Patients with oral tongue squamous cell carcinoma and co-existing diabetes exhibit lower recurrence rates and improved survival: Implications for treatment

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Abstract. Locoregional recurrences and distant metastases are major problems for patients with squamous cell carcinoma of the head and neck (SCCHN). Because SCCHN is a heterogeneous group of tumours with varying characteristics, the present study concentrated on the subgroup of squamous cell carcinoma of the oral tongue (SCCOT) to investigate the use of machine learning approaches to predict the risk of recurrence from routine clinical data available at diagnosis. The approach also identified the most important parameters that identify and classify recurrence risk. A total of 66 patients with SCCOT were included. Clinical data available at diagnosis were analysed using statistical analysis and machine learning approaches. Tumour recurrence was associated with T stage (P=0.001), radiological neck metastasis (P=0.010) and diabetes (P=0.003). A machine learning model based on the random forest algorithm and with attendant explainability was used. Whilst patients with diabetes were overrepresented in the SCCOT cohort, diabetics had lower recurrence rates (P=0.015 after adjusting for age and other clinical features) and an improved 2-year survival (P=0.025) compared with non-diabetics. Clinical, radiological and histological data available at diagnosis were used to establish a prognostic model for patients with SCCOT. Using machine learning to predict recurrence produced a classification model with 71.2% accuracy. Notably, one of the findings of the feature importance rankings of the model was that diabetics exhibited less recurrence and improved survival compared with non-diabetics, even after accounting for the independent prognostic variables of tumour size and patient age at diagnosis. These data imply that the therapeutic manipulation of glucose levels used to treat diabetes may be useful for patients with SCCOT regardless of their diabetic status. Further studies are warranted to investigate the impact of diabetes in other SCCHN subtypes.

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Introduction

Squamous cell carcinoma of the head and neck (SCCHN) comprises tumours of different origin, including mucosa of the upper airways, the oral cavity and sinuses. Patients have a high mortality rate (1) and critical prognostic factors at diagnosis are tumour size and metastatic lymph nodes in the neck. A major problem for these patients is the high rate of tumour relapse, where locoregional recurrences develop in 30-40% of patients and distant metastases in 20-30% (2).

The best current predictive tool for SCCHN survival is the tumour-node-metastasis (TNM) staging system based on tumour morphology, without considering patient-specific factors such as age (3), sex and comorbidity (4). Immunohistochemistry and molecular genetics can also provide important information for prognosis and targeted therapy (5). However, molecular analyses are uncommon outside of research institutes and are not performed routinely in the clinical setting, highlighting the importance of analysing the prognostic impact of widely available clinicopathological factors that are easily accessible at the time of diagnosis. Diabetes, characterised by sustained hyperglycemia, represents one such factor, and is known to associate with an increased risk for many cancers including SCCHN, where higher levels of blood glucose and various lipids have been seen up to 30 years before diagnosis (6). Data from The Cancer Genome Atlas (TCGA) or other sources, including genomic, transcriptomic and clinical information have often been used to identify prognostic indicators in patients with SCCHN, often using computational algorithms and artificial intelligence (AI) approaches to produce lists of potential biomarkers, comprising differential expression of specific mRNAs, microRNAs, lncRNAs etc (7-11). However, genomic and transcriptomic data are not commonly available in routine clinical practice, and patient management is

therefore based on clinical, histological and radiological data. In addition, SCCHN is a heterogenous set of tumours that have different biologies and prognoses according to their site of origin, indicating that site-specific factors are involved in patient outcome (12).

Therefore, we focused on squamous cell carcinoma of the oral tongue (SCCOT), the most common subgroup of oral SCCHN, employing machine learning to investigate medical and clinicopathological data available at diagnosis and identify parameters that are important to predict recurrence in the routine clinical situation.

