Oral Oncology 168 (2025) 107584

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Association of quality of life with mortality in patients with adenoid cystic carcinoma using an internationally-validated QoL questionnaire (EQ-5D-5L)

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ARTICLE INFO

Keywords:
Adenoid cystic carcinoma
Salivary gland cancer
Quality of life
EQ-5D-5L

ABSTRACT

Background/objectives: An evaluation of quality of life (QoL) is increasingly required for approval and reimbursement of new drug therapies. To support the evaluation of the impact of new drug therapies on QoL in single-arm studies in adenoid cystic carcinoma (ACC), we sought to determine the QoL baseline in a cohort of patients with ACC during routine follow up visits and to assess for associations with clinical or prognostic factors. **Methods:** An internationally-validated QoL questionnaire (EQ-5D-5L) was completed by patients with ACC referred to an experimental medicine centre. EQ-5D value scores (EQV) were calculated from each questionnaire using the EuroQol England value set. A Cox proportional hazards model was built with EQV as a time-dependent variable. Non-linear mixed effects modelling (NLME) was used to test the relationship between EQV and predictors (time, NOTCH1 status, age at diagnosis, sex, local and/or metastatic recurrence, and primary site of disease). **Results:** Between 2019 and 2023, 563 questionnaires were completed by 161 patients with ACC. Median EQV was 0.81 (range −0.22 to 1.0) and mean EQV was 0.79. A decrease in EQV from 1 to 0 was associated with an eightfold increase in risk of death in the total population (HR = 0.118, 95 % CI 0.057 to 0.244, p=<0.001). No predictor had a significant impact on EQV in NLME except time (p=<0.001). **Conclusions:** For patients with ACC, a worse QoL as measured by EQ-5D-5L was associated with a significantly increased risk of death. It remains unclear if poorer QoL has a causal relationship with mortality.

Introduction

An evaluation of impact on quality of life (QoL) is required for reimbursement of drug therapies in many healthcare systems [1,2]. Additionally, many jurisdictions are increasingly considering QoL in the regulatory approval process for new drug therapies [1,2].

Adenoid cystic carcinoma (ACC) is a rare cancer with limited treatment options [3,4]. ACC typically follows an indolent disease course [5], and drug therapies are generally reserved until significant clinical or radiological progression, with current options offering only limited response rates [3,4]. These features make patients with ACC difficult to recruit to clinical trials, and studies of new therapies in ACC are almost invariably small, non-randomised, and lacking a comparator QoL measure [3]. In addition, no baseline of QoL in patients with ACC has been published in the non-curative setting to provide a comparator.

To assist in understanding QoL in ACC, we aimed to characterise the baseline QoL and its associations with time and other clinical factors in a cohort of patients with ACC. EQ-5D value scores (EQV) are the key QoL measure used during appraisals of new drug therapies through the UK National Institute for Health and Care Excellence (NICE) [2]. As there

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https://doi.org/10.1016/j.oraloncology.2025.107584
Received 1 May 2025; Received in revised form 30 July 2025; Accepted 31 July 2025

are no published datasets including EQV for ACC patients outside of interventional clinical trials (which are typically single arm), we sought to determine the EQV in this cohort of patients.

Materials and methods

This study was a retrospective analysis of data collected during standard practice. The cohort was selected from patients with ACC who attended a tertiary cancer centre. Patients were included in the study if they had provided written, informed consent to analysis of their clinical data. All patients had histopathological confirmation of ACC. An internationally-validated QoL questionnaire (EQ-5D-5L) was sent to patients prior to clinic appointments using an electronic patient-reported outcome measures system as part of standard-of-care. The timing of clinic appointments was determined by clinical need at any point following diagnosis and not specifically linked to disease milestones, such as diagnosis or recurrence. An individual patient could complete more than one questionnaire at different timepoints.

EQ-5D-5L comprises 5 dimensions and a visual analogue scale (VAS) [6]. The dimensions are: anxiety/depression; mobility; pain/discomfort; self-care; and usual activities. Each dimension is scored using 5 levels: none/no impairment (1); slight (2); moderate (3); severe (4); and extreme/unable (5) [6]. A set of 5 dimension scores for an observation is a health state [6]. The VAS is a self-assessed interpretation of overall health out of 100- the patient gives a value they feel represents their current health, with 100 being perfect health and 0 being the worst health possible [6]. EQ-5D value scores (EQV) were calculated from the dimensions of each EQ-5D-5L questionnaire; the EQV is derived from a health state weighted by national interpretations of QoL using country-specific value sets [6]. The EuroQol England EQ-5D-5L (2017) value set was used for this study [7]. An EQV of 1 equates to perfect QoL, whilst an EQV of 0 is a state considered comparable to death. EQV can be negative for states considered worse than death [8].

Median, mean, and decile EQV values were calculated based on the first EQ-5D-5L questionnaire completed by each patient, as subsequent observations for the same individual were not independent. Subsequent modelling, described below, accounts for within-group dependent observations.

