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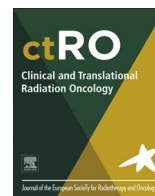
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Original Research Article

The influence on survival of glucocorticoid induced diabetes in cancer patients with metastatic spinal cord compression



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ABSTRACT

Background and purpose: The influence of glucocorticoid induced hyperglycemia on survival in patients with metastatic spinal cord compression (MSCC) is unknown.

Materials and methods: In a prospective, observational cohort study 131 patients with MSCC referred to radiotherapy, 30 Gray (Gy) in 10 fractions, and treated with ≥ 100 mg prednisolone a day were followed with daily blood glucose measurements during radiotherapy.

Results: During follow-up a total of 56 patients 43% (95% CI = 35–52%) presented plasma glucose values diagnostic of diabetes. Sixteen patients who developed diabetes were treated with insulin, 12% (95% CI = [6%; 18%]) of the total population. The patients developing diabetes with need for insulin therapy during glucocorticoid therapy had a significantly increased mortality compared to those with normal glucose metabolism and with diabetes without need for therapy, hazard ratio = 2.1 (95% CI = 1.08–4.09, $p = 0.0285$).

Discussion: To our knowledge this is the first prospective study to describe the influence of glucocorticoid induced diabetes on survival in patients with MSCC from different primary tumors.

Conclusions: The results indicate that development of diabetes during high-dose glucocorticoid therapy needing insulin treatment in patients with MSCC from different primary tumors is associated with reduced survival.

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Introduction

Patients with metastatic spinal cord compression (MSCC) are treated with high doses of glucocorticoids to reduce local edema from the diagnosis is suspected and during radiotherapy [1]. Glucocorticoids may induce hyperglycemia and diabetes because of insulin resistance, decreased pancreatic insulin secretion and increased hepatic gluconeogenesis [2]. The risk of developing diabetes during high-dose glucocorticoid therapy in cancer patients ranges between 11% and 34.3% [3–5] in different patient categories and with divers definitions of diabetes.

A potential impact of diabetes on survival in cancer patients remains controversial. Thus, preexisting diabetes at the time of cancer diagnosis increase all-cause mortality [6] but there is contradicting evidence as to whether hyperglycemia and diabetes, preexisting or induced by glucocorticoids, affect survival in cancer patients negatively [7–11] or not [12,13]. This may be explained by pre-existing diabetes which potentially may contribute to excess mortality both through already established cardiovascular disease and through metabolic pathways including catabolism and increased oxidative stress. In contrast, glucocorticoid-induced diabetes is mainly a metabolic disorder. No previous studies have excluded cancer patients with preexisting diabetes and assessed the influence on mortality of glucocorticoid induced diabetes per se.

We performed a prospective, observational cohort study aiming to determine the incidence and consequence of glucocorticoid induced diabetes in 131 patients with MSCC [14]. In this analysis

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we address the question whether development of glucocorticoid induced diabetes in previously non-diabetic cancer patients with M5CC influence survival.

Materials and methods

Design

Patients with a tentative diagnosis of M5CC are referred to the Department of Radiation Oncology at hospital X in city X 24 h a day 7 days a week from country X, an area with approximately 2.4 million inhabitants. From May 2013 to December 2014 we included patients in a prospective, observational cohort study on glucocorticoid induced diabetes in this department.

Once the diagnosis of M5CC is confirmed by magnetic resonance imaging (MRI), the patient is conferred with the Spine Unit to decide whether surgery is a possibility or not [15]. Approximately 20% of the patients are offered surgery before radiotherapy [16] and the remainder are offered radiotherapy alone. If the patient is believed to live for more than six months, based on the clinical evaluation by the oncologist and a scoring system (Tokuhashi Revised score [17,18]), the patient is treated with 30 Gy in 10 fractions. The patients are offered a single fraction of 8–10 Gy if they are expected to live for less than three months.

High-dose glucocorticoid therapy has proven beneficial as an adjunct to radiotherapy [1] and is most often initialized in the local hospital, alternatively prescribed at the first visit at hospital X. The standard dose was 300 mg prednisolone a day during radiotherapy. Radiotherapy is given on an outpatient basis and patients who need to be hospitalized are admitted to their local hospital in the treatment period.