Materials and methods

Material. The study was approved by the Regional Ethical Committee in Umea, Umeå University, Sweden (dnr 2014-193-32M), giving consent to achieve clinical information from the files from patients retrospectively and prospectively. Written informed consent was achieved from the patients after oral information given by ENT-staff. Medical records were retrieved for 139 patients with a verified diagnosis of SCCOT treated during 1997-2019 at the University Hospital, Umea. Patients lacking clinical data, such as complete anamnestic information, or not having radiological data available, and/or not having diagnostic slides available for re-examination were excluded, leaving 66 patients that were included in the study. No tumour had positive M-stage and this factor was thus excluded from further analyses. In addition to the standard parameters used in TNM and histopathological classification, and known high-risk factors such as smoking status, we also retrieved information on common comorbidities such as allergies, cardiovascular problems and symptoms of metabolic syndrome. Patient data are summarised in Table I.

Worst pattern of invasion (WPOI) and Lymphocytic response (LR). Tumours were also analysed for Worst Pattern of Invasion (WPOI) and Lymphocytic Response (LR) using haematoxylin/eosin stained slides. According to the evaluation scale of Brandwein-Gensler *et al* (13), WPOI scores range from 1-5 (1=broad pushing tumour front, 2=pushing tumour fingers and separate tumour islands, 3=tumour islands comprising >15 cells, 4=tumour islands comprising <15 cells and 5=tumour satellites found at a distance of ≥1 mm from the tumour). LR has a three grade-scale, where 1=continuous dense rim of lymphoid tissue, 2=patches of lymphoid tissue and 3=limited or no lymphocytic response (13).

Principal component analysis (PCA). Soft independent modelling of class analogies (SIMCA) is a multivariate data analysis tool that identifies patterns and relationships between many variables simultaneously. We used SIMCA 16 (MKS data analytics solutions, Umeå, Sweden) with unsupervised principal component analysis (PCA) to identify clusters or trends in the clinical and histopathological parameters investigated.

Statistical analysis. Two-tailed Fisher exact tests were used to determine associations between different clinicopathological features, and Kaplan-Meier with log rank test was used for survival analysis. SPSS version 25 was used for calculations and P-values <0.05 were considered statistically significant.

Random forest. We used the python library 'Lazy Predict' (https://lazypredict.readthedocs.io/en/latest) for initial performance assessment of different machine learning models for our data. Random Forrest (RF) was identified as the best machine learning model for our data. The RF approach has the additional advantage of explainability by identifying the specific features that are principally responsible for prediction. RF is a machine learning algorithm based on randomly constructed decision trees using bootstrap aggregating to improve stability and accuracy (14). Thus, as well as identifying suitable features for classification, RF also ranks the relative importance of each variable in the classification scheme. The importance scores for features are calculated based on their contribution to the reduction of impurity in the decision trees that make up the forest. It allows RF to identify and rank features according to their predictive power. Features with higher importance scores are considered more significant in the model's decision-making process. The RF classification model and its features of importance were calculated using leave-one-out cross validation (LOOCV) (15).

Results

Principal component analysis (PCA). Unsupervised PCA was performed to get an overview of subject distributions based on clinical, radiological and histopathological factors available at diagnosis. However, no distinct clustering of patients with recurrence and those without was found (Fig. 1).

Statistical analysis. Significant associations were seen between recurrence and T stage (P=0.001), radiological signs of neck metastasis (P=0.010) and diabetes (P=0.003) (Table I).

Random forest. The RF classifier was built from 14 clinical and histopathological features available at diagnosis for the 66 patients (listed in Table II). Performance was assessed by LOOCV and the optimized classification RF model (n_estimators=70, max_depth=10) achieved an accuracy of 71.2% (ROC_AUC=0.729, sensitivity=0.583, specificity=0.786, balanced accuracy=0.685, F-score=0.595) for risk of recurrence. The three factors that were significantly associated with risk of recurrence in the statistical analysis-T-stage (high risk), radiological signs of neck metastasis (high risk), and diabetes (low risk)-were also among the five most important features in model building (Fig. 2).

