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Otero Rico

PhD Thesis

Diagnostic delay and survival in squamous cell carcinoma of the oral cavity

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TESIS DE DOCTORADO

DIAGNOSTIC DELAY AND SURVIVAL IN SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY

Ana Otero Rico

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Título de la tesis: **Diagnostic delay and survival in squamous cell carcinoma of the oral cavity**

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Diagnostic delay and survival in squamous cell carcinoma of the oral cavity

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Diagnostic delay and survival in squamous cell carcinoma of the oral cavity

D. Jose Luis López-Cedrún Cembranos

INFORMA:

Que la presente tesis, se corresponde con el trabajo realizado por Dª. Ana Otero Rico, bajo mi dirección/tutorización, y autorizo su presentación, considerando que reúne los requisitos exigidos en el Reglamento de Estudios de Doctorado de la USC, y que como director de esta no incurre en las causas de abstención establecidas en la Ley 40/2015.

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En A Coruña, 14 de Octubre de 2022

Fdo. Jose Luis López-Cedrún Cembranos

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DEDICATION

To my mother.

Thank you for teaching me to never give up.

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RESUMO

INTRODUCIÓN

O carcinoma oral e orofarínxeo de células escamosas é o duodécimo cancro máis frecuente a nivel mundial, cunha incidencia combinada de 476.125 casos e un total de 225.900 mortes durante o ano 2020. Neste contexto, a supervivencia do cancro oral non mellorou de forma significativa, a pesar dos avances terapéuticos, e probablemente en relación coa demora diagnóstica, entre outros factores independentes.

A maior parte dos carcinomas orais diagnostícanse en etapas avanzadas, o que resulta en baixas taxas de supervivencia ós 5 anos (20-50%). Aínda que hai estudos que mostran resultados pouco conclusivos respecto da asociación entre longos períodos ata o diagnóstico/ tratamento e os resultados no tratamento do cancro de cabeza e pescozo, varios estudos apoian unha potencial asociación entre a demora diagnóstica e a baixa supervivencia.

En xeral, suxeriuse que un diagnóstico precoz é o factor máis importante para a supervivencia global, e que se estes tumores fosen diagnosticados e tratados en estadios máis iniciais, as taxas de supervivencia serían superiores ao 80%. Observouse que a demora diagnóstica é un factor de risco ligado á estadiaxe TNM no momento do diagnóstico, e á vez un factor de risco independente, xunto co estadio, o contido de ADN e a expresión de oncoxenes. Con todo, os estudos que intentan inferir a capacidade preditiva da demora

diagnóstica no cancro oral carecen dunha metodoloxía sólida e non permiten establecer unha asociación clara.

Na maior parte dos países o cancro oral é máis frecuente en homes que en mulleres, porén hai unha tendencia á alza na poboación feminina, que é consistente cos patróns de consumo de alcol e tabaco a nivel global. O carcinoma oral tamén está ligado á situación económica e social, coas taxas máis altas nos sectores máis desfavorecidos da poboación. Tradicionalmente considerouse unha enfermidade da vida adulta e das idades máis avanzadas, e en relación coa duración e intensidade da exposición a carcinóxenos. As localizacións máis frecuentes son o chan da boca e a lingua (predominantemente bordo lateral, zona posterior e ventral). A mucosa xugal e o trígono retromolar son máis frecuentes naquelas zonas do mundo onde o consumo de noz de betel é habitual. Finalmente e en orde de frecuencia decrecente, tamén se localiza no padal brando, xinxiva, mucosa labial e padal duro.

A etioloxía do cancro oral é multifactorial. Os factores etiolóxicos máis importantes son o tabaco, consumo de alcol en exceso e uso de noz de betel. Estes factores poden actuar de forma separada ou sinérxica. Tamén hai outros factores de risco para subtipos específicos: o virus do papiloma humano asóciase a tumores na rexión orofarínxea en determinadas subpoboacións dalgúns países (homes, en xeral novos, de orixe europea e de alto nivel socioeconómico), mentres que os carcinomas de beizo asócianse coa exposición ultravioleta. No que se refire ó prognóstico, o estadio non é sempre un bo factor preditivo, pois hai tumores de pequeno tamaño que se comportan de forma máis agresiva que outros de maior tamaño. Aínda que hai moitas publicacións que intentan identificar factores pronósticos sociodemográficos, clínicos e histolóxicos, aínda existe unha controversia acerca da relativa importancia destes factores, con excepción do estadio TNM. O estadio da lesión no momento do

diagnóstico, a presenza de extensión extracapsular no contexto de afectación nodal e as marxes afectas aínda seguen sendo os factores prognósticos máis importantes para o cancro oral. A comorbilidade, definida como aqueles procesos patolóxicos que coexisten e que non están relacionados coa enfermidade primaria, tamén poden afectar á supervivencia do paciente con carcinoma oral de células escamosas, e algúns estudos demostraron a asociación entre enfermidades coexistentes e períodos libres de recidiva, así como a influencia negativa destas na supervivencia específica.

Pack e Galo estableceron o concepto de demora diagnóstica hai xa máis de 75 anos, e dende entón os investigadores usaron unha variedade de criterios para cuantificar e estudar o impacto do tempo transcorrido ata o diagnóstico. As taxas de supervivencia ós 5 anos para cancro oral varían entre o 20 e o 50%, con mínimas melloras (<5%) nos últimos 20 anos. A alta taxa de mortalidade está en relación directa co feito de que moitos destes cancros se presentan en estadios avanzados. Desafortunadamente, polo menos dous terzos dos pacientes con carcinoma oral aínda son diagnosticados en estadios avanzados (III e IV), cunha taxa de supervivencia ós 5 anos dun 50% ou menos, que comparada coa taxa de supervivencia do 80% naqueles pacientes cunha patoloxía máis localizada, supón unha marcada diferenza de mortalidade baseada no estadio. O tamaño do tumor á hora do diagnóstico segue sendo o factor máis importante para o carcinoma oral de células escamosas, e os estadios avanzados asócianse a unha taxa de mortalidade máis elevada.

En canto á definición dos intervalos temporais na investigación, os criterios son heteroxéneos, o cal crea un obstáculo á hora de comparar diferentes estudos. Unha ferramenta útil para resolver este problema é a declaración de Aarhus, que foi desenvolvida por un grupo de consenso internacional co fin de mellorar o deseño e a

comunicación de resultados dos estudos que se centran no diagnóstico precoz do cancro oral.

OBXECTIVOS

A hipótese de traballo deste estudo é que a demora diagnóstica se asocia á supervivencia do cancro oral, e que intervalos máis prolongados condicionarían peores resultados para os pacientes e unha taxa de mortalidade máis elevada.

O obxetivo principal é cuantificar a "demora diagnóstica" de acordo cos intervalos propostos pola declaración de Aarhus, a súa influencia na supervivencia do cancro oral e os factores asociados. Hai poucos estudos que inclúan a supervivencia dos pacientes como resultado da investigación, e este foi foco de atención deste estudo. Como obxectivos secundarios cuantificamos e analizamos o impacto dos seguintes intervalos na supervivencia: intervalo do especialista, intervalo hospitalario e intervalo total.

MATERIAL E MÉTODOS

A colección de datos para este estudo obtívose das historias clínicas de pacientes diagnosticados e tratados de carcinoma oral/orofaríngeo de células escamosas entre os anos 1998-2009 no Hospital Universitario da Coruña (Galicia, España). O estudo foi observacional, cun compoñente retrospectivo e prospectivo, xa que se realizou seguimento dos pacientes ata o ano 2016. Todas as análises estatísticas leváronse a cabo utilizando o software R.

O proxecto de investigación foi aprobado polo Comité Autonómico de Ética na Investigación (CAEI) de Galicia co número de rexistro 2014/097, o cal confire oficialmente dereitos e condicións éticas adecuadas ós pacientes durante a investigación de acordo cos requisitos da Declaración de Helsinqui.

O modelo dos itinerarios de tratamento para pacientes sintomáticos con cancro e a declaración de Aarhus utilizáronse como marco teórico e conceptual. O síntoma inicial definiuse como o primeiro síntoma que o paciente refire na súa presentación en Atención Primaria, sendo ese paciente diagnosticado despois cun carcinoma oral de células escamosas.

RESULTADOS

No primeiro estudo, unha regresión multivariable confirmou unha asociación significativa entre un intervalo do especialista máis curto e un estadio TNM avanzado. No segundo artigo, o modelo multivariante de Cox que incluía o intervalo hospitalario (T14) discretizado en terciles, mostrou un risco de mortalidade 2.8 veces maior para o estadio III-IV, e un risco dúas veces maior para o sexo masculino. O intervalo hospitalario (T14) e a mortalidade mostran unha asociación en "V", na que os pacientes con intervalos T14 curtos (3-18 días), e aqueles con intervalos T14 longos (26–55 días) teñen unha mortalidade máis elevada que aqueles con intervalos T14 intermedios (19-25 días). Finalmente, no terceiro artigo, a análise univariable atopou asociacións significativas para o sexo ($p = 0.03$) e estadio TNM (I-II vs. III-IV) ($p = 0.001$). Considerando o intervalo total (T5) como unha variable continua, non se atopou asociación significativa ($\exp \beta = 1.0$; $p = 0.13$), aínda que isto xa se viu no modelo Cox multivariable de supervivencia cando o intervalo total (T5) foi discretizado en cuartiles. Nesta situación observouse un risco de mortalidade 1.8 veces superior no sexo masculino e un risco 2.5 veces superior para estadios avanzados III-IV. O intervalo total (T5) e a mortalidade mostraron unha asociación en "U", na que pacientes con intervalos T5 curtos (24-55.5 días) e aqueles con intervalos T5 prolongados (127.5-420 días) mostraban unha mortalidade máis elevada que aqueles con intervalos T5 intermedios (55.5-127.5 días).

A caracterización dos pacientes incluídos no primeiro cuartil do T5, con intervalos curtos e alta mortalidade, permitiu a identificación de variables importantes para a clasificación dentro deste grupo con intervalos de recidiva máis curtos, como a presenza de infiltración vascular, cun erro de predición aceptable (20%).

DISCUSIÓN

O obxectivo principal deste estudo foi cuantificar a "demora diagnóstica" de acordo cos intervalos temporais propostos pola declaración de Aarhus, a súa influencia na supervivencia do carcinoma oral e os factores asociados. Hai moitos estudos que se centran na demora asociada aos pacientes e Atención Primaria, pero os intervalos asociados á atención especializada ou período hospitalario non foron explorados de forma exhaustiva.

A causa principal que condiciona intervalos prolongados desde o primeiro síntoma ata o diagnóstico histolóxico definitivo atribúese á presentación tardía por parte do paciente. Como tal, o intervalo relacionado co paciente é o intervalo máis longo no itinerario dos pacientes ata o tratamento, aínda que se descoñecen as causas que condicionan esta situación. Algúns destes factores inclúen comportamentos de negación, falta de coñecemento ou conciencia da enfermidade e os seus síntomas, automedicación e barreiras físicas ou económicas no acceso á atención sanitaria. Por outra banda, e de acordo cos nosos resultados, a contribución relativa do intervalo do especialista ao tempo total ata o diagnóstico parece relativamente pequeno (6/64 días). Só aqueles pacientes con tumores máis grandes (T3/T4) mostran unha menor demora relacionada co especialista que aqueles con tumores máis pequenos (T1/T2), e os nosos resultados mostran unha asociación significativa entre intervalos do especialista máis curtos e estadio TNM máis avanzado, e exclúen asociacións hipotéticas entre o intervalo do especialista e outras variables

relacionadas co paciente ou o tumor. As razóns que xustifican dar prioridade a pacientes con enfermidade máis avanzada non están claras, aínda que este fenómeno tamén se observa nas listas de espera cirúrxicas, onde intervalos de espera máis prolongados afectan a aqueles pacientes en estadios iniciais da enfermidade. Nesta situación, a explicación pode ser un intento de empezar o tratamento canto antes para evitar que o tumor se converta en irresecable ou que metastatice. Tendo en conta que os intervalos do especialista máis prolongados se producen naqueles pacientes con estadios TNM máis precoces (I-II), e que intervalos máis longos desde o diagnóstico ata o tratamento se asocian cun aumento no risco de mortalidade, en particular para pacientes en estadio iniciais, deberíase optimizar o intervalo hospitalario para estes pacientes para que poidan empezar o seu tratamento canto antes. Considerando as limitacións deste estudo, conclúese que o intervalo do especialista é un intervalo curto, e que supón só unha pequena parte da carga temporal no contexto do intervalo total ata o diagnóstico. Con todo, poderíase mellorar, e a redución do intervalo do especialista podería ser o obxectivo de futuras intervencións, especialmente para aqueles pacientes con estadios precoces da enfermidade.

O noso segundo estudo centrouse no estudo do intervalo hospitalario. Os resultados deste estudo permiten contextualizar a atención especializada no itinerario terapéutico dos pacientes. Varias revisións sistemáticas mostraron unha asociación inconsistente entre a demora diagnóstica e o risco de recorrencia, estadio no momento do diagnóstico e a supervivencia do carcinoma oral. Os estudos mostran que o cancro de cabeza e pescozo (así como o de mama, colorrectal, testicular e melanoma) ten un intervalo máis curto ata o diagnóstico, o cal se asocia con mellores resultados. Un intervalo longo ata o diagnóstico constitúe un factor de risco moderado para a mortalidade no carcinoma de cabeza e pescozo. O intervalo total no noso estudo

resultou ser significativamente máis curto que a media para este intervalo de acordo cos cálculos doutros estudos publicados na última década en Australia, India e Irán. A asociación entre o intervalo desde o diagnóstico ao tratamento e a supervivencia do cancro oral na contorna hospitalaria só foi estudada recentemente, e os resultados son contraditorios. Na nosa serie, a mediana do intervalo hospitalario son 23.4 días, e os pacientes con intervalos hospitalarios máis curtos teñen unha mortalidade significativamente máis elevada. Esta asociación contraditoria débese ao paradoxo do tempo de espera (factor de confusión por indicación), na que aos pacientes que están gravemente enfermos con tumores agresivos e unha alta taxa de mortalidade asociada se lles dá prioridade para previr a extensión tumoral ou a irresecabilidade do tumor. Este fenómeno tamén se describiu en gliomas, cancro de endometrio e cervical, cancro de mama e colorrectal. Con todo, este factor de confusión por severidade non explica por que os intervalos hospitalarios máis prolongados para o cancro oral (>26 días) se asocian significativamente a unha mortalidade máis elevada, o que suxire unha asociación positiva entre intervalos hospitalarios máis longos e peores taxas de supervivencia para o cancro oral.

O intervalo hospitalario depende das características da práctica clínica e do sistema sanitario, polo que pode variar dependendo do contexto. Considerando o rumbo de severidade á hora de dar prioridade aos pacientes cun peor prognóstico para o diagnóstico e o tratamento do cancro oral, e tendo en conta que se identificou que os pacientes máis afectados, en termos de supervivencia, pola demora no tratamento son aqueles en estadios iniciais (I-II) que requiren tratamento cirúrxico, deberíanse implementar estratexias para tratar a estes pacientes de forma precoz e impedir a progresión da patoloxía. Asumindo que os intervalos hospitalarios prolongados xeran unha

mortalidade máis elevada, acurtar este intervalo aumentaría a supervivencia para pacientes con esta patoloxía.

Se se teñen en conta os resultados do noso primeiro estudo, que se centraba no intervalo do especialista, pódese deducir que a contribución á demora do intervalo "pre-tratamento" no intervalo hospitalario é moito máis importante en termo de días, e que os esforzos deberían orientarse a axilizar o inicio do tratamento unha vez que o diagnóstico se clarificou. As estratexias baseadas nunha consulta hospitalaria multidisciplinaria (cirurxía oral e maxilofacial, otorrinolaringología, oncoloxía e radioterapia) demostraron que poden reducir significativamente os procesos diagnósticos e o atraso no inicio do tratamento.

A última parte deste estudo é a única que avaliou o impacto do intervalo total na mortalidade do cancro oral ata agora. Aínda que é o primeiro estudo publicado sobre a asociación da supervivencia co intervalo total ata o tratamento en pacientes con carcinoma oral sintomático dentro do marco conceptual dos itinerarios ata o tratamento, hai certos sesgos que deben asumirse, xa que son inherentes ó deseño retrospectivo deste estudo. A investigación neste campo tradicionalmente consideraba as demoras totais ata o diagnóstico histolóxico, culpabilizando o paciente e o médico. A demora atribuída ó paciente, como se discutiu previamente, débese á falta de coñecemento ou conciencia da patoloxía, crenzas relixiosas e culturais e automedicación; mentres que a atribuída ó profesional sanitario se achaca á existencia de barreiras no acceso ó sistema sanitario, falta de coñecemento da patoloxía e erros no diagnóstico.

Os autores atoparon unha asociación en "U", na que aqueles pacientes con intervalos máis curtos (24-55.5 días) e máis longos (127.5-420 días), tiñan unha mortalidade máis elevada que aqueles con intervalos intermedios. Outros tumores (pulmón, colorrectal, mama e ovario) mostraron este comportamento paradóxico, no que

intervalos máis curtos asócianse a taxas de mortalidade máis altas. As taxas de mortalidade máis altas en pacientes con intervalos máis curtos poderíanse xustificar polo sesgo de indicación e a agresividade tumoral. Esta circunstancia explícase por un sesgo de indicación na que os profesionais sanitarios dan prioridade á hora de diagnosticar os pacientes máis graves, pero tamén podería explicarse por outro sesgo que non se mediu: a velocidade de crecemento tumoral (agresividade tumoral). Dedúcese que pacientes con tumores de crecemento rápido, o cal leva a presenza de máis síntomas e unha progresión máis rápida, esixirían atención profesional de forma máis rápida que aqueles con tumores de crecemento lento. Esta hipótese estaría corroborada polo feito de que no noso estudo os pacientes co intervalo total máis curto teñen como variable preditiva máis importante un menor intervalo libre de enfermidade ata a recidiva, o cal se correlaciona coa taxa de progresión tumoral. A pesar da escasa evidencia nos resultados dos tempos de espera no cancro oral, esta investigación mostra por primeira vez unha asociación máis significativa entre intervalos máis longos e mortalidade, que con intervalos intermedios. Este resultado indica a necesidade de acurtar o intervalo total a través de campañas dirixidas a pacientes para mellorar o seu coñecemento e toma de conciencia de lesións de crecemento lento con sintomatología menos marcada. Os nosos resultados tamén indican unha necesidade de mellorar e optimizar os procesos en atención primaria, a interconsulta e o intervalo hospitalario, para evitar os rumbos por severidade. Este estudo tamén mostra un amplo intervalo hospitalarios, no que hai unha clara marxe de mellora.

Está claro que o tamaño do tumor primario afecta tanto á elección do tratamento como ós resultados do mesmo, e que os estadios iniciais asócianse cun mellor prognóstico, supervivencia e calidade de vida. O tamaño tumoral é un factor determinante para que o cirurxián poida realizar unha resección completa e obter marxes

libres de enfermidade, así como á hora de decidir a necesidade de radioterapia. Un gran tamaño tumoral no momento da presentación asóciase cun risco aumentado de recidiva local, maior probabilidade de metástasis cervicais, un tratamento máis agresivo xunto con máis efectos secundarios derivados do mesmo e unha peor taxa de supervivencia. Mesmo no caso de que a resección completa sexa factible, asúmese de forma intuitiva que un maior tamaño tumoral require unha maior resección, e por tanto hai un maior risco potencial de complicacións, efectos secundarios derivados do tratamento e maior dificultada á hora de conseguir marxes libres de enfermidade nunha localización tan anatomicamente complexa como a cabeza e o pescozo. Por iso mesmo, tamén se deduce de forma intuitiva que o tratamento do cancro oral en estadios iniciais (cando as lesións son pequenas e están localizadas) é a forma máis efectiva de reducir a mortalidade, morbilidad e a deformidade por esta patoloxía.

As estratexias para diagnosticar o cancro oral de forma precoz poderían incluír campañas de detección precoz (screening) en grupos de alto risco, e mesmo a realización de exploracións sistemáticas en consultas por parte do profesional sanitario. Isto reduciría os intervalos ata o diagnóstico e tratamento do cancro oral, pois as probas de screening non teñen como obxectivo obter un diagnóstico, senón o acelerar a interconsulta e a indicación de probas de diagnóstico máis específicas por parte do especialista.

En xeral, hai unha falta de coñecemento por parte da poboación no que se refire a síntomas e factores de risco, e a implementación de campañas informativas non só dirixidas ao público, senón tamén aos profesionais sanitarios sería de gran importancia para facilitar a detección precoz.

Os equipos multidisciplinares son unha peza fundamental no itinerario de cada paciente a nivel individual, así como un sistema de interconsultas eficiente, así como a estreita colaboración cun equipo

ben coordinado a nivel local. Deberían realizarse auditorías dos procesos con certa frecuencia para detectar fallos potenciais no sistema e aquelas áreas nas que se pode mellorar. O modelo dos itinerarios terapéuticos e a declaración de Aarhus tamén constitúen un mecanismo de seguridade para asegurar un acceso igualitario á atención sanitaria e para pór de relevo desigualdades en certas poboacións, se existisen.

Dende o punto de vista clínico, queremos proporcionarlle ós nosos pacientes a mellor atención posible para conseguir os mellores resultados posibles. Para mellorar a atención que reciben os nosos pacientes e asegurar o diagnóstico precoz do carcinoma oral de células escamosas, non só debemos investir en investigación en ciencias básicas co fin de desenvolver modelos predictivos, intelixencia artificial e tecnoloxías que permitan predicir o potencial de malignización dunha lesión aparentemente inocente; tamén hemos de preguntarnos que é o que podemos facer dende o punto de vista clínico. A implementación de vías rápidas de interconsulta foi útil para reducir o tempo transcorrido entre a consulta e o inicio do tratamento. A actualización de guías clínicas máis precisas tamén é necesaria para clarificar o papel dos médicos de atención primaria e os dentistas no itinerario dos pacientes, así como intervencións dirixidas a reducir o intervalo pre-interconsulta. Debemos esforzarnos en educar á poboación para aumentar o seu coñecemento e conciencia do cancro oral, así como facilitar a formación continuada dos profesionais sanitarios neste ámbito. Poderiamos considerar a implementación dun programa de screening para cancro oral, que podería ter lugar á vez que as revisións dentais anuais ou semestrais. Por outra banda, debería garantirse o acceso igualitario e universal de todos os subgrupos poboacionais, e deberían implementarse determinadas intervencións para aqueles grupos que puidesen considerarse de alto risco debido ás súas características sociodemográficas. Está claro que moitas destas intervencións han de

ser implementadas no marco xeral do sistema de saúde. Con todo, algunhas delas poden ser implementadas na práctica diaria polo facultativo clínico, contribuíndo igualmente a implementar cambios e inducir melloras na atención sanitaria. Sen ir máis lonxe, unha acción aparentemente trivial, como a sinxela adopción do marco teórico proposto por Aarhus á hora de realizar a historia clínica, podería inducir cambios. Este marco teórico, que propón criterios claros e ben definidos para os eventos claves no itinerario dos pacientes, facilitaríanos a análise das nosas intervencións, e permitiría comparar os resultados futuros e pasados con maior precisión da que foi posible ata agora.

