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End of life care in cancer patients: how much chemotherapy and how much palliative care? Record linkage study in Northern Italy

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Abstract (word count: 298 words)

Objectives

Investigating use of chemotherapy and of palliative care services in the last month of life, and whether they are inversely associated.

Design

Population based cohort linked to mortality registry and administrative databases.

Setting

Emilia-Romagna Region (Northern Italy – 4,4 million residents).

Participants

55,625 residents who died of cancer between 2017 and 2020.

Primary and secondary outcome measures

Multivariate analyses were carried out to assess the relationship between chemotherapy and palliative care services, and their association with factors related to tumour severity.

Results

15.3% of study population received chemotherapy and 40.2% received palliative care services in the last month of life, with variation across eight local health authorities (LHA). The likelihood to receive chemotherapy or palliative care services may have depended on LHA of residence. Chemotherapy was inversely associated to receiving home care or hospice services during the last 30 days, surgery within the last 30 days, aggressive tumours and increasing age, whereas they increased in case of haematologic tumours and previous hospital admissions. The likelihood to receive palliative care went in the opposite direction in case of haematologic tumours and hospital admissions within the last 30 days and in presence of aggressive tumours whereas surgery within the last 30 days, receiving chemotherapy during the last 30 days and increasing age were inversely associated to it.

Conclusion

Use of chemotherapy and palliative care in the last month of life appear to be inversely associated, with relatively high variability across different LHAs that may be explained to a higher degree by different prescribing attitudes rather than by local epidemiology/case mix or availability of services. While administrative data have obvious limits, our findings are in line with conclusions of other studies. Shifting resources from aggressive pharmacological treatments to comprehensive approaches to palliative care services is ideally a priority in cancer care.

Article summary: strengths and limitations of this study

- Inclusion of all people deceased from cancer in a Region with 4,4 million residents, linking information on use of chemotherapy and palliative care services with tumour characteristics and severity, are major strengths of this study.
- Results are discussed in-depth in light of scientific literature on multidisciplinary approaches to favour end of life transitions from aggressive treatments to palliative care
- Our data should be taken with caution since administrative data could not capture all the elements that may contribute to clinical decision making
- Moreover, although multivariate analyses provide adjustment for factors associated with tumour severity, residual confounding can be present

Keywords:

- End of life care
- Chemotherapy
- Palliative care
- Cancer

TEXT (word count: 3068 words, excluding tables, figures and references)

Introduction

The appropriate use of chemotherapy in the end-of-life care is increasingly debated, both for clinical and economic reasons. [1,2] Aggressive treatments, facilitated by the availability of newer anticancer agents that have fewer side effects, [3] often do not alleviate patients' suffering or provide hope for extending significantly life of decent quality. Focus on clinically irrelevant treatments may lead to the underuse of palliative care, [4,5,6] defined by WHO as "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through … assessment and treatment of pain and other problems, physical, psychosocial and spiritual". [7] Palliative care is generally provided in dedicated hospices or as home care services by a specially trained team of doctors, nurses and other specialists who work together with a patient's other doctors to provide an extra layer of support. Expectations of patients' and parents on one side, [8,9,10] and difficulties in predicting and communicating patients' prognosis on the other, [11,12] are among the main determinants of the chemotherapy overuse. Some patients may perceive continued active treatment as the only acceptable option. [10] For example, in a prospective cohort of terminally ill patients with cancer (n = 386), 31% preferred life-extending care rather than comfort care and as many as 77% preferred to receive chemotherapy even if it would extend their life by only one week. [12] Communication between the care team, patient and family seem to be a central element that can influence this phenomenon. [13] A qualitative study in the US identified three distinct patterns, from the caregiver's point of view of patient-caregiver-physician communication, that can influence the transition from disease-oriented to comfort-oriented care: [14] the first two patterns involve explicit discussions about EOL care and treatment choices, either with or without a shared understanding about prognosis, therefore favoring (or not) seamless transitions from active cancer treatment to comfort-oriented care, usually in hospice; in the third one no such explicit discussion on EOL occur, often leading to an unanticipated decline of the patient's condition, discontinuation of chemotherapy only when the patient become too sick and a sense of abandonment by and anger at the oncology team.

From the clinicians' point of view, withdrawal of drugs during the final, but not exactly predictable, stages of life is challenging [15]: early withdrawal can cause potential harm, whereas late withdrawal would involve unnecessary treatment and stress. Research findings suggest that culture may impact the utilization of aggressive treatment in patients with advanced cancer. For example, a study from Japan stated that only 3.7% of patients receive chemotherapy in their last 2 weeks of life [16]

However, chemotherapy itself is frequently considered a form of palliative care, aimed at reducing tumour-related symptoms, so that boundaries between curative and palliative intent of chemotherapy are sometimes difficult to establish. [17,18,19] According to the American Society of Clinical Oncology (ASCO), chemotherapy can potentially improve QOL in late stages of life even if it doesn't impact survival length [20]. In this regard, it promotes a simultaneous care approach, using palliative care alongside usual oncology care as the standard of care for any patient with advanced cancer. [21]

Several studies have analysed use of chemotherapy in the last weeks of life with results that, although variable, show a tendency to prolong treatment beyond realistic expectations of a favourable benefit-risk ratio.[18,22,23,24,25,26,27] Analysis of data available in administrative and clinical databases can inform about prescribing patterns and the utilization of health care services in the end of life, in order to provide useful basis for discussion helping clinicians and health care managers identify areas of improvement, enhance the appropriateness and value of cancer care and make judicious use of available resources. In keeping with these targets, this study aims at providing insights on the use of chemotherapy, hospital, hospice and home care services in the last month of life in a region of Northern Italy with more than 4 million residents, also to assess whether palliative care services are inversely associated with overuse of chemotherapy.

Methods

A cohort of residents in the Emilia-Romagna Region dying of cancer between 2017 and 2020 (ICD-X classification: *C00-C97, D00-D09, D37-D48)* were selected from the regional mortality registry. This cohort was linked with the routinely available administrative databases, which include hospital discharge,

pharmacological prescriptions at discharge or outpatient (use of drugs within ATC classes L01 and L02), ambulatory services, hospice and domiciliary care (also collectively considered as palliative care services), received within the last 30 days of life. Data were anonymized and record linkage procedures were performed according to the unique identification number, assigned to each resident.

Analyses were specifically aimed at describing frequency of chemotherapy, palliative care services or both received within the last 30 days of life among eight Local Health Authorities (LHA). Logistic multivariate two-level analyses [28] were carried out to assess whether 1) chemotherapy use, 2) palliative care services 3) or both within the last 30 days of life could be associated to each other as well as to type of tumour (solid vs haematological), patients' age, surgery and hospital admissions, considering LHA clustering as the second level (random intercept) to eliminate the effect of a possible correlation of results of residents in the same province. One-level models, [29] adding each LHA as covariates (each compared to a reference LHA) were subsequently used to assess whether use of chemotherapy and of palliative care could present variability among LHA. Odds ratio with 95% confidence intervals were calculated. SAS version 8.2 (SAS Institute inc., Cary, NC, USA) and STATA/SE version 16.1 (STATACorp, College Station, TX 77845) were used for statistical analyses.

Patient and Public Involvement: no patient involved.

Results

Between January 1, 2017 and December 31, 2020 in Emilia-Romagna, 55,625 people died from cancer. Table 1 quantifies the main cancer diagnosis associated to death, by LHA; no substantial differences are shown among different LHA. Table 2 shows use of chemotherapy and of palliative care services within the last 30 days of life by main cancer diagnosis in the whole cohort. Breast, prostate and haematologic tumours are those where use of chemotherapy is highest (in more than 20% of patients), whereas nervous system and urinary tumours are those with the lowest use (in less than 10%). Use of palliative care services appears relatively uniform across tumour types, except for a lower observed use in genital tumours in men and haematologic tumours. Overall, 15.3% of patients received chemotherapy within the last 30 of life,

with an increasing trend from 2017 to 2020 (respectively 14.6, 15.0, 15.7 and 16.2). About palliative care services, 40.2% (39.7, 40.3, 40.1 and 40.8 from 2017 to 2020) of patients received them. 4.1% received surgery within the last 30 days.

Among the eight local health authorities, there was variability in the use of chemotherapy (from 12.5% to 16.9% - Fig.1) and of palliative care (from 36.2% to 43.7% - Fig.2) in the last 30 days of life. 39.1% of patients died in hospital, with wide variability among the LHAs (range: from 29.4% to 44.0%).

A multivariate two-level model with random intercept (LHA) shows that the likelihood to receive chemotherapies, during the last 30 days of life, increased by 115% in case of haematologic tumours and of 63% in case of hospital admissions within the last 30 days, whereas it was reduced of 41% for surgery within the last 30 days, of 12% for aggressive tumours, of 8% for receiving home care or hospice services during the last 30 days and of 5% for every year of increasing age (table 3a). Intracluster correlation coefficient (ICC) (0.3%) shows low intra-LHA correlation.

A second two-level cluster multivariate model shows that the likelihood to receive palliative care during the last 30 days of life goes in the opposite direction, decreasing of 48% in case of haematologic tumours and of 30% for hospital admissions within the last 30 days, and increasing of 12% in presence of aggressive tumours, whereas it decreased of 56% in case of surgery within the last 30 days, of 10% if receiving chemotherapies during the last 30 days and of 5% for every year of increasing age (table 3a). Also in this case the intracluster correlation coefficient (0.3%) shows no intra LHA correlation.

A third two-level cluster multivariate model shows that aggressive tumours reduce of 16% the likelihood to receive concurrent chemotherapy and palliative care during the last 30 days of life, in keeping with the result of the first model, suggesting that clinicians in such cases tend not to insist on chemotherapies (table 3a). Also in this case the intracluster correlation coefficient (0.4%) shows no intra-LHA correlation.

Since no effect of clustering of subjects in the 8 LHAs was shown, in order to assess variability among LHA we replicated the latter models without LHA clustering and including LHA as covariates (table 3b). Covariate coefficients are the same as in the cluster models, confirming no effect of LHA clustering on the outcome.

As raw data suggested in fig. 1 and fig. 2, place of residence may also be associated with the likelihood to receive end-of-life chemotherapies and palliative care after adjusting for the other covariates.

Discussion

This study shows that use of chemotherapy and of palliative care services in the last month of life are inversely associated rather than complementary, suggesting the need to further explore the hypothesis that palliative care services may have a role in preventing inappropriate use of chemotherapy. A variable use of chemotherapy and palliative care services in different LHAs and across different tumours in the last month of life is also shown. Compared to solid cancers, haematologic tumours tend to be treated more frequently with chemotherapy and to be provided less frequently with palliative care, probably in light of the more frequent availability of effective in-hospital therapies leading to longer survival [30] or of perceiving a more favourable benefit-risk ratio of "not giving up", and of the often rapid pace of decline near death. This has also been observed in other studies. [31,32,33,34] An opposite pattern is associated to aggressive tumours, treated more frequently with palliative care and less with chemotherapy.
Variability among different LHAs may depend either on a different epidemiological distribution of the tumours and of their severity, or on different prescribing attitudes and availability of palliative services in the areas of residence. Main cancer diagnosis associated to death appear similar across different LHA. In addition, multivariate analyses provide adjustment for factors associated with tumour severity (age, haematologic tumour, previous surgery and hospital admission) and, although residual confounding can be reasonably present, we consider unlikely that it could provide the main explanation for the observed variability. Therefore, despite limits in our data and taking unobserved factors (residual confounding) into account, we consider that this variability may be explained to a higher degree by different prescribing-management attitudes rather than by local epidemiology/case mix. As for the availability of palliative services in the areas of residence, the Emilia-Romagna Region has been quite active in implementing a national law issued in 2010 [35] to guarantee such availability as well as adequate access to these services.

[36] Further qualitative research could analyse whether attitudes and level of endorsement in different LHA may in part explain their differential use/access, aside from their availability which is relatively homogeneous across the region.