Features. That diabetic SCCOT patients showed a lower risk of recurrence than patients without diabetes was an unexpected result. More detailed investigation revealed that all diabetic patients were >50 years old, compared to 57% (31/54) of non-diabetics (P=0.005), and the majority of diabetics (9/12, 75%) also had cardiovascular disease, compared to 22% (12/54) of non-diabetics (P=0.001). Half of the patients with diabetes (6/12) showed a lymphocytic response (either as a continuous dense rim or as patches of lymphocytes), compared to 85% (46/54) of patients without diabetes (P=0.014; Table III). Of the 12 patients with diabetes, five were treated with metformin, four with insulin and three with diet only to control their hyperglycaemia. Information on T- and N-stage was not available for one diabetic patient, and the remaining 11 patients all had

Table I. Clinicopathological features of patients with squamous cell carcinoma of the oral tongue (n=66).

Clinicopathological features	No. (%)
Sex	
Female	31 (47.0)
Male	35 (53.0)
Age, years	
≤50	23 (34.8)
>50	43 (65.2)
Localisation	
Oral tongue, unspecified	17 (25.8)
Lateral border	39 (59.1)
Tongue with overgrowth outside the oral tongue	10 (15.1)
T stage	
T1, T2	56 (85.0)
T3, T4	9 (13.6)
Missing	1 (1.5)
N stage	
N0	60 (90.9)
N1, N2	5 (7.6)
Missing	1 (1.5)
Radiology	
Neck metastasis	13 (19.7)
No neck metastasis	48 (72.7)
Reactive nodes	5 (7.6)
Degree of differentiation	
Poor	4 (6.1)
Poor-moderate	14 (21.2)
Moderate	19 (28.8)
Moderate-high	27 (40.9)
High	2 (3.0)
Worst pattern of invasion[a]	
Broad pushing fingers; separate tumour islands	1 (1.5)
Invasive islands (>15 cells/island)	10 (15.1)
Invasive islands (<15 cells/island), including single cell invasion	51 (77.3)
Tumour satellites with ≥1 mm distance from tumour	4 (6.1)
Lymphocytic response[a]	
Continuous dense rim of lymphoid tissue	27 (40.9)
Patches of discontinuous dense lymphoid infiltrate	25 (37.9)
Limited or no response	14 (21.2)
Smoking	
Yes	37 (56.0)
No	25 (37.9)
Unknown	4 (6.1)
Diabetes	
Yes	12 (18.2)
No	54 (81.8)
Asthma	
Yes	8 (12.1)
No	58 (87.9)
Cardiovascular disease	
Yes	21 (31.8)
No	45 (68.2)
Combination treatment[b]	
Yes	50 (75.8)
No	16 (24.2)
Recurrence within 2 years	
Yes	24 (36.4)
No	42 (63.6)
Status	
Dead	26 (39.4)
Alive	40 (60.6)

[a]Data previously reported for some patients (31). [b]Combination of surgery, radiotherapy and/or chemotherapy.

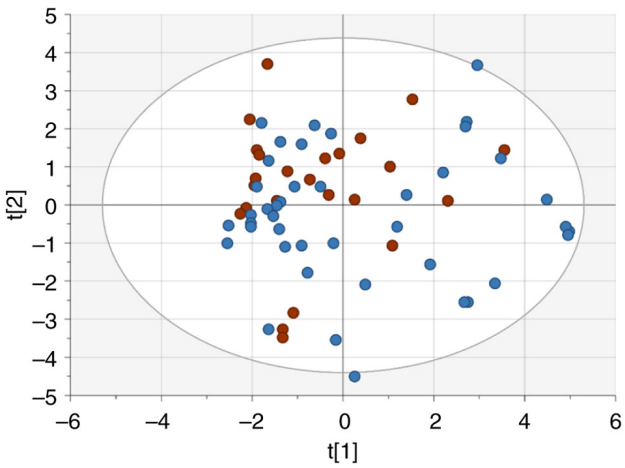

Figure 1. Principle component analysis of clinicopathological features at diagnosis in patients with squamous cell carcinoma of the oral tongue. Patients with recurrence are shown as red dots and patients without recurrence are shown as blue dots.