CONCLUSIÓNS

1. O intervalo do especialista é un intervalo curto no cancro oral, e supón unha carga relativamente menor no contexto do intervalo total ata o diagnóstico. Este intervalo atópase básicamente condicionado pola extensión tumoral, e con todo non se atopou asociación das outras características do paciente ou do tumor coa magnitude deste intervalo. Hai marxe para implementar melloras e un posible obxectivo para intervencións futuras sería acurtar o intervalo do especialista, en particular para aqueles pacientes en estadios precoces unha vez que xa foron diagnosticados.

2. O intervalo hospitalario é un intervalo relevante no itinerario do paciente con cancro oral de cara ó tratamento, chegando a representar unha cuarta parte do intervalo total. A pesar de que a extensión tumoral atópase fortemente asociada a unha maior mortalidade, o noso traballo mostra unha asociación non intuitiva onde os pacientes con intervalos hospitalarios curtos teñen unha mortalidade sisgnificativamente máis elevada, debido o paradoxo do tempo de espera. A presenza deste importante sesgo clínico,

un sesgo de confusión por indicación, podería condicionar a supervivencia de pacientes diagnosticados en estadios precoces, os que constitúen o grupo máis sensible ós retrasos no tratamento do cancro oral.

3. A mediana do tempo do intervalo total é superior a 2.5 meses. Este intervalo e a mortalidade por cáncer oral mostran unha asociación en "U", na que pacientes con intervalos totais máis curtos (pacientes con tempos de recidiva máis curtos e presenza de infiltración vascular) e aqueles con intervalos totais máis longos, teñen unha mortalidade máis elevada que aqueles con intervalos intermedios. As taxas de mortalidade máis elevadas asócianse cos intervalos de tempo máis curtos e máis longos, e esta asociación non-monotónica entre o intervalo temporal e a mortalidade pode inducir a subestimación da asociación cando os intervalos de tempo se analizan de forma dicotómica. Para conseguir reducir o intervalo total, os esforzos deberían centrarse naqueles factores que contribúen no itinerario do paciente de cara ó tratamento, así como en intervencións destinadas a promover tanto o coñecemento da patoloxía entre a poboación xeral, como a mellora das habilidades diagnósticas entre os facultativos sanitarios de atención primaria á vez que se reducen os tempos hospitalarios pretratamento.

RESUMEN

INTRODUCCIÓN

El carcinoma oral y orofaríngeo de células escamosas es el duodécimo cáncer más frecuente a nivel mundial, con una incidencia combinada de 476.125 casos y un total de 225.900 muertes durante el año 2020. En este contexto, la supervivencia del cáncer oral no parece haber mejorado de forma significativa, a pesar de los avances terapéuticos, y probablemente en relación con la demora diagnóstica, entre otros factores independientes.

La mayor parte de los carcinomas orales se diagnostican en etapas avanzadas, lo que resulta en bajas tasas de supervivencia a los 5 años (20-50%). Aunque hay estudios que muestran resultados poco concluyentes respecto a la asociación entre largos periodos hasta el diagnóstico/ tratamiento y los resultados en el tratamiento del cáncer de cabeza y cuello, varios estudios apoyan una potencial asociación entre la demora diagnóstica y la baja supervivencia.

Se ha sugerido que un diagnóstico temprano es el factor más importante para la supervivencia global, y que si estos tumores fueran diagnosticados y tratados en estadios más tempranos, las tasas de supervivencia sería superiores al 80%. Se ha visto que la demora diagnóstica es un factor de riesgo ligado al estadiaje TNM en el momento del diagnóstico, y a la vez un factor de riesgo independiente, junto con el estadio, el contenido de ADN y la expresión de oncogenes. Sin embargo, los estudios que intentan inferir la capacidad

predictiva de la demora diagnóstica en el cáncer oral carecen de una metodología sólida y no permiten establecer una asociación clara.

En la mayor parte de los países el cáncer oral es más frecuente en hombres que en mujeres, sin embargo hay una tendencia al alza en la población femenina, que es consistente con los patrones de consumo de alcohol y tabaco a nivel global. El carcinoma oral también está ligado a la situación económica y social, con las tasas más altas en los sectores más desfavorecidos de la población. Tradicionalmente se ha considerado una enfermedad de la vida adulta y de edades más avanzadas, y en relación con la duración e intensidad de la exposición a carcinógenos. Las localizaciones más frecuentes son el suelo de la boca y la lengua (predominantemente borde lateral, zona posterior y ventral). La mucosa yugal y el trígono retromolar son más frecuentes en aquellas zonas del mundo donde el consumo de nuez de betel es habitual. Finalmente y en orden de frecuencia decreciente, también se localiza en el paladar blando, encía, mucosa labial y paladar duro.

La etiología del cáncer oral es multifactorial. Los factores etiológicos más importantes son el tabaco, consumo de alcohol en exceso y uso de nuez de betel. Estos factores pueden actuar de forma separada o sinérgica. También hay otros factores de riesgo para subtipos específicos: el virus del papiloma humano se asocia a tumores en la región orofaríngea en determinadas subpoblaciones en algunos países (hombres, en general jóvenes, de origen europeo y de alto nivel socioeconómico), mientras que los carcinomas de labio se asocian con la exposición ultravioleta. En lo que se refiere al pronóstico el estadio no siempre es un buen factor predictivo, pues hay tumores de pequeño tamaño que se comportan de forma más agresiva que otros de mayor tamaño. Aunque hay muchas publicaciones que intentan identificar factores pronósticos sociodemográficos, clínicos e histológicos, todavía existe una

controversia acerca de la relativa importancia de estos factores, con excepción del estadio TNM. El estadio de la lesión en el momento del diagnóstico, la presencia de extensión extracapsular en el contexto de afectación nodal y los márgenes afectos todavía siguen siendo los factores pronósticos más importantes para el cáncer oral. La comorbilidad, definida como procesos patológicos que coexisten y que no están relacionados con la enfermedad primaria, también pueden afectar a la supervivencia del paciente con carcinoma oral de células escamosas, y algunos estudios han demostrado la asociación entre enfermedades coexistentes y periodos libres de recidiva , así como la influencia negativa de estas en la supervivencia específica.

Pack y Gallo establecieron el concepto de demora diagnóstica hace ya más de 75 años, y desde entonces los investigadores han usado una variedad de criterios para cuantificar y estudiar el impacto del tiempo transcurrido hasta el diagnóstico. Las tasas de supervivencia a los 5 años para cáncer oral varían entre el 20 y el 50%, con mínimas mejoras (<5%) en los últimos 20 años. La alta tasa de mortalidad está en relación directa con el hecho de que muchos de estos cánceres se presentan en estadio avanzados. Desafortunadamente, al menos dos tercios de los pacientes con carcinoma oral todavía son diagnosticados en estadios avanzados (III y IV), con una tasa de supervivencia a los 5 años de un 50% o menos, que comparada con la tasa de supervivencia del 80% en aquellos pacientes con una patología más localizada, supone una marcada diferencia de mortalidad basada en el estadio. El tamaño del tumor a la hora del diagnóstico sigue siendo el factor más importante para el carcinoma oral de células escamosas, y los estadios avanzados se asocian a una tasa de mortalidad más elevada.

En cuanto a la definición de los intervalos temporales en la investigación, los criterios son heterogéneos, lo cual crea un obstáculo a la hora de comparar diferentes estudios. Una herramienta útil para

resolver este problema es la declaración de Aarhus, que fue desarrollada por un grupo de consenso internacional con el fin de mejorar el diseño y la comunicación de resultados de los estudios que se centran en el diagnóstico temprano del cáncer oral.

OBJETIVOS

La hipótesis de trabajo de este estudio es que la demora diagnóstica se asocia a la supervivencia del cáncer oral, y que intervalos más prolongados condicionarían peores resultados para los pacientes y una tasa de mortalidad más elevada.

El objetivo principal es cuantificar la "demora diagnóstica" de acuerdo con los intervalos propuestos por la declaración de Aarhus, su influencia en la supervivencia del cáncer oral y los factores asociados. Hay pocos estudios que incluyan la supervivencia de los pacientes como resultado de la investigación, y este fue el foco de atención de este estudio. Como objetivos secundarios cuantificamos y analizamos el impacto de los siguientes intervalos en la supervivencia: intervalo del especialista, intervalo hospitalario e intervalo total.

MATERIAL Y MÉTODOS

La colección de datos para este estudio se obtuvo de las historias clínicas de pacientes diagnosticados y tratados de carcinoma oral/orofaríngeo de células escamosas entre los años 1998-2009 en el Hospital Universitario de A Coruña (Galicia, España). El estudio fue observacional, con un componente retrospectivo y prospectivo, ya que se realizó seguimiento a los pacientes hasta el año 2016. Todos los análisis estadísticos se llevaron a cabo utilizando el software R.

El proyecto de investigación fue aprobado por el Comité Autonómico de Ética en la Investigación (CAEI) de Galicia con el número de registro 2014/097, el cual confiere oficialmente derechos y

condiciones éticas adecuadas a los pacientes durante la investigación de acuerdo con los requisitos de la Declaración de Helsinki.

El modelo de los itinerarios de tratamiento para pacientes sintomáticos con cáncer y la declaración de Aarhus se utilizaron como marco teórico y conceptual. El síntoma inicial se definió como el primer síntoma que el paciente refiere en su presentación en Atención Primaria, siendo ese paciente diagnosticado después con un carcinoma oral de células escamosas.

RESULTADOS

En el primer estudio, una regresión multivariable confirmó una asociación significativa entre un intervalo del especialista más corto y un estadio TNM avanzado. En el segundo artículo, el modelo multivariante de Cox que incluía el intervalo hospitalario (T14) discretizado en terciles, mostró un riesgo de mortalidad 2.8 veces mayor para los estadio III-IV, y un riesgo dos veces mayor para el sexo masculino. El intervalo hospitalario (T14) y la mortalidad muestran una asociación en "V", en la que los pacientes con intervalos T14 cortos (3-18 días), y aquellos con intervalos T14 largos (26–55 días) tienen una mortalidad más elevada que aquellos con intervalos T14 intermedios (19-25 días). Finalmente, en el tercer artículo, el análisis univariable encontró asociaciones significativas para el sexo ($p = 0.03$) y estadio TNM (I-II vs. III-IV) ($p= 0.001$). Considerando el intervalo total (T5) como una variable continua, no se encontró asociación significativa ($\exp \beta = 1.0$; $p = 0.13$), aunque esto ya se había visto en el modelo Cox multivariable de supervivencia cuando el intervalo total (T5) fue discretizado en cuartiles. En esta situación se observó un riesgo de mortalidad 1.8 veces superior en el sexo masculino y un riesgo 2.5 veces superior para estadios avanzados III-IV. El intervalo total (T5) y la mortalidad mostraron una asociación en "U", en la que pacientes con intervalos T5 cortos (24-55.5 días) y

aquellos con intervalos T5 prolongados (127.5-420 días) mostraban una mortalidad más elevada que aquellos con intervalos T5 intermedios (55.5-127.5 días). La caracterización de los pacientes incluídos en el primer cuartil del T5, con intervalos cortos y alta mortalidad, permitió la identificación de variables importantes para la clasificación dentro de este grupo con intervalos de recidiva más cortos como la presencia de infiltración vascular, con un error de predicción aceptable (20%).

DISCUSIÓN

El objetivo principal de este estudio fue cuantificar la "demora diagnóstica" de acuerdo con los intervalos temporales propuestos por la declaración de Aarhus, su influencia en la supervivencia del carcinoma oral y los factores asociados. Hay muchos estudios que se centran en la demora asociada a los pacientes y Atención Primaria. Sin embargo, los intervalos asociados a la atención especializada o periodo hospitalario no han sido explorados de forma exhaustiva.

La causa principal que condiciona intervalos prolongados desde el primer síntoma hasta el diagnóstico histológico definitivo se atribuye a las presentación tardía por parte del paciente. Como tal, el intervalo relacionado con el paciente es el intervalo más largo en el itinerario de los pacientes hasta el tratamiento, aunque se desconocen las causas que condicionan esta situación. Algunos de estos factores incluyen comportamientos de negación, falta de conocimiento o conciencia de la enfermedad y sus síntomas, auto-medicación y barreras físicas o económicas en el acceso a la atención sanitaria. Por otra parte, y de acuerdo con nuestros resultados, la contribución relativa del intervalo del especialista al tiempo total hasta el diagnóstico parece relativamente pequeño (6/64 días). Solo aquellos pacientes con tumores más grandes (T3/T4) muestran una menor demora relacionada con el especialista que aquellos con tumores más

pequeños (T1/T2), y nuestros resultados muestran una asociación significativa entre intervalos del especialista más cortos y estadio TNM más avanzado, y excluyen asociaciones hipotéticas entre el intervalo del especialista y otras variables relacionadas con el paciente o el tumor. Las razones que justifican dar prioridad a pacientes con enfermedad más avanzada no están claras, aunque este fenómeno también se observa en las listas de espera quirúrgicas, en donde intervalos de espera más prolongados afectan a aquellos pacientes en estadios tempranos de la enfermedad. En esta situación, la explicación puede ser un intento de empezar el tratamiento lo antes posible para prevenir que el tumor se convierta en irresecable o que metastatice. Teniendo en cuenta que los intervalos del especialista más prolongados se producen en aquellos pacientes con estadios TNM más tempranos (I-II), y que intervalos más largos desde el diagnóstico hasta el tratamiento se asocian con un aumento en el riesgo de mortalidad, en particular para pacientes en estadio iniciales, se debería optimizar el intervalo hospitalario para estos pacientes para que puedan empezar su tratamiento lo antes posible. Considerando las limitaciones de este estudio, se concluye que el intervalo del especialista es un intervalo corto, y que supone solo una pequeña parte de la carga temporal en el contexto del intervalo total hasta el diagnóstico. Sin embargo, se podría mejorar, y la reducción del intervalo del especialista podría ser el objetivo de futuras intervenciones, especialmente para aquellos pacientes con estadios tempranos de la enfermedad.

Nuestro segundo estudio se centró en el estudio del intervalo hospitalario. Los resultados de este estudio permiten contextualizar la atención especializada en el itinerario terapéutico de los pacientes. Varias revisiones sistemáticas han mostrado una asociación inconsistente entre la demora diagnóstica y el riesgo de recurrencia, estadio en el momento del diagnóstico y la supervivencia del

carcinoma oral. Los estudios muestran que el cáncer de cabeza y cuello (así como el de mama, colorrectal, testicular y melanoma) tiene un intervalo más corto hasta el diagnóstico, lo cual se asocia con mejores resultados. Un intervalo largo hasta el diagnóstico constituye un factor de riesgo moderado para la mortalidad en el carcinoma de cabeza y cuello. El intervalo total en nuestro estudio resultó ser significativamente más corto que la media para este intervalo de acuerdo con los cálculos de otros estudio publicados en la última década en Australia, India e Irán. La asociación entre el intervalo desde el diagnóstico al tratamiento y la supervivencia del cáncer oral en el entorno hospitalario solo ha sido estudiada recientemente, y los resultados son contradictorios. En nuestra serie, la mediana del intervalo hospitalario son 23.4 días, y los pacientes con intervalos hospitalarios más cortos tenían una mortalidad significativamente más elevada. Esta asociación contradictoria se debe a la paradoja del tiempo de espera (factor de confusión por indicación), en la que a los pacientes que están gravemente enfermos con tumores agresivos y una alta tasa de mortalidad asociada se les da prioridad para prevenir la extensión tumoral o la irresecabilidad del tumor. Este fenómeno también se ha descrito en gliomas, cáncer de endometrio y cervical, cáncer de mama y colorrectal. Sin embargo, este factor de confusión por severidad no explica por qué los intervalos hospitalarios más prolongados para el cáncer oral (>26 días) se asocian significativamente a una mortalidad más elevada, lo que sugiere una asociación positiva entre intervalos hospitalarios más largos y peores tasas de supervivencia para el cáncer oral.

El intervalo hospitalario depende de las características de la práctica clínica y del sistema sanitario, por lo que puede variar dependiendo del contexto. Considerando el sesgo de severidad a la hora de dar prioridad a los pacientes con un peor pronóstico para el diagnóstico y el tratamiento del cáncer oral, y teniendo en cuenta que

se ha identificado que los pacientes más afectados, en términos de supervivencia, por la demora en el tratamiento son aquellos en estadios iniciales (I-II) que requieren tratamiento quirúrgico, se deberían implementar estrategias para tratar a estos pacientes de forma temprana e impedir la progresión de la patología. Asumiendo que los intervalos hospitalarios prolongados generan una mortalidad más elevada, acortar este intervalo aumentaría la supervivencia para pacientes con esta patología. Si se tienen en cuenta los resultados de nuestro primer estudio, que se centraba en el intervalo del especialista, se puede deducir que la contribución a la demora del intervalo "pre-tratamiento" en el intervalo hospitalario es mucho más importante en término de días, y que los esfuerzos deberían orientarse a agilizar el inicio del tratamiento una vez que el diagnóstico se ha clarificado. Las estrategias basadas en una consulta hospitalaria multidisciplinaria (cirugía oral y maxilofacial, otorrinolaringología, oncología y radioterapia) han demostrado que pueden reducir significativamente los procesos diagnósticos y el retraso en el inicio del tratamiento.

La última parte de este estudio es la única que ha evaluado el impacto del intervalo total en la mortalidad del cáncer oral hasta ahora. Aunque es el primer estudio publicado sobre la asociación de la supervivencia con el intervalo total hasta el tratamiento en pacientes con carcinoma oral sintomático dentro del marco conceptual de los itinerarios hasta el tratamiento, hay ciertos sesgos que deben asumirse ya que son inherentes al diseño retrospectivo de este estudio. La investigación en este campo tradicionalmente consideraba las demoras totales hasta el diagnóstico histológico, culpabilizando al paciente y al médico. La demora que se atribuye al paciente, como se ha discutido previamente se debe a la falta de conocimiento o conciencia de la patología, creencias religiosas y culturales y auto-medicación; mientras que la atribuída al profesional sanitario se achaca a la

existencia de barreras en el acceso al sistema sanitario, falta de conocimiento de la patología y errores en el diagnóstico.

Los autores encontraron una asociación en "U", en la que aquellos pacientes con intervalos más cortos (24-55.5 días) y más largos (127.5-420 días), tenían una mortalidad más elevada que aquellos con intervalos intermedios. Otros tumores (pulmón, colorrectal, mama y ovario) han mostrado este comportamiento paradójico, en el que intervalos más cortos se asocian a tasas de mortalidad más altas. Las tasas de mortalidad más altas en pacientes con intervalos más cortos se podrían justificar por el sesgo de indicación y la agresividad tumoral. Esta circunstancia se explica por un sesgo de indicación en la que los profesionales sanitarios dan prioridad a la hora de diagnosticar a los pacientes más graves, pero también podría explicarse por otro sesgo que no se ha medido: la velocidad de crecimiento tumoral (agresividad tumoral). Se deduce que pacientes con tumores de crecimiento rápido, lo cual conlleva la presencia de más síntomas y una progresión más rápida, exigirían atención profesional de forma más rápida que aquellos con tumores de crecimiento lento. Esta hipótesis estaría corroborada por el hecho de que en nuestro estudio los pacientes con el intervalo total más corto tienen como variable predictiva más importante, un menor intervalo libre de enfermedad hasta la recidiva, lo cual se correlaciona con la tasa de progresión tumoral. A pesar de la escasa evidencia en los resultados de los tiempos de espera en el cáncer oral, esta investigación muestra por primera vez una asociación más significativa entre intervalos más largos y mortalidad, que con intervalos intermedios. Este resultado indica la necesidad de acortar el intervalo total a través de campañas dirigidas a pacientes para mejorar su conocimiento y toma de conciencia de lesiones de crecimiento lento con sintomatología menos marcada. Nuestros resultados también indican una necesidad de mejorar y optimizar los procesos en atención

primaria, la interconsulta y el intervalo hospitalario, para evitar los sesgos por severidad. Este estudio también muestra un amplio intervalo hospitalario, en el que hay un claro margen de mejora.

Está claro que el tamaño del tumor primario afecta tanto a la elección del tratamiento como a los resultados del mismo, y que los estadio tempranos se asocian con un mejor pronóstico, supervivencia y calidad de vida. El tamaño tumoral es un factor determinante para que el cirujano pueda realizar una resección completa y obtener márgenes libres de enfermedad, así como a la hora de decidir la necesidad de radioterapia. Un gran tamaño tumoral en el momento de la presentación se asocia con un riesgo aumentado de recidiva local, mayor probabilidad de metástasis cervicales, un tratamiento más agresivo junto con más efectos secundarios derivados del mismo y una peor tasa de supervivencia. Incluso en el caso de que la resección completa sea factible, se asume de forma intuitiva que un mayor tamaño tumoral requiere una mayor resección, y por lo tanto hay un mayor riesgo potencial de complicaciones, efectos secundarios derivados del tratamiento y mayor dificultada a la hora de conseguir márgenes libres de enfermedad en una localización tan anatómicamente compleja como la cabeza y el cuello. Por eso mismo, también se deduce de forma intuitiva que el tratamiento del cáncer oral en estadios iniciales (cuando las lesiones son pequeñas y están localizadas) es la forma más efectiva de reducir la mortalidad, morbilidad y la deformidad por esta patología.

Las estrategias para diagnosticar el cáncer oral de forma temprana podrían incluir campañas de detección precoz (screening) en grupos de alto riesgo, e incluso la realización de exploraciones sistemáticas en consultas por parte del profesional sanitario. Esto reduciría los intervalos hasta el diagnóstico y tratamiento del cáncer oral, pues las pruebas de screening no tienen como objetivo obtener un

diagnóstico, sino el acelerar la interconsulta y la indicación de pruebas de diagnóstico más específicas por parte del especialista.

En general, hay una falta de conocimiento por parte de la población en los que se refiere a síntomas y factores de riesgo, y la implementación de campañas informativas no sólo dirigidas al público, sino también a los profesionales sanitarios sería de gran importancia para facilitar la detección precoz.