We followed the patients who were referred to 30 Gy in 10 fractions and treated with high dose glucocorticoid [19], ≥ 100 mg prednisolone per day or an equivalent dose of another glucocorticoid.

All procedures followed were in accordance with the Helsinki Declaration [20], the study was approved by The Regional Committee on Health Research Ethics (file number H-4-2012-004) and reported to the Danish Data Protection Agency (file number HIH-2011-22). Oral and written information was given by the primary investigator (HS), who also obtained written, informed consent to participate.

Subjects

Cancer patients with a histologically confirmed diagnosis, were eligible for inclusion if they were 18 years or more of age, were diagnosed with M5CC, treated with ≥ 100 mg prednisolone daily and were referred to radiotherapy treatment with 30 Gy in 10 fractions. Known diabetes was the only exclusion criterion and the classification was based on self-reporting from the patients, prescription of antidiabetic medication according to medical records and measurement of HbA1c at baseline (in 118 out of 131 patients).

Clinical and laboratory data

At the time of inclusion, we obtained information on age, sex, height and body weight, primary tumor, medical history, diabetes in first- and second-degree relatives, tobacco and alcohol consumption and medications data. Venous blood samples were collected and performance status (PS) was assessed using the toxicity and response criteria of the Eastern Cooperative Oncology Group (ECOG) [21]. On the last day of radiotherapy venous blood

samples were repeated. The dose of prednisolone was registered on a daily basis.

Monitoring of blood glucose and classification of diabetes

During the subsequent 12 days one to four capillary blood glucose measurements daily were performed using a Medisense Precision XceedPro glucometer (Abbott Diabetes Care Inc. Alameda, USA). In inpatients, we aimed at three measurements a day in their local hospital and one measurement in the Section of Radiotherapy, while outpatients had one measurement in conjunction with radiotherapy.

Diabetes was defined according to a modification of WHO guidelines from 2006: two random plasma glucose measurements ≥ 11.1 mmol/L [22]. Fasting glucose measurements and oral glucose tolerance test were not feasible in this acute setting and due to the short time of observation diabetes defined by HbA1c was not an option.

There were no study instructions on treatment of hyperglycemia or diabetes. The decision to initiate glucose lowering therapy was taken by the physicians at the department where the patient was admitted following local guidelines.

Insulin was the preferred choice for all patients who had glucose lowering therapy. Patients were defined as having insulin treated diabetes from their first injection of insulin.

Survival data

Inclusion took place between May 2013 and December 2014. 5 months after inclusion was ended, in May 2015, we registered if the patients were dead or alive using the medical records and the Central Office of Civil Registration.

Statistics

The study was powered to detect a prevalence of glucocorticoid induced diabetes of 15% with an accuracy of $\pm 5\%$ (140 participants) and subsequently we explored survival for patients with and without diabetes.

Kaplan-Meier estimates stratified by primary tumor were used to describe survival for all the patients. Log-rank tests were used to test for equality of the survival functions and pairwise comparisons were adjusted for multiplicity by Holm's method.

The effect of glucocorticoid induced diabetes on mortality was modeled by the multistate model shown in Fig. 1. The boxes in the figure represent the four different states that a patient can be

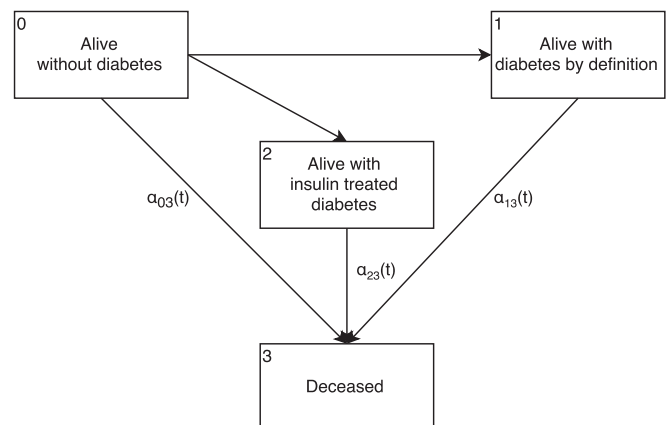


Fig. 1. Illustration of the multistate model.

in at any given time under the study period and the arrows represent the possible transitions between the states.