A linear Cox proportional hazards model was built with EQV as a time-dependent variable and mortality as the event of interest. A second Cox proportional hazards model was constructed using penalised smoothing splines to assess linearity by comparing to the first model using the Chi-squared test.

A base non-linear mixed effects model was constructed between time and EQV. Variant models were built for other clinical and prognostic factors (NOTCH1 gain-of-function alteration status, age at diagnosis, sex, local and/or metastatic recurrence, and primary site of disease), with one model per predictor. These were tested against the base model using the Chi-squared test.

Kaplan-Meier survival analysis was also performed on the overall cohort and for subgroups of each factor above to assess whether the cohort was representative of patients with ACC. P-values were calculated using the log-rank test.

All analyses were completed using R Statistical Software (v4.3.2) in Rstudio (v2023.12.0.0) [9]. The following packages were used for statistical analysis: survival [10,11], nlme [12,13], and eq5d [14]. The ggplot2 [15], ggsurvfit [16], and ggpubr [17] packages were used for graphical analysis. The dplyr package was used for data processing [18].

Results

Between 2019 and 2023, 161 patients with ACC were identified who had completed at least one EQ-5D-5L questionnaire. A total of 563 EQ-5D-5L questionnaires were completed with a median of two responses per patient (range 1 to 20). Median age was 49 and 60 % were female, consistent with previous analyses in this cohort [19]. At the time of analysis, 41 % had died. Table 1 summarises their clinical characteristics.

Multiple primary site locations were included in the analysis, reflective of the fact ACC can arise from exocrine structures throughout the body and that clinical trials of new drugs in this setting are typically based on histology, independent of primary site. NOTCH1 gain-of-function alterations were found in 8 % of patients, consistent with previous reports in this disease of ~ 8.5 %-26.3 % [19–22].

One hypothesis we sought to test was that the site of recurrence (local recurrence vs distant metastatic recurrence) had an impact on the patient's QoL scores. These subgroups were well represented in this study, with 40 % local recurrence (14 % local recurrence only; 26 % local and metastatic recurrence) and 72 % metastatic recurrence (46 % metastatic recurrence only; 26 % both local and metastatic recurrence) for the 86 % of patients with recurrent disease (139/161).

To determine whether this cohort was comparable to previously published cohorts of patients with ACC [19,21–23], we analysed overall survival from diagnosis (Fig. 1A) and from recurrence (Fig. 1F). As expected, median overall survival from diagnosis was 13.9 years (95 % confidence interval: 9.39 – 17.8), and median survival from disease recurrence was 6.0 years (95 % confidence interval: 5.42 – 9.88). We then sought to determine the association between clinical parameters and survival from diagnosis (Fig. 1B-1E) and from recurrence (Fig. 1G-1J). Of these parameters, an activating NOTCH1 mutation is known to be prognostic [19,21,22] and we found NOTCH1 status to be significantly associated with both survival from diagnosis ($p = 0.040$) and survival from recurrence ($p = 0.007$) in our cohort. The other parameters evaluated were location of primary site, sex, and recurrence status, with no significant associations found.

For all 161 patients, median EQV was 0.81 (range −0.22 to 1.0) and mean EQV was 0.79. The EQV by decile is shown in Table 2. The EQV is derived from the 5 EQ-5D-5L dimension scores evaluating anxiety/depression, mobility, pain/discomfort, self-care, and usual activities. The distribution of EQ-5D-5L dimension scores is shown in Fig. 2A. The median EQ-5D-5L dimension scores were 2 for anxiety/depression (IQR 1–2), 1 for mobility (IQR 1–2), 2 for pain/discomfort (IQR 1–3), 1 for

Table 1
Clinical characteristics of the studied population.

Characteristic	No. of Patients (%)
Overall population	161
Age at diagnosis, years	
Median	49
Mean	50.8
Range	17–81
Sex	
Female	97 (60.2)
Male	64 (39.8)
Primary site	
Major salivary gland	58 (36.0)
Minor salivary gland	31 (19.3)
Sinonasal	44 (27.3)
Tracheobronchial	20 (12.4)
Lacrimal	4 (2.5)
Skin	3 (1.9)
Breast	1 (0.6)
Status at time of analysis	
Alive	95 (59.0)
Deceased	66 (41.0)
Disease recurrence	
Yes	139 (86.3)
No	22 (13.7)
Pattern of recurrence	
None	22 (13.7)
Local recurrence only	23 (14.3)
Metastatic recurrence only	74 (46.0)
Both local and metastatic recurrence	42 (26.1
NOTCH1 alteration status	
No known pathogenic alteration	148 (91.9)
Gain-of-function alteration	13 (8.1)