Los equipos multidisciplinares son una pieza fundamental en el itinerario de cada paciente a nivel individual, así como un sistema de interconsultas eficiente, así como la estrecha colaboración con un equipo bien coordinado a nivel local. Deberían realizarse auditorías de los procesos con cierta frecuencia para detectar fallos potenciales en el sistema y aquellas áreas en las que se puede mejorar. El modelo de los itinerarios terapéuticos y la declaración de Aarhus también constituyen un mecanismo de seguridad para asegurar un acceso igualitario a la atención sanitaria y para poner de relieve desigualdades en ciertas poblaciones, si existiesen. Desde el punto de vista clínico, queremos proporcionarle a nuestros pacientes la mejor atención posible para conseguir los mejores resultados posibles. Para mejorar la atención que reciben nuestros pacientes y asegurar el diagnóstico precoz del carcinoma oral de células escamosas, no sólo debemos invertir en investigación en ciencias básicas con el fin de desarrollar modelos predictivos, inteligencia artificial y tecnologías que permitan predecir el potencial de malignización de una lesión aparentemente inocente; también hemos de preguntarnos qué es lo que podemos hacer desde el punto de vista clínico. La implementación de vías rápidas de interconsulta ha sido útil para reducir el tiempo transcurrido entre la consulta y el inicio del tratamiento. La actualización de guías clínicas más precisas también es necesaria para clarificar el papel de los médicos de atención primaria y los dentistas en el itinerario de los pacientes, así como intervenciones dirigidas a reducir el intervalo pre-

interconsulta. Debemos esforzarnos en educar a la población para aumentar su conocimiento y conciencia del cáncer oral, así como facilitar la formación continuada de los profesionales sanitarios en este ámbito. Podríamos considerar la implementación de un programa de screening para cáncer oral, que podría tener lugar a la vez que las revisiones dentales anuales o semestrales. Por otra parte, debería garantizarse el acceso igualitario y universal de todos los subgrupos poblacionales, y deberían implementarse determinadas intervenciones para aquellos grupos que pudieran considerarse de alto riesgo debido a sus características sociodemográficas. Está claro que muchas de estas intervenciones han de ser implementadas en el marco general del sistema de salud. Sin embargo, algunas de ellas pueden se implementadas en la práctica diaria por el facultativo clínico, contribuyendo igualmente a implementar cambios e inducir mejoras en la atención sanitaria. Sin ir más lejos, una acción aparentemente trivial, como la sencilla adopción del marco teórico propuesto por Aarhus a la hora de realizar la historia clínica, podría inducir cambios. Este marco teórico, que propone criterios claros y bien definidos para los eventos claves en el itinerario de los pacientes, nos facilitaría el análisis de nuestras intervenciones, y permitiría comparar los resultados futuros y pasados con mayor precisión de la que ha sido posible hasta ahora.

CONCLUSIONES

1. El intervalo del especialista es un intervalo corto en el cáncer oral, y supone una carga relativamente menor en el contexto del intervalo total hasta el diagnóstico. Este intervalo se encuentra básicamente condicionado por la extensión tumoral, sin embargo otras características del paciente o del tumor no parecen asociarse a la magnitud de este intervalo. Hay margen para implementar mejoras y un

posible objetivo para intervenciones futuras sería acortar el intervalo del especialista, en particular para aquellos pacientes en estadios tempranos una vez que se les ha diagnosticado.

2. El intervalo hospitalario es un intervalo relevante en el itinerario del paciente con cáncer oral hacia el tratamiento, llegando a representar una cuarta parte del intervalo total. A pesar de que la extensión tumoral se encuentra fuertemente asociada a una mayor mortalidad, nuestro trabajo muestra una asociación no intuitiva donde los pacientes con intervalos hospitalarios cortos tienen una mortalidad significativamente más elevada, debido a la paradoja del tiempo de espera. La presencia de este importante sesgo clínico, un sesgo de confusión por indicación, podría condicionar la supervivencia de pacientes diagnosticados en estadios precoces, y que constituyen el grupo más sensible a los retrasos en el tratamiento del cáncer oral.

3. La mediana del tiempo del intervalo total es superior a 2.5 meses. Este intervalo y la mortalidad por cáncer oral muestran una asociación en "U", en la que pacientes con intervalos totales más cortos (pacientes con tiempos de recidiva más cortos y presencia de infiltración vascular) y aquellos con intervalos totales más largos, tienen una mortalidad más elevada que aquellos con intervalos intermedios. Las tasas de mortalidad más elevadas se asocian con los intervalos de tiempo más cortos y más largos, y esta asociación no-monotónica entre el intervalo temporal y la mortalidad puede inducir la subestimación de la asociación cuando los intervalos de tiempo se

analizan de forma dicotómica. Para conseguir reducir el intervalo total, los esfuerzos deberían centrarse en aquellos factores que contribuyen en el itinerario del paciente hacia el tratamiento, así como en intervenciones destinadas a promover tanto el conocimiento de la patología entre la población general, como la mejora de las habilidades diagnósticas entre los facultativos sanitarios de atención primaria a la vez que se reducen los tiempos hospitalarios pre-tratamiento.

SUMMARY

INTRODUCTION

Oral and oropharyngeal cancer is the 12th most common malignancy worldwide, with a combined incidence of 476.125 cases and a total of 225.900 deaths during the year 2020.

In this context, survival to oral cancer does not seem to have significantly improved despite therapeutic advances, probably because of delay in diagnosis, among other independent factors. Oral carcinomas are mostly diagnosed at advanced disease stages, which results in poor 5-year survival rates (20–50%). Although a number of studies have shown inconclusive results when evaluating the association between long periods to diagnosis/treatment and poor outcomes in head and neck cancer, various studies have supported a potential association between diagnostic delays and low survival.

It has been suggested that an early diagnosis is the most important prognostic factor for overall survival, and also that if these malignancies were diagnosed and treated at earlier stages, survival rates would exceed 80%. Oral cancer diagnostic delay has been found to be both a risk factor linked to TNM stage at diagnosis and an independent risk factor, together with disease stage, proliferative markers, DNA content and oncogene expression. However, studies inferring prognostic capability for diagnostic delay in oral cancer are methodologically weak and do not allow the establishment of a clear association.

In most countries, oral cancer is more common in men than in women, however the rising trend in incidence in females is consistent with the global patterns and trends in tobacco and alcohol consumption. Oral cancer is also linked to social and economic status and deprivation, with the highest rates occurring in the most disadvantaged sections of the population. It has traditionally been considered a disease of adult life and older age, mostly related to the duration and intensity of carcinogen exposure. The most frequent locations are floor of mouth and tongue (lateral border predominantly, posterior and ventral surfaces). Buccal mucosa and retromolar triangle are more frequent in those areas of the world where betel quid is a habit. Finally, and in order of decreasing frequency it can also be found in the soft palate, alveolar ridge, labial mucosa and hard palate

The etiology of oral cancer is multifactorial. The most important etiological factors are tobacco, excess consumption of alcohol and betel quid usage. These factors can act separately or synergistically. There are other risk factors for specific subtypes: high-risk Human Papillomavirus has been linked to cancers in the oropharyngeal regions in subpopulations in selected countries (men, younger ages, of European origin, higher socioeconomic status), whereas lip cancers are strongly associated with ultraviolet radiation from sunlight exposure.

Regarding prognosis, stage is not always a good predictor, as small tumours can behave more aggressively than larger ones. Although there are many publications which try to identify the sociodemographic, clinical and histological prognostic factors, there is still controversy over the relative importance of different prognostic factors, apart from the TNM stage. The stage of the presenting lesion at diagnosis, the presence of extracapsular spread in the context of nodal involvement and positive margins still are the most important prognostic markers for oral cancer. Comorbidity, defined as disease

processes that coexist and are not related to the index disease, can also impact overall survival of the newly diagnosed patient with HNSCC, and some studies have proven association between coexisting diseases and shorter recurrence-free intervals, as well as negatively influencing disease-specific survival.

Pack and Gallo established the basis of the concept diagnostic delay over 75 years ago, and ever since researchers have used a variety of criteria in order to quantify and study the impact of the time to diagnosis. The 5-year survival rates reported for oral cancer vary between 20–50%, with only minor improvements (<5%) in the last 20 years. The high mortality rate is in direct relation to the fact that many oral cancers present at a late stage of the disease. Unfortunately, at least two thirds of patients with oral cancer are still diagnosed at an advanced stage of disease (stage III and IV), with a 5-year survival rate of 50% or less, which compared to the more than 80% survival rate in those with localized disease, makes the differences in mortality rates based on staging very marked. Tumour stage at diagnosis continues to be the most important prognostic factor for OSCC, with advanced stages associated to higher mortality.

There is a heterogeneity in the criteria used to describe time intervals in research, which makes comparisons between studies difficult. An useful tool to navigate this conundrum is the guideline known as “The Aarhus statement” which was developed by an international Consensus Work Group in order to improve the design and reporting of studies on early cancer diagnosis.

OBJECTIVES

The working hypothesis of this study is that diagnostic delay is linked to oral cancer survival, and that longer time intervals lead to worse patient outcomes and increased mortality.

The main objective is to is to quantify "diagnostic delay" according to the time intervals proposed by the Aarhus statement, their influence in oral cancer survival and the associated factors. Studies on early diagnosis including patient survival as an outcome are scarce, and this was the focus of this study. As secondary objectives we quantified and analysed the impact on survival of the following intervals: specialist interval, hospital interval and total/overall interval.

MATERIAL AND METHODS

The data relevant to this study was obtained from the records of patients diagnosed and treated with oral/oropharyngeal squamous cell carcinoma between 1998–2008 at the University Hospital A Coruña (Galicia, Spain), in North-Western Spain. The study was observational, with a retrospective and prospective component, as the patients were followed up until 2016. All statistical analyses were performed using the R software.

This investigation project was approved by the Galician Research Ethics Committee (CAEI) under the registration number 2014/097, which officially grants patients' rights and the adequate ethics conditions during research and complies with the requirements of the Declaration of Helsinki.

The model of pathways to treatment of symptomatic cancer patients and the Aarhus Statement were used as the conceptual framework. The presenting symptom was defined as the first symptom reported at presentation at a primary care setting by a patient later diagnosed with an oral squamous cell carcinoma.

RESULTS

In the first study, multivariate regression confirmed a significant association between shorter STI and advanced TNM stage. In the second article the multivariate Cox survival model that included the hospital interval (T14) discretised by terciles, showed a 2.8-fold greater mortality risk for stages III-IV and a 2-fold greater risk for men. The hospital interval (T14) and mortality show a V-shaped association, where patients with short T14 intervals (3–18 days) and those with long T14 intervals (26–55 days) had higher mortality than those with medium T14 intervals (19–25 days). Finally, in the third article, univariate analysis found significant associations for gender ($p = 0.03$) and TNM stage (I-II vs. III-IV) ($p = 0.001$). Considering the overall interval (T5) a continuous variable, no significant association could be identified ($\exp \beta = 1.0$; $p = 0.13$), although this was acknowledged in the multivariate Cox survival model when the overall time interval (T5) was discretized by quartiles. In this situation, a 1.8-fold greater mortality risk for men and a 2.5-fold greater risk for stages III-IV could be disclosed. Overall time interval (T5) and mortality showed a U-shaped association, where patients with short T5 intervals (24–55.5 days) and those with long T5 intervals (127.5–420 days) had higher mortality than those with medium T5 intervals (55.5–127.5 days). The characterization of patients included in the first T5 quartile, with short time intervals and high mortality, permitted the identification as important variables for classification within this group shorter recurrence times and presence of vascular infiltration, with an acceptable prediction error (22%).

DISCUSSION

The primary objective of this study to was to quantify “diagnostic delay” according to the time intervals proposed by the Aarhus statement, their influence in oral cancer survival and the

associated factors. There is extensive knowledge of the intervals associated with patients and primary care. However, the secondary care intervals have been scarcely explored.

The main cause of longer time intervals from the first symptom to definitive histological diagnosis of an oral cancer is reported to be the late presentation of the patient. As such, the patient interval accounted for the longest period in the patients' pathway to treatment, although its causes are poorly understood. Some of these factors include denial behaviours, lack of knowledge/awareness, self-treatments and physical or economic barriers in the access to care. Conversely, according to our results, the relative contribution of the specialist time interval to the total time until diagnosis seems to be relatively small (6/64 days). Only patients with larger tumours (T3/T4) have shown significantly less specialist delay than those with smaller ones (T1/T2), and our results show a significant association between shorter STI and advanced TNM stage, and exclude hypothetical links between the STI and other variables related to the patient or to the tumour. The reasons behind the prioritisation of patients with advanced disease for pathological diagnosis remain unclear, although this phenomenon also occurs in surgical waiting times, where longer time intervals affect patients at early stages of the disease. In the latter situation, the explanation may be an attempt to start treatment as early as possible in order to prevent the tumour to become unresectable or to metastasize. Bearing in mind longest STI is found in patients at early stages (TNM stages I-II) and also that long intervals since diagnosis to treatment increase the mortality risk, particularly for patients at early stages, the optimisation of hospital intervals for these patients is encouraged to begin their treatment as quickly as possible. Considering the limitations of this study, it is concluded that the specialist time interval (STI) is a short time interval in oral cancer diagnosis, imposing a limited time burden in the context

of the whole interval until diagnosis. However, there seems to be room for improvement and a possible target for future interventions is to shorten STI, particularly for patients at early stages of their disease.

Our second observational study was aimed at assessing the hospital interval. The results of this study permit a contextualization of the secondary care in the patients' path to treatment. Various systematic reviews have shown an inconsistent relationship between diagnostic delay and the risk of recurrence, stage at diagnosis and survival for oral cancer. Reports have shown that head and neck cancer (as well as breast, colorectal, testicular cancer and melanoma) has a shorter time to diagnosis, which is associated with better outcomes. A long interval until diagnosis seems to be a moderate risk factor for mortality in head and neck carcinoma. The total interval in our study resulted to be significantly lower than the average for this time-period calculated from the reports published in the last decade from Australia, India, and Iran. The association between the diagnosis-to-treatment interval and survival for oral cancer in the hospital setting has only recently been studied and has yielded conflicting results. In our series, the mean hospital interval was 23.4 days, and patients with short hospital intervals had significantly higher mortality. This counterintuitive association is due to the waiting time paradox (confounding by indication), where seriously ill patients with aggressive tumours and higher associated mortality are prioritised to prevent the tumour from becoming unresectable or metastasising. This phenomenon has also been reported in gliomas, cervical and endometrial cancer, breast cancer and colorectal cancer. However, this confounding by severity cannot explain why the longer hospital intervals for oral cancer (>26 days) are significantly associated with higher mortality, suggesting a positive association between long hospital intervals and poorer oral cancer survival rates.

The hospital interval is dependent on the characteristics of the clinical practice and the health system and can therefore vary between contexts. Considering the severity bias in the prioritisation of patients with a poorer prognosis for the diagnosis and treatment of oral cancer and that studies have identified that patients undergoing surgical treatment in early stages (I-II) are most affected (in terms of survival) by treatment delay, strategies should be implemented to promptly treat early-stage patients and prevent stage progression. Given that long hospital intervals generate higher mortality, shortening this interval would increase survival for patients with this neoplasm.

Taking into account the results from our first study, which focused on the specialist interval, it can be deducted that the contribution to delay of the pre-treatment interval in the hospital interval is much more important in terms of days, and that efforts should be aimed at streamlining the start of treatment once the diagnosis has been ascertained. Strategies based on multidisciplinary first-day hospital consultations (oral and maxillofacial surgery; ear, nose and throat; radiotherapy; and medical oncology) have shown the ability to significantly reduce the duration of diagnostic procedures and the delay to the start of the first treatment.

The final part of the study is the only one that has assessed the impact of the total time-interval on mortality from oral cancer to date. Despite the fact that this is the first report on the association of survival with the overall time interval to treatment in patients with symptomatic oral cancer within the framework of the model of pathways to treatment, certain biases have to be assumed which are inherent to the retrospective nature of the current investigation. Research on this issue has traditionally considered total delays until histological diagnosis, blaming both patients and clinicians. The delay attributed to the patient (patient interval), as previously discussed, is due to lack of knowledge, poor symptom interpretation,

cultural/religious beliefs, and self-treatment, whereas the delay attributed to clinicians (professional/provider delay) has been put down to the existence of barriers to access primary healthcare, lack of oral cancer awareness, and misdiagnosis.

The authors found a U-shaped association, where patients with short time-intervals (24–55.5 days) and with long time-intervals (127.5–420 days) had a higher mortality than those with medium time-intervals. Different neoplasms (lung, colorectal, breast, and ovarian) have shown a paradoxical behaviour where shorter intervals are linked to higher mortality. Higher mortality rates in patients with shorter time-intervals could be explained by confounding by severity and tumour aggressiveness This circumstance has been explained by an indication confounder (waiting time paradox) where professionals prioritize severely ill patients for diagnosis, but it could also be explained by another unmeasured confounding: tumour growth velocity (tumour aggressiveness). Thus, patients with fast-growing tumours, implying more symptoms and rapid progression, would demand professional care faster than those with slower growing ones. This hypothesis would be supported by the finding that patients in our study with shorter overall intervals have, as their most important predictive variable, less time to recurrence, which correlates with tumour progression rate. Despite the limited evidence on waiting time outcomes in oral cancer, the current investigation shows for the first time a stronger association between the longest time intervals with mortality than for middle-length intervals. This finding suggests the importance of shortening the overall time interval by increasing patient awareness about slower-growing tumours with “less intense” symptomatology. Our findings also seem to point at a need for optimizing the primary care, referral, and hospital intervals to avoid bias by severity. The current research also describes a broad overall time interval, with wide margins for improvement.

It is clear that the size of the primary tumour affects both the choice and outcome of treatment, and earlier stages are associated with better prognosis, survival and quality of life. Tumour size is an important factor in determining the surgeon's ability to resect and obtain tumour-free margins, as well as in deciding the necessary radiotherapeutic dose. Large size at presentation is associated with an increased risk of local recurrence, increased cervical lymph node metastasis, more extensive therapy/toxicity and poor survival. Even in a context of resectability, it is intuitive to assume that bigger tumour size encompasses a larger resection and hence a higher potential for complications, side effects and potentially worse outcome due to tumour extension and the difficulty to achieve free margins in a complex anatomical area such as the head and neck. Hence, it is also intuitive to deduct that treating oral cancer at an early stage (when lesions are small and localized) is believed to be the most effective intervention to reduce death, morbidity and disfigurement from this disease.

Strategies for diagnosing oral cancer at an early stage could include population screening of high-risk groups and opportunistic screening by healthcare providers. This would result in a reduction of the time intervals in diagnosis and treatment of oral cancer because a screening test is not intended to be diagnostic, but aims to accelerate the referral and application of more specific diagnostic procedures by a specialist.

There is a generalised low awareness and knowledge of risk factors ad symptoms amongst the general population, and educational awareness campaigns aimed not only at the general public, but also at primary care health providers are of paramount importance in order to enable early detection.

In order optimise the cancer journey of each individual patient, multidisciplinary teams are a fundamental cornerstone of the process

as well as a streamlined referral process, working in parallel with a well-coordinated local team. Audits on the processes involved should be carried out regularly in order to detect potential system failings and areas where there is room for improvement. The model of pathways to treatment and the Aarhus statement could also constitute a fail-safe mechanism to ensure equal access to healthcare and to highlight existing inequalities in certain populations.

From the clinician standpoint, we are interested in providing the best available care to our patients in order to ensure the most favourable outcomes. In order to continuously improve patient care and ensure early diagnosis and treatment of OSCC, not only do we need to encourage research in basic science with the aim of developing predictive models, machine learning and technologies that can ascertain the likelihood of malignant progression of apparently innocent lesions; we must also consider what we can improve from the clinical standpoint. The establishment of fast-tracks referral systems has been useful in diminishing the time between referral and the beginning of cancer treatment. Refining and updating referral guidelines is also necessary to clarify the roles of GDPs and GPs in the patient referral pathway, as is the implementation of new interventions aimed at reducing the prereferral interval of patients with oral cancer. We should work on increasing the patient´s awareness of oral cancer and provide ongoing education for primary care clinicians on this topic. We could consider the implementation of oral screening programs that could even take place at the same time as a yearly or six-monthly scheduled dental check-up. Equal access to healthcare for all the different sectors of the population should be ensured, and certain interventions should be aimed at those groups who may be high-risk due to their sociodemographic characteristics. It is clear that some of these interventions have to be implemented in the wider framework of the healthcare system. However, other

interventions can be implemented by clinicians in their daily practice, equally contributing to change and improvement in patient care. Without looking any further, a seemingly small action, such as the effortless adoption of the theoretical framework proposed by the Aarhus statement at the time of clinical documentation, could induce change. This framework, which provides clear and well-defined criteria for key events in the patient´s pathway, will enable us to assess the outcome of our interventions, and compare future and past results with more accuracy than we ever have up to now.

CONCLUSIONS

1. Specialist time interval is a short time interval in oral cancer diagnosis, imposing a limited time burden in the context of the whole interval until diagnosis. This interval is fundamentally conditioned by tumoral extension, however other patient or tumour characteristics do not seem to be associated with the length of this interval. There seems to be room for improvement and a possible target for future interventions would be to shorten specialist time interval particularly for patients at early stages after their disease has been disclosed.

2. The hospital interval is relevant in the pathway to treatment of the patient with oral cancer, representing a quarter of the total length of the overall interval. Even though tumoral extension is frequently associated with an increased mortality, our results show a counterintuitive association where patients with short hospital intervals had significantly higher mortality, due to the waiting time paradox. The presence of this important clinical bias, confounding by indication, could condition survival of patients diagnosed at

early stages, as they constitute the most sensitive population in regards to delays in the treatment of oral cancer.

3. The median of the overall interval is greater than 2.5 months. This interval and the mortality attributed to oral cancer showed a U-shaped association, where patients with short overall intervals -patients with shorter recurrence times and presence of vascular infiltration- and those with long overall intervals had higher mortality than those with medium overall intervals. The highest mortality rates are linked to the shortest and longest time intervals and this non-monotonic association between time interval and mortality may induce an underestimation of the association when time intervals are considered dichotomously. In order to diminish the overall time interval, efforts focused on the contributing factors in the patient's pathway to treatment should be implemented, as well as interventions aimed at increasing both the awareness among the general population and the diagnostic capabilities among primary care clinicians while decreasing hospital pre-treatment times simultaneously.

Introduction

1. INTRODUCTION

Oral and oropharyngeal cancer is the 12th most common malignancy worldwide[1], with a combined incidence of 476.125 cases and a total of 225.900 deaths during the year 2020. According to the GLOBOCAN report which focuses primarily on the description of cancer incidence and mortality at the global level and an assessment of the geographic variability observed across 20 predefined world regions, there is a trend to a global increasing incidence. The results of the study and report are based on data from 185 countries and 36 cancers.

In this context, survival to oral cancer does not seem to have significantly improved despite therapeutic advances[2–5], probably because of delay in diagnosis[3, 6], among other independent factors. Oral carcinomas are mostly diagnosed at advanced disease stages, which results in poor 5-year survival rates (20–50%). Although a number of studies have shown inconclusive results when evaluating the association between long periods to diagnosis/treatment and poor outcomes in head and neck cancer[7], various studies have supported a potential association between diagnostic delays and low survival[8].

It has been suggested that an early diagnosis is the most important prognostic factor for overall survival, and also that if these malignancies were diagnosed and treated at earlier stages, survival rates would exceed 80% [6].

