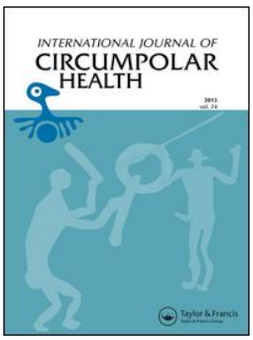

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Is there a seasonal variation of survival after systemic chemotherapy for metastatic castration-resistant prostate cancer in a rural part of North Norway?

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ABSTRACT

The winter darkness or polar night induces endocrine and metabolic mechanisms, which might reduce the efficacy of cancer treatment and thus contribute to shorter survival. Moreover, season- and weather-related treatment delays and irregularities might also cause reduced efficacy of anti-cancer drugs. Therefore, this study evaluated the prognostic impact of timing of chemotherapy (start during winter darkness or outside of this season), in terms of overall survival, in patients with metastatic castration-resistant prostate cancer (MCRPC) who received oncology care at the Nordland hospital Bodø. The study included 111 patients treated with first-line docetaxel chemotherapy for MCRPC. Twenty patients (18%) started their treatment during winter darkness (arbitrarily defined as ±4 weeks around 21 December). In unadjusted univariate analysis, survival was shorter in this group (median 10.2 vs. 18.9 months, p = 0.055). However, not all baseline parameters were equally distributed between the two groups. In multivariable-adjusted Cox regression analysis accounting for several confounding variables, only one factor was statistically significant: pre-chemotherapy serum lactate dehydrogenase level (a surrogate marker of disease burden). Thus, the present results suggest that seasonal variation is not a major contributor to the diverging survival outcomes observed after docetaxel chemotherapy.

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Prostate cancer; distant metastases; chemotherapy; systemic therapy; survival; pattern of care

Introduction

Prostate cancer is a disease with long natural history and variable outcomes, which depend on cancer biology and host factors, including but not limited to age and comorbidity. Death from non-cancer-related causes is common, however some patients develop metastatic, life-threatening disease. In the early phase, endocrine treatment (surgical or chemical castration) is able to slow the progression of prostate cancer metastases. Eventually, the disease evolves into a castration-resistant state. Several palliative, yet life-extending options for systemic therapy of metastatic castration-resistant prostate cancer (MCRPC) are currently available, e.g. cytotoxic chemotherapy (docetaxel, cabazitaxel), endocrine-based therapy (enzalutamide, abiraterone acetate) and the bone-affine radionucleotide Ra-223 (for patients without visceral metastases) [1–3].

Commonly, patients with performance status 0–1 (corresponding to Karnofsky score 80–100) and without contraindications to one or several of these approved drugs receive sequential treatment [4,5]. There is no universally agreed sequence of choice. Individual decisions are required, taking into account patient preference, drug toxicity, and disease characteristics, such as the presence of visceral metastases or the prostate-specific antigen (PSA) doubling time, to name a few. Aggressive disease is often treated with first-line docetaxel, while limited or slowly progressing disease can be managed with enzalutamide or abiraterone acetate. While the latter two oral medications can be taken at home, the other drugs require hospital visits for intravenous injection and monitoring. In rural North Norway, travel distance to the hospital-based chemotherapy units exceeds 200 km, and weather conditions during the winter months often create difficulties, e.g. closed roads and airports, which cause treatment delays [6,7]. In addition, the winter darkness or polar night is known to influence biological rhythms [8,9], and, amongst others, promote vitamin D deficiency, which in turn may negatively affect cancer treatment [10]. In theory, the efficacy of intravenous chemotherapy for MCRPC during winter darkness might be affected by these biological risk factors. Moreover, season-related treatment delays and irregularities might also cause reduced efficacy, eventually shortening the survival that can be obtained with optimal chemotherapy. In this context, a troublesome start of chemotherapy might create bigger problems than treatment breaks or delays after successful induction of response. In

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fact, it is common to introduce treatment breaks after several cycles of docetaxel, e.g. 6–10 cycles with intervals of 3 weeks, because continuous treatment is tolerated poorly. Eleven percent of patients stopped treatment due to adverse events in the pivotal trial, 12% needed a dose reduction and 24% had delayed the administration of at least one injection (data for an interval of 3 weeks) [11]. In a different prospective study, the median progression-free survival was 10 months [12]. Patients with disease progression are taken off treatment and consult with their clinical oncologist regarding other available options, as outlined earlier. To test the hypothesis that administration of the first dose of docetaxel chemotherapy during winter darkness is disadvantageous, we analysed overall survival stratified by date of treatment initiation.

