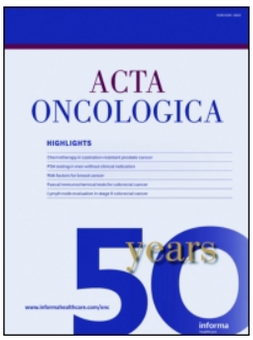

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End-of-life anticancer treatment – a nationwide registry-based study of trends in the use of chemo-, endocrine, immune-, and targeted therapies

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ORIGINAL ARTICLE

End-of-life anticancer treatment – a nationwide registry-based study of trends in the use of chemo-, endocrine, immune-, and targeted therapies

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ABSTRACT

Background: Anticancer treatments near the end of a patient's life should generally be avoided, as it leaves the patient with no significant anticancer effect but increases the risk of severe side effects. We described the pattern of all end-of-life anticancer treatment in a population of Danish cancer patients.

Methods: Using the Danish national health registries, we identified all patients deceased due to cancer 2010–2015. Anticancer treatment registered in the last 30 days of life was categorized as end-of-life treatment. Predictors of such treatment were investigated using logistic regression models.

Results: We identified 42,277 patients (median age 70 years) of whom 16% received end-of-life anticancer treatment. This proportion did not change during the study period ($p = .09$). Chemotherapy alone was the most frequent treatment, accounting for 78% of all end-of-life treatment in 2010, decreasing to 71% in 2015. In contrast, end-of-life use of immunotherapy, targeted therapy and endocrine therapy increased during the study period. Breast cancer as index cancer was associated with the highest frequency of end-of-life treatment (23%), followed by malignant melanoma (21%), and prostate cancer (18%). Factors associated with lower odds for end-of-life treatment were female sex, older age, high burden of comorbidity, and being diagnosed >6 months prior to death.

Conclusions: We found a stable overall rate at 16% of patients receiving anticancer treatment within one month prior to death in this nationwide sample of cancer deaths. Further research is needed to assess whether this level of end-of-life treatment is justified or reflects inappropriate use.

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KEYWORDS
Epidemiology; end-of-life anticancer treatment; palliative; cancer

Background

Anticancer treatment near the ending of a patient's life should generally be avoided as it leaves the patient with no significant anticancer effect, and at risk of severe side effects. Studies on chemotherapy at the end-of-life show, it may impair the quality of life [1] and the access to palliative end-of-life care [1,2], without providing a survival benefit. End-of-life chemotherapy has also been associated with a higher risk of dying at a hospital than at home, which is against the wish of most patients [3–5]. Yet, use of chemotherapy at the end of life has been reported as high as 43% of the patients [6]. Focus on 'first do no harm' when prescribing anticancer treatment [7–9] is increasing with the rapid introduction of new anticancer therapies, as clinicians struggle to balance anticancer effect against possible adverse effects. Although the use of chemotherapy at the end of life has been studied, the use of combination therapies and newer therapies, such as immunotherapy and targeted therapy at the end of life in a 'real-life' population, is still by large unknown.

The aim of this study was to provide a nationwide description of the pattern of anticancer end-of-life treatment in Danish clinical oncology. Secondly, we aimed at identifying subpopulations of patients, likely to receive anticancer treatment at the ending of their life.

Methods and materials

By use of the Danish health registries, we performed a cohort study describing end-of-life anticancer treatment in Danish cancer patients deceased from January 1st, 2010 to December 31st, 2015.

Data sources

The CanEpid database at Open Patient data Explorative Network (OPEN) in Odense, Denmark contains trajectories of all Danish cancer patients with selected solid cancer forms (see Supplementary Table S1 for the ICD codes for the solid cancer forms included in CanEpid). Incident cases of cancers were ascertained from the Danish Cancer Registry [10] and we obtained information on diagnosis by International Classification of Disease (ICD) codes. Using the unique

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Supplementary data for this article can be accessed here.

personal identification number assigned to all Danish inhabitants by birth or first immigration in the Danish Civil Registration System [11], data were linked to all relevant nationwide health registers, including the Danish National Patient Registry [12] (for information on hospital contacts and treatment), The Danish Register of Causes of Death [13] (for information on cause of death) and the Danish Civil Registration System (for information on sex, birth date, date of death, and migration) [11].