T1/T2 tumours, compared to 45/54 non-diabetics (P=0.204). None of the 11 diabetic patients with T1/T2 tumours had a recurrence, whereas 36% (16/45) of non-diabetics with T1/T2 tumours had a recurrence (P=0.023). To reduce heterogeneity in clinicopathological features, we analysed the subgroup of non-diabetic patients over 50 years of age with a T1/T2 tumour, comparable to diabetic patients regarding age and T-stage. Kaplan-Meier analysis showed that diabetic patients had better 2-year overall survival than non-diabetics (P=0.025; Fig. 3A). Of these patients, 42% (10/24) non-diabetics developed recurrence, compared to none of the eleven in the diabetic group (P=0.015, Fisher's exact test). Longer-term follow up of these diabetic (11) and non-diabetic (24) patients using Kaplan-Meier analysis showed that diabetic patients had better recurrence-free survival than non-diabetics although this was not statistically significant (P=0.287; Fig. 3B).

Table II. Association between clinicopathological features and recurrence.

Clinicopathological features	Recurrence		P-value
	Yes, n	No, n	
Sex			
Female	13	18	0.446
Male	11	24	
Age, years			
≤50	8	15	>0.999
>50	16	27	
Localisation			
Localized tumour on lateral border or unspecified	19	37	0.477
Overgrowth outside the oral tongue	5	5	
T stage[a]			
T1, T2	16	40	0.001
T3, T4	8	1	
N stage[a]			
N0	20	40	0.058
N1, N2	4	1	
Radiology			
Neck metastasis	9	4	0.010
No neck metastasis or reactive nodes	15	38	
Degree of differentiation			
Poorly, poorly-moderately or moderately differentiated	15	22	0.453
Moderately-well or well differentiated	9	20	
WPOI			
Broad pushing fingers; separate tumour islands or invasive islands (>15 cells/island)	2	9	0.303
Invasive islands (<15 cells/island) or tumour satellites with ≥1 mm distance from tumour	22	33	
LR			
Continuous dense rim of lymphoid tissue or patches of discontinuous dense lymphoid infiltrate	22	30	0.066
Limited or no response	2	12	
Smoking[b]			
Yes	15	22	0.419
No	7	18	
Diabetes			
Yes	0	12	0.003
No	24	30	
Asthma			
Yes	3	5	>0.999
No	21	37	
Cardiovascular disease			
Yes	6	15	0.422
No	18	27	
Combination treatment			
Yes	20	30	0.375
No	4	12	

[a]Information about T and N stage was lacking for 1 patient. [b]Information about smoking was lacking for 4 patients. WPOI, worst pattern of invasion; LR, lymphocytic response.