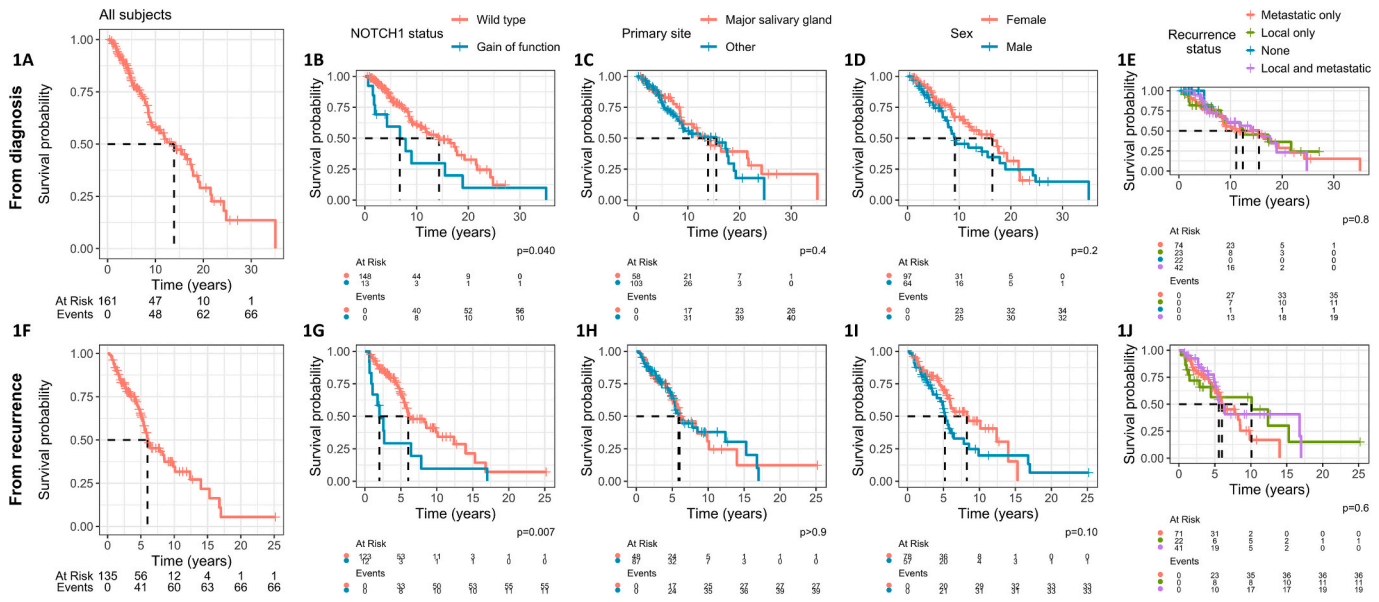

Fig. 1. Kaplan-Meier survival analysis of the cohort of 161 patients with ACC from diagnosis (1A-1E) and 135 patients with ACC from first confirmed recurrence of disease (1F-1 J); The complete cohort were included in figures 1A and 1F, the remainder are for clinical covariates of interest.

Table 2
Mean EQ value and EQ value by decile.

Mean EQ value	**0.79**
Decile	**EQ value**
1st	0.57
2nd	0.68
3rd	0.75
4th	0.78
5th (median)	0.81
6th	0.86
7th	0.88
8th	0.92
9th	0.94

self-care (IQR 1–1), and 2 for usual activities (IQR 1–3). The patient-reported visual analogue scale for best health (VAS) is shown in Fig. 2B. Median VAS was 70 (IQR 30–80). The distribution of EQV is left-skewed (Fig. 2C). We next sought to compare the mean QoL as determined by EQV in this cohort of patients with ACC with the age-matched general population [24]. The mean EQV of 0.79 for patients with ACC is lower than the age-matched general population mean of 0.86 (Fig. 2C, orange dashed line is the general population mean, black dashed line is the studied population mean).

We hypothesized that poorer QoL was associated with a higher mortality rate, and developed a linear Cox proportional hazards model to test this. This revealed a decrease in EQV from 1 to 0 was associated with an eightfold increase in risk of death in the total population (HR =