In Denmark systemic anticancer treatment for solid tumors are exclusively prescribed and administered through the departments of oncology.

Study population

The study population comprised all adult cancer patients in the CanEpid database who died between January 1st, 2010 and December 31st, 2015. The sample was further restricted to those at risk of receiving unnecessary anticancer treatment near their end of life by requiring that they (i) were to have a solid tumor diagnosis defined by ICD-10 codes at any stage, (ii) were evaluated within 12 months prior to their death at a clinical oncology department related to above diagnosis, (iii) and had cancer listed as the primary cause of death. If a patient had more than one type of cancer diagnosed, the latest cancer diagnosed was considered as the index cancer.

Outcomes

We defined use of anticancer medications at the 'end-of-life' as an anticancer treatment received during the last 30 days of life whether it was an ongoing treatment initiated prior to the last 30 days of life, or a treatment initiated within that period. Anticancer treatment was defined by all approved oral and intravenous therapies, including conventional chemotherapies, endocrine therapies, immunotherapies, and targeted therapies such as check point inhibitors, nonspecific immunotherapies, monoclonal antibodies, and small molecule kinase inhibitors.

Descriptive variables

End-of-life anticancer treatment were categorized according to Danish examination and treatment codes [14,15] as chemotherapy (procedure code BWHA*), immunotherapy (BOHJ*, BWHB1, BWHB2, BWHB8), and endocrine therapy (BWHC*).

Patient demographic data included sex and age at time of death. From the Danish National Patient Registry, we obtained data on medical diagnoses and stage of cancer disease, all hospital contacts (admissions, evaluations, and ambulatory visits), and specific treatment, including dates of treatment provided upon visits. We calculated the Charlson Comorbidity Index (CCI) [16], based on both primary and secondary diagnoses, with exception of cancer diagnoses, 1 to 10 years prior to death. If the patient died during a hospital or hospice admission, the place of death was defined as at hospital or at hospice, in all other cases the place of death was defined as patient's home. In Denmark nursing homes are considered and registered as the patient's own home. We calculated and categorized time from diagnosis to death as days from first diagnosis of index cancer till death ($<$6 months, 6–12 months, 1–5 years, 5+ years).

Statistical analysis

We used descriptive statistics to evaluate the extent of end-of-life anticancer treatment. Factors associated with receiving end-of-life treatment were described using logistic regression with the characteristics of the deceased as independent variables. We estimated crude and mutually adjusted odds ratios (OR) with 95% confidence intervals (CI) for receiving end-of-life treatment within 30 days prior to death according to sex, age group, cancer group, CCI, and time since diagnosis. To account for an increasing age at the time of death, we also conducted the adjusted analysis age standardized according to age distribution in 2010. To describe the association between age (continuous) and end-of-life treatment in more details, we also generated restricted cubic splines with 70 years (median age) as reference, and 6 knots allowing for a non-linear association. As supplementary analyses, we repeated the analysis stratified by cancer group. All data was stored, handled, and analyzed pseudo anonymized on a secure server with logging, in accordance with Danish law.

Ethical considerations

The CanEpid database is approved by the Danish Health Authorities. The project was reported to the Danish Data Protection Agency under the Region of Southern Denmark (project number 18/14895). According to Danish legislation, purely register-based research needs no further approval including approval from a Research Ethics Committee [17].

Results

The final population of deceased cancer patients comprised 42,377 patients (Figure 1).

The population characteristics show an equal distribution between sexes, a distribution of age with a median age of 70 years (interquartile range 63–77 years). Lung cancer was the most frequent index cancer (35%) followed by colorectal cancer (15%) and breast cancer (10%) (Table 1). Overall, 37% had a CCI $>$0. The majority (88%) received their index cancer diagnosis less than five years prior to death, and 47% were diagnosed within 12 months prior to death.