Oral cancer diagnostic delay (long time intervals until diagnosis) has been found to be both a risk factor linked to TNM stage at diagnosis[9] and an independent risk factor[8], together with disease stage, proliferative markers, DNA content and oncogene expression[10]. However, studies inferring prognostic capability for diagnostic delay in oral cancer are methodologically weak and do not allow the establishment of a clear association[8].

1.1. MAGNITUDE OF THE PROBLEM

The GLOBOCAN 2018 report showed that there were 354.864 new diagnoses and 177.374 deaths estimated in 2018 from oral cavity and lip cancer, representing the 16th most common neoplasm worldwide. Cancers of the lip and oral cavity were highly frequent in Southern Asia (India, Pakistan, Sri Lanka and Taiwan), the Pacific Islands (Melanesia and Papua New Guinea, the latter with the highest incidence rate worldwide in both sexes) and Latin America (Brazil, Uruguay, Puerto Rico and Cuba)[3, 11–14]. These cancers collectively constitute the most common form of cancer in males in India and Pakistan, and the second most common in Papua New Guinea[14]. Of these oral cancers, more than 90% are oral squamous cell carcinomas (OSCC)[15, 16].

European countries with a rising incidence of oral and lip cancer include Latvia, Czech Republic, United Kingdom[17, 18], Denmark, Estonia, Slovenia, Finland, Norway and Sweden. Other areas of increased incidence include Japan, India and the United States[3, 4, 14, 19].

At the national level, incidence rates in males were highest in Papua New Guinea (27.5 per 100, 000 persons-year), Pakistan (16.3), Latvia (14.6), followed by India (13.9) and Bangladesh (12.4), respectively. In females, the very same countries presented the highest

rates, namely Papua New Guinea (15.1), Pakistan (8.1), Bangladesh (6.5), Afghanistan (4.6) and India (4.3). Similarly, the highest mortality rates in males were in Papua New Guinea (12.4), Pakistan (10.9), India (7.7), Bangladesh (7.4) and Afghanistan (7.3), and in females in Pakistan (6.4), Papua New Guinea (5.4), Bangladesh (5.0), Afghanistan (4.0) and India (3.4)[14].

According to the GLOBOCAN 2020[20] estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer (IARC), cancer of the lip and oral cavity continues to be the 16th most frequent neoplasm worldwide, with and incidence of 377.713 cases and 177.757 deaths in 2020. This represents an increase in incidence and mortality when compared to the prior report. The areas with the highest reported incidence were Melanesia, South-Central Asia, Central and Eastern Europe , followed by Australia and New Zealand, Western and Northern Europe and Northern America. The areas with the highest mortality rate were Melanesia, South-Central Asia and Central and Eastern Europe[21]. In high-risk countries such as Sri Lanka, India, Pakistan and Bangladesh, oral cancer is the most common cancer in men, and may contribute up to 25% of all new cases of cancer[4].

On the other hand, there were 98.412 new cases of cancer of the oropharynx and the total accumulated deaths were 48.143[1]. There is an increased incidence when compared to the previous report, however the number of deaths decreased slightly from 51.005 in the 2018 report, to 48.143. The regions with the highest incidence of oropharyngeal cancer were Europe (in particular Western Europe), Northern America and Australia and New Zealand. The highest mortality rates were found in Western, Central and Eastern Europe, Melanesia and South-Central Asia. Regarding mortality rates, an increase for both males and females from 177, 384 cases in 2018 to 275, 164 in 2040 can be expected[20].

The combined figures for both oral and oropharyngeal cancer show an incidence of 476.125 with a total of 225.900 deaths in 2020, thus being the 12th most common combined location for neoplasms in the world. The global epidemiology of cancers of the lip, tongue and mouth (oral cavity) [ICD-10: C00-06], and oropharynx [ICD-10: C09-C10], was measured excluding the salivary glands [C07-08] and other pharyngeal sites [C11-13] such as nasopharynx and hypopharynx.

The interpretation of the global estimates of lip, oral cavity cancer and oropharynx should be undertaken with some caution. For example, an important limitation is the definition of oral cancer in GLOBOCAN 2018, which includes the base of tongue (ICD-10 C01) combined with other and unspecified parts of tongue (C02). In addition, the robustness of national estimates in GLOBOCAN varies by country, depending on the availability of high quality incidence and mortality data. However, an increase in incident cases of over 40% is expected for the next 20 years, along with the subsequent associated mortality[20], which highlights the fact that it is a global public health problem.

1.2. DISTRIBUTION

1.2.1. Sex

In most countries around the world, oral cancer is more common in men than in women. The reported sex differences are attributable to heavier indulgence in risk habits by men and exposure to sunlight (for lip cancer) as a part of outdoor occupations.

Globally, incidence and mortality were consistently higher among males than females. Increasing rates in mouth cancers among females were observed in some populations[14, 22]. The observed rising trend in incidence in females is consistent with the global patterns and

trends in tobacco and alcohol consumption[23–25] and the causal role of smoking and smokeless tobacco consumption on oral cancers[26, 27].

1.2.2. Age

It has traditionally been considered a disease of adult life and older age. This is mostly because of the duration and intensity to carcinogen exposure[28]. The risk of developing oral cancer increases with age and the majority of cases occur in people aged 50 or over, and from 2000 to 2004, the median age of diagnosis in USA was 62 years[29]. About 6% of oral cancers occur in young people under the age of 45 years[30]. In high-incidence countries of the world, many cases are reported before the age of 40. The rising incidence in oral and oropharyngeal cancer and mortality rates in young adults is reported from many countries in the European Union and parts of United States[31–33]. In Scotland, where this trend was first reported, the incidence rate between 1990 and 1999 in males under 45 has more than doubled from 0.6 to 1.3 per 100, 000. Fortunately, the disease is not more aggressive than that occurring in older adults either in the USA or in Southern England[33, 34].

1.2.3. Location

Tongue is the most common site for intraoral cancer amongst European and US populations, amounting to 40–50% of oral cancers. Buccal cancer is more common among Asian populations due to betel quid/tobacco chewing habits. In Sri Lanka, where this habit is widespread, 40% of oral cavity cancers are found on the buccal mucosa[35].

The most frequent locations are floor of mouth and tongue (lateral border predominantly, posterior and ventral surfaces). Buccal mucosa and retromolar triangle are more frequent in those areas of the

world where betel quid is a habit. Finally, and in order of decreasing frequency it can also be found in the soft palate, alveolar ridge, labial mucosa and hard palate[36–38]. Some groups have found that the tongue is the most frequent location for OSCC, independent of age[39, 40], while other series have found that the floor of mouth was the most common site of OSCC localization, followed by the tongue[41]. This trend in location could be explained probably because the floor of the mouth is more exposed to the carcinogenic effects of tobacco and the accumulation of chemicals as suggested by Sturgis et al. who suggested that the pooling of saliva in gravity-dependent regions contributes to the development of cancer along the lateral and ventral surfaces of tongue, and in the floor of the mouth[42]. In addition, the absence of keratin in the floor of mouth and ventral tongue might increase the vulnerability of these sites to carcinogens.

1.2.4. Socioeconomic deprivation

Oral cancer is linked to social and economic status and deprivation, with the highest rates occurring in the most disadvantaged sections of the population[11, 12, 18, 43–46]. The association is particularly strong for men, and it is also worth noting that regular consumption of fruit and vegetables tends to be more rare in people with low incomes.

1.3. RISK FACTORS

The etiology of oral cancer is multifactorial. The most important etiological factors are tobacco[26, 27, 47], excess consumption of alcohol[48] and betel quid usage[49]. These factors can act separately or synergistically[22]. There are other risk factors for specific subtypes: high-risk Human Papillomavirus (HPV) has been linked to cancers in the oropharyngeal regions (including base of tongue, lingual tonsil and soft palate) in subpopulations in selected countries (men, younger

ages, of European origin, higher socioeconomic status), whereas lip cancers are strongly associated with ultraviolet radiation (UVR) from sunlight exposure[50, 51]. Oral cancers may be preventable either by reducing exposure to risk factors, or by screening for oral potentially malignant disorders.

1.3.1. Tobacco and alcohol

It is more than 20 years now since the IARC (International Agency for the Research on Cancer) stablished that tobacco [47] and alcohol[48] were the main risk factors for oral cancer. Attributable risk of oral cancer due to both tobacco and alcohol is estimated to be more than 80%. The risk in smokers increases between 3-12 fold in comparison to non-smokers, and it is directly related to the quantity and duration of the habit. Alcohol is a carcinogenic in itself, however it has a synergic effect with tobacco, potentiating its effects. Heavy drinkers and smokers have 38 times the risk of abstainers from both products[22]. Cancers of the oral tongue have been traditionally associated with tobacco and alcohol consumption[52], with the highest incidence rates found in India. Sankaranaryanan et al.[53] reported a positive association between the consumption of tobacco smoking and alcohol, with the higher risk of cancer in the oral tongue and floor of mouth in a case control study in Kerala. Tobacco chewing was also associated with oral cancer in both sexes, independent of the use of tobacco[54]. In addition, marijuana consumption is suspected to increase the risk of oral cancers, particularly in the oropharynx, although its association with oral tongue remains unclear[55].

Alcohol consumption is associated with oral cancer, and the risk increases with the quantity consumed[56], as well as its interaction with tobacco smoking[57]. All forms of tobacco are carcinogenic and evidence for smokeless tobacco causing oral and pharyngeal cancer has recently been evaluated and confirmed (IARC n.d.).

The impact of cigarette smoking on the historical trends of mouth cancer is seen in the similarity of mouth cancer trends with lung cancer two decades on; lung cancer rates continue to decrease in males but increase in females in several European countries, coinciding with time-lagged tobacco consumption[58].

Decreasing the morbidity and mortality from oral cavity cancers in transitioning regions with the highest burden remains a priority; in South Asia, for example, the major risk factors remain oral tobacco consumption, which includes the consumption of betel quid, with or without tobacco[59].

Some studies have found differences in location distribution based on the type of habit, whilst others have not[41]. Perry et al.[60] found that non- smokers had a higher incidence on the edge of the tongue, possibly in relation of ongoing dental irritation, whereas Luce et al.[61] reported no location differences in the male or female population with regards to daily tobacco consumption. However, these authors did find that in the female population the proportion of drinkers was high for patients with cancer of the hypopharynx and low for those with lip cancer. Alcohol has also been associated with second primary cancers of the oral cavity and pharynx in two cohorts of patients with a first primary cancer[62, 63]. Pentenero et al. have reported that when compared to all the other subsites, the relative frequency of smokers with lesions was statistically significantly higher in the buccal mucosa and in the floor of the mouth, while it was lower in the tongue[64]. Dhar et al. on the other hand, suggested that alcohol may pose a higher risk for buccal mucosa and floor of mouth, than for the tongue[65].

1.3.2. Betel nut

Both tobacco and alcohol consumption are well established risk factors, however, the high prevalence of the chewing of betel quid is a

major determinant in the high-risk countries in South Central Asia[66], with the risk factor classified as carcinogenic by IARC in 2009[67]. A study in India has reported that betel quid chewing, with or without added tobacco, increases the risk of oral cancer, independently of other tobacco and alcohol use[68]. The similarly elevated rates of overall lip and oral cavity cancers found in Papua New Guinea and other countries in the Pacific are likely linked to the same causes, with betel quid chewing commonly practised in the region[69].

1.3.3. Human papillomavirus (HPV)

Among young people (under the age of 45 years) there is a small sub-group of patients (approximately 25%) who had little, if any, exposure to the major risk factors[30, 43]. There is strong evidence to suggest that Human Papillomavirus (HPV) plays a role in this subgroup and increases the risk of cancers in the oropharyngeal region (including base of tongue, lingual tonsil and soft palate)[33, 70, 71]. This group of head and neck cancers constitutes a different entity in terms of their epidemiologic, clinical and molecular characteristics, as well as outcome and survival[72, 73]. Overall, the presence of HPV infection results in improved overall survival and disease-free survival[74–76].

High-risk Human Papillomavirus (HPV) has been linked to cancers in the oropharyngeal regions (including base of tongue, lingual tonsil and soft palate) in subpopulations in selected countries (men, younger ages, of European origin, higher socioeconomic status)[77]. Chaturvedi et al. and other groups[78, 79] reported an increasing incidence of HPV-related cancer (which includes certain sites of the tongue) in white men but not white women in the Unites States, possibly implicating changes in sexual behaviour as a critical driver.

1.3.4. Dysplastic/ precancerous lesions

Oral potentially malignant disorders (OPMD) represent a range of architectural and cytologic changes that carry an increased risk of malignant transformation[80]. Clinically, these lesions include leukoplakia, erythroleukoplakia, erythroplakia, proliferative verrucous leukoplakia, oral lichen planus, lupus erythematosus, oral submucous fibrosis, dyskeratosis congenita, palatal lesions in reverse smokers and epidermolysis bullosa. Recently oral lichenoid lesions and chronic graf-versus-host disease have also been added to this group. These lesions may have overlapping clinical appearances, such as lichenoid features, nonspecific erosions, or ulcerations[81]. It is estimated that 16%–62% of cases of oral squamous cell carcinoma (OSCC) arise from pre-existing lesions[82]. The reported malignant transformation rate of OPMD is variable, though it is reported to be in the range of 0.13%–24.0%[82, 83]. Oral leukoplakia, the most common[84], has a 1% prevalence and reported malignant transformation rates of 2-5%, although a recent meta-analysis from 2021 shows a pooled malignant transformation rate of 9.8% [85] .

Immunosuppression was associated with malignant transformation of OPMD, and steroid treatment could increase the probability of transformation[81], although it is difficult to clearly differentiate between the possible direct effect of topical steroids on progression or if progressing lesions with chronic or lichenoid inflammation are symptomatic and require more use of steroids to control symptoms.

Tobacco smoking and alcohol consumption are established risk factors for OSCC[86], though their roles as risk factors for progression OPMD are less defined, but their influence would be expected based on their known association with OSCC. It is important to mention the high-risk nature of these lesions in non-smokers, Previous studies have proposed a higher risk of transformation in non-smokers[87],

particularly for floor of mouth lesions[88]. A possible explanation for this could be that leukoplakia in non-smokers may have a higher genetic predisposition for transformation and therefore should be treated more aggressively.

Histological grading of OPMD is the gold standard for risk stratification of malignant transformation, and it guides the clinical management[83, 89]. Despite this, the mechanism of progression is still not well understood, and it is difficult to predict which lesions will progress to cancer, hence lesions with a lichenoid appearance should always be biopsied to confirm the diagnosis and to rule out dysplasia.

1.3.5. Deficient nutrition

The consumption of fruit and vegetables is found to be associated with a reduced risk of oral cancer, and each portion of fruit or vegetable reduces the risk by at least a quarter[90]. This suggests that a diet deficient in antioxidants is a further factor that predisposes towards the development of oral cancer[91–94] and precancer[95]. Also, it is worth considering that many alcoholic patients present with malnutrition and diet modifications due to their habit[96], which would also contribute to a poorer outcome in this subpopulation.

1.4. PROGNOSTIC FACTORS

The management of OSCC is largely dependent on the TNM staging system, which is based on clinical variables (tumour size, lymphatic spread and presence of metastasis). However, the stage is not always a good predictor of prognosis, as small tumours can behave more aggressively than larger ones. Although there are many publications which try to identify the sociodemographic, clinical and histological prognostic factors[97–99], there is still controversy over the

relative importance of different prognostic factors, apart from the TNM stage. The stage of the presenting lesion at diagnosis, the presence of extracapsular spread in the context of nodal involvement and positive margins still are the most important prognostic markers for oral cancer[100, 101].

1.4.1. Sociodemographic factors

Although several studies have looked into age, sex, race and lifestyle; sociodemographic factors are regarded as of being of weak prognostic value[102].

There is a lack of consensus in the literature regarding age as a prognostic factor in patients with tongue cancer. The debate continues as to whether younger patients (<40 years) fare worse than older patients, and there are conflicting results regarding the effect of age in the prognosis. Some studies show that patients below the age of 40 have an increased frequency of tumour recurrence, distant metastases and mortality[103–105]. Other studies report that younger age is associated with a better survival[106–109]. Some investigators have found no difference between age and prognosis[105, 110–113], whilst others report that patient´s older age significantly shortened the disease-specific survival time[109].

Regarding sex, some studies have shown that 5 year survival rates in men are worse than in women with tongue cancer[114–117], while others did not find such association[118, 119].

Worse outcomes have been reported for the black African-American adult male population when compared with whites[33, 46], as they tended to present more often at later stages. This could be in probable relation to inequality in the access to healthcare facilities and socioeconomic deprivation[120] , which also played a role in the drop of survival rates in Scotland, between 1968 and 1987, from 47% to 39%

in people below 65 years, and most notably in the population of the more socially deprived areas[45].

Smoking and chewing tobacco was found to have an adverse effect on survival in populations where alcohol usage was uncommon[121], and alcohol usage has also been associated with a decreased survival in patients with stage III-IV[109]. This would lead to expecting better survival for the non-smoking and non-alcohol drinking patient population, however, this is likely due to the reduced incidence of other chronic diseases[122].

1.4.2. Comorbidity

The anatomic extent of cancer alone is not the most accurate way to predict the outcome of an individual patient. Disease processes that coexist and are not related to the index disease can impact overall survival of the newly diagnosed patient with HNSCC. The presence of coexisting disease can also predict the survival from oral cancer, and studies have proved the association between coexisting diseases and shorter recurrence-free intervals, thus constituting a prognostic factor[123].

Several instruments have been used to quantify comorbidity including the Adult Comorbidity Evaluation 27 (ACE-27), the Charlson Comorbidity Index (CCI) and the Cumulative Illness Rating Scale. The ACE-27 and CCI are the most frequently used indexes. The information on comorbidity at the time of diagnosis can be abstracted from patient records, and it has been noted that self-reporting is less reliable than record review, as it tends to under-represent the comorbid burden[124].

The ACE-27, as its name suggests, has 27 elements that need to be graded and has been extensively validated for predicting survival in HNC[125], particularly in the elderly[126]. In particular, comorbidity

measured with ACE-27 was a prognostic factor for overall survival in patients older than 70 years with head and neck cancer[127]. This index was derived from the Kaplan-Feinstein index, which was initially developed for assessing comorbidity in diabetes mellitus, and subsequently modified and adapted by Piccirillo[125] to include items relevant to cancer. There is a clear distinction between the impact of the four ACE-27 severity grades. The impact of an ACE-27 grade 3 is comparable to the impact of a T4 tumour or an N2 neck[128]. The CCI[129] is simpler, it uses 22 elements and has also been validated for its use in HNC[130]. The CCI was and independent prognostic factor even in the HPV-adjusted oropharyngeal cancers[131] , however it does not classify comorbid conditions by severity, which decreases its predictive power.

Several studies have compared the different indexes and have come to the conclusion that they all have similar prognostic ability[132, 133] and that there was no apparent advantage to using a disease-specific index when attempting to predict overall survival[133]. Other studies have shown the ACE-27 to be the best for stratifying HNC patients, with a prognostic ability comparable to that of nodal stage[128, 134, 135].

Comorbidity increases mortality in patients with head and neck cancer, and this effect is greater in the early years following treatment[136, 137]. In addition to reducing overall survival, many studies have shown that comorbidity influences disease-specific survival negatively, most likely because patients with high comorbidity tend to have a delay in diagnosis[138], often presenting with advanced stage tumours. These patients do not necessarily present with early stage tumours, despite having increased contact with healthcare providers. A plausible explanation could be that although patients with comorbidities are more likely to seek medical care than their healthy peers, the early symptoms from cancer are diffused in the presence of

other pressing concerns from comorbid conditions that dominate the care of the patient, leading to delayed cancer diagnosis. On the other hand, Reid et al.[139] observed that among patients with no alcohol and tobacco-related comorbidities, increasing numbers of physician visits were independently associated with a reduced risk of advanced stage at diagnosis for all anatomic sites.

Although patients younger than 45 year with HNC have less comorbidities[140], advanced comorbidity in this group has been shown to have a detrimental effect on the disease-free interval and tumour-specific survival in patients with head and neck cancer, independent of other factors[141]. As the age of the population increases, so does the prevalence of comorbidity[127], but nonetheless, it continues to play a prognostic role in the elderly group[127, 139]. Nevertheless, its impact is much more marked in the relatively younger patients than in the elderly, as the former have fewer competing causes of death[126]. A recent study by Schimansky et al.[142] showed a dose-response relationship between comorbidity and survival that was consistent across tumour sites and independent of adjustment for lifestyle confounding factors.

This data should be integrated with tumour-specific staging systems in order to develop better instruments for prognostication, that would result in better treatment choices and outcome of patients with head and neck cancer[142–144].

1.4.3. Tumour staging and clinical factors

The TNM staging system by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC)[142, 145, 146], along with other adverse features, have long been used to guide therapeutic decisions and in the treatment planning of OSCC, and the TNM continues to be the most important tool for

predicting disease outcome. Tumour stage at diagnosis is still the most important prognostic factor for OSCC, with advanced stages linked to a higher rate of mortality[147].

The simplicity of TNM staging makes it the most accepted and used system in clinical practice. In order to increase acceptance and compliance, by design the TNM staging system has to be kept simple and user-friendly[148].

However, TNM staging, although simple, leaves out multiple adverse pathological features such as lymphovascular invasion, perineural invasion, and histologic differentiation, which have been shown to have significant negative prognostic value in literature[99, 149, 150]. TNM staging alone may be insufficient to fully address the needs for treatment selection and escalation[151], but although a highly complex staging system may be most accurate, it may not be easy to accept in clinical practice, and thus will have poor compliance[148].

The current AJCC/UICC TNM staging (8th edition, 2017) of OSCC has included significant modifications[152] through the incorporation of:

- Depth of invasion in the T stage: Traditionally, the greatest dimension of the tumour (diameter) was the most important characteristic for the T stage categories in oral cancer. Since depth of invasion (DOI) has been shown to have prognostic implications, with deeper tumours showing an increased risk of nodal metastases and decreased disease-specific survival, this parameter was included in the categorization of T stages in the AJCC 8th edition[153].
- Extracapsular spread/extranodal extension in the N stage: Extranodal extension (ENE) has been shown to have a profound effect on prognosis of most head and neck cancers,

except for tumours associated with HPV, and therefore, it was incorporated in the N category[154].

- Human papillomavirus (HPV) related or p16-positive oropharyngeal cancer is a different entity with a higher incidence in younger individuals with little or no tobacco exposure. Its incidence has been rising since 1990 and it shows an excellent response to treatment even in patients with advanced stage disease[78, 155]. Taking into account that it behaves as a completely different disease when compared to p16-negative OSCC, a separate staging system has been created for HPV-related OSCC[156].