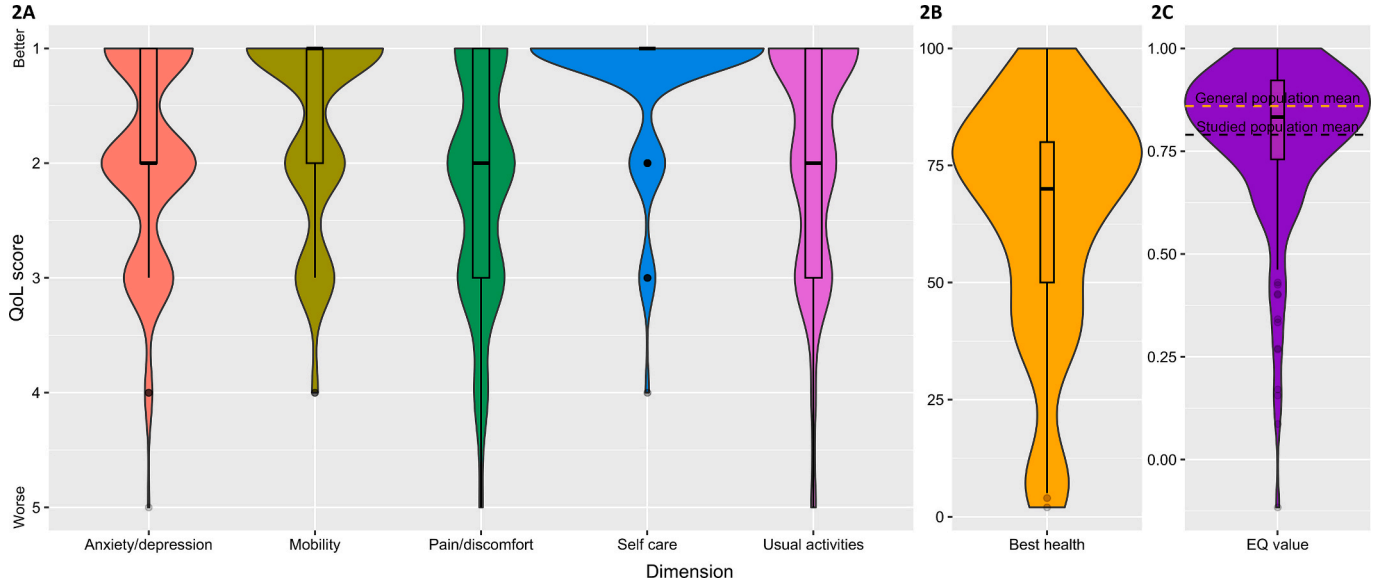

Fig. 2. Violin and box-and-whisker plots showing distribution of quality-of-life dimensions as measured by the EQ-5D-5L questionnaire in the studied population (2A). The distribution of visual analogue scales for best health is shown in 2B. EQ values are calculated from the dimensions (2C). An age-adjusted EQ value mean for the UK general population is shown in orange, and the sample EQ value mean in black. An EQ value of 1 equates to perfect health, 0 equates to a state considered as bad as death, and values below 0 are states considered worse than death. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

0.118, 95 % CI 0.057 to 0.244, p=<0.001; Table 3). However, there was a significant non-linear relationship between EQV and survival over time (p = 0.011; Table 3). Fig. 3 shows the modelled non-linear survival probability over time per EQV decile. A greater marginal effect on survival was seen for the difference in EQV above the median value of 0.81.

We also sought to determine whether QoL changes over time, as it is expected that patients become more symptomatic during their disease course. A non-linear mixed effects model was used to test this and revealed a significant negative association between time and EQV (slope −0.027, p=<0.001), with the negative slope indicating QoL declining over time (Table 4). Clinical variables including NOTCH1 status, location of primary site, sex, age, recurrence status and type of recurrence were evaluated by incorporating them into variant models, tested against the time model as a base (Table S1). No variant model with an additional clinical variable significantly improved the fit of the base model, suggesting the other variables do not have a significant impact on QoL (Table S1).

Discussion

This is the first study to characterise the baseline QoL in the ACC population outside of an interventional clinical trial. We have demonstrated that QoL does significantly decrease over time in patients with ACC, but have identified no other significant risk factors for deteriorating QoL.

QoL has rarely been reported in the literature for ACC. Locati et al collected QoL data including EQ-5D-5L questionnaires during a single-arm interventional study of 28 Italian patients treated with Lenvatinib [25]. Mean EQV at baseline was reported at 0.8, comparable with our findings, whilst they also found that QoL decreased over the study period of 12 months to a mean EQV of 0.7. However, the results of this study must be interpreted with caution as Locati et al only reported EQV to a single decimal place. The study also collected QoL data using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Items (EORTC QLQ-C30) and the EORTC Quality of Life Questionnaire–Core Module Head and Neck Module (EORTC QLQ-H&N35), which also showed a modest drop in QoL across the duration of the study. However, as there was no comparator arm, it is not possible to determine whether the decline in QoL was due, in part or in whole, to the introduction of Lenvatinib, or simply reflective of a deterioration over time, as demonstrated in our study.

The importance of patient-reported outcomes as a measure of QoL are increasingly being recognised by regulatory bodies, with the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) both recommending their inclusion in oncology clinical trials [26,27]. Furthermore, many health technology assessment agencies use patient-reported outcomes as part of the technology assessment process to inform decisions regarding the reimbursement of therapies, with generic measurement tools generally being favoured due to their consistency and comparability across disease areas [1]. Germany and the United Kingdom particularly favour the EQ-5D family of questionnaires, with EQ-5D widely used during health technology assessments by their national agencies, the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) and NICE respectively [1]. As a result, QoL data collected via patient-reported outcomes can have significant implications on drug approval and drug reimbursement in major healthcare markets. However, clinical trials in ACC are typically single-arm studies without a comparator arm due to the rarity of the disease [3]. Therefore, it is difficult to make inferences about the effect of new therapies on QoL based on these studies alone. The data presented in this study provides a representative baseline for the ACC population from which inferences can be drawn, and could help industry and health technology assessment agencies in appraising the impact of future therapies.