The closer to death, the fewer patients received anticancer treatment (Figure 2). A total of 6748 (16%) patients received at least one anticancer treatment during the last 30 days before death. The proportion of patients receiving end-of-life anticancer treatment was stable during the study period ranging between 15–17% (Supplementary Figure S1). Chemotherapy in single use, or in combination with endocrine therapy, was the most frequently used type of treatment accounting for 75% of all end-of-life treatment with a

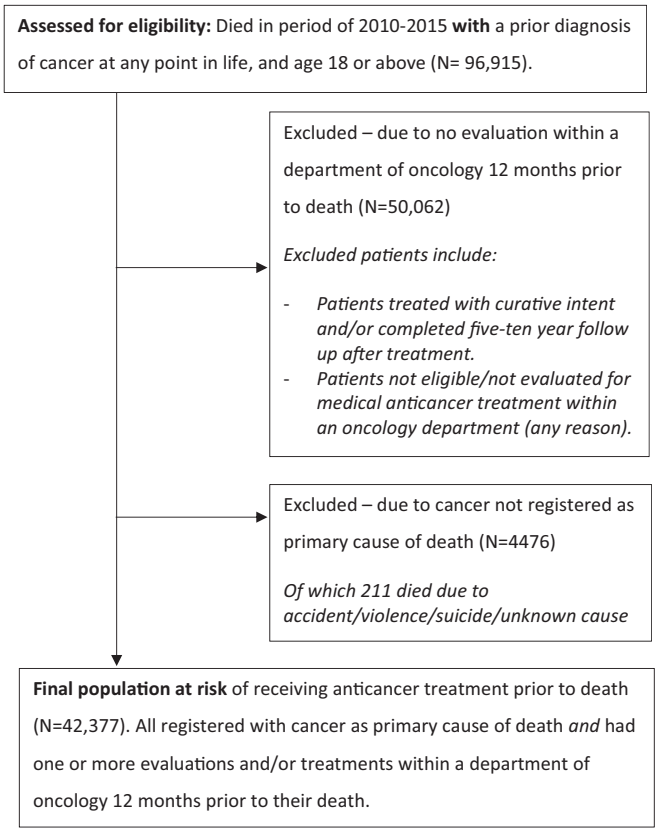

Figure 1. Flowchart of the study population – all cancer patient (> 18 years) in Denmark dying of cancer between 2010 and 2015 and in risk of receiving end-of-life treatment.

Table 1. *Characteristics of all deceased with cancer as primary cause of death and at least one visit to a department of oncology 12 months prior to death in Denmark (2010–2015).*

	Oncology population ($n = 42,377$)
Sex	
Male	21,010 (49.6%)
Female	21,367 (50.4%)
Age	
Median (IQR, years)	70 (63-77)
18–44	1013 (2.4%)
45–59	6306 (14.9%)
60–74	20,725 (48.9%)
75–89	13,709 (32.4%)
90+	624 (1.5%)
Index cancer diagnosis	
Lung	14,752 (34.8%)
Colorectal	6272 (14.8%)
Breast	4213 (9.9%)
Prostate	2986 (7.0%)
Female genital organ	3015 (7.1%)
Pancreas	2777 (6.6%)
Urinary Tract	2908 (6.9%)
Upper gastrointestinal	1923 (4.5%)
Brain/Central nervous system	1935 (4.6%)
Melanoma skin	1070 (2.5%)
Other	526 (1.2%)
Charlson Comorbidity Index	
0	25,875 (62.7%)
1-2	6161 (14.9%)
3+	9260 (22.4%)
Time since diagnosis	
0 - < 6 mo	11,463 (27.1%)
6 mo ≤ 1 year	8554 (20.2%)
1 ≤ 5 years	17,433 (41.1%)
5+ years	4927 (11.6%)
Missing	
Charlson Comorbidity Index	1081 (2.6%)

slight change toward use of immunotherapy and endocrine treatment, increasing in single use from 3.2% and 10% in 2010 to 7.2% and 16% in 2015, respectively (Supplementary Figure S2). Chemotherapy in combination with immunotherapy decreased from 9.0% in 2010 to 6.1% in 2015. Patients with breast cancer, as index cancer, had the highest proportion of end-of-life anticancer treatment (23%), followed by patients with malignant melanoma of the skin (21%), patients with pancreatic cancer (18%), and patients with prostate cancer (18%) (Figure 3). Patients with urinary tract cancer, as index cancer, were least likely to be treated by the end of life (10%). As a post hoc explanatory analysis of patients receiving end-of-life treatment, we found 32% of the breast cancer patients and 78% of the prostate cancer were treated with endocrine treatment alone.