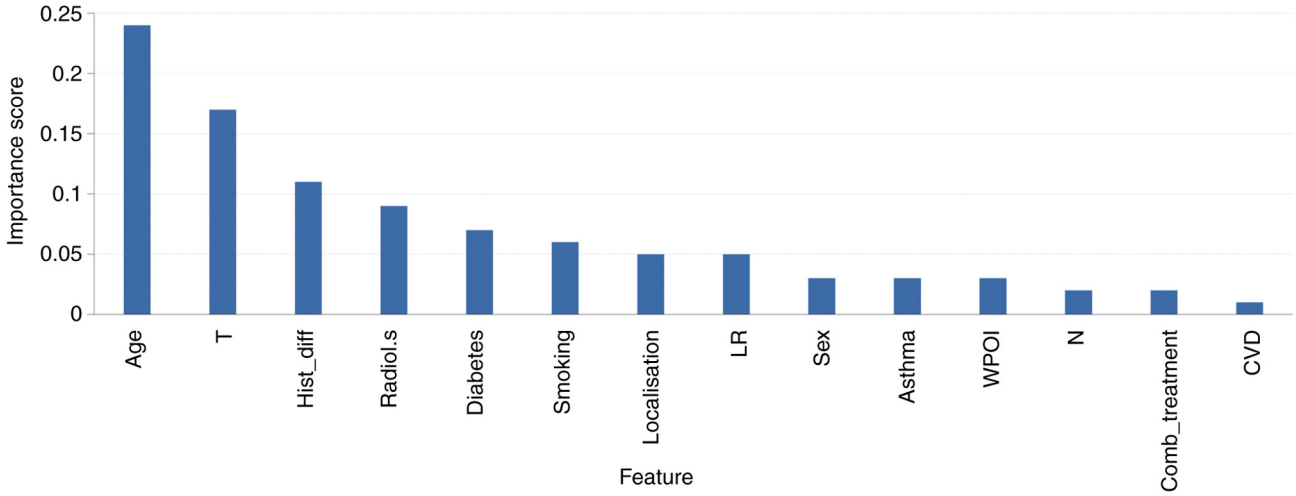

Figure 2. Clinical feature importance of the random forest model. T, tumour size; Hist_diff, histological differentiation; Radiol.s, radiological signs of neck metastasis; LR, lymphocytic response; WPOI, worst pattern of invasion; N, tumour spread to lymph node; Comb_treatment, combined treatment (surgery, irradiation and/or chemotherapy); CVD, cardiovascular disease.

Discussion

Tumour recurrence is a major problem for SCCHN patients, and, with a local recurrence rate of 30-40% (2), there is an urgent need for tools to predict the risk of relapse to ensure appropriate treatment and patient monitoring. Many studies have used various approaches to improve the prognostic prediction for SCCHN patients, including the ability to estimate outcomes from clinical and genomic data, and AI and machine learning methods have been applied to large 'omic' datasets and other data for this purpose (16-19). Here, we investigated whether similar machine learning approaches using only clinically available data at diagnosis are useful for improving models of risk recurrence in SCCOT, the most common subgroup of SCCHN tumours. Using consecutive samples of SCCOT and data available from routine clinical investigations at diagnosis and medical histories, we identified that the machine learning model RF is a valuable approach, able to generate a model to predict SCCOT recurrence with an accuracy of 71.2% using only these simple data.

Despite the relatively low performance of the overall model, unlike some AI approaches our modelling procedure provided information into the specific features responsible for prediction. Surprisingly, diabetes as a co-morbidity showed a strong positive influence on outcome; patients with diabetes had lower rates of recurrence than non-diabetic patients and a correspondingly better survival. According to the Swedish diabetes register, approximately half a million people have diabetes, and 85-90% of these have type II diabetes (https://www.diabetes.se/diabetes). In our study, 18% (12/66) of patients were diabetics ($P<0.001$ compared to the general population) and eight had type II diabetes judged by their medication. Thus, our data are compatible with the general findings that diabetes is associated with an increased risk of cancer development, including SCCHN and the oral SCC subtype (20). Paradoxically, our data show that patients with diabetes have a decreased risk of recurrence.

Hyperglycaemia in diabetes is caused by improper function or reduced secretion of insulin from pancreas, and the correlation between diabetes and increased carcinogenesis risk is therefore thought to be due to hyperinsulinemia, hyperglycaemia and insulin resistance (21). Despite the association of hyperglycaemia with increased risk of developing cancer, none of the diabetic patients we studied showed tumour recurrence within the first 50 months of follow-up. The link between diabetes and lack of recurrence was retained when comparing the diabetic group, all of whom were over 50 years of age and with a T1/T2 tumour, to the group of non-diabetics who were also over 50 years of age and with a T1/T2 tumour, where 42% of the non-diabetic patients showed a recurrence compared to none of the diabetic patients. This presents an apparent paradox, where hyperglycaemia associated with clinical diabetes is expected to cause an increased risk of cancer development, yet co-existing diabetes reduces the risk of cancer recurrence. The most plausible explanation for this discrepancy between expectation and reality is that patients diagnosed with diabetes receive one or more treatments and/or lifestyle changes to control their disease, and are regularly monitored in wealthy countries to prevent hyperglycaemia. Thus, advanced health care procedures ensure that diabetics show high hyperglycaemic levels only before their diagnosis, which is rapidly and effectively reduced by anti-diabetic therapy.