At time zero, determined by start of prednisolone treatment, all patients belong to the initial state (alive without diabetes). Over time, each patient can then either die without getting diabetes or develop diabetes (either by definition or insulin treated) and then subsequently move to the deceased state. Deaths were censored at the end of study (May 2015) and diabetes events were censored 12 days after start of prednisolone treatment.

The parameters of interest are the three transition-specific hazard functions going to the absorbing death state. The transition probabilities were estimated by the Aalen-Johansen estimator and the equality of the associated transition hazards was tested under a proportionality assumption. The covariates (age, sex, body mass index (BMI), PS, primary tumor and C-reactive protein (CRP)) were included through a stratified Cox model where each stratum corresponds to a transition and the covariates were allowed to have different effects across the strata.

Results

Recruitment/response

Of 324 patients assessed for eligibility 140 were recruited (43%) and 131 were included in the analyses on incidences, risk factors and time course. One patient with overt diabetes, HbA1c = 79 mmol/mol, was excluded from the survival analysis, further seven with slightly elevated values were included as a single HbA1c measurement is not diagnostic of diabetes [23]. For baseline characteristics see Table 1.

Characteristics of the sample

The patients were grouped according to primary tumor in 4 categories, lung cancer n = 36 (27%), breast cancer n = 25 (19%), prostate cancer n = 31 (24%) and other cancer forms n = 39 (30%) including unidentified tumors and tumors of unknown origin.

During follow-up a total of 56 patients (43%, 95% CI = [35%; 52%]) presented plasma glucose values diagnostic of diabetes. 40 (31%, 95% CI = [23%; 39%]) patients had diabetes that was left untreated and 16 patients (12%, 95% CI = [6%; 18%]) were treated with insulin [14]. No patients received oral antidiabetic medicine.

Diabetes and mortality

In six months (180 days), from the first day of prednisolone, 78 (60%) of the patients died: 28 (78%) patients with lung cancer, 15 (48%) patients with prostate cancer, 5 (20%) patients with breast cancer and 30 (77%) the patients with other cancer forms, see Fig. 2. The overall p-value for equality of survival function was less than 0.0001 and the pairwise comparisons showed that all survival functions were significantly different from each other at the 5% level except for lung cancer vs. other cancer type and breast cancer vs. prostate cancer with adjusted p-values equal to 0.4406 and 0.1481 respectively.

Out of the 75 patients that did not develop diabetes 57 (76%) died, out of the 40 patients with untreated diabetes 28 (70%) died, and out of the 16 patients with diabetes treated with insulin 14 (87.5%) died.

At the end of study in May 2015, 32 patients were still alive and had a median follow up of 234 days (min–max; 159–723)

Table 1
Baseline characteristics. IQR = interquartile range.

Variable	All	No diabetes	Untreated diabetes	Diabetes treated with insulin
N (%)	131 (100)	75 (57)	40 (31)	16 (12)
Female sex (%)	42 (32)	43 (33)	45 (34)	31 (24)
Age (years), mean (min; max)	68 (46; 88)	68 (48; 88)	68 (46; 87)	69 (50; 86)
BMI (kg/m ²), mean (min; max)	25 (14; 44)	25 (15; 44)	24 (14; 31)	25 (18; 33)
		N = 73	N = 38	N = 15
Performance status (%)				
0	6 (4)	6 (8)	0	0 (0)
1	52 (40)	36 (48)	13 (32)	3 (19)
2	44 (34)	18 (24)	19 (48)	7 (44)
3	29 (22)	15 (20)	8 (20)	6 (37)
Primary tumor (%)				
Lung	36 (27)	22 (29)	10 (25)	4 (25)
Breast	25 (19)	16 (21)	7 (17)	2 (13)
Prostate	31 (24)	14 (19)	12 (30)	5 (31)
Others	39 (30)	23 (31)	11 (28)	5 (31)
Brain metastases (%)	5 (4)	4 (5)	0	1 (6)
Lung metastases (%)	51 (39)	35 (47)	13 (33)	3 (19)
Liver metastases (%)	30 (23)	16 (21)	9 (23)	5 (31)
Bone metastases (%)	129 (99)	74 (99)	39 (98)	16 (100)
Hospitalisation or not				
Outpatient	56 (43)	41 (55)	15 (38)	0
Inpatient	53 (40)	21 (28)	19 (47)	13 (81)
Alternating	22 (17)	13 (17)	6 (15)	3 (19)
Prednisolone start dose, mg, mean (min; max)	261 (100; 2500)	234 (100; 350)	307 (100; 2500)	275 (150; 300)
Cumulated dose of prednisolone in twelve days treatment, mg, mean (min; max)	2919 (1000; 6750)	2835 (1200; 3650)	3040 (1000; 6750)	2966 (1400; 3600)
Daily prednisolone dose in twelve days treatment, mg, mean (min; max)	247 (83; 563)	240 (100; 304)	255 (83; 563)	259 (150; 300)
Number of plasma glucose measurements, median (IQR)	9 (8–20)	8 (7–12)	13 (8–28)	30 (18–33)

