPC), symptom assessment, advanced cancer, end of life chemotherapy, patient-centered care

Introduction

There is mounting evidence on the crucial role of early activation of palliative care in patients' cancer journey, especially in the advanced stage of the disease (1). Indeed, numerous studies have shown that this approach improves the quality of life and, in some cases, even patients' survival (2–6). As a result, early palliative care is now recommended by most prominent international oncology scientific societies and is included in their guidelines (7–10).

Despite such evidence, outcomes obtained with this approach are not consistently reported and appear to be related to several key elements through which early palliative care benefits patients and caregivers (11). In addition, the heterogeneity related to different organizational models, the availability of palliative care teams, as well as the cultural and social-health aspects across different countries, to date, do not allow suggesting a unique model for early palliative care delivery (11, 12).

The Veneto Institute of Oncology (IOV) takes charge of more than 5,000 new cancer patients in need of systemic treatment per year. IOV is an Organization of European Cancer Institutes (OECI) certified Comprehensive Cancer Center, and since 2012, the Oncology Department has obtained the European Society of Medical Oncology (ESMO) certification as a Designated Center of integration of oncology and palliative care (ESMO-DC). Since 2017, the Institute has adopted a procedure with standardized referral criteria through (1) routine screening of supportive care needs at oncology visits; (2) filling in a referral form by oncologists at the time of the visit; the form was defined by oncology and palliative care teams for identifying patients with palliative care needs; (3) a system in place to trigger referral when patients meet the criteria; and (4) activation of simultaneous care outpatients clinic (SCOC), in which the oncologist and the palliative care team (a palliative care physician, a physician specialized in clinical nutrition, a psycho-oncologist, and a nurse navigator) assess together, through validated tools, the needs of patients with the aim to deliver personalized, timely patient-centered care and improve patient and caregiver outcomes (13). This embedded model meets internationally agreed criteria for optimizing the early inclusion of palliative care in the care pathway (14, 15). In order to ensure an early referral of patients with metastatic disease, patients' assessment is based on symptom's burden and life expectancy, and through the activation of a simultaneous care clinic, the oncologist and the palliative care team share the patient's journey (13). Recently, we reported the data on our series of 753 patients evaluated at SCOC from January 2018 to December 2021 in terms of indicators of appropriateness, process, and outcome provided by the Institute's procedure (13). In this work, we report the data from further analyses performed in the same group of 753 patients, evaluating a number of other parameters and the correlation between symptom intensity, gender, age, and survival.

Patients and methods

Patients

This study was conducted at the Veneto Institute Oncology (IOV), Padua, Italy. The study population was composed of patients referred to SCOC between January 2018 and December 2021. Selection criteria were the availability of the referral form filled in by the oncologist and cancer-directed treatment planned. SCOC data were retrieved from a prospectively maintained database: demographic and clinic information, distress thermometer (DT), Edmonton Symptom Assessment Scale (ESAS), and Malnutrition Universal Screening Tool (MUST). These three scales (DT, ESAS, and MUST) are used because of the following characteristics:

- The DT is a simple tool developed by the National Comprehensive Cancer Network (NCCN), which provides effective screening for symptoms of distress. The instrument is a self-reported tool using a Likert rating scale (0 to 10) and additionally identifies sources of distress using a Problem List (PL) (16).
- The ESAS is a measure of symptom burden that includes a Likert rating of nine symptoms, on a scale from 0 (best) to 10 (worst), which has been adopted for routine needs screening during the SCOC visit (17).
- The MUST identifies patients who are malnourished or are at risk of malnutrition; a score of 0 indicates a low risk of malnutrition, a score of 1 indicates medium risk, and a score ≥ 2 indicates a high risk (18, 19).

We also analyzed whether there were significant differences by gender, age (age less than, or equal to, and over 70 years), and type of cancer, with regard to a series of variables:

1. DT
2. ESAS: type of symptoms and intensity
3. MUST
4. Awareness of the cancer prognosis (total, partial, absent)
5. Systemic anticancer treatment (SAT) at the end of life (last 60, 30, and 14 days)
6. Unplanned visits to the emergency room (ER)
7. Place of death (hospital *vs*. hospice or home)
8. Actual survival at the time of SCOC referral

Statistical analysis

The patients' characteristics were described by descriptive analysis. The comparisons were tested using chi-square tests, Fisher' exact tests, and log-rank tests, as appropriate. For the survival analysis, all patients entered into the study at the date of SCOC were followed up until 31 January 2022 or the date of death, whichever came first. Median survival was calculated with the Kaplan–Meier method. The following variables were analyzed: ESAS, MUST, territorial services activation, prognosis awareness, chemotherapy within the last 30 days of life, unplanned access in the ER, place of death, actual and estimated survival; figures were drawn for gender and age comparisons including only the significant results. The place of death and the end-of-life chemotherapy were assessed for deceased patients. Cox's proportional hazards model was fitted to the data to evaluate the association between the actual survival and the variables of interest (gender, age class, and tumor site). Logistic, multinomial, and cumulative logit models were used to test the association between the category variables, previously considered in the bivariate analysis, and the variables of interest. R Version 4.2.0 was used to perform all statistical analyses. The level of significance was set at 5%.

Results

Demographic and patients' clinical characteristics are shown in Table 1. Among the patients, 318 were women (42.2%), and the median age was 68 years (range: 60–76 years), with 352 patients (46.7%) aged 70 years and older. The most prevalent disease type was gastrointestinal cancer (566 patients, 75.2%). A total of 661 (87.8%) patients had a Karnofsky performance status (KPS) ≥70, 684 (90.9%) patients had metastatic disease, and 223 (29.6%) patients received more than two lines of therapy. The time from cancer diagnosis to the first SCOC visit was less than 1 year for 351 patients (51.8%). The median survival of the overall population from SCOC visit was 7.3 months (95% CI: 6.5–8.0).

Symptom's burden

The median score for DT was 4 (range: 0–9), with the vast majority of patients (98.6%) reporting physical problems and more than half (69.4%) presenting emotional issues, as shown in Figure 1. Family and practical problems and spiritual concerns were present in a small percentage of patients (1.0%, 0.7%, and 0.0%, respectively). Younger women reported a significantly greater median distress compared with other patients (5 *vs*. 4, p=0.0018, Figure 2).

ESAS symptoms by three levels of severity are shown in Figure 3. Almost all symptoms had a higher prevalence in the 0–3 score range, except for fatigue, which was experienced with an intensity of 7–10 in 281 patients (41.7%). A total of 175 patients had three or more symptoms with an intensity of 7–10. The median survival for these patients was 5.6 months (95% CI: 4.7–7.4), whereas the median survival for the other patients was 7.7 months (95% CI: 6.8–8.6; log-rank test's p-value=0.0232) (Table 2).

TABLE 1 Patients' characteristics.

Characteristics	Patients (n) 753	(%) 100
Gender:		
Men	435	(57.8)
Women	318	(42.2)
Age at referral (years):		
Median (IQR)	68	(60–76)
< 70 years	401	(53.3)
≥ 70 years	352	(46.7)
Tumor site:		
Gastrointestinal (GI)	566	(75.2)
Genitourinary (GU)	113	(15.0)
Other (sarcoma, lymphoma, gynecological)	74	(9.8)
Karnofsky Performance Status:		
≥70	661	(87.8)
50-60	92	(12.2)
Tumor stage:		
Locally advanced	47	(6.2)
Metastatic	684	(90.9)
Missing	22	(2.9)
Treatment line:		
First line	338	(44.9)
Second line	192	(25.5)
Third or further lines	223	(29.6)
Years since cancer diagnosis:		
≤1	351	(51.8)
>1	326	(48.2)
Survival from the SCOC visit (months):		
Median (95% CI)	7.3	(6.5-8.0)

Systemic anticancer treatment at the end of life

As of 31 January 2022, 552 (73.3%) patients were deceased. The median number of days between the last administration of SAT and patient death was 66 (range: 1–1193 days). A total of 242 patients (43.8%) received SAT in the last 60 days of life, among which 83 (15.0%) received SAT during the last month and 17 (3.1%) in the last 2 weeks of life (Table 3). The median age of patients who received SAT in the last 30 days was 63 years (IQR: 57–69), which is lower than the rest of the group (68 years, IQR: 60–76, p=0.0005). Nearly half (47.0%) of the patients who received SAT in the last 30 days of life were being treated in the first line. The median survival from the SCOC visit for these patients was 3.4 months (95% CI: 1.8–4.5) compared with 5.9 months (95% CI: 5.5–6.4) for the other patients (p <0.0001). For this group of patients, the hospital was the more frequent place of death (60.0% *vs.* 25.5% in other patients, p<0.0001). There were no differences with regard to unplanned access to the ER, hospital admission, number of lines of treatment, and years for patients treated or not treated with SAT in the last month of life.

Results by gender

ESAS symptoms with intensity greater than 3 were differently distributed according to gender, with women reporting higher prevalence of appetite loss, pain, wellbeing, depression, and anxiety compared with men (see Figure 4). No difference was observed for dyspnea, which was the only symptom more frequent in men (women: 14.8% *vs.* men: 18.6%, p=0.2388, data not shown).

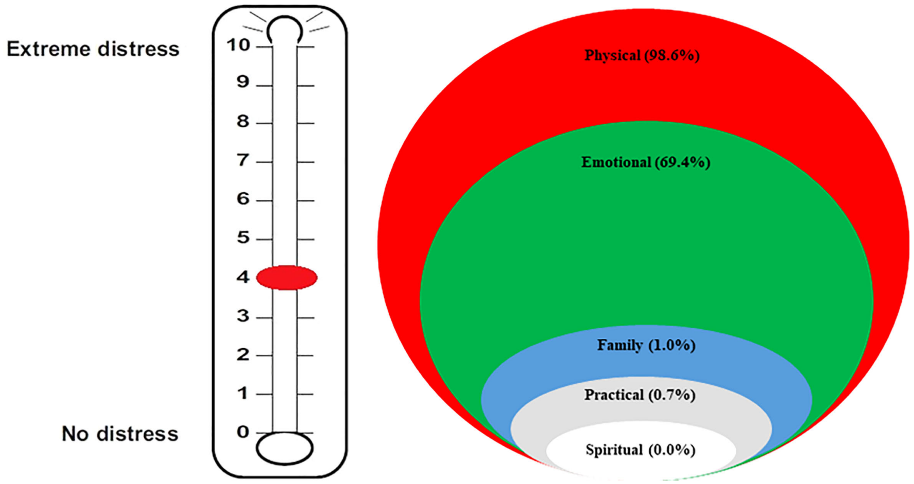

FIGURE 1
Results according to distress thermometers: median score and burden of distress in the different areas.

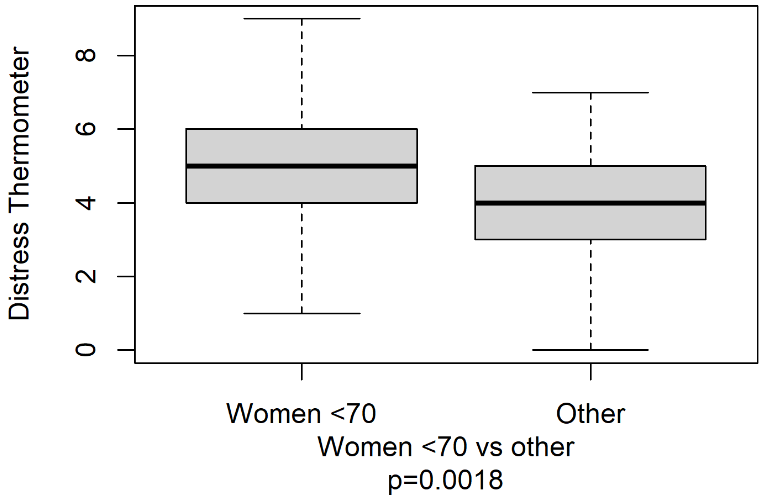

FIGURE 2
Distress thermometer's boxplot by women under 70 years versus others.

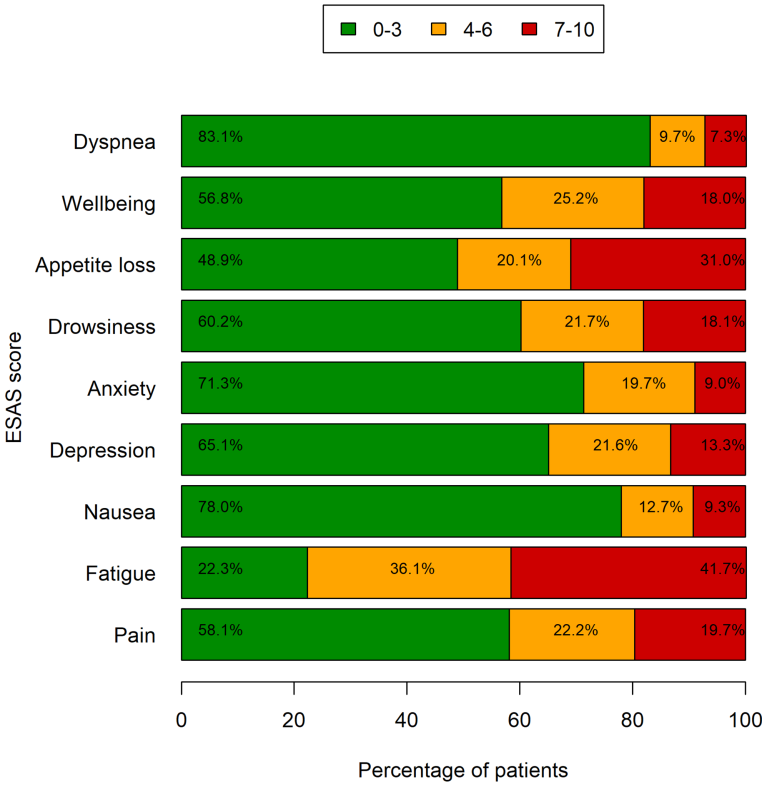

FIGURE 3
Symptom severity by ESAS. Bars represent the frequencies of symptoms grouped by three levels of severity (data missing in up to 92 patients).

TABLE 2 Survival according to worse symptom's burden by ESAS.

≥ 3 ESAS, score 7–10	Patients (%)	Events	Median survival (months)	95% CI	p-value
Yes	175 (23.2)	128	5.6	[4.7–7.4]	0.0232
No	578 (76.8)	423	7.7	[6.8–8.6]	

MUST scores were worse for women, with 117 (43.0%) having a score ≥ 2 (patients at higher risk of malnutrition), compared with men (130, 34.2%, p=0.0276).

More women were found to have complete awareness of the disease prognosis compared to men (66.5% *vs*. 52.6%). Moreover, men presented more unplanned access to the ER (26.0% *vs*. 17.9% for women, p=0.0117). No significant differences according to gender were found in territorial services activation, the number of patients undergoing SAT in the last 30 days of life, the place of death, and survival.

Results by age

Figure 5 summarizes significant differences according to the age of patients. With regard to ESAS, pain (p=0.0373) and nausea (p=0.0296) had a higher prevalence in younger compared to older patients. As for prognosis awareness, 209 patients (64.3%) aged <70 years reported total prognosis awareness compared with 148 (51.9%) patients aged ≥ 70 years. SAT in the last 30 days of life was administered to 63 (20.0%) adults aged <70 years and to 20 (8.4%) older patients (p=0.0003). Also, a significant difference was observed with regard to the place of death, occurring in hospital for 38.4% younger subjects compared with 22.7% for older patients. Moreover, older patients had better survival, with median survival for adults aged <70 years being 6.3 months (95% CI: 5.7–7.2) compared with 8.8 months (95% CI: 7.5–10.1) for patients aged ≥ 70 years (p=0.0006). No other significant differences were found.

Multivariate analysis

Regression models were developed taking into account the variables of interest. As reported in Table 4, multivariate analysis confirmed the statistically significant difference in the ESAS score by gender (women's ESAS score >3 for the symptoms pain, nausea, depression, anxiety, appetite loss, and wellbeing), MUST (lower risk of having a score ≥ 2 in men), and a higher awareness of cancer prognosis in women. Patients aged 70 years and older also had 20% lower risk of death (p=0.0072). Elderly patients received less SAT within the last 30 days of life as well as in the last 2 months (OR=0.6, p=0.0058, data not shown). With regard to the tumor site, only mortality risk resulted significant in multivariate analysis, being 1.5 times higher for GI cancers compared with other cancer types (p=0.0099).

Discussion

Early integration of palliative care in the cancer patient's care path is today regarded as an essential goal to optimize the quality of life in the advanced stage of the disease and is best delivered in outpatient clinics (1). There is no single model of palliative care that is appropriate for all settings (11). The embedded model put in place in our Department, in which the palliative care team shares the SCOC with the oncologist, meets all the criteria proposed by international consensus to ensure timely activation of palliative care (20). This innovative organizational model allows intercepting cancer patients in an advanced stage of disease who need global care. The needs of each patient are addressed through the systematic use of validated Patient Reported Outcome Measures (PROMs), and this allows the customization of the patient's journey and future end-of-life care decisions. In particular, the joint presence of an oncologist together with the palliative care team facilitates dialogue with patients and caregivers on advance care planning, end-of-life provisions, and preferential death location (21). Sharing resources between oncology and palliative care services is also cost-effective and may encourage collaborative education and research (11, 15). New organizational models are a challenge and an important resource to guarantee assistance to cancer patients also in the COVID era and in every phase of the illness trajectory (Andrè Ilbawi, WHO Cancer Control Officer, Opening Session at ASCO 2022 congress, the 4th June 2022).

TABLE 3 Systemic anticancer treatment (SAT) at the end of life.

SAT	Last 60 days n (%)	Last 30 days n (%)	Last 14 days n (%)	Median survival (months)	95% CI	p-value
Yes	242 (43.8)	83 (15.0)	17 (3.1)	3.4	[1.8–4.5]	<0.0001
No	310 (56.2)	469 (85.0)	535 (96.9)	5.9	[5.5–6.4]	

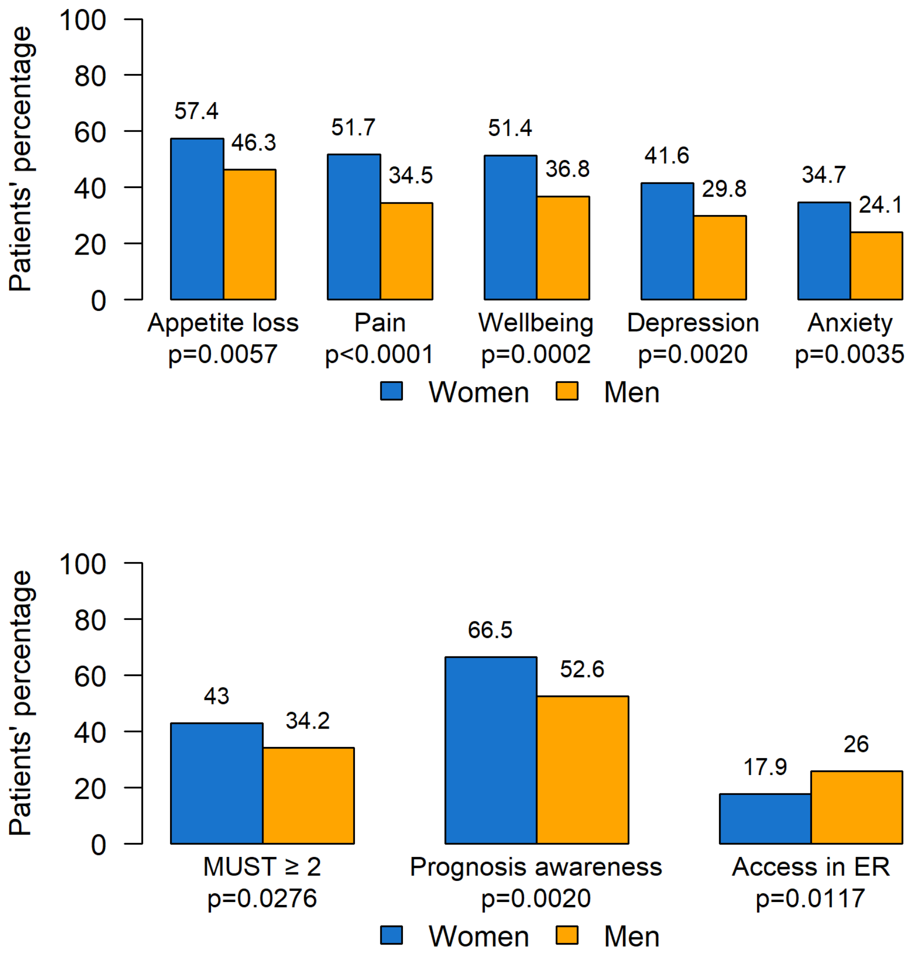

FIGURE 4
Statistically significant difference according to gender. ER, Emergency room.

A previous paper by our group described the organizational model of embedded systemic early palliative care for patients with advanced cancer and the results of the last 4 years of activity as assessed through indicators of outcome, process, and appropriateness (13). The present work reports the results concerning symptoms burden, SAT at the end of life, difference by age, gender, and survival in the same group of 753 patients referred to SCOC in the period 2018–2021.

The *DT*, first described by Roth et al. in 1998, was developed for assessing distress in cancer patients (16). Since then, several experiences have been published regarding this easy-to-use tool with the ability to intercept at a glance the main problems of the patient (22, 23). A wide proportion of cancer patients, ranging between 25% and 60%, report distress when they are assessed (24). The median DT score in our patients was 4 (range: 0–9), with 98.6% of the patients experiencing physical problems, 69.4% emotional problems, and only 1.0%, 0.7%, and 0.0% reporting familiar, practical, and spiritual problems, respectively. This very low frequency of practical, family, and spiritual problems might look surprising, taking into account other studies, particularly American experiences, in which up to 80% of the patients with cancer attribute their distress to financial stressors (25, 26). This may be due to several reasons, including the different Italian healthcare system (which guarantees the coverage of most of cancer therapies compared with the American insurance system), the different social aspects of family relationships, and more widespread religious beliefs, as well as the patients' reluctance to involve the doctor on problems other than oncological disease.

Fatigue was highly relevant in our patients' population, reported by 92.7% with the DT and confirmed by the ESAS assessment. Notably, for ESAS > 3, fatigue was detected in 77.8% of the patients. Indeed, fatigue constitutes the most distressing patient-related symptom in terms of intensity and frequency that negatively affects their quality of life (27–29), although, unfortunately, nothing at this time has been shown to effectively

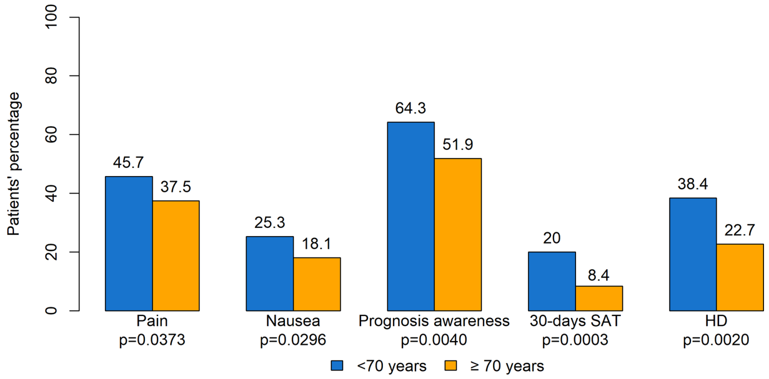

FIGURE 5
Statistically significant difference according to age. SAT, systemic anticancer therapy; HD, hospital death.

relieve this symptom (30). Fatigue is multifactorial, related both to the treatment (surgery, chemotherapy, and radiation therapy) and to the tumor itself. It is usually underestimated by physicians, and its management remains one of the greatest unmet needs for patients with advanced cancer. Fatigue has been inadequately discussed and undertreated (31) due to lack of agreement on its measurement, inadequate understanding of the biology, and difficulty in conducting clinical trials of fatigue interventions (32). According to systematic meta-analyses and recently published studies, evidence-based management of cancer-related fatigue should be focused on behavioral and psychological interventions (33, 34), since pharmacological intervention has shown limited effect. Also, literature report on cancer-related fatigue seems to be more pronounced in women than in men, especially at the end of life (35).

ESAS was confirmed in our experience as one of the most valuable tools for detecting type and intensity of symptoms in metastatic cancer patients. In line with literature data (36), nearly one-fourth of the patients with advanced cancer in our cohort experienced three or more symptoms with an intensity of 7/10 or greater, exhibiting a strong correlation with survival. ESAS is confirmed as an important tool for identifying a group of patients with high symptom burden who require immediate support and assistance by the palliative care team (36, 37). Assessment of patient's needs allows providing more effective support, relevant to every person's individual experience, and it is necessary for setting priorities for resource allocation (31).

With regard to *SAT at the end of life*, our study showed that 43.8% of the patients received anticancer therapy during the last 60 days of life, of which 15% was within the last 30 days and 3.1% within the last 2 weeks of life. These figures can be partially justified by the good KPS that, on average, patients presented at the time of their first SCOC visit and that guides oncologists in their decision-making. In fact, almost half of the patients who received SAT in the last 30 days of life are therapy naïve. Furthermore, younger patients were more often treated with SAT at the end of life likely due to oncologists' attitude of offering at least one opportunity for treatment even though cancer was in the advanced stage at diagnosis. SAT use in the last 14 days in our series compares favorably with the rate of 7% reported by Bakitas (4), 9.3% of an Italian study (38), as well as the rate of 13.6% observed by Greer et al. (39). Based on the analysis of SEER-Medicare, an overly aggressive care is associated with more than 10% of patients receiving SAT in the last 14 days (40). As for the patients who received SAT within 30 or 60 days, our results are in line with those reported in the literature in Italy (41, 42) and in other countries (43–45). Although the use of SAT in patients who are close to death has been increasing over time (46), little information is available about the clinical effect of such treatment (47). The extent of the contribution of SAT at the end of life and the role of advanced state of disease *per se* in hastening patients' death cannot be further assessed in our experience, just like other reports in the literature, i.e., Zhu et al. (44). Indeed, our data confirm those by an American report in which SAT in the last 30 days of life was associated with an increased rate of death in the hospital (48, 49). Interestingly, older patients were found to receive less SAT during the last 60 days of life, in line with literature data (44, 48); they lived longer and died more frequently in hospice or at home. Indeed, as reported by Wright et al., perceptions of better end-of-life care are associated with earlier hospice enrolment, avoidance of ICU admission in the last 30 days of life, and deaths outside the hospital, among family members of elderly patients who died with lung or colorectal cancer (50). These findings are supportive of advance care planning consistent with patients' preferences (50, 51) and may help both granting patients' wishes regarding the place of death (52) as well as reducing caregivers' distress (53).

TABLE 4 Results by multivariate analysis.