Updates to the AJCC/UICC TNM staging are important to reflect current scientific advances. The 8th edition of AJCC had a lower Akaike information criterion and improved concordance index values compared with the 7th edition[157]. Hence the update allows better risk stratification, a more precise counselling of patients with OSCC who were previously considered at low risk and was a significant predictor for both OS and DSS. Based on the treatment guidelines recommended by the National Comprehensive Cancer Network (NCCN)[158], patients can be divided into three distinct groups: low, intermediate, and high risk. However, stratification within these groups has remained difficult; locoregional recurrence still takes place in one third of correctly treated early-stage OSCC despite clear surgical margins, whilst survival for advanced cancers (stages III/IV) is prognosticated solely based on nodal stage[152, 159].

The current practice for OSCC management is largely directed by multidisciplinary meeting discussions, which take into consideration the cancer stage, adverse pathological factors, individual patient factors, and the likely functional consequences and morbidity of each treatment approach[159]. Pathological staging by AJCC8 TNM staging is considered together with adverse pathological variables

such as primary tumour site, histologic differentiation, ENE, perineural, lymphovascular, and bone invasion for prognostic risk stratification. As such, TNM staging alone remains insufficient in directing treatment decisions reliably[160, 161].

Models that assess the need for treatment escalation based on objective pathological features are still lacking, making treatment guidance clinically challenging[151, 161]. A simple system like the TNM classification will not enable the use of an accurate personalized prognostic tool, as it does not include histopathological features of the tumour such as perineural invasion, patient factors such as comorbidity or smoking, functional status of the anatomy or response to therapy. Hence, there will likely be a development towards prognostic tools that will predict overall and cancer-related mortality and risk of recurrence in individual patients with oral cancer taking into account numerous variables based on tumour and host characteristics beyond those covered by the traditional TNM staging system[162]. An example of such predictive models are nomograms, and they have been widely tested in a variety of different cancers, including in the head and neck region[162–166]. Nomograms are statistical prognostic models that generate a probability of a clinical event for a particular individual based on their specific characteristics, and take into account various host and tumour variables. They not only enable the clinician to make a rational therapeutic decision based on estimated risk, but also empower patients to understand the implications of their decision in terms of potential benefits versus complications/side-effects of treatment. The current TNM system is static as opposed to dynamic, as it does not include the "response to therapy" and only stages patients at the time of initial diagnosis. Nomograms, on the other hand, are dynamic and personalized prediction tools and can estimate prognosis individually with a higher accuracy. Therefore, nomograms will likely be widely used in the near

future[148, 162] and they will prove to be useful tools for personalised accurate risk stratification, individualised risk of recurrence, cancer-specific survival and precision therapy planning[142, 145, 146] for OSCC patients. In the future, a dynamic nomogram with an user friendly interface for the physician and the patient, that could be readily accessed in the clinical setting, such as a smartphone, may be a standard of care for risk estimation and prognosis.

1.4.4. Histopathologic factors

1.4.4.1. Cellular related markers

- **Tumour site**

The gradual decrease in five year overall survival the more posteriorly the tumour is located has been recognised for many years[167–169], and it is in direct relation to the tumour´s site influence on nodal metastasis[170], stage at presentation and the surgeon´s ability to achieve complete resection and clear margins as well as the presence of second primary tumours[102, 171, 172]. However, some studies have found that no intraoral subsite influenced disease relapse at early stages[123, 173].

- **Depth of invasion**

The differentiation among thin (≤ 5 mm), intermediate (> 5 mm and ≤ 10 mm) and thick (> 10 mm) lesions not only is important preoperatively due to its implications in treatment planning, but also postoperatively. Tumour depth is an independent prognostic factor with a consistently adverse effect on lymph node metastasis, local recurrence and survival rate[64, 174–177]. The depth of invasion can be assessed preoperatively via MRI imaging[178, 179] and has been added to

the AJCC8 TNM staging. The histological analysis once the tumour is excised would confirm or add accuracy to this measurement.

- **Histological grading**

Traditionally OSCC has been graded according to the method originally described by Broders[180], and adopted by the WHO[181] which recommends three categories: grade 1 (well differentiated); grade 2 (moderately differentiated) and grade 3 (poorly differentiated). In a tumour showing different grades, the higher grade determines the final categorization. The grading system takes into account a subjective assessment of the degree of keratinisation, cellular and nuclear pleomorphism, and mitotic activity, and because of this subjectivity it is prone to variation between pathologists as well as inadequate sampling of histologically heterogeneous tumours. The other downside is that it focuses on morphological features rather than functional features[181].

- **Apoptosis**

It is generally recognised that the failure of physiological apoptosis (programmed cell death in the absence of inflammation and damage to adjacent cells) is one of the causes of tumour growth. There are two routes: mitochondria-independent (directly activated by caspases) and mitochondria-dependent which is regulated by the BCL-2 protein family (Bcl-2 inhibits apoptosis, whilst Bax promotes it). A low apoptotic index (AI) (percentage of apoptotic cells and bodies in a given tumour cell population) and low expression of Bax has been correlated with a worse outcome, while low expression of Bcl-2 has been correlated with a better clinical outcome[182].

- **Nuclear DNA content**

Some investigators have found aneuploidy to be related to poor prognosis[183, 184], while others have not found such association[185]. In a study by Rubio et al.[186] the analysis of tumour DNA by flow cytometry appeared to useful as a supplement to clinical and histologic evaluation in predicting the tendency of OSCC to metastasize to regional lymph nodes.

Aneuploidy analysis could also help identify dysplastic lesions with a high risk of malignant progression[187]. It is also important to mention that non-diploid tumours also responded poorly to radiotherapy, hence DNA content could be a significant prognostic marker for the evaluation of OSCC in patients receiving radiation therapy[188].

- **Gene expression profiling**

Gene expression profiling or genetic signatures generated from high-output technologies have been used to study the progression and outcome of different cancers. In particular the microarray technique developed in the last decades has made it possible to study the expression of several thousands of genes simultaneously, enabling the identification of different gene patterns in tumours with different outcomes[189] as well as prognosis-based treatment[190].

Studies have focused on whether gene expression profiling could permit early detection of lymph node metastases for primary head and neck squamous cell carcinomas[191–193].

However, it has become obvious that the actual gain in predictive precision due to the use of gene classifiers derived from expression profiling needs to be carefully evaluated. The prognostic model based on gene expression has to be externally validated by providing evidence that the model works satisfactorily on other

patients than those from whose data it was derived[194]. Larger patient series are needed to obtain more precise results. It is highly plausible that gene expression profiling will, in the future, improve diagnosis and treatment of oral cavity and oropharyngeal squamous cell carcinomas, particularly by providing a tool for the selection of optimum treatment strategies for individual patients, and by reducing adverse side effects related to overtreatment. In years to come, it could help achieve tailored therapeutic strategies which would be adapted to the severity of the disease in each individual case[195, 196].

- **Viruses**

Human papilloma virus (HPV) infection with serotypes HPV-16 and HPV-18[75] is found in a small proportion of OSCCs, and in up to 50% of tonsillar and oropharyngeal SCCs[197]. The action of these viruses is by inserting specific DNA fragments into the host cell genome that leads to an inactivation of cellular tumour suppressor proteins (Rb and p53), the absence of which allow the cells to proliferate indefinitely. The most frequent sites associated with HPV are the base of the tongue and palatine tonsils, followed by oral cavity, larynx, and sinonasal mucosa[197, 198]. Patients with HPV-associated HNSCC are younger, have minimal tobacco exposure[199] and survival is better than in the absence of HPV[197, 198, 200, 201].

- **Molecular markers**

The relatively unchanged rate of mortality in patients with OSCC despite efforts to improve management strategies and detection has led to studies focused on finding molecular markers that could predict the behaviour of the tumour and tailor the treatment to avoid under/overtreating as well as targeted therapies and clinical trial inclusion.

Many molecular markers affecting cellular pathways have been studied, such as growth factors (EGFR), cell motility and adhesion markers (tight-junction proteins, E-cadherin, integrins, CD44), those related to cell cycle (cyclins B1/D1, Ki-67)[202] and its regulation (p16, p53, p27, PRb), matrix metalloproteinases, apoptosis (Bcl-2, Bax), as well as angiogenesis markers within the tumour mass (VEGF, CD34, CD31, factor VIII-related antigen)[203]. However, the results have not been uniform across all studies due to a lack of uniformity in study design, evaluation and reporting. Some results are even conflicting, which has hindered their clinical implementation[99, 150]. Moreover, many of this studies have a relatively small sample size, which makes it difficult to translate the results obtained to clinical practice.

1.4.4.2. Microenvironment related markers

Tumour growth and metastasis formation are not just determined by the division rate of malignant tumour cells, but also by various cell types and the extracellular matrix. The tumour microenvironment is a mixture of extracellular matrix molecules, tumour cells, endothelial cells, fibroblasts and immune cells that is believed to play a key role in tumour progression.

- **Angiogenesis**

The formation of new vessels is one of the key events in tumour progression. Sufficient blood supply is an important factor that enables a tumour to reach a clinically detectable size and to ensure its maintenance and continued growth it needs a process of neovascularization[204]. Tumour angiogenesis is determined morphologically by evaluating the microvascular density of the tumour, which is achieved by staining the section with markers such as CD34, CD31, factor VIII-related antigen, or more recently, CD105 (endoglin) which seems to be more specific[205] and it correlates with

the metastatic potential, constituting a potential target for therapy[206]. High microvascular density has been associated with a poor prognosis in early OSCC[207], while other studies have not been able to validate this finding[109, 208–210]. This difference in findings could be due to major differences in study design.

- **Lymphovascular invasion**

The presence of aggregates of tumour cells within endothelial lined channels or invasion of the media of a vessel with ulceration of the intima has long been associated with a poor prognosis in OSCC. It is closely associated to cervical nodal metastasis, locoregional recurrence, or both[102, 149, 211]. Some studies have reported a correlation between lymphovascular invasion and regional disease, but not with survival[212, 213]. Other studies have showed that the presence of histological evidence of lymphovascular invasion in oral carcinoma has a significant impact on survival outcome in OSCC patients[211, 214, 215]. However, it has been pointed out that this characteristic is difficult to define and recognise with certainty[102].

- **Perineural invasion**

Infiltration of the perineural space of nerves at the advancing front of the tumour is related to the site, the diameter and thickness of the tumour, pattern of invasion at the advancing tumour front, presence of nodal metastasis, close/involved resection margins and survival[102, 171, 172]. It is a widely recognized indicator of poor prognosis in oral cancer patients, strongly correlating with aggressive tumor behavior, disease recurrence, and increased morbidity and mortality[216]. Most of the studies that found a statistical association between lymphovascular invasion and poor prognosis in OSCC also found a similar or even stronger association with perineural invasion[211, 212, 215]. It has also been associated with both regional

recurrence and distant metastasis[217, 218]. Sparano et al.[219] reported that perineural invasion was an independent factor for occult nodal metastasis on multivariate analysis, while lymphovascular invasion was not, in a series of 45 clinically negative neck (N0) patients with early tongue OSCC (T1/T2). The identification of this characteristic was increased by more than 50% after careful reviewing of slides and staining with S-100[220] .

- **Cancer associated fibroblasts**

Cancer initiation and progression are believed to be associated with the tumour microenvironment, which contains various cell types, including fibroblasts, immune cells, neoplastic epithelial cells, endothelial cells and pericytes. Cancer-associated fibroblasts (CAFs) show a distinct phenotype from normal fibroblasts and become synthetic machines that produce many different tumour components, subsequently playing a role in all stages of disease progression, including metastasis. CAFs have a role in creating the extracellular matrix structure and metabolic and immune reprogramming of the tumour microenvironment with an impact on adaptive resistance to chemotherapy[221]. Within the last decade, emerging evidence has indicated that the tumour micro-environment is critical to the initiation and progression of tumours[222–224] by directly being sources of pro-tumorigenic signals and recruitment of pro-tumorigenic inflammatory cells[224–226].

The origin of these cells is still unknown. Based on different studies, CAFs are presently thought to originate from four sources: local fibroblasts or fibroblast precursors, bone marrow-derived precursor cells, malignant or normal epithelial cells undergoing epithelial–mesenchymal transition (EMT) and endothelial cells[225].

Stromal response in OSCC comprises liberation of multiple cytokines and factors, such as TGF-β, vascular endothelial growth factor A (VEGFA), hepatocyte growth factor (HGF), epidermal growth factor (EGF), tumour necrosis factor (TNF), interferon-γ (IFN-γ), C-X-C motif chemokine ligand 5 (CXCL5) and C-C motif chemokine ligand 5 (CCL5), which act as mediators in processes that are essential to tumour initiation and survival, such as neoangiogenesis and the differentiation of fibroblasts into CAFs. Increasing evidence indicates that TGF-β plays a dual role not only in stimulating fibroblasts to become CAFs but also in enhancing tumorigenesis and progression in OSCC . Furthermore, activated CAFs tend to secrete more TGF-β to act back on tumour cells. Recent studies have shown that TGF-β1 can be secreted by CAFs to promote OSCC invasion in vitro[227]. Many studies have demonstrated the increased expression of CAFs to be associated with poor prognosis. Vered et al. reported that increased amount of CAFs in the stroma is an adverse independent predictor of local recurrence in tongue OSCC[228]. It has also been shown that they are present not only in primary, but also in metastatic OSCC tumours, prompting the hypothesis that they promote tumour invasion and facilitate metastases by either accompanying the tumour cells while metastasizing, or by being recruited from the surrounding environment[229].

- **Inflammatory response**

It has been recognized that systemic inflammatory markers, such as neutrophil-to-lymphocyte ratio, are associated with patient survival in various types of cancer. Research on interactions between tumour development and systemic inflammation indicates that chronic inflammation can stimulate carcinogenesis, and the degree of systemic inflammation correlates with the outcomes. These markers could help identify the patients who are at risk of shorter survival and higher

recurrence preoperatively[230, 231], and they were independent predictors for poor overall survival and disease-free survival[232, 233]. It has been suggested that they could be valuable in predicting survival outcomes during preoperative and postoperative assessment. Inflammatory plasma protein biomarkers could also be used to assist in the early detection of OSCC[234].

1.5. DIAGNOSTIC DELAY

Pack and Gallo[235] established the basis of the concept diagnostic delay over 75 years ago, and ever since researchers have used a variety of criteria in order to quantify and study the impact of the time to diagnosis.The 5-year survival rates reported for oral cancer vary between 20–50%[100], with only minor improvements (<5%) in the last 20 years[3, 4]. The high mortality rate is in direct relation to the fact that many oral cancers present at a late stage of the disease. Unfortunately, at least two thirds of patients with oral cancer are still diagnosed at an advanced stage of disease (stage III and IV)[109, 236–239] with a 5-year survival rate of 50% or less[100, 147, 238], which compared to the more than 80% survival rate in those with localized disease, makes the differences in mortality rates based on staging very marked[240–242]. Tumour stage at diagnosis continues to be the most important prognostic factor for OSCC, with advanced stages associated to higher mortality[147, 243] .

Studies examining time to diagnosis report that patients usually delay seeking professional advice for periods up to 3 months after having become aware of an oral symptom that could be linked to oral cancer. It is important to note that the proportion of patients presenting with advanced disease has not changed in 40 years despite public education[147]. When they are finally diagnosed, they tend to have a considerable size, depth of invasion and frequently present with

metastases to regional lymph nodes, despite the fact they tend to be located in an area which could have easily been diagnosed at earlier stages[244, 245]. The relationship between delay from onset of symptoms to referral to a specialist centre and stage at presentation has been described in the literature[246], and several meta-analyses have linked diagnostic delays (>1 month) to advanced disease stage at diagnosis[7–9, 247–251]. However, there are also studies that have found no correlation between delay and more advanced stage at presentation[252–263], but this could be in relation to the definition of the time intervals and study design.

Early diagnosis is presumed to be a key factor in improving the outcome[264], as longer times from the first symptom to diagnosis and treatment of symptomatic oral cancers have been linked to poorer outcomes in terms of disease stage and patient survival[7, 8, 246]. However, it is difficult to quantify the impact of early diagnosis and to assess the significance of diagnostic delay in terms of survival, quality-of-life outcomes[265, 266] or tumour stage at presentation.

Regarding survival, a study by Ho et al. found the delay from presentation to cancer diagnosis in patients with oropharyngeal cancer to be, on average, 3 months or longer; however, this delay did not appear to significantly impact survival[267]. Caudell et al. examined the interval from diagnosis to treatment initiation among patients with locally advanced HNC treated with primary radiation and did not find a statistically significant adverse effect of a prolongation of this interval on survival[268]. There is limited knowledge on the effects of any interventions that have been aimed at reducing the diagnostic delay[269], but it has been suggested that if these malignancies were detected and treated early, the survival rate could exceed 80% [6]. It is important to mention that patients with early stage, particularly those who are surgically resectable, tend to experience less delays than those with advanced stage requiring multidisciplinary treatment by a

variety of subspecialty physicians, including medical oncologists, radiation oncologists, and maxillofacial surgeons. This is consistent with the intuitive notion that multidisciplinary coordination of care takes more time[243]. It has also been reported that outcomes in radiotherapy only treatment do not seem to be influenced by time from biopsy to treatment[268]. Although it would also be intuitive to expect that longer delays would always translate to worse outcomes in cancer, in certain types of cancer (such as endometrial) a paradoxical relationship has been identified, and those patients who experience the longest delay in treatment are those more likely to survive[270]. In oral cancer, the association found is that a longer time interval from the first symptom to referral for definitive diagnosis is a significant risk factor for mortality from oral cancer, and the chances of presenting at a more advanced stage at diagnosis are also significantly higher than in patients with shorter intervals[8, 271].

There are no standardised definitions for describing time intervals, with diverse criteria used in the literature to describe the patient´s pathway from their first awareness of symptoms to the initiation of treatment[272]. The absence of a standardised theoretical framework and the lack of consensus as to what constitutes a time-point beyond which a cancer should be considered delayed[273] has led to the use of a wide range of arbitrary endpoints for defining "delay" in research. Hence, there is a heterogeneity in the criteria used in research in this topic, which makes comparisons between studies difficult[101]. An useful tool to navigate this conundrum is the guideline known as "The Aarhus statement" which was developed by an international Consensus Work Group in order to improve the design and reporting of studies on early cancer diagnosis[271, 274].

The vast majority of research in the literature focuses on two intervals: the time since first symptom until consultation with a healthcare professional (referred to as "patient delay")[249, 255, 261, 275–277]

and the period the patient is under the care of a healthcare professional until a final pathological diagnosis is reached (referred to as "provider/professional/clinician delay") (138, 249, 250, 253, 255, 261, 278–281). The "overall or total diagnostic delay" would include the period elapsed since the first symptom or sign until the definitive diagnosis. But even these most widely used intervals are not consistent in the literature because of different landmarks used to define them, and variations can be marked, particularly in "total delay" as the endpoint varies amongst studies. The process as a whole consists of four steps: the first is from the onset of symptoms /signs associated with cancer until the first contact with a clinician; the second is from the initial visit to the patients' receipt of a referral letter to the specialist; the third is from receipt of the letter to a visit to a specialized service; the fourth is from the visit to the specialist until a final diagnosis is reached[259]. The lengths of the first and third steps are dependent on the patients, and the second and fourth steps depend on the professionals. There are other factors to be considered that influence tumour stage at presentation, such as biological behaviour, and studies relating to other tumour sites have proposed that this could be more important than delay[282, 283].

1.5.1. Patient related diagnostic delay

As many of the initial symptoms of oropharyngeal HNSCC are nonspecific, patients may delay in seeking advice from their General Practitioner (Primary Care Provider). However, when the presenting symptoms are more specific or worrying to the patient, such as painful ulceration[276, 284] or bleeding, presentation tends to be earlier[260, 276]. This is in keeping with the findings by Brouha et al. that oral cancer with dysphagia, a sore throat, a neck mass, irritation, or a painful lesion showed a shorter appraisal delay than did patients with a lesion, a mass, or pain without a visible lesion, as they tended to attribute the

symptoms to a common cold or an infection, tended to consider the symptom harmless or trivial[285] and only sought attention if the symptom persisted[247]. Usually the persistence of a bodily change beyond three weeks would make the patient seek professional advice[286, 287], as the lesion should be regarded as "suspicious", "unexplainable" and should trigger "uncertainty".

Estimates indicate that on average 30% of patients delay seeking help for more than 3 months following the self-discovery of symptoms/signs of oral cancer[288]. Several studies have reported an average patient delay of 45 days for pharyngeal cancer and 18 days for oral cancer[247], with a median duration of patient delay ranging from 2 weeks to 4 months, most commonly from 3 weeks to 1.6 months[249, 255, 258, 259, 263, 278, 289]. Other authors[237] have summarised different studies to quantify this time interval as ranging from 1.6 to 5.4 months[259, 290–292]. In north-western Spain, the period since the first cancer-related sign/symptom is detected until the patient demands an appointment at primary care resulted to be the longest interval in the subject's pathway to diagnosis and treatment (median: 31.5 days) and accounts for more than 60% of the interval since the onset of the symptoms until the patient is referred for specialized care[293].

The responsibility for delay when apportioned to the patient or physician, mostly accounts due to patients' delay[100, 147, 259, 294]. In younger people, this delay could be longer as cancer is not suspected by primary care practitioners[295].

Cultural, psychosocial[296] factors and socioeconomic determinants[43, 44] such as symptom interpretation[297], belief that the symptom is trivial[298] or that it will improve, emotions such as fear of consultation[299], denial[300, 301], stoicism, disclosure of the symptoms to significant others, use of herbal medication before professional consultation[284] and lack of knowledge about oral cancer[302] influence the decision to seek help and the attendance to a healthcare provider[276, 301,

[303, 304]. Certain emotional representations of a health threat such as anxiety and emotional distress can also be motivating factors for action[305, 306]. However, the lay public do not necessarily associate an intraoral ulcer with oral cancer, or as a trigger for seeking advice[307], and heavy drinkers may delay attendance due to the guilt or fear of medical judgement[308]. Among those patient-based variables we must also consider socioeconomic factors[309] like educational barriers, limited access to transportation, lack of paid leave from work, language barriers, and homelessness[243]. Llewelyn et al.[295] found that those patients who had no further education beyond high school experienced more patient delay. The length of this interval is also conditioned by the healthcare system and accessibility to care[237, 310, 311].

Efforts to minimize the delay attributed to patients should be centered in the importance of patient education[250, 258, 278, 301, 302, 312, 313], as well as the recommendation for screening by means of a regular examination by a professional for patients with a high risk of oral cancer[253, 255, 258], due to the complexity of patients´ help-seeking behaviour and the tendency to misdiagnose or miss certain sites during self-examination such as the palate[314]. Improving the knowledge of the existence of oral cancer among the general population is vital to more accurate symptom interpretation[285, 315], as the non-recognition of the symptoms (mainly related to lack of knowledge about the disease) is the predominant risk factor for patient delay[316, 317].

1.5.2. Professional delay

The delay attributable to the medical profession was equally distributed between general practitioners and the hospital service[147], however the risk of hospital delay was increased if the patient was referred to a general rather than a cancer-specific service particularly if the lesion presented as an apparently benign lump[318].

