Impact of Palliative Care in Evaluating and Relieving Symptoms in Patients with Advanced Cancer. The DEMETRA Study

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Abstract

Background: Cancer patients experience a number of symptoms throughout the course of the disease. We aimed to provide a comprehensive analysis of the symptom burden in patients with advanced cancer at admission to specialist palliative care (PC) services and seven days later, to estimate the immediate impact of PC intervention.

Patient and methods: The analysis was based on an observational, prospective, multicenter study (named DEMETRA) conducted in Italy to outline the profile of patients, families and PC services in different care settings (hospital, hospice and home care). The prevalence and intensity of symptoms were assessed using three tools, including the Edmonton Symptom Assessment System (ESAS).

Results: Five PC centers recruited 865 cancer patients. Thirty-three different symptoms were observed at baseline, the most frequent being asthenia (85%) and lack of appetite (71%). Two-thirds of patients experienced six to twelve simultaneous symptoms. The intensity of the most frequent symptoms according to ESAS varied from 5.5 for asthenia to 3.9 for nausea. The presence and intensity of physical symptoms increased with increasing levels of anxiety and depression. After seven days, prevalence decreased significantly only for nausea and breathlessness, while intensity diminished significantly for almost all symptoms. At admission we noted a correlation between patients' symptoms and the care setting. After one week, the symptom intensity was uniformly reduced in all settings.

Conclusions: The study confirmed the considerable symptom burden of patients with advanced cancer. PC intervention significantly lessened the severity of symptoms, despite the patients' advanced disease and short survival.

Introduction

Palliative care (PC) is mainly addressed to the evaluation and treatment of physical, functional, psychological, social, and spiritual symptoms throughout the course of chronic and progressive diseases, especially in the advanced and terminal phases [1, 2], with the aim of improving, or at least preserving, patients' quality of life.

Most evidence in recent decades has been related to the treatment of symptoms in cancer patients, at any stage of the disease and of whatever causal origin. In fact, symptoms may derive from the primary disease or its secondary localizations, but also from cancer therapies and even from treatments aimed to control comorbidities or other symptoms such as pain [3–9]. Nausea and vomiting, for instance, may be due to the localization of the tumor, to impaired gastric emptying or delayed gastrointestinal transit, to antineoplastic agents or radiation therapy, or to opioids given to relieve pain [10, 11]. In the patient's evaluation the distinction of the symptom's causal factors may be irrelevant, but for the physician understanding the pathogenetic mechanisms is fundamental to setting up specific therapies according to the cause. Moreover, the prevalence and severity of symptoms vary across the phases of illness [12]. Pain, nausea and depression have been reported to be relatively stable over the last six months of life,

while dyspnea, drowsiness, poor well-being, lack of appetite and asthenia tend to increase in severity over time. In particular, the patient's symptom burden changes during the last days of life, when PC becomes the specific and often only therapeutic approach [13]. The management of this clinical picture – with some symptoms tending to disappear and others taking their place – is a central and crucial issue in controlling patients' suffering.

In previous studies, only selected aspects of these symptoms were considered. We therefore carried out this analysis with the objective of providing a comprehensive evaluation of the symptom burden in patients with advanced cancer from the moment of admission to a PC service. We estimated the prevalence and intensity of symptoms, the number of symptoms experienced simultaneously, their prevalence based on the primary tumor site, and the way in which the presence and severity of anxiety and depression could modify the physical symptoms. We reassessed symptom prevalence and intensity after seven days to estimate the immediate impact of PC, paying attention also to the influence of the care setting on the clinical expression of symptoms.

Methods

Study design

The data of this analysis derive from an observational, prospective, multicenter study (named DEMETRA) aimed at outlining the profile of patients, families, care services and clinical features from the moment of admission to PC centers. The general presentation of DEMETRA has been published elsewhere [14]. Given the considerable extension of the information collected and the results achieved, the Scientific Committee decided to divide its contents into separate publications, each deepening a specific theme.