		OR	95% CI	p-value
ESAS (ref: score ≤ 3)				
- Pain				
Gender (ref: Women)	Men	0.5	(0.3–0.6)	<0.0001
Age class (ref: < 70 years)	≥ 70	0.7	(0.5–0.9)	0.0149
Tumor site (ref: Other)	GU	2.3	(1.2–4.6)	0.0155
- Nausea				
Gender (ref: Women)	Men	0.7	(0.4–1.0)	0.0276
Age class (ref: < 70 years)	≥ 70	0.6	(0.4–0.9)	0.0103
- Depression				
Gender (ref: Women)	Men	0.6	(0.4–0.8)	0.0008
- Anxiety				
Gender (ref: Women)	Men	0.6	(0.4–0.8)	0.0016
- Appetite loss				
Gender (ref: Women)	Men	0.6	(0.5–0.8)	0.0031
- Wellbeing				
Gender (ref: Women)	Men	0.5	(0.4–0.7)	<0.0001
Tumor site (ref: Other)	GU	2.4	(1.2–4.8)	0.0111
- Dyspnea				
Tumor site (ref: Other)	GI	0.5	(0.3–1.0)	0.0440
MUST (ref: score 0–1)				
Gender (ref: Women)	Men	0.7	(0.5–1.0)	0.0311
PROGNOSIS AWARENESS (ref: Absent)				
Gender (ref: Women)	Men	0.6	(0.4–0.8)	0.0011
Age class (ref: < 70 years)	≥ 70	0.6	(0.5–0.9)	0.0049
SAT^ AT THE END OF LIFE (ref: > 30 days)				
Age class (ref: < 70 years)	≥ 70	0.4	(0.2–0.7)	0.0006
UNPLANNED ER* VISITS (ref: No)				
Gender (ref: Women)	Men	1.6	(1.1–2.3)	0.0110
PLACE OF DEATH (ref: Hospital)				
Gender (ref: Women)	Men	0.6	(0.4–1.0)	0.0294
Age class (ref: < 70 years)	≥ 70	2.1	(1.3–3.3)	0.0028
SURVIVAL		**HR**		
Age class (ref: < 70 years)	≥ 70	0.8	(0.7–0.9)	0.0072
Tumor site (ref: Other)	GI	1.5	(1.1–2.0)	0.0099

^SAT, systemic anticancer therapy.
*ER, emergency room.
OR, odds ratio; HR, hazard ratio.

The *role of oncologists* is strategic not only for the proper management of SCOC patients but also for an accurate estimation of prognosis in order to avoid therapeutic aggressiveness at the end of life when not justified. Continuing education of medical oncologists in palliative care remains critical for both providing the first level of palliative care, with systematic use of PROMs in clinical practice, and facilitating early access to an integrated SCOC (13). Prognosis, indeed, needs to be taken into account in the decision-making process, and several tools may help in the prognosis assessment, such as the Pap score (54). A systematic review of mortality predictors in patients with advanced cancer has been recently published (55). The "surprise question" and general clinical and laboratory variables are non-tumor-specific predictors of mortality within 3–24 months in patients with advanced cancer. This translates in the recommendation to pay more attention in the advanced stage of disease to clinical and laboratory parameters, which are not cancer-related, rather than to the type of tumor. In fact, a new validated machine-learning model to predict 6-month prognosis in patients with advanced solid tumors has been proposed (56), which can be useful and may support shared decision-making discussions between oncologists and patients with regard to considering a further line of SAT.

In addition, our data prove that there are *significant differences with regard to gender and age*. Women experienced a higher frequency of pain, anxiety, depression requiring psychological support in 22% of the subjects, loss of appetite, and higher MUST score values (100% requiring nutritional support), together with a higher frequency of total awareness of cancer prognosis compared with men. In particular, subgroup analysis by DT results showed that adult women had a significantly higher median distress compared with the rest of the cancer patient population.

Evaluation by age revealed a significantly lower median survival in younger subjects; in the same group, prevalence of pain was higher, along with awareness of prognosis. Such differences were confirmed in *multivariate analysis*. Indeed, age and gender might be differently impacted by early palliative care interventions, as reported in the study by Nipp et al. (57). No significant differences were found in our cohort by disease subgroups, except for lower dyspnea and lower survival in patients with GI cancer, as well higher pain and lower wellbeing in patients with GU cancer. This suggests, as reported by Chalkidis et al. and confirmed by a systematic review of mortality predictors in patients with advanced cancer, that patients with advanced solid tumors may converge to a common pathway at end of life, regardless of the cancer type, at which point patient-specific factors unrelated to cancer are the most important (55, 56).

In conclusion, to summarize it with the metaphor that Zimmermann has recently proposed, our study confirms the importance of introducing early palliative care as an umbrella for cancer patients and caregivers that must be opened before it starts to rain (58).

Limitations

This study has some limitations. Although the results are in line with other similar reports in the literature, data collection was limited to one single center, which restricts the extrapolation of the results to the general population. Given the observational nature of this study, it was not possible to evaluate the effectiveness of this approach in comparison with a control group. The oncologist's reasons for referring patients to SCOC and anticancer treatment decision-making were not factored in, although they would provide additional information.

Implications

Our data confirm the importance of assessing PROMs by oncologists in clinical practice for a thorough evaluation of type and extent of needs of advanced cancer patients undergoing systemic cancer treatment. Oncologists must also be trained in the use of validated prognostic tools in order to refrain from proposing anticancer therapy at the end of life when not indicated. A fully embedded model in which the oncologist evaluates patients with advanced stage disease together with a palliative care team can facilitate the patients' approach to palliative care and allows for direct sharing among the palliative care team regarding treatment options, life expectancy, and patient awareness of prognosis. Proper resources should be allocated in order to fulfill model requirements (59).

Conclusions

Our data confirm the importance of assessing PROMs in order to acknowledge the type and extent of needs of advanced cancer patients. Italian cultural, social, and healthcare background may partly justify the low prevalence of social and spiritual issues detected in a relevant group of cancer patients with advanced stage of disease, and confirm the general presence of good family support, which is also assessed by the high percentage of patients who died at home (37.8%). Our study identified two subgroups of patients who require special attention and support due to the important symptom's burden detected by PROMs: women who experienced higher frequency of pain, anxiety, depression, loss of appetite, and higher MUST scores, together with a higher frequency of total awareness of the prognosis; and younger adult subjects who have a shorter life expectancy, experience more intense pain and nausea, are more aware of the prognosis, and die more often in a hospital. These categories of patients with advanced stage of disease, regardless of the tumor type, require special attention to provide early referral to SCOC for adequate symptoms' relief and proper care planning.

The overall SCOC performance was good as evaluated by some parameters such as the low percentage of patients receiving SAT at the end of life, the place of death, and the number of unplanned visits at the ER.

The role of the oncologist remains crucial to identify all patients in need of early palliative care through the systematic use of PROMs, which are now part of clinical practice (60). Assessment of patients' needs should be done across the board on all patients with metastatic cancer, and then, through joint evaluation at SCOC, the categories of patients in greatest need can be identified. Changing perspective in the evaluation of patients is mandatory for oncologists in order to intercept the true needs of patients with cancer in advanced disease. Defining an accurate estimate of prognosis remains strategic in order to avoid SAT at the end of life, especially as second or further treatment line, which can contribute to being detrimental for patients' survival and/or the quality of life for patients and caregivers.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was reviewed and approved by Veneto Institute of Oncology Ethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization, VZ, AG, SS, AB, and SL. Data collection, VZ, AG, SS, MN, IG, AP, RM, MB, SM, CS, DM, FD, CDT, CP, BC, AAP, DB, FN, MC, FB, RI, AB and SL. Statistical analysis: CDT; original draft preparation, VZ, AG, AB, CDT, SS, and SL. Review and editing, all authors. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Gratitude among advanced cancer patients and their caregivers: The role of early palliative care

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Objective: A cancer diagnosis represents a unique trauma, given its life-threatening, multidimensional, and uncertain nature. Gratitude is a construct representing the emotional state that arises when individuals recognize that a benefit has been received as a result of someone else's action or a spiritual entity's intervention. Based on the positive psychological wellbeing, gratitude has been associated with improved health outcomes even in the disease setting. Thus, the models of care that foster gratitude should be adopted in the clinical context. This study aims to explore whether and how gratitude may originate in patients with advanced cancer and their caregivers undergoing early palliative care (EPC).

Methods: We analyzed 251 reports from 133 patients and 118 caregivers describing their clinical experience in two EPC units. The sources of gratitude were identified and ranked based on their frequencies. Words expressing gratitude and words referring to communication and spirituality were collected by means of the Linguistic Inquiry and Word Count software and correlated.

Results: In total, 123 (92.5%) of 133 patients' and 97 (82.2%) of 118 caregivers' reports, respectively, included explicit or implicit expressions of gratitude. Gratitude was associated specifically with successful physical symptom management, emotional support, improved attitude toward death, better information, humanity, and the familiar environment. The use of words of gratitude in patients' reports was positively correlated with the use of words referring to communication (r = .215, p = .026) and spirituality (r = .612, p <.001).

Conclusion: Our results suggest that interventions within the EPC model based on doctor–patient–caregiver communication may allow patients and caregivers to experience a feeling of gratitude, and this may represent a resource to be exploited to improve their physical and psychosocial wellbeing.

KEYWORDS

early palliative care, cancer, patients, caregivers, qualitative research, gratitude, spirituality, communication

Introduction

A cancer diagnosis and its treatment represent a unique trauma for most patients. The detection of an abnormality on self- or routine examination, the following laboratory tests and screening procedures, and the communication of a life-threatening illness are shocking and cause patients to face an escalation of fear and uncertainty that leaves them vulnerable and apparently with no control over events (1). Once on standard oncology care (SOC), patients are overwhelmed by the side effects (2) that may not get fully addressed by oncologists (3) and trigger cascading consequences on their physical and psychosocial wellbeing (2). Their primary caregivers experience similar feelings, exacerbated by the burden of their responsibility (2). Apparently, there are no reasons to feel grateful in such a situation.

In psychology, gratitude is defined as a transient, emotional state arising from a two-stage process: the recognition that a benefit has been received and the acknowledgment that such a benefit is derived from someone else's action (4–8). When gratitude is experienced more regularly over time, in the form of a more general disposition in noticing and appreciating positive aspects in the world, it is conceptualized as a personality trait more than an emotional state (9). In any case, it is commonly accepted that gratitude occurs in interpersonal contexts (10). From an evolutionary perspective, it has been proposed that gratitude is functional to identify those who have demonstrated responsiveness to their needs and preferences in order to create bonds with them (11). In some cases, the source of recognized benefits or positive aspects in the world may also be attributed to impersonal or non-human sources like God, nature, or the universe, suggesting that gratitude could also be related to the concept of spirituality beyond that of interpersonal relationship (6, 9, 12–14).

Based on the idea of positive psychological wellbeing, a construct representing positive thoughts, emotions, and strategies people use to evaluate their life positively (15), specific positive emotions like gratitude might be potent predictors of improved health outcomes during the periods of chronic stress, including life-limiting illness (10). In this sense, gratitude has received considerable attention in health research over the last two decades, also in relation to the oncological populations (6, 10, 16, 17). There is a strong literature linking gratitude to psychological wellbeing and positive social relationships, and the research linking gratitude to physical health, although more limited, is insightful (18–20). In consideration of the extreme influence that gratitude might have in a cancer population facing a life-threatening diagnosis, clinicians should adopt the models of care that foster it.

Only recently, the role of gratitude has been investigated in the context of palliative care (7, 9, 18, 21–23). The interest raises from the consideration that gratitude has been specifically linked with psychological constructs relevant for palliative care as anxiety (24) and death anxiety (25, 26), depression (12, 27–30), and psychological distress (30). Recently, Centeno and colleagues (31) analyzed the content of 110 thank-you letters sent from bereaved caregivers to two palliative care units to understand the reasons behind the gratitude felt toward the palliative team. Results showed that caregivers' gratitude arose from the essential characteristics and principles of palliative care, like humanity, professionalism, emotional support, and holistic interventions, that address the unmet needs usually recognized by patients with advanced cancer and their caregivers (2). The only study on gratitude in palliative care involving patients has been conducted by Althaus and colleagues (9). By administering validated questionnaires to 64 cancer patients on palliative care, the authors found that gratitude arises in this context mainly through relationships with family and friends. They also found that gratitude is positively associated with the health status, quality of life (QoL), and appreciation of life, and a post-traumatic growth dimension and negatively associated with psychological distress, supporting the hypothesis that gratitude may have a positive impact on the QoL and reduce psychological distress in palliative care patients at the end of life.

Early palliative care (EPC) integrates palliative care with SOC early in the course of the disease for patients with cancer and their caregivers (32–34). In this model of care, the interpersonal context, i.e., the relationship between the palliative care team, the patient, and the caregiver, which is expressed by an attentive and honest style of communication, plays a key role (2). High-quality communication is the means by which the palliative care team addresses patients' and caregivers' unmet physical, psychosocial, and spiritual needs in the long term, by taking charge early on. It is unlikely for patients with cancer to express spontaneously their doubts and fears, and they are grateful when their physicians are proactive in confronting distressing issues (35, 36). Thus, it could be speculated that EPC could trigger, although unsolicited, an emotional state of gratitude in both the patient and the caregiver towards the palliative team and function as a positive psychological intervention.

In this exploratory study, we analyzed 251 reports from patients with advanced cancer and their caregivers under EPC talking about their clinical experience with the model, in order to verify the hypotheses that an emotional state of gratitude might be commonly encountered among cancer patients and their caregivers on EPC and that the long-term, high-quality relationship and communication with the palliative team as well as the inclusion of spiritual needs among the goals of care may have a role in its elicitation. Specifically, the objectives were to (1) assess the proportion of patients and caregivers feeling gratitude in the EPC context; (2) record their sources of gratitude; (3) identify associations between gratitude and doctor–patient–caregiver communication, as a measure of their relationship; and (4) identify associations between gratitude and spirituality.

Materials and methods

Participants

This study was conducted in two EPC units: the outpatient Oncology and Palliative Care Unit, Civil Hospital Carpi, USL, Modena (Italy) and the outpatient Palliative Care Unit, Section of Hematology, Azienda Ospedaliera Universitaria di Modena (Italy). A total of 133 patients with advanced cancer and 118 caregivers of alive or deceased patients were enrolled between July 2020 and June 2022. Patient and caregiver eligibility required at least four visits at the EPC unit, willingness to complete the task, and age ≥18 years. At the time of the enrollment, patients had a life expectancy of more than 6 months and were not on interim evaluations to be referred to hospice or home care. All participants provided written informed consent prior to data collection.

The study was performed in accordance with the ethical standards of the 2013 Declaration of Helsinki and was approved by the Ethics Committee of Modena (N. 0026448/20).

Study setting

Our outpatient EPC oncology and hematology units were established in 2006 and 2012, respectively, and integrate primary oncology and hematology specialists with a palliative/supportive care team composed of one physician assistant, one fellow, and one nurse specialized in palliative care (PC), to provide comprehensive symptom management and psychosocial, spiritual, and emotional support to patients with cancer and their families, from the time of diagnosis to advanced/metastatic disease according to established guidelines (3, 32, 37, 38). Patients with an advanced/metastatic cancer diagnosis (with distant metastases, in the case of solid tumors, late-stage disease, and/or a prognosis of 6–24 months) with high symptom burden are electively referred by the oncologists to receive an EPC intervention. The EPC team follows on average 20–30 patients/week and each patient on a regular basis one-to-two times/week. Outpatient EPC interventions are integrated with both specialized nurse home care services and hospices (32, 37, 39).

Procedure

The task was described to patients and caregivers by the EPC team during a dedicated, face-to-face encounter, also to offer easier opportunities to ask for clarifications. Patients completed a self-administered pen-and-paper questionnaire (Table 1) in which they were asked to answer three questions about their experience with the disease prior to and during the EPC intervention and possible changes in the perception and

TABLE 1 Questionnaires for patients and caregivers.

Patients
Talk about your disease experience prior to the EPC.
Talk about your disease experience during the EPC.
Talk about your perception and expectations of the future and your thoughts and feelings about the end of life.
Is there anything more that you would like to say?
Caregivers
For how long did your relative come to the EPC Unit?
What do you think EPC treatments meant for your loved one? And what did they mean to you?
Is there an episode you would like to share with us from the period when you were caring for your loved one?
Would you like to add something else?

expectations of their future, including at the end of life. A fourth, open question allowed them to openly express their thoughts on the topic. The questionnaire was completed once, at a time of their preference and availability during the weekly appointments at the units. They were free to complete it all at once or in separate sessions. Caregivers completed the same task at home. Both patients and caregivers were asked to submit their responses within 1 month. Self-administered questionnaires were chosen over face-to-face interviews as the best option to respond with comfort to possibly painful questions and to anonymize the process, in order to minimize the risk of social desirability and obsequiousness biases. The sample characteristics were collected with the support of our database and chart reviews.

Statistical analysis

Descriptive statistics was performed on the sample characteristics.

The analyses were performed separately for patients and caregivers. The answers to the questionnaire of each participant were analyzed together as a unique report. Two researchers, a physician and psycholinguist (EBa and EBo), independently read the reports and analyzed them based on a common strategy involving a three-step process. The first step consisted of categorizing reports as reporting the expressions of explicit gratitude, implicit gratitude, or no gratitude. Reports reporting the expressions of explicit gratitude were considered those in which the respondent wrote words or expressions of gratitude (e.g., "thank you" and "I am grateful for"). Reports reporting the expressions of implicit gratitude were considered those not mentioning, explicitly, words of gratitude, but involving the use of positive, high-intensity words, expressions, or metaphors conveying great warmth and enthusiasm when talking about the experience with the EPC (e.g., "EPC unit has been a *lifeline*" and "These doctors are *outstanding*"). Reports that could not be categorized as reporting the expressions of explicit or implicit gratitude were categorized as reports reporting no gratitude. The second step consisted of identifying reasons for gratitude. Reasons for gratitude were considered those aspects of the EPC experience reported in association to explicit or implicit expressions of gratitude. This means that if participants wrote that, once referred to the EPC unit, the pain was resolved, physical symptom management was not considered as associated to gratitude but more as an expected and given-for-granted result. Conversely, if participants wrote that, once referred to the EPC unit, the pain was resolved, thanks to the palliative care team or that the pain that they have been suffering for years was miraculously resolved in a few days, giving them their life back, physical symptom management was considered as associated to gratitude (explicitly or implicitly, respectively). The third step consisted of aggregating reasons for gratitude into broader categories and ranking them based on their frequency. At the end of the three-step process analysis, the two researchers shared the results and refined them through periodic meetings and discussions.

Quantitative analysis was performed on reports reporting the expressions of explicit gratitude through the Italian version of the Linguistic Inquiry and Word Count (LIWC) software (40). This is a psychometrically validated, automated, text-analysis program that measures the percentage of the use of theoretically defined categories of words in either text or speech (41). By uploading *ad hoc* dictionaries of the language of interest, the words of any target text can be filed into one or more categories and subcategories. Categories and subcategories represent dozens of word domains through which LIWC compiles a text. For example, the word "cried" belongs to five word categories/subcategories (overall affect, negative emotions, sadness, verb, and past tense verb); hence, every time the word "cried" is found in the target text, the scores referring to each of these five categories/subcategories will increase (40). Interestingly, LIWC allows to customize *ad hoc* dictionaries by adding the categories/subcategories of interest.

We coded three categories of interest that allowed us to investigate the relationship between the use of words associated to gratitude (e.g., "grateful" and "thank you"), communication (e.g., "to listen" and "to talk"), and spirituality (e.g., "soul" and "redemption"). While the categories related to communication and spirituality were already coded by the LIWC Italian dictionary, we added the category referring to gratitude that coded words like *gratitudine* ("gratitude"), *grata/o* ("grateful"), *grazie* ("thank you"), *ringraziamenti* ("thanks"), and *ringraziare* ("to thank"). Reports including implicit expressions of gratitude were excluded from the analysis because implicit contents cannot be detected by the software.

Through a series of bivariate Pearson correlations, we correlated the coded category of gratitude with the coded categories of communication and spirituality. In accordance with the exploratory approach of our study, we set a significance level at $p = .05$.

Results

A total of 133 patients and 118 caregivers took part in the study, for a total of 251 participants. Among participants who were originally approached, 28 patients and 38 caregivers refused to participate because they were feeling uncomfortable or were not interested, resulting in a response rate of 83% for patients and 76% for caregivers. The patients' mean age was 68.4 years. A total of 118 patients were diagnosed with solid cancer, whereas 15 had a hematologic malignancy. The mean time receiving EPC was 9.8 months. The caregivers' mean age was 56.7 years, of whom 93 cares/cared for patients with solid cancer and 25 for patients with hematologic cancer. Additional details are reported in Table 2.

TABLE 2 Demographic and clinical/caregiving characteristics of the sample (n = 251).

			Patients (n = 133)	Caregivers (n = 118)
Age at enrollment	Years	Mean (sd)	68.4 (11)	56.7 (13.7)
		Range	35–87	20–82
Sex	Female	n (%)	60 (45.1)	77 (65.3)
	Male	n (%)	73 (54.9)	39 (33.1)
Education	Primary school	n (%)	24 (18)	10 (8.5)
	Secondary school	n (%)	40 (30.1)	22 (18.6)
	College	n (%)	54 (40.6)	43 (36.4)
	Graduation’s degree	n (%)	0 (0)	4 (3.4)
	Bachelor’s degree	n (%)	9 (6.8)	32 (27.1)
	Missing data	n (%)	6 (4.5)	7 (5.9)
Ethnicity	Caucasian	n (%)	122 (91.7)	106 (89.8)
	African	n (%)	0 (0)	1 (0.8)
	Arabian	n (%)	3 (2.3)	2 (1.7)
	Indo-European	n (%)	0 (0)	1 (0.8)
	Missing data	n (%)	8 (6)	8 (6.8)
Religion	Catholic	n (%)	92 (69.2)	81 (68.6)
	Muslim	n (%)	3 (2.3)	2 (1.7)
	Evangelic	n (%)	1 (0.8)	1 (0.8)
	Orthodox	n (%)	3 (2.3)	2 (1.7)
	Jehovah’s Witness	n (%)	1 (0.8)	1 (0.8)
	Animist	n (%)	0 (0)	2 (1.7)
	Atheist/Agnostic	n (%)	25 (18.8)	21 (17.8)
	Missing data	n (%)	8 (6)	7 (5.9)
Cancer diagnosis	Solid	n (%)	118 (88.7)	93 (78.8)
	Head, neck, larynx	n (%)	7 (5.9)	–
	Rectum, sigma	n (%)	3 (2.5)	–
	Colon	n (%)	12 (10.2)	–
	Gastric	n (%)	17 (14.4)	–
	Pancreas	n (%)	9 (7.6)	–
	Breast	n (%)	20 (16.9)	–
	Lung	n (%)	19 (16.1)	–
	Genitourinary (kidney, testis, prostate, ovary)	n (%)	24 (20.3)	–
	Skin	n (%)	2 (1.7)	–
	Sarcoma	n (%)	3 (2.5)	–
	Missing data	n (%)	2 (1.7)	–
	Hematologic	n (%)	15 (11.3)	25 (21.2)
Time since first EPC consult	Months	Mean (sd)	9.8 (13.9)	14 (14.7)
		Range	2–96	2–72
KPS score at first EPC consult	0–100	Median (IQR)	60 (50–60)	–
NRS pain score at first EPC consult	0–10	Median (IQR)	7 (6–8)	–
Active CT at first EPC consult		n (%)	52 (72.2)	–
Status of the patient (alive/deceased) at the moment of the caregiver enrollment	Alive	n (%)	–	81 (68.6)
	Deceased	n (%)	–	37 (31.4)
In case of deceased patient, months since death	Months	Mean (sd) Range	–	13.4 (10.1) 1–36

(Continued)

TABLE 2 Continued

			Patients (n = 133)	Caregivers (n = 118)
Relationship to patient	Mother/father	n (%)	–	1 (0.8)
	Spouse/partner	n (%)	–	53 (44.9)
	Daughter/son	n (%)	–	51 (43.2)
	Sister/brother	n (%)	–	4 (3.4)
	Other family members	n (%)	–	5 (4.2)
	Missing data	n (%)	–	4 (3.4)

-, no data; CT, chemotherapy; EPC, early palliative care; IQR, interquartile range; KPS, Karnofsky Performance Status; NRS, numerical rating scale.

Of 133 patients' reports, 123 (92.5%) include explicit or implicit expressions of gratitude. The remaining 10 (7.5%) did not report expressions of gratitude. However, none reported any complaint and all reported positive feedback.

Expressions of gratitude were explicit in 100 (75.2%) reports and implicit in 23 (17.3%) (Figure 1 and Table 3).

The reasons for gratitude cited by patients can be summarized into six categories: physical symptom management (cited in 83.5% of the reports), emotional support (46.6%), improved attitude toward death (33.8%), better information (24.1%), humanity (22.6%), and familiar environment (12%) (Tables 4, 5).

Of 118 caregivers' reports, 97 (82.2%) include explicit or implicit expressions of gratitude. The remaining 21 (17.8%) did not report expressions of gratitude. None reported any complaint, and all reported positive feedback.

Expressions of gratitude were explicit in 88 (74.6%) reports and implicit in 9 (7.6%) (Figure 1 and Table 3).

The reasons for gratitude cited by caregivers were physical symptom management (78%), emotional support (39%), better information (22%), humanity (16.1%), familiar environment (14.4%), and improved attitude toward death (11%) (Tables 4, 5).

Physical symptom management included, on a broader perspective, competence in relieving pain, medical skills, and high levels of scientific competences and professionalism. Emotional support included listening, encouragement, empowering, relieving from the psychological burden, and dedication to participants' needs. Improved attitude toward death was obtained through discussions, relieving of pain, and positive emotions. Better information referred to prognostic understanding and end-of-life care awareness. Humanity referred to kindness and being treated like persons and not patients. Familiar environment referred to the feeling of calm and peace patients experienced while in the unit.

In patients' reports, but not in caregivers' report, the use of words associated to gratitude was positively correlated with words referring to communication (r = .215, p = .026) and spirituality (r = .612, p <.001).

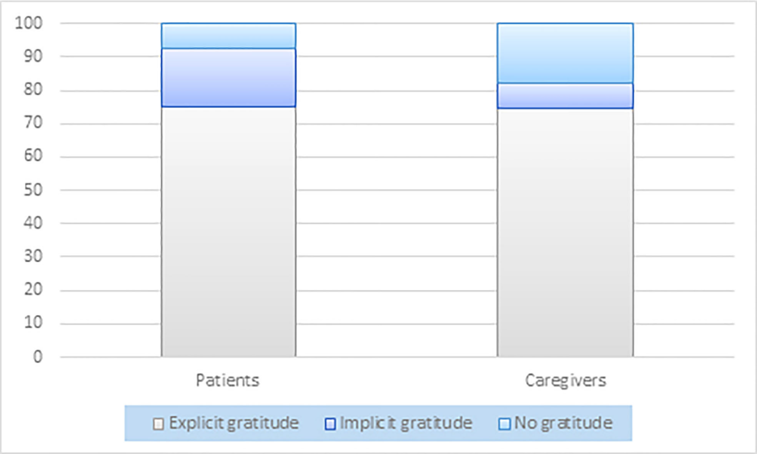

FIGURE 1
Graphical representation of the percentage proportion between reports showing explicit, implicit, and no gratitude for patients and caregivers.

TABLE 3 Quotations of explicit, implicit, and no gratitude from patients and caregivers.

	Patients	Caregivers
Explicit gratitude	001-P-008 "Thanks to doctors' explanations I was able to go on" 001-P-010 "I thank the team for the emotional support" 002-P-009 "Through the years, my life has improved thanks to the palliative cares" 002-P-022 "I would like to thank from the bottom of my heart for the attention, dedication, care that have always been guaranteed to me, both professionally and humanely. I have always felt entrusted; I would almost dare to say loved." 002-P-050 "I must say that I am lucky to being able to count on such care, and I must say thank you."	001-C-001 "A sincere, heartfelt thanks to the people who accompanied us through this very difficult journey. For the humanity, the availability, the professionalism and the patience they have shown day after day." 001-C-007 "I would like to thank the palliative team for never making us feel alone." 002-C-017 "I will never stop saying heartfelt thanks for the kindness, respect, humanity as well as the highest professionalism of the clinic staff." 002-C-009 "As a family member I can only say thank you." 002-C-016 "Beyond expressing my gratitude, I would like to reiterate the crucial importance of these treatments for everyone."
Implicit gratitude	002-P-003 "Once arrived here, they gave me my smile back in one week. This is the unit that, as a side effect, has the wellbeing." 002-P-116 "I must say that here I found a unit that I didn't even think could exist." 002-P-102 "The palliative care for me was miraculous, (…). It seemed like a dream to me. I have started to live a life worthy of the name again." 002-P-006 "To me, the cure received in this unit was truly a godsend"	001-C-005 "All the doctors and the nurses who helped us made us feel like humans and not just the number of a bed, and this really makes the difference." 002-C-025 "They have been of utmost importance, not only to stem the pain, they have been much more." 002-C-092 "They have been a lifesafer."
No gratitude	001-P-002 "In my opinion this clinic was necessary to have a passable standard of living." 002-P-078 "I did not know the palliative care unit, and I am very sorry, because if I had known earlier I would have been better. I had a great time, pains reduced a lot after only 2 visits. It is an excellent service, I would say necessary."	001-C-003 "Palliative care was a choice to have some more time, with a good quality of life." 001-C-011 "Palliative cares have been treatments that allow him to stay active and in a decent physical shape."