The majority of newly diagnosed diabetics are initially treated with Metformin as an anti-glycaemic treatment. Metformin directly inhibits tumour cell proliferation, including SCCHN cells (21) and has cytostatic effects when used therapeutically in non-diabetic women with operable breast cancer (22). Metformin users may also have a reduced risk of acquiring cancers such as colorectal, liver, lung, prostate and breast (23), although recent data suggest that this issue is controversial and remains to be proven (24). There is also evidence that the increased risk of recurrence of OSCC seen in type II diabetic patients is reduced in those who use Metformin (25). In this large retrospective study of more than 800 patients with oral SCC (OSCC), patients with type II diabetes showed worse survival. However, when taking Metformin treatment into account, survival improved significantly. Metformin has

Table III. Association between clinicopathological features and diabetes.

Clinicopathological features	Diabetes		P-value
	Yes, n	No, n	
Sex			
Female	3	28	0.117
Male	9	26	
Age, years			
≤50	0	23	0.005
>50	12	31	
Localisation			
Localised tumour on lateral border or unspecified	12	44	0.187
Overgrowth outside the oral tongue	0	10	
T stage[a]			
T1, T2	11	45	0.337
T3, T4	0	9	
N stage[a]			
N0	11	49	0.579
N1, N2	0	5	
Radiology			
Neck metastasis	1	12	0.434
No neck metastasis or reactive nodes	11	42	
Degree of differentiation			
Poorly, poor-moderate or moderately differentiated	5	32	0.341
Moderately-well or well differentiated	7	22	
WPOI			
Broad pushing fingers; separate tumour islands or invasive islands (>15 cells/island)	4	7	0.104
Invasive islands (<15 cells/island) or tumour satellites with ≥1 mm distance from tumour	8	47	
LR			
Continuous dense rim of lymphoid tissue or patches of discontinuous dense lymphoid infiltrate	6	46	0.014
Limited or no response	6	8	
Smoking[b]			
Yes	8	29	0.501
No	3	22	
Asthma			
Yes	1	7	>0.999
No	11	47	
Cardiovascular disease			
Yes	9	12	0.001
No	3	42	
Combination treatment			
Yes	8	42	0.465
No	4	12	

[a]Information about T and N stage was lacking for 1 patient. [b]Information about smoking was lacking for 4 patients. WPOI, worst pattern of invasion; LR, lymphocytic response.

also shown a positive effect on histological grade of dysplasia in non-diabetics with oral premalignant lesions through its actions on mTOR signalling (26). Although these studies imply a specific effect of Metformin on inhibiting cancer formation and progression (25,26), only 42% of diabetics in our cohort were treated with Metformin and the remaining diabetic patients were controlled with insulin (33%) or dietary modification (25%). As all diabetics were free of recurrence >50 months of follow-up, the data indicate that not only Metformin but also other antiglycaemic treatments may have a