Five Italian PC units based in Florence, Forlì, Lecco, Palermo and Rome participated in the study, which comprised a total of 1013 individuals suffering from various advanced chronic diseases. Most were cancer patients (85%), treated in three different care settings: home, hospice and hospital. The analysis of symptoms reported here concerns only cancer patients, given the high prevalence of cancer among the population studied and the specificity of the clinical conditions and symptoms associated with cancer compared to other advanced diseases.

The inclusion criteria for the DEMETRA study were age ≥ 18 years; presence of a chronic and progressive illness requiring palliative intervention; and written informed consent for study participation and personal data processing. Patients who were already in the care of a PC network and those who could not ensure regular follow-up were excluded.

Eligible patients were recruited over a six-month period (May to November 2017). Each patient was followed up for 12 months, until November 2018.

Data collection

Among the patient information collected in the DEMETRA study were sociodemographic data, primary tumor site, presence and sites of metastasis, number of concomitant diseases, care setting (hospice, home care or hospital) and symptoms [14]. Data were collected at the baseline visit (day 0) and after seven days (day 7), to assess the first impact of palliative treatments.

Symptoms were assessed using three tools: 1) the interRAI-PC, an instrument evaluating a wide range of PC issues, including items related to symptoms [15]; 2) a supplementary list of items to detect symptoms and clinical aspects not covered by the interRAI-PC including rattle, dysphagia, dysgeusia, neuropathic pain, bowel occlusion, liver and kidney functional impairment, paresis, motor disorders, spinal cord compression, pleural effusion and intracranial hypertension; 3) the Edmonton Symptom Assessment System (ESAS), which estimates the prevalence of nine main symptoms (pain, asthenia, nausea, depression, anxiety, drowsiness, breathlessness, poor well-being, lack of appetite) and their intensity, measured with a numeric rating scale from 0 to 10 [16, 17].

Statistical analysis

Categorical variables were described by absolute and relatives frequencies, while continuous variables were summarized using mean values with the corresponding standard deviation (SD). The differences in the prevalence of symptoms across levels of anxiety and depression were evaluated using Pearson's chi-squared test, while the Kruskal-Wallis rank-sum test was used to evaluate differences in mean symptom intensity between different levels of anxiety and depression. McNemar's chi-squared test was used to evaluate differences in the prevalence of symptoms between days 0 and 7. To compare symptom intensity at day 0 and day 7, we applied the paired-samples Wilcoxon test. All data were analyzed using the R software package (version 3.6.1/2019).

Results

The flowchart of patients evaluated in the present study is shown in Fig. 1. From a total of 1013 patients, we selected 865 cancer patients. Of these, 780 answered the ESAS questionnaire and were considered for the intensity of symptoms at baseline, while 508 (65%) were also evaluated at day 7.

The baseline characteristics of patients are summarized in Table 1. Fifty-two percent were women and the mean age was 74 years. Fifty-five percent of patients were assisted at home. The most frequent primary tumor sites were the digestive system, lung, urinary and reproductive system. About 80% of patients had metastases, the most frequent sites being liver, lung and bone.

Table 1
Demographic and clinical characteristics of the 865 study patients at baseline.

Characteristics	Patients N (%)
Female	447 (51.7)
Age (years), mean (SD)	74.2 (12.8)
Palliative care centers	
Florence	80 (9.3)
Forlì	160 (18.5)
Lecco	211 (24.4)
Palermo	296 (34.2)
Rome	118 (13.6)
Palliative care setting	
Home	473 (54.7)
Hospital	191 (22.1)
Hospice	201 (23.2)
Primary tumor site	
Lung	181 (20.9)
Digestive system	248 (28.7)
Urinary/reproductive system	167 (19.3)
Head/neck	29 (3.4)
Breast	51 (5.9)
Other	189 (21.9)
Patients with metastasis	683 (79.1)
Site of metastasis	
Liver	298 (43.6)
Lung	277 (40.6)
Bone	227 (33.4)

SD, standard deviation.

Characteristics	Patients N (%)
Brain	96 (14.1)
Other sites	442 (51.1)
Patients with concomitant diseases	486 (56.2)
SD, standard deviation.	