At the beginning of each quotation, the ID of the participant is reported: the first three numbers indicate the unit (001 for the Hematology Unit, Azienda Ospedaliero Universitaria Policlinico, University of Modena and Reggio Emilia Azienda Ospedaliera of Modena and 002 for the Oncology and Palliative Care Unit, Civil Hospital Carpi), the letter indicates patient (P) or caregiver (C), and the last three numbers indicate the recruitment progressive number).

Discussion

In this study, we investigated the frequency and sources of gratitude as well as their association with communication and spirituality in the context of EPC through the analysis of 251 reports from patients and caregivers, talking about their clinical experience with EPC. To our knowledge, this is the first study to examine the presence of gratitude in the EPC context.

Relative to our first objective, i.e., to assess the proportion of patients and caregivers feeling gratitude in the EPC context, our data show that gratitude arises in most patients and caregivers on EPC. Among patients' and caregivers' reports, 92.5% and 82.2% reported explicit or implicit words of gratitude. The study from Centeno and colleagues (31) did not report a proportion between the patients followed by the two palliative care units and the number of caregivers' thank-you letters received, raising the doubt, as recognized by the authors themselves, that only the most satisfied would write a thank-you letter spontaneously. Our study fills this gap by assessing the frequency of gratitude in the palliative care context not only for caregivers but also for patients. The high percentages of expressions of gratitude found may indicate that gratitude in the EPC context is not linked to personality dispositions but, rather, to an indirect, secondary benefit arising from the well-known, primary benefits attributed to EPC, like symptom control (2, 37, 42), reduced therapy aggressiveness (3, 42–44) and risk of severe pain (32, 37), improved QoL (2, 3, 37, 44–47), mood (2, 3, 37, 44–47), and prognostic awareness (2, 48, 49). Most of SOC interventions have primary benefits on cancer itself but lead to secondary, indirect issues (2, 37). The availability of a model of cancer care that allows, beyond the resolutions of such issues, secondary benefits such as the elicitation of gratitude is of utmost value, given its potential relevance as an indicator of the clinical outcome.

TABLE 4 Emerging reasons for gratitude and illustrative quotations.

Reasons for gratitude	Percentage	
	Patients	Caregivers
Physical symptoms	83.5%	78%
Emotional support	46.6%	39%
Improved attitude toward death	33.8%	11%
Better information	24.1%	22%
Humanity	22.6%	16.1%
Familiar environment	12%	14.4%

In the oncological setting, patients could still experience positive thoughts and emotions, as shown by studies on post-traumatic growth and benefit finding (50, 51). However, the presence of a positive attitude during the cancer experience often relies on the personal resources of patients and caregivers (e.g., personality and environment). As a positive attitude may be improved by positive psychology interventions (15), these should be systematically provided in the oncology setting. Thus, if the EPC model acts itself as a positive psychological

TABLE 5 Emerging reasons for gratitude and illustrative quotations from patients and caregivers.

Reasons for gratitude	Patients	Caregivers
1. Physical symptom management	002-P-009: "When I first came here, I didn't desire to live because I had so many pains and I was in a severe depressive crisis. Over the years my life has improved thanks to palliative care. As the pain subsided, the wish to live became bigger and bigger." 002-P-044: "For me they (EPCs) were a salvation, a light. My pains are now more tolerable, my belly has deflated, and I no longer have to do the paracentesis every few days." 001-P-005: "I am very satisfied with how I have been medicated and informed about the course of the disease. I was brought back to an autonomous and conscious life."	001-C-007: "We felt so cared for by nurses and doctors who came to our home with an incredible cadence and interacted with us flawlessly." 002-C-052: "So much relief, my husband had no pain and lived well. And even more, he was peaceful, with me by his side all the time (…). Of course, if he had been suffering I would not have made it." 002-C-063: "To me they (EPC) represented everything; to see her calm and without pain allowed me to make it."
2. Emotional support	001-P-004: "I immediately felt welcomed, protected and taken into consideration." 002-P-003: "This is the clinic which, as a side effect, has the well-being, the feeling well. I come in already knowing that when I will come out, I will be fine. I will be fine in every sense. Physically, emotionally (…)." 002-P-043: "But I would like to say that I feel very well cared for, listened to and understood; in other words, I feel no longer alone but now I am confident. I have full confidence in these people who take care of me (…)."	002-C-092: "I found kindness, hospitality and solidarity, as it should always be when you face such a problem." 001-C-005: "I start by saying that personally I am not frightened by death, but by the suffering that can be experienced along the way, so this journey reassured me that, feeling helped and "pampered" by doctors and nurses, I will have a lot of relief in dealing with my husband's disease." 001-C-006: "I have talked many times with my father about the path we have faced together through palliative care and I can say that for him it was a path of emotional relief, as well as physical, decisive."
3. Improved attitude toward death	002-P-003: "(…) and life becomes easier, more livable, so when I come here, I don't think about death." 002-P-040: "In these last months I have often addressed with the doctor these aspects in conversations, and this is what, personally, I have appreciated the most. Being able to talk about certain things, which is not easy for me (for example with my loved ones), has really helped me a lot to understand and to accept." 002-P-043: "I am having some interesting conversations with the team on death issues which honestly are helping me a lot in understanding and accepting and getting rid of my fear. I can't speak to my family about this, thus being able to talk about such topic with those who can actually help you can really be a great help."	001-C-001: "There was a time when the idea of letting my mother go was unacceptable. (…). It took time, the path of palliative care was also fundamental in this, to learn to let her go and respect her wishes." 002-C-017: "The beauty of the first meeting with the clinic staff. We went out and, I can't explain, but we were smiling. Each visit has always been filled with serenity, even when the situation worsened, and the disease progressed. Knowing that you are not alone and that you can count on someone who guarantees you control over your suffering and respect for your will is a lot. And maybe that's what helped me most in accepting the idea of death." 002-C-082: "I have been able to prepare myself and it was fundamental for me considering what I will have to face later, at the "end of life". But I have well understood that, if there hadn't been this part of early referral here, the so-called "end of life" would have been a real failure. You need time to be able to prepare, otherwise it is all useless."
4. Better information	002-P-022: "They also allowed me to take the most delicate decisions, for example when I decided to stop oncological therapies because they are no longer effective." 002-P-027: "These treatments help me to know what I need in order to choose the best care options while respecting my dignity as a person." 002-P-050: "They talk to me, they listen to me, and they explain things to me, while before no one explained to me what was happening. Now I no longer do cancer treatments because they made me feel bad. Now I'm fine."	002-C-022: "They helped me in preparing myself for my father's death, they did it through conversations in which they gradually informed me of the progress of the disease, the prognosis and what to expect. In doing so, they accompanied me and helped me to make the best decision every time, for example the transfer to hospice at the very end." 002-C-047: "(…), knowing what is happening, knowing the prognosis of the disease, being able to talk to doctors about possible choices, makes me more aware, prepared, and allows me to be able to better follow my mother." 002-C-051: "If the doctor had not talked to me and informed me step by step of what was going on, I would have gone mad, I would not have made it."
5. Humanity	002-P-074: "(…) coming here every week and always being able to count on such a trained team, able of making you feel not just a patient, but a person in his entirety (…)." 002-P-093: "I feel respected in my dignity as a human being, before I felt like a number, a tumor, I didn't feel like a person, as I do now." 002-P-007: "When I say, "You know, doctor, I feel better with this treatment", she says "But I WANT you to feel better", I think that a doctor cannot tell you more than that."	001-C-005: "All the doctors, the nurses who supported us, made us feel like people and not just the number of a bed and this makes the difference." 001-C-001: "It was a priority for the doctors to understand what made my mother happy: once she understood that her greatest desire was to go on doing the little things of every day, she was always put in a position to do them and, overall, she was encouraged to do them." 001-C-001: "I remember that during a visit at which my brother and I were not present, the doctor told my mum some episodes of his personal life referred to his son. When I met my mother in the afternoon, she told me right away and I noticed that the doctor's confidence had made her happy. It meant that he didn't just consider her a patient, but a person with whom to joke, with whom to be able to share a private piece of his life."
6. Familiar environment	002-P-004: "The luck is that a beautiful, almost familiar environment has been created." 002-P-050: "I love the doctor and the nurse, because they make	002-C-053: "My mum feels at home and not in hospital." 002-C-073: "To see my mother so welcomed, accompanied, as if she was in a family environment, as if she was at home, by very professional but also human doctors and

(Continued)

TABLE 5 Continued

Reasons for gratitude	Patients	Caregivers
	me feel at home 002-P-045: "By thinking that I always see the kind and smiling faces welcoming me, when I go to the EPC unit, means a lot."	nurses was a surprise. I didn't know there was such a thing." 002-C-008: "Dad was a person full of life, sunny and witty, and he was able to pass all this to his fellow adventurers too. Sincere feelings were born with the staff and with the patients, there were moments of important sharing of emotions and feelings."

At the beginning of each quotation, the ID of the participant is reported: the first three numbers indicate the unit (001 for the Hematology Unit, Azienda Ospedaliero Universitaria Policlinico, University of Modena and Reggio Emilia Azienda Ospedaliera of Modena and 002 for the Oncology and Palliative Care Unit, Civil Hospital Carpi), the letter indicates patient (P) or caregiver (C), and the last three numbers indicate the recruitment progressive number).

intervention, triggering an emotional state of gratitude, it should be preferred over other models of care.

Relative to our second objective, i.e., to record the sources of gratitude from patients on EPC and their caregivers, we found that gratitude was associated with EPC interventions and specifically with successful physical symptom management, emotional support from the EPC team, improved attitude toward death, better information, humanity, and the familiar environment. Our results confirm and extend the results from Centeno and colleagues (31). Moreover, they mostly overlap with patients' and caregivers' perspectives on benefits achieved through EPC (2, 3, 39, 52).

The main EPC interventions soliciting gratitude are symptom management and emotional support for both patients and caregivers. Symptom management often referred to pain relief. The importance of symptom resolution for patients with advanced cancer is in keeping with studies showing that a reduction in pain severity is associated with an improvement in functional status, as early as the first week (37, 42), and that symptom management is necessary to restore physical functioning, mood, and social life (2). Once again, data show that the keystone of EPC is the resolution of physical symptoms. Once symptoms are controlled, more psychological resources are available to cope with the other, equally burdening, issues (2, 53).

Emotional support is the second most cited source of gratitude. Interestingly, emotional support is often reported jointly with better information, i.e., the opportunity to discuss honestly about the disease and its treatments with the medical staff. This may be explained by the fact that emotional support is mainly required when sharing information about the clinical situation. Healthcare professionals often fear removing hope from patients by revealing the truth about their condition (36). However, uncertainty often forces patients and caregivers to take into consideration all the possible scenarios, an extremely energy- and resource-consuming process. Contrary to intuitions, knowing the truth in an emotionally supporting context may help to focus on the real scenario and elaborate it. Moreover, to be aware of the situation allows patients, and even more caregivers, to plan not only the care path but also how to communicate with the other members of the family.

Palliative care was not identified as a source of gratitude by patients in the study by Althaus and colleagues (9). Our additional result may be due to our participants' longstanding involvement in palliative care. The EPC unit was described by some as a habit, an awaited weekly appointment. An early introduction to palliative care may have led to a better relationship and to a stronger positive impact of its benefits. However, it may also be possible that the different methodologies gave origin to the different results. Indeed, Althaus and colleagues explicitly asked their participants which life domains were identified as a source of gratitude, whereas we identified spontaneously reported sources in the context of a questionnaire focusing on the clinical experience.

Conversely, our results are similar to those by Centeno and colleagues (31), whose methodology was similar to ours (31) but involved the traditional, late, and end-of-life palliative care setting and focused only on caregivers. It is possible that patients more than caregivers could require an early referral to palliative care in order to appreciate its benefits and experience a feeling of gratitude for them.

Relative to our third and fourth objectives, i.e., to identify the associations of gratitude with communication and spirituality, as expected, we found that the more patients were grateful the more they talked about their communication with the palliative team and used words associated to spirituality.

The sources of gratitude we identified are or arise from interventions that distinguish palliative care from SOC. SOC does not always contemplate an honest, empathetic, and truthful communication with patients and caregivers on their unmet needs (3). On the other hand, communication is the main means that the palliative doctor has to understand how to support a patient with advanced cancer in achieving the optimal QoL (54). In fact, communication is upstream to all the sources of gratitude identified. Thus, communication should be further promoted in the EPC setting.

Spirituality refers to the way people find meaning and purpose in the world and how they perceive their connection to self, others, the significant, or sacred (55). Illness can trigger spiritual concerns, both existential and religious (56). Thus, spirituality is properly and comprehensively tackled by palliative care, as a mediating variable affecting care outcomes in terms of the QoL and coping resources (56), as extensively demonstrated (57).

The relationship between gratitude and spirituality is not a new topic in literature. Our results confirm data from studies in both oncological and non-clinical settings reporting that the indexes of spirituality are significantly correlated with the frequency of gratitude feelings (58–61). It may be possible that belonging to an organized religion may contribute to eliciting gratitude by improving social support. The spiritual support received from the religious community may lead to higher wellbeing, eliciting, in turn, feelings of gratitude (6, 13, 62). In our samples, only 18.8% of patients and 17.8% of caregivers did not belong to a religious denomination. However, spirituality can also be described as “an intrinsic private relationship with a divine and spiritual transcendence” (6) and no studies investigate the presence of gratitude in a sample of spiritual, non-religious individuals. Literature suggests a link between spirituality and gratitude and between spirituality and well-being (57, 63). Spirituality can therefore be a resource of strength for patients, and it may play an essential role in the relationship between gratitude and wellbeing, during an experience of illness. Thus, it should be evaluated in the EPC setting.

The present study has several limitations. First, gratitude as a personality trait was not assessed in the sample; thus, we cannot exclude that the high expression of gratitude found among our participants is to be attributed to a widespread predisposition to gratitude and not to an emotional state elicited by the model of care. Second, our analyses do not allow us to draw conclusions on cause–effect relationships. A model representing how gratitude works in the context of EPC should be implemented to run more informative regression analyses. Third, the refusal to participate in the study from 17% of patients and 24% of caregivers might be due to or associated with a lack of gratitude, thus biasing the results. However, 7.5% of patients and 17.8% of caregivers took part in the study even though they did not express any feelings of gratitude. Moreover, the referral bias is still lower than that from the study of Centeno and colleagues (31) since we did not look at letters spontaneously sent by grateful families but rather at responses to a questionnaire on the experience with the disease prior to and during the EPC intervention.

Although unsolicited, gratitude may represent a resource in EPC interventions. Thus, its assessment as well as gratitude-based interventions could be useful in the context of EPC Future directions should be focused on the biological links between gratitude and clinical outcomes in the cancer population (15) in the setting of EPC.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Modena (N. 0026448/20). The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conception/design: EBo, SB, LP, FG, FA, GP, CP, FE, EBr, ML, and EBa. Provision of patients: LP, FG, FA, ML, and EBa. Collection and/or assembly of data: EBo, LP, FG, FA, ML, and EBa. Data analysis and interpretation: EBo, SB, LP, FG, FA, GP, CP, FE, EBr, ML, and EBa. Manuscript writing: EBo, SB, LP, FG, FA, GP, CP, FE, EBr, ML, and EBa. Final approval of manuscript: EBo, SB, LP, FG, FA, GP, CP, FE, EBr, ML, and EBa.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Communication about early palliative care: A qualitative study of oncology providers' perspectives of navigating the artful introduction to the palliative care team

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Background: Despite robust evidence for the integration of early palliative care for patients with advanced cancer, many patients still access this approach to care late. Communication about the introduction of Early Palliative Care is an important skill of healthcare providers working in this setting. In the context of limited community understanding about palliative care, patients and their families may express fear or negative reactions to its early introduction. Health professionals may lack the confidence or skill to describe the role and benefits of early palliative care.

Aim: This study sought to explore clinicians' perspectives on communication about referral to early palliative care, specifically identifying facilitators in undertaking this communication task.

Methods: An exploratory qualitative study set within a tertiary oncology service in Victoria, Australia. Semi-structured interviews were conducted with purposively sampled oncology clinicians exploring their perspectives on communication about referral to early palliative care. A reflexive thematic analysis was undertaken by two researchers, including both latent and semantic coding relevant to the research question. Reporting of the research was guided by the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist.

Results: Twelve oncology clinicians (58% female, with 67% > 15 years clinical experience) from medical oncology, surgical oncology, and haematology participated. The artful navigation of communication about early palliative care was characterised by the need for a 'spiel' involving the adoption of a series of strategies or 'tactics' when introducing this service. These themes included: *1) Using carefully selected and rehearsed language; 2) Framing in terms of symptom control; 3) Framing as additive to patient care; 4) Selling the* *service benefits of early palliative care; 5) Framing acceptance of referral as an altruistic act; and 6) Adopting a phased approach to delivering information about palliative care.*

Implications: This study highlights the wide ranging and innovative communication strategies and skills required by health professionals to facilitate referral to early palliative care for cancer patients and their families. Future focus on upskilling clinicians around communication of this topic will be important to ensure successful implementation of models of early palliative care in routine cancer care.

KEYWORDS

early palliative care, oncology, referral, communication, qualitative study

Introduction

Palliative care, concerned with the relief of physical, psychological, social, and spiritual suffering (1), is associated with improved clinical outcomes for patients and their families. Several meta-analyses demonstrate benefits for patients including greater health-related quality of life, reduced symptom burden, improved mood, and even prolonged survival (2–4). As such, there is growing impetus to integrate palliative care earlier in the cancer care pathway (5), reflected in the ASCO guideline that patients with advanced cancer receive dedicated palliative care services concurrent with anticancer treatment (6). Yet, late referral of cancer patients to palliative care specialists continues to be identified across international settings (7–9).

The realisation of early integration of palliative care is hampered, in part, by the unique communication barriers in this context (10, 11). Communication between patients and clinicians is a relational process underpinning all oncology and palliative care (11). Communication is broadly considered a core determinant of quality end-of-life care (12), and has ensuing implications for the health of the caregiver in bereavement (13). Despite population-level preferences of >70% who want to be informed about options regarding palliative care in the event of serious illness such as cancer (14), patients and their caregivers report inadequate communication about palliative care, including a tendency to use euphemistic or technical language that is difficult to understand (15, 16). Underlying such challenges in care are the clinician-perceived communication barriers related to the introduction of palliative care (17).

Among these clinician-reported communication barriers are a fear of diminishing patients' morale (18), prognostic uncertainty (19, 20), perceived lack of adequate training for such discussions (21, 22), language and cultural factors (17), and difficulty judging the appropriate time for these discussions (23). These factors are compounded by variable levels of community understanding about palliative care (24), with perceptions of relevance only for those imminently dying (25), meaning patients may also be fearful or avoidant of discussing early palliative care (15). Thus the communication landscape in the setting of early palliative care is fraught, with communication paradoxically representing both a core component of and barrier to early integration with oncology (26).

While the introduction of 'Early Palliative Care' is an important skill of clinicians working in the advanced cancer setting, there has been limited empirical focus on communication facilitators or strategies to navigate this specific task (27). This task is one largely reliant on professionals who are not routinely trained in this specific aspect of care and whose core focus is a different specialty (22). In short, the referral communication task occurs 'outside' the field of palliative care where many have the training and skill sets to undertake such complex conversations.

While communication skills training for cancer care clinicians appears effective in improving support for patients in consultations such as when "difficult news" is delivered, uptake of such training is not yet widespread (26, 28–31). As such, the informal, self-adopted strategies of clinicians therefore remain particularly relevant. This study sought to explore oncology healthcare professionals' perspectives on communication about referral to early palliative care, specifically identifying facilitators when undertaking this communication task.

Methods

Study design

This study employed an exploratory, qualitative, cross-sectional design using semi-structured interviews to elucidate oncology clinicians' perspectives on communication of a palliative care referral. The epistemological position adopted by the researchers reflects social constructionism in which positivist notions of mapping reality in a decontextualized sense were rejected in favour of a view of knowledge that is circumscribed, in part, by social context (32). Methodological rigour was conceptualized in line with Lincoln and Guba favouring trustworthiness (transferability, dependability, credibility, confirmability) (33) over quantitative notions of reliability and validity (34). Activities to enhance trustworthiness included the following: AC and LG (both researchers in palliative care, and experienced in qualitative analysis) engaged in an ongoing process of reflexivity through co-analytic sessions during which varying interpretations of the data were questioned and challenged; an audit trail of the data analytic process was kept; and diverse participant perspectives were triangulated *via* a purposive sampling framework. The reporting of this research is consistent with the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist (35).

Ethics

Ethics approval was provided by the Institutional Human Research Ethics Committee in St. Vincent's Hospital Melbourne (LRR 070/15). Informed consent was obtained from each participant prior to study participation.

Study participants and setting

Participants were recruited through the oncology service of a tertiary hospital in the metropolitan centre of Melbourne, Victoria, Australia. A purposive sampling strategy was utilised to identify a group of clinicians currently providing care to patients with advanced cancer who routinely required referral to palliative care. Purposive sampling ensured that both male and female perspectives were included in the sample, in addition to representation across oncological specialties, and a range of clinical experience. No participants who were invited declined participation.

Data collection

Data from participants were collected by one researcher (AC) using semi-structured interviews (n = 4) and focus groups (n = 8) of 40-65 minutes duration. These were conducted face-to-face in the hospital setting during 2018. Interviews were included to allow broader participation where purposively sampled participants were unavailable at the focus group times. Demographic information on participants was collected *via* a brief survey including gender, profession, and number of years' clinical experience. The interview guide (Table 1) used for all data collection included an initial open exploration of clinicians' experiences with referring patients to palliative care. Subsequent questions related to views of the timing of palliative care referral, communication about palliative care, and barriers and enablers relating palliative care referral. Supportive affirmations and direct probes were used to encourage dialogue and prompt further discussion around these topics of interest. In the present research, data on communication about palliative care were analysed and are presented herein, with other procedural and systemic barriers to palliative care referral to be published elsewhere.

Data analysis

Audio recordings were transcribed verbatim, de-identified, before being subjected to analysis. The researchers adopted an inductive, reflexive approach to thematic analysis, using a combination of latent and semantic codes (36, 37). This reflexive process first involved initial data immersion and familiarization through repeated reading of the transcript and initial coding to identify latent content within the data. Subsequently, these codes were further abstracted to identify conceptual similarities and differences between codes with related codes then clustered together. Codes that were not coherent in the context of the meaningfulness across the dataset or irrelevant to the research aims were removed. Themes were constructed with the remaining related codes, and themes were then defined and refined to ensure appropriate wording. The write-up process then ensued with the use of illustrative quotations accompanying the themes presented. Trustworthiness in the analytic process was ensured through ongoing meetings between L.G and A.C, to discuss and justify the phrasing and content of codes, and the conceptual relations and organization between codes, themes, and subthemes. This process reflected peer debriefing, which can enhance the credibility of the analysis (33).

Results

Sample description

Twelve oncology clinicians (58% female) from medical oncology (n = 8), surgical oncology (n = 3) and haematology (n = 1) participated (Table 2). Eight (67%) of the participants reported over 15 years in practice, with 4 (33%) who reported less than 15 years' experience.

Findings - artful navigation of palliative care conversations: *"You have to tiptoe around it"*

The artful navigation of communication about early palliative care was characterised by the need for a 'spiel'

TABLE 1 Interview guide.

Topic	Question	Prompts, as needed
PREAMBLE: Thank-you for giving up your time today to attend this focus group/interview. You may recall the purpose of the session is to discuss issues pertinent to the introduction of early palliative care for patients with advanced cancer and their families.		
Topic 1: **Discussion of past cases when the clinician has referred a person for early palliative care**	*To begin, can you reflect back upon a previous patient that you have referred to early palliative care. Please discuss this case and share some of the circumstances leading up to this referral, the discussion that took place, and how this was received.*	• What prompted the referral/ conversation? • How was the referral/ conversation received? • How did the patient and their family respond? • Did you feel it was appropriate timing? • If so/why? Why not earlier? Why not later?
Topic 2: **Views of the timing of palliative care referral early in the illness**	*Now I would like to discuss how you see early palliative care fitting into the overall management and support offered for patients with advanced cancer. How would you define the timing of ‘early’ palliative care?*	• What are the key needs and concerns at the time of introduction to early palliative care? - For patients? - For families? - For you as a health care provider? • At what time in the person’s illness might you consider referring to early palliative care? • What prompts you to think you should get palliative care involved early on?
Topic 3: **Communication about early palliative care**	*I wonder now, if we can discuss, how you might go about talking about early palliative care with patients and their families once you’ve you identified they may benefit from it.* *Given some of the complexities of talking about early palliative care, how might you explain this to patients and their families?*	• What might you say? • What works well? • What doesn’t work so well? • What strategies do you use to introduce early palliative care? • What is difficult about this discussion?
Topic 4: **Barriers and enablers relating early palliative care referral.**	Lastly I would like to discuss your views of the barriers and enablers associated with referral to early palliative care. When you see a role for early palliative care, what do you see to be the key inhibiting and enabling factors in raising this?	• Patient understanding of palliative care? ■ If so/what do they understand • Patient hopes • Communication • Time • Relationships • Others?

involving the adoption of a series of strategies or ‘tactics’ when introducing this service. Healthcare Professionals (HCPs) described the various techniques they carefully executed to skillfully introduce the concept of ‘early palliative care’ to patients with advanced cancer. These strategies reflected clinicians’ attention to the timing of the introduction, the quantity of information presented, and the specific content or framing of the message itself.

Six constructed themes represented healthcare professionals’ perspectives on these key strategies for navigating the communication landscape in palliative care referral, namely: *Using Carefully Selected and Rehearsed Language; Framing Palliative Care in Terms of Symptom Control; Framing Palliative Care as Additive to patient care; Selling Service Benefits of Adding Palliative Care to Standard Oncology; Framing Palliative Care Referral Acceptance as an Altruistic Act;* and *Adopting a phased approach to delivering information about palliative care.* Each theme is described in turn, with illustrative examples from the clinicians’ data.

1. Using carefully selected and rehearsed language: *“Mention the ‘palliative care’ word and you can see the face drop”*

HCPs in this study described their carefully selected and rehearsed language in consultations where they sought to introduce early palliative care to patients with advanced

TABLE 2 Characteristics of participating health care professionals.

	N=12	%
Gender		
Male	5	42
Female	7	58
Discipline		
Medical oncology	8	67
Haematology	1	8
Surgical oncology	3	25
Years of experience in discipline		
< 5	3	25
5-15	1	8
15+	8	67
Focus group or interview		
Focus group	8	67
Interview	4	33

cancer. In particular, this related to clinicians' perceived need to avoid the term 'palliative care' when discussing referral with patients:

> "Mention the 'palliative care' word and you can see the face drop".

The need to avoid the use of this term was described in relation to negative, patient-held connotations of this name, and specifically end-of-life connotations:

> "As soon as you mention 'palliative care', people think you're talking about end of life".