Primary care healthcare professionals should be aware of the mantra "urgent 2-week referral for suspected head and neck cancer", however blame for this delay must be shared almost equally by the dentist and the doctor. The latter were far more prone to treat the oral lesions by some form of drug, whereas the former were more prone to blame the denture or the teeth[319]. In general, dentists performed more oral cancer examinations, although physicians saw more high-risk patients[320]. The fact that the tongue is one of the most common sites for OSCC[275, 280, 321] reiterates the readily accessible nature of these lesions to visual inspection by the willing clinician.

The primary care interval has consistently shown to be shorter than the patient interval[237, 294], and the main causes for delay include a low index of suspicion and a lack of knowledge about oral cancer[322], as well as lack of familiarity and experience with the disease[101, 323].

It is paramount in order to make a histological diagnosis to obtain an appropriate and adequate sample, and although biopsies could be undertaken in the primary care level, the most frequent approach is not to biopsy and opt for an immediate referral[322]. Studies have reported that there was no difference in delay between those patients who were biopsied prior to referral to the specialist, and those who were biopsied after being seen by a specialist, suggesting that the timing of the biopsy was not a significant contributor to the treatment delay[321].

The specialist interval (time from first contact with a medical specialist until definitive or histological diagnosis) has been rarely studied, and the factors influencing its length remain unclear[291, 324].

The median duration associated with the professional delay ranged from 11 days to 18 days[249, 255, 261, 278]. Onizawa et al.[259] reported an average duration of 14 days, which is comparable to prior studies, and compatible with the recommendation by clinical guidelines[325].

Ongoing educational interventions could be useful in order to reduce professional delay in oral cancer diagnosis[317, 326], as proven by a pilot educational intervention on spanish dentists[327]. Education in this field should be a regular part of continuing professional development both for doctors and dentists[281, 321, 328, 329]. Moreover, education at university level is also important, as shown by an UK study which revealed that significantly more final year dental students had an opportunity to examine patients with oral lesions compared to their medical colleagues (88% versus 61%)[330]. Other studies have concluded that doctors and medical students are inadequately educated about oral diseases with obvious consequence [331], which would lead to missed diagnoses in primary care due to a lack of awareness. It is also interesting to note that most dentists preferred to consult with medical specialists such as a dermatologist or an internist[332] if they had difficulties in establishing a diagnosis for an oral mucosal lesion, despite the fact that a priori they were better trained in the recognition of these lesions[332, 333].

The implementation of the NICE guidelines in 2005 already showed a positive impact in the reduction of diagnostic intervals of those patients who presented with NICE-qualifying symptoms in the UK[334].

1.5.3. Tumour features related to diagnostic delay

It would seem obvious to deduct that the longer the time to diagnosis, the more advanced the cancer is and that the prognosis is worse. However, some studies found no correlation between delay and stage of disease at presentation or survival[147, 253, 254, 256, 257, 260–262, 278]. It is important to remember that although tumours may appear similar, their growth rates may be very different, as well as their aggressiveness[239]. Hence, patients with fast-growing tumours may be diagnosed earlier but at advanced stages[261, 335], which could explain

why shorter patient and professional delays have been linked to advanced stages in some studies[8, 138, 255].

The lack of correlation between delay and outcome also applies to lung, bowel, oesophagus, and gastric cancer[252, 336–339]. It seems that some tumours are silent until they are advanced. This is important because it conveys certain limitations to the expectation of identifying the disease through public education, and it could call for risk stratification and selective screening in order to reliably detect them at an early stage[147]. Seoane et al.[340] demonstrated in a multivariate study that when the statistical analysis is adjusted for tumour stage at diagnosis (I-II vs. III-IV), proliferative activity is an independent factor for survival and diagnostic delay has no influence on the outcome. Survival in oral cancer may be more affected by the tumour growth rate than by time intervals to diagnosis. Although Brouha et al.[247] associated diagnostic delay to tumour stage, it could be that the "silent tumour" hypothesis[239] acts as a confounding factor, as patients with aggressive tumours and poor prognosis usually do not have delayed diagnosis, whereas tumours that grow more slowly demonstrate good prognosis despite long diagnostic delays[241]. The paradoxical relationship between delay and survival, in which shorter delays are associated with worse outcomes in terms of survival has been described not only in tongue cancer[138, 323], but also in endometrial, cervix, lung, colon, renal and urethral cancer. This paradox is in favour of the role of the biological aggressiveness of the cancer[101, 269, 270]. The differences in tumour aggressiveness would explain the tumour´s stage at diagnosis and patient survival better than the length of the diagnostic intervals, and the biological behaviour of the tumour would account for the discrepancies observed in the association between delay and tumour stage and survival.

1.5.4. Theoretical frameworks and the Aarhus statement

It is important to highlight that most studies on diagnostic delay in oral cancer do not use any theoretical framework or standardised definitions for data collection or reporting. In the literature, there is a general lack of consistency in the definition and measurement of key time points and intervals. The use of the term "cancer diagnostic delay" has been largely discouraged, given its use outside a conceptual framework, as it fosters heterogeneous criteria that hinder comparisons among studies and provides inconsistent results. It is more appropriate to describe "time intervals" along with the stages and landmarks from symptom recognition to diagnosis and initiation of treatment[341]. It is believed that reducing diagnostic delays may result in improved prognosis, as well as increasing the proportion of early stage cancers identified. Investigation in this field would greatly benefit and be facilitated by the use of a robust theoretical framework that would enable consistency in reporting, better comparison of data and the development of effective interventions[342, 343].

Several theoretical models have been developed in order to describe the events and processes that lead to symptomatic cancer diagnosis. The most relevant models are the framework developed by Olesen et al.[344] (Figure 1) and the "Model of Pathways to Treatment"[341] (Figure 2). The latter is a refinement of the prior "Andersen Model of Total Patient Delay"[298] (Figure 3), which is based on an earlier model proposed by Safer et al.[345].

A systematic review by Walter et al.[341] proved that "Andersen Model of Total Patient Delay" did not match the complex and dynamic pathways of the healthcare system pathways, neither did it provide a clear framework for research, as it lacked the specification of the time intervals measured, and there were differences in the way it was understood and applied, as well as variation in the wording used to ask patients about the time intervals. Several refinements were introduced to try and convey the

dynamic nature of symptom perception, interpretation and self-management, as not only perceptions and responses may change over time[287], but there can also be variations in the course to the final diagnosis. This consensual research model has been recommended for identifying targets for interventions aimed at early diagnosis with the ultimate goal to improve the prognosis of the disease[287, 341]. It can be applied to different types of cancer and across healthcare systems. It describes a series of events that define landmarks or milestones (detection of bodily changes, perception of the need to discuss symptoms with a healthcare professional, first consultation with a healthcare professional, diagnosis and start of treatment) which define four time intervals (appraisal, helps-seeking, diagnostic and pre-treatment).

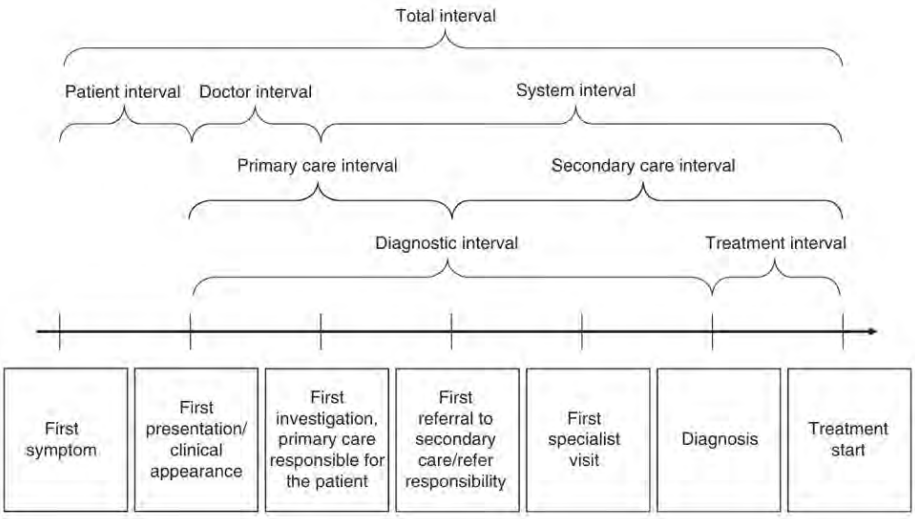

Figure 1- The categorisation of delay as proposed by Olesen et al. (2009). Reproduced with permission from the British Journal of Cancer © Cancer Research UK[344]

With the aim to simplify, standardise and monitor studies and interventions aimed at reducing the time to diagnosis and the start of treatment for patients with symptomatic cancer, an international

Consensus Working Group was formed in November 2009. The result was the "Aarhus statement", a series of recommendations for definitions and methodological approaches within the theoretical framework of the "Model of Pathways to Treatment", which identifies different key points and time intervals for oral cancer patients, along with their contributing factors (patients, healthcare provider/system, and disease factors)[271, 273, 274, 342] from the first symptom (detection of bodily change) to the start of treatment[274, 342]. This model provides guidance for researchers, a checklist for early cancer-diagnosis research and 15 different intervals to be reported in oncology studies[7] and up to 8 intervals for oral cancer[271, 273] (Figure 4), and simultaneously allows the identification of targets for intervention strategies for improving survival, as well as minimising biases. It also recommends the replacement of the term "delay" for "time-intervals" as the former term is considered inaccurate and unspecific[341]

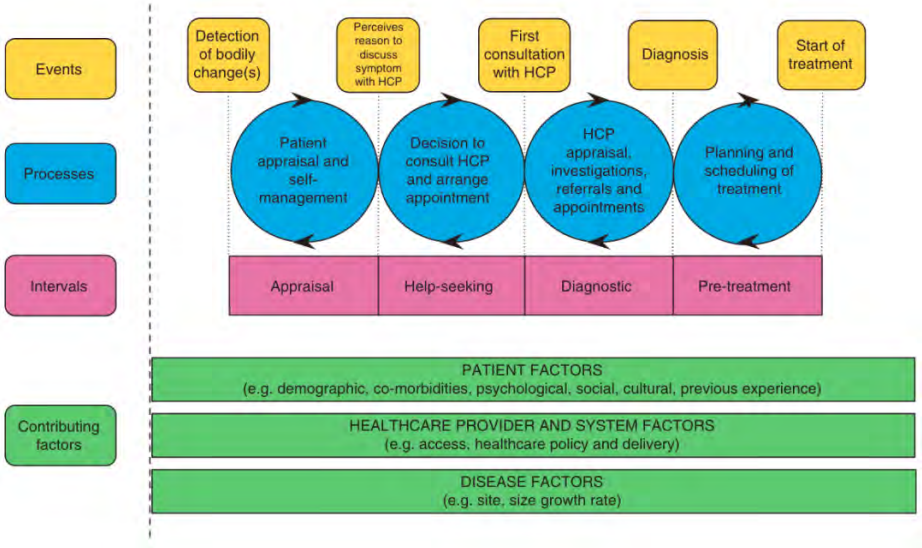

Figure 2- The categorisation of delay as proposed by Walter et al. (2012). Reproduced with permission from the Journal of Health Services Research and Policies © The Royal Society of Medicine Press Ltd[341]

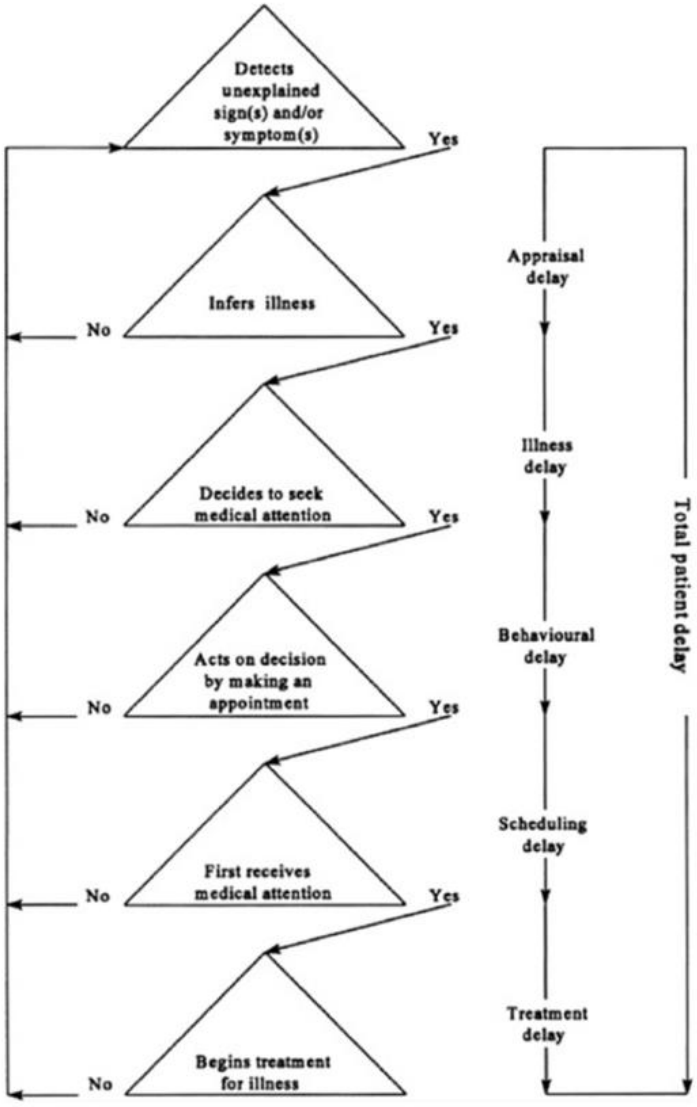

Figure 3- The General Model of Total Patient Delay as proposed by Andersen et al. (1995). Reproduced with permission from the British Journal of Social Psychology © The British psychological Society[298]

The "Aarhus statement", based on the "Model of Pathways to Treatment" establishes five events or key timepoints[274]:

- *Date of first symptom*: It should be defined as "the" time point when the first bodily changes and /or symptoms are noticed. Ideally it should include several components: the date of the first bodily change, the date when the first symptom is noticed, the date when the person perceives a reason to discuss the symptom with a healthcare professional and the date when the first "high-risk symptom" was noticed. It is also important to recognise that symptoms are medically defined and that those definitions may not necessarily align with the patients perception or may be inconsistent with lay-symptom definition.

The term "appraisal interval" and "help-seeking interval" should be used instead of "patient delay" to describe the "patient interval" as they are more descriptive both of the time taken to interpret bodily changes/symptoms and the period of time taken to act upon those interpretations and seek help.

- *Date of first presentation*: This would be the date of first consultation with a healthcare professional, which is usually in primary care. It should be considered as the time point at which it would be possible for the clinician seeing the patient to have started the investigation or referral for possible important pathology.

- *Date of referral:* This is the date in which there is a transfer of care from one health provider (usually primary care) to a specialist service (secondary care).

- *Date of diagnosis:* Taking into account the guidance provided by the European Network of Cancer Registries the most accurate definition of diagnosis is the date of first histological confirmation of the malignancy, which would ideally be the date the specimen/sample was obtained.

- *Date of start of treatment:* When treatment is initiated in the secondary care setting by the specialist team.

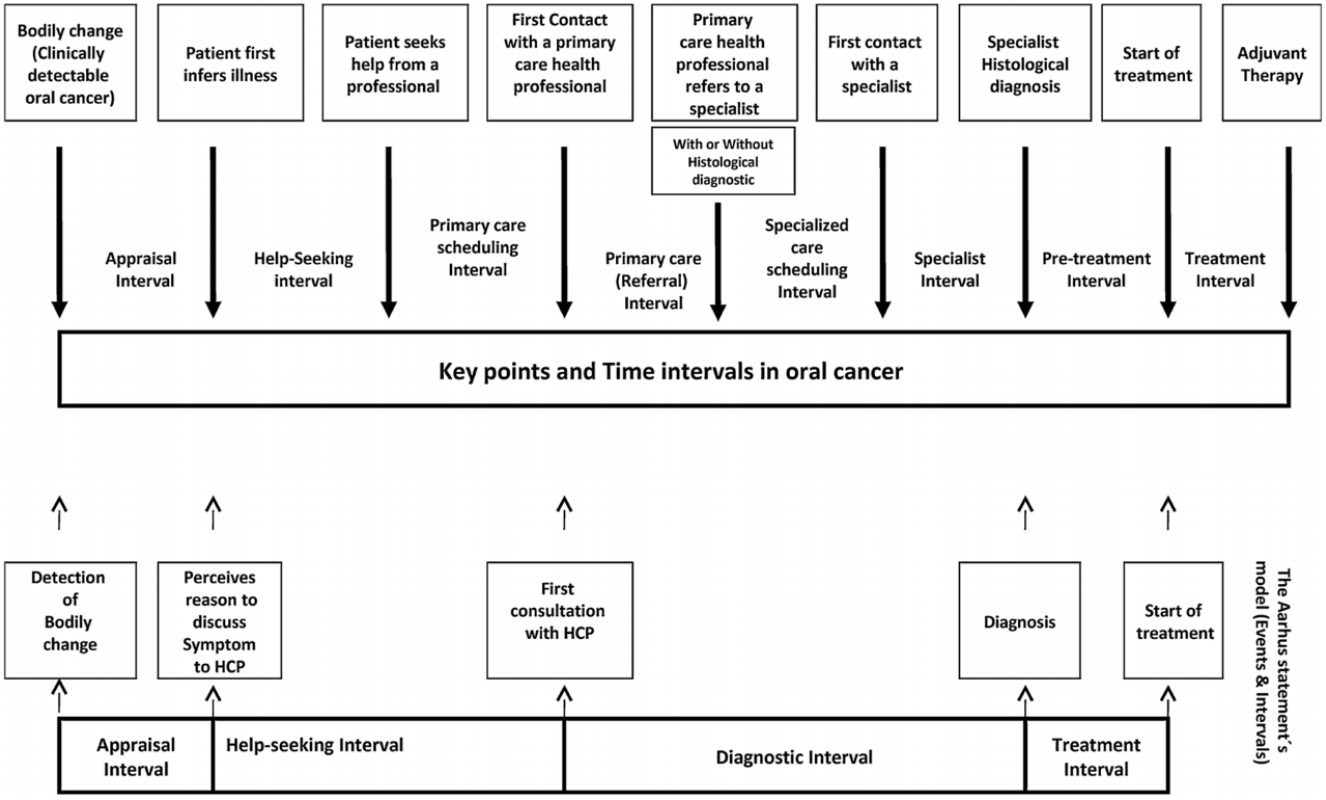

Figure 4- Key points and time intervals in oral cancer: relationship with the Aarhus Statement model as proposed by Varela-Centelles et al. (2017). Reproduced with permission from the International Journal of Oral and Maxillofacial Surgery © International Association of Oral and Maxillofacial Surgeons[273]

These landmarks in the timeline define four time intervals[274], and the total time interval would be the time elapsed from the first symptom to the beginning of the treatment (Figure 4) as summarised by Varela-Centelles et al.[273]:

- *Appraisal interval*: time from first bodily change to perceived reason to discuss symptom with a healthcare provider.
- *Help-seeking interval*: time from decision to consult a healthcare provider to first consultation with a healthcare provider.
- *Diagnostic interval*: the time elapsed from the first consultation with a healthcare provider to histological diagnosis. This interval can be further divided in a primary care/referral interval (from first consultation in primary care to referral to the specialist or secondary care), a specialized care scheduling interval and a specialist interval.
- *Pre-treatment interval*: interval from diagnosis to the start of treatment.

The patient interval is defined as the time between the patient´s first awareness of signs and/or symptoms and their first consultation with a healthcare provider and comprises both the appraisal and help-seeking intervals. It is reported to be the most significant contributor to the total time-interval, comprising 1.6 to 5.6 months approximately[237, 258, 272, 292].

The Aarhus statement approach and its definitions should be used by researchers in order to standardise and achieve uniform criteria when reporting on oral cancer, which will enable interventions directed at diminishing the time to treatment and improving the prognosis of the disease. One of the current limitations of these studies is that they tend to be retrospective and are inherently linked to a recall bias, and there is usually a selection bias too as most studies were performed in hospitals.

Objectives

2. OBJECTIVES

- The working hypothesis of this study is that diagnostic delay is linked to oral cancer survival, and that longer time intervals lead to worse patient outcomes and increased mortality.

- The general objective is to is to quantify "diagnostic and treatment delay" according to the time intervals proposed by the Aarhus statement, their influence in oral cancer survival and the associated factors. Studies on early diagnosis including patient survival as an outcome are scarce[261, 323, 340], and this was the focus of this study.

- As specific objectives we stablished:

  1. To quantify the specialist interval (STI) for oral cancer patients and its influence on survival.
  2. To quantify the hospital interval for patients with oral cancer and to evaluate its association with survival.
  3. To quantify the total time interval since the first bodily change (sign/ symptom) until the start of treatment in symptomatic oral cancer patients and to assess its impact on survival.

- These specific objectives are dealt with in the following scientific papers:
    - Objective 1: Shorter specialist time intervals are associated with advanced stage on symptomatic oral cancer. Oral Dis. 2018 Mar;24(1-2):112-114. doi: 10.1111/odi.12754.
    - Objective 2: Association between hospital interval and survival in patients with oral cancer: A waiting time paradox.PLoS One. 2019 Oct 25;14(10):e0224067. doi: 10.1371/journal.pone.0224067. eCollection 2019.
    - Objective 3: Overall time interval ("Total diagnostic delay") and mortality in symptomatic oral cancer: A U-shaped association. Oral Oncol. 2020 May;104:104626. doi: 10.1016/j.oraloncology.2020.104626.

Material and Methods

3. MATERIAL AND METHODS

The data relevant to this study was obtained from the records of patients diagnosed and treated with oral/oropharyngeal squamous cell carcinoma between 1998–2008 at the University Hospital A Coruña (Galicia, Spain). This is one of the two large Units of Oral and Maxillofacial Surgery of the Galician Health Service (SERGAS), which serves a population of 2, 701, 743 people through a free, universal, public scheme in North-Western Spain. The study was observational, with a retrospective and prospective component, as the patients were followed up until 2016. All statistical analyses were performed using the R software[346].

This investigation project was approved by the Galician Research Ethics Committee (CAEI) under the registration number 2014/097 (see Appendix), which officially grants patients' rights and the adequate ethics conditions during research and complies with the requirements of the Declaration of Helsinki.

For the three studies the general inclusion and exclusion criteria used for data acquisition were as follows:

a) Inclusion criteria:

- Symptomatic patients with histological diagnosis of OSCC.
- Locations: tongue, floor of mouth, gingiva, buccal mucosa, retromolar triangle, hard palate and oropharynx.