Table 2 lists the 33 symptoms observed at baseline in decreasing order of prevalence. The most frequent symptoms were asthenia, poor well-being, lack of appetite, drowsiness, pain, depression, constipation, anxiety, breathlessness and insomnia. More than half of patients had six to twelve simultaneous symptoms and one-tenth had 15 or more symptoms (**Supplementary Table 1**). The most frequent combinations of concomitant symptoms at baseline are shown in **Supplementary Table 2**. These combinations often included asthenia, lack of appetite, drowsiness and poor well-being, all of which were present in 46% of patients, while three of these symptoms, variously combined, occurred in over half of patients. **Supplementary Table 3** shows the prevalence of the main symptoms observed at baseline according to the primary tumor site. Breathlessness was mainly frequent in lung cancer, pain in pancreatic cancer, anxiety and drowsiness in breast cancer, and lack of appetite in colorectal cancer.

Table 2
Prevalence of symptoms in decreasing in order of frequency among 865 patients at baseline.

Symptoms	Patients	
	N	%
Asthenia	734	84.9
Poor well-being	614	71.0
Lack of appetite	610	70.5
Drowsiness	543	62.8
Pain	523	60.5
Depression	482	55.7
Constipation	465	53.8
Anxiety	456	52.7
Breathlessness	423	43.5
Insomnia/disturbed sleep	357	41.3
Nausea	348	40.2
Dysgeusia	294	34.0
Dysphagia	277	32.0
Edema	258	29.8
Dry mouth	257	29.7
Bloating/flatulence	188	21.7
Vomiting	176	20.4
Recent falls	160	18.5
Gastroesophageal reflux	151	17.5
Dry cough	137	15.8
Fever	117	13.5
Dizziness/vertigo	80	9.3
Jaundice	80	9.3
Hemorrhage/bleeding	78	9.0
Diarrhea	74	8.6

Symptoms	Patients	
	N	%
Profuse sweating	67	7.8
Hallucinations	55	6.4
Hiccups	40	4.6
Fecalomas	36	4.2
Muscle cramps	36	4.2
Death rattle	31	3.6
Seizures	27	3.1
Myoclonus	14	1.6

Nine of the 10 most frequent symptoms were included in the ESAS questionnaire. This allowed us to measure the intensity of these symptoms in the whole population and in symptomatic patients, as shown in Table 3. In the first group, the intensity ranged from 5.2 (asthenia) to 1.7 (nausea); in the second, from 5.5 (asthenia) to 3.9 (nausea). The prevalence and intensity of the four main physical symptoms (pain, breathlessness, nausea and asthenia) significantly increased with increasing levels of anxiety and depression (**Supplementary Table 4**).

Table 3
Intensity of most frequent symptoms in 780 patients at baseline.

Symptoms	All patients	Symptomatic patients	
	Mean intensity (SD)	N	Mean intensity (SD)
Asthenia	5.17 (2.53)	734	5.50 (2.25)
Poor well-being	3.98 (2.90)	614	5.05 (2.30)
Lack of appetite	3.93 (3.01)	610	5.03 (2.47)
Drowsiness	3.10 (2.85)	543	4.45 (2.37)
Pain	3.03 (2.78)	523	4.51 (2.19)
Depression	2.68 (2.87)	482	4.33 (2.48)
Anxiety	2.41 (2.70)	456	4.12 (2.33)
Breathlessness	2.10 (2.79)	423	3.43 (3.03)
Nausea	1.75 (2.49)	348	3.91 (2.33)
SD, standard deviation.			

In Table 4, the prevalence and intensity of symptoms are compared in patients evaluable at both visits, on day 0 and day 7. After one week there was a significant decrease in the prevalence of breathlessness and nausea only, but the intensity decreased significantly for all symptoms except anxiety, depression and drowsiness. Among patients with severe symptom intensity at baseline (score ≥ 6) we observed a reduction in intensity for all symptoms (**Supplementary Table 5**).

Table 4
Changes in prevalence and intensity of main symptoms from day 0 to day 7 in 508 patients.