Our data should be taken with caution since administrative data are grossly descriptive and have obvious limits in capturing all the elements that may contribute to clinical decision making. Nonetheless, our findings are in line with conclusions of several other studies. There may be a potential to limit use of end of life chemotherapies increasing at the same time the provision of palliative care services. In general, shifting resources from aggressive pharmacological treatments to comprehensive approaches to palliative care services should be a priority in cancer care, and palliative care may be one of the determinants “protecting” against the overuse of chemotherapy. While the high variability observed among Local Health Authorities in the use of these services is worrying, it also suggests that a huge potential exists to better organize end of life care for cancer patients.

Clinical and administrative data can help to promote discussion among oncologists, specialists in palliative care, general practitioners, pharmacists, health care managers and (ideally) patients' representatives to maximize quality of end of life care, especially in blood malignancies, in light of available resources. Local multidisciplinary groups can/should use data to analyse possible determinants of inappropriate care, discuss to what extent chemotherapies can be used as palliative care and propose strategies to offer patients and their families the best possible support. This especially in light of the increasing availability and accelerated approval of new therapies [37] often with a limited added value but with a wide range of indications, targeting resistant cases and/or administered by oral route. These circumstances may favour an increase in the use of chemotherapies sometimes (or often) without a real clinical benefit, and may hinder or delay access to palliative care services.

The availability of adequate prognostic tools is key to discuss appropriateness of end-of-life care and, in theory, performance status can be used as such to guide clinicians and palliative care specialists to make choices for appropriate health care.[38] Aside from ECOG performance status, that may be variably weighed by physicians often leading to optimistic assessments, [39] other prognostic tools should be

warranted. In 2005, the European Association for Palliative Care made recommendations in this regard [40] and prognostic tools have been developed and validated.[41] Yet, most of them depend on the evaluation of functional status, which is largely subjective and may lead to optimistic estimates to justify the use of aggressive therapies. Objective assessment of functional status have been advocated, for example the measurement of a surrogate like skeletal muscle mass through imaging techniques. [31] A palliative prognostic score integrating subjective judgments with a series of more objective parameters has been validated and extensively discussed, showing a good balance between accuracy and applicability in clinical practice. [42,43,44,45] Routine use of this kind of prognostic tools would certainly require adequate promotion among clinicians. Again, the objective should be to warrant the most appropriate care given the patients' clinical status, avoiding overtreatments that could worsen their quality of life diverting attention from "truly palliative" care.

However, to fulfil this goal, the use of more accurate prognostic assessments does not seem sufficient. Physicians should be prepared to address patients' and relatives' concerns and expectations by refining their communication skills in specific kinds of situations like communication at diagnosis, discussion of prognosis, decision-making about palliative anticancer therapy, transitions to palliative care and preparation of patients and families for dying and death, more widespread use of advanced care planning (ACP) [46] ACP enables individuals "to define goals and preferences for future medical treatment and care, to discuss these goals and preferences with family and healthcare providers, and to record and review these preferences if appropriate". ACP interventions have the potential to prepare patients for decision-making when they are unable to make their own decisions, typically including one or more focused, personal conversations between patients and healthcare professionals about patients' personal values, life goals, and preferences regarding future medical treatment and care. [47]. Interventions that include communication about ACP and care preferences have been found to improve concordance between care preferences and actual care delivered. [48]

To better align care with preferences, the National Academy Medicine and American Society of Clinical Oncology recommend patients and providers have goals-of-care (GOC) conversations [49] all of which may

occur in ACP [50] and that palliative care, which typically involves such discussions, [51] be integrated into standard oncology care. [52]

Although the capacity for it is inborn, even empathy is considered a learned behaviour.[53] Lack of communication skills is one of the main barriers to adequate communication and decision-making, but physicians' misconception that skills training is not needed, that "you have to be born with this skill" and about the efficacy of training may hinder specific efforts to fill that gap. [54] Doctors' attitudes towards death, their focus on clinical parameters and their lack of confidence in their own judgment of their patient's true condition may also play a negative role. [55]

Nurses play a pivotal role as well in accompanying patients and their families through their cancer journey. Nursing practice covers a broad continuum of care, from health promotion to disease prevention, coordination of care, cure (when possible) and palliative care when cure is not possible [49]. Given the frequency and continuity of contact that nurses have with patients and their families, they are in an ideal position to assume an important role in health care delivery processes, [56, 57] to provide cancer patients and their families with emotional and social support, together with adequate communication about the diagnosis, prognosis and treatment alternatives [56, 58]. Cancer care is multidisciplinary, requiring effective communication also within the team and the importance of recognizing being part of a team. In this regard, it is essential to propose shared training between the entire care team and to develop organizational models and work tools to fulfil this goal. [56, 59]

Promotion of enhanced health professional-patient communication and shared decision making can be effectively achieved [60] but would benefit from a system-wide approach considering several elements like inclusion of communication skills in clinical competencies needed for credentialing, incentives to provide and to seek effective training, system capacity to record communication with patients in electronic medical records and multi-focal and interdisciplinary team support for serious illness communication.[39,61]

Conclusion

A multidisciplinary approach involving clinicians, nurses, specialists in palliative care, pharmacists, health care managers and members of the public is needed to investigate macro issues highlighted through administrative data, to promote the use of better prognostic tools and a more comprehensive approach to end-of-life cancer care, limiting use of aggressive treatments that are not beneficial or that could even worsen quality of life. We are implementing this approach in our Local Health Authority. However, we advocate that such local efforts should be nested within a system-wide approach to promote effective physician-patient communication, thoroughly integrating communication skills among the clinical competencies doctors need to achieve. These are especially needed in end-of-life care.

Table 1 – Study population of patients dying for cancer in Emilia-Romagna between 2017 and 2020, by tumour site and local health authority: number (white background) and percentage (grey background)

	LHA1	LHA2	LHA3	LHA4	LHA5	LHA6	LHA7	LHA8	Region
Head & neck	105	137	157	221	296	43	164	316	1,439
	2.6	2.5	2.7	2.7	2.6	2.7	3.1	2.3	2.6
Digestive	1,422	1,803	1,825	2,571	3,507	504	1,638	4,305	17,575
	35.3	33.2	31.4	31.9	30.4	31.5	30.6	31.2	31.6
Respiratory	778	857	1,084	1,501	1,993	279	957	2,649	10,098
	19.3	15.8	18.7	18.6	17.3	17.5	17.9	19.2	18.2
Muscoloskeletal	31	51	52	62	63	18	30	102	409
	0.8	0.9	0.9	0.8	0.6	1.1	0.6	0.7	0.7
Skin	122	129	193	171	319	68	110	360	1,472
	3.0	2.4	3.3	2.1	2.8	4.3	2.1	2.6	2.7
Nervous system	109	181	187	302	387	57	163	506	1,892
	2.7	3.3	3.2	3.7	3.4	3.6	3.0	3.7	3.4
Breast	278	355	370	517	789	102	382	790	3,583
	6.9	6.5	6.4	6.4	6.8	6.4	7.1	5.7	6.4
Genital (women)	196	243	262	385	598	74	204	586	2,548
	4.9	4.5	4.5	4.8	5.2	4.6	3.8	4.2	4.6
Genital (men)	9	21	14	32	50	6	29	54	215
	0.2	0.4	0.2	0.4	0.4	0.4	0.5	0.4	0.4
Urinary	247	397	389	566	918	103	461	962	4,043
	6.1	7.3	6.7	7.0	8.0	6.5	8.6	7.0	7.3
Prostate	181	237	275	323	486	56	204	491	2,253
	4.5	4.4	4.7	4.0	4.2	3.5	3.8	3.6	4.1
Haematologic	359	607	563	870	1,241	188	546	1500	5,874
	8.9	11.2	9.7	10.8	10.8	11.8	10.2	10.9	10.6
Other/metastatic	191	406	440	547	883	100	469	1,188	4,224
	4.7	7.5	7.6	6.8	7.7	6.3	8.8	8.6	7.6
Region	4,028	5,424	5,811	8,068	11530	1,598	5,357	13,809	55,625
	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Table 2 - Percentage of use of chemotherapy and palliative care (home or hospice care) during the last 30 days of life

Cancer type	Treatment during the last 30 day of life			
	% chemotherapy	% home care	% hospice care	% overall palliative
Head & neck	13.0	19.3	28.7	41.3
Digestive	10.3	23.1	27.7	44.8
Respiratory	19.3	21.5	28.0	43.3
Musculoskeletal	10.4	20.5	21.8	38.1
Skin	16.5	25.1	30.9	47.8
Nervous system	6.1	20.3	31.9	45.2
Breast	27.1	20.8	25.5	40.4
Genital (women)	16.4	20.8	29.6	44.6
Genital (men)	13.0	15.8	11.2	24.2
Urinary	8.7	19.2	22.9	37.4
Prostate	26.1	18.4	23.2	37.1
Haematologic	24.7	15.3	13.2	26.2
Other/metastatic	8.4	18.2	15.8	30.8
Region	***15.3***	***20.7***	***24.9***	***40.2***

Table 3a - Factors associated with receiving chemotherapy, palliative care or both during the last 30 days in Emilia-Romagna (random intercept two-level multivariate model considering LHA clustering)

Factor	Chemotherapy	Palliative care	Chemotherapy palliative care
	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)
Chemotherapy within the last 30 days	-	0.90* (0.85-0.94)	-
Palliative care within the last 30 days	0.92* (0.87-0.97)	-	-
Haematologic tumour (*ref. solid/metastatic*)	2.15* (2.00-2.30)	0,52* (0.49-0.56)	1.03 (0.92-1.16)
Age (continuos, in year)	0.95* (0.95-0.95)	0.99* (0.99-0.99)	0.96*(0.96-0.96)
Hospital admission within the last 30 days	1.63* (1.55-1.72)	0.70* (0.67-0.72)	1.05 (0.98-1.14)
Surgery within the last 30 days	0.59* (0.52-0.67)	0.44* (0.39-0.49)	0.42*(0.33-0.54)
Aggressive tumour	0.88* (0.84-0.93)	1.12* (1.08-1.16)	0.84*(0.78-0.90)

**significance at p≤0.05*

Table 3b- Factors associated with receiving chemotherapy, palliative care or both during the last 30 days in Emilia-Romagna (logistic multivariate model)

Factor	Chemotherapy	Palliative care	Chemotherapy palliative care
	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)
Chemotherapy within the last 30 days *(ref.NO)*	-	0.90*(0.85-0.94)	-
Palliative care within the last 30 days *(ref.NO)*	0.92*(0.87-0.97)	-	-
Haematologic tumour (*ref. solid/metastatic*)	2.15*(2.01-2.30)	0.52*(0.49-0.56)	1.03 (0.92-1.17)
Age (continous, in year)	0.95*(0.95-0.95)	0.99*(0.99-0.99)	0.96*(0.96-0.96)
Hospital admission within the last 30 days *(ref.NO)*	1.63*(1.55-1.72)	0.70*(0.67-0.72)	1.05 (0.98-1.14)
Surgery within the last 30 days *(ref.NO)*	0.59*(0.52-0.68)	0.44*(0.39-0.49)	0.42*(0.33-0.54)
Aggressive tumour *(ref.NO)*	0.88*(0.84-0.92)	1.12*(1.08-1.16)	0.84*(0.78-0.90)
LHA 3 *(reference)*			
LHA 1	1.09 (0.97-1.22)	0.86*(0.79-0.93)	1.03 (0.87-1.21)
LHA 2	0.79*(0.71-0.89)	0.77*(0.72-0.84)	0.69*(0.58-0.81)
LHA 3	1.04 (0.94-1.14)	0.80*(0.74-0.85)	0.91 (0.79-1.05)
LHA 4	0.91*(0.84-1.00)	0.92*(0.86-0.98)	0.84*(0.73-0.96)
LHA 5	0.75*(0.63-0.89)	1.07 (0.96-1.20)	0.76*(0.59-0.98)
LHA 6	0.92 (0.83-1.02)	0.96 (0.89-1.04)	0.89 (0.76-1.04)
LHA 7	0.99 (0.90-1.07)	1.04 (0.97-1.10)	1.03 (0.91-1.17)