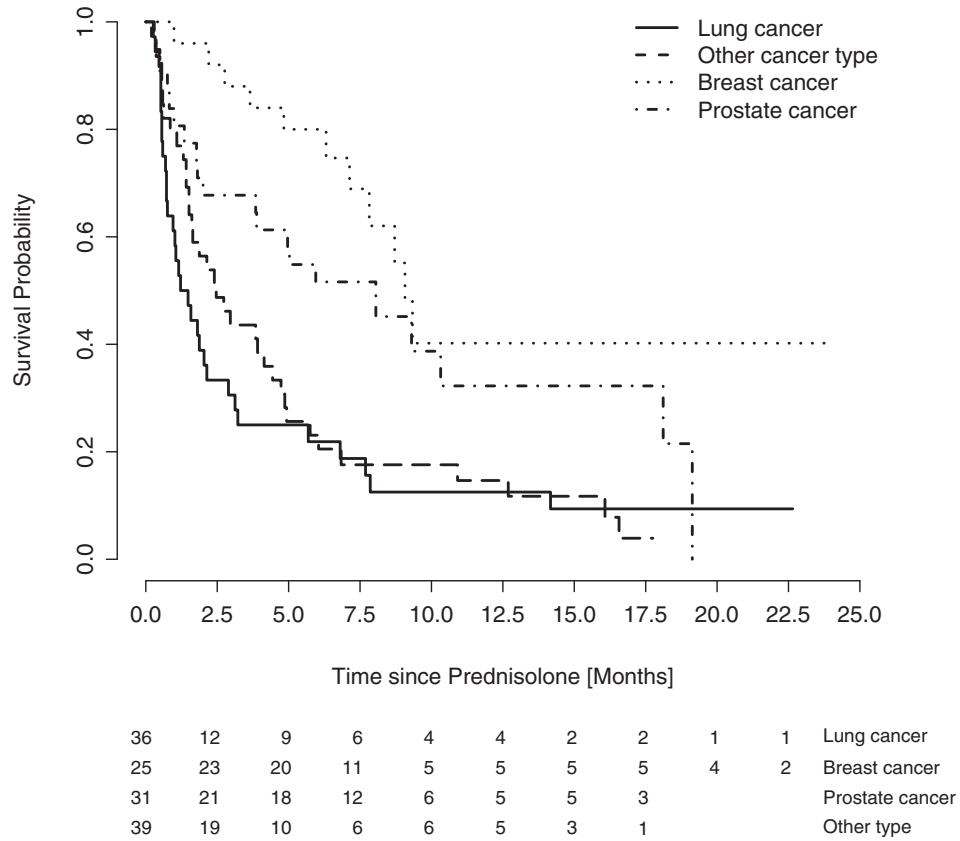


Fig. 2. Survival based on primary tumor in 131 patients with metastatic spinal cord compression treated with high doses of glucocorticoids and followed for a mean of 355 days. The numbers under the figure refer to the number of patients at risk at the time points above stratified by tumor group.