The fact that reduced QoL is associated with an increased risk of mortality is consistent with findings from studies in non-small cell lung cancer, which also confirm that a lower EQ value correlates with an increased risk of death [28]. NOTCH1 gain-of-function alteration is associated with a significantly poorer prognosis in ACC [19,21,22]; our findings were consistent with the published literature and showed a significantly poorer prognosis for patients with NOTCH1 gain-of-function. However, this did not correlate with a significant impact on QoL, suggesting that an increased rate of disease progression is not related to QoL. This was contrary to our assumptions prior to the study where we hypothesised that a more aggressive disease course would be associated with a poorer QoL.

No significant differences in QoL were observed between different patterns of recurrence; local recurrence was not demonstrated to have a significantly different QoL to metastatic recurrence, or both types of recurrence together. Furthermore, origin of primary site (major salivary glands or other sites) did not show a significant difference in QoL.

The main limitation of this study was that the timepoints of the questionnaire completion dates were determined by the clinical need for follow-up, rather than at specifically pre-determined time points in the disease course, such as diagnosis, recurrence, or initiation of treatment. For the same reason, there are variable numbers of responses per patient. Furthermore, the data is time-dependent and, whilst this has been accounted for by the modelling methods applied, it reduces the generalisability of the findings. However, the most parsimonious models have been used, where possible, to reduce the impact of this [29].

The EQ-5D-5L questionnaire was used in this study as it has been adopted by the UK regulatory authorities [2]. However, it is brief, not cancer-specific, and considered, by some, to be too general to adequately assess QoL in specific indications [30]. Despite these concerns, the EQ-5D-5L is generally found to correlate well with other measures of health status and QoL, and is a reliable and moderately responsive tool [31]. There are also advantages of EQ-5D-5L being generalisable and comparable between different diseases and nations [32], and patient compliance is higher when completing a more-concise questionnaire [33].

Whilst this study shows that a poorer QoL is predictive of increased mortality, it is unclear whether deteriorating QoL is merely a surrogate marker of increasing disease burden, or whether QoL has a causal relationship with reduced prognosis that could be targeted by interventions, such as enhanced supportive care. Research has suggested that active and early input from supportive care teams can improve QoL and survival in the non-curative setting in patients with advanced cancer [34,35]. However, future studies are needed to determine whether providing supportive care interventions to patients with ACC with a poorer QoL can improve QoL and prognosis.

Table 3
Time-dependent linear Cox proportional hazard model showing significant relationship between quality of life and risk of death. The linear model is compared to a non-linear Cox proportional hazards model built using penalised splines using the Chi squared test.

Time-dependent Cox proportional hazards model (linear)	
Hazard ratio (95 % confidence intervals)	0.118 (0.057–0.244)
Standard error	0.371
P value	<0.001
Chi squared comparison to non-linear Cox proportional hazards model built using penalised splines	
P value	0.011

Conclusions

For patients with ACC, a poorer QoL, as measured by EQ-5D-5L, was associated with a significantly increased risk of death. It remains unclear whether poorer QoL is a surrogate marker of increasing disease burden or whether there is a causal relationship with mortality. NOTCH1 status and pattern of disease recurrence were not associated with a poorer QoL in this cohort.