* *significance at p≤0.05;* LHA = local health authority

Figure legends

Figure 1 - Percentage of chemotherapy use during the last 30 days of life, by LHA of residence (all tumours)

Figure 2 - Percentage of home care services use during the last 30 days of life, by LHA of residence (all tumours)

Author contributions

GF: conception and design, interpretation of data, drafting the article

MM: conception and design, analysis and interpretation of data

MG: interpretation of data, revising the article critically for important intellectual content

RGG: conception and design, interpretation of data, revising the article critically for important intellectual content

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All authors approved the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Name of the Ethics Committee: Comitato Etico dell'Area Vasta Emilia Nord, Reggio Emilia (Italy)

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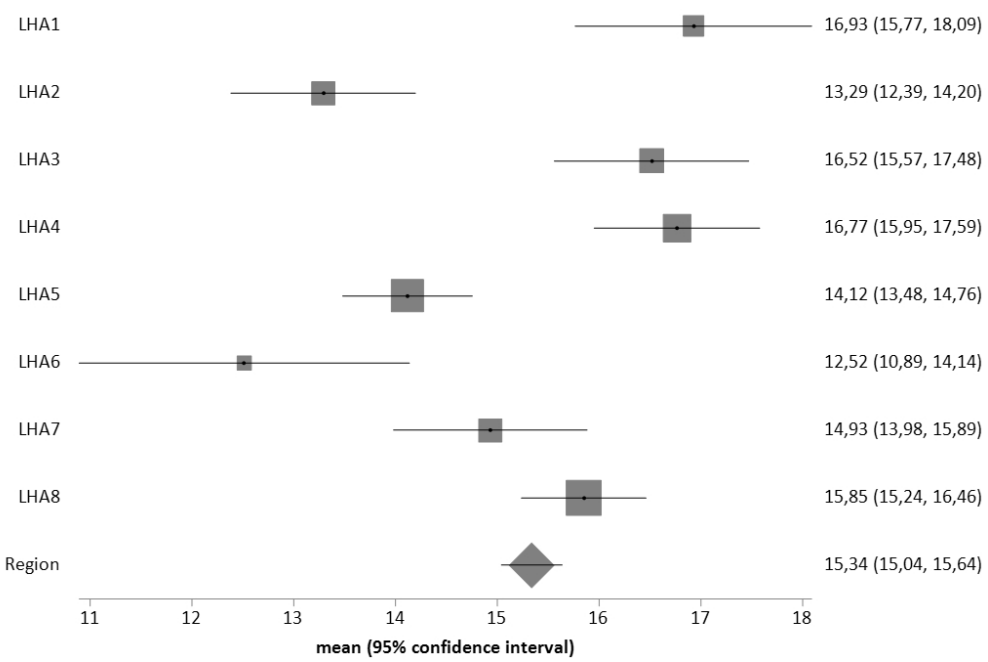

Figure 1 - Percentage of anticancer drug use during the last 30 days of life, by LHA of residence (all tumours)

86x57mm (300 x 300 DPI)

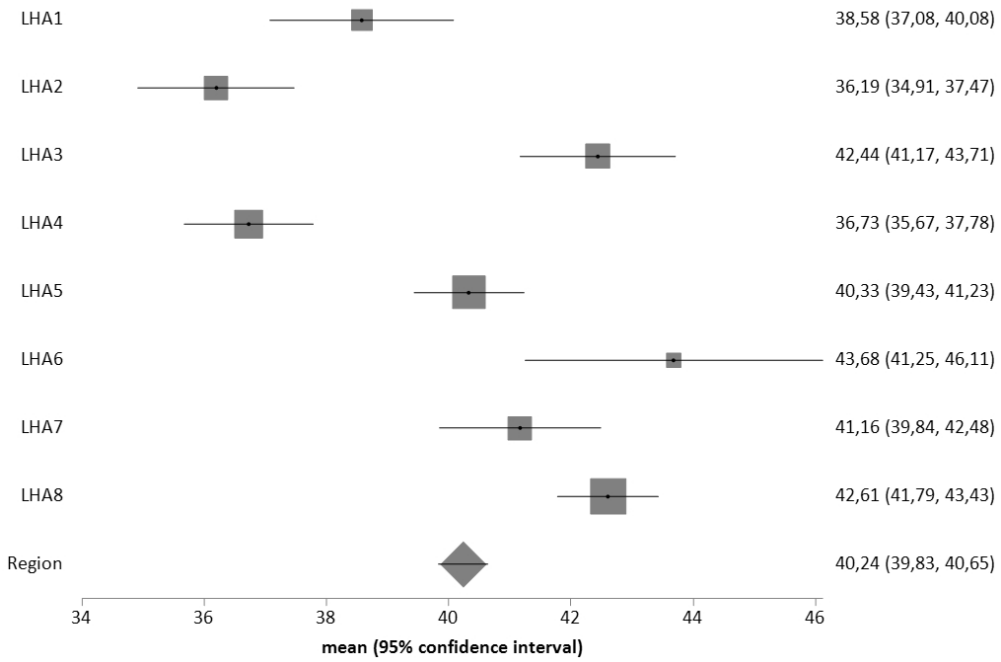

Figure 2 - Percentage of home care services use during the last 30 days of life, by LHA of residence (all tumours)

85x58mm (300 x 300 DPI)

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End of life care in cancer patients: how much drug therapy and how much palliative care? Record linkage study in Northern Italy

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End of life care in cancer patients: how much drug therapy and how much palliative care? Record linkage study in Northern Italy

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Participant consent: not required (the study cohort was made up of deceased patients)

Abstract (word count: 298 words)

Objectives

Investigating use of anticancer drugs and of palliative care services in the last month of life.

Design

Population based cohort linked to mortality registry and administrative databases.

Setting

Emilia-Romagna Region (Northern Italy – 4,4 million residents).

Participants

55,625 residents who died of cancer between 2017 and 2020.

Primary and secondary outcome measures

Multivariate analyses were carried out to assess the relationship between cancer drug therapy and palliative care services, and their association with factors related to tumour severity.

Results

In the last month of life, 15.3% of study population received anticancer drugs (from 12.5% to 16.9% across the eight local health authorities - LHA) and 40.2% received palliative care services (from 36.2% to 43.7%). The likelihood to receive anticancer drugs or palliative care was associated with LHA of residence. Drug therapy was inversely associated with receiving palliative care services within the last 30 days (odds ratio 0.92), surgery within the last 6 months (OR 0.59), aggressive tumours (OR 0.88) and increasing age (OR 0.95), whereas they increased in case of haematologic tumours (OR 2.15) and hospital admissions within the last 6 months (OR 1.63). The likelihood to receive palliative care went in the opposite direction in case of haematologic tumours (OR 0.52) and hospital admissions within the last 6 months (OR 0.70), and in presence of aggressive tumours (OR 1.12); surgery (OR 0.44), receiving anticancer drugs during the last 30 days (OR 0.90) and increasing age (OR 0.99) were inversely associated with it. All these results were statistically significant.

Conclusion

Use of anticancer drugs and palliative care in the last month of life were inversely associated, with relatively high variability across different LHAs in spite of similar epidemiology/case mix and availability of services. While administrative data have limits, our findings are in line with conclusions of other studies.

Article summary: strengths and limitations of this study

- Inclusion of all people deceased from cancer in a Region with 4,4 million residents, linking information on use of anticancer drugs and palliative care services with tumour characteristics and severity, are major strengths of this study.
- Caution should be taken since administrative data could not capture all the elements that may contribute to clinical decision making
- Moreover, although multivariate analyses provide adjustment for factors associated with tumour severity, residual confounding may be present

Keywords:

- End of life care
- Anticancer drug therapy
- Palliative care
- Cancer

TEXT (word count: 3049 words, excluding tables, figures and references)

Introduction

The appropriate use of anticancer drugs in end-of-life care is increasingly debated, both for clinical and economic reasons. [1,2] Aggressive treatments, facilitated by the availability of newer anticancer agents that have fewer side effects, [3] often do not alleviate patients' condition or provide hope for extending significantly life of decent quality. Focus on clinically irrelevant treatments may lead to the underuse of palliative care, [4,5,6] defined by WHO as "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through … assessment and treatment of pain and other problems, physical, psychosocial and spiritual". [7] Palliative care is generally provided in dedicated hospices or as home care services by a specially trained team of doctors, nurses and other specialists who work together with a patient's other doctors to provide an extra layer of support.

[8,9] Expectations of patients' and parents on one side, [10] and difficulties in predicting and communicating patients' prognosis on the other, [11,12] are among the main determinants of overuse of anticancer drugs (box). Some patients may perceive continued active treatment as the only acceptable option. [10] For example, in a prospective cohort of terminally ill patients with cancer (n = 386), 31% preferred life-extending care rather than comfort care and as many as 77% preferred to receive drug treatment even if it would extend their life by only one week. [12] Communication between the care team, patient and family seem to be a central element that can influence this phenomenon. [13]

From the clinicians' point of view, withdrawal of drugs during the final, but not exactly predictable, stages of life is challenging [14]: early withdrawal can cause potential harm, whereas late withdrawal would involve unnecessary treatment and stress (box). Research findings suggest that culture may impact the utilization of aggressive treatment in patients with advanced cancer. For example, a study from Japan stated that only 3.7% of patients receive chemotherapy in their last 2 weeks of life [15]

However, anticancer therapy itself is frequently considered a form of palliative care, aimed at reducing tumour-related symptoms, so that boundaries between curative and palliative intent are sometimes difficult to establish (box). [16,17,18] According to the American Society of Clinical Oncology (ASCO), anticancer drugs

can potentially improve QOL in late stages of life even if they don't impact survival length [19]. In this regard, their use promotes a simultaneous care approach, using palliative care alongside usual oncology care as the standard of care for any patient with advanced cancer. [20]

Several studies have analysed use of anticancer drugs in the last weeks of life with results that, although variable, show a tendency to prolong treatment beyond realistic expectations of a favourable benefit-risk ratio.[16,21,22,23,24,25,26] Analysis of data available in administrative and clinical databases can inform about prescribing patterns and the utilization of health care services in the end of life, in order to provide useful basis for discussion helping clinicians and health care managers identify areas of improvement, enhance the appropriateness and value of cancer care and make judicious use of available resources. In keeping with these targets, this study aims at providing insights on the use of anticancer drugs, hospital, hospice and home care services in the last month of life in a region of Northern Italy with more than 4 million residents, also to assess whether palliative care services are inversely associated with overuse of antineoplastic therapy.

Methods

A cohort of residents in the Emilia-Romagna Region who had cancer as the underlying cause of death between 2017 and 2020 (ICD-X classification: *C00-C97, D00-D09, D37-D48)* were selected from the regional mortality registry. This cohort was linked with the routinely available administrative databases, specifically: 1) hospital discharge records (including inpatient use of anticancer drugs, type of tumour, patients' age, surgery and hospital admissions); 2) ambulatory services (specifying use of anticancer drugs); 3) outpatient pharmacological prescriptions (use of drugs within ATC classes L01 and L02); 4) hospice and 5) domiciliary care databases (also collectively considered as palliative care services). Data were anonymized and record linkage procedures were performed according to the unique identification number, assigned to each resident and available in each of the databases. A list of codes used to select hospital discharge information and ambulatory care is available in the appendix.

Analyses were specifically aimed at describing frequency of anticancer drug use, palliative care services or both received within the last 30 days of life among eight Local Health Authorities (LHA). Logistic multivariate

two-level analyses [27] were carried out to assess whether 1) anticancer drug use, 2) palliative care services 3) or both within the last 30 days of life could be associated with each other as well as with type of tumour (solid vs haematological, or aggressive tumours - see list in the appendix), patients' age, any surgery and hospital admissions within the last 6 months, considering LHA clustering as the second level (random intercept) to eliminate the effect of a possible correlation of results of residents in the same province. One-level models, [28] adding each LHA as covariates (each compared to a reference LHA) were subsequently used to assess whether use of anticancer drugs and of palliative care could present variability among LHA. Odds ratio with 95% confidence intervals were calculated. SAS version 8.2 (SAS Institute inc., Cary, NC, USA) and STATA/SE version 16.1 (STATACorp, College Station, TX 77845) were used for statistical analyses.