A variety of strategies were proposed by HCPs for managing or circumventing this anticipated issue in the referral process. Commonly, clinicians described the strategy of first dispelling patient-held negative connotations before using the term. One HCP noted that they preface the use of this term with an instruction for the patient to disregard any end-of-life preconceptions they have about this service:

> "I've been prefacing it by saying 'I want you to ignore the terminal connotations of this referral'"

Another HCP described the strategy of delaying the use of the 'palliative care' term until late during the referral discussion, owing to the fact that patients' families do not engage with the remainder of what the clinician has to say, once they hear the word:

> "Often I don't mention the word 'palliative' until … late … because I think that once a patient's family hears the word 'palliative' they have an immediate impression. And [I find] they almost don't hear the conversation, if you're introducing it."

In the absence of a different name for palliative care, some clinicians described favouring an approach to 'get them in the door' by introducing the concept of early palliative care using different terms. Some clinicians adopted the strategy of simply avoiding the term 'palliative care' completely:

> "I don't even mention palliative care."

Related to this, several HCPs in this study raised the suggestion of changing the name of 'palliative care' in general:

> "They should just change the name of 'palliative care' anyway."

2. Framing palliative care in terms of symptom control: *"It's for us to manage your symptoms a little bit better"*

HCPs in the study described framing Palliative Care in terms of symptom control when introducing early palliative care with patients. The approach of directly aligning palliative care with symptom control involved characterizing this service as the best approach to manage the symptoms that the person is presently experiencing:

> "I say, 'Look, you've got symptoms. The best people to manage symptoms are the palliative care service.' And I actually … frame it in the symptom management kind of way."

Similarly, two participants noted that they specifically frame the palliative care service in terms of being the "pain team" or as specialists in pain control:

> "I think I found it easy to introduce palliative care as the pain specialists."

HCPs noted that they opt for the term 'symptom control' specifically due to the stigma associated with the term palliative care:

> "I think you have to frame it [palliative care] as symptom control. I think it's like a stigma.

The approach of framing palliative care as symptom control was therefore perceived by HCPs as an effective strategy, describing that it was helpful to avoid negative patient-held reactions:

> "Because I frame it a bit differently, maybe I don't see so many people reacting [negatively] so much now."

However, one HCP in the sample noted that, when patients are asymptomatic, this makes it difficult to discuss PC:

> "I guess I would have difficulty broaching, or more difficulty broaching pall(iative) care when a patient has no symptoms whatsoever from their cancer."

Indeed, one HCP expressed skepticism with respect to the effectiveness of symptom control framing, noting that irrespective of the framing used, palliative care will hold different connotations for some patients:

> "It's easy to say 'it's just how you sell it' but that's not really true. I mean, yes, it's how we're going to get a group of people who can help us see if we can … to remove the pain or whatever it is. But it still sends a slightly different message to a lot of people."

3. Representing palliative care as additive to patient care: *"[Palliative Care] is about adding extra things in. It's not about taking things away"*

In introducing early palliative care, HCPs in the study described representing this concept as an additional layer of support to their care. One HCP described explaining to patients that it involves adding elements to their care, as opposed to withdrawing care:

> "I sort of emphasize that [palliative care] is about adding extra things in. It's not about taking things away"

In this context, this participant also noted a perceived obligation to reassure their patients that a referral for early palliative care does not mean discontinuation of their oncologic care:

> "I feel I'm obliged to say 'Just because you go to palliative care doesn't mean I'm going to stop seeing you.'"

Moreover, HCPs raised their strategy of explicitly offering the patient a choice of which professionals are involved in their care, in this way framing the addition of palliative care to the team of professionals to work with the oncologist:

> "I say, 'Look, do you want me to be involved? Would you prefer me to involve somebody fresh and new who specializes in this area? Would you prefer us to work as a team?"

One HCP also noted that they frame palliative care professionals as 'experts' who are even 'better' than the referring clinician, being an added pair of eyes who can make better recommendations for care:

> "I've found it's good to sell it as them being experts even better than me. I'll say 'They are a lot better than me at this. I could prescribe something, but an extra pair of eyes, they can find key things, or suggest something better.'"

4. Selling service benefits of adding palliative care to standard oncology: *"Usually what I'm talking about is services"*

HCPs noted how they inform patients of the specific service benefits of adding palliative care to their standard oncologic care. One HCP described framing palliative care in terms of necessary services which could solve existing anxieties or concerns of patients and their family members:

> "Usually what I'm talking about is services, and trying to identify things that family might already be worried is going to be a problem."

Another HCP enumerated several specific service benefits of palliative care including the role to facilitate patients staying at home or out of the hospital, or if admitted, to align with a person's desire to go home:

> "I sort of sell the role of palliative care in discharge planning. The importance of not just going home, but being comfortable at home, being able to stay home for a significant amount of time."

The availability of advice or care 24 hours a day and seven days a week was another specific service benefit described by HCPs as a strategy when describing early palliative care to patients. Palliative care was framed as the point of contact for patients and their family if they found themselves at home with concerns and needing help, in this away avoiding the emergency department:

> "Another selling point I've used is, let's say you're at home and your symptoms get worse. It's nice to have someone to call, people who can visit, rather than coming back to ED waiting for hours."

The 'pace' of palliative care was also described by one HCP as a selling point used when discussing palliative care with patients, whereby they note that the service affords more time for care:

> "I sell the pace. I say you won't be rushed on the pall care ward."

5. Framing palliative care referral acceptance as an altruistic act: *"We're not just doing this for you. We're actually doing it for your wife"*

Several HCPs described framing early palliative care as a service needed by family members or even by themselves as their health professional when attempting to convince patients to accept an early referral to palliative care. Two HCPs noted that family members are eager to avail themselves for support:

> "I think the partner is desperate for help…"

This HCP notes that such help for a patient's partner may be provided by palliative care:

> "[palliative care] is support for the partner."

Similarly, HCPs on occasion noted that they inform patients that, by accepting an early referral to palliative care, they would help them as their doctor, knowing that they have support in the community who can contact them when needed:

> "I often say that 'it will be helpful for me if we organize this.' I say it makes my life much easier if I know you've got this support in the community and they can contact me when they need to. And it would be helpful for me."

6. Adopting a phased approach to delivering information about palliative care: *"They get so much information in the beginning, and they just haven't got a clue"*

HCPs discussed the benefits of raising palliative care early, when it is 'not needed', giving an opportunity to address misperceptions. At the same time, HCPs also perceived that patients with advanced cancer are presented with copious amounts of information at diagnosis. In this context, HCPs described difficulty in introducing the discussion of palliative care early following diagnosis, owing to the perception that it may be overwhelming for the patient:

> "I personally find I just explained the cancer alone, even without getting treatment, that might be too overwhelming at first consultation. No doubt they need pal care, but personally I feel like maybe it might be too early [to discuss]"

One HCP noted that this is particularly true of younger cancer patients as, in their perspective, these patients find palliative care particularly difficult to understand at this initial stage:

> "We're increasingly seeing these younger patients with metastatic cancer … I just find bringing up pal care at [the initial] stage is even harder for them to comprehend."

Related to this, another HCP described not introducing the topic of palliative care at diagnosis, but wait for the consultations that follow:

> "Maybe within a time frame so get over the period where they're just taking cancer as a word, digesting the treatment. And just have a person say within two or three weeks to find them".

When introducing the conversation about early referral to palliative care, HCPs described the careful balancing act of the need for providing the patient with information about the service, while at the same time recognising that too much detail may also lead the patient to close the conversation. In response, some HCPs adopted the strategy of introducing the concept of palliative care in broad terms only:

> "I start to maybe outline some of the things that pall care can offer, but maybe not in a lot of nitty-gritty details".

Responding to this tension, some HCPs also described the strategy of delivering the introduction to palliative care in a piecemeal or 'drip feed' approach, involving a brief mention in one consultation and then following up at a later visit:

> "I find it's good just to sort of plant the seed [of palliative care] one time, follow it up the next time. And it might actually be two or three visits before you actually get them to say 'yes'".

Discussion

With the implementation of early palliative care far from being standard of care across many international settings, communication around the task of referral is one key issue that requires further attention. This study sought to explore oncology clinicians' perspectives on communication about palliative care, highlighting some key strategies adopted to underpin the content, framing, and timing of the communication about early referral. The 'artful' navigation of introducing early palliative care, characterised by the need to employ various strategies executed overtime to enable referral, point to the complexity of this clinical communication task. To ensure the successful implementation of models of early palliative care in routine cancer care, further empirical studies to distill the effectiveness of these strategies, and interventions to support clinicians around communication of this topic are needed.

This study has revealed strategies adopted by oncology clinicians who must frequently broach referral to early palliative care. These strategies were largely focused around referring clinicians' perceived need for a rehearsed 'spiel' to introduce this concept in a manner perceived to be 'gentler', 'easier' or more palatable for patients. This involved carefully selected words and framing of palliative care: for symptom control; as experts – mostly in pain management; to help loved ones; to help the treating clinician; to add to the care team; to access specific services or tasks; to support patient hopes to go home; to support a focus on quality of life. Interestingly, some of this framing is also consistent with the palliative care discourse which has seen messaging used by palliative care professionals focused on actions (e.g. availability, family care, wellbeing), values (e.g. individualized care – 'you matter') or alignment with immediate needs (e.g. support to go home), rather than identity (11, 38).

The approach used by clinicians also involved considered timing as to when to optimally raise this discussion – timing not necessarily defined based upon the best evidence but instead framed around enhancing patient acceptability through a phased, 'drip-fed' approach. This has resonance with a stepwise questioning strategy observed in other studies, allowing opportunities for the person to engage in difficult talk without explicitly inviting such talk or placing patients in this potentially delicate position (39).

The finding that clinicians avoid using the term 'palliative care' is consistent with prior literature indicating stigma associated with this term (10, 15, 16, 40) and that many referring clinicians and patients dislike and opt to avoid this term (15), frequently in favour of re-branding as 'supportive care' (41–45). In this study some clinicians also broadly suggested that the name of the discipline should be changed. The extant debate in the literature regarding the need to re-name 'palliative care' has seen a spectrum of perspectives. This includes proponents, often from referring specialities, who argue that a name change is necessary due to the stigma associated with the name.

Conversely, opponents, often from palliative care, point to the risk of a 'euphemistic treadmill' (46), citing the limited (or short-term) increase in palliative care referral following a name change in a given setting (47) or arguing that the limitations of the term are a cultural artefact and hence would not be readily ameliorated by a name change (48, 49). Indeed surveys of palliative care clinicians suggest that although many recognise patients perceive the term "palliative care" negatively, few believe a name change to supportive care would encourage early referral, and <21% support renaming the specialty (7, 50). Others point to the opportunities for a re-branding of message which conveys the benefits, re-focuses the message, and builds the service accordingly, while still maintaining the name, palliative care (51–53). In any case, the results of this study highlight the complexity of palliative care discourse and potential for mixed messaging underpinning 'early palliative care' (38, 49, 51). Further, the results support the need for greater clarity of message within the communication underpinning referral to early palliative care, explaining the intended role and service offerings to health professionals and patients (10).

While clinicians spoke of using different terms and strategies to avoid patient distress while enabling palliative care referral, it is possible that they are also seeking to avoid their own discomfort. While there is little literature in the area, the use of euphemisms, different names, and discussion of activities of palliative care such as pain relief enable the patient and the physician to avoid talking of end-of-life care and death (15). It is possible that the use of this avoidant strategy serves to not only protect patients from distress, but also to lessen their own discomfort in discussing palliative care and its implications. Exploring this possibility and undertaking to directly evaluate clinicians' distress in performing an early referral may provide opportunities for redress. Importantly, these communication aspects, as a seemingly major barrier, will be crucial to address in any future implementation of systematic screening for palliative care referral. The finding in this study of framing palliative care referral acceptance as an altruistic act is consistent with the literature on oncology trial participation. Such research has demonstrated that altruism is a frequent motivation for clinical trial participation (54), with patients demonstrating high agreement for scale items such as 'contributing to research that can help others in the future' as a motivation for their participation. However, cancer patients are not monolithic in these altruistic motivations, with patients with a poorer prognosis demonstrating a lesser altruistic motivation for research participation than for those with a better prognosis (55). There is a dearth of literature exploring the role of altruism in palliative care referral acceptance among cancer patients. However, it is conceivable that the framing of referral acceptance in terms of supporting others (e.g., family, primary clinician) may capitalize on altruistic motivations among cancer cohorts and thereby facilitate referral. Further research is necessary to investigate altruism as a motivator of palliative care referral acceptance in this cohort. Potential ethical implications of this framing, for example in terms of coercion, must also be explored.

Study strengths and limitations

When exploring the nature of communication in healthcare, observational research methods such as conversation analysis offer an alternative approach which may elucidate different issues. Additionally, triangulation of the findings with a patient sample would further add to the interpretation, which in this analysis, was limited to the clinician's perspectives of how they communicate about early referral to palliative care. Similarly, other referring clinicians such as General Practitioners working in community settings may provide additional important perspectives around this task. Finally, the prior communication skills training of clinicians participating in this study was not recorded. Such training has been demonstrated to influence cancer care consultations and would likely enhance confidence and practices in this important task of introducing early palliative care. Nonetheless, this well-designed and analysed qualitative study, albeit small, provides new insights into the strategies used by clinicians in this communication task which can form the basis of further study, highlight the role for formal communication skills training, and support other clinicians seeking peer guidance on introducing early palliative care.

Conclusion

This study reveals the complex task of communicating about early referral to palliative care and the communication skills required by health professionals to 'artfully' navigate this task. Oncology clinicians conveyed their self-adopted strategies which underpinned their 'spiel' to ease the introduction of early palliative care for patients and their families, and perhaps for the clinicians themselves. This was characterised by careful rehearsed language, framing and attention to the timing of the introduction- none of which was necessarily straightforward or overt. While there are apparent opportunities and also limitations of such an approach, the attention given to this clinical task equivalent to a "breaking bad news" conversation gives weight to its importance. The future successful implementation of models of early palliative care integration in oncology will require support for communication skills training specific to introducing early referral to palliative care.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by St Vincent's Hospital Melbourne Human Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AC was the lead investigator, obtained the study funding, was responsible for the study conduct, had access to the data, and co-authored the first draft. AC, LG, and OW were involved in the data analysis. All authors contributed to the study protocol, interpretation and, contributed to the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Screening versus multidimensional assessment of symptoms and psychosocial distress in cancer patients from the time of incurability

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Objective: Previous symptom prevalence studies show a diverse spectrum of symptoms and a large diversity in symptom intensities in patients being just diagnosed as having incurable cancer. It is unclear, how physical symptoms and psychosocial burden should be recorded in order to determine the variable need for palliative care and further support. Therefore, we compared two different strategies for detecting physical symptoms and psychosocial burden of patients with newly diagnosed incurable cancer and their effects on the further course of the disease.

Methods: SCREBEL is a controlled, randomized, non-blinded, longitudinal study of the research network of the Palliative Medicine Working Group (APM) of the German Cancer Society (DKG). We compared: a less complex repeated brief *screening* for symptoms and burden in patients using the NCCN Distress Thermometer and IPOS questionnaire versus a multidimensional comprehensive *assessment* using the FACT-G and their entity-specific questionnaires, the PHQ4 scales, SCNS-34-SF, IPOS and NCCN Distress Thermometer. The primary study endpoint was quality of life (QoL), measured using FACT-G, after six months. Secondary study endpoints were QoL by using evaluation of secondary scores (NCCN DT, IPOS, PHQ4, SCNS-SF-34G) at time 6 months, the number of hospital days, the utilization of palliative care, emergency services, and psychosocial care structures. To assess effects and differences, multiple linear regression models were fitted and survival analyses were conducted.

Results: 504 patients were included in the study. 262 patients were lost to follow-up, including 155 fatalities. There were no significant differences between the low-threshold *screening* approach and a comprehensive *assessment* with respect to symptoms and other aspects of QoL. Using the IPOS, we were able to measure an improvement in the quality of life in the low-threshold *screening* arm by a decrease of 0.67 points (95%-CI: 0.34 to 0.99) every 30 days. (p<0.001). Data on the involvement of emergency facilities and on supportive services were insufficient for analysis.

Conclusion: A comprehensive, multidimensional *assessment* did not significantly differ from brief *screening* in preserving several dimensions of quality of life. These findings may positively influence the implementation of structured low-threshold screening programs for supportive and palliative needs in DKG certified cancer centers.
DRKS -No. DRKS00017774 https://drks.de/search/de/trial/DRKS00017774.

KEYWORDS

multidimensional assessment, screening, cancer patients, palliative medicine, quality of life

Introduction

There is abundant evidence from clinical studies that various quality of life (QoL) parameters and the implementation of patient's goals of care and preferences (1–3) may be improved by an early (timely) inclusion of a palliative care perspective in patients suffering from incurable cancers (4–8).

Here, stage-dependent approaches (for instance, all distantly metastasized/incurable/stage IV patients should be addressed) concur with red-flags concepts (for instance, patients with typically burdensome cancer entities, with malnutrition or frailty should be addressed) (9, 10).

In an epidemiologic study, physicians estimated that 15.8% of all cancer patients who are discharged from hospital would require further palliative support (11). Other studies demonstrated a high variance in physical and psychosocial symptoms of patients with newly diagnosed incurable cancer (12, 13), which can be detected *via* assessment tools (13, 14).

An *assessment* is able to capture various symptoms and burden of patients and thus detect the need for care, which can improve the patient's QoL and health (14). A repeated and brief, low-effort (in this paper defined as "low-threshold") *screening*, however, appears to enhance symptom capturing and can improve quality of life and even overall survival (15, 16). All these findings suggest the usefulness of a *screening* or *assessment* approach in order to gather these symptoms and needs in a timely and structured manner. (6, 7).

The structural policy developments in Germany, for example in the context of the certification process of cancer centers of the German Cancer Society (DKG), already demand a structured screening approach for psychosocial distress by psycho-oncology. They suggest a similar approach for physical symptoms and other complaints that are relevant in pain therapy and palliative care (17). The "evidence-based guideline: Palliative Care for patients with incurable cancer" (4) recommends the repeated recording of physical, psychological, social and spiritual needs. It emphasizes the need for information on palliative issues for incurable cancer patients. However, a standard on how to most effectively capture these symptoms and needs is still missing.

In other fields of medicine, a low-threshold and easy-to-perform *screening* (like screening for psychosocial distress in psycho-oncology) competes with comprehensive, multi-dimensional *assessment* strategies (like formal baseline assessments in specialized palliative care or pain therapy, for instance). The low-threshold *screening* is a brief strategy to identify potential physical symptoms and psychosocial stress in patients, while an *assessment* is a comprehensive, multi-dimensional recording and evaluation of the patient's symptoms and distress by using various questionnaires. A low-threshold *screening* may thus be preferred due to its resource-saving properties in patients and health care providers. However, a multi-dimensional *assessment* may suggest a more differentiated view on the complexity of physical symptoms and psychosocial distress in advanced stages of disease, even if it takes much more time and attention of patients and personnel.

Therefore, we aimed to evaluate in our SCREBEL (Screening versus multidimensional assessment of symptoms and psychosocial distress in cancer patients from the time of incurability) study the impact of two different recording strategies on QoL, the inclusion of palliative care and psychosocial support structures, emergency care structures and hospitalizations, in relation to the remaining survival time.

Material and methods

Study population

There were 24 study sites recruited by the research network of the Palliative Medicine Working Group (APM) of the DKG. In these cancer centers patients over 18 years with solid tumor entities were identified at the time of diagnosis of incurability (i.e., prior to initiation of palliative anti-cancer therapy and according to the definition of incurability as established in the former APM study (13)) *via* outpatient clinics, oncological wards or multidisciplinary tumor boards by treating physicians. Non-compliance and age being under 18 years were the only exclusion criteria. After study inclusion, the PI (Göttingen) assigned the patients to the two intervention arms (low-threshold *screening* versus comprehensive *assessment*) by using block randomization, stratified by center and tumor entity at a ratio of 1:1 (Figure 1). Within this study, patient intervention took place only *via* conducting surveys. The patients were requested to complete simple screening surveys autonomously on regular follow-up visits to their disease.

A population of 504 patients was estimated to be recruited for this study including an expected dropout rate of 20%. For the primary endpoint in the SCREBEL study we expected a standard deviation of 17.26 based on the experience of the former APM study (12, 13). Thus, a non-parametric test on differences between groups regarding FACT-G with a two-sided significance level $\alpha = 5\%$ yields a power of 80% if differences are at least 5 points, which represents a clinically relevant difference (18).

Outcome definitions

As the physicians were advised to include the results from the latest assessment into their treatment decision in order to improve the patient's QoL we chose QoL as the primary endpoint. Quality of life was assessed using the following questionnaires:

The **FACT-G (**Functional Assessment of Cancer Therapy) (19) is a 27-item questionnaire designed to measure four domains of QoL in cancer patients: Physical, social, emotional, and functional well-being. The items are measured on a five-point Likert-scale from 0 (not at all) to 4 (very much). The score is the sum of all items and ranges from 0 to 108. The higher the score, the better the QoL.

The **NCCN Distress Thermometer** (National Comprehensive Cancer Network distress thermometer) (20) is a validated, widely used screening measure. The screening contains a single-item visual numeric scale ranging from 0 ("no distress") to 10 ("extreme distress") to quantify the global level of distress experienced in the past week. A higher score indicates a higher distress and thus a lower QoL (21).

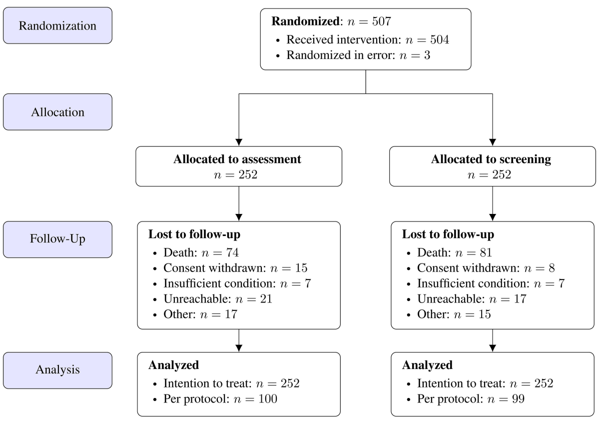

FIGURE 1
CONSORT flow diagram of patient randomization, allocation, follow-up and study analysis.

IPOS (Integrated Palliative Care Outcome Scale) (22) is a 10 question survey developed to measure palliative care needs of patients and their families. The questions address how limited the individual is due to the symptoms rather than the severity of the symptoms themselves. Of all questions, only the questions 2 (with again 10 subitems) and 3-9 contribute to the overall score, resulting in 17 contributing items. All items are measured on a five-point Likert scale (0 to 4). The IPOS is the sum of the 17 items mentioned above, thus ranging from zero to 68. A higher IPOS score indicates a lower QoL. Moreover, in the presence of at least two questions answered with "3" or at least three questions answered with "2", further exploration and medical treatment is recommended.

PHQ-4 (Patient Health Questionnaire) (23) is a four item questionnaire addressing a patient's psychosocial condition regarding anxiety and depression. The items are measured on a four-point Likert-scale from 0 (not at all) to 3 (nearly every day). The total score is the sum of all items and ranges from 0 to 12. A total score ≥ 3 for the first two questions indicate anxiety. A total score ≥ 3 for the last two questions suggests depression. The higher the score, the lower the QoL.

SCNS-SF-34-G (Supportive Care needs Survey – short form 34 German Version) (24) is a 34-item questionnaire and comprises of subgroups for psychological needs (10 items), health system and informational needs (11 items), physical and daily life needs (5 items), patient care and support needs (5 items) and sexuality and other problems (3 items). The items are measured on a five-point Likert scale separated into two classes: no need (scale 1-2) and some need (scale 3-5). The overall score used for evaluation is the sum of all items of the questionnaire. High SCNS-SF-34-G scores indicate the need for more support for patients. The version used is a modified version of the SCNS-SF-34-G including only 25 questions, thus the score ranges from 25 to 125.

Analysis populations

Analysis of participants was done in accordance with the ICH E9 guidelines for data analysis considerations (25). All randomized patients were considered as part of the intention-to-treat population. Participants of the *assessment* group were considered as per-protocol if baseline intervention took place. For the *screening* group we required at least 2 additional interventions between baseline and 6 months visit. Moreover, we require for the per-protocol population that the final visit took place 6 months after their inclusion ± 2 month. Sensitivity analyses revealed that the length of the timeframe around 6 months allowed for protocol adherence had no relevant impact on our results.

Trial design

We performed a multicenter, controlled, randomized, non-blinded, longitudinal study and evaluated two different strategies for capturing physical symptoms and psychosocial needs.

For this purpose, the *screening* arm screened for symptoms and distress by using IPOS (15) and NCCN distress thermometer (16) repeatedly in three to six week intervals (adjusted to usual tumor therapy application cycles and oncology presentations). We did not influence whether or how palliative care was adjusted according to the screening results. IPOS was chosen as a questionnaire in the *screening* arm, since it is a validated and widely used tool in European countries to evaluate patients' well-being and monitor their need for care (26–28). The NCCN was selected in adherence to the preceding APM study (13).

In the *assessment* arm, an initial single comprehensive recording of several dimensions of quality of life using IPOS (15), NCCN Distress Thermometer (16), plus FACT-G (general and organ-specific) (17), PHQ-4 (18), and SCNS-SF-34-G (19) has been performed. The questionnaires were again selected in adherence to the preceding APM study (13).

The study concept was designed to detect symptoms or distress, so that support measures could be initiated promptly if required. The test results were supposed to be made apparent in the institutional clinical patient´s charts, and the resulting interventions were left to the discretion of the treating team.

After 6 months, a QoL assessment was performed in both intervention arms, again using IPOS, NCCN Distress Thermometer, plus FACT-G, PHQ-4, and SCNS-SF-34-G to compare QoL. We chose this observation period as a trade-off between observing long-term effects of the intervention and avoiding excessive dropout rates, based on the data from the previous APM study (13) where data was sufficiently available after 6 months but not after 12 months, due to dropout.

In addition, study centers were asked for further data from the hospital documentation system about hospital days, emergency admissions, inclusion of specialized palliative care and other supportive services up to at most six months after start of participation.

General patient data and case report form items (CRF) were recorded in an electronic format (secuTrial).

A statistical analysis plan was written, registered and signed by the principal investigators and the responsible statistical team before analysis.

Statistical analysis

Descriptive statistics are reported as numbers and proportions or median with corresponding range as appropriate. If not stated otherwise, tests were performed two-sided on a significance level of 5%. Parameter estimates are provided with corresponding 95% confidence intervals (95%-CI).

Primary endpoint was the FACT-G score at time t = 6 months. Differences in the relative intervention effect between study arms were tested non-parametrically using a two sample t-test for the nonparametric Behrens-Fisher problem (29). In addition, a multiple linear regression model for the FACT-G was fitted with the factor study arm (*screening* vs. *assessment*) and with additional influencing factors (tumor entity, study sites, and important prognostic baseline factors such as sex, age, personal living status and lost-to-follow-up-state). Primary and survival analysis were performed on the intention-to-treat population, and secondary and sensitivity analyses were done on the per-protocol population. Secondary endpoints at time t = 6 months (NCCN Distress Thermometer, IPOS, PHQ4, SCNS-SF-34-G) are evaluated analogously to the primary score; multiple linear regression models were fitted accordingly.

Survival rates within 6 months were estimated using Kaplan-Meier curves with additional 95% confidence bands. Comparison of the two intervention groups was performed using a log-rank test. Number of hospitalizations and mean length of stay were analyzed using negative binomial regression and zero-inflated Poisson-regression, respectively. Additionally, we fitted a Cox proportional hazards model to investigate additional factors.

For the *assessment* arm, the change of the QoL scores between initial assessment and 6 months visit was analyzed using multiple linear regression regarding the stratification factors and taking into account further covariates such as age and sex. For the *screening* arm, physical symptoms and psychosocial strains (measured *via* IPOS) were analyzed descriptively over time.