- Any TNM stage (the 7th edition of AJCC was used during data collection).
- Surgical treatment with curative intention +/- chemotherapy +/- radiotherapy.

b) Exclusion criteria:

- Other locations than those mentioned in the inclusion criteria.
- Recurrence of a prior OSCC.
- Surgical treatment with palliative intent.
- Salvage surgery indication.

The model of pathways to treatment of symptomatic cancer patients and the Aarhus Statement were used as the conceptual framework[271, 273, 274]. The presenting symptom was defined as the first symptom reported at presentation at a primary care setting by a patient later diagnosed with an oral squamous cell carcinoma[294].

The intervals considered in this study were the following (see Figure 5):

- Patient interval: time from symptom onset to first consultation with a healthcare professional.
- Primary care interval: time from first consultation to referral for further investigation.
- Pre-referral/prehospital interval: time elapsed from symptom onset to referral to secondary care.
- Secondary care interval: time from the first consultation in secondary care to treatment.
- Pre-treatment interval: time from diagnosis to the start of the treatment.
- Total/ overall time interval: time from first symptom to the beginning of treatment.

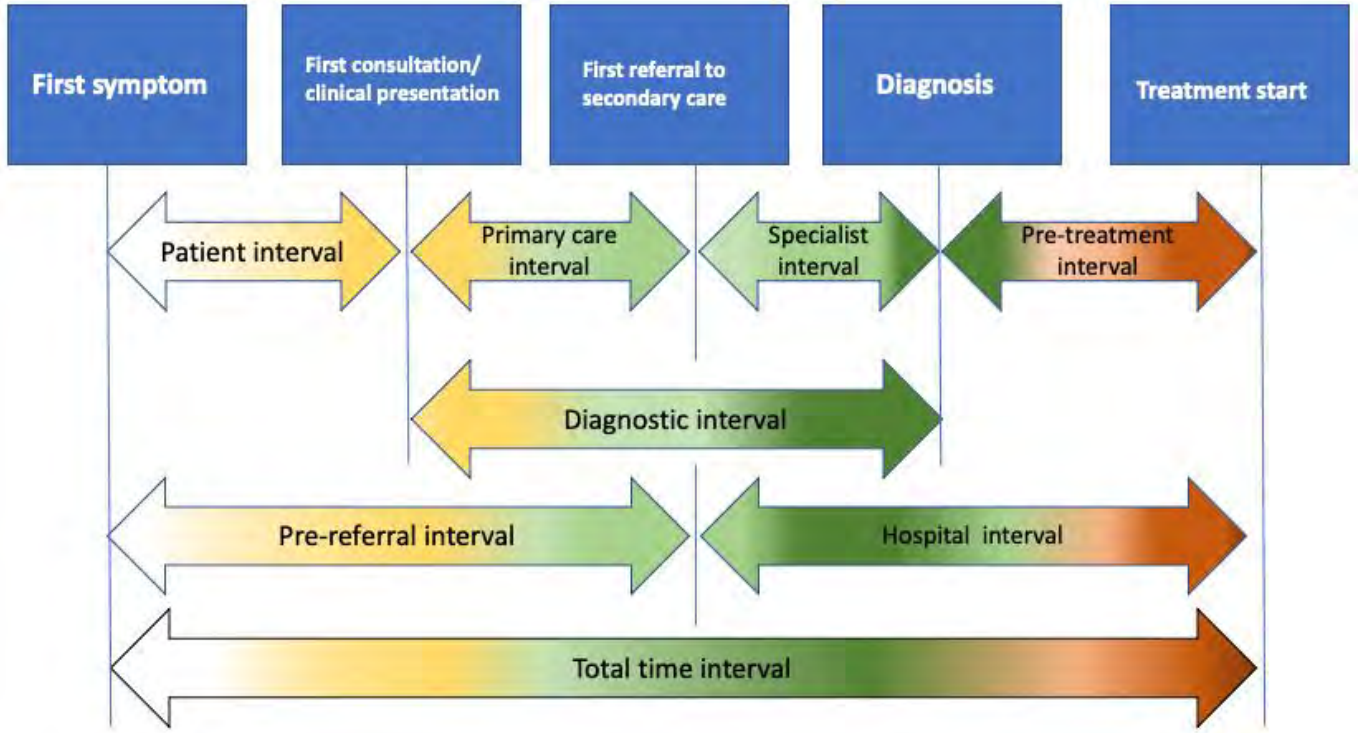

Figure 5- The model of pathways to treatment of symptomatic cancer patients: Aarhus statement. Based on Varela-Centelles et al. (2017). Reproduced with permission from the International Journal of Oral and Maxillofacial Surgery © International Association of Oral and Maxillofacial Surgeons[273]

The focus of this study were the specialist interval, the hospital interval and the total or "overall" time interval as defined by the Aarhus Statement framework (Figure 6).

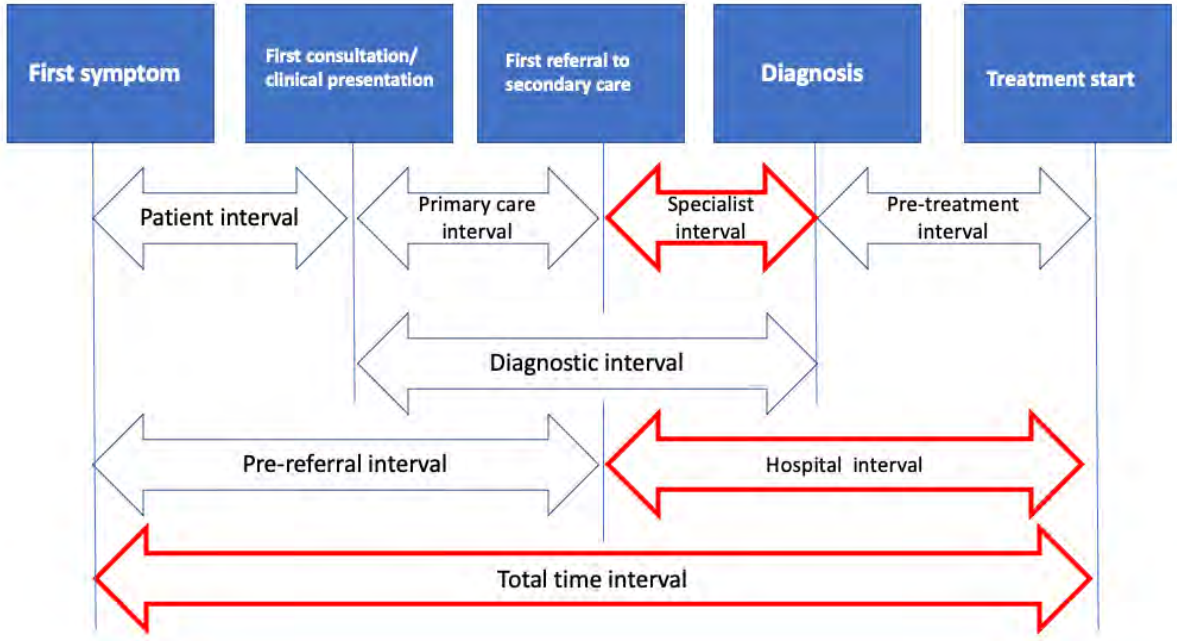

Figure 6- Time intervals (outlined in red) which were quantified and assessed during the present study. Based on Varela-Centelles et al. (2017). Reproduced with permission from the International Journal of Oral and Maxillofacial Surgery © International Association of Oral and Maxillofacial Surgeons[273]

3.1. ARTICLE 1- ANALYSIS OF THE SPECIALIST INTERVAL (STI), AND ITS IMPACT ON SURVIVAL.

The specialist interval (time from first contact with a medical specialist until definitive or histological diagnosis) has been rarely studied, and the factors influencing its length remain nuclear[247, 291]. Thus, the aim of this investigation was to quantify this time interval and to assess its related factors.

3.1.1. Statistical analysis

The time interval from first symptom to definitive diagnosis was calculated to determine the relative length of the specialist time interval (STI). To work out linear regression models, variables like age, gender, comorbidity, tumour site, macroscopic pattern and TNM stage were also recorded. The criterion for selecting the best model was based on the Akaike information criterion (AIC), so the model with the lowest AIC was considered the best, under the assumption that models with presence of multicollinearity are rejected.

3.2. ARTICLE 2- ANALYSIS OF THE HOSPITAL INTERVAL, AND ITS IMPACT ON SURVIVAL.

Our study divided the diagnostic/treatment pathway into two components:

1) the total prehospital or pre-referral interval[347] from the first symptom of oral cancer to when the patient consulted the hospital doctor (patient + primary care interval)

2) the secondary care interval (from the first consultation in secondary care to treatment)[8, 274, 342, 347].

Our study focused on the latter hospital interval in the Model of Pathways to Treatment[274, 342, 347]. Few studies (all outside of the proposed theoretical framework) have considered the hospital delay as a whole in the pathway to diagnosis[242, 277, 312] and the start of treatment[348] for patients with oral cancer. A clear association between the magnitude of this time period and tumour staging at the time of diagnosis has also not been established[242, 277, 312]. The present study is the first to evaluate the secondary care delay in the hospital setting for oral cancer and the association between hospital time and survival. Our study's objective was therefore to quantify the interval between the first contact with the specialist and the start of treatment for patients with oral cancer and to evaluate whether there was a link between this interval and disease survival.

3.2.1. Study design

Sample size estimation was based on the principal objective of the study, that was the relation between survival and the interval from the first specialist visit to the start of treatment. The sample size equation selected was based on test for equality for Cox s Proportional Hazards Model. Different sample size curves were estimated based on different values for hazard ratios (obtained from different publications with similar objectives) and with different values for overall probability of the occurrence of the event, death by oral cancer (based on regional oral cancer studies). A value of hazard ratio of 1.75 was considered as clinically relevant (in the need for a compromise between the theoretical required sample size and the regional data available). The selected levels for alpha and power (1-beta) were 0.05 and 0.80 respectively. The required sample size estimated range from 224 (when probability of event isas lower as 45%) to 125 (probability of event of 80%). The study interval was defined in the context of the "treatment path" model as the interval from the first specialist visit (start point) to the start of treatment (end point), also known as T14[7, 274, 342, 344].

3.2.2. Statistical analysis

We calculated the total interval (from first symptom to treatment: T5) to evaluate the relative length of the hospital interval (T14 /T5). Survival time was defined as the interval from the first treatment to death or censoring. The variables age, gender, comorbidity, tumour location, macroscopic pattern and tumour, node and metastasis (TNM) status were considered when estimating the linear regression models. To determine the presence of a relationship between the levels of the variables and patient survival, we adjusted a univariate proportional hazards Cox regression model, including all previously described variables. The model took the following form:

$$\lambda(t) = \lambda 0\ (t) \exp\ \{ßX\}$$

where X is one of the explanatory variables,

λ (t) represents the risk for a given time t and

λ0 (t) is the baseline risk.

We then incorporated all the non-temporal explanatory variables into a multiple regression model, which was adjusted with a stepwise regression based on the Akaike information criterion (AIC). We therefore selected the model with the lowest AIC as the best, under the assumption that models presenting multicollinearity are to be rejected. Flexible models were considered for the continuous covariates; however, all covariates behaved linearly and therefore only models with linear effects were considered. The univariate model whose explanatory variable is the TNM stage did not meet the hypothesis of risk proportionality. We therefore calculated the Kaplan-Meier estimator for the survival function and performed a log-rank test to determine any differences between the various stages.

We employed the mean and median as the central tendency statistics and the interquartile range and 90th centile as the spread indicators when describing the intervals (days). We also calculated the ratio between the mean and the secondary care interval and the total treatment interval (T14 /T5), assuming the conditions for using the test. To estimate the global survival curve, we employed the Kaplan-Meier method and calculated the estimators associated with the tumour stages (I-II vs. III-IV), applying the log-rank test to identify differences in survival. We then adjusted the multivariate Cox models. The time variable was discretised, as were the non-temporal explanatory variables. We employed the T14 terciles and considered the mean tercile (19–25 days) as the reference level in the adjusted models. All studies were performed using the R software (R Core Team, 2015), with the alpha value indicating significance at the 0.05 level.

3.3. ARTICLE 3- ANALYSIS OF THE TOTAL TIME INTERVAL SINCE THE FIRST BODILY CHANGE (SIGN/ SYMPTOM) UNTIL THE START OF TREATMENT, AND ITS IMPACT ON SURVIVAL.

3.3.1. Study design

The study interval was defined within the conceptual framework of the Model of Pathways to treatment (The Aarhus Statement)[271, 274], and included the overall time from first symptom (start point) to the beginning of treatment (end point) (T5). Survival time was defined as the interval from the first treatment to death or censoring. Sample size was determined according to the aim of the study, and its equation was based on the test for equality for Cox's proportional hazards model. Different sample size curves were estimated based upon different values for hazard ratio (obtained from different reports with

similar objectives) with different values for overall probability of the occurrence of the event: death by oral cancer (based on regional cancer studies). A value of hazard ratio of 1.75 was considered as clinically relevant. The selected levels for alpha and power (1-beta) were 0.05 and 0.80 respectively. The estimated sample size ranged between 224 and 125 depending on the probability of the event.

3.3.2. Inclusion/exclusion criteria

The inclusion criteria was symptomatic patients, whose physical changes or symptoms prompted them to seek care from a primary care health professional.

Patients with a previous history of potentially malignant oral disorders were excluded, as well as those diagnosed at different centres, recruited through screening interventions or experiencing a second primary tumour, multiple carcinomas, secondary metastatic cancer or recurrent neoplasms.

From the initial sample of 231 patients, 48 cases were excluded because of incomplete data regarding one or more time-milestones defining the study interval (overall time interval-T5). In order to rule out a potential selection bias linked to missing values; the nonparametric test of Jamshidian & Jalal was undertaken for the determination of fully random patterns of loss. In addition, the mean and standard deviation for continuous variables and the absolute and relative frequencies were also determined to assess differences between the fraction with missing values (missing) and the fraction without them (not missing).

3.3.3. Statistical analysis

We employed the mean and median as the central tendency statistics and the interquartile range as the spread indicators when

describing the intervals (days). To estimate the global survival curve, we employed the Kaplan-Meier method and calculated the estimators associated with the tumour stages (I-II vs. III-IV), applying the log-rank test to identify differences in survival. We then adjusted the multivariate Cox models. The time variable was discretised, as were the non-temporal explanatory variables. We employed the T5 quartiles, combining the two central ones (Q2 + Q3) (55.5–127.5 days) as the reference level in the adjusted models. The profiles of patients classified within a given time interval were assessed using the Baggin methodology (bootstrap aggregating) to generate prediction-classification models. The measurement for prediction capability was the prediction error (0: perfect prediction to 100% zero prediction).

Results

4. RESULTS

The results of this dissertation are collated in the following scientific papers:

4.1. 1ST ARTICLE

ANALYSIS OF THE SPECIALIST INTERVAL (STI), AND ITS IMPACT ON SURVIVAL

Seoane J, Otero-Rico A, López-Cedrún JL, Varela-Centelles P. Shorter specialist time intervals are associated with advanced stage on symptomatic oral cancer. Oral Dis. 2018 Mar;24(1-2):112-114. doi: 10.1111/odi.12754. PMID: 29480638.

Journal: Oral Diseases

Impact factor: 2.310

Quartile: Q1

Position:21/92

Link to the article:
https://onlinelibrary.wiley.com/doi/10.1111/odi.12754

4.2. 2ND ARTICLE

ANALYSIS OF THE HOSPITAL INTERVAL, AND ITS IMPACT ON SURVIVAL

Lopez-Cedrún JL, Otero-Rico A, Vázquez-Mahía I, Seoane J, García-Caballero L, Seoane-Romero JM, Varela-Centelles P. Association between hospital interval and survival in patients with oral cancer: A waiting time paradox. PLoS One. 2019 Oct 25;14(10):e0224067. doi: 10.1371/journal.pone.0224067. PMID: 31652279.

Journal: PLoS One

Impact factor: 2.740

Quartile: Q2

Position: 27/71

Link to the article:
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0224067

4.3. 3RD ARTICLE

ANALYSIS OF THE TOTAL TIME INTERVAL SINCE THE FIRST BODILY CHANGE (SIGN/ SYMPTOM) UNTIL THE START OF TREATMENT, AND ITS IMPACT ON SURVIVAL.

Lopez-Cedrún JL, Varela-Centelles P, Otero-Rico A, Vázquez-Mahía I, Seoane J, Castelo-Baz P, Seoane-Romero J. Overall time interval ("Total diagnostic delay") and mortality in symptomatic oral cancer: A U-shaped association. Oral Oncol. 2020 May;104:104626. doi: 10.1016/j.oraloncology.2020.104626. Epub 2020 Mar 5. PMID: 32146387.

Journal: Oral Oncology

Impact factor: 5.337

Quartile: Q1

Position: 7/92

Link to the article:
https://doi.org/10.1016/j.oraloncology.2020.104626

Discussion

5. DISCUSSION

The primary objective of this study to was to quantify "diagnostic delay" according to the time intervals proposed by the Aarhus statement, their influence in oral cancer survival and the associated factors. There is extensive knowledge of the intervals associated with patients and primary care[349, 350]. However, the secondary care intervals have been scarcely explored. Even though survival is a recommended outcome for research in early diagnosis in symptomatic cancer, reports considering survival as a dependent variable are scarce[138, 261, 323, 340, 351]. Moreover, these kind of studies have not considered a conceptual framework and have assessed intermediate intervals with a high heterogeneity: patient delay[138, 261], professional delay[138, 261], total delay[261], total diagnostic delay[138, 237, 240, 261, 271, 272, 274, 279, 284, 290, 321, 323, 340, 349, 351–354], referral delay[7, 138, 237, 240, 271, 272, 279, 284, 290, 321, 349, 352, 353], and more recently, the interval between diagnosis and treatment (DTI)[355–359].

Therefore, the focus of this study was to quantify three distinct time intervals (the specialist interval, the hospital/secondary care interval and the total/overall time interval) as defined by the Aarhus statement, and analyse their association with survival (Figure 6).

We conducted the study by following the model of pathways to treatment[274, 342], adopting the events and intervals generated in the adaptation of the Aarhus guidelines to symptomatic oral cancer[271, 273, 274]. However, a number of limitations need to be considered. This was a retrospective, hospital-based study, which could be subject to a

selection bias, making it difficult to generalise the results to the general population, but the influence of socioeconomic features is highly unlikely due to the characteristics of the Galician health system. In addition, this type of study has a lower tendency toward information biases (errors in the collected data). In this sense, the memory biases inherent to retrospective studies that could compromise the information recalled by the patients would also affect prospective studies on diagnostic delay. Taking into account that these studies gather information about time intervals in patients' pathways from the detection of a bodily change, fully prospective designs are virtually impossible. Potential recall biases could be prevented by double-checking the information provided by patients against details given by their relatives and the data recorded in primary care clinical charts[360]. On the other hand, and being the investigation focused on hospital times using clinical records, the chances for this bias are minimized. However, the fact that researchers involved in the design of the study had also undertaken data retrieval tasks may have resulted in a potential information bias, but the type of data used in our study and the retrospective nature of our investigation makes the existence of this particular systematic error highly improbable. The impossibility of randomized designs must also be highlighted because of obvious ethical reasons. The strengths of this investigation include the fact that the features of the sample are similar to the European average for oral cancers, which increases the external validity of the study; and the use of a conceptual framework (the theoretical model of Andersen and the Aarhus guidelines)[274, 341] and the procedures employed for controlling confounding factors in observational studies (regression modelling and stratified analyses), which confer internal validity to the study.

The main cause of longer time intervals from the first symptom to definitive histological diagnosis (patient interval + diagnostic

interval) of an oral cancer is reported to be the late presentation of the patient[237]. As such, the patient interval accounted for the longest period in the patients' pathway to treatment, although its causes are poorly understood. Some of these factors include denial behaviours, lack of knowledge/awareness, self-treatments and physical or economic barriers in the access to care[275, 349]. Conversely, according to our results, the relative contribution of the specialist time interval (STI) to the total time until diagnosis seems to be relatively small (6/64 days). Only one group has previously quantified this interval for oral cancer (7 days)[361], and the reported times for head and neck carcinomas seem to be slightly longer (18.8 days)[362]. The factors influencing this period are unclear, although patients being treated by the "wrong" specialty appear to experience "delays in cancer diagnosis" at secondary care[7]. In the particular case of head and neck cancer, an influence of variables like patient interval, comorbidity or tumour features on STI could not be proved[361]. Only patients with larger tumours (T3/ T4) have shown significantly less specialist delay than those with smaller ones (T1/T2), and our results show a significant association between shorter STI and advanced TNM stage and exclude hypothetical links between the STI and other variables related to the patient or to the tumour. The reasons behind the prioritisation of patients with advanced disease for pathological diagnosis remain unclear, although this phenomenon also occurs in surgical waiting times, where longer time intervals affect patients at early stages of the disease. In the latter situation, the explanation may be an attempt to start treatment as early as possible in order to prevent the tumour to become unresectable or to metastasize[265]. Bearing in mind that longer STIs are found in patients at early stages (TNM stages I-II) and also that long intervals since diagnosis to treatment increase the mortality risk, particularly for patients at early stages; the optimisation of hospital intervals for these patients is encouraged in order to begin their treatment as quickly as possible. Considering the

limitations of this study, it is concluded that STI is a short time interval in oral cancer diagnosis, imposing a limited time burden in the context of the whole interval until diagnosis. However, there seems to be room for improvement and a possible target for future interventions is to shorten STI, particularly for patients at early stages of their disease.

Our second observational study was aimed at assessing the hospital interval (specialist interval + pre-treatment interval) and included a large patient sample recruited consecutively with a high inclusion rate (96.5%), making the presence of selection biases unlikely. Eight patients were lost because of the impossibility to retrieve information related to some of the dates defining the interval being studied (hospital interval/T14). To avoid the presence of confounders (mixing of effects), we considered the exposure variable as the dependent time and adjusted the results of the association according to other prognostic factors (e.g., age, sex, comorbidity, etc.). However, a potential for a classification bias has to be assumed due to the poor discernment between stages II and III in terms of survival, and which is inherent to those editions of the AJCC/UICC TNM classifications which do not consider depth of invasion (DOI) nor extranodal extension (ENE). Tumour aggressiveness could also have been a confounding factor in the association between delay and survival[340]. Calculating the survival interval from the "start of treatment" instead of from "symptom onset" could generate a "lead-time bias" (errors in the survival measurement associated with the early detection of cancer)[245, 363]. However, this possibility is limited in studies of diagnostic delay in symptomatic oral cancer[363].