The setting of care was the publicly funded Norwegian healthcare system, which aims at equal access to treatment without financial barriers, e.g., by providing travel and accommodation [13,14]. Norway has been known for a policy that minimises poverty and offers public health insurance to all inhabitants. The main hospital in our region is the only one with a department of oncology and is located in the city of Bodø. Chemotherapy is also administered at five smaller local hospitals, which consult with an oncologist via weekly virtual, web-based meetings.

Material and methods

This retrospective study included 111 men (all Caucasian) with MCRPC who received oncology care at the Nordland hospital Bodø (academic teaching hospital in rural North Norway) and started treatment with intravenous chemotherapy consisting of first-line docetaxel. All patients were in good general condition (performance status 0–1, which means able to work). Some patients presented with metastases at the time of diagnosis with prostate cancer (synchronous distant metastases), others later during the disease trajectory. In all cases, systemic treatment for MCRPC was started between 2007 and 2018. Drug therapy was given according to the national Norwegian guidelines, which however leave room for individual sequencing. Treatment did not include early docetaxel during the hormone-sensitive stage in this study. After docetaxel chemotherapy, further sequential options included enzalutamide and abiraterone acetate, as well as cabazitaxel and Ra-223. Drug doses and intervals were chosen by the treating clinical oncologist and adjusted according to toxicity. For example, docetaxel could be administered every 3 weeks (most effective regimen), every 2 weeks or once weekly (easier to tolerate due to lower doses).

The electronic patient record (EPR) system was used to collect all follow-up, treatment and baseline data. Actuarial survival from the first day of docetaxel treatment for MCRPC was calculated with the Kaplan-Meier method and compared between subgroups with differing baseline characteristics with the log-rank test. Winter darkness was arbitrarily defined as the time period around 21 Decemberst (±4 weeks around this date; 23 November–18 January; approximately 4–5 h of daylight). Explorative analyses of different definitions of winter darkness were performed, too (such as ±3 or 6 weeks around 21 December). Associations between different variables of interest were assessed with the chi-square or Fisher's exact probability test (two-tailed). A multivariable-adjusted Cox regression analysis of prognostic factors for survival was performed (stepwise regression for model fit). The original 4-week cut-off was included, together with the presence of visceral metastases (yes/no) and serum LDH (continuous variable). All parameters with p-value <0.2 in univariate log-rank test were included. A p-value ≤0.05 was considered statistically significant.

Results

Five patients were still alive and censored at the time of last follow-up (18–46 months, median 23 months). Twenty of 111 patients (18%) started with intravenous docetaxel chemotherapy during winter darkness. These 20 patients had less favourable baseline characteristics compared with the remaining patients (higher serum PSA, alkaline phosphatase (ALP) and lactate dehydrogenase (LDH), higher rates of visceral metastases, weekly docetaxel use, and no further line(s) of treatment), as shown in Table 1.

Figure 1 displays the Kaplan-Meier survival curves with median values of 10.2 and 18.9 months, respectively (p = 0.055). The explorative analyses of different definitions of winter darkness showed comparable trends towards shorter survival. Regarding the 3-week definition (n = 14), median survival was 11.8 and 17.6 months, respectively (p = 0.3). For the 6-week cut-off (n = 27), the respective figures were 12.5 and 18.9 months (p = 0.076). In the multivariable-adjusted Cox regression analysis, only serum LDH was significantly associated with overall survival (p = 0.0001; visceral metastases: p = 0.44, winter darkness: p = 0.27).

Discussion

This retrospective single-institution analysis was inspired by non-oncological studies, which have suggested that the winter darkness influences biological rhythms [8,9], and, amongst others, promotes vitamin D deficiency, which in turn may negatively affect cancer treatment [10,15]. Due to both biological and geographical risk factors (e.g. potential treatment irregularity

Table 1. Patient characteristics, n = 111.