For non-parametric testing we employed a composite testing strategy and imputed missing values with the worst possible value (e.g. for FACT-G we imputed the value zero), thus associating drop-out with the least possible value for QoL. This was then interpreted as the evaluation of the full analysis set according to a worst-case approach for handling intercurrent events (25). Additionally, we performed a complete-cases-analysis as sensitivity analysis to assess possible impairments or biases of our study results resulting from dropouts.

Differences in QoL regarding IPOS and NCCN between study arms at baseline and after 6 months, were assessed using non-parametric testing. Pre-post comparison of QoL regarding IPOS and NCCN were analysed stratified by group using paired t-testing.

For all additional analyses, missing items were imputed as proposed in the corresponding scoring guidelines. In the case of missing total scores, we imputed ten times using predictive mean matching (30) based on study center, sex, age, entity, time of diagnosis and study arm. All data were analyzed using R version 4.2.1 (31) with additional packages mice, nparcomp, survminer for multiple imputation, nonparametric testing and survival analysis, respectively.

Ethics and consent

The study protocol was approved by the ethics committees of all 24 study sites (PI study site no. 23/2/19) and followed the Declaration of Helsinki Ethical Principles for Medical Research. SCREBEL was registered in the German Registry for Clinical Studies (DRKS No. 00017774). Patients were included after written information, clarifications of the study and written consent.

The study was sponsored by the Innovation Funds of the German Federal Joint Committee.

Results

The study randomized 507 patients from 24 different study centers. Three patients were randomized in error and could not be included in the study.

Of the recruited patients, 233 were female and 271 were male, with a mean age of 66.6 years. The median age was 67 years, ranging from 29 to 90 years (range 61 years). Of these patients, 314 were married/living in a relationship, 121 were living alone and two were living in a care facility. 67 did not state their personal living condition. Engagement of services of additional palliative care, psychosocial support and emergency structures has been recorded for only 34 patients with 16 patients documented to have frequented emergency or supportive services. Thus, this complementary data collection turned out to be insufficient for further analysis.

Of the included 504 patients, 262 were lost to follow-up after 6 months, including 155 fatalities (see Figure 1 below).

In the study, 13 different tumor entities were included, whereby patients suffering from lung cancer were most prevalent in both study arms, followed by patients with hepatobiliary and pancreatic cancer and by skin cancers (Table 1).

Primary analysis

The primary analysis revealed no significant differences in the intervention effects on QoL (measured *via* FACT-G) between the two groups at t = 6 months, neither using the worst-case approach nor in a complete-case-analysis where the relative effects in intervention were estimated to be 0.504 (95%-CI: 0.458 to 0.549) and 0.509 (95%-CI: 0.431 to 0.587), respectively. Within the linear regression model, none of the included variables turned out to have a significant non-zero influence on QoL. (see Table 2 below)

With respect to the patient's lost-to-follow-up-state we did observe only not-significantly smaller values in QoL. Moreover, we observed slightly smaller values for patients in the *screening* group whereas male patients seemed to have slightly higher QoL than females. Regarding the influence of age, QoL seemed to be insensitive.

TABLE 1 Distribution of patient demographics within the two study arms.

	Assessment (n = 252)		Screening (n = 252)	
Age (mean ± s.d.)	66.0 ± 11.0		67.2 ± 10.4	
Sex (n/%)*				
Female	126	50%	107	42%
Male	126	50%	145	58%
Personal living condition (n/%)*				
Married/in a relationship	148	59%	166	66%
Living alone	67	27%	54	21%
Care facility	0	0%	2	0%
No answer	37	15%	30	12%
Entity (n/%)*				
Lung cancer	68	27%	70	28%
Hepatobiliary tumors and pancreatic carcinoma	49	19%	51	20%
Skin cancer	37	15%	35	14%
Colorectal cancer	24	10%	23	9%
Head and neck tumors	23	9%	25	10%
Breast cancer	15	6%	19	8%
Endometrial and ovarian cancer	15	6%	9	4%
Gastric cancer/carcinoma	6	2%	6	2%
Urological tumors (kidneys and urinary tract)	6	2%	7	3%
Esophageal cancer	4	2%	1	0%
Brain tumors	3	1%	3	1%
Cervical and vulvar carcinoma	1	0%	1	0%
Prostate cancer	1	0%	2	1%

* Frequency (percent), s.d., standard deviation.

TABLE 2 Pairwise contrasts between *assessment* and *screening* group within multiple linear regression with respect to different questionnaires (first column), cf. also the outcome definitions section.

Questionnaire	Estimated difference (Assessment – Screening)	95%-CI	p-value
FACT-G	0.728	[-2.601; 4.058]	0.667
NCCN DT	0.169	[-0.645; 0.982]	0.683
IPOS	1.344	[-1.924; 4.612]	0.418
PHQ4	-0.002	[-0.186; 0.182]	0.986
SCNS-SF-34	1.322	[-6.005; 8.650]	0.722

FACT-G, Functional Assessment of Cancer Therapy – General; NCCN DT, National Comprehensive Cancer Network Distress Thermometer; IPOS, Integrated Palliative Care Outcome Scale; PHQ4, Patient Health Questionnaire 4; SCNS, Supportive Care Needs Survey short form 34.

Secondary analyses

In accordance with our primary analysis, non-parametric testing for differences in the intervention effect on QoL measured by the secondary scores revealed no significant results likewise, both for the worst case-approach and the corresponding sensitivity analysis. Moreover, in the linear regression models the included variables did not turn out to have significant non-zero influences on QoL even though males seemed to have a somewhat smaller stress level of -0.25 points (95%-CI: -0.47 to -0.04) measured by PHQ4 than females, p = 0.023. The tendencies of the influences of the included factors direct in the same direction as outlined for FACT-G above. The estimated differences between *assessment* and *screening* group using primary and secondary outcome questionnaires are summarized in Table 2.

Survival analysis

The course of estimated Kaplan-Meier survival curves up to six months is shown in Figure 2. A log-rank test for differences in survival times revealed no significant difference in the survival distribution between the two study arms, p = 0.309.

Within regression modelling, the probability of hospital admission within 6 months for the *assessment* and the *screening* group were estimated as 51% (95%-CI: 45% to 58%) and 61% (95%-CI: 55% to 67%), respectively, and turned out to differ significantly, p = 0.033. Given a hospital admission, the length of stay in *assessment* and screening group was estimated as 7.2 (95%-CI: 6.9 to 7.6) and 8.0 (95%-CI: 7.6 to 8.3) days, respectively, being significantly different (p = 0.003). The number of hospitalizations within 6 months was estimated to be 0.38 (95%-CI: 0.30 to 0.48) in the *assessment* group and 0.51 (95%-CI: 0.41 to 0.64) in the *screening* group. The difference was not significant (p = 0.07).

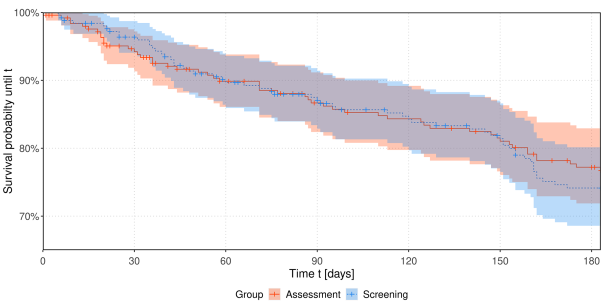

FIGURE 2
Estimated survival probabilities over time up to 6 months stratified by intervention group. Considering a Cox proportional hazards model none of the included factors study group, sex, age, study center, entity or personal living status turned out to have a significant influence on the hazard function. Affiliation to the screening group does not seem to significantly increase the hazard by a factor of 1.37 (95%-CI: 0.97 to 1.94), p = 0.073.

Additional analyses on primary and secondary endpoints

In a linear regression model for FACT-G within the *assessment* group, none of the explaining factors age, sex and visit time (baseline vs. six months) turned out to have a significant influence. The difference in FACT-G after – before intervention was 2.2 (95%-CI: -3.0 to 7.3) which turned out to be no significant increase of QoL over time, p = 0.406.

Multiple linear regression of the change of IPOS with respect to baseline depending on inclusion time in the study, age and sex yielded a significant decrease over time (p < 0.001), indicating a relief of burden. Per 30 days within study inclusion, IPOS decreased by -0.54 (95%-CI:-0.84 to -0.24) points, cf. Figure 3A. Within the same period of time, psychological strains could be reduced by -0.16 (95%-CI: -0.28 to -0.05) and physical symptoms by -0.20 (-0.39 to -0.02), see Figures 3B, C, respectively.

Additionally, we analyzed the change of QoL regarding IPOS and NCCN DT over time within and between groups. Neither at baseline nor after 6 months, IPOS, its subscores for psychological strains and physical symptoms or NCCN DT differed significantly between *assessment* and *screening* group. In the *assessment* group, a significant improvement of QoL could only be achieved with respect to the psychological strains subscore. In contrast, the *screening* group exhibited a significantly better quality of life after 6 months regarding all considered scores (see Table 3). The distribution of QoL changes within study arms are visualized in Figure 4.

Discussion

There were no significant differences in the improvement in QoL after a six months period between the *assessment* arm and the

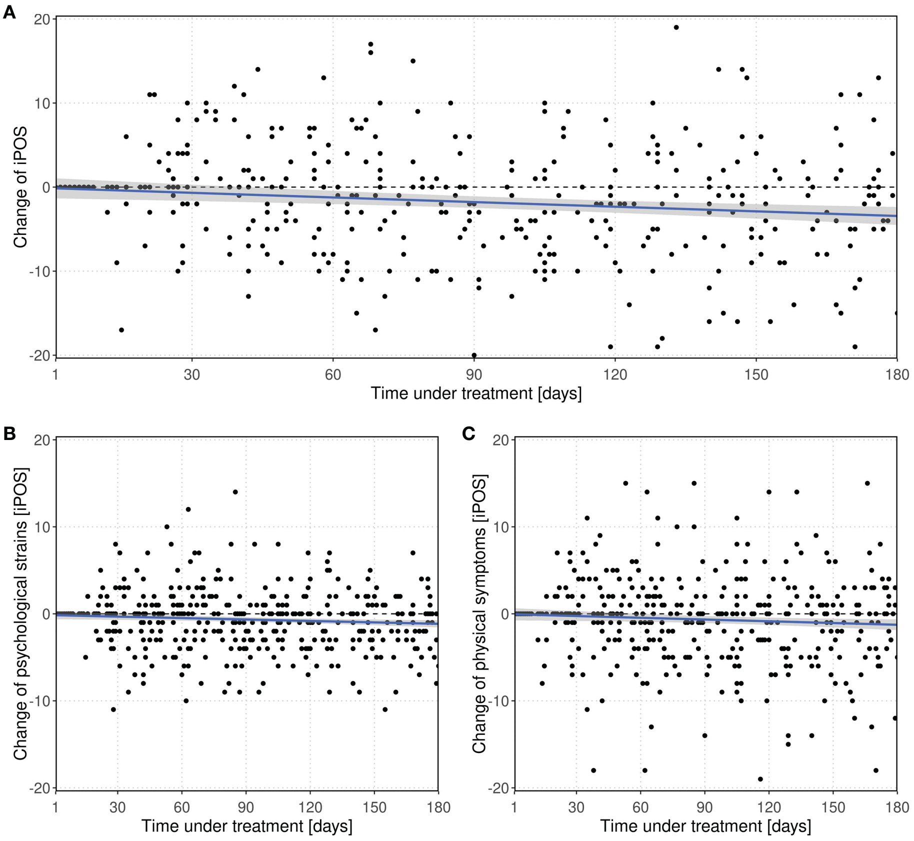

FIGURE 3
Change of **(A)** IPOS and subscores **(B)** psychological strains and **(C)** physical symptoms with respect to baseline value over time within the study within the *screening* group. Every point represents a score difference of a visit during the observation period. The dashed line at zero represents no change with respect to baseline.

screening arm. Based on our data, both low-threshold *screening* and comprehensive *assessment* might be an appropriate strategy to record symptoms and stress for patients in order to best maintain the patients' QoL. Since low-threshold screening saves resources and time, this strategy could be favored in day-to-day clinical practice.

A preceding study of the APM research network was able to provide data on physical symptoms and psychosocial burden of 500 patients after the diagnosis of incurability by using an assessment strategy in a non-comparative longitudinal cohort study (12, 13). Patients in this preceding study showed quite variable symptom and distress levels, suggesting quite variable needs for supplementing specialized, multi-professional palliative care for some patients, and suggesting the usefulness of one kind of *screening/assessment* in order to detect patients in need (12, 13). The scope and perceived intensity of physical symptoms and psychosocial distress was comparable between the two studies.

Within the *screening* group, we found evidence that the quality of life according to IPOS can be maintained or even improved despite the course of the disease. The IPOS, which was periodically recorded in the *screening* arm, showed that the quality of life increased slightly. This may be explained, for instance, by the effect of palliative anti-cancer therapies (that began after enrollment by definition), by a response shift phenomenon related to increasing resilience towards the constraints of their illness (32), or by other positive factors such as successful palliative care interventions. A systematic review of

TABLE 3 Changes in mean QoL after 6 months visit with respect to baseline with corresponding 95%-CI and p-values of paired t-tests.

	Assessment	P-value	Screening	P-value
IPOS	−1.52 [−3.68; 0.65]	0.166	−3.49 [−5.42; −1.57]	<0.001
IPOS – Psychological strains	−1.19 [−2.00; −0.38]	0.005	−1.17 [−1.79; −0.55]	<0.001
IPOS – Physical symptoms	−0.54 [−1.63; 0.54]	0.321	−1.11 [−2.20; −0.02]	0.046
NCCN DT	−0.28 [−0.86; 0.30]	0.339	−0.89 [−1.39; −0.38]	<0.001

quantitative studies suggests that resilience and hope, independence, social support, spirituality, fatigue, emotional distress, and coping skills are interrelated factors in patients with terminal illnesses. Prior experience with illness and life adversity, meaning-making, reconciling with life's finiteness, acceptance of illness, control, and other factors for resilience were additionally found in qualitative studies (33). Another study points to the importance of medical communication, which can have a significant impact on the patient's well-being and remaining life (34). However, the questionnaires cannot provide clues on which reasons the patients themselves would attribute to an eventual improvement in their quality of life.

A significant improvement in QoL (psychological strains and physical symptoms, see Table 3) as per NCCN DT and IPOS was also observed within the *screening* group compared to baseline. In contrast, in the *assessment* group, significant improvement was only recorded in the IPOS subscore for psychological strains. This could indicate that low-threshold screening is better suited to record psychological stress and symptom stress and to react by the treating physicians. As there was insufficient data on palliative treatments or psycho-oncological care during the study, no precise statement to this end can be made.

On the other hand, the probability of hospitalization and the amount of days of hospitalization was higher in the *screening* group than in the *assessment* group. It is up for debate whether a regular screening encourages hospital stays or whether the patients' condition in the *screening* group was worse and therefore needed longer treatment.

Strength and limitations

The study not only compares two distinct symptom recording strategies, but also provides more detailed insight into reported quality of life shortly after the diagnosis of incurable cancer. We demonstrated the variability in symptom spectrum and intensity, and provided data that the perceived quality of life may also improve even in advanced, eventually progressive disease. Due to the recruitment of a large number of study sites (24), some of them with specialization on few cancer entities, a large spectrum of different cancer entities could be included, and sub-group analyses are pending.

A major limitation of the study was the concurrent COVID-19 pandemic and its profound logistical implications, which severely

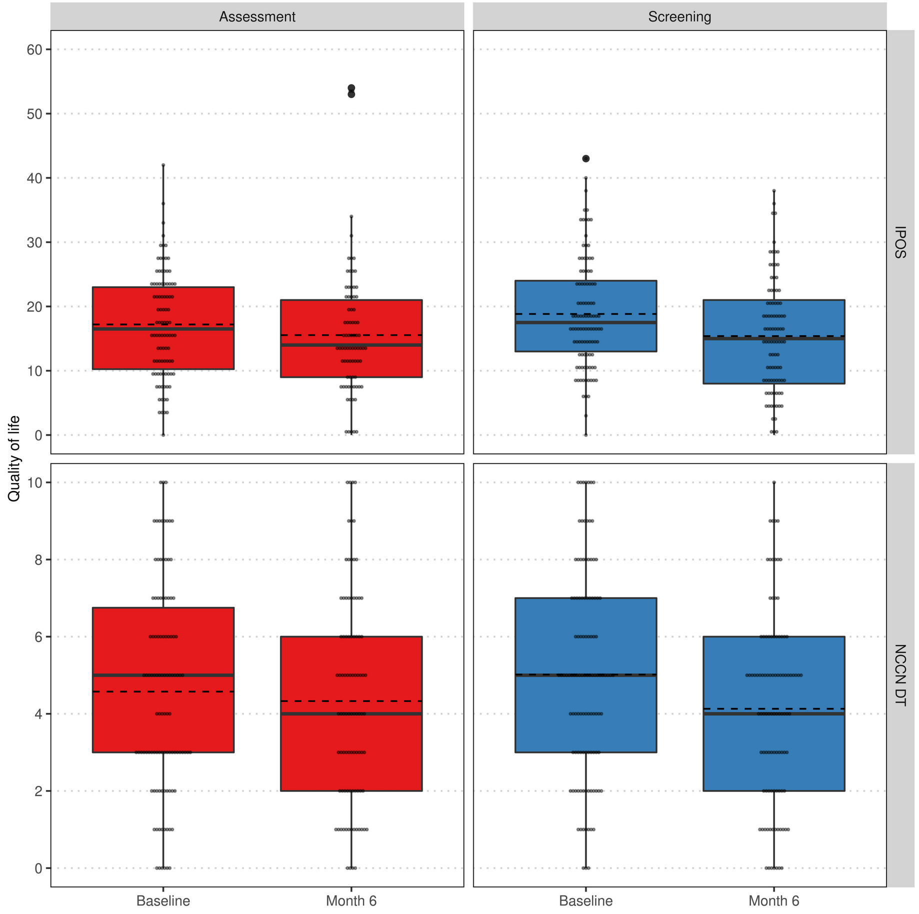

FIGURE 4
Comparison of QoL regarding IPOS (top) and NCCN DT (bottom) at baseline and 6 months visit stratified by groups *assessment* (left) and *screening* (right) within the per-protocol population. Lower values indicate a higher QoL. Individual values as small grey dots, mean within group and visit as dashed line.

impacted patient recruitment at many study sites. Study personnel were often not allowed to visit in-patients on a regular basis, and during the pandemic, staff resources were spent even more focused on patient care compared to study activities, and on-site study monitoring was not possible. Forwarding test results to clinical charts and utilization was likewise impaired by pandemic restrictions. Digital study monitoring would have eventually ensured data integrity by displaying prompts in case of missing input or errors even under pandemic study conditions. Especially smaller study sites were filled to personal capacity more quickly than larger facilities. Therefore, particularly data about the inclusion of palliative care and other emergency or supportive structures was insufficiently obtained, and no reasonable results on these proposed secondary objectives were gathered. Furthermore, the planned documentation of the reasons of patients not to participate was affected by the very special circumstances in the years 2020–22.

Another limitation of the study might be a potential learning bias by the recruiting physicians. Due to the nature of the study, there may have been a learning effect that could prompt recruiting physicians to ask patients more frequently about their well-being, regardless to which group the patients were assigned to. This cannot be prevented without allocating the various study sites to just one intervention arm. This idea, however, was discarded because the unequal structure of the institutions involved (university hospitals, medical practices, community clinics) would have made it difficult to compare the data.

The therapeutic consequences of the information gathered from the questionnaires for the further treatment of a patient (for instance, to refer to palliative or other supportive services) lay with the treating physicians. Since the study intervention focused on the recording of symptoms and needs only, no criteria were established as to how physicians should act in case of positive test results. This limitation may also have contributed to the fact that both arms exhibited a similar development in QoL.

Conclusion

A comprehensive, multidimensional *assessment* did not significantly differ from low-threshold *screening* in preserving several dimensions of quality of life. Even if no significance level was reached in neither direction, it might be suggested that low-threshold, resource-saving, and easy-to-handle screening may be prioritized in day-to-day clinical practice. Survival rates did not differ significantly between the two groups. However, QoL scores had improved significantly by the end of the observation period in the *screening* arm. Further research is required to find out the reasons for this improvement in QoL and the associated reduction in distress and symptom burden. Like other studies, this study is constrained by the data available. Also, the combination of *screening/assessment* and resulting intervention (test-driven intervention) should be focused on in further trials.

Our findings may positively stimulate the implementation of structured screening programs for supportive and palliative care needs in certified cancer centers.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics committee of the University Medical Center Göttingen. The patients/participants provided their written informed consent to participate in this study. The study protocol was approved by the ethics committees of all 24 study sites (PI study site no. 23/2/19) and followed the Declaration of Helsinki Ethical Principles for Medical Research. SCREBEL was registered in the German Registry for Clinical Studies (DRKS No. 00017774). Patients were included after written information, clarifications of the study and written consent.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supportive care of neurodegenerative patients

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Neurodegenerative illnesses are notorious for paucity of treatments and relentless clinical progression. Illness may follow a relatively acute presentation, as is seen with primary brain tumors such as glioblastoma or have a more insidious onset with a slower yet unyielding course, such as that seen in Parkinson's disease. Though disparate in presentation, these neurodegenerative illnesses are universally terminal, and both the patients and their families benefit from the intervention of supportive care in conjunction with primary disease management. Supportive palliative care has been shown to improve quality of life, enhance patient outcomes, and often extend patient life—but such care needs to be tailored. This clinical commentary examines the role of supportive palliative care in the management of neurologic patients, comparing and contrasting glioblastoma patients with idiopathic Parkinson's disease patients. Both patient populations are high utilizers of healthcare resources, require active management of multiple symptoms, and have high caregiver burden which underscores the need for supportive services in conjunction with disease management provided by the primary care team. Review of prognostication, patient and family communication, trust and relationship building, and complementary medicinal approaches are explored for these two diseases which broadly represent two differing poles of incurable neurological illness.

KEYWORDS

glioblastoma, supportive care, Parkinson's disease, neurodegenerative disease, palliative care

The two poles of neurodegenerative disease

The needs of neuro-oncology patients with serious illness are unique and differ from other terminal illnesses and particularly from other neurodegenerative disorders. When considering neuro-oncologic illnesses such as glioblastoma (WHO grade IV), the trajectory of the disease is short and aggressive, characterized by rapid functional and cognitive impairment (1, 2). The diagnosis is given when the disease is more advanced. An early palliative care referral is recommended and set as standard of care by the American Society of Clinical Oncology to improve quality of life, ensure a dignified death, and ease caregiver burden and grief (3, 4). In contrast, other neurodegenerative disorders such as Parkinson's disease may smolder for years before active symptoms present, and the progression is slow and proceeds over an extended period. These differences in disease progression and prognosis underscore the vastly different approaches needed in palliation of terminal neurological disorders. This article is a professional commentary on neurodegenerative disease in a palliative setting based on the authors' clinical observations and personal experience from three established subspecialty departments (neuro-oncology, movement disorders, and palliative care) in a Level 1 medical center in central Texas USA and supported by the evidence-base. We will look at glioblastoma and Parkinson's disease patients as archetypal of rapid versus protracted neurodegenerative disorders, comparing and contrasting their unique end of life needs. The diagnosis, progression and prognostication for these two diseases will be compared and contrasted, as well as an in-depth look at caregiver burden. Discussion on individual symptom management is beyond the scope of this paper.

The diagnosis, progression, and prognostications of the two diseases

The diagnosis of glioblastoma, after symptom presentation, is a grade 4 diagnosis with a prognosis of 15-18 months assuming aggressive medical intervention (5), Hemminger et al. (2) note a mean survival of 12.6 months. For the glioblastoma patient, palliative care should be engaged early (3) ideally on first diagnosis, regardless of presenting symptomology due to the aggressive nature of the disease and overall poor prognosis. Patients move from independent to fully dependent over months, requiring rapid shifts in how the patient views themselves and how they function day to day. Due to the speed of disease progression, relationship building and trust development between clinician, patient and patient's family needs to be accomplished quickly. The focus is therefore on clear and compassionate communication, with frequent supportive medical interactions resulting in rapid confidence building.

At time of presentation in Parkinson's disease there is already a 60% dopaminergic neuronal loss in the substantia nigra (6), but it may be a decade before disability becomes significantly life-limiting. Death may be anticipated 15 – 26 years from first prognosis, with disability occurring in a non-linear fashion (7, 8). Parkinson's disease is distinctive of other neurological disorders in the wide presentation of symptomology and variability in prognosis at time of diagnosis (9). Palliation of symptoms early in Parkinson's disease may be provided by the primary neurological treatment team and specialist palliative care is appropriately called in many years after first diagnosis for more complex symptom management.

Communication in both a disease that has a rapid decline and one that has a prolonged decline can be aided by structured information sharing. There are several communication models and frameworks that can aid the provider in navigating these complex skills and practices (10, 11). The Ask-Tell-Ask method is one such method and involves first asking the patient to share their understanding of their disease (12, 13). This sharing allows the provider to assess what level of communication is needed in patient education and helps prevent repeating information that the patient already knows. The "Tell" then allows the provider, with permission, to share further information on the disease and prognosis personally tailored to the patient based on their initial disease description. The presence of uncertainty in prognostication and the limitation of prognostic tools should also be communicated. The last "Ask" allows the palliative provider to reassess patient understanding, correct misconceptions and fill in gaps in knowledge (14).

Glioblastoma patients benefit from decision making addressed up front, while the patient still has the cognitive abilities to understand and make their own decisions. Advanced directives should be completed soon after diagnosis, and it is preferable for the family to be brought in to hear the patient's preferences firsthand. The loss of cognitive abilities in Parkinson's disease is slower and can be anticipated, allowing the patient's wishes to be documented with ample time while the patient is still competent to make their own decisions.

Although life expectancy for glioblastoma patients has increased with the advent of new therapies, the outlook for most patients is still dire. Glioblastoma is well understood; however, many patients have poor awareness of disease trajectory and short life-expectancy (15). Good prognostic awareness is associated with a more favorable quality of life for the patient and reduced psychosocial stress for the caregiver (16). Prognostication is more complex in Parkinson's disease due to the longer disease trajectory, variable stages of disease at diagnosis, non-linear manifestation of symptoms and other comorbidities which have more opportunity to impact disease progression and overall patient disability. Unlike glioblastoma patients, Parkinson's patients can improve with exercise, which is known to modify disease progression (17). Optimized sleep, nutrition, stress control can help manage symptom manifestation, and patient engagement in disease modifying life-style changes can further challenge prognostication for the Parkinson patient.

Symptoms that affect social participation, reduced mobility, reduce ability to perform activities of daily living, and increase depression in both patient populations have a profound effect on patient quality of life. Discussion on symptom management for both the glioblastoma patient and the Parkinson's patient is outside of the scope of this discussion, and there are some excellent articles to which we would refer the reader (6, 7, 18–20). In addition to disease treatment and symptom management, we would offer that patient and caregiver support in these areas are foundational to adaptation to disease. Having a clear understanding of the disease processes, expected progression and how to adapt to the changing landscape normalizes change and can significantly enhance acceptance and provide emotional peace and resiliency on both the part of the patient and the care giver. A reasonably recent framework for the support and palliation of patients with high grade gliomas was proposed by Philip et al. (21) which is an interesting guide for provider teams and worth exploring. We hope more research will be done in this area to support their findings.