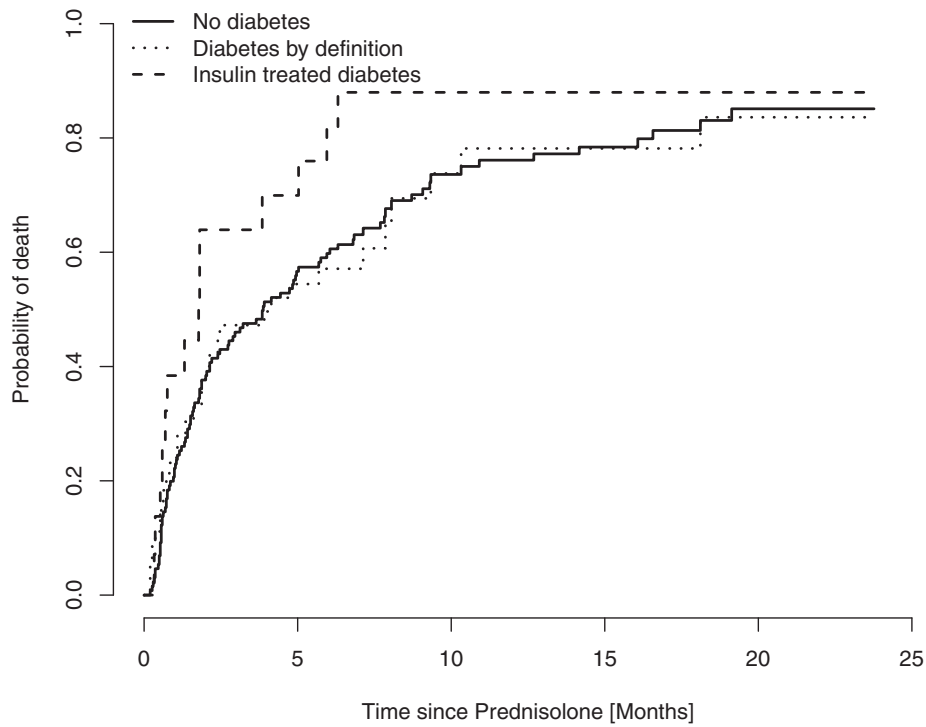


Fig. 3. Nonparametric estimates of the transition probabilities to death according to three states: No diabetes, diabetes by definition and insulin treated diabetes.

Fig. 3 shows the estimated transition probabilities in the unadjusted model. Under the proportionality assumption the mortalities for patients that did not develop diabetes and the patients with diabetes left untreated were alike with a hazard ratio of 0.99 (95% CI = 0.63–1.56, $p = 0.9698$). Patients developing glucocorticoid induced diabetes with need for insulin therapy had a significantly increased mortality compared to those with normal glucose metabolism and with diabetes without need for therapy, hazard ratio = 2.1 (95% CI = 1.08–4.09, $p = 0.0285$).

Tumor group significantly affected the transition hazards from alive without diabetes to death, from untreated diabetes to death and from insulin treated diabetes to death (p -values for likelihood ratio test equal to 0.0151, 0.0221 and 0.051 respectively). Patients with lung cancer had the highest mortality. Furthermore, there was a significant positive association between CRP and transition from alive without diabetes to death ($p = 0.0124$). Table 2 shows the estimated hazard ratios and 95% confidence intervals. None of the other covariates showed any significant effects on the transition hazards. We note that with only 14 observed events in the transition from insulin treated diabetes to death there is little information available for adjustments.

The baseline hazards function in the Cox model for insulin treated diabetes was still significantly different from the baseline mortality of patients with normal glucose metabolism and for diabetes without need for therapy when adjusting for tumor group, $p = 0.0017$.

To assess potential confounding from misclassification: diabetes at baseline or not, need for insulin therapy or not, inpatient or not, we made a sensitivity analysis based on whether the patients had any glucose measurement >15 mmol/L during the observation period. This analysis only included patients with HbA1c <48 mmol/mol. A log-rank test showed that patients who had at least one glucose measurement >15 mmol/l ($n = 17$) had statistically significant worse survival, $p = 0.00639$, Fig. 4. This is also true if we include all the patients in the analysis or remove only the patient with HbA1c = 79 mmol/mol at baseline.

Discussion

Main findings

In this study, which is the first to assess the isolated impact of glucocorticoid induced diabetes on mortality in MSCC, development of diabetes needing insulin treatment was associated with a doubled mortality risk. The mortality of the patients as a whole is comparable to other cohorts of patients with MSCC in Danish hospitals [16,24] and not influenced by other risk factors in the adjusted model.