Symptoms	N patients (%)		p value[a]	Intensity, mean (SD)			p value[a]
	Day 0	Day 7		Day 0	Day 7	Difference (Day 7 – Day 0)	
Asthenia	472 (92.9)	474 (93.3)	NS	4.89 (2.59)	4.47 (2.52)	-0.42 (2.37)	< 0.001
Poor well-being	396 (78.0)	399 (78.5)	NS	3.81 (2.85)	3.4 (2.70)	-0.35 (2.38)	< 0.001
Lack of appetite	374 (73.6)	362 (71.3)	NS	3.61 (3.03)	3.19 (2.93)	-0.43 (2.63)	< 0.001
Drowsiness	357 (70.3)	351 (69.1)	NS	3.00 (2.74)	2.77 (2.60)	-0.23 (2.48)	NS
Pain	343 (67.5)	319 (62.8)	NS	2.96 (2.66)	2.19 (2.27)	-0.76 (2.15)	< 0.001
Depression	304 (59.8)	319 (62.8)	NS	2.58 (2.85)	2.60 (2.74)	0.02 (2.33)	NS
Anxiety	290 (57.1)	301 (59.3)	NS	2.27 (2.63)	2.27 (2.57)	0.01 (2.34)	NS
Breathlessness	233 (45.9)	192 (37.8)	< 0.05	1.92 (2.69)	1.56 (2.49)	-0.36 (1.72)	< 0.001
Nausea	255 (50.2)	192 (37.8)	< 0.05	1.61 (2.35)	1.28 (2.12)	-0.33 (1.87)	< 0.001

NS, not statistically significant.

[a]p value for difference between day 7 and day 0.

After one week, breathlessness was significantly reduced in patients treated at home, while nausea was significantly reduced in those treated at home or in hospice (**Supplementary Table 6**). Anxiety and depression significantly increased in those treated at home and in hospital, respectively. Pain significantly decreased in all care settings; anxiety only in patients treated in hospital; breathlessness, poor well-being, lack of appetite, nausea and asthenia in those treated at home; and lack of appetite, nausea and asthenia in those in hospital (Table 5).

Table 5.
Changes in intensity of main symptoms between day 0 and day 7 according to setting of care in 508 patients overall and in those symptomatic at baseline.

Symptoms	Setting	All patients			Symptomatic patients		
		Intensity, mean (SD)			Intensity, mean (SD)		
		Day 0	Day 7	p value[a]	Day 0	Day 7	p value[a]
Asthenia	Home	4.81 (2.59)	4.57 (2.48)	<0.05	5.15 (2.34)	4.80 (2.34)	<0.01
	Hospice	5.12 (2.52)	4.16 (2.45)	<0.01	5.54 (2.12)	4.33 (2.40)	<0.001
	Hospital	5.00 (2.74)	4.25 (2.98)	NS	5.64 (2.18)	4.08 (2.85)	<0.01
	p value[b]	NS	NS		NS	NS	
Poor well-being	Home	3.99 (2.79)	3.70 (2.70)	<0.01	4.92 (2.24)	4.35 (2.46)	<0.001
	Hospice	3.28 (3.01)	2.84 (2.68)	NS	4.79 (2.44)	3.37 (2.68)	<0.001
	Hospital	3.34 (2.88)	2.66 (2.45)	NS	4.74 (2.25)	2.90 (2.45)	<0.001
	p value[b]	<0.05	<0.01		NS	<0.001	
Lack of appetite	Home	3.65 (3.00)	3.30 (2.86)	<0.01	4.85 (2.47)	4.06 (2.70)	<0.001
	Hospice	3.99 (3.27)	3.10 (3.19)	<0.01	5.40 (2.61)	3.68 (3.09)	<0.001
	Hospital	2.50 (2.51)	2.45 (2.86)	NS	4.23 (1.80)	3.31 (2.75)	NS
	p value[b]	<0.05	NS		NS	NS	
Drowsiness	Home	2.98 (2.68)	2.80 (2.55)	NS	4.20 (2.23)	3.57 (2.43)	<0.001
	Hospice	3.00 (2.89)	2.90 (2.74)	NS	4.31 (2.51)	3.69 (2.56)	NS
	Hospital	3.09 (2.96)	2.25 (2.71)	NS	4.69 (2.39)	2.55 (2.85)	<0.01
	p value[b]	NS	NS		NS	NS	
Pain	Home	3.14 (2.63)	2.45 (2.29)	<0.001	4.38 (2.06)	3.15 (2.17)	<0.001