Patients receiving end-of-life anticancer treatment were more likely to die in hospital and least likely to die at a hospice: Relative to dying at home adjusted ORs of 2.4 (95% CI 2.2–2.5) and 0.7 (95% CI 0.7–0.8), respectively.

When analyzing factors associated with the use of end-of-life treatment (Figure 4) we found that women were less likely to be treated than men (OR 0.91; 95% CI 0.86–0.97). We found decreasing likelihood of receiving end-of-life treatment by increasing age group, when compared to the age group 18–45 years. This was confirmed, when age was fitted, as a continuous variable, into a spline ($p < .05$) (Supplementary Figure S3). The risk of receiving end-of-life treatment varied among the specific cancer diagnoses (Figure 4): Using lung cancer patients as a reference group (due to numeric size), patients, diagnosed with breast cancer, prostate cancer, and malignant melanoma of the skin, had 1.5–2.2 higher odds of treatment. Conversely, patients with brain/central nervous system cancer, upper gastrointestinal cancer, and urinary tract cancer, had a reduction in likelihood between 30–40% compared to lung cancer patients. Patients with increased CCI had less likelihood of receiving end-of-life treatment, with a reduction of approximately 20% for patients with CCI 0. A small variance was observed in the study period between the proportion of patients receiving end-of-life treatment, with OR ranging from 0.9–1.1 compared to year 2010. Patients, diagnosed with cancer within the last 6 months prior to their death, had the highest odds of being treated near end of life. Standardizing by age, according to 2010, did not change the estimates significantly (Supplementary Figure S4).

For all cancer groups, older age was associated with decreasing likelihood of end-of-life treatment. In most cancer groups, a CCI >0 was associated with a lower likelihood of treatment (Supplementary Figures S5-15). To be noted, within some diagnosis groups, due to small categories, confidence intervals were wide, and estimates may consequently be imprecise.

Discussion

During 2010–2015, 16% of deceased cancer patients received anticancer treatment in the last month of their life. The likelihood of being treated was associated with type of cancer,

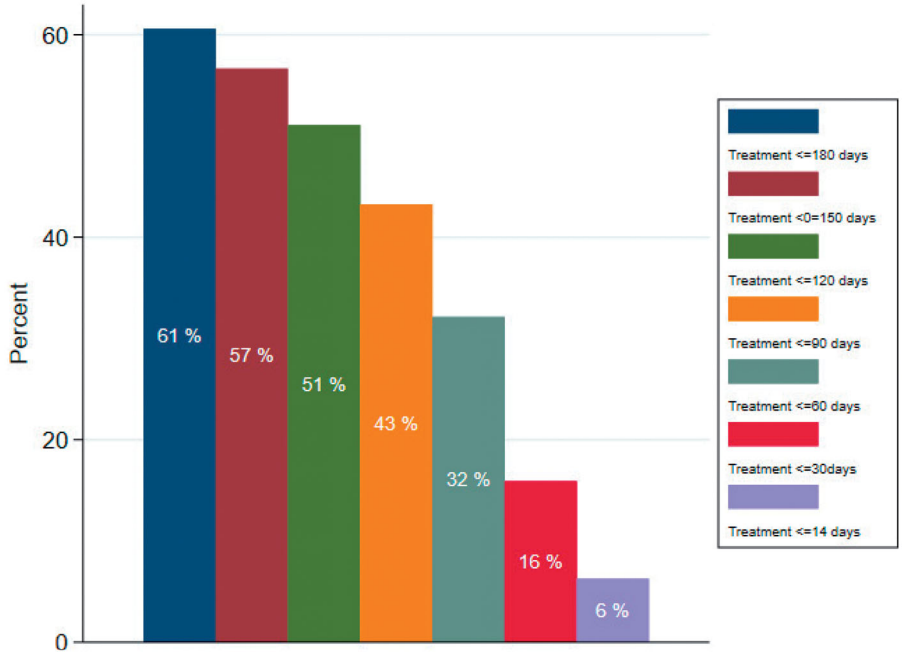

Figure 2. Frequency of end-of-life treatment prior to death in Denmark, 2010–2015.