Comparison of findings with those reported in the literature

In a meta-analysis Barone et al. conclude that preexisting type 1 and 2 diabetes in cancer patients at the time of diagnosis was associated with an HR of 1.41 for the risk of all-cause mortality compared with individuals without diabetes. The meta-analysis

included 23 studies with patients with various types of cancer [6]. Suggested explanations for the increased all-cause mortality are several: Facing a cancer diagnosis patients with diabetes and their doctors maybe don't pay enough attention to the management of hyperglycemia, blood pressure and dyslipidemia; the diabetic patients with comorbidity often may not be offered the same anti-cancer treatment as the non-diabetic patients and maybe they respond less well; tumor cell proliferation may be increased in a hyperglycemic, hyperinsulinaemic environment and finally diabetes in itself carries an increased risk of cardiovascular death [6].

Studies looking at hyperglycemia and diabetes in cancer patients, with and without preexisting diabetes and treated with glucocorticoids or not, predominantly find a negatively influence on survival. Patients with grade III and IV astrocytomas and persistent hyperglycemia had a median survival of 5 months compared to patients without hyperglycemia who had a median survival of 11 months. Hyperglycemia was secondary to preexisting diabetes in 7 patients (25%) and secondary to Decadron use in 21 patients (75%) [10]. Derr et al. found an inverse relationship between mean glucose level and survival period in patients with newly diagnosed glioblastoma multiforme with and without preexisting diabetes, that is the higher the mean glucose the shorter the survival [8]. In low grade gliomas, patients with persistent outpatient hyperglycemia had a five year survival rate of 43% versus 84% in the group without hyperglycemia, a result that remained statistically significant after controlling for various other factors known to influence survival [7]. In a prospective study, again including patients with preexisting diabetes, of hematologic patients with acute lymphocytic leukemia (ALL) who had high dose glucocorticoid as part of a chemotherapy regime, hyperglycemia was associated with a shorter time to remission, an increase in overall mortality and an increased risk for developing complicated infections [11].

No previous studies have focused solely on glucocorticoid induced diabetes and survival. As mentioned in the introduction the distinction between preexisting diabetes and glucocorticoid induced diabetes is however important because cardiovascular disease, along with other comorbidity, as a complication to long standing diabetes might influence survival in patients with preexisting diabetes. Glucocorticoid induced diabetes seems to be mainly characterized by metabolic changes as described by Simmons et al. who found that patients with glucocorticoid induced diabetes had less family history of diabetes, weighed less, had less retinopathy and had significantly fewer macrovascular complications than patients with type 2 diabetes receiving or not receiving glucocorticoid [25]. Further supporting a metabolic effect of hyperglycemia on survival in cancer, Chaichana et al., mentioned above, found that persistent outpatient hyperglycemia (not in diabetic levels), is associated with decreased survival in patients with low grade glioma, also when excluding patients with preexisting diabetes from analysis and patients who were on steroids in the observation period. This indicates that a metabolic state with hyperglycemia, even in the absence glucocorticoids, may also worsen the prognosis [7].

Table 2

Impact of tumor group and CRP on transitions between the states. Patients with lung cancer generally have the highest mortality in each transition.

	No diabetes → Death	Untreated diabetes → Death	Insulin treated diabetes → Death
Lung cancer	1 (ref.)	1 (ref.)	1 (ref.)
Breast cancer	0.326 [0.139; 0.765]	0.226 [0.045; 0.133]	0.048 [0.004; 0.578]
Prostate cancer	0.367 [0.157; 0.859]	0.587 [0.194; 1.765]	0.287 [0.068; 1.231]
Other cancer type	0.767 [0.389; 1.513]	1.997 [0.650; 6.134]	0.182 [0.033; 1.003]
CRP	1.011 [1.002; 1.019]	–	–