Parameter	n (outside WD)	%	n (WD)	%	Difference*
Median age, range (years)	70	56–82	70.5	58–86	0.29
Median PSA, range (ng/ml)	116	10–3855	182	46–1165	0.41
Median haemoglobin (g/dl)	13.0	9.0–15.9	13.4	9.3–16.0	0.76
Median ALP, range (U/l)	156	39–1340	205	49–1723	0.33
Median LDH, range (U/l)	249	144–1097	241	162–1983	0.006
Visceral metastases	12	13	6	30	0.09
Synchronous distant metastases	34	37	6	30	0.61
CCI zero	64	70	15	75	0.67
Weekly docetaxel	38	42	12	60	
Docetaxel every 3 weeks	45	49	6	30	
Other docetaxel regimen	8	9	2	10	0.27
Concomitant bisphosphonate	42	46	8	40	0.63
Further line(s) after docetaxel	53	58	8	40	0.21

*p-value (Fisher's exact or chi-square test).
WD: winter darkness, PSA: prostate-specific antigen, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, CCI: Charlson comorbidity index.
The difference in serum LDH mainly relates to mean values (286 in the outside WD group vs. 462 in the WD group).

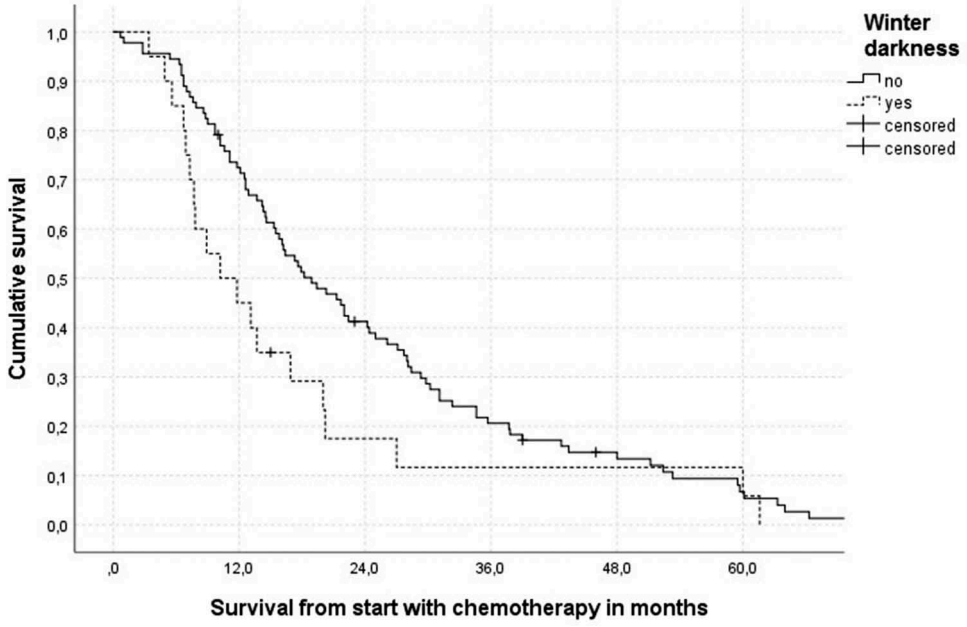

Figure 1. Actuarial Kaplan-Meier survival curves for patients who started treatment during winter darkness vs. other seasons. The median was 10.2 and 18.9 months, respectively (p = 0.055).

due to closed roads or airports) for inferior outcomes of intravenous docetaxel chemotherapy for MCRPC during winter darkness, we analysed overall survival stratified by date of treatment initiation. The study cohort consisted mainly of elderly, retired men (median age 70 years) with bone-only metastases. Typically, metastatic disease developed after an initial period of locally or locoregionally confined cancer. These characteristics resemble those reported in other studies from non-arctic regions [4,5,12].

In principle, weekly low-dose docetaxel may be inferior to higher doses administered every 3 weeks [1,16]. Only a minority of patients in the present study received docetaxel every 3 weeks. In particular, patients who started chemotherapy during winter darkness often received other dosing regimens. Moreover, they were less likely to proceed to additional systemic therapy after docetaxel. These imbalances can be explained by different disease characteristics, e.g. serum PSA, ALP and LDH levels, as well as the presence of visceral metastases (biologically aggressive cancer with poor prognosis). Due to the long natural history of prostate cancer and the fact that a minority of patients had synchronous metastatic disease, we believe that seasonal variation is not the main explanation for these findings. As shown in multivariable-adjusted analysis, treatment start during winter darkness was not an independent predictor of unfavourable survival. Much larger studies are needed to provide solid support to hypotheses about seasonal variation of growth and

metastasis of tumours, hypotheses which already have been discussed in previous reviews, such as ref [16].