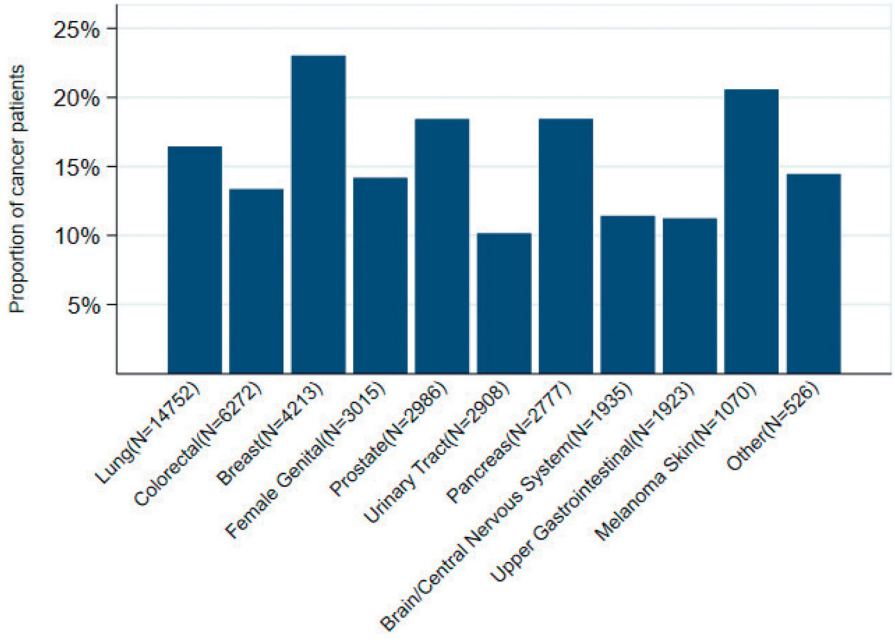

Figure 3. Proportions and total number of patients receiving end-of-life anticancer treatment by cancer diagnosis in the Danish cancer population dying of cancer 2010–2015 ($n = 43{,}377$).

age, sex, comorbidity, and time since diagnosis, whereas the proportion of patients being treated near end of life was stable over time.

The American Association of Clinical Oncologists (ASCO) recommends that chemotherapy at the end of life should be avoided, as it may solemnly cause the patient harm, as well as delayed entry into hospice or palliative care, and could prevent patients from preparing themselves for death in a meaningful way [18]. Yet, new treatment modalities and combinations are continuously evolved [8,19,20] and the use of endocrine therapies, immunotherapies, and targeted therapies are increasing [8] also in our population. Despite criticism [21,22], clinical trials continue to test new treatment in protocols on strictly selected populations. This leaves clinicians with the difficult task of extrapolating results on expected anticancer effect and possible harm to an unselected real-life cancer patient population. A population most likely to be older [23], more comorbid [21,24], physically frail [25], and having received several previous treatment options, than the populations included in the trials [8,19,22].

Studies show clinicians tend to be overly optimistic regarding effect of the treatment [8,26] and patients tend to have a great wish for treatment [7,27], especially if patients are offered new treatment possibilities such as