Patient and family education

A patient's understanding of their disease and treatment options is foundational to their ability to make educated and meaningful medical decisions. Posing such conversations in the "Hope and Worries" framework preserves the crucial element of hope that impacts a patient's ability to face the future and share their worries. This allows for a greater understanding of the realities of the disease and leaves the patient with a realistic perspective in which to plan, so that the element of surprise is limited. The literature suggests that patients prefer prognostic information communicated in a manner that preserves hope (1). Patients vary in their wishes to know their prognosis and in the level of detail they want. Ariadne Labs' Serious Illness Conversations Program (https://www.ariadnelabs.org/serious-illness-care/) may serve as foundational when beginning to understand and care for the patient on their own terms. They have developed clinician conversation guides, patient and caregiver workbooks and resources to guide these difficult conversations. Conversations can start simply with asking the patient to share what they understand about their diagnosis, what their treating provider shared about prognosis and how much information they would be comfortable receiving (big picture, detailed information or only the good news.) It helps to explore the benefits of having such conversations when the patient and provider have the time and space to do this in a thoughtful and calm manner, emphasizing that beginning such conversations during a time of crisis is incredibly challenging.

Building relationships with Parkinson's patients spans months to years. The Parkinson's communities nationally are well established with patient resources and support for care givers. There is active outreach by national and international organizations such as the Parkinson's Foundation (https://www.parkinson.org/), Michael J Fox foundation (https://www.michaeljfox.org/) The Davis Phinney Foundation (https://davisphinneyfoundation.org/, Parkinson's UK (https://www.parkinsons.org.uk/information-and-support), Parkinson's Europe (https://www.parkinsonseurope.org/) where patients can educate and empower themselves and come prepared to their medical appointments.

In a similar fashion there are online resources for brain cancer patients. The Glioblastoma Foundation (https://glioblastomafoundation.org/), and the Glioblastoma Support Network (https://glioblastomasupport.org/) offer glioblastoma patients and families patient-focused education and support in the USA and worldwide. The International Brain Tumor Alliance (https://theibta.org/brain-tumour-support-advocacy-and-information-organisations/) has a worthwhile listing of support groups and organizations internationally. Overall, there are fewer universal sources of patient-centered education for glioblastoma patients, which results in a patient relying more heavily on their clinicians, nurses, and other members of their interdisciplinary medical team for disease education. To support the patient fully, follow-up appointments are closer together than for the Parkinson patient. The high healthcare utilization underscores the need for supportive palliative care to be involved right from the time of diagnosis to walk the disease path with the patient, provide education and symptom control. This sharing of load reduces the burden on the rest of the healthcare team.

Caregiver burden

Burden as a function of disease progression

Caregivers in both Parkinson's disease and glioblastoma can suffer a lot of stress and the burden can be high. Regardless of the rapidity of the disease process, there are changes in relationships and roles due to disability and increased dependency on family and caretakers (22). In glioblastoma the stressors include hasty adaptation to rapid changes in patient capabilities, and less time to be educated and connect with others who have a similar disease to understand the benchmarks, norms, and prognosis of the glioblastoma patient. With the slow evolution of Parkinson's disease and a robust national social and educational infrastructure, there is greater time for adaptation, education and understanding. Although the long duration of disease wears heavily on caregiving, this eases the pressure on the clinician to provide all the education, and it allows the caregiver time to adapt to change. The slow progression of Parkinson's disease also allows space for discussion around the disease, treatments, and current and future available research.

Burden due to disease complexity

There may be complex needs at any stage during neurological illness. Parkinson's patients may present with very variable symptomology and have a wide variety of care requirements (9) which results in the Parkinson patient and caregiver leaning on the provider to normalize expectations and provide a more tailored vision of what to expect in the future. Complexity of care may depend on the ability and skills of the caregiver (22). Motor symptoms define Parkinson's disease: tremor, slowness, rigidity and, later in the disease, falls. In a similar fashion, glioblastoma patients are hampered by reduced mobility as their disease progresses, depending on their tumor location. Caregivers contend with reduced mobility which affects not only the patient's quality of life, but also increases the caregiver demand in time and attention, as well as physical strain. Non-motor symptoms of the disease can be as much, if not more burdensome to the caregiver (23). Symptoms such as rem sleep behavior disorder, constipation, micrographia, apathy, anxiety and depression are seen early on in disease presentation often before the diagnosis is fully fleshed out. As non-motor symptoms in Parkinson's disease often present well before motor manifestations of the disease, it adds complexity to the diagnosis, understanding and care for the patient (9). Being a caregiver in any relationship can be difficult and may come with negative health outcomes (24). Parkinson's caregivers have been found to have higher rates of depression, increased susceptibility to illness and poorer quality of life even when compared to caregivers in other diseases (25). This may be in part related to the duration of the disease and the slow, but relentless patient decline over years which affords the caregiver little respite. The interdisciplinary team in palliative care practice can attend to caregivers in addition to the patient's needs. Social work, chaplain services, child life specialists and psychology are core in this integrative support, be it an intense and rapid decline of a glioblastoma patient or the relentless decline of the Parkinson's patient over years wearing the caregiver down.

Assessing disease burden

There are numerous validated scales that can help measure and quantify caregiver burden. There are three common scalers: The Zarit Caregiver Burden Inventory (26), The Caregiver Burden Inventory

(27) and The Caregiver Strain Index (28). The scales are designed to assess the level of burden that the caregiver experiences for the patient, caregiver, and provider to have a better understanding of how quality of life can be improved.

Signs of caregiver burden

Signs of caregiver burden include: Denial of the severity of the disease or management; Anger at the disease or towards the patient, or difficulty managing emotions; Social withdrawal from hobbies, social support, or activities; Anxiety about the future, the unexpected or even day-to-day routines; Depression impacting perceptions as well as the ability to cope with stress; Fatigue, lacking energy to get through each day; Poor sleep which may be due to poor sleep hygiene or interruptions in sleep to provide care; Difficulty concentrating, completing tasks, or staying focused; Health problems, possibly because of deferring their own care for the care of the patient.

Interventions for the care giver

There is an increasing awareness of the value of specific caregiver training in the management of both cancer and neurological patients. The support groups discussed above have sections devoted to caregiver education and support, and research is emerging on the benefits of informal training by the patient's professional team. Empowerment of both the patient and the caregiver are key which includes the "caregivers' confidence that they can help alleviate their loved ones' symptoms" (29–31). Interventions for the caregiver may include such things as training caregivers in daily care skills, medication management, mechanics of movement to reduce patient falls and improve mobility. Caregivers can experience strain in multiple dimensions including emotionally, socioeconomically and financially, and caregiver strain is also known to be influenced by their attitude and sense of empowerment (32). Interventions should include empathic listening and asking open ended questions by all members of the palliative interdisciplinary team to better understand caregiver pressure points, as not all patients will experience all symptoms and resources should match their needs (33, 34). Caregivers can be encouraged to use mind-body techniques for stress reduction and mood control (35). A well-rounded palliative program may offer caregiver support groups to normalize some of these feelings and experiences. Caregivers can be encouraged to take time for self-care and utilize respite care services, as it is the intensity (number of hours) of caregiving that correlates to caregiver strain (33). The provider should also consider optimizing the patient's medication regimen to appropriately control symptoms which makes caretaking easier and thus reduces burden.

Grief

Processing grief in both the Parkinson patient and the glioblastoma patient is complex and multifactorial. Much of this occurs with and through the patient's family, community and foundational support systems, for example the patient's primary care providers or spiritual leaders. This burden of processing for both the patient and the family, which is deep and often complex, can be further supported by interdisciplinary palliative services including psychology, child life specialists, social work and chaplains.

Due to the long disease trajectory of Parkinson's disease, anticipatory grief is possible and common (36). Patients and caregivers have time to work through the mourning process for lost functionality and separation from loved ones through impending death. Palliative psychologists may lead a patient and their caregivers through these feelings and bring peace to the space that the patient occupies. Seyama and Kanda (37) elegantly describe the challenge that families face when living with "" conflicting emotions that never go away" [which] are present from the time of diagnosis until death and that the family must live while reconciling the polar emotional states of hope and pain". In glioblastoma patients, due to the rapidity of the disease process there is less time to come to terms with the diagnosis, change, fear, loss and death. Just the concept that the disease is rapid and relentless can be overwhelming, with the knowledge that there is little time to achieve life goals. The palliative health psychologist's role focuses more on acceptance of diagnosis and preparation for end-of-life, which is done in months, not years.

Good prognostic awareness from time of diagnosis can help with caregiver grief (16) Child life specialists become especially critical in families with children involved with the patient. The rapid decline of a loved one can be frightening and poorly understood. Children notice change, disease and decline even when not spoken about if they do not have context, they may create their own interpretation of what is happening to the patient or assign blame inappropriately. Child life specialists help children understand change and come to terms with the impending loss of a loved one in a non-threatening manner. Child life can also work on legacy building with the patient and the child while the patient is still alive, leaving more than just memories to ease grief and memorialize the patient.

Conclusion

Supportive palliative care is adjunct and integral to quality care of a terminally ill patient. Palliative care specialists function as an added layer of support for terminally ill patients. The patient is not required to change any treatment for their disease or treatment provider. While not interfering with active disease treatments, symptoms and side effects from the disease process and its treatment can be managed proactively. Engagement early in the disease process provides optimal patient care.

Engaging supportive palliative care is the engagement of a team. The medical provider may lead the patient and family care, but the true value of the palliative team is the sum of the individual members of the associated interdisciplinary team. A team consists of physicians, advanced practice providers, nurses, social worker, psychologist, chaplain, and child life specialist.

There are many similarities between the palliative management of a neurooncological patient, such as glioblastoma and a neurodegenerative patient such as Parkinson's disease. The differences, although nuanced, are important to successful patient management.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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A distress thermometer with a cutoff score of ≥ 6 is the optimal point to identify highly distressed patients with advanced cancer stages in resource-limited countries without palliative care services

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Purpose: Although the distress thermometer (DT) scale has been widely validated and used in different cancer types and settings, an optimal cutoff score of DT is not defined to screen advanced cancer patients. The study aimed to define the optimal DT's cutoff score among advanced cancer patients in resource-limited countries without palliative care services and to assess the prevalence and factors associated with psychological distress among this population.

Methods: A secondary analysis was performed. Three hundred seventy-nine patients were recruited from Palestine. Participants completed the DT and the Hospital Anxiety and Depression Scale (HADS). Receiver operating characteristic analysis (ROC) was used to define the optimal cutoff score for the DT against HADS-Total ≥15. Multiple logistic regression was utilized for identifying the factors associated with psychological distress of the DT.

Results: A DT cutoff score ≥ 6 correctly identified 74% of HADS distress cases and 77% of HADS non-distress cases, with a positive predictive value (PPV) and negative predictive value (NPV) of 97% and 18%, respectively. The prevalence of distress was found to be 70.7%, and the major sources of distress were related to physical (n = 373; 98.4%) and emotional problems (n = 359; 94.7%). Patients with colon (OR = 0.44, 95% CI: 0.31 – 0.62) and lymphoid cancers (OR = 0.41, 95% CI: 0.26 – 0.64) were less likely to have psychological distress than patients with other types of cancer, whereas patients with lung (OR = 1.80, 95% CI: 1.20 – 2.70) and bone cancers (OR = 1.75, 95% CI: 1.14 – 2.68) were more likely to experience it.

Conclusion: A cutoff DT score of 6 appeared acceptable and effective for screening distress in patients with advanced cancer stages. Palestinian patients exhibited a high level of distress, and the high prevalence supports the argument of using a DT within the standard delivery of cancer care to identify highly distressed patients. These highly distressed patients should then be involved in a psychological intervention programme.

KEYWORDS

advanced cancer patients, distress thermometer, healthcare system, palliative care, screening

Introduction

Patients with cancer experience considerable distress through their illness journeys, such as fear, coping with isolation, loss, anxiety, depression, and dependency (1). Distress is defined by the National Comprehensive Cancer Network (NCCN) as an "unpleasant emotional experience of a psychological (cognitive, behavioural, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment" (2). Psychological distress is relatively common among cancer patients, which has been recognized as the "sixth vital sign" in cancer care (3, 4). Psychological distress is an essential outcome associated with reduced treatment compliance (5) and increased risk of health deterioration and death (6). The most common types of psychological distress patients with advanced cancer confront are anxiety and depression (7, 8). Anxiety and depression have profound negative influences on patients' health and are associated with poor quality of life (QOL) (9) and a low level of satisfaction with medical treatments (10). Thus, identifying unrecognized cancer patients with psychological distress on time and promptly treating them is crucial in reducing the consequences of cancer side effects and enhancing their lives (11).

Several tools are available to identify psychologically distressed patients, including the Distress Thermometer (DT) (12, 13), Hospital Anxiety and Depression Scale (HADS) (14, 15), Brief Symptom Inventory-18 (BSI-18) (16) and Symptom Checklist-90 (17). Considering the length and time required to complete the previous tools, the NCCN Distress Management Panel has recommended using DT as a screening tool for distress (18). The NCCN also recommended adopting DT with a cutoff score of ≥ 4 to identify distressed cancer patients (12). Some studies adopted the recommended NCCN cutoff score for a general cancer population (19, 20). In contrast, other studies accepted a cutoff score of 3 (21, 22), a cutoff score of 5 (23, 24), or a cutoff score of 6 (25, 26). The variations in the optimal cutoff score were attributed to the cancer type (19, 20, 24, 26, 27), cultural and religious background of patients (19, 28), and clinical settings (20, 23, 29).

Despite the abundance and diversity of previous studies, most studies have been conducted in countries with high-quality cancer and palliative care (PC) services (20, 23, 29, 30). This makes it difficult to generalize the DT cutoff score in countries where PC has not been introduced in the healthcare system. No study has been conducted to define the optimal DT cutoff point in advanced cancer patients treated in a setting with no PC services introduced in the healthcare system. This study was carried out in Palestine-Gaza Strip, a country ranked by the WHO at the "capacity building activity-country" with an initiative designed to create a workforce, organizational and policy capacity for PC development (31), but no services have been integrated into their healthcare system (HCS) (32). Initiatives have been applied in PC-related areas, and most have focused on training healthcare professionals. PC services are the top priority of the Ministry of Health to be introduced into the HCS in the upcoming five years, as stated in the strategic plan for 2021–2025 (33). However, till now, PC services have not been introduced into oncological clinical practice in the Palestine-Gaza Strip. Most Gazan cancer patients' are diagnosed in advanced stages, putting them under a high level of distress and needing psychological support. This study's primary aim was to define the optimal cutoff score for DT among advanced cancer patients in resource-limited countries without PC services. It also aimed to find the best DT cutoff score for identifying highly distressed advanced cancer patients in stages III or IV. In addition, it identified the prevalence and factors associated with psychological distress among this population in relation to the DT data.

Materials and methods

Design and procedure

A secondary analysis was performed using primary data from a larger study on the unmet needs of PC patients. The study was conducted from May 2020 to August 2020 in the two hospitals in the Gaza Strip (Al-Shifa Hospital and the European Gaza Hospital) that provide cancer services for adult patients. The parent study adopted a multi-method research approach to comprehensively explore the factors and needs associated with the provision of PC services in the HCS from patients with advanced cancer, healthcare professionals and policymakers' perspectives (34).

Participants' characteristics and sample size calculation

Only patients who had been diagnosed with an advanced stage (diagnosed with stages III or IV), were 18 years of age or above;

were treated at one of the two hospitals that provide cancer services and who gave written consent were recruited through the convenience sampling approach. Patients with brain tumours and those exhibiting symptoms of cognitive impairment were excluded.

The patients who had appointments to visit the outpatient clinics in the hospitals were selected to participate. To identify the eligible participants, a list of patients' names was printed from the information technology department after getting approval from the general directors of the two aforementioned hospitals. The printed list was forwarded to the heads of the oncology departments, asking them to exclude the non-eligible patients from the list. The final list of eligible patients was passed to the assigned oncology nurses who were asked to reach the selected patients and invite them to participate in the study, informing them that participation was voluntary and that they had the right to withdraw from the study at any time. Those who agreed to participate signed the informed consent form. Utilizing the sample size calculation formula described by Thompson (35), the required sample size was 368 patients. In this study, 379 patients at two hospitals in the Gaza Strip participated in the study.

Measures

Self-administered questionnaires were adopted to collect data in this study, utilizing two instruments: the DT and HADS scales. Prior permission for their use was obtained by the original scale's authors. Socio-demographic and medical-related variables were also collected.

Distress Thermometer

The Arabic version of the DT scale was used (20). It is a screening tool that has been widely used in psycho-oncologic research to identify clinically high levels of distress among cancer patients (20). The DT is a one-item measure that assesses the level of distress patients have experienced in the preceding week (36). The scale ranges from 0 (no distress) to 10 (high distress). The DT includes 36 problems answered with "*no*" or "*yes*" clustered into five domains: practical problems, family problems, emotional problems, spiritual problems, and physical problems.

Hospital Anxiety and Depression Scale

The Arabic version of the HADS was utilized to assess cancer patients' anxiety and depression levels (37). It is a 14-item scale encompassing two subscales: anxiety and depression. The scores in each subscale are computed and determined to fall under one of the following three categories: normal cases (score of 0-7), borderline cases (score of 8-10), and cases (score of 11-21) (15). The cut-off point of the Arabic version of HADS for the total score was ≥ 15 and for anxiety and depression, it was ≥ 6/7. In this study, the HADS-T Arabic version had a good internal consistency with a Cronbach's α coefficient was 0.69, with a subscale of HADS-anxiety of 0.60 and a subscale of HADS-depression of 0.62. Validation of the DT versus HADS has been adopted in many studies, showing that a total score of HADS-T ≥ 15 was the optimal cutoff score for screening distress (38, 39).

Socio-demographic and medical characteristics

Patient's demographic and medical data variables were collected, such as age, gender, marital status, level of education, living conditions, cancer site, stage, type, duration since diagnosis, and current and completed treatments.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 25 software. Descriptive statistics were utilized to present the mean score and frequency of demographic characteristics, DT, and HADS scales. The percentages of the top 10 frequent problems/items for the distressed patients were also presented. The receiver operating characteristic (ROC) analysis was calculated to identify the optimal DT's cutoff score against HADS-T ≥ 15. The optimal cutoff score was determined according to the point at the top left level of the curve. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive utility index (UI+) were calculated for each DT cutoff point against HADS-T ≥ 15. The area under the curve (AUC) of a ROC of 1 corresponded to a perfect test with 100% of sensitivity and 100% specificity was considered an optimal point to identify the DT's cutoff score. The Youden index (*J*) was calculated to confirm the optimal cutoff DT score. Chi-square (χ^2) analyses and t-tests were utilized as appropriate to assess for differences between the distressed and not-distressed groups with participant variables. Multivariate logistic regression analysis was performed for the purpose of identifying the factors associated with psychological distress. All statistical tests were two-tailed, and *p* values of less than 0.05 were significant.

Results

Participants' characteristics

A total of 404 advanced cancer patients were approached, 25 (6.2%) refused participation, and 379 (93.8% response rate) were included in the final analysis. Participants ranged in age from 18 to 90 years old, with a mean age of 50.13 ± 14.04 years. More than half of the participants (n = 193) were male. The majority were married (n = 316; 83.4%). 50.9% of patients had stage IV cancer, and 81% received chemotherapy treatment. About 21.8% of patients had breast cancer, followed by lung cancer at15.3%. Detailed characteristics of the study participants are presented in Table 1.

The mean DT score was 6.72 ± 2.48, ranging from 0 to 10. The HADS-T score ranged from 3 to 42, with a mean score of 22.50 ± 5.52. For HADS-D, about 89.5% of patients reported signs of depression (30.9% borderline; 58.6% definitive, with a mean depression HADS score of 11.15 ± 3.09). While for the HADS-A,

TABLE 1 Demographic and clinical characteristics of the study subjects (N=379).

Participants' characteristics	Total N = 379 (%)
Age in years	
Mean + SD	50.13 ± 14.04
Gender	
Male	193 (50.9)
Female	186 (49.1)
Marital status	
Married	316 (83.4)
Not married[a]	63 (16.6)
Education	
Primary and less	51 (13.5)
Secondary	243 (64.1)
University	85 (22.4)
Working status	
None	177 (46.7)
Employee	102 (26.9)
Homemaker	100 (26.4)
Monthly Income (USD) (N=359)	
Less than 250 USD	249 (69.4)
More than 250 USD	110 (30.6)
Diagnosis/type	
Breast	83 (21.8)
Colon	58 (15.3)
Lung	34 (9.0)
Bone	28 (7.4)
Prostate	20 (5.3)
Bladder	12 (3.2)
Thyroid	27 (7.1)
Lymphoid	26 (6.9)
Brain and neck	25 (6.6)
Stomach	17 (4.5)
Other	49 (12.9)
Stage	
III	186 (49.1)
IV	193 (50.9)
Current treatment	
Chemotherapy	307 (81.0)
Radiation	27 (7.1)
Surgical	16 (4.2)
Other	29 (7.7)
DT (mean ± SD)	6.71 ± 2.48
HADS-T (mean ± SD)	22.50 ± 5.52
HADS-A (mean ± SD)	11.35 ± 3.38
HADS-D (mean ± SD)	11.15 ± 3.09

SD, Standard deviation; USD, United States Dollar.
[a]Includes those who are single, widowed, or divorced;
[b]Missing data 5.3%.

87.9% of patients reported signs of anxiety (26.4% borderline; 61.5% definitive, with a mean score of 11.35 ± 3.38) (Table 1).

Receiver operating characteristic analysis and the optimal cutoff score

For patients with advanced cancer stages (stage III and IV), results showed that DT had good discriminating accuracy (AUC = 0.772, 95% CI: 0.658–0.885) between distress and no distress against HADS-T ≥15. A cutoff score of 6 on DT correctly identified 74% of HADS distress cases and 77% of HADS non-distress cases, with PPV and NPV of 97% and 18%, respectively. The *J* index and UI calculation demonstrated an accuracy of DT in screening cases (*J* = 0.51, UI + = 0.72). Details of the accuracy of measures for DT scores according to HADS-T are presented in Figure 1 and Table 2.

A subgroup analysis was also conducted to confirm whether a cutoff score of ≥ 6 is an appropriate point to identify highly distressed advanced cancer patients in either stage III or IV. DT had good discriminating accuracy (AUC = 0.785, 95% CI: 0.584–0.987) between distress and no distress in patients with stage III when compared to HADS-T ≥15. The cutoff score of 6 on DT also correctly identified 71.1% of HADS distress cases and 81.8% of HADS non-distress cases. The same with patients diagnosed with stage IV, the cutoff score of 6 on DT also correctly identified 78.8% of HADS distress cases and 75% of HADS non-distress cases, with good discriminating accuracy (AUC = 0.854, 95% CI: 0.757–0.950) between distress and no distress against HADS-T ≥15 (Figures 2A, B).

χ^2 test of the index test results (DT ≥6) against the results of the reference standard (HADS-T ≥15) is presented in Table 3. The index test correctly identified 74.5% of HADS-A distress cases and 56.5% of HADS-A non-distress cases. Moreover, the index test correctly identified 73.2% of HADS-D distress cases and 51.3% of HADS-D non-distress cases. The association between index test results and HADS-A and HADS-D reached a significant level (*P*-value = < 0.000 and 0.001, respectively).

Prevalence of distress at a cutoff score ≥ 6

At DT (≥6), 70.7% of the patients (n = 268) were found to be distressed. 15% of patients reported distress at the level of 10, indicating extreme distress (Figure 3). The major sources of distress were related to physical (n = 373, 98.4%), emotional (n = 359,

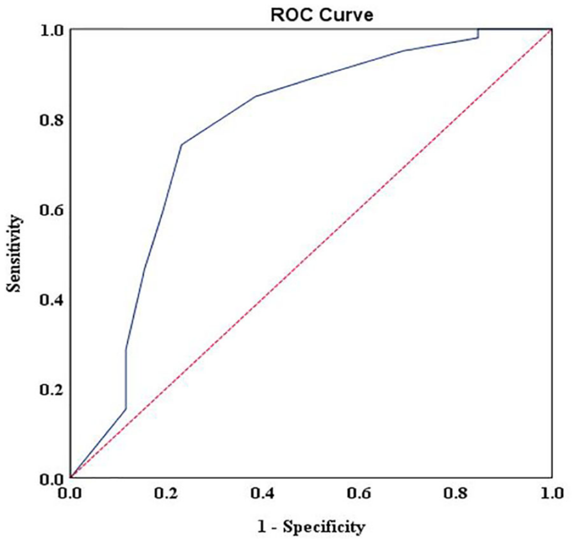

FIGURE 1
Receiver operating characteristic curve of the distress thermometer score against the Hospital Anxiety and Depression Scales-Total cutoff score > 15 for patients with advanced stages.

94.7%), and practical problems (n = 324, 85.5%). Nervousness (n = 281, 73.9%), depression (n = 276, 72.8%), and fear (n = 275, 72.6%) were the main emotional sources of distress among advanced cancer patients. The top 10 frequent problems checked as a source of distress are presented in Table 4.

Factors influencing distress among patients with advanced cancer

All variables with a *p*-value ≤ 0.25 in univariate analysis were selected for multivariate logistic regression. Findings underscored that patients with colon (OR = 0.44, 95% CI: 0.31 – 0.62) and lymphoid cancers (OR = 0.41, 95% CI: 0.26 – 0.64) were less likely to have psychological distress than patients with other types of cancer, whereas patients with lung (OR = 1.80, 95% CI: 1.20 – 2.70) and bone cancers (OR = 1.75, 95% CI: 1.14 – 2.68) were more likely to experience it. Results also indicated that patients with stage IV (OR 1.30, 95% CI: 1.06 – 1.60) and those with emotional distress (OR 2.69, 95% CI: 1.71 – 4.23) were more likely to have psychological distress than patients with stage III and those without emotional problems (Table 5).

Discussion

This study was conducted to define the optimal cutoff score of DT in patients with advanced cancer stages in resource-limited countries without PC services. The study furthered the knowledge about the prevalence and risk factors associated with psychological distress among this population. A cutoff score of ≥ 6 on the DT scale is the most sensitive to be adopted for identifying advanced cancer patients with psychological distress. Patients exhibited a high level of psychological distress, anxiety, and depression. Physical and emotional related problems were the leading source of distress. The multiple logistic regression model underpinned the findings that cancer diagnosis, stage, and emotional distress were independently associated with psychological distress.

The cutoff point is crucial to dichotomize the continuous scale levels of people at risk for developing diseases and those not (40, 41). The commonly utilized methods for evaluating scale effectiveness and determining the optimal cutoff point are the AUC and the Youden index (*J*) methods (40), of which both are applied in this study to identify the cutoff point of the DT scale. The AUC is based on mapping the sensitivity by one minus specificity, where the optimal cutoff point is closed to 1 (41, 42). Our study underscored that DT at a cutoff score of 6 showed a good

TABLE 2 Accuracy measures for DT scores according to HADS-T.

DT cut off score	Sensitivity	Specificity	Youden index (*J*)	Positive predictive value	Negative predictive value	Utility index +
Against HADS-T						
0/1	1.000	0.15	0.156	94.1	100	94.1
1/2	0.980	0.15	0.136	94	36.4	92.1
2/3	0.952	0.31	0.263	94.9	32	90.3
3/4	0.890	0.50	0.395	96	25	85.4
4/5	0.850	0.62	0.471	96.8	32.2	82.3
5/6†	**0.742**	**0.77**	**0.519**	**97.8**	**18.0**	**72.6**
6/7	0.595	0.81	0.411	97.7	12.8	58.1
7/8	0.465	0.85	0.319	97.6	10.4	45.3
8/9	0.286	0.89	0.180	97.1	8.4	27.8
9/10	0.153	0.89	0.156	94.7	7.1	14.5

DT, Distress Thermometer; HADS-T, Hospital Anxiety and Depression Scale-Total.
†Bold values signify the balanced cutoff point with the highest Youden index.