Patient and Public Involvement: no patient involved.

Results

In Emilia-Romagna, 55,625 people died from cancer between January 1, 2017 and December 31, 2020. Table 1 quantifies the main cancer diagnosis associated with death, by LHA: no substantial differences are shown among different LHAs. Table 2 shows use of anticancer drugs and of palliative care services within the last 30 days of life by main cancer diagnosis in the whole cohort. The highest use of anticancer drugs was in people with breast, prostate and haematologic tumours (in more than 20% of patients), whereas the lowest use was in people with nervous system and urinary tumours (in less than 10% of patients). Use of palliative care services appears relatively uniform across tumour types, except for a lower observed use in genital tumours in men and in haematologic tumours. Overall, 15.3% of patients received anticancer drugs within the last 30 days of life, with an increasing trend from 2017 (14.6%) to 2020 (16.2%). About palliative care services, 40.2% of patients received them (from 39.7% in 2017 to 40.8% in 2020). 4.1% received surgery within the last 30 days. Among the eight local health authorities, there was variability in the use of anticancer drugs (from 12.5% to 16.9% - Figure 1) and of palliative care (from 36.2% to 43.7% - Figure 2) in the last 30 days of life. 39.1% of patients died in hospital, with wide variability among the LHAs (range: from 29.4% to 44.0%).

The likelihood to receive anticancer drugs during the last 30 days of life increased by 115% in case of haematologic tumours, and by 63% in case of hospital admissions within the last 30 days. It was reduced by 41% for surgery within the last 30 days, by 12% for aggressive tumours, by 8% for receiving home care or hospice services during the last 30 days and by 5% for every year of increasing age (Table 3). The intracluster correlation coefficient (ICC) is 0.3%, showing low intra-LHA correlation.

The likelihood to receive palliative care during the last 30 days of life increased by 12% in presence of aggressive tumours. It was reduced by 48% in case of haematologic tumours, by 30% for hospital admissions within the last 30 days, by 56% in case of surgery within the last 30 days, by 10% if receiving anticancer drugs during the last 30 days and by 5% for every year of increasing age (Table 3). Also in this case, the intracluster correlation coefficient (0.3%) shows no intra LHA correlation.

The likelihood to receive concurrent anticancer drugs and palliative care during the last 30 days of life was reduced by 16% in case of aggressive tumours, in keeping with the result of the first model, suggesting that clinicians in such cases tend not to insist on drug therapy (Table 3). Also in this case, the intracluster correlation coefficient (0.4%) shows no intra-LHA correlation.

Since no effect of clustering of subjects in the 8 LHAs was shown, we replicated the latter models without LHA clustering and including LHA as covariates, in order to assess variability among LHAs (Extra table). Covariate coefficients are the same as in the cluster models, confirming no effect of LHA clustering on the outcome. As raw data suggested in Figure 1 and Figure 2, place of residence may also be associated with the likelihood to receive end-of-life drug therapies and palliative care after adjusting for the other covariates.

Discussion

This study shows that use of anticancer drugs and of palliative care services in the last month of life are inversely associated rather than complementary, suggesting the need to further explore the hypothesis that palliative care services may have a role in preventing inappropriate use of anticancer drugs. A variable use of

anticancer drugs and of palliative care services in different LHAs and across different tumours in the last month of life is also shown. Compared to solid cancers, haematologic tumours tend to be treated more frequently with anticancer drugs and to be provided less frequently with palliative care. This circumstance could be related to the more frequent availability of effective in-hospital therapies leading to longer survival [29], to perceiving a more favourable benefit-risk ratio of "not giving up", and to the often rapid pace of decline near death. This has also been observed in other studies. [30,31,32,33] An opposite pattern is associated with aggressive tumours, treated more frequently with palliative care and less frequently with anticancer drugs.

Variability among different LHAs may depend either on a different epidemiological distribution of the tumours and of their severity, or on different prescribing attitudes and availability of palliative services in the areas of residence. Main cancer diagnosis associated with death appear similar across different LHA. In addition, multivariate analyses provide adjustment for factors associated with tumour severity (age, haematologic tumour, previous surgery and hospital admission) and, although residual confounding can be reasonably present, we consider unlikely that it could provide the main explanation for the observed variability. Therefore, despite limits in our data and taking the possibility of unobserved factors (residual confounding) into account, we consider that this variability may be explained to a higher degree by different prescribing and management attitudes rather than by local epidemiology/case mix. As for the availability of palliative services in the areas of residence, the Emilia-Romagna Region has been quite active in implementing a national law issued in 2010 [34] to guarantee such availability as well as adequate access to these services. [35] Further qualitative research could analyse whether attitudes and level of endorsement in different LHA may in part explain differential use/access, aside from their availability which is relatively homogeneous across the region.

Inclusion of all people deceased from cancer in a Region with 4,4 million residents, linking information on use of anticancer drugs and palliative care services with tumour characteristics and severity, are major strengths of this study. However, our results should be taken with caution since administrative data are grossly descriptive and have obvious limits in capturing all the elements that may contribute to clinical decision making. As for quality and completeness of available data, they are collected as part of the patient's care: reimbursements to

health services depend on their completeness, which can be assumed and which should exclude the possibility of major biases. However, no scientific validation of the databases used and of the record-linkage procedures is available, although the unique patient identification number present in all the databases should ensure that no data is lost.

Nonetheless, our findings are in line with conclusions of several other studies. There may be a potential to reduce use of end of life anticancer therapies increasing at the same time the provision of palliative care services. In general, shifting resources from aggressive pharmacological treatments to comprehensive approaches to palliative care services should be a priority in cancer care, and palliative care may be one of the determinants “protecting” against the overuse of anticancer drugs. While the high variability observed among Local Health Authorities in the use of these services is worrying, it also suggests that a huge potential exists to better organize end of life care for cancer patients.

Clinical and administrative data can help promote discussion among oncologists, specialists in palliative care, nurses, general practitioners, pharmacists, health care managers and (ideally) patients' representatives to maximize quality of end of life care, especially in blood malignancies, in light of available resources. Local multidisciplinary groups can/should use data to analyse possible determinants of inappropriate care and propose strategies to offer patients and their families the best possible support. This especially in light of the increasing availability and accelerated approval of new therapies [36] that often have a limited added value but a wide range of indications, targeting resistant cases and/or administered by oral route. These circumstances may favour an increase in the use of anticancer drugs, sometimes (or often) without a real clinical benefit, and may hinder or delay access to palliative care services.

Data on pharmacoutilization can also help local multidisciplinary groups to discuss to what extent anticancer drugs are used with a palliative intent, and to foster the design of research protocols aimed at evaluating the impact of drug utilization on patients’ quality of life (QoL). Record linkage studies generally cannot provide such specific information, since QoL information is generally unavailable in administrative databases, and this is also one of the limits of our study. A few RCTs and systematic reviews addressing different types of tumours have shown some effect of different anticancer therapies on reducing pain and improving patients’ quality of

life [37,38,39,40,41,42]. However, this issue is largely debated as evidence is controversial or lacking, so that the guideline from the European Society for Medical Oncology (ESMO) explicitly contraindicates the use of anticancer drugs in the last weeks of life. [43]

The availability of adequate prognostic tools is key to discuss appropriateness of end-of-life care: in theory, performance status can be used as such to guide clinicians and palliative care specialists to make choices for appropriate health care. [44] Aside from ECOG performance status that may be variably weighed by physicians, often leading to optimistic assessments, [45] other prognostic tools should be warranted. In 2005, the European Association for Palliative Care made recommendations in this regard [46] and prognostic tools have been developed and validated. [47] Yet, most of them depend on the evaluation of functional status, which is largely subjective and may lead to optimistic estimates to justify the use of aggressive therapies. Objective assessment of functional status has been advocated, for example the measurement of a surrogate like skeletal muscle mass through imaging techniques. [31] A palliative prognostic score integrating subjective judgments with a series of more objective parameters has been validated and extensively discussed, showing a good balance between accuracy and applicability in clinical practice. [48,49,50,51] Routine use of this kind of prognostic tools would certainly require adequate promotion among clinicians. Again, the objective should be to warrant the most appropriate care given the patients' clinical status, avoiding overtreatments that could worsen their quality of life, diverting attention from "truly palliative" care.

However, to fulfil this goal, the use of more accurate prognostic assessments does not seem sufficient. Physicians should be prepared to address patients' and relatives' concerns and expectations by refining their communication skills in specific kinds of situations like communication at diagnosis, discussion of prognosis, decision-making about palliative anticancer therapy, transitions to palliative care and preparation of patients and families for dying and death, and more widespread use of advanced care planning (ACP) [52]. [53]. Interventions that include communication about ACP and care preferences have been found to improve concordance between care preferences and actual care delivered. [54]

To better align care with preferences, the National Academy of Medicine and the American Society of Clinical Oncology recommend patients and providers have goals-of-care (GOC) conversations, [55] all of which may

occur in ACP, [56] and that palliative care, typically involving such discussions, [8] be integrated into standard oncology care. [57] Also nurses play a pivotal role in accompanying patients and their families through their cancer journey, being in an ideal position [58, 59] to provide cancer patients and their families with emotional and social support, together with adequate communication about the diagnosis, prognosis and treatment alternatives [58,60]. Cancer care is multidisciplinary: it requires effective communication also within the team, and recognizing to be part of a team. In this regard, it is essential to propose shared training between the entire care team and to develop organizational models and work tools to fulfil this goal. [9,58]
Promotion of enhanced health professional-patient communication and shared decision making can be effectively achieved [61] but would benefit from a system-wide approach considering several elements like inclusion of communication skills in clinical competencies needed for credentialing, incentives to provide and to seek effective training, system capacity to record communication with patients in electronic medical records and multi-focal and interdisciplinary team support for serious illness communication.[45,62]

Conclusion

A multidisciplinary approach involving clinicians, nurses, specialists in palliative care, pharmacists, health care managers and members of the public is needed to investigate macro issues highlighted through administrative data, to promote the use of better prognostic tools and a more comprehensive approach to end-of-life cancer care, limiting use of aggressive treatments that are not beneficial or that could even worsen quality of life. We are implementing this approach in our Local Health Authority. However, we advocate that such local efforts should be nested within a system-wide approach to promote effective physician-patient communication, thoroughly integrating communication skills among the clinical competencies doctors need to achieve. These are especially needed in end-of-life care.