	Hospice	2.08 (2.59)	1.42 (2.04)	<0.01	4.24 (2.11)	2.64 (2.29)	<0.001
	Hospital	3.20 (2.74)	1.66 (2.07)	<0.001	4.55 (2.11)	2.06 (2.22)	<0.001
	p value[b]	<0.001	<0.001		NS	<0.01	
Depression	Home	2.55 (2.82)	2.63 (2.78)	NS	4.24 (2.45)	3.88 (2.60)	<0.05
	Hospice	3.32 (3.00)	2.89 (2.70)	NS	4.55 (2.60)	3.61 (2.64)	<0.05
	Hospital	1.25 (2.25)	1.73 (2.42)	NS	4.23 (2.13)	3.15 (2.54)	NS
	p value[b]	<0.001	<0.05		NS	NS	
Anxiety	Home	2.22 (2.61)	2.43 (2.65)	NS	3.95 (2.30)	3.55 (2.50)	<0.05
	Hospice	2.47 (2.80)	2.04 (2.53)	NS	4.05 (2.53)	2.71 (2.74)	<0.001
	Hospital	2.32 (2.52)	1.34 (1.57)	<0.05	4.08 (1.98)	1.64 (1.66)	<0.001
	p value[b]	NS	<0.05		NS	<0.001	
Breathlessness	Home	1.97 (2.65)	1.64 (2.50)	<0.001	4.02 (2.48)	3.15 (2.72)	<0.001
	Hospice	1.75 (2.69)	1.38 (2.51)	NS	4.47 (2.51)	3.25 (3.17)	<0.05
	Hospital	1.86 (3.01)	1.23 (2.41)	NS	5.47 (2.59)	2.87 (3.42)	<0.05
	p value[b]	NS	NS		NS	NS	
Nausea	Home	1.86 (2.45)	1.59 (2.28)	<0.01	3.70 (2.26)	2.82 (2.46)	<0.001
	Hospice	1.05 (2.02)	0.51 (1.43)	<0.001	3.23 (2.36)	1.17 (1.84)	<0.001
	Hospital	0.66 (1.67)	0.32 (0.83)	NS	3.62 (2.20)	0.62 (1.41)	<0.05
	p value[b]	<0.001	<0.001		NS	NS	

NS, not statistically significant; SD, standard deviation.

[a]p value for difference between day 7 and day 0; [b]p value for difference between care settings.

Discussion

This study evaluated the symptom burden in a cancer patient population during the last days of life, at the time of admission to specialist PC. The decision to appraise only cancer patients was prompted by the need for a clinically homogeneous population but also by the high proportion of cancer patients among those included in the DEMETRA study. In addition, cancer patients' average life expectancy is generally short at the time of admission to PC. The median survival in our population was 29 days, and only about 65% of patients were evaluable after the first seven days. Due to the advanced phase of disease, PC health professionals had little time to reach therapeutic goals, which were mainly to alleviate symptoms. We sought to evaluate whether and how the symptom profile of patients could be changed in a few days as a result of PC intervention.

We observed the presence of many symptoms at the time of PC admission. Asthenia was the most frequent, followed by poor well-being, lack of appetite, drowsiness, pain, depression, constipation, anxiety, breathlessness and sleep disorders, which were present in 40–70% of patients. The large number of symptoms is characteristic of the advanced stage of cancer, as previously documented [18].