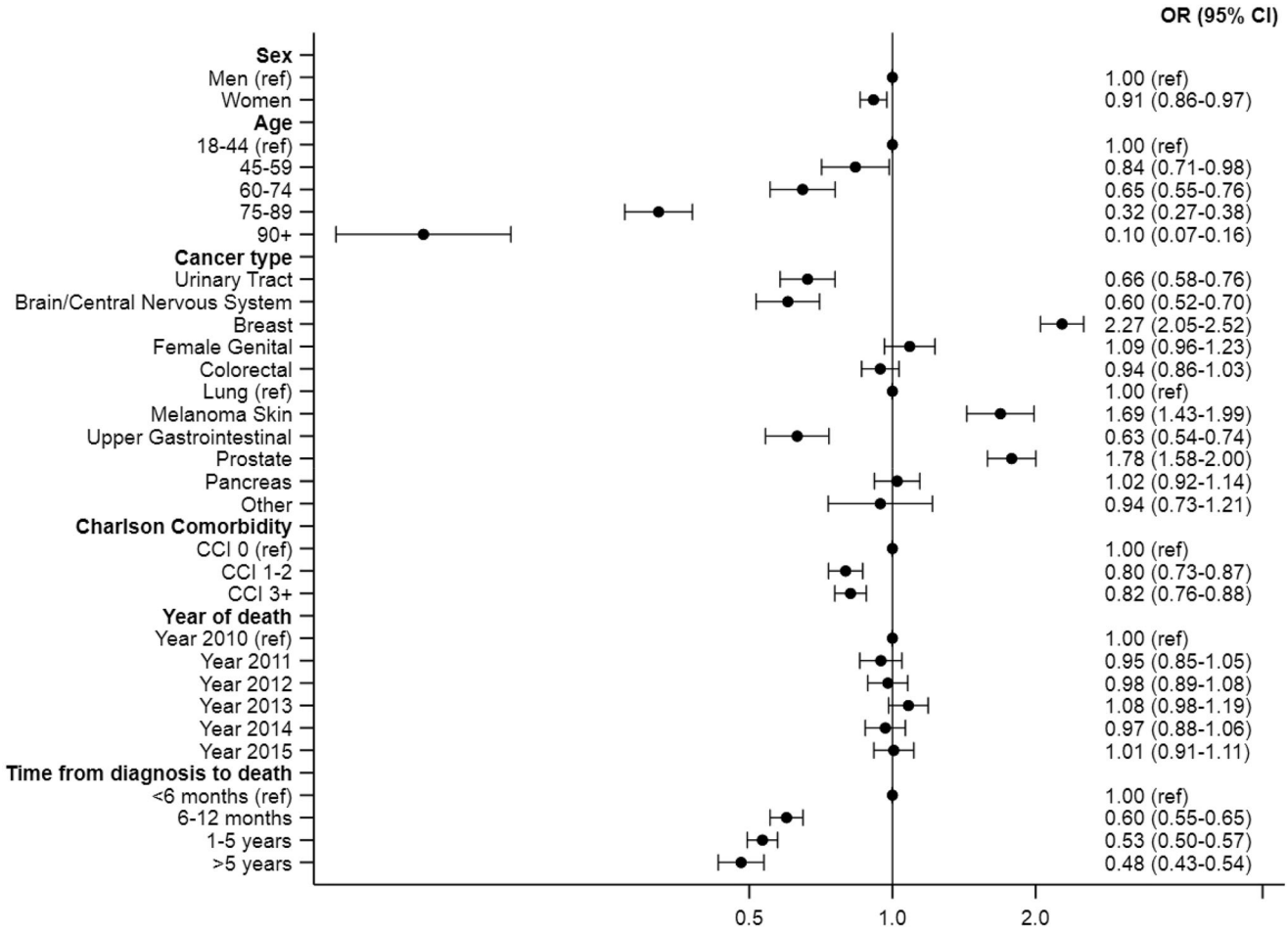

Figure 4. Forest plot of odds ratios (OR) with 95% confidence intervals (95% CI) for risk of receiving end of life treatment according to sex, age, cancer type, Charlson Comorbidity Index, year of death, and time to death from diagnosis, mutually adjusted. Plotted on a logarithmic scale.

immunotherapy and targeted therapies [8]. A problem that is most likely to be exaggerated by the introduction of new anti-cancer agents [8]. Since some of the new treatments might have a quick and pronounced response in some patients, as seen, e.g., with targeted agents in BRAF mutated malignant melanoma [28] In such cases, hope of response this might lead to treatment of patients with a high tumor burden, and – in the absence of response – an increased end-of-life treatment.

A study, exploring clinicians' rationales for administering end-of-life treatment, revealed that oncologists believe that many patients equate a continued treatment with hope, and prescription of therapy is done not to deprive patients of all hope [29]. Our results, on overall use of end-of-life treatment, are in line with the findings of previous reports focused on the use of chemotherapy [30–34], as well as smaller studies on targeted agents [35,36], and immune therapy [37].

Many prior studies have indicated that the use of end-of-life treatment is increasing [6,38]. We found a largely stable proportional use between 2010 and 2015, despite an increasing use of immune therapies, targeted therapies, and endocrine therapies. The cancer population is both increasing and getting older at the time of diagnosis and treatment [23]. To some extent, this may explain the observed stable proportion of end-of-life treatment, since older patients seem less likely to receive end-of-life treatment. It could also be assumed that when clinicians prescribe anticancer treatment to 'eligible' patients, new therapies are replacing old therapies rather than increasing the percentage of patients treated near the end of their lives and thus suggesting the stable proportion of 'eligible' patients.