Box. Main determinants of potential overuse of anticancer drugs

- Expectations of patients' and parents (and "never give up" attitude)
- difficulties in predicting patients' prognosis
- difficulties in communicating patients' prognosis
- physician's perception of potential harm by early withdrawal
- therapy seen as a form of palliative care

Table 1 – Study population of patients dying for cancer in Emilia-Romagna between 2017 and 2020, by tumour site and local health authority (LHA): number (white background) and percentage (grey background)

	LHA1	LHA2	LHA3	LHA4	LHA5	LHA6	LHA7	LHA8	Region
Head & neck	105	137	157	221	296	43	164	316	1,439
	2.6	2.5	2.7	2.7	2.6	2.7	3.1	2.3	2.6
Digestive	1,422	1,803	1,825	2,571	3,507	504	1,638	4,305	17,575
	35.3	33.2	31.4	31.9	30.4	31.5	30.6	31.2	31.6
Respiratory	778	857	1,084	1,501	1,993	279	957	2,649	10,098
	19.3	15.8	18.7	18.6	17.3	17.5	17.9	19.2	18.2
Muscoloskeletal	31	51	52	62	63	18	30	102	409
	0.8	0.9	0.9	0.8	0.6	1.1	0.6	0.7	0.7
Skin	122	129	193	171	319	68	110	360	1,472
	3.0	2.4	3.3	2.1	2.8	4.3	2.1	2.6	2.7
Nervous system	109	181	187	302	387	57	163	506	1,892
	2.7	3.3	3.2	3.7	3.4	3.6	3.0	3.7	3.4
Breast	278	355	370	517	789	102	382	790	3,583
	6.9	6.5	6.4	6.4	6.8	6.4	7.1	5.7	6.4
Genital (women)	196	243	262	385	598	74	204	586	2,548
	4.9	4.5	4.5	4.8	5.2	4.6	3.8	4.2	4.6
Genital (men)	9	21	14	32	50	6	29	54	215
	0.2	0.4	0.2	0.4	0.4	0.4	0.5	0.4	0.4
Urinary	247	397	389	566	918	103	461	962	4,043
	6.1	7.3	6.7	7.0	8.0	6.5	8.6	7.0	7.3
Prostate	181	237	275	323	486	56	204	491	2,253
	4.5	4.4	4.7	4.0	4.2	3.5	3.8	3.6	4.1
Haematologic	359	607	563	870	1,241	188	546	1500	5,874
	8.9	11.2	9.7	10.8	10.8	11.8	10.2	10.9	10.6
Other/metastatic	191	406	440	547	883	100	469	1,188	4,224
	4.7	7.5	7.6	6.8	7.7	6.3	8.8	8.6	7.6
Region	4,028	5,424	5,811	8,068	11530	1,598	5,357	13,809	55,625
	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Table 2 - Percentage of use of anticancer drugs *and palliative care (home or hospice care) during the last 30 days of life, by cancer type*

	Treatment during the last 30 day of life			
Cancer type	**%** anticancer drugs	**% home care**	**% hospice care**	**% overall palliative**
Head & neck	13.0	19.3	28.7	41.3
Digestive	10.3	23.1	27.7	44.8
Respiratory	19.3	21.5	28.0	43.3
Musculoskeletal	10.4	20.5	21.8	38.1
Skin	16.5	25.1	30.9	47.8
Nervous system	6.1	20.3	31.9	45.2
Breast	27.1	20.8	25.5	40.4
Genital (women)	16.4	20.8	29.6	44.6
Genital (men)	13.0	15.8	11.2	24.2
Urinary	8.7	19.2	22.9	37.4
Prostate	26.1	18.4	23.2	37.1
Haematologic	24.7	15.3	13.2	26.2
Other/metastatic	8.4	18.2	15.8	30.8
Region	***15.3***	***20.7***	***24.9***	***40.2***

Table 3 – Odds ratios of receiving anticancer drugs, *palliative care or both given each covariate (two-level multivariate model considering LHA clustering)*

Factor	Anticancer drugs	**Palliative care**	Anticancer drugs **+ palliative care**
	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)
Anticancer drugs within the last 30 days	-	0.90* (0.85-0.94)	-
Palliative care within the last 30 days	0.92* (0.87-0.97)	-	-
Haematologic tumour (*ref. solid/metastatic*)	2.15* (2.00-2.30)	0,52* (0.49-0.56)	1.03 (0.92-1.16)
Age (continuos, in year)	0.95* (0.95-0.95)	0.99* (0.99-0.99)	0.96*(0.96-0.96)
Hospital admission within the last 30 days	1.63* (1.55-1.72)	0.70* (0.67-0.72)	1.05 (0.98-1.14)
Surgery within the last 30 days	0.59* (0.52-0.67)	0.44* (0.39-0.49)	0.42*(0.33-0.54)
Aggressive tumour	0.88* (0.84-0.93)	1.12* (1.08-1.16)	0.84*(0.78-0.90)

**significance at p≤0.05*

Figure legends

Figure 1 - Percentage of use of anticancer drugs *during the last 30 days of life, by LHA of residence (all tumours)*

Figure 2 - Percentage of home care services use during the last 30 days of life, by LHA of residence (all tumours)

Author contributions

GF: conception and design, interpretation of data, drafting the article

MM: conception and design, analysis and interpretation of data

MG: interpretation of data, revising the article critically for important intellectual content

RGG: conception and design, interpretation of data, revising the article critically for important intellectual content

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All authors approved the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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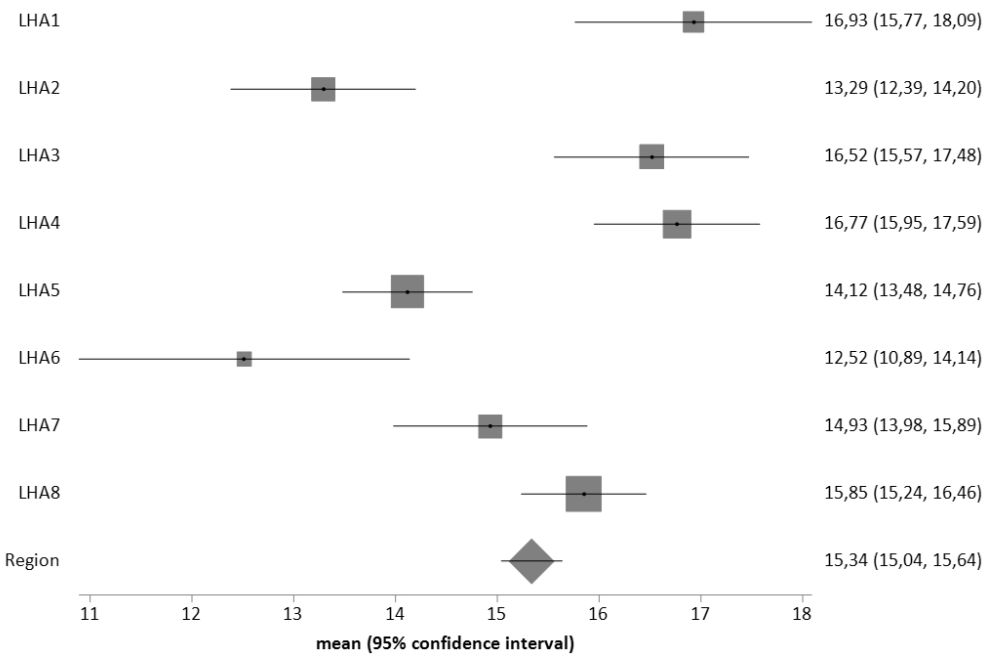

Figure 1 - Percentage of anticancer drug use during the last 30 days of life, by LHA of residence (all tumours)

86x57mm (300 x 300 DPI)

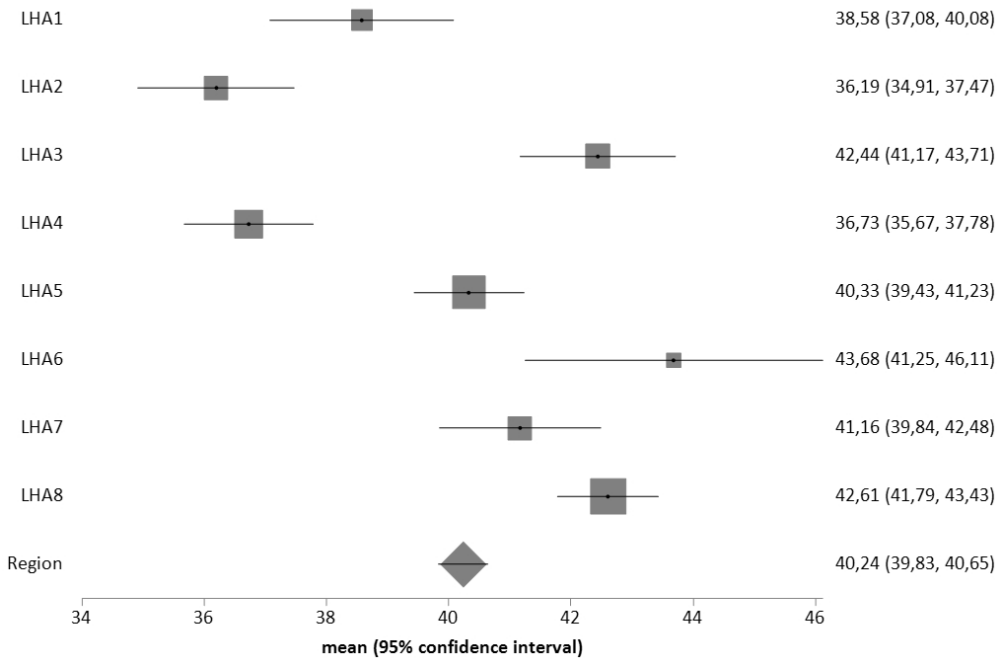

Figure 2 - Percentage of home care services use during the last 30 days of life, by LHA of residence (all tumours)

85x58mm (300 x 300 DPI)

Extra table - Odds ratios of receiving anticancer drugs, *palliative care or both given each covariate (logistic multivariate model without LHA clustering)*

Factor	Anticancer drugs	**Palliative care**	Anticancer drugs **+ palliative care**
	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)
Anticancer drugs within the last 30 days *(ref.NO)*	-	0.90*(0.85-0.94)	-
Palliative care within the last 30 days *(ref.NO)*	0.92*(0.87-0.97)	-	-
Haematologic tumour (*ref. solid/metastatic*)	2.15*(2.01-2.30)	0.52*(0.49-0.56)	1.03 (0.92-1.17)
Age (continous, in year)	0.95*(0.95-0.95)	0.99*(0.99-0.99)	0.96*(0.96-0.96)
Hospital admission within the last 30 days *(ref.NO)*	1.63*(1.55-1.72)	0.70*(0.67-0.72)	1.05 (0.98-1.14)
Surgery within the last 30 days *(ref.NO)*	0.59*(0.52-0.68)	0.44*(0.39-0.49)	0.42*(0.33-0.54)
Aggressive tumour *(ref.NO)*	0.88*(0.84-0.92)	1.12*(1.08-1.16)	0.84*(0.78-0.90)
LHA 3 *(reference)*			
LHA 1	1.09 (0.97-1.22)	0.86*(0.79-0.93)	1.03 (0.87-1.21)
LHA 2	0.79*(0.71-0.89)	0.77*(0.72-0.84)	0.69*(0.58-0.81)
LHA 3	1.04 (0.94-1.14)	0.80*(0.74-0.85)	0.91 (0.79-1.05)
LHA 4	0.91*(0.84-1.00)	0.92*(0.86-0.98)	0.84*(0.73-0.96)
LHA 5	0.75*(0.63-0.89)	1.07 (0.96-1.20)	0.76*(0.59-0.98)
LHA 6	0.92 (0.83-1.02)	0.96 (0.89-1.04)	0.89 (0.76-1.04)
LHA 7	0.99 (0.90-1.07)	1.04 (0.97-1.10)	1.03 (0.91-1.17)

* *significance at p≤0.05;* LHA = local health authority

APPENDIX. Relevant codes for cohort selection and use of health services

Cohort selection:

from mortality registry, deceased subjects with cancer as underlying cause of death (ICD X: C00-C97; D00-D09; D37-D48)

Anticancer drugs from hospital records and ambulatory care:

- Hospital records: ICD 9-CM pathology code V58.1x and/or*/ICD9 CM intervention code =99.25 and/or DRG code 410
- ambulatory care: administrative codes (from tariff nomenclator) 99.25, 992501, 8901F0

Anticancer drugs for outpatients:

ATC code L01 or L02

ICD-9 codes for aggressive tumours

150.x malignant tumor of the esophagus
151.x malignant tumor of the stomach
155.x malignant tumor of the liver and intrahepatic bile ducts
156.x malignant tumor of the gallbladder and extrahepatic ducts
157.x malignant tumor of the pancreas
162.x Malignant tumor of the trachea, bronchi and lungs
163.x malignant tumor of the pleura
179.x malignant tumor of the uterus
191.x malignant brain tumor
192.0 malignant tumor of the cranial nerves
192.1 malignant tumor of the brain meninges
202.4 leukemic reticuloendotheliosis
204.x lymphoid leukemia
205.x acute myeloid leukemia
206.x monocytic leukemia
207.x other specific leukemias
208.x unspecified cell-type leukemia

ICD-9 codes for metastases

196.xx-199.xx

ICD-X codes for haematologic tumors

C81 Hodgkin's disease
C82 Follicular (nodular) non-Hodgkin's lymphoma
C83 Diffuse non-Hodgkin's lymphoma
C84 Peripheral and cutaneous T-cell lymphoma