Furthermore, patients experienced a large number of symptoms simultaneously, as also previously observed [9, 19]. This is an important and underestimated clinical problem. For patients the multitude of symptoms is very distressing, while for physicians treating all the symptoms is complex due to the number of drugs needed, their potential toxicity, and the risk of drug-to-drug interactions. This makes it necessary to decide which symptoms should be primarily treated, with which drugs, and what results are expected, important aspects that open a window on future insights. In our study, frequent combinations of simultaneous symptoms nearly always included asthenia, lack of appetite, drowsiness and poor well-being, consistent with the findings of others [20, 21]. Such combinations entail a negative physical and psychological condition, with lack of energy and interests and detachment from life.

The prevalence of symptoms at baseline differed according to the site of the primary tumor, as also reported elsewhere [22, 23]. The association between specific tumor sites and cancer symptoms is clear, even at advanced stages of the disease when widespread metastasis can dilute this specificity. Instead, some symptoms, such as pain and asthenia, tend to occur in all tumors.

The intensity of symptoms ranged from 5.2 for asthenia to 1.7 for nausea in the overall population, and from 5.5 for asthenia to 3.9 for nausea in symptomatic patients, showing analogies to earlier observations [24, 25]. Interestingly, the prevalence and intensity of physical symptoms such as pain, breathlessness, nausea and asthenia correlated with the presence and severity of anxiety and depression, reflecting the integration between physical and mental suffering.

We also evaluated whether and to what extent PC treatments could change the symptom profile of patients after one week. A week is a short period of time, but not for patients with terminal cancer. Their life expectancy is very limited, and as a consequence every therapeutic intervention must be immediately effective. The results obtained in one week are therefore an important measure of the clinical impact of

PC. In our study, the prevalence of symptoms between day 0 and 7 was unchanged except for breathlessness and nausea, which tended to decrease significantly. Considering that the clinical situation quickly worsens in advanced cancer, even the containment of a few symptoms should be seen as positive. Conversely, symptom intensity was significantly reduced after one week of treatment, with the exception of depression, anxiety and drowsiness. This was an important clinical result, indicating the relief of suffering at such a highly critical time.

Finally, changes in the prevalence and intensity of symptoms between day 0 and 7 were evaluated in the three settings of care: home, hospice and hospital. Some symptoms had a different initial prevalence depending on the setting. Poor well-being, pain and nausea were more frequent in patients at home, while lack of appetite and depression prevailed in hospice patients. After one week, the reduction of intensity was almost uniform for all symptoms, with negligible differences related to the setting of care.

The main strength of this study is that it provides a comprehensive analysis of various aspects of the symptoms experienced by cancer patients in the final period of life. Its main limitation is the impossibility of describing the treatments given for such symptoms and the subsequent clinical results, because the DEMETRA study protocol did not include the collection of these data.

Conclusions

The primary aim of this study was to define the clinical symptom profile of 865 patients with advanced cancer from the moment they accessed PC services. The study confirmed that the number and severity of symptoms in these patients was substantial. Multiple symptoms were present and many were perceived as severe. Our results make it clear that PC intervention can significantly lessen the severity of symptoms, even at the advanced stages of cancer. This further confirms the need for these patients to receive competent PC. In our opinion, such competence concerns not only PC specialists but also oncologists, general practitioners and any other physicians dealing with patients at an advanced stage of disease.

Declarations

Ethics approval and consent to participate:

The DEMETRA study was approved by the ASST Lecco Ethics Committee on 1st December 2016 and subsequently by the institutional review boards of each participating center. Written informed consent for participation in the study and processing of personal data was collected from all recruited patients before any study-related activities were carried out.

Consent for publication:

not applicable

Availability of data and materials:

The datasets generated during and/or analysed during the current study are not publicly available because the data are owned by the socio-health agency that participated in the study but specific demend are available from the corresponding author on reasonable request.

Competing interests:

The authors declare no conflict of interest.

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Author contributions:

Conceptualization, O.C, G.S.; formal analysis, G.P; methodology, O.C., C.B; Investigation, L.R, supervision, G.S.; writing—original draft, O.C., G.P, C.B.; writing—review & editing, O.C, G.P, C.B, L.R, M.C, G.S.