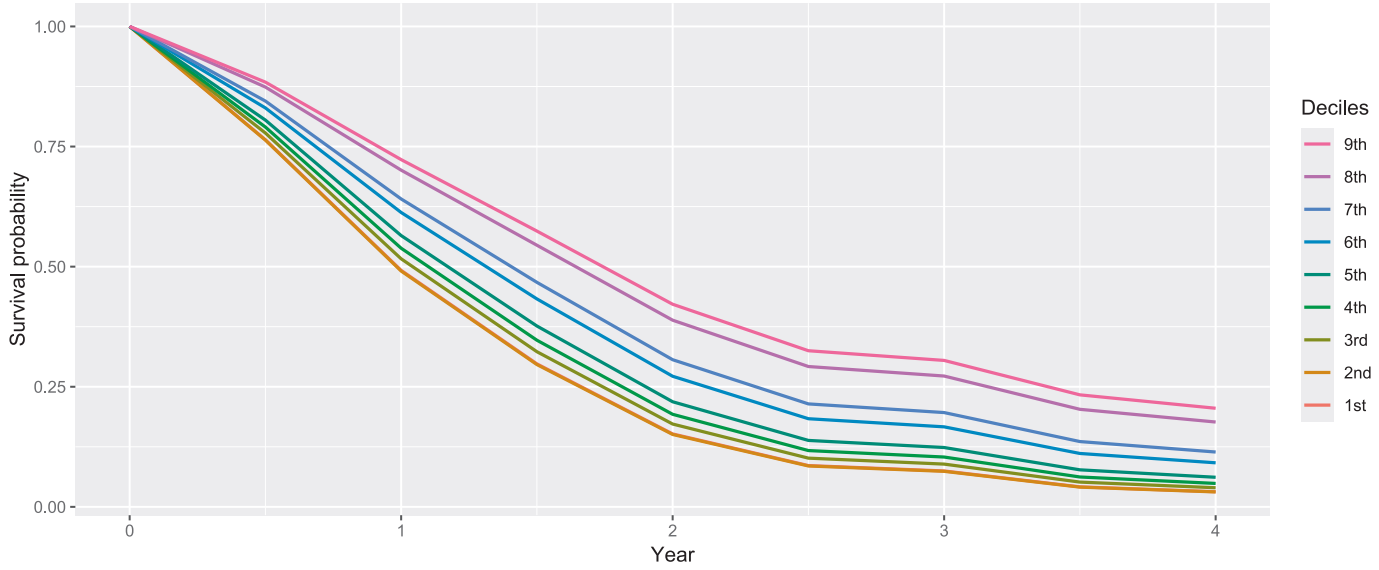

Fig. 3. Non-linear Cox proportional hazards model predicting probability of survival over time per EQ value decile.

Table 4
Time-dependent non-linear mixed effects model showing relationship between time and EQ value. This was the base model used as a reference for further analysis of covariates..

Fixed effects	Value	Standard error	Degrees of freedom	T-value	P-value (Sig. < 0.05)	Correlation
Intercept	0.763	0.015	342	50.48	N/A	N/A
Slope	−0.027	0.008	342	−3.48	<0.001	0.572
Random effects	**Standard deviation**	**Correlation**				
Intercept	0.171	N/A				
Slope	0.050	0.825				

Institutional Review Board Statement: The analysis was conducted in accordance with the UK Policy Framework for Health and Social Care Research and the Declaration of Helsinki. Written informed consent was obtained under the MCRC Biobank Research Tissue Bank Ethics (NHS NW Research Ethics Committee 18/NW/0092 was approved on 22 May 2018, superseded by 22/NW/0237 approved on 30 August 2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

CRediT authorship contribution statement

Joseph Edward Haigh: Methodology. **Karan Patel:** Methodology, Investigation, Conceptualization. **Lucy Shepherd:** Writing – review & editing, Validation, Methodology, Formal analysis. **Emily Heathcote:** Investigation. **Samuel Rack:** Investigation. **Guy Betts:** Investigation. **Laura Spurgeon:** Investigation. **Robert Hodgson:** Methodology. **Hitesh Mistry:** Software, Methodology, Formal analysis. **Kevin Joseph Harrington:** Writing – review & editing. **Robert Metcalf:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Funding

Funding support is provided to the head and neck research team by The Christie Charity, Syncona Foundation, and The Infrastructure Industry Foundation. There is no applicable grant number.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Robert Metcalf reports financial support was provided by The Christie Charity. Robert Metcalf reports financial support was provided by Syncona Foundation. Robert Metcalf reports financial support was provided by The Infrastructure Industry Foundation. Robert Metcalf reports a relationship with Bristol-Myers Squibb Co that includes: speaking and lecture fees. Robert Metcalf reports a relationship with Merck Sharp & Dohme that includes: speaking and lecture fees. Robert Metcalf reports a relationship with Roche that includes: speaking and lecture fees. Robert Metcalf reports a relationship with Bayer that includes: speaking and lecture fees. Robert Metcalf reports a relationship with Achilles Therapeutics UK Limited that includes: speaking and lecture fees. Robert Metcalf reports a relationship with Aptus Clinical that includes: speaking and lecture fees. Robert Metcalf reports a relationship with PCI Biotech that includes: speaking and lecture fees. Robert Metcalf reports a relationship with Ayala Pharmaceuticals, Inc. that includes: speaking and lecture fees. Robert Metcalf reports a relationship with OxSonics Ltd that includes: speaking and lecture fees. Kevin Joseph Harrington reports a relationship with Arch Oncology (Inst) that includes: consulting or advisory and speaking and lecture fees. Kevin Joseph Harrington reports a relationship with AstraZeneca (Inst) that includes: consulting or advisory, funding grants, and speaking and lecture fees. Kevin Joseph Harrington reports a relationship with Bristol-Myers Squibb Co that includes: consulting or advisory and speaking and lecture fees. Kevin Joseph Harrington reports a relationship with Boehringer Ingelheim (Inst) that includes: consulting or advisory and speaking and lecture fees. Kevin Joseph Harrington reports a relationship with Merck Serono that includes: consulting or advisory and speaking and lecture fees. Kevin Joseph Harrington reports a relationship with Merck Sharp & Dohme that includes: consulting or advisory, funding grants, and speaking and lecture fees. Kevin Joseph Harrington reports a relationship with Oncolys Biopharma Inc that includes:

consulting or advisory and speaking and lecture fees. Kevin Joseph Harrington reports a relationship with Pfizer that includes: speaking and lecture fees. Kevin Joseph Harrington reports a relationship with Replimune that includes: consulting or advisory and speaking and lecture fees. Kevin Joseph Harrington reports a relationship with Inzen Therapeutics that includes: consulting or advisory and speaking and lecture fees. Kevin Joseph Harrington reports a relationship with Codiak Biosciences that includes: speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper..