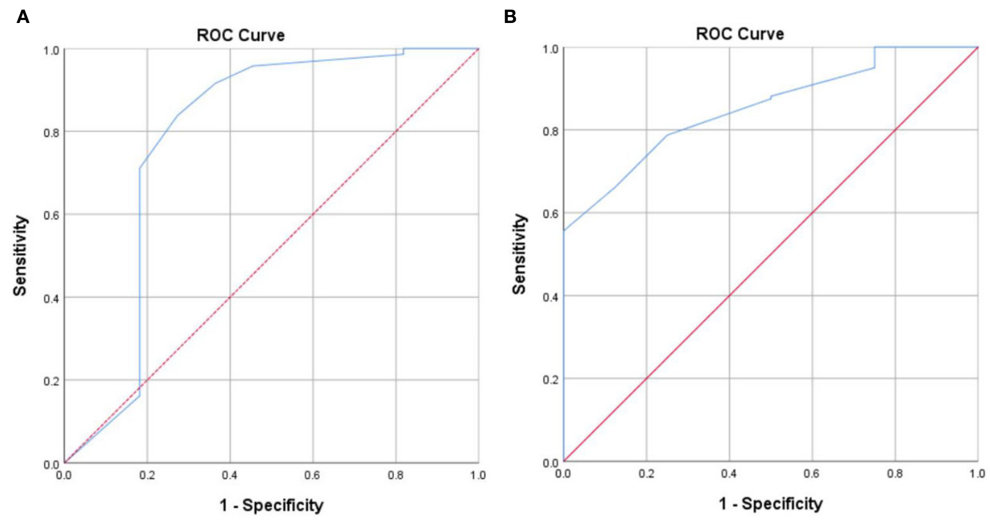

FIGURE 2
(A) Receiver operating characteristic curve of the distress thermometer score against the Hospital Anxiety and Depression Scales-Total cutoff score 15 for patients with stage III. **(B)** Receiver operating characteristic curve of the distress thermometer score against the Hospital Anxiety and Depression Scales-Total cutoff score ≥ 15 for patients with stage IV.

TABLE 3 Classification rates using a DT cutoff of 6 concerning HADS cases.

	Index test (DT) cutoff score ≥ 6			
Reference test (HADS) cutoff score	Above cutoff, N (%)	Below cutoff, N (%)	Chi-square OR (95% CI)	p-values
HADS-T ≩ 15			30.586 9.59 (3.73-24.64)	0.000
Above cut-off	262 (74.2)	91 (25.8)		
Below cut-off	6 (23.1)	20 (76.9)		
HADS-A ≩ 8			18.750 3.79 (2.01-7.14)	0.000
Above cut-off	248 (74.5)	85 (25.5)		
Below cut-off	20 (43.5)	26 (56.5)		
HADS-D ≩ 8			10.155 2.88 (1.47-5.64)	0.001
Above cut-off	249 (73.2)	91 (26.8)		
Below cut-off	19 (48.7)	20 (51.3)		

DT, Distress Thermometer; HADS-T, Hospital Anxiety and Depression Scale total score.

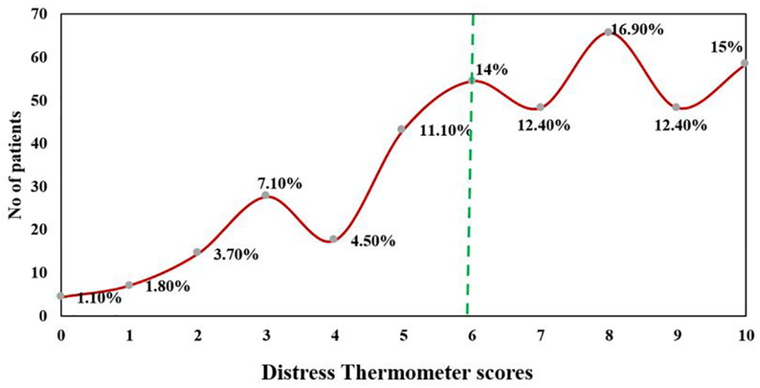

FIGURE 3
The frequency distribution of DT score under and above DT cutoff scores 6.

TABLE 4 Top 10 frequent problem list items checked as a source of distress among study participants.

Rank	List of problems	n (%)	Domain
1	Nervousness	281 (74.1)	Emotional
2	Depression	276 (72.8)	Emotional
3	Fears	275 (72.6)	Emotional
4	Loss of interest in activities	275 (72.6)	Emotional
5	Spiritual/religious	274 (72.3)	Spiritual
6	Sadness	265 (69.9)	Emotional
7	Fatigue	262 (69.1)	Physical
8	Worry	258 (67.5)	Emotional
9	Pain	248 (65.4)	Physical
10	Eating	246 (64.9)	Physical

discriminating accuracy, which is congruent with previous literature reporting a good AUC (19, 27, 43). The Youden index (*J*) (44) is another method that based on combining sensitivity and specificity into a single measure (Sensitivity + Specificity - 1) and has a value between 0 and 1 (42). In our study, the *J* index demonstrated an accuracy of DT at a cutoff score of 6 in screening distress patients. Furthermore, the PPV and NPV were also calculated at a cutoff score of 6, resulting in fewer false-positive

TABLE 5 Multivariate logistic regression model .

Variables	β	S.E.	Wald	OR (95% CI)	*P value*
Stage					
III	Ref.	–	–	–	–
IV	0.266	0.104	6.534	1.305 (1.06-1.60)	**0.011**
Diagnosis/type					
Breast	-0.252	0.157	2.574	0.777 (0.57-1.05)	0.109
Colon	-0.810	0.171	22.247	0.445 (0.31-0.62)	**0.000**
Lung	0.592	0.206	8.232	1.807 (1.20-2.70)	**0.004**
Bone	0.560	0.217	6.610	1.75 (1.14-2.68)	**0.010**
Prostate	10.120	0.249	0.231	0.887 (0.544-1.44)	0.631
Thyroid	-0.218	0.221	0.966	0.804 (0.52-1.24)	0.804
Lymphoid	-0.887	0.225	15.49	0.412 (0.26-0.64)	**0.000**
Brain and neck	0.323	0.229	1.97	1.38 (0.88-2.16)	0.160
Other	Ref.	–	–	–	–
Emotional problems					
No emotional problems	Ref.	–	–	–	–
Have emotional distress	0.991	0.230	18.47	2.695 (1.71-4.23)	**0.000**
Physical problems					
No physical problems	Ref.	–	–	–	–
Have physical problems	-0.991	0.230	1.073	0.653 (0.29-1.46)	0.300

HADS, Hospital Anxiety and Depression Scale.
Bold values denote statistical significance at the P < 0.05 level.

and false-negative rates. These are notable results that were not measured in most previous studies, based mainly on the sensitivity and specificity of the scales.

Timely identification and management of highly distressed patients are critical to enhancing their lives, which can be achieved using efficient and accurate screening tools (11). The optimal cutoff of DT is not well defined in patients with advanced cancer. There is no conclusive data regarding the optimal cutoff point because no single cutoff score has been found that increases the accuracy of DT (45). The DT with a cutoff score of ≥ 6 against HADS-T ≥ 15 is an efficacious tool for screening distress in patients with advanced cancer stages, as reported in this study. This result aligns with previous studies (25, 26). It does, however, contradicts NCCN guidelines, which recommend a cutoff score of ≥ 4 as the optimal point for screening distress (12), as well as previous studies conducted in Italy (46), Saudi Arabia (20), the United States (47) and China (48). The variations in the optimal cutoff point can be attributed to the clinical settings in which highly developed countries provided optimal care to patients, as opposed to Palestine, which has a fragmented HCS, inadequate staffing and unavailability of pain medications (32, 49), making it unable to meet the baseline needs of patients (32, 50).

Findings showed that DT ≥ 6 correctly identified 74% of advanced cancer patients as distressed and 77% as not distressed patients. Our study's sensitivity and specificity levels are somewhat similar to a Chinese study (25), but higher than that reported in a Saudi Arabia study (20). The variations across studies are attributed to the studies' methodological underpinnings as the former study was limited to intracranial cancer patients, while the latter study focused on all cancer stages, compared with this study that focused on cancer patients with stage III and IV cancer. Thus, a cutoff score of ≥ 6 is optimal to generalize across different cancer populations in settings with no PC services. The cutoff score of ≥ 6 will help decrease overdiagnosis due to false-positive results. Misdiagnosis of patients may burden non-distressed patients with unnecessary interventions. It may also burden and overstress the healthcare system with higher service use and costs.

Findings underscored that no associations were reported between DT and demographic and clinical variables, except for cancer diagnosis and stage. The results are in accordance with earlier studies that were also unable to find associations between DT and demographic and clinical variables (12, 51, 52). In contrast, other studies have identified an association between distress and younger patients (53), female patients and illiterate patients (54). Previous studies reported an independent association between distress and head and neck cancer, which contradicts this study that found lung and bone cancers were associated with higher distress than other cancer diagnoses (55). Psychological distress is common among patients with lung and bone cancers (56, 57). Lung cancer is the second most commonly diagnosed cancer in Palestine, comprising 11.4% of the total cancers (58). The fragile Palestinian HCS, shortage of healthcare professionals (59), and limited resources impede achieving optimal cancer services and meeting the needs of cancer patients, including lung cancer (60, 61). Furthermore, Palestinian patients with lung cancer are unfortunately diagnosed at a late stage, and they experience shortness of breath, coughing up blood, and severe chest pain (62). They are in need of oxygen therapy to alleviate their dyspnea, and prolong their survival (63, 64). However, the long-term oxygen therapy may impede their daily activities and may influence their psychological status (65).

Thus, more attention should be paid to these group of cancer patients in Palestine through psychological interventional programs to alleviate their distress.

This study reports certain limitations; adopting a cross-sectional design with non-probability sampling methods made it difficult to generalize our findings to all patients and determine the causation for any observed association. The authors determine the optimal cutoff DT score based on specific criteria, including the use of HADS; other external criteria can be used and may influence the generalizability of the findings. Despite these limitations, our findings show that determining the optimal cutoff DT score for patients with advanced cancer stages in resource-limited countries without PC services, as well as understanding the sources of distress can help healthcare professionals in identifying patients in need of urgent intervention to reduce the sources of those distresses for cancer patients. Adopting several methods for determining the optimal cutoff point is also one contribution of this study.

Conclusion

Identifying advanced cancer patients with high distress is crucial. A cutoff DT score of 6 appeared acceptable and effective for screening of distress in this population. Palestinian patients had a high level of distress. The high prevalence supports the argument of using a DT within the standard delivery of cancer care. The highly distressed patients should then be involved in a psychological intervention programme.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical approvals to undertake the study was obtained from the Human Subjects Ethics Sub-committee at The Hong Kong Polytechnic University, Hong Kong (reference number: HSEARS20200414006). Administrative approval was also obtained from the Palestinian Ministry of Health-Gaza (reference number: 476303). The patients/participants provided their written informed consent to participate in this study.

Author contributions

HA-O, AM, and JL planned the study. HA-O and AM analyzed the data, and HA-O, AM, and JL together interpreted the findings. H-AO wrote the first draft of the manuscript and AM and JL made the final revision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Doing palliative care research on hematologic cancer patients: A realist synthesis of literature and experts' opinion on what works, for whom and in what circumstances

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Background: Research in PC (Palliative Care) is frequently challenging for patient's frailty, study design, professional misconceptions, and so on. Little is known about specificity in PC research on Hematologic cancer patients, who have distinct characteristics that might influence the enrollment process.

Aims: What works, how and for whom, in increasing enrollment in studies in PC on patients with hematologic malignancies?

Methods: Realist review: a qualitative review whose goal is to identify and explain the interaction between Contexts, Mechanisms, and Outcomes (CMOs). The theory was informed by a narrative, theory-based literature research, including an initialsystematic research, and the addition of papers suggested by experts of the field. We also used 7 interviews with experts in PC about patients with hematologic malignancies research and our own experience from a PC pilot study on patients with hematologic malignancies to refine the initial theory.

Results: In our initial theory we hypothesize that:

- Access to palliative care could be beneficial to hematologic patients, even in early stages
- Hematologists tend to under-use palliative care services in general, due to unpredictable disease trajectories and cultural barriers.
- These factors may negatively impact the patients' enrollment in PC research

We included secondary literature as narrative reviews, if they presented interesting propositions useful for our theoretical construction. 23 papers met our inclusion criteria.We also searched for relevant CMOs impacting referral in palliative care, and we selected a list of CMOs that could be relevant also in hematology. We accordingly theorized a group of interventions that could increase the enrollment in PC research and presented them using "social exchange theory" (SET) as a theoretical framework.Prominent researchers in PC in hematologic malignancies were interviewed on their opinion on our results, and additional CMOs.

Conclusions: Before conducting research in PC on patients with hematologic malignancies, it's probably advisable to assess:

- The perception of the different actors (physicians, nurses, other professionals involved), in particular the hematologists, in terms of pros and cons of referral to PC and enrollment in PC trials
- The existing relationship between PC and the Hematology department

Accordingly, it's possible to tailor different interventions on the various actors and choose a model of trial to increase the perception of benefits from PC and, consequently, enrollment.

KEYWORDS

realist sinthesys, hematologic palliative care, research in hematologic palliative care, research in palliative care, enrollment in palliative care, oncology, hemato oncology

Background

In this section we are presenting the known difficulties met when recruiting PC (palliative care) patients in research projects, and the goal of this paper: investigating how these difficulties apply to PC patients with hematologic malignances. We used the realist (see Box 1) approach for this, as we developed an Initial theory (presented at the beginning of the "results" section) and we "refined it" through an evidence informed process, consisting of different steps (see "data collection and analysis" in "materials and methods" section) and produced a more refined, final theory of what works, for whom and in what circumstances in enrollment of palliative care patients with hematological malignances (reported at the end of the "results" section).

Patients with advanced hematological malignancies suffer from a very high symptom burden and psychological, spiritual, social, and physical symptoms comparable with patients with metastatic non-hematological malignancy (1–4).

In agreement with the new World Health Organization recommendation (5) the evidence from studies performed in patients with solid tumors and hematologic patients' symptom burden suggests that an earlier and integrated provision of specialized palliative care has the potential to improve their quality of life and reduce resource consumption through effective management of psychological and physical symptoms, appropriate relationships, effective communication, and support in decision-making. Palliative Care study design must take into account intrinsic methodological challenges, such as the unpredictability of disease progression, recruiting difficulties, and high attrition rates (6). Moreover, outcome measures that assessed the acceptance of the study by the participants were frequently absent (7) and RCT (Randomized Controlled Trial) design may be more frequently connected with people who are unwilling to be enrolled, aseven the use of words like "randomization" and "placebo" (6), can be negatively perceived by the patients. In the other hand,a language perceived as clear, and non-technical in that specific culture, and the use of words more oriented to symptom management then to palliation could have a positive impact.

Trials encountered enrollment challenges; for example, the consent approach rate in the ENABLE III trial of early versus delayed initiation of concurrent palliative care was 44%, with a variety of reasons given by approached patients for declining participation (7, 8).

Thespecialist's opinion about the experimental arm involved in the trial proposal can also influence the enrollment (6, 9).

If they have the perception of "failing the patient", or adding burden, or if they lack faith in the proposed intervention, when referring to palliative care, because they lack faith in the specific research or intervention proposed, fears to speak about prognosis, or perceive the enrollment procedure as too demanding for the

Box 1 Glossary of terms of realist methodology.

Realism: theory-driven research approach, which produces evidence-informed theories, to better understand how an intervention works, for whom and under what circumstances, through the search for underpinning mechaninsms ("retroduction").
CMO configuration:
Context: environmental backdrop elements of an intervention or program (ig: laws, cultural norms). Context in realist theory describes "in what circumstances and why interventions or programs 'work'".
Mechanism: resources offered in a specific context (ig: information) and reactions of people involved (ig: trust or engagement). It should provide an "an explanatory account of how and why programs gives rise to outcomes".
Outcome: effects of specific mechanisms in a defined context, both intended or unintended (ig: adherence to a treatment).
Initial Rough theory (IRT): hypothesis of underpinning mechanisms in a program or intervention, usually, in the form of "if…then" statements, that need to be furtherly tested.
Refined theory: theorization resulting from the testing of IRT through the analysis of the gathered evidence.

usual care staff, this might have a negative impact on the overall enrollment (10). In their study, White et al. state that over three quarters of interviewed patients stated that they would be interested in trial participation if their doctor made it clear that he/she was keen for participation (6). The absence of symptoms can decrease patients' motivation, and in general patients need to see some relevant potential personal gain, as the access to additional care or a better symptom management (when they are already present), or feel that their contribution can be helpful to others. Organizational factors can also have an effect, such as if the patient must attend multiple visits or travel further to receive the offered service.

Little is known about specific research in PC regarding *hematologic* cancer patients.

Studies showed heterogeneity in the population, PC intervention, disease trajectory and treatment phase (11). Only in the last 2 years some evidences on effectiveness arose on high symptomatic hospitalized patients by EL-Jawahri et al. (12).

Following the WHO recommendation, we initially developed a PC intervention integrated with standard hematological care (13). This pilot study was primarily focused on assessing the feasibility of the PC intervention. Secondary aims included exploring its acceptability by patients, professionals and caregivers and collecting preliminary information on its effectiveness. Our study design was discussed with hematology colleagues to better understand how to propose it and the inclusion criteria suitable for the feasibility trial including patients at their last active treatment (see Table 1).

However, the enrollment for this protocol has been difficult; it started in November 2018 with patients and caregivers; we enrolled 15 patients in 3 years.

It's essential for our research team to understand the reason for this low accrual, related to patients, professionals, trial itself or organization. We believe it should be interesting to compare our experience with other realities all over the world.

In this paper we described a realist synthesis (14, 15) (read Box 1 for details on realist methodology), based on our previous Review, a rapid review on Hematologic cancer patient and research in Palliative Care (final check March 2022) and experts 'opinion on PC trials for hematologic cancer patients.

Eventually, We (11) integrated these data with our experience. Hence, the aims of the current study were:

- to provide an overview of difficulties in patients enrollment in palliative care studies, specifically in hematologic malignancies, exploring the experts' point of view, literature overview, our experience.
- to elaborate a realist synthesis of enrollment in palliative care intervention for hematologic cancer patients

The results of this study might be relevant for developing structured intervention proposals regarding hematologic cancer patients in PC trials or to give some suggestions to our colleagues involved in research protocol in this complex topic.

With this in mind, as expected by the realist approach, we aimed at producing a theoretical contribution, starting from an "Initial Rough Theory" (IRT) at the beginning of the process and finishing with a more refined version of it, as a result of our research work.

Materials and methods

The process that we followed could be considered a process of realist synthesis; we decided to include secondary studies in our revision, which is not typical, and we tested our Initial rough theory with an independent study.

This part of the process is compatible with the realist logic, but it's not a fixed stage of usual research strategies in realist synthesis. We considered as our guide for this manuscript the "Quality

TABLE 1 Our pilot intervention.

Our intervention: difficulties met, and initiatives taken in response
Before we started writing the protocol: • we met with the 2 referring hematologists expert in myeloma multiple and chief of department to discuss inclusion criteria of the trial. • a focus group was conducted to explore difficulties in enrollment As a result, some initiatives were placed from the start, as: • hand-delivery of written reminders for the office desk of hematologists • weekly in-person reminder, at scheduled ward's meeting • periodical reminders to formal leaders of the ongoing trial
During the enrolment stage, Hematologists listed some difficulties: • it's hard to keep in mind the possibility of enrollment in non-pharmacological protocol through ordinary care • the suggested timeline (*before* starting the last active treatment) for the enrollment can be an obstacle, as: - some patients potentially eligible for the intervention needed urgent access to palliation, and so were excluded from the protocol (as they couldn't be randomized and enrolled in the study) - sometimes clinicians needed to start the allegedly last line of therapy in a really short time, making the enrollment process impossible • trial's design was aimed to maximize safety and benefit for the patient: when control group patients asked to receive palliative care, they were immediately redirected to it. This might have negative influenced the clinicians' perceptions of the relevance of the trial intervention.
as additional possible improvement strategies we tried to: • engage "trial champions", as we asked to hematologists that showed particular interest in the trial to sponsor the trial enrollment • involve the formal ward's leadership, to explore their perceptions on ongoing difficulties

standards for realist synthesis for researchers and peer-reviewers" (16, 17) of the Rameses project.

According to realist analysis methodology, our first literature consultation aimed at the development of a rough theory (IRT), that further research and expert consultation aimed to refine the IRT, focusing on what seems to work better, for whom, and how, describing it through Context-Mechanism-Outcome (CMO) configurations (see Box 1 "glossary of terms of realist methodology").

The initial rough theory was based on a previous systematic revision of literature from our team (11) and our knowledge from our personal experience in conducting a trial on PC with hematologic patients (see Table 1 "*Our intervention: difficulties met, and initiatives taken in response*").

We then better specified our focus and decided to extend our search of possible mechanisms that might have an impact on the enrollment process to contiguous fields. In addition to the search for CMOs regarding the enrollment of hematologic patients into PC studies, we searched for articles describing CMOs relevant in the referral to palliative care in hematological patients. (Research strategy reported in Table 2, where we reported both the shift of focus of our research and the correspondent article selection process, as suggested in "quality standards for realist synthesis", standard 5 and 6) (17). This is an example of "progressive focusing", a well-established technique in qualitative research in which the focus of the inquiry is iteratively clarified by reflection on emerging data (50).

We derived an interview guide (see appendix 1 "the interview guide") to collect data about the different research teams that are conducting similar studies. The interview was developed following the recommendations by the RAMESES project for "realist interviews" (17, 51).

Data collection and analysis

Steps in developing our final theory were shown in Figure 1 "phases of research".

They were:

- STEP 1: we developed our IRT starting from literature review on Early Palliative Care and Hematologic cancer patients and our experience in a pilot feasibility trial

TABLE 2 Articles' selection.

rationale of articles' selection and correspondent shift of research's focus	research strategy
initial literature systematic review (Tanzi, S., et al. (2020). "Early palliative care in hematological patients: a systematic literature review." BMJ supportive & palliative care 10(4): 395-403.): aim of the review was to synthesize the evidence on the impact of early palliative care on hematologic cancer patients' quality of life and resource use	Embase,Cochrane, CINHAL and Scopus searched for: • (early OR integrated OR simultaneous care OR concurrent) AND palliative care OR early palliative care OR simultaneous care AND (haematologic* OR haematologic* OR onco-haematologic*); english, up to 7/2/2020. - 296 articles retrieved, - 8 articles included in the review (18–25):
Second literature research for theory refinement March 2021: after developing an RCT experience our research team focused on how and why hematologic enrollment in palliative care research proved to be so difficult in our and other professionals' experience.	Pubmed: • research[Title/Abstract] AND palliative[Title/Abstract] AND (hematologic*[Title/Abstract] OR haematologic*[Title/Abstract]) Filters: Adult: 19+ years, from 2011 – 2021: - 53 records retrieved, - 12 records included in the review (7, 12, 18, 26–34):
After interviewing 7 main experts in the fields that resulted eligible as authors of the main works retrieved in the previous articles retrieval, as appropriate in realist synthesis, we then decided to "seek out data from situations outside the program under study where it can be reasonably inferred that the same mechanisms(s) might be in operation" (Rameses project's standards), and retrieved additional records from bibliographies, considered articles and interviewees indications, exploring the contiguous fields difficulties in hematologic research in general, and difficulties in palliative care research in general, searching for relevant CMOs for our research question("why enrollment in palliative care studies on patients with hematologic malignancies is so difficult?").	16 articles selected for the realist synthesis (6, 8, 9, 35–46)
After iteratively analyzing the selected articles, we decided to focus on the more specific aspects of difficulties in hematologic referral and difficulties in palliative care research on patients with hematologic malignancies, as the information and CMOs configurations retrieved in the articles about the difficulties in PC research in general where mainly already reported in the other two groups.	selected as highly contributors to our research's question: FINAL ARTICLES' SELECTION: 22 articles (7, 12, 18, 20, 26–33, 35–37, 42, 43, 46–49):

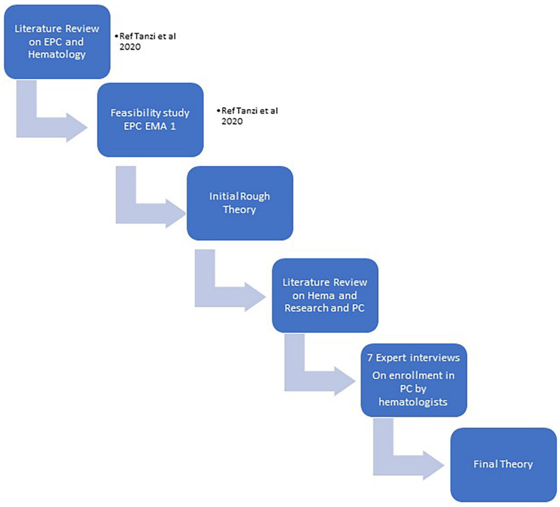

FIGURE 1
The phases of research.

- STEP 2: we searched for relevant palliative care studies conducted with hematologic patients and for ongoing trials.

We analyzed the available materials (published papers, protocols and abstract), using an appraisal process in which we made a first selection based on abstract's pertinence, and then a second appraisal rating the full-text articles based on their relevance ("high", "medium", "low", "none"). Study characteristics (e.g. sample type and size, type of research, grade of evidence) and theoretical contribution (e.g. 'how', 'why, 'in what circumstances') were tabulated on an Excel spreadsheet.

- STEP 3: we developed a list of the retrieved CMOs, linking them to the different studies, to have an operative summary of the main mechanism that seemed likely to have an impact on hematologic studies' enrollments (see appendix 2).
- STEP 4: we developed an interview guide based on the CMOs' list and the suggested guidelines for authors' interviews in realist evaluations; we then contacted the authors of the research that we analyzed to gather additional information on their studies and to compare our findings with the experts' opinion (see appendix 1).

In October 2020, we sent a first email to ask the availability for an interview; in December 2020 -March 2021 we conducted 7 interviews to the researchers involved in palliative care on patients with hematologic malignancies interventions. GM conducted audio-recorded phone interviews with key informants of researcher teams, purposively selected according to the following characteristics: having conducted a palliative care study on hematologic cancer patients published in literature, trials ongoing (referring to trial.gov registration, last research July 2020) or published research protocols. Two experts were also contacted based on their works presented in congresses' abstract. The semi-structured interviews were transcribed verbatim by GM. The authors of the 2 trials ongoing did not answer to our invitation.

Both authors searched the transcripts and the articles for possible context, mechanisms, ad outcomes configurations that could emerge and refine the initial rough theory (see Table 3).

Ethics

This Research project did not include the collection, processing, or analysis of personal or sensitive data of an interested party. Accordingly, the research did not require review or approval by the Ethics Committee. Nevertheless, specific participant protection procedures were adopted: researchers asked participants to agree to participate in the survey and interviews on a voluntary basis by email, and to give their informed consent orally during the audio registered phone call.

Results

Initial rough theory

We developed our IRT through a published systematic review (11) and the testing in our context through a trial (13). We tried to apply some suggested improvements during the enrolment of our research study: some attentions were planned just from the beginning of the study and others were added during the enrolment process (see Table 1 "our intervention").

Enrollment in palliative interventions have its difficulties, but hematology has some specific obstacles, leading to additional difficulties to enrollment and subsequent development of new high-quality knowledge.

Additional features that might negatively impact enrollment *in* PC interventions on patients with hematologic malignancies probably are:

- Difficulty in prognostication by hematologists:
- Disease development: uncertainty in its trajectory (also for the advent of potential lifesaving therapies-as CAR T-cell) and consequently on referring to PC.
- On the other end, patients suitable of a PC intervention were identified between very "end of life" population (life expectancy of days/few weeks)
- Defining target population: Difficulty to understand which hematologic population could benefit most from PC service, based on patients' needs as perceived by hematologists
- Organizational challenges: especially for ambulatory outpatients, it's hard to keep in mind the possibility of enrollment in non-pharmacological protocol through ordinary care. Moreover, sometimes clinicians needed to start the allegedly last line of therapy in a really short time, and palliative care evaluation and randomization was not possible

Theory refinement process

We refined our initial theory through a) literature research for relevant mechanisms and b) interviews to experts in the fields.