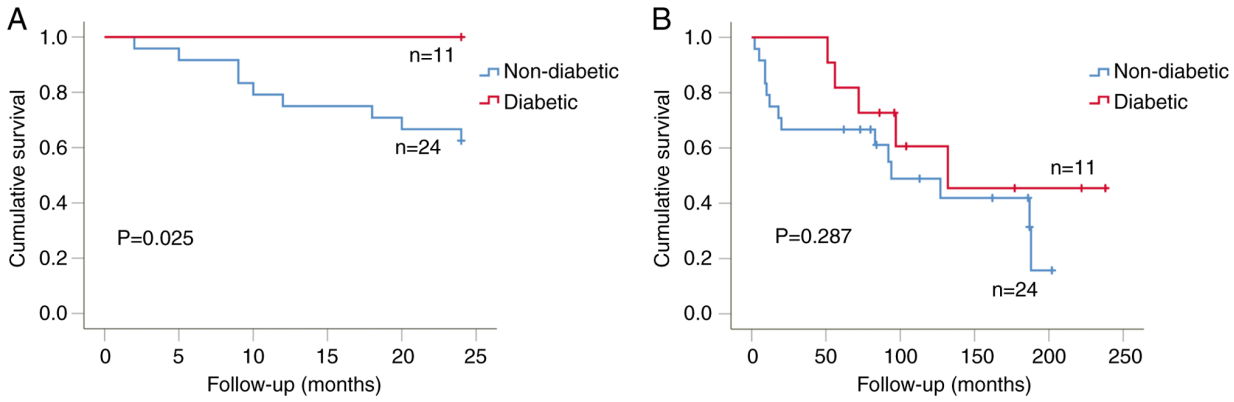

Figure 3. Kaplan-Meier recurrence-free survival analysis of patients >50 years old with a T1/T2 tumour, divided into patients with diabetes (red line) and without diabetes (blue line). (A) First 2 years follow-up (P=0.025). (B) Available follow-up time (P=0.287). Tick marks indicate censored cases.

positive impact on survival, in keeping with the lack of specific effects of Metformin versus other methods of control seen in other studies of Type II diabetic patients with SCCHN (27). That the improved overall survival of diabetic SCCOT patients was reduced after longer follow-up may be explained by the majority of diabetics (75%) also suffering from cardiovascular disease as an additional comorbidity. The effect of controlling (reducing) circulating glucose levels on tumour growth is presumably linked to the extreme reliance of cancer cells on high glucose levels, where tumour cells require high levels of energy but use the inefficient process of aerobic glycolysis (the Warburg effect), which has been suggested as a therapeutic avenue for many cancers, irrespective of diabetes (28). The use of aerobic glycolysis by tumour cells is also important for DNA repair and helps to promote resistance to standard genotoxic therapeutic agents (29), which may also help to explain our observations of improved response in controlled diabetic patients. In addition to direct effects on tumour cell growth, diabetes also influences tumour associated altered immune responses. An inflammatory response has previously been shown to have a positive prognostic impact in SCCOT (24), and the majority of non-diabetics in our study (85%) showed a higher LR than diabetics. That diabetics showed a lower frequency of CD3+ T-cells due to metabolic inhibition, lactic acidosis inhibiting T-cell viability and function (30) is in concordance with our results, where 50% of diabetics showed limited or no LR.

In conclusion, we used clinical, radiological and histological data available in the routine care at diagnosis of patients with SCCOT to establish a prognostic model. Using machine learning to provide a risk of recurrence classification procedure produced a model with 71.2% accuracy. An unexpected but important finding from feature importance was that none of the patients with diabetes showed tumour recurrence after > 50 months follow-up. Although patients with diabetes are over-represented among patients with SCCOT, diabetics showed less recurrence and improved survival compared to non-diabetics, even after accounting for the independent prognostic variables of tumour size and patient age at diagnosis. Even if the number of patients with diabetes and cardiovascular disease may seem a bit high in our study, 18.2 and 31.8% respectively, there was no selection performed other than the availability of clinical, histological and radiological data.

Notwithstanding the limitations of our study in terms of cohort size, the major strength of the present study is the use of a single subtype of SCCHN, where data imply that reduction of glucose levels may be beneficial for all patients with SCCOT, not just patients undergoing treatment for their diabetes. In addition, irrespective of the genetic and clinical differences between SCCOT and other SCCHN tumours, our data also indicate that reduction of glucose levels may be useful for similar tumours in the head and neck region (larynx, jaw, thyroid, etc), which is an area for future investigations.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

AMS, LW, PJC and KN designed the study. AMS and LW retrieved and analysed data. LNS, NS and XG participated in data analysis. AMS, LW, PJC and KN wrote the manuscript. AMS, LW, LNS, XG, NS, PJC and KN edited the manuscript. AMS and KN confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments. The present

study was approved by the local ethics committee (Regionala Etikprövningsnämnden, Umeå University, Umeå, Sweden; approval no. 2014-193-32M). Written informed consent was obtained from the patients after oral information given by Ear, Nose and Throat-staff.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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