Acknowledgement

The authors acknowledge the support of the Manchester Cancer Research Centre (MCRC) Biobank. The MCRC biobank was granted research ethics approval for the collection of demographic and clinical data for patients whose clinical images have been included in this study under the MCRC Biobank Research Tissue Bank Ethics (NHS NW Research Ethics Committee 18/NW/0092, superseded by 22/NW/0237 approved on 30 August 2022). However, the MCRC biobank does not endorse specific studies or the interpretation of results. We are grateful for the assistance of Jenni Hill in the preparation of the manuscript for submission.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2025.107584.

Data availability

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to the requirement to uphold the data sharing with relevant approved researchers as stipulated in the ethical approval.

References

[1] Shaw C, Longworth L, Bennett B, Ruane P, Watson C, Francis LE, et al., P59 to what extent Is EQ-5D used as a tool for clinical outcome assessment? Value in Health, Volume 25, Issue 1, S13. DOI: 10.1016/j.jval.2021.11.057.
[2] National Institute for Health and Care Excellence, NICE health technology evaluations: the manual [internet]. [London]: NICE; 2022/revised 2023 [cited 2024 May 02]. (NICE process and methods [PMG36]). Available from: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation.
[3] Geiger JL, Ismaila N, Beadle B, Caudell JJ, Chau N, Deschler D, et al. Management of Salivary Gland Malignancy: ASCO Guideline. JCO 2021;39:1909–41. https://doi.org/10.1200/JCO.21.00449.
[4] Van Herpen C, Poorten VV, Skalova A, Terhaard C, Maroldi R, van Engen A, et al. Salivary gland cancer: ESMO—European Reference Network on Rare Adult Solid Cancers (EURACAN) Clinical Practice Guideline for diagnosis, treatment and follow-up. ESMO Open 2022;7:100602 [CrossRef] [PubMed].
[5] Cantù, G. Adenoid cystic carcinoma. An indolent but aggressive tumour. Part A: from aetiopathogenesis to diagnosis. *Acta Otorhinolaryngol Ital.* 2021 Jun;41(3): 206-214. doi: 10.14639/0392-100X-N1379. PMID: 34264913; PMCID: PMC8283400.
[6] EuroQol Research Foundation. EQ-5D-5L User Guide, 2019. Available from: https://euroqol.org/publications/user-guides.
[7] Devlin N, Shah K, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of Life: an EQ-5D-5L Value Set for England. Health Econ 2017:1–16. https://doi.org/10.1002/hec.3564.
[8] EuroQol Group. *Terminology*. https://euroqol.org/support/terminology/ [Accessed 15 Jan 2024].
[9] R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2021. https://www.R-project.org/.
[10] Therneau, T.M. (2023). _A Package for Survival Analysis in R_. R package version 3.5-7, https://CRAN.R-project.org/package=survival.
[11] Therneau TM, Grambsch PM. Modeling Survival Data: Extending the Cox model_. New York: Springer; 2000.
[12] Pinheiro. J.; Bates, D.; R Core Team (2023). _nlme: Linear and Nonlinear Mixed Effects Models_. R package version 3.1-163, https://CRAN.R-project.org/package=nlme.
[13] Pinheiro JC, Bates DM. _Mixed-Effects Models in S and S-PLUS_. Springer, New York 2000. https://doi.org/10.1007/b98882.
[14] Morton F, Nijjar JS. _eq5d: Methods for Analysing 'EQ-5D' Data and calculating 'EQ-5D' Index scores_. R package version 2024;(15):3. https://CRAN.R-project.org/package=eq5d.
[15] Wickham H. ggplot2: Elegant Graphics for Data Analysis. New York: Springer-Verlag; 2016.
[16] Sjoberg D, Baillie M, Fruechtenicht C, Haesendonckx S, Treis T. _ggsurvfit: Flexible Time-to-Event figures_. R package version 2023;1. https://CRAN.R-project.org/package=ggsurvfit.
[17] Kassambara A. _ggpubr: 'ggplot2' based Publication Ready plots_. R package version 2023;(6). https://CRAN.R-project.org/package=ggpubr.
[18] Wickham, H.; François, R.; Henry, L.; Müller. K.; Vaughan. D. (2023). dplyr: A Grammar of Data Manipulation. R package version 1.1.4, https://github.com/tidyverse/dplyr, https://dplyr.tidyverse.org.
[19] Feeney L, Hapuarachi B, Adderley H, Rack S, Morgan D, Walker R, et al. Clinical disease course and survival outcomes following disease recurrence in adenoid cystic carcinoma with and without NOTCH signaling pathway activation. Oral Oncol 2022;133.