TABLE 3 CMOs from the interviews.

Mechanisms	*Verbatim*	Cod	Effects on enrollment +/-	already retrieved in literature research? Y/N
Early access to PC for ALL transplant patients	*.we decided that it would be a good idea to try to see if we can have all of our patients going to transplant the at least evaluated by palliative care.* *I mean, having the patient having met you and having some sort of therapeutic relationship with you, even if in the beginning when you're seeing them, you're focusing on and patients with myeloma on neuropathy and you're focusing on not able to sleep. And then if things change, you're focusing on other things, you're what you're talking about, doesn't it evolves and that's that feels natural to a patient, which I think is good.*	1	+	Y
Use other term than Palliative care	*or we called it supportive care here, not palliative care.* *We change the name for you know, we didn't choose and we don't use palliative care physicians, we use supportive care.* *i miei colleghi ematologi spesso presentano il servizio di cure domiciliari parlando di cure domiciliari, non di cure palliative.*	Cod 1, cod 2 4	+	y
Proposal Pc as a extra layer support	*. The goal is to figure out how you're going to get through this better.* *You know, an extra layer of support. And we are delighted if these patients are cured.*	Cod 2, 3,6	+	y
Systematically propose PC	*Part of that also is seeing supportive care and the cancer center. They see a dietician. They see a social worker. They see a financial counselor. They see supportive care.*	1	+	y
To propose PC for its impact on outcomes	*So the idea is that it could also impact on the outcomes of the, you know, the process to not just be on the comfort of the patient*	1	+	y
Dedicated PC physician	*And here she works solely in our cancer center, basically. And so she doesn't have to go to see heart failure patients or ICU patients. She can focus on cancer care*	1	+	y
Favorable organization	*Our cancer center and our hospital are right beside each other, so it's literally twenty five yards away to get to the inpatient side* *And one other thing is linking the visits with other visits, like getting the palliative care visit on the same day as the oncologist visits.* *una unità di cure palliative all'interno dell'ematologia dove il paziente viene intercettato all'interno dell'ospedale*	1 4	+	y
Pc as symptoms control in first instance	*I think that that's not going to work as well because the patients will never want to do anything more than they have to do.*	1	+	y
Good relationship between PC and hematology teams	*I have a really good relationship with the hematology oncology team, so I'm able to talk to them on a daily basis. I can just walk into their work room and say, Hey, this patient has this issue or this patient is doing really well. I'm really excited about it. So there's a really good working relationship.*	1	+	y
Inclusion criteria included term as "incurable"		2	–	N
Hematologist do not recognize PC needs	*they told me that patients were not in a palliative state for that kind of disease.*		+	y
Developing a research protocol togheter	*And we thought that developing research together might be a great opportunity to develop collaboration and improvement in that with hematological malignancies patients. So we use research in order to improve clinical collaboration*	Cod 2, cod 3	+	y
Identify specific hematology population	*. I think it might highlight the need for them to come up with some specific patients.*	2	+	y

(Continued)

TABLE 3 Continued

Mechanisms	*Verbatim*	Cod	Effects on enrollment +/-	already retrieved in literature research? Y/N
Starting from hematologists needs	*I think it wasn't for symptoms management, it was more like a bed management problem,… even if it's a hematological patients and we can manage and improve the symptoms management as well.* *Blood transfusion* *Antibiotic treatments* *Hemorrhagic events* *These are often elderly patients, with many issues, both social and... physical, and therefore they cannot access the service, they cannot come to the day hospital, and so our colleagues make requests for us... but not because they know what simultaneous palliative care is.* *But also through subcutaneous or intravenous routes, medications can be administered, medications for the disease, and we do that, so it's easier, so to speak, to entrust, how should I put it, entrust it to the group.*	2 4	+	Y
Misconception about PC by hematologist	*And when you try to say, like, you can be in palliative care situation, and still have oncological treatments. This is not something that many of them actually, they don't really integrate … OK, it's great for patients when we don't have any treatment to propose.* *So, I believe it's really a communication issue among peers, meaning that, in the end, a hematologist recognizes someone who is a hematologist. But who also has skills in palliative care... and so even I, I am convinced that we...*	2 4	–	y
Having always a therapeutic line to propose	*And in hematological field, there are improvements. I mean, major improvements may be more than sort of to us. I don't know if that can be. And so I think maybe innovations for oncological treatments might be something which is not helpful for us. Because there always. It's always … moving that line,*	2	–	Y
Don't talk about the prognosis	*the official reason is about the prognosis. They don't talk about the prognosis of the patients.*	2	–	y
Local Reality/ specific local context	*They [oncologists] had participated to our two earlier trials […] Because of that, they were so positive about the idea of early palliative care that the idea that we were going to do a delayed trial was not very positively received […]*	Cod 2, 4	–	
Caregiver opinion	*obviously in research, yeah, the the caregivers opinions are very important. And they should be maybe one point to that might improve enrollment as well.*	6	-/+	y
Using an embedded model	*So in the outpatient clinic, we were embedded in the clinic. And so from a practical standpoint … We would sort of either sequentially see the patient while they were there or sometimes we would go together.*	Cod 3	+	Y
Having similar department (pain clinic) can influence/having drug trial	*we have something kind of difficult for palliative care. I mean, like we have a pain team and palliative care team.* *, they just aren't going to do it, because they're so busy worrying about treating the leukemia, or maybe trying to get the patient onto a drug trial,*	Cod 2 5	–	y
Having strict criteria to defined advanced hematological cancer	*if you looked at the additional materials, you would have seen that we had very specific criteria To describe Advanced, … right and so … yeah. Yeah. And so the hematologic ones there were … chromosomal markers … There were all sort of things.* *Cioè ci sono tanti elementi che uno dovrebbe prendere per poi costruire una sorta di semaforo giallo rosso per dire questo è un paziente da segnalare…* *High risk patient*	3 4 5	- + +	y
Symptomatic patients	*this was a great, great intervention and palliative care is great, but I really didn't need it right then; I needed it later. And so you'll some of the patients told us they preferred not having it. Maybe it was too early for that…. They weren't feeling symptoms. They weren't all the stuff that we were working with them on. You know, as far as decision making and problem solving and all that stuff, those weren't their big issues, right? That they didn't, they didn't have them, but they weren't till later.* *So for these patient it was actually in my mind an easier sell, because they were already overwhelmed. They were already distressed. Some of them are already symptomatic, and so they, they appreciated any extra layer of support they can have*	Cod 3 Cod 4 Cod 6	+	y
Strength collaboration within a research	*which is what we're teaching them in, you know, working with them in palliative care about. And these are skills and education that's going to be helpful to them, whether they are cured or not cured. So there's nothing harmful about what we're doing. So they had to learn* *we had to create that culture first, before going into and doing sort of a study that focus on end-of-life for optimizing end-of-life care*	Cod 2 Cod 3 6	+	y

(Continued)

TABLE 3 Continued

Mechanisms	*Verbatim*	Cod	Effects on enrollment +/-	already retrieved in literature research? Y/N
Previous good collaboration with hema team	*And so before I was starting this trial, we had kind of grown up together and I helped support their, their ability to do bone marrow transplant, clinically trained, all the nurses, all the problematic staff.*	Cod 3 4	+	y
Being an insider/finding a champion in the hematology team	*But these are hematologists who have... created a path, instead of going out, they have created an essentially in-hospital palliative care unit.* *that has been a very essential to the success of this study, is the fact that those of us who are leading them, are part of the leukemia and Transplant teams.*	Cod 4 5	+ +	y
Simultaneus care model	*The fear of a break, of an interruption in the relationship with the institution responsible for the patient, and therefore the "tearing" of care towards an unknown team;*	4	+	y
Sharing *crossroad* visits	*And so we have these meetings, where we call back the hematologist who was in charge, who certainly has more authority in saying, "Look, things have changed."*	4	+	y
Systematically approach all eligible patient	*The research staff were screening from the inpatient roster.*	6 5		y
Not involved the hematology in the proposal	*think that obviously impacts all of these of my studies is how do you present the fact that you may be randomized to usual care, and not to have these clinicians involved, and so …* *is to not rely on the oncologist for referrals.*	6 5	+	
Coaching to a standard research proposal	*a huge part of actually the challenge was training research coordinators across institutions to approach the process of describing the study, describing what palliative care is in a consistent fashion* *to have prepared a sort of a script and to train the research coordinators or any research staff about how to talk to the patient, About palliative care.*	6 5	+	y
Stress to participate for altruistic reason	*and honestly most patients sign up for my studies for altruistic reasons*	6	+	y
Not been PC an extra cost	*f these studies that the cost of healthcare is part of their inpatient Hospital stay, and so they were not receiving extra personal cost of them,*	6	+	y
Not been perceived as a survey	*he concern about being in usual care, the concerns about "I don't wanna fill out surveys"*	6	+	y
Avoiding use jargon for randomization		5	+	y
Training in giving difficult communication for research staff	*We have actually had in-person training sessions for the research staff. So you practice that in in a pretend way as part of the training for becoming a coordinator on this on these trials.*	5	+	y

We are presenting our results based both on their source of retrieval ("CMOs literature research" and "CMOs in interviews"), and as our "refined theory", a possible global theorization of how the different CMOs might be theoretically related.

CMO in literature research

In our literature research, we selected some relevant mechanisms that might have an impact on the enrollment process. We hypothesize that if hematologists do not refer to PC at the same time, they don't enroll in a palliative care trial.

So, for the aim of this project we wrote 2 tables (see appendix 2):

CMO on patterns on referral to PC by hematologists

CMO on specific patterns on PC research for hematologic cancer patients

Palliative care referral for hematologic cancer patients

This group of CMOs focuses on the difficulties of referring to PC by hematologists and the mechanisms which have an impact on it.

Some of these M regard the *model of integration* between hematology and PC and other *organizational difficulties*: strict criteria to access to hospice, for example, lack of space and time to discuss about PC, hospital culture focused on curing, being in different department and not having access 24/24 hours to PC service, could reduce referral to PC. A linear (from beginning to end) model more than a sequential one (PC only when hematologic care is concluded) could improve PC referral as having clear leadership on patients between the 2 staffs. Poor communication between staffs is detrimental even for PC referral.

Relation between hematologist and pc professionals with reciprocal acknowledgment could improve PC referral, not seeing referring to PC as a failure or a deskilling. Perceived self-efficacy by hematologists and misconceptions about palliative care could reduce referral to PC service. The term PC itself could be avoided. *Patient's conditions* as asymptomatic patients or patients with unrealistic expectations could reduce the integration between the 2 staffs. Hematologic patients could have specific needs not addressed by PC and unexpected disease trajectory makes difficult to recognize PC needs. *Hematologists difficulties* to propose a consultant inside a long-time relationship with patient, late end of life discussions and unrealistic expectations from active treatments could reduce PC referral by hematologists.

Palliative care research for hematologic cancer patients

In this group we analyzed mechanisms suggested from the scarce literature on enrolment in PC for hematologic cancer patients (7, 18, 35–37). The mechanisms underlying the low enrollment seem to be quite similar to the well-known mechanisms in PC in general (8, 9, 38–42, 52, 53), with some more specificity regarding this subgroup as the difficulty to define a clear prognosis. Identifying patients with highest supportive needs may improve feasibility and acceptability of future primary palliative care in hematologic malignancy trials. Moreover, lack of patient interest in the topic of palliative care research also potentially affected the feasibility.

CMOs in interviews

The interviews with expert partially agreed with the results from the literature, but they also contributed to add some significant insight into our research question (see Table 3 "interviews' mechanisms" and Table 4 "interviewers characteristics"). Experts' interviews suggested that the initial identified population should be rich in symptoms burden to start building a collaboration with hematologists.

Consequently, in a second time, end-of-life patients could be co-managed between the two staffs, with a simultaneous approach. Moreover, being part of the hematologic team or being perceived like an insider seem to be the winning element in the RCTs realized until now.

Finally, trials with inpatients -as transplanted patients, for example - could be easier to conduct, due to the high symptoms burden and the access facility to the ward.

On the other hand, failure experience collected from the interviewed experts are described as linked to the population target definition as "incurable", a criterion hard to recognize for hematologists.

Moreover, the hematologist point of view on Palliative Care is essential for both refer to PC and propose a PC trial.

Refined theory

An important finding of this review was that 'success features' did not seem to be intrinsic to any specific single study design or type of research, but the result of many different interactions between different contexts and mechanisms. "Social exchange theory" by Homans was used by Salins to explain the possible problems in referral in palliative care (47), including hematology. We selected this theory as flexible and useful enough to be used to explain the problems in enrollment in PC studies in hematologic patients too. According to this interpretation, referral is a social interaction, and depends on the perception of social actors of this interaction as capable of providing a sort of reward and avoid a cost. As represented in Figure 2, it's plausible that every actor involved can create attrition in the enrollment process. But as stated both in the reviewed literature and in the experts 'opinions, it's possible to design a study or a clinical environment to create a perception of a more favorable reward/costs relation for all the actors involved: this might be seen as the "intermediate mechanism", on which different kind of interventions might have an impact.

It's possible to intervene on the perception of patients and caregivers, where the "double awareness" (26) of potentially fatal development of the disease and at the same time potentially life-

TABLE 4 Interviewee characteristics.

Code	Study type	setting	In/outpatient	Personal experience
Cod 1	Retrospective review	Hospital	In/out	+
Cod 2	Pilot study	Hospital	In	–
Cod 3	RCT	Hospital	In/out	+
Cod 4	Observational	Home care/ambulatory	out	+
Cod 5	RCT	Hospital	In/out	+
Cod 6	RCT	Hospital	In/out	+
Cod 7	Pilot study	Hospital	In/out	–

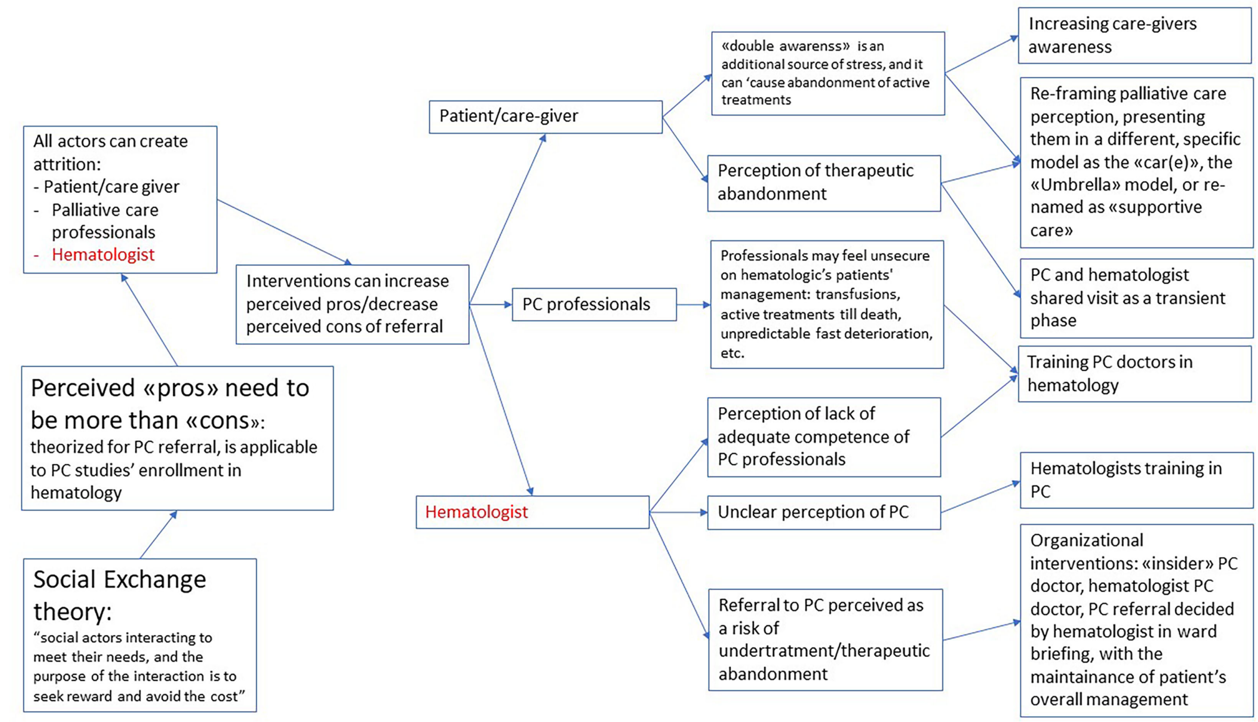

FIGURE 2
Refined theory: what works, for whom and in which circumstaces, when enrolling hematologic cancer patients in palliative care?

prolonging intervention creates a high stress. For instance, reframing their perception of palliative care through the use of a different term (as "supportive care") (27) or the explanation of a different framework for palliative care for patients with hematologic malignancies as the "CAR(E)" or "Umbrella" model (43), or even with an explicit decision to create a higher involvement of the care giver in partial substitution of the patient.

It's also possible to increase the self-efficacy of palliative care doctors, through specific hematologic training, considering the specific differences of this patients' population.

But it's highly likely that the more relevant actor in the process might be the hematologist. Many possible interventions might lead to a better perception of the advantages of PC referral.

An unclear perception of referral as a possible source of undertreatment might be addressed with organizational adjustments, as having a PC hematologist, or a palliative care consultation that is discussed in the ward meeting and keeps the patient under the hematologic management.

As a consequence, (see Figure 3) the perception of the different actors might be the key element to lead to an intervention modulated on the characteristics of the specific environment in which the study might be developed, in particular the perception of hematologists. A stronger, already existing relationship between the two teams might imply the chance of working on highly complex needs. On the other end, a new relationship might require an easier task to start, as addressing highly symptomatic patients (ig, patients undergoing transplantation).

Discussion

This synthesis from literature and experts 'opinions allows us to deepen the topic of enrolment in PC trial in hematologic cancer patients.

As highlighted by our results, the problem of enrolling hematological patients in palliative care trials overlaps with dynamics inherent in the referral to PC services by hematologists, in general.

We defined our general refined theory as a "ecological theory of enrollment in palliative care research on patients with hematologic malignancies".

As a refinement to our initial list of CMOs impacting the enrollment process, we selected the "social exchange theory" (SET) of Salins (47) as a relevant model for our theoretical construction. In his SET, he theorizes that oncologists need to have a clear perception of the advantages that they might get from the referral to palliative care, and that these advantages need to outbalance the costs.

This model is useful to explain the difficulty of enrollment in palliative care intervention in hematologic patients too and could be integrated with other theoretical aspects specific for this field. We face in hematologic patients the specific difficulty of "double awareness" (as theorized by Gerlach (26)) that puts the patients and the caregivers on a specific tension due to the double possibility of having a rapid deterioration of health conditions to death or getting to a disease-free period of time thanks to the medicines.

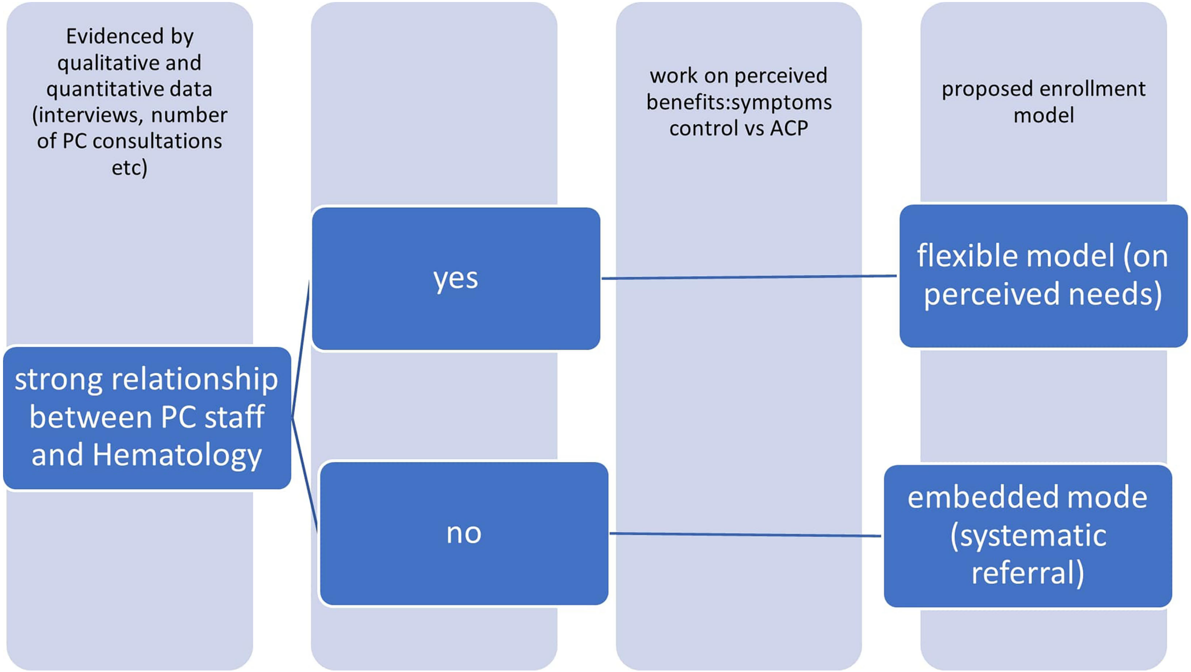

FIGURE 3
Teams' relationship and enrollment.

Applying the SET model to hematology intervention, we might see how this aspect of "double awareness" needs to be managed both by health professionals and patients and caregivers. Health professionals will then be assessing their pros and cons of referral, knowing that the costs of the referral might result in less awareness of curing possibilities and less focus on available treatments.

Another relevant CMO that we added to our initial theory, is that palliative care needs the PC professionals to be really flexible, to increase referral to PC of patients with hematologic malignancies, searching for the most suitable model for their environment. While we listed several aspects that could have an impact and need to be addressed while designing the intervention, if we start from the SET theory, it seems safe to theorize that every intervention should start from the assessment of the perception of the hematologists of the possible advantages and disadvantages of the referral to palliative care. A first distinction should be between interventions that are built on a strong relationship between PC staff and hematologists, and interventions that are developed independently from an already relationship between the teams. Often, these interventions might implicitly be designed to build a better relationship by the leaders of the program.

Quantitative elements could be informative on the level of integration; while qualitative data could help selecting the elements that could be addressed by an intervention aimed at reaching a more cooperative environment.

The successful experiences reported of enrollment of hematologic patients in palliative care were all based on a previous positive experience of cooperation between the two teams (7, 18). It might be unlikely that the enrollment process could be successful in a context where the intervention itself aims at obtaining a better interaction between the two teams.

Some interventions are possible and seem more likely to work, and all of them might be interpreted as an effort to increase the pros/cons ratio and the perception of the palliative care contribution in the hematologists.

Mere technical improvements (such as a remembering email or a phone call from the researcher) as well as simply hypothesizing a different study design (42) seem to not be able to solve the question and might lead to miss the more relevant points.

The contamination of knowledge with a Palliative care/hematology model that is not only integrated but embedded (44) would respond both to organizational problems and to those related to misconceptions on PC; both expert interviews and data from literature confirm this suggestion.

The health care professionals gate keeping-where the professionals don't recognize PC needs- was recognized as a barrier to PC enrolment by the literature (42) and seems to be logically applicable in the hematologic setting too. An integrative model "fluctuant, flexible and based on patients' needs", where these needs are detected by hematologists has been suggested as a possible model of optimal integration (3). But it might be beneficial to consider the possibility of an even more embedded model, where PC is almost "forced" in hematology ward's daily work. It could minimize the burden of the intervention both for patients and clinical staff and overcome the difficulties by hematologist to recognize PC needs especially in asymptomatic patients. Moreover, having a PC physician/nurse as a member of the hematologic team could lead to perceive palliative care as a routine component of the patient care.

According to this, an additional mechanism that might be beneficial in terms of integration is the training of hematological professionals in palliative care and in understanding deeply the palliative care approach, while training palliative care practitioners as well to the specificities of the hematological patient, as suggested by many authors (26, 28–30, 45).

Our experts' interviews also suggested that enrolling only symptomatic patients could be a more initial intervention; however, an early approach also for asymptomatic patients could change the culture/improve the acceptance between palliative care professionals and hematologist. The referral not only for physical needs but also social, psychological, ethical and spiritual ones, should be learnt and improved (26, 46).

Unpredictable course of hematologic malignancies could negatively impact the enrollment.

Using objective and systematic criteria for enrollment (as conducing a first assessment on the list of transplants, or having an automatic flagging and reporting of patients with bad prognosis criteria) would avoid this lack. Artificial intelligence has had a growing improvement for this kind of problems (54).

Limitations

The overall quality of a review is strongly influenced by the quality of the primary studies considered. The difficulty in gathering firsthand data on palliative care patients is the very reason why this approach might be interesting, as we tried to produce a theoretical contribution based on what is known, what is guessable and what is not known to help navigate this difficult field.

A realist review is an evidence-informed review, who is only partially evidence based, as part of the effort in this specific type of review is trying to produce a theoretical contribution from the available data. We attempted to suggest possible solutions and useful links between what is perceived as connected in this field, trying to start from making explicit what is "obvious" for the researchers in the field but not so obvious for the readers.

This approach limits the exact generalizability of our suggestions, but encourages researchers to try and confirm or challenge our hypothesis, as expected by realist methodologies.

Conclusions

The referral to PC- as the enrollment in a PC trial - should be tailored on patients' needs and recognizing these palliative care needs is not simple for Hematologists.

To recognize the relationship between PC staff and Hematology is mandatory to propose the right approach, an integration flexible model or on an embedded model.

Consequently, we suggest that expected outcomes should be different, based on a preliminary evaluation of the context of the intervention: while an intervention based on a new relationship might have as a starting stage the aim to address complex symptoms control, and might also explicitly be part of a wider intervention that might result in building stronger relationships between the different stakeholders. On the other side, when a strong, previous relationship between the staffs is already present, it might increase the chance to address more complex topics as advance care planning.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements.

Author contributions

Both authors contributed to all parts of the manuscripts. In particular, ST worked more on background and discussion and GM worked more on "methods" and results. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.991791/full#supplementary-material

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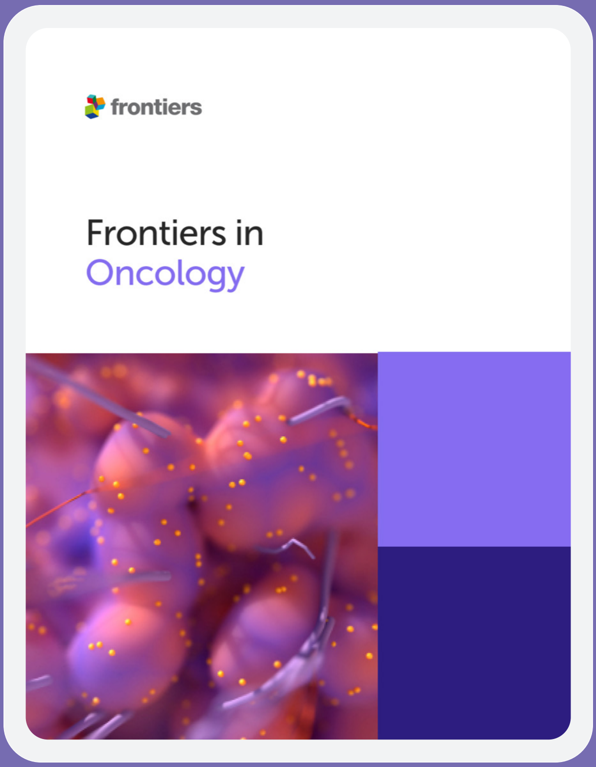

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