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Figures

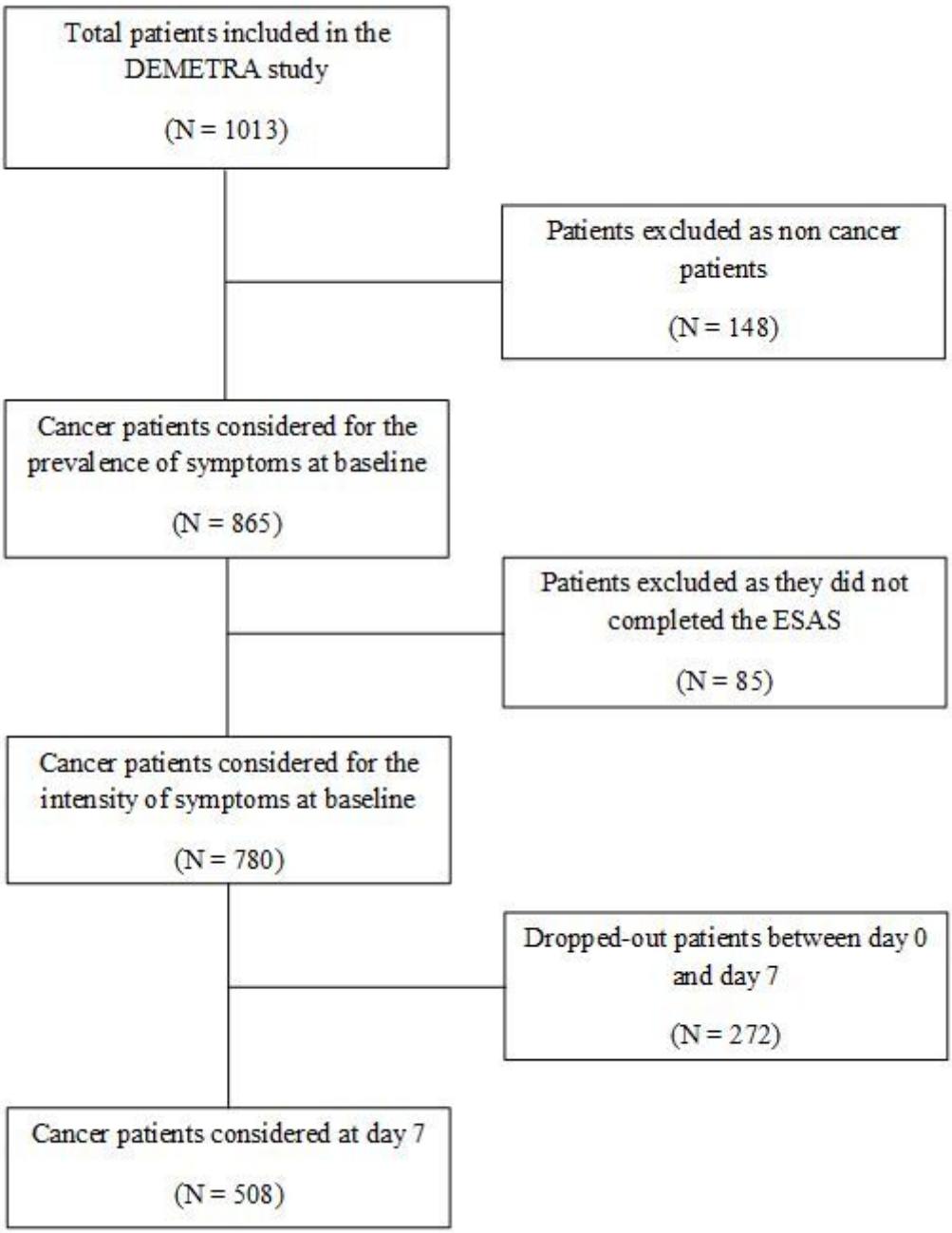

Figure 1

Flowchart of patients included in the study. ESAS, Edmonton Symptom Assessment System.

Supplementary Files

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