[20] Ho AS, Ochoa A, Jayakumaran G, Zehir A, Valero Mayor C, Tepe J, et al. Genetic hallmarks of recurrent/metastatic adenoid cystic carcinoma. J Clin Invest 2019; 129:4276–89.
[21] Ferrarotto R, Mitani Y, Diao L, Guijarro I, Wang J, Zweidler-McKay P, et al. Activating NOTCH1 mutations define a distinct subgroup of patients with adenoid cystic carcinoma who have poor prognosis, propensity to bone and liver metastasis, and potential responsiveness to notch1 inhibitors. J Clin Oncol 2017;35:352–60.
[22] Patel K, Manzo M, Hapuarachi B, Rack S, Jermann P, Feeney L, et al. Gene expression patterns in adenoid cystic carcinoma with and without diffuse NOTCH1 intracellular domain (NICD1) immunohistochemistry staining. Oral Oncol 2023 Nov;146:106542. https://doi.org/10.1016/j.oraloncology.2023.106542. Epub 2023 Aug 22 PMID: 37619521.
[23] Jang S, Patel PN, Kimple RJ, McCulloch TM. Clinical Outcomes and Prognostic Factors of Adenoid Cystic Carcinoma of the Head and Neck. Anticancer Res 2017 Jun;37(6):3045–52. https://doi.org/10.21873/anticanres.11659. PMID: 28551643; PMCID: PMC7238770.
[24] Hernández Alava M, Pudney S, Wailoo A. Estimating EQ-5D by Age and sex for the UK. NICE DSU. Report 2022.
[25] Locati LD, Galbiati D, Calareso G, Alfieri S, Singer S, Cavalieri S, et al. Patients with adenoid cystic carcinomas of the salivary glands treated with lenvatinib: activity and quality of life. Cancer 2020;126:1888–94. https://doi.org/10.1002/cncr.32754#.
[26] European Medicines Agency. *Integrating patients' views in clinical studies of anticancer medicines*. https://www.ema.europa.eu/en/news/integrating-patients-views-clinical-studies-anticancer-medicines [Accessed 16 Jan 2025].
[27] US Food and Drug Administration. *Core Patient-Reported Outcomes in Cancer Clinical Trials*. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/core-patient-reported-outcomes-cancer-clinical-trials [Accessed 16 Jan 2025].
[28] Liao K, Wong DC, Gomes F, Faivre-Finn C, Moliner L, Sperrin M, et al. Exploring the value of routinely collected data on EQ-5D-5L and other electronic patient-reported outcome measures as prognostic factors in adults with advanced non-small cell lung cancer receiving immunotherapy: BMJ. Oncology 2024;3:e000158.
[29] Bates, D.M.; Kliegl, R.; Vasishth, S.; Baayen, H. (2015). Parsimonious Mixed Models. arXiv: Methodology.
[30] Efthymiadou O, Mossman J, Kanavos P. Health related quality of life aspects not captured by EQ-5D-5L: results from an international survey of patients. Health Policy 2019 Feb;123(2):159–65. https://doi.org/10.1016/j.healthpol.2018.12.003. Epub 2018 Dec 14 PMID: 30598239.
[31] Feng, Y.S.; Kohlmann, T.; Janssen, M.F.; Buchholz, I. Psychometric properties of the EQ-5D-5L: a systematic review of the literature. Qual Life Res. 2021 Mar;30(3): 647-673. doi: 10.1007/s11136-020-02688-y. Epub 2020 Dec 7. PMID: 33284428; PMCID: PMC7952346.
[32] Devlin, N.; Pickard, S.; Busschbach, J. The Development of the EQ-5D-5L and its Value Sets. 2022 Mar 24. In: Devlin N, Roudijk B, Ludwig K, editors. Value Sets for EQ-5D-5L: A Compendium, Comparative Review & User Guide [Internet]. Cham (CH): Springer; 2022. Chapter 1. Available from: https://www.ncbi.nlm.nih.gov/books/NBK589306/ doi: 10.1007/978-3-030-89289-0_1.
[33] Rolstad S, Adler J, Rydén A. Response burden and questionnaire length: is shorter better? A review and meta-analysis Value Health 2011 Dec;14(8):1101–8. https://doi.org/10.1016/j.jval.2011.06.003. Epub 2011 Aug 2 PMID: 22152180.
[34] Berman, R.; Davies, A.; Cooksley, T.; Gralla, R.; Carter, L.; Darlington, E.; *et al.* Supportive Care: An Indispensable Component of Modern Oncology. Clin Oncol (R Coll Radiol). 2020 Nov;32(11):781-788. doi: 10.1016/j.clon.2020.07.020. Epub 2020 Aug 16. PMID: 32814649; PMCID: PMC7428722.
[35] Scotté F, Taylor A, Davies A. Supportive Care: the "Keystone" of Modern Oncology Practice. Cancers (Basel) 2023 Jul 29;15(15):3860. https://doi.org/10.3390/cancers15153860. PMID: 37568675; PMCID: PMC10417474.