Unfortunately, few other studies provided results that are relevant in the present context. To the best of our knowledge, none of these studies were related to chemotherapy for MCRPC. In an Italian analysis of first-line chemotherapy in 1610 newly diagnosed patients with metastatic colorectal cancer, a strong circannual rhythm in response rate was evident, with the higher proportion of responding patients in the subgroup diagnosed in January [17]. Moreover, a circannual rhythmicity of the proportion of patients progressing at 6 months and surviving at 1 year was demonstrated, with acrophases located both in winter (February and January, respectively). Several interpretations about the underlying reasons were discussed: the rhythm in sunlight exposure and, as a consequence, of vitamin D serum levels and folate degradation, the variability in toxic effect intensity of chemotherapy, and the rhythm in the biological behaviour of tumour cells. While not directly related to the cancer type and geographical region covered in the present study, these results lend support to the scientific justification and background discussed earlier, because they suggest the existence of seasonal influences unrelated to travel problems and treatment delay.

A research group from Spain assessed whether yearly seasons and climate could influence the chemotherapy toxicity profile based on data from the phase III GEICAM 9906 study, which was run in geographically and climatically distinct regions in Spain [18]. In this trial of adjuvant chemotherapy for early breast cancer, 1246 patients were randomised. The results showed differences in haematological and non-haematological toxicities in relation to the season of the year and the climate of the area in which the treatment was administered. There was higher haematological toxicity in warm seasons (spring and summer) and in Oceanic climate regions. Asthenia frequency was greater in the summer period. Myalgias and sensory neuropathy caused by paclitaxel chemotherapy were recorded more frequently during autumn. Efficacy endpoints, e.g. survival or progression-free survival, were not included. The present study did not assess the toxicity profile of docetaxel chemotherapy and was performed in a different setting (palliative vs. adjuvant; prostate vs. breast cancer). As illustrated by these not perfectly matching examples from the literature, additional work, and especially from circumpolar regions, is needed to answer the open questions. Further studies might also inform the development of clinical strategies, which minimise the negative impact of seasonal variations. There is always a risk of publication bias, meaning that studies which did not detect any seasonal variation may have remained unpublished and therefore the literature may be dominated by the (spuriously or incidentally?) positive studies.

Limitations of the present study include the very small sample size, limited statistical power of subgroup analyses, presence of confounding factors, and retrospective design. Vitamin D levels were not known. The same is true for actual treatment irregularities and docetaxel-related side effects. The choice of time-period is also a matter of debate, as is the generalisability of our findings. Nevertheless, studies from circumpolar rural regions are of interest to the clinicians who provide cancer care in the respective regions.

We have previously shown that all cancer patients in our region have equal access to systemic therapy and radiotherapy [6,7,19]. The availability of smaller and less specialised local hospitals, which can provide chemotherapy infusions and participate in video-streamed multidisciplinary tumour boards and virtual meetings with oncologists, provides a framework for quality care also in the most remote areas of our sparsely populated county. In other studies from different healthcare settings, geographical disparities and problems with rural and circumpolar health care have been identified [20–22]. Given that anticancer treatment usually can not be delayed for several weeks or even months, healthcare providers need to ensure continuous high-quality care during all seasons of the year, and they should also support further research projects that will shed more light on winter darkness-related issues.

Conclusions

The present results suggest that seasonal variation was not a major contributor to the variable survival outcomes observed after docetaxel chemotherapy for MCRPC. The latter were driven mainly by differences in burden and patterns of disease.

Authors' contributions

CN participated in the design of the study and performed the statistical analysis. EH and AD collected patient data. CN and EH conceived of the study and drafted the manuscript. All authors read and approved the final manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

Ethics approval

As a retrospective quality of care analysis, no approval from the Regional Committee for Medical and Health Research Ethics (REK Nord) was necessary (national policy in Norway). This research project was carried out according to our institutions' guidelines and with permission to access the patients' data.

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Availability of data and materials

Data will not be shared, but a copy of relevant baseline parameters can be provided to researchers attempting to pool data from several institutions for large-scale analyses.

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