C85 Other and unspecified types of non-Hodgkin's lymphoma
C88 Immunoproliferative malignant diseases
C90 Multiple myeloma and malignant plasma cell tumors
C91 Lymphoid leukemia
C92 Myeloid leukemia
C93 Monocytic leukemia
C94 Other specified cell type leukemias
C95 Unspecified cell type leukemia
C96 Other and unspecified malignant tumor of lymphoid, hematopoietic and related tissues
D45 Polycythemia vera
D46 Myelodysplastic syndromes
D47 Other tumors of uncertain or unknown behavior of lymphatic, hematopoietic and tissues

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **(Pag. 1-2)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **(Pag. 2)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **(Pag. 5-6)**
Objectives	3	State specific objectives, including any prespecified hypotheses **(pag. 6)**
Methods		
Study design	4	Present key elements of study design early in the paper **(pag. 6)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **(pag. 6)**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **(pag. 6)**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **(pag. 6-7, appendix)**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **(pag. 6-7, appendix)**
Bias	9	Describe any efforts to address potential sources of bias **(pag. 7, appendix for multivariate statistical models)**
Study size	10	Explain how the study size was arrived at **We considered all deceased subjects in a four-year period (pag. 6). No formal hypothesis was pre-specified**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **(pag. 6-7, appendix)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **(pag. 7)**
		(*b*) Describe any methods used to examine subgroups and interactions **(pag. 7)**
		(*c*) Explain how missing data were addressed **(we commented on completeness of data at pag. 10)**
		(*d*) If applicable, explain how loss to follow-up was addressed **(not applicable)**
		(*e*) Describe any sensitivity analyses **(pag. 7 – LHA clustering vs not clustering)**

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Pag. 6-7 and table 1 (included all deceased subjects – cancer as underlying cause of death)**
		(b) Give reasons for non-participation at each stage **(not applicable)**
		(c) Consider use of a flow diagram **(not applicable)**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **(pag. 7 – see covariates of the statistical models, table 3 and table in appendix)**
		(b) Indicate number of participants with missing data for each variable of interest **(55,625 subjects were included - pag. 7)**
		(c) Summarise follow-up time (eg, average and total amount) **(exposures were assessed in the last 30 days of life)**
Outcome data	15*	Report numbers of outcome events or summary measures over time **(% use of anticancer drugs and palliative care during the last 30 days of life has been reported by cancer type – see tab. 2)**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence intervals). Make clear which confounders were adjusted for and why they were included **We provided results from multivariate analyses (OR and confidence intervals -– see pag. 7-8, tab 3a and table in the appendix)**
		(*b*) Report category boundaries when continuous variables were categorized **Not applicable**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **Not relevant**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **See table in appendix**
Discussion		
Key results	18	Summarise key results with reference to study objectives **(pag. 9)**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **(pag. 10)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **(pag. 9-11)**
Generalisability	21	Discuss the generalisability (external validity) of the study results **(pag. 10)**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **(not applicable – authors work within the Italian NHS and this research was**

within the scope of their job)

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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End of life care in cancer patients: how much drug therapy and how much palliative care? Record linkage study in Northern Italy

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End of life care in cancer patients: how much drug therapy and how much palliative care? Record linkage study in Northern Italy

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Participant consent: not required (the study cohort was made up of deceased patients).

The "Area Vasta Emilia Nord" Ethics Committee waived the need for next of kins' consent

Abstract (word count: 300 words)

Objectives

Investigating end-of-life use of anticancer drugs and of palliative care services.

Design

Population based cohort linked to mortality registry and administrative databases.

Setting

Emilia-Romagna Region (Northern Italy).

Participants

55,625 residents who died of cancer between 2017-2020.

Primary and secondary outcome measures

Multivariate analyses were carried out to assess the relationship between cancer drug therapy and palliative care services, and their association with factors related to tumour severity.

Results

In the last month of life, 15.3% of study population received anticancer drugs (from 12.5% to 16.9% across the eight local health authorities - LHA) and 40.2% received palliative care services (from 36.2% to 43.7%). Drug therapy was inversely associated with receiving palliative care services within the last 30 days (odds ratio 0.92, 95% CI 0.87-0.97), surgery within the last 6 months (OR 0.59, 95% CI 0.52-0.67), aggressive tumours (OR 0.88, 95% CI 0.84-0.93) and increasing age (OR 0.95, 95% CI 0.95-0.95). Drug therapy was more likely among those with haematologic tumours (OR 2.15, 95% CI 2.00-2.30) and in case of hospital admissions within the last 6 months (OR 1.63, 95% CI 1.55-1.72). Palliative care was less likely among those with haematologic compared with other tumours (OR 0.52, 95% CI 0.49-0.56), in case of surgery (OR 0.44, 95% CI 0.39-0.49) or hospital admissions (OR 0.70, 95% CI 0.67-0.72) within the last 6 months, if receiving anticancer drugs during the last 30 days (OR 0.90, 95% CI 0.85-0.94) and for each year of increasing age (OR 0.99, 95% CI 0.99-0.99). Palliative care was more likely in presence of aggressive tumours (OR 1.12, 95% CI 1.08-1.16).

Conclusion

Use of anticancer drugs and palliative care in the last month of life were inversely associated, showing variability across different LHAs. While administrative data have limits, our findings are in line with conclusions of other studies.

Article summary: strengths and limitations of this study

- Inclusion of all people deceased from cancer in a Region with 4,4 million residents, linking information on use of anticancer drugs and palliative care services with tumour characteristics and severity, are major strengths of this study.
- Caution should be taken since administrative data could not capture all the elements that may contribute to clinical decision making
- Moreover, although multivariate analyses provide adjustment for factors associated with tumour severity, residual confounding may be present

Keywords:

- End of life care
- Anticancer drug therapy
- Palliative care
- Cancer

TEXT (word count: 2667 words, excluding tables, figures and references)

Introduction

The appropriate use of anticancer drugs in end-of-life care is increasingly debated, both for clinical and economic reasons. [1,2] Aggressive treatments, facilitated by the availability of newer anticancer agents that have fewer side effects, [3] often do not alleviate patients' condition or provide hope for extending significantly life of decent quality. Focus on clinically irrelevant treatments may lead to the underuse of palliative care, [4,5,6] defined by WHO as "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through … assessment and treatment of pain and other problems, physical, psychosocial and spiritual". [7] Palliative care is generally provided in dedicated hospices or as home care services by a specially trained team of doctors, nurses and other specialists who work together with a patient's other doctors to provide an extra layer of support.

[8,9] Expectations of patients' and parents on one side, [10] and difficulties in predicting and communicating patients' prognosis on the other, [11,12] are among the main determinants of overuse of anticancer drugs (box). Some patients may perceive continued active treatment as the only acceptable option. [10] For example, in a prospective cohort of terminally ill patients with cancer (n = 386), 31% preferred life-extending care rather than comfort care and as many as 77% preferred to receive drug treatment even if it would extend their life by only one week. [12] Communication between the care team, patient and family seem to be a central element that can influence this phenomenon. [13]

From the clinicians' point of view, withdrawal of drugs during the final, but not exactly predictable, stages of life is challenging [14]: early withdrawal can cause potential harm, whereas late withdrawal would involve unnecessary treatment and stress (box). Research findings suggest that culture may impact the utilization of aggressive treatment in patients with advanced cancer. For example, a study from Japan stated that only 3.7% of patients receive chemotherapy in their last 2 weeks of life [15]

However, anticancer therapy itself is frequently considered a form of palliative care, aimed at reducing tumour-related symptoms, so that boundaries between curative and palliative intent are sometimes difficult to establish (box). [16,17,18] According to the American Society of Clinical Oncology (ASCO), anticancer drugs

can potentially improve QOL in late stages of life even if they don't impact survival length [19]. In this regard, their use promotes a simultaneous care approach, using palliative care alongside usual oncology care as the standard of care for any patient with advanced cancer. [20]

Several studies have analysed use of anticancer drugs in the last weeks of life with results that, although variable, show a tendency to prolong treatment beyond realistic expectations of a favourable benefit-risk ratio.[16,21,22,23,24,25,26] Analysis of data available in administrative and clinical databases can inform about prescribing patterns and the utilization of health care services in the end of life, in order to provide useful basis for discussion helping clinicians and health care managers identify areas of improvement, enhance the appropriateness and value of cancer care and make judicious use of available resources. In keeping with these targets, this study aims at providing insights on the use of anticancer drugs, hospital, hospice and home care services in the last month of life in a region of Northern Italy with more than 4 million residents, also to assess whether palliative care services are inversely associated with overuse of antineoplastic therapy.

Methods

A cohort of residents in the Emilia-Romagna Region who had cancer as the underlying cause of death between 2017 and 2020 (ICD-X classification: *C00-C97, D00-D09, D37-D48)* were selected from the regional mortality registry. This cohort was linked with the routinely available administrative databases, specifically: 1) hospital discharge records (including inpatient use of anticancer drugs, type of tumour, patients' age, surgery and hospital admissions); 2) ambulatory services (specifying use of anticancer drugs); 3) outpatient pharmacological prescriptions (use of drugs within ATC classes L01 and L02); 4) hospice and 5) domiciliary care databases (also collectively considered as palliative care services). These databases do not include any personal details (e.g. name or fiscal code) that can allow direct identification of included subjects: anonymity is warranted since each resident is associated to a unique identification number, allowing record linkage procedures. A list of codes used to select hospital discharge information and ambulatory care is available in the appendix.

Analyses were specifically aimed at describing frequency of anticancer drug use, palliative care services or both received within the last 30 days of life among eight Local Health Authorities (LHA). Logistic multivariate two-level analyses [27] were carried out to assess whether 1) anticancer drug use, 2) palliative care services 3) or both within the last 30 days of life could be associated with each other as well as with type of tumour (solid vs haematological, or aggressive tumours - see list in the appendix), patients' age, any surgery and hospital admissions within the last 6 months, considering LHA clustering as the second level (random intercept) to eliminate the effect of a possible correlation of results of residents in the same province. One-level models, [28] adding each LHA as covariates (each compared to a reference LHA) were subsequently used to assess whether use of anticancer drugs and of palliative care could present variability among LHA. Odds ratio with 95% confidence intervals were calculated. SAS version 8.2 (SAS Institute inc., Cary, NC, USA) and STATA/SE version 16.1 (STATACorp, College Station, TX 77845) were used for statistical analyses.

Patient and Public Involvement: no patient involved.

Results

In Emilia-Romagna, 55,625 people died from cancer between January 1, 2017 and December 31, 2020. Table 1 quantifies the main cancer diagnosis associated with death. Extra table 1 also provides specific data on each LHA: no substantial differences are shown among them. Table 2 shows use of anticancer drugs and of palliative care services within the last 30 days of life by main cancer diagnosis in the whole cohort. The highest use of anticancer drugs was in people with breast, prostate and haematologic tumours (in more than 20% of patients), whereas the lowest use was in people with nervous system and urinary tumours (in less than 10% of patients). Use of palliative care services appears relatively uniform across tumour types, except for a lower observed use in genital tumours in men and in haematologic tumours. Overall, 15.3% of patients received anticancer drugs within the last 30 days of life, with an increasing trend from 2017 (14.6%) to 2020 (16.2%). About palliative care services, 40.2% of patients received them (from 39.7% in 2017 to 40.8% in 2020). 4.1% received surgery within the last 30 days.

Among the eight local health authorities, there was variability in the use of anticancer drugs (from 12.5% to 16.9% - Figure 1) and of palliative care (from 36.2% to 43.7% - Figure 2) in the last 30 days of life. 39.1% of patients died in hospital, with wide variability among the LHAs (range: from 29.4% to 44.0%).

The likelihood to receive anticancer drugs during the last 30 days of life mostly increased in case of haematologic compared to other tumours; it also increased in case of hospital admissions within the last 6 months. It was reduced in case of surgery within the last 6 months and (less) in case of aggressive compared to other tumours, receiving home care or hospice services during the last 30 days and for every year of increasing age. Detailed data are available in Table 3. The intracluster correlation coefficient (ICC) is 0.3%, showing low intra-LHA correlation.