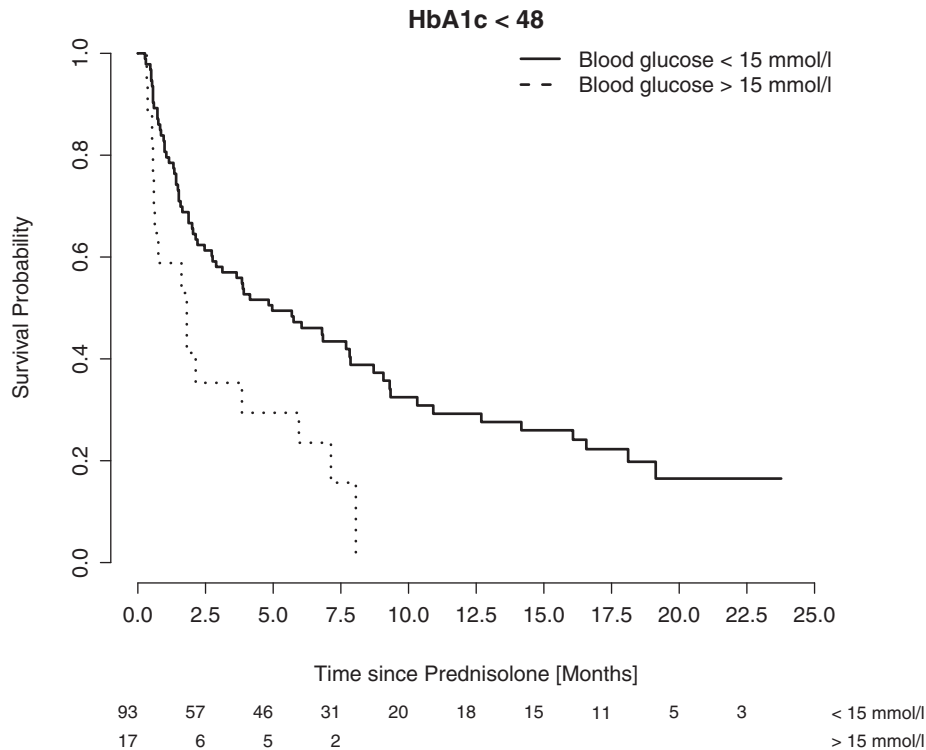


Fig. 4. Sensitivity analysis. A log-rank test showed that patients who had at least one glucose measurement >15 mmol/l (n = 17) had statistically significant worse survival, p = 0.00639. This analysis only included patients with HbA1c <48 mmol/mol.

Strengths and limitations

The main strength of our study was that data on glucocorticoid induced diabetes was systematically gathered prospectively and more detailed than in previous studies, making diabetes classification of patients with diabetes by definition more certain.

Patients were categorized as having insulin treated diabetes based on the local doctor's decision to start treatment. There were no study instructions when to give insulin and that might have been a limitation due to misclassification. The Joint British Diabetes Societies for inpatient care (JBDS-IP) recommend that if blood glucose values in patients treated with glucocorticoids are consistently greater than 12 mmol/L anti-diabetic treatment is instituted, but in specific clinical situations (e.g. end of life care) you might be less conservative and aim for values below 15 mmol/L [26]. Out of 16 patients treated with insulin in our study, 14 had blood glucose measurements >15 mmol/l before insulin treatment was initiated thus reflecting typical clinical recommendations. The last two patients had insulin after blood glucose measurements >14.0 and 14.4 mmol/l. So although the decision to initiate insulin treatment was based on clinical judgement from different physicians we believe that the patients with need for insulin therapy were overall correctly identified. Furthermore the analyses resulted in similar outcome when using insulin therapy or plasma glucose >15 mmol/l as grouping criterion.

The patients were homogeneous in the sense that they were all referred to the same radiotherapy regimen and had the same dose of glucocorticoids, but compared to the regimen in other radiotherapy clinics the dose of glucocorticoid was relatively high. The prospective design also made it possible to systematically collect data on risk factors for diabetes and PS.

The study was powered to identify the incidence of glucocorticoid induced diabetes and this secondary analysis on survival is limited by the small number of patients with glucocorticoid induced diabetes although the results reach statistical significance.

Conclusions

In the present study of patients with MSCC of different tumor origin development of glucocorticoid induced diabetes needing insulin therapy during fractionated radiotherapy reduced survival significantly. This is the first study to assess the influence on survival of glucocorticoid induced diabetes since patients with known preexisting diabetes were excluded. The results suggest a metabolic effect of hyperglycaemia on mortality or alternatively a common underlying mechanism simultaneously promoting diabetes and mortality. This question warrants a trial assessing the effect of treatment of glucocorticoid induced diabetes on survival in cancer patients.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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