In line with prior studies on risk factors associated with end-of-life chemotherapy [31,34,39] we found younger patients more likely to receive end-of-life treatment. A qualitative study, using a grounded theory approach, found that most decisions to continue aggressive anticancer treatment were guided by ethical reasons such as preferences of the patient, and perceptions of injustice associated with dying young from both the patient, relatives and the prescribing doctors [40]. Our finding with the younger patients more likely to receive end-of-life treatment may also partly be explained by this. In this interpretation our findings support the need of a qualified shared decision between patient and healthcare personnel prior to initiating or continuing treatment.

Patients with breast cancer, malignant melanoma, and pancreatic cancer, as index cancers, had a higher likelihood of end-of-life anticancer treatment compared to other types of cancers. Both prostate cancer and breast cancer patients may receive endocrine anticancer treatment, alone or in combination with other therapies. Suggesting expected toxicity of the anticancer treatment may play a role, hence

prescription of endocrine therapies near the end of life may continue when severe side effects are considered less likely to occur. The finding of higher rates among breast cancer patients supports earlier findings on risk factors associated with end-of-life treatment with chemotherapy in hospitalized patients [34]. Breast cancer patients are generally younger, i.e., more physically fit patients with several available standard treatments in different combinations, despite high tumor burden. This allows treatment to continue over longer periods of time. In these cases, overestimation of effect and underestimation of harm, as well as not wanting to deprive patients of hope, may play a more significant role as death approaches. During the study period, treatments have changed dramatically, especially for malignant melanoma and lung cancer, as new and more effective targeted treatments and immunotherapies have been introduced. Estimating effect and harm of these novel treatments is difficult due to radical differences in time to response, side effects, and measurement of treatment failure between these newer treatments and conventional chemotherapy. The chemosensitivity of tumors has been considered a risk factor for receiving end-of-life treatment [31,34]. Yet we found both breast cancer and prostate cancer to be at a higher risk of receiving end-of-life treatment than more chemo sensitive cancers as pancreatic cancer, lung cancer (including small cell lung cancer) and female genital organs (including ovarian cancer). A significant proportion of these patients received endocrine treatment alone. This suggests that other factors, such as, balancing benefits and harms of treatment, type of anticancer treatment and not wanting to deprive patients of hope, may play a larger role than chemosensitivity. Recent studies suggest early access to specialized palliative care as a mean of reducing the use of end-of-life anticancer treatment and increasing quality of life and be opportunity cost near end of life [41,42]. In this register-based study it has not been possible to distinguish between death due to an unforeseeable medical complication/toxicity or due to failure of the indication of treatment. It is therefore not possible to assess to what extend this level of end-of-life treatment is justified. Hence more prospective studies in this area is needed studying the combination of end-of-life treatment, quality of life and cost-effectiveness, to assess whether this level of end-of-life treatment is justified or reflects inappropriate use, as well as evaluate effect of interventions.

Strengths and limitations

The study is based on combined data from the Danish nationwide health registers that are assumed to be complete, because the Danish health care system is paid by taxes and is covering the entire population. This combined with the fact that data have been registered independently of the present study, ensures a virtually complete study population without selection bias.

We based the selection of the final population at risk solely on patients with cancer as primary cause of death. Correct registration of cause of death may be difficult as death often has multiple causes. Consequently, cancer patients with other morbidities or specific side-effect listed as primary cause of death may have been excluded. We had no information neither about the stage at diagnosis or at death, the curative or palliative intent of treatment, nor the patients' performance status. The assessment of comorbidity was purely index-based and may not capture all relevant comorbidities.

Conclusion

In our nationwide cohort of cancer patients, we found a stable rate of 16% receiving anticancer treatment during the last month prior to their death, despite an increasing use of immunotherapies and targeted treatments near the end of life. Further research is needed to assess whether this level of end-of-life treatment is justified or reflects inappropriate use and should explore the effects of implementing shared decision making on the use of end-of-life treatment overall and within specific cancer groups. Monitoring the use of end-of-life treatment and its correlation to quality of life, may also add to the discussion on use of scarce resources in the health care system.

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