The likelihood to receive palliative care during the last 30 days of life shows a limited increase in presence of aggressive compared to other tumours. It was reduced in case of haematologic compared to other tumours, hospital admissions within the last 6 months, surgery within the last 6 months and (less)in case of receiving anticancer drugs during the last 30 days and for every year of increasing age (Table 3). Also in this case, the intracluster correlation coefficient (0.3%) shows no intra LHA correlation.

The likelihood to receive concurrent anticancer drugs and palliative care during the last 30 days of life was reduced in case of surgery within the last 6 months and (less) in case of aggressive compared to other tumours, in keeping with the result of the first model, suggesting that clinicians in such cases tend not to insist on drug therapy (Table 3). Also in this case, the intracluster correlation coefficient (0.4%) shows no intra-LHA correlation.

Since no effect of clustering of subjects in the 8 LHAs was shown, we replicated the latter models without LHA clustering and including LHA as covariates, in order to assess variability among LHAs (Extra table 2). Covariate coefficients are the same as in the cluster models, confirming no effect of LHA clustering on the outcome. As raw data suggested in Figure 1 and Figure 2, place of residence may also be associated with the likelihood to receive end-of-life drug therapies and palliative care after adjusting for the other covariates.

Discussion

This study shows that use of anticancer drugs and of palliative care services in the last month of life are inversely associated rather than complementary. A variable use of anticancer drugs and of palliative care services in different LHAs and across different tumours in the last month of life is also shown. Compared to solid cancers, haematologic tumours tend to be treated more frequently with anticancer drugs and to be provided less frequently with palliative care. This circumstance could be related to the more frequent availability of effective in-hospital therapies leading to longer survival [29], to perceiving a more favourable benefit-risk ratio of "not giving up", and to the often rapid pace of decline near death. This has also been observed in other studies. [30,31,32,33] An opposite pattern is associated with aggressive tumours, treated more frequently with palliative care and less frequently with anticancer drugs.

Variability among different LHAs may depend either on a different epidemiological distribution of the tumours and of their severity, or on different prescribing attitudes and availability of palliative services in the areas of residence. Main cancer diagnosis associated with death appear similar across different LHA. In addition, multivariate analyses provide adjustment for factors associated with tumour severity (age, haematologic tumour, previous surgery and hospital admission) and, although residual confounding can be reasonably present, we consider unlikely that it could provide the main explanation for the observed variability. Therefore, despite limits in our data and taking the possibility of unobserved factors (residual confounding) into account, we consider that this variability may be explained to a higher degree by different prescribing and management attitudes rather than by local epidemiology/case mix. As for the availability of palliative services in the areas of residence, the Emilia-Romagna Region has been quite active in implementing a national law issued in 2010 [34] to guarantee such availability as well as adequate access to these services. [35] Further qualitative research could analyse whether attitudes and level of endorsement in different LHA may in part explain differential use/access, aside from their availability which is relatively homogeneous across the region. Inclusion of all people deceased from cancer in a Region with 4,4 million residents, linking information on use of anticancer drugs and palliative care services with tumour characteristics and severity, are major strengths of this study. However, our results should be taken with caution since administrative data are grossly descriptive

and have obvious limits in capturing all the elements that may contribute to clinical decision making. As for quality and completeness of available data, they are collected during the patient's care for the purpose of reimbursements to healthcare rather than for research. No scientific validation of the unique patient identification number is available.

Nonetheless, our findings are in line with conclusions of several other studies. There may be a potential to reduce use of end-of-life anticancer therapies increasing at the same time the provision of palliative care services. In general, shifting resources from aggressive pharmacological treatments to comprehensive approaches to palliative care services should be a priority in cancer care, and palliative care may be one of the determinants "protecting" against the overuse of anticancer drugs. While the high variability observed among Local Health Authorities in the use of these services is worrying, it also suggests that a huge potential exists to better organize end of life care for cancer patients.

Clinical and administrative data can help promote discussion among oncologists, specialists in palliative care, nurses, general practitioners, pharmacists, health care managers and (ideally) patients' representatives to maximize quality of end-of-life care, especially in blood malignancies, in light of available resources. Local multidisciplinary groups can/should use data to analyse possible determinants of inappropriate care and propose strategies to offer patients and their families the best possible support. This especially in light of the increasing availability and accelerated approval of new therapies [36] that often have a limited added value but a wide range of indications, targeting resistant cases and/or administered by oral route. These circumstances may favour an increase in the use of anticancer drugs, sometimes (or often) without a real clinical benefit, and may hinder or delay access to palliative care services.

Data on pharmaco-utilization can also help local multidisciplinary groups to discuss to what extent anticancer drugs are used with a palliative intent, and to foster the design of research protocols aimed at evaluating the impact of drug utilization on patients' quality of life (QoL). Record linkage studies generally cannot provide such specific information, since QoL information is generally unavailable in administrative databases, and this is also one of the limits of our study. A few RCTs and systematic reviews addressing different types of tumours have shown some effect of different anticancer therapies on reducing pain and improving patients' quality of

life [37,38,39,40,41,42]. However, this issue is largely debated as evidence is controversial or lacking, so that the guideline from the European Society for Medical Oncology (ESMO) explicitly contraindicates the use of anticancer drugs in the last weeks of life. [43]

In any case, the availability of adequate prognostic tools is key to improve the appropriateness of end-of-life care. In theory, ECOG performance status can be used as such to guide clinicians and palliative care specialists to make choices for appropriate health care, [44] although it is subjectively assessed and may lead to optimistic assessments. [45] A palliative prognostic score integrating subjective judgments with a series of more objective parameters has been validated and extensively discussed, showing a good balance between accuracy and applicability in clinical practice. [46,47,48,49] Physicians should be also prepared to address patients' and relatives' concerns and expectations by refining their communication skills. Interventions that include communication about advanced care planning (ACP) and care preferences with goals-of-care (GOC) conversations, [50] have been found to improve concordance between care preferences and actual care delivered. [51] Nurses play a pivotal role too in accompanying patients and their families through their cancer journey, being in an ideal position [52, 53] to provide cancer patients and their families with emotional and social support, together with adequate communication about the diagnosis, prognosis and treatment alternatives [52,54].

Conclusion

By showing, through administrative data, that use of anticancer drugs and of palliative care services in the last month of life may be inversely associated rather than complementary, this study suggests the need to further explore the hypothesis that palliative care services may have a role in preventing inappropriate use of anticancer drugs. Administrative data may help highlight macro issues that should be addressed with a multidisciplinary approach involving clinicians, nurses, specialists in palliative care, pharmacists, health care managers and members of the public, eventually helping the promotion of palliative care and limiting the use of aggressive treatments that may not be beneficial.

Box. Main determinants of potential overuse of anticancer drugs

- Expectations of patients' and parents (and "never give up" attitude)
- difficulties in predicting patients' prognosis
- difficulties in communicating patients' prognosis
- physician's perception of potential harm by early withdrawal
- therapy seen as a form of palliative care

Table 1 – Study population of patients dying for cancer in Emilia-Romagna between 2017 and 2020, by tumour site: number (white background) and percentage (grey background)

Head & neck	1,439
	2.6
Digestive	17,575
	31.6
Respiratory	10,098
	18.2
Muscoloskeletal	409
	0.7
Skin	1,472
	2.7
Nervous system	1,892
	3.4
Breast	3,583
	6.4
Genital (women)	2,548
	4.6
Genital (men)	215
	0.4
Urinary	4,043
	7.3
Prostate	2,253
	4.1
Haematologic	5,874
	10.6
Other/metastatic	4,224
	7.6
Region	55,625
	100.0

Table 2 - Percentage of use of anticancer drugs *and palliative care (home or hospice care) during the last 30 days of life, by cancer type*

	Treatment during the last 30 day of life			
Cancer type	**%** anticancer drugs	**% home care**	**% hospice care**	**% overall palliative**
Head & neck	13.0	19.3	28.7	41.3
Digestive	10.3	23.1	27.7	44.8
Respiratory	19.3	21.5	28.0	43.3
Musculoskeletal	10.4	20.5	21.8	38.1
Skin	16.5	25.1	30.9	47.8
Nervous system	6.1	20.3	31.9	45.2
Breast	27.1	20.8	25.5	40.4
Genital (women)	16.4	20.8	29.6	44.6
Genital (men)	13.0	15.8	11.2	24.2
Urinary	8.7	19.2	22.9	37.4
Prostate	26.1	18.4	23.2	37.1
Haematologic	24.7	15.3	13.2	26.2
Other/metastatic	8.4	18.2	15.8	30.8
Region	***15.3***	***20.7***	***24.9***	***40.2***

Table 3 – Odds ratios of receiving anticancer drugs, *palliative care or both given each covariate (two-level multivariate model considering LHA clustering)*

Factor	Anticancer drugs	**Palliative care**	Anticancer drugs **+ palliative care**
	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)
Anticancer drugs within the last 30 days	-	0.90* (0.85-0.94)	-
Palliative care within the last 30 days	0.92* (0.87-0.97)	-	-
Haematologic tumour (*ref. solid/metastatic*)	2.15* (2.00-2.30)	0,52* (0.49-0.56)	1.03 (0.92-1.16)
Age (continuos, in year)	0.95* (0.95-0.95)	0.99* (0.99-0.99)	0.96*(0.96-0.96)
Hospital admission within the last 6 months	1.63* (1.55-1.72)	0.70* (0.67-0.72)	1.05 (0.98-1.14)
Surgery within the last 6 months	0.59* (0.52-0.67)	0.44* (0.39-0.49)	0.42*(0.33-0.54)
Aggressive tumour	0.88* (0.84-0.93)	1.12* (1.08-1.16)	0.84*(0.78-0.90)

**significance at p≤0.05*

Figure legends

Figure 1 - Percentage of use of anticancer drugs *during the last 30 days of life, by LHA of residence (all tumours)*

Figure 2 - Percentage of home care services use during the last 30 days of life, by LHA of residence (all tumours)

Author contributions

GF: conception and design, interpretation of data, drafting the article

MM: conception and design, analysis and interpretation of data

MG: interpretation of data, revising the article critically for important intellectual content

RGG: conception and design, interpretation of data, revising the article critically for important intellectual content

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All authors approved the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Ethics statement: this study involves human participants and was approved by an Ethics Committee.

Name of the Ethics Committee: Comitato Etico dell'Area Vasta Emilia Nord, Reggio Emilia (Italy)

Reference number for ethics approval : 1032/2020/OSS/AUSLREreceived from the Ethics Committee of “Area Vasta Emilia Nord”

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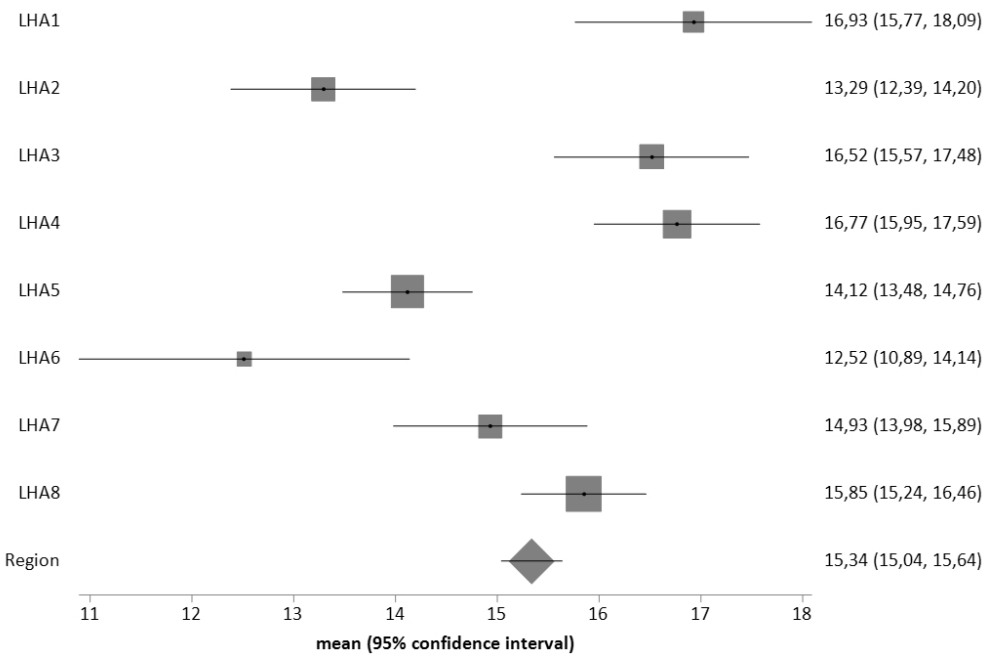

Figure 1 - Percentage of anticancer drug use during the last 30 days of life, by LHA of residence (all tumours)

86x57mm (300 x 300 DPI)

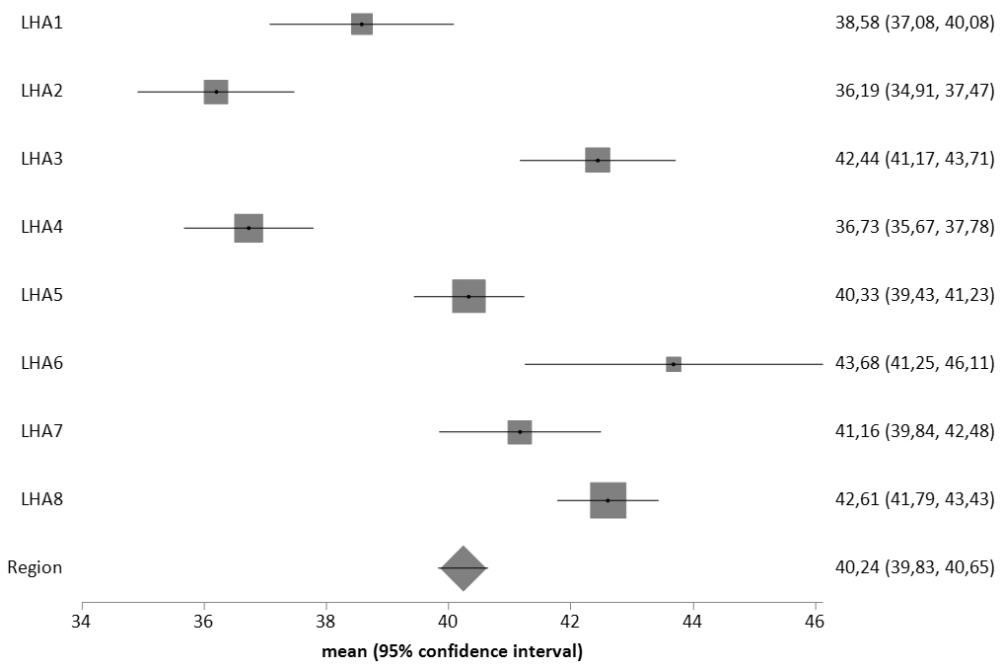

Figure 2 - Percentage of home care services use during the last 30 days of life, by LHA of residence (all tumours)

85x58mm (300 x 300 DPI)

Extra table 1 – Study population of patients dying for cancer in Emilia-Romagna between 2017 and 2020, by tumour site and local health authority (LHA): number (white background) and percentage (grey background)

	LHA1	LHA2	LHA3	LHA4	LHA5	LHA6	LHA7	LHA8	Region
Head & neck	105	137	157	221	296	43	164	316	1,439
	2.6	2.5	2.7	2.7	2.6	2.7	3.1	2.3	2.6
Digestive	1,422	1,803	1,825	2,571	3,507	504	1,638	4,305	17,575
	35.3	33.2	31.4	31.9	30.4	31.5	30.6	31.2	31.6
Respiratory	778	857	1,084	1,501	1,993	279	957	2,649	10,098
	19.3	15.8	18.7	18.6	17.3	17.5	17.9	19.2	18.2
Muscoloskeletal	31	51	52	62	63	18	30	102	409
	0.8	0.9	0.9	0.8	0.6	1.1	0.6	0.7	0.7
Skin	122	129	193	171	319	68	110	360	1,472
	3.0	2.4	3.3	2.1	2.8	4.3	2.1	2.6	2.7
Nervous system	109	181	187	302	387	57	163	506	1,892
	2.7	3.3	3.2	3.7	3.4	3.6	3.0	3.7	3.4
Breast	278	355	370	517	789	102	382	790	3,583
	6.9	6.5	6.4	6.4	6.8	6.4	7.1	5.7	6.4
Genital (women)	196	243	262	385	598	74	204	586	2,548
	4.9	4.5	4.5	4.8	5.2	4.6	3.8	4.2	4.6
Genital (men)	9	21	14	32	50	6	29	54	215
	0.2	0.4	0.2	0.4	0.4	0.4	0.5	0.4	0.4
Urinary	247	397	389	566	918	103	461	962	4,043
	6.1	7.3	6.7	7.0	8.0	6.5	8.6	7.0	7.3
Prostate	181	237	275	323	486	56	204	491	2,253
	4.5	4.4	4.7	4.0	4.2	3.5	3.8	3.6	4.1
Haematologic	359	607	563	870	1,241	188	546	1500	5,874
	8.9	11.2	9.7	10.8	10.8	11.8	10.2	10.9	10.6
Other/metastatic	191	406	440	547	883	100	469	1,188	4,224
	4.7	7.5	7.6	6.8	7.7	6.3	8.8	8.6	7.6
Region	4,028	5,424	5,811	8,068	11530	1,598	5,357	13,809	55,625
	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Extra table 2 - Odds ratios of receiving anticancer drugs, *palliative care or both given each covariate (logistic multivariate model without LHA clustering)*

Factor	Anticancer drugs	**Palliative care**	Anticancer drugs **+ palliative care**
	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)
Anticancer drugs within the last 30 days *(ref.NO)*	-	0.90*(0.85-0.94)	-
Palliative care within the last 30 days *(ref.NO)*	0.92*(0.87-0.97)	-	-
Haematologic tumour (*ref. solid/metastatic*)	2.15*(2.01-2.30)	0.52*(0.49-0.56)	1.03 (0.92-1.17)
Age (continous, in year)	0.95*(0.95-0.95)	0.99*(0.99-0.99)	0.96*(0.96-0.96)
Hospital admission within the last 30 days *(ref.NO)*	1.63*(1.55-1.72)	0.70*(0.67-0.72)	1.05 (0.98-1.14)
Surgery within the last 30 days *(ref.NO)*	0.59*(0.52-0.68)	0.44*(0.39-0.49)	0.42*(0.33-0.54)
Aggressive tumour *(ref.NO)*	0.88*(0.84-0.92)	1.12*(1.08-1.16)	0.84*(0.78-0.90)
LHA 3 *(reference)*			
LHA 1	1.09 (0.97-1.22)	0.86*(0.79-0.93)	1.03 (0.87-1.21)
LHA 2	0.79*(0.71-0.89)	0.77*(0.72-0.84)	0.69*(0.58-0.81)
LHA 3	1.04 (0.94-1.14)	0.80*(0.74-0.85)	0.91 (0.79-1.05)
LHA 4	0.91*(0.84-1.00)	0.92*(0.86-0.98)	0.84*(0.73-0.96)
LHA 5	0.75*(0.63-0.89)	1.07 (0.96-1.20)	0.76*(0.59-0.98)
LHA 6	0.92 (0.83-1.02)	0.96 (0.89-1.04)	0.89 (0.76-1.04)
LHA 7	0.99 (0.90-1.07)	1.04 (0.97-1.10)	1.03 (0.91-1.17)

* *significance at p≤0.05;* LHA = local health authority

APPENDIX. Relevant codes for cohort selection and use of health services

Cohort selection:

from mortality registry, deceased subjects with cancer as underlying cause of death (ICD X: C00-C97; D00-D09; D37-D48)

Anticancer drugs from hospital records and ambulatory care:

- Hospital records: ICD 9-CM pathology code V58.1x and/or*/ICD9 CM intervention code =99.25 and/or DRG code 410
- ambulatory care: administrative codes (from tariff nomenclator) 99.25, 992501, 8901F0

Anticancer drugs for outpatients:

ATC code L01 or L02

ICD-9 codes for aggressive tumours

150.x malignant tumor of the esophagus
151.x malignant tumor of the stomach
155.x malignant tumor of the liver and intrahepatic bile ducts
156.x malignant tumor of the gallbladder and extrahepatic ducts
157.x malignant tumor of the pancreas
162.x Malignant tumor of the trachea, bronchi and lungs
163.x malignant tumor of the pleura
179.x malignant tumor of the uterus
191.x malignant brain tumor
192.0 malignant tumor of the cranial nerves
192.1 malignant tumor of the brain meninges
202.4 leukemic reticuloendotheliosis
204.x lymphoid leukemia
205.x acute myeloid leukemia
206.x monocytic leukemia
207.x other specific leukemias
208.x unspecified cell-type leukemia

ICD-9 codes for metastases

196.xx-199.xx

ICD-X codes for haematologic tumors

C81 Hodgkin's disease
C82 Follicular (nodular) non-Hodgkin's lymphoma
C83 Diffuse non-Hodgkin's lymphoma
C84 Peripheral and cutaneous T-cell lymphoma

C85 Other and unspecified types of non-Hodgkin's lymphoma
C88 Immunoproliferative malignant diseases
C90 Multiple myeloma and malignant plasma cell tumors
C91 Lymphoid leukemia
C92 Myeloid leukemia
C93 Monocytic leukemia
C94 Other specified cell type leukemias
C95 Unspecified cell type leukemia
C96 Other and unspecified malignant tumor of lymphoid, hematopoietic and related tissues
D45 Polycythemia vera
D46 Myelodysplastic syndromes
D47 Other tumors of uncertain or unknown behavior of lymphatic, hematopoietic and tissues

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **(Pag. 1-2)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **(Pag. 2-3)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **(Pag. 5-6)**
Objectives	3	State specific objectives, including any prespecified hypotheses **(pag. 6)**
Methods		
Study design	4	Present key elements of study design early in the paper **(pag. 6)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **(pag. 6)**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **(pag. 6)**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **(pag. 7, appendix)**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **(pag. 6-7, appendix)**
Bias	9	Describe any efforts to address potential sources of bias **(pag. 7, appendix for multivariate statistical models)**
Study size	10	Explain how the study size was arrived at **We considered all deceased subjects in a four-year period (pag. 6). No formal hypothesis was pre-specified**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **(pag. 6-7, appendix)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **(pag. 7)**
		(*b*) Describe any methods used to examine subgroups and interactions **(pag. 7)**
		(*c*) Explain how missing data were addressed **(we commented on completeness of data at pag. 10)**
		(*d*) If applicable, explain how loss to follow-up was addressed **(not applicable)**
		(*e*) Describe any sensitivity analyses **(pag. 7 – LHA clustering vs not clustering)**

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Pag. 7 and table 1 (included all deceased subjects – cancer as underlying cause of death)**
		(b) Give reasons for non-participation at each stage **(not applicable)**
		(c) Consider use of a flow diagram **(not applicable)**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **(pag. 7-8 – see covariates of the statistical models, table 3 and extra tables)**
		(b) Indicate number of participants with missing data for each variable of interest **(55,625 subjects were included - pag. 7)**
		(c) Summarise follow-up time (eg, average and total amount) **(exposures were assessed in the last 30 days of life)**
Outcome data	15*	Report numbers of outcome events or summary measures over time **(% use of anticancer drugs and palliative care during the last 30 days of life has been reported by cancer type – see tab. 2)**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence intervals). Make clear which confounders were adjusted for and why they were included **We provided results from multivariate analyses (OR and confidence intervals -- see tab 3 and extra table 2)**
		(*b*) Report category boundaries when continuous variables were categorized **Not applicable**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **Not relevant**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **See extra tables**
Discussion		
Key results	18	Summarise key results with reference to study objectives **(pag. 9)**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **(pag. 9-10)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **(pag. 9-11)**
Generalisability	21	Discuss the generalisability (external validity) of the study results **(pag. 9-10)**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **(not applicable – authors work within the Italian NHS and this research was**

within the scope of their job)

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.