The results of this study permit a contextualization of the secondary care in the patients' path to treatment. Various systematic reviews have shown an inconsistent relationship (positive association, no association, and even inverse relationship) between diagnostic

delay and the risk of recurrence, stage at diagnosis and survival for oral cancer (7, 248). Reports have shown that head and neck cancer (as well as breast, colorectal, testicular cancer and melanoma) has a shorter time to diagnosis, which is associated with better outcomes[7]. A long interval until diagnosis seems to be a moderate risk factor for mortality in head and neck carcinoma[8]. A meta-analysis showed that the probability of presenting an advanced-stage tumour at diagnosis is significantly higher for patients with oral cancer with long intervals to diagnosis than for similar patients with no delay to diagnosis[9]. The total interval in our study resulted to be significantly lower than the average of this time-period calculated from the reports published in the last decade from Australia, India, and Iran[349]. The association between the diagnosis-to-treatment interval (DTI) and survival for oral cancer in the hospital setting has only recently been studied and has yielded conflicting results. Two population based cancer registry studies have shown poorer survival, with DTIs >20 and >30 days, respectively[355, 356]. However, other studies with similar sample sizes have not been able to demonstrate this association for the same time interval[357–359], with DTIs ranging from 22 days[359] to 38 days[357]. The hospital interval also presented wide variability in the literature (15 days to 45 days)[312, 348]. In our series, the mean hospital interval was 23.4 days, and patients with short hospital intervals had significantly higher mortality. This counterintuitive association is due to the waiting time paradox (confounding by indication), where seriously ill patients with aggressive tumours (the "sick-quick group") and higher associated mortality are prioritised to prevent the tumour from becoming unresectable or metastasising[265, 364, 365]. This phenomenon has also been reported in gliomas, cervical and endometrial cancer, breast cancer[282, 366] and colorectal cancer[352]. However, this confounding by severity cannot explain why the longer hospital intervals for oral cancer (>26 days) are significantly associated with

higher mortality, suggesting a positive association between long hospital intervals and poorer oral cancer survival rates.

The hospital interval is dependent on the characteristics of the clinical practice and the health system and can therefore vary between contexts[367]. Considering the severity bias in the prioritisation of patients with a poorer prognosis for the diagnosis and treatment of oral cancer and that studies have identified that patients undergoing surgical treatment in early stages (I-II) are most affected (in terms of survival) by treatment delay[265, 282, 352, 366, 367], strategies should be implemented to promptly treat early-stage patients and prevent stage progression. Given that long hospital intervals generate higher mortality, shortening this interval would increase survival for patients with this neoplasm.

Taking into account the results from our first study, which focused on the specialist interval, it can be deducted that the contribution to delay of the pre-treatment interval in the hospital interval is much more important in terms of days, and that efforts should be aimed at streamlining the start of treatment once the diagnosis has been ascertained. Strategies based on multidisciplinary first-day hospital consultations (oral and maxillofacial surgery; ear, nose and throat (ENT); radiotherapy; and medical oncology) have shown the ability to significantly reduce the duration of diagnostic procedures and the delay to the start of the first treatment[368]. Future studies on the early diagnosis of symptomatic oral cancer which focus on survival as an outcome and that follow the Aarhus criteria should control the confounding by indication present in this type of study, thereby establishing the true impact of the intervals to the start of treatment. Hospital delays represent a significant interval in the patient's path to treatment. These "delays" have prognostic implications and are susceptible to severity biases (waiting time paradox) that should be prevented.

The final part of the study is the only one that has assessed the impact of the total time-interval on mortality from oral cancer to date. Despite the fact that this is the first report on the association of survival with the overall time interval to treatment in patients with symptomatic oral cancer within the framework of the model of pathways to treatment, certain biases have to be assumed which are inherent to the retrospective nature of the current investigation. In an attempt to minimize a potential memory bias, hospital data were checked against primary care records. A hypothetical selection bias linked to missing values has been discarded due to the absence of differences between the "missing" and "not-missing" groups: gender ($p = 0.69$); comorbidity ($p = 0.19$); tumour site ($p = 0.32$); TNM stage ($p = 0.55$); recurrence ($p = 0.29$); exitus ($p = 0.38$), which prove a random loss of values. However, the presence of an unmeasured confounding cannot be rule ruled out, particularly the tumour aggressiveness, which may well behave as a potential confounding factor in studies on early cancer diagnosis. In this study, we avoided using dichotomous values for time intervals and fractioning the range of this exposition factor in terciles or quartiles, as recommended by previous reports[352].

Research on this issue has traditionally considered total delays until histological diagnosis, blaming both patients and clinicians. The delay attributed to the patient (patient interval), as previously discussed, is due to lack of knowledge, poor symptom interpretation, cultural/religious beliefs, and self-treatment[237, 284], whereas the delay attributed to clinicians (professional/provider delay) has been put down to the existence of barriers to access primary healthcare, lack of oral cancer awareness, and misdiagnosis[237, 240, 272, 284]. A more recent perspective includes the analysis of the whole time until treatment (overall time interval), which has been found to average 187 days for oral cancer[349]. The length of this interval shows wide variations

according to the times and regions studied: 157 days in Iran[279], 195 days in Australia[321], 206 days in the USA[290], and 210 in India[353]. This interval resulted to be slightly shorter in the current investigation (107 days). These wide variations may be due to the fact that the contributing factors in "pathway to treatment" are dependent from the actual neoplasia, as well as from demographical, psychological, and sociocultural aspects of the patient[274]. Agents such as healthcare providers, factors of the healthcare system (accessibility and health policies) also behave as conditioning factors of this time interval[274].

Time increments until diagnosis and treatment of different cancers (breast, colorectal, testicular and melanoma) seem to be associated to poorer outcomes[7]. Although this finding has been described also for head and neck carcinomas[8], this phenomenon was not observed for oral cancer in the current research. In this line of research, reports focused on partial intervals in the oral cancer patient's path to treatment have shown equivocal results[138, 261, 323, 323, 340, 354–359]. Perhaps this lack of consistency could have been due to methodological weaknesses mostly related to the absence of a theoretical framework, with different definitions of key-points in the intervals, the use of time intervals in dichotomous terms ("delays"), and differences in the control for confounders.

The authors found a U-shaped association, where patients with short time-intervals (24–55.5 days) and with long time-intervals (127.5–420 days) had a higher mortality than those with medium time-intervals. Different neoplasms (lung, colorectal, breast, and ovarian) have shown a paradoxical behaviour where shorter intervals are linked to higher mortality. Higher mortality rates in patients with shorter time-intervals could be explained by confounding by severity and tumour aggressiveness This circumstance has been explained by an indication confounder (waiting time paradox) where professionals prioritize severely ill patients for diagnosis[364]. This confounder by

severity has also been identified for oral cancer, with shorter specialist intervals associated to advanced-stage symptomatic cancer[365], and in short hospital intervals associated to higher mortality than medium hospital intervals[369]. However, and bearing in mind that the interval from the detection of a bodily change to the first consultation to a healthcare professional (patient interval) represents the longest time interval to treatment[349], this bias cannot explain on its own the U-shaped association disclosed by our study, which implies higher mortality for both the shortest and the longest time-intervals. This U-shaped association may well be explained by another unmeasured confounding: tumour growth velocity (tumour aggressiveness). Thus, patients with fast-growing tumours, implying more symptoms and rapid progression, would demand professional care faster than those with slower growing ones. This hypothesis would be supported by the finding that patients in our study with shorter overall intervals have, as their most important predictive variable, less time to recurrence, which correlates with tumour progression rate[370]. The existence of tumour heterogeneity in head and neck carcinomas, with different kinetic patterns[370], can also explain this phenomenon together with the importance of the tumour proliferative activity for patient survival with different lengths of diagnostic intervals of oral carcinomas[340, 370]. In addition, different carcinomas in different locations have also shown a non-monotonic behaviour, similar to U-shaped, where the association between time intervals and survival does not increase or decrease in a constant way[352, 371]. Despite the limited evidence on waiting time outcomes in oral cancer, the current investigation shows for the first time an association between the longest time intervals with mortality stronger than for middle-length intervals. This finding suggests the importance of shortening the overall time interval by increasing patient awareness about slower-growing tumours with "less intense" symptomatology[372]. Our findings also seem to point at a need for optimizing the primary care, referral, and hospital intervals to

avoid bias by severity[240, 373]. The current research also describes a broad overall time interval, with wide margins for improvement.

Although it had been previously reported that a longer pre-referral interval (patient interval + primary care interval) has been associated with more advanced stage at diagnosis (2- fold risk) as well as constituting a significant risk factor for mortality from oral cancer[271], the findings differed when the secondary care environment was analysed. We not only found that shorter specialist intervals are associated to advanced-stage symptomatic cancer[365], but also that shorter hospital intervals are associated to higher mortality than medium hospital intervals[369]. We found that there is a non-monotonic association between the total time interval and mortality. The highest mortality rates are linked to the shortest and longest overall time intervals[374]. The higher mortality rates in patients with shorter time-intervals could be explained by confounding by severity and tumour aggressiveness. This circumstance has been explained by an indication confounder (waiting time paradox) where professionals prioritize severely ill patients for diagnosis. From a methodological perspective, and apart from recommending the use of a conceptual framework and observance of the Aarhus guidelines, this investigation highlights the need for undertaking stratified analyses of the time interval in combination with the use of makers of biological activity of the tumour (HPV-status, Ki-67, or mitotic index). If these analyses are not taken into account, the heterogeneity of this confounder in oral cancer would lead towards a null hypothesis (negative bias), masking the association of these variables. Research designs considering homogeneous groups of patients could also increase the internal validity of this kind of studies. In addition, and in order to diminish the overall time interval, efforts focused on the contributing factors in the patient's pathway to treatment should be implemented, as well as interventions aimed at increasing both the awareness among the

general population and the diagnostic capabilities among primary care clinicians while dismissing hospital pre-treatment times. There is an emerging body of evidence supporting the impact of prolonged pre-treatment and treatment intervals with poorer survival and worse oncologic and/or functional outcomes from HNC which needs to be further clarified by high-quality synthesis of studies[375].

It is clear that the size (T) of the primary tumour affects both the choice and outcome of treatment[102], and that earlier stages are associated with better prognosis[8] , survival and quality of life. Tumour size is an important factor in determining the surgeon's ability to resect and obtain tumour-free margins, as well as in deciding the necessary radiotherapeutic dose. Large size at presentation is associated with an increased risk of local recurrence, increased cervical lymph node metastasis, more extensive therapy/toxicity and poor survival[376]. Even in a context of resectability, it is intuitive to assume that bigger tumour size encompasses a larger resection and hence a higher potential of complications, side effects and potentially worse outcome due to tumour extension and the difficulty to achieve free margins in a complex anatomical area such as the head and neck. Hence, it is also intuitive to deduct that treating oral cancer at an early stage (when lesions are small and localized) is believed to be the most effective intervention to reduce death, morbidity and disfigurement from this disease[377].

Strategies for diagnosing oral cancer at an early stage could include population screening of high-risk groups[378, 379] and opportunistic screening by healthcare providers[379]. This would result in a reduction of the time intervals in diagnosis and treatment of oral cancer because a screening test is not intended to be diagnostic, but aims to accelerate the referral and application of more specific diagnostic procedures by a specialist. Because five-year survival is directly related to stage at diagnosis, prevention and early detection

efforts have the potential not only for decreasing the incidence, morbidity and mortality; but also for improving the survival of those who develop this disease. Thus, screening programs could be beneficial, particularly when oral cancer is preceded by a premalignant lesion which is accessible on visible inspection[380]. Although both the UK National Screening Committee[381] and the US Preventive Services Task Force have concluded that the available evidence was insufficient to assess the balance of benefits and harms of screening for oral cancer in asymptomatic adults[382], counterarguments[383] have been proposed as the screening of asymptomatic individuals by systematic visual oral examination is a feasible objective. Moreover, there is the possibility of reducing costs and increasing efficiency through the application of telemedicine. Mobile phone applications have been developed and piloted for oral cancer screening in India[384], in Corboda (Argentina), and more recently in Malaysia[385]. These applications allow transmission of oral images deemed as high risk[386] to a "remote" specialist, and could be very useful for application in secluded areas[380, 387, 388].

One of the more striking reasons given by patients in a 2010 study for delay in the event of new lesions that were eventually diagnosed as cancer, was the administration of self-treatment provided by a pharmacy. In addition to purchasing off-the shelf items, 50% of patients who had resorted to self-treatment had done so with the counsel of a pharmacist[389]. This situation showcases the generalised low awareness and knowledge of risk factors amongst the general population[390, 391]. Educational awareness campaigns[273, 392] aimed not only at the general public, but also at primary care health providers are of paramount importance in order to enable early detection. However, there are few investigations on the impact of awareness campaigns on cancer outcomes[392], and some studies have found limited evidence regarding the effectiveness of educational interventions to promote

early presentation[372]. The available evidence shows just a modest short-term increase of oral cancer knowledge at the individual level with the use of written information, such as leaflets[393–396]. On the other hand, short-term mass campaigns aimed at the general public have shown inconsistent results[315, 397–399].

Education and awareness of oral cancer is also important for clinicians, including dentists and physicians[400], who may not be knowledgeable about the risk factors, diagnosis, and early detection of these cancers and/or are not performing routine oral cancer examinations[320, 328, 401–406]. Oral cancer is particular in the sense that it is the only neoplasm which can be referred for specialized care by both dentists and primary care physicians, and both healthcare professionals refer patients in similar proportions[321, 323, 407]. Varela-Centelles et al.[360] found significant differences in the primary care interval and the prereferral interval depending on the referral pattern: patients referred by GDPs had shorter prereferral intervals. In addition, most dentists referred directly to hospital oral and maxillofacial surgery, ensuring a more efficient pathway through the healthcare system with shorter time intervals, but there was no evidence that GPs performed less well than dentists[240]. Varela-Centelles et al.[408] also found in a recent community-based study in Galicia, that patients with a persistent oral ulceration -the most frequent presenting symptom - preferred to consult a GP. Other UK-based studies have found that thirty-eight percent of electronic two-week wait referrals from GDPs were deemed inappropriate and that ongoing education is required to minimise these inappropriate referrals, as the poor rate of guideline adherence from GDPs could be related to the pressure to refer defensively or to a lack of knowledge of referral guidelines or oral pathology[409].

The introduction of a fast-track policy for urgent referrals for suspected cancer in the UK (NICE guidelines for primary care) in

2005 has shown some effectiveness in reducing the diagnostic interval from several cancers since its implementation, including HNC, with a mean reduction of 21 days[334]. In a similar fashion, a national fast track program policy was introduced in Denmark in 2007, and there has been a significant reduction in delay of diagnosis and treatment of head and neck cancer[410]. The results provided showed a significant reduction in pre-treatment waiting time for HNC patients of 41% from 2002 to 2010[411]. When comparing these results to healthcare systems from other countries, like Canada, where there was no implementation of a fast-track referral system, the wait times for head and neck cancer treatment from the time of initial consultation with an oncologist have increased from 1995 to 2005[412]. These results clearly indicate that the implementation of a fast-track policy is essential to decrease waiting times in cancer[413], and in particular in head and neck cancer. The study by Toustrup et al. showed that it is possible to reduce waiting times in head and neck cancer through logistic changes to almost half. After the implementation of change, the reported overall time from first suspicion of cancer until treatment start was reduced from 57 calendar days to 29 calendar days[414].

There is also evidence that two-week referral conversion rates are falling in the UK, while detection rates are rising because of an increased number of referrals. This would point towards a misuse of the two-week referral pathway, with the potential of these increasing inappropriate numbers to eventually overwhelm the system[415]. A falling conversion rate with an increasing detection rate reflects an increasing number of two-week referrals, and the increasing detection suggests that approximately two thirds of UK head and neck cancers were diagnosed via other routes[416, 417]. In short, it seems that over the years more head and neck patients are being referred, but proportionally less are actually being diagnosed with cancer[418]. The yield of the cancer conversion rate could be improved by focusing on

more targeted guidelines[418, 419] and ensuring sufficient resources in secondary care[415] to enable timely assessment of patients referred via the two-week referral pathway.

In the context of the UK and the NHS, improvements in utilizing the fast-track system need to be made in order to bring about an improvement in early diagnosis of head and neck cancer. As things stand, it may actually be detrimental for most cancer patients, as the time from referral to initial consultation using standard referral letters was generally much longer than the recommended period of 2 weeks[281, 416]. This may require a revision of the referral guidelines on oral cancer symptoms developed by NICE[420].

A combined approach, which tackles both physician awareness and the need to update and adapt the guidelines[421] could prove to be the optimal solution to the conundrum on how to optimise and improve the two-week wait referral for head and neck cancer within the NHS. Tikka et al.[422] proposed a significantly refined version of the referral guidelines which demonstrated greater diagnostic efficacy than the current NICE guidelines. Guidelines should not be static, and further iterative refinements of referral criteria should be considered in the pathway of patients with suspected HNC.

From the governance standpoint, reduced waiting times would have an effect on cost-effectiveness in the healthcare system. It is important to consider that oropharyngeal tumours in stages I-II are generally given single-modality treatment, but stages III-IV require multimodal treatment. Also, patients in stages III-IV are more likely to relapse and require palliative care. For both of these reasons, reducing delay in referral by increasing patient and GP awareness of this disease should reduce health costs, as well as saving patients' lives and improving survival as well as functional outcome.

A study by Simons et al. demonstrates that the redesign of a care process resulted in significantly better long-term patient outcomes and cost savings for particular patient groups. In particular, for oral cancer, the 95% confidence interval for incremental costs showed a cost reduction ranging from €187 to €1437 per patient treated for an oral cavity tumour, and a reduction in the waiting time of 5 days for patients treated for oropharynx and hypopharynx tumours after achieving a "lean process" redesign[423]. Other studies however have not found a difference in costs, but have demonstrated that optimising the diagnostic track and quality of care results in better oncological outcomes, improved overall survival and increased patient satisfaction[424].

In order optimise the cancer journey of each individual patient, multidisciplinary teams are a fundamental cornerstone of the process as well as a streamlined referral process, working in parallel with a well-coordinated local team[425]. Audits on the processes involved should be carried out regularly in order to detect potential system failings and areas where there is room for improvement.

The optimal performance of a referral system is also important from the legal perspective, as delay in diagnosis is one of the most common reasons for litigation in HNSCC[426]. Litigation in patients with cancer of the oral cavity is relatively rare. Those who pursue litigation against their physicians are frequently younger than their counterparts who do not sue, and often have poor oncological outcomes. The most common allegations that led to suits were failure to diagnose, failure to perform biopsy, failure to refer[290], and surgical complications[426]. If we look closely at those failures they seem eerily familiar and almost mirror the keypoints in the timeline as proposed by the Aarhus statement. Guidelines must attempt to prevent delays in diagnosis by all means possible, as it is clear that an earlier diagnosis would allow for lesser surgery or, possibly, eliminate the need for

adjuvant chemotherapy or radiotherapy[246], and in turn lead to greater patient satisfaction. The medicolegal implications of a delayed or missed diagnosis of oral malignant disease can be severe. Cases alleging failure to diagnose cancer and failure to refer patients for an additional opinion and treatment, are likely to be cases with large damage claims owing to the cost of the medical care, pain and suffering, potential permanent disfigurement, lost wages or income claims and loss of spousal companionship, which all are attributed to the injury[427]. It is interesting to note that allegations more commonly involved the initial workup of what would ultimately be found to be oral cavity cancer, rather than iatrogenic complications incurred during treatment of the cancer following appropriate diagnosis[428]. In this sense, the theoretical framework proposed by the Aarhus statement could also be considered a safety-netting mechanism for patients, as it can help ensure the correct timing of each step of the cancer pathway, and allows the detection of system failings or areas that require improvement within the process, by potentially highlighting significant differences in the duration of the time intervals when comparing different health providers.

The model of pathways to treatment and the Aarhus statement could also constitute a fail-safe mechanism to ensure equal access to healthcare and to highlight existing inequalities in certain populations. This potential application could be of special importance in the context of universal and government-funded healthcare systems such as the NHS (National Health Service) in the UK and the SNS (Sistema Nacional de Salud) in Spain.

There are several studies hailing from the United States that highlight that a prolonged pre-treatment interval in head and neck cancer was associated with African-American race, Hispanic ethnicity, lack of insurance or Medicaid coverage, lower education levels and distance of primary residence from treatment facility[429, 430]; all of

which reflect the barriers and difficulties of social determinants of health in the initial access to healthcare, and that are inherent to the organization of the healthcare system in that country.

Shiboski et al.[431] found racial disparity with detriment of the African-American communities with respect to stage at diagnosis and relative survival among cases with oral cavity cancer, associating the poorer relative survival among African–Americans with oral cavity cancer with delayed diagnosis, as they were diagnosed at more advanced stages and had larger tumours at the time of diagnosis than their American counterparts. Socioeconomic factors such as poverty, inadequate education, and lack of healthcare insurance coverage seemed to better explain racial disparities than biological differences, and some studies have focused on the inequalities in the access to healthcare[432–435].

Recent studies within the UK healthcare system, which is public and government funded have found ethnic inequalities in the diagnostic interval of several cancers[436]. It is interesting to note that this study does use the Aarhus conceptual framework for their definition of diagnostic interval. It is precisely the use of the conceptual framework in cancer diagnostic delay that enables the comparison between different population groups, as the timepoints that define the intervals are standardised by the Aarhus framework. The study found site-specific ethnic differences in the diagnostic interval that should concern policymakers and primary care providers, as the deleterious effect of cancer diagnostic delay has now been estimated, with a worse 10-year survival rate of up to 5% for a two-month delay, depending on age. Another research group[437] focused in the different survival outcomes of head and neck cancer in a cohort of 21966 patients from different ethnic minority groups. The findings of this study indicate that Black individuals fare worse in terms of head and neck cancer specific mortality and stage at presentation, compared

with individuals of other racial and ethnic minority groups, and this could be related to unexplored factors associated with social determinants of health.

The standardization of time intervals through the use of the theoretical framework and the Aarhus statement could also ensure a more equal access to healthcare, by allowing to highlight inequalities in access to the system in certain populations, and facilitating targeted actions such as screening in high risk groups, in order to improve outcomes and patient care for all the population.

The impact of the COVID-19 pandemic on cancer outcomes and excess mortality is yet to be determined. In what refers to diagnostic delay, the pandemic generated an undesired experimental bubble, during which increased timeframes were forced upon patients and physicians alike[438]. Several short communications have reported fewer oral cancer diagnoses during the pandemic, as well as a lack of control of potentially malignant oral disorders and an increase in the proportion of cancers diagnosed at advanced stages, accompanied by longer therapeutic delays compared to the same period of the previous year[439].

During the pandemic, delaying surgical treatments and favouring non-surgical approaches was a common occurrence, and emergency guidelines were proposed[440, 441]. In general, these guidelines tended to favour not to postpone or interrupt HNSCC treatment in SARS-CoV-2 negative patients unless there were significant clinical reasons to prevent the patient from being treated. The patient interval as defined by the Aarhus statement was influenced by negative emotions due to the ongoing situation (fear, anxiety, distress, uncertainty) and their toll on mental health[442], disruptions in treatment, inadequate infrastructures and personnel, as well as by the unavoidable lockdowns, which acted almost like physical barriers to healthcare access[443].

The pandemic itself created an enormous burden on the healthcare system not only due to the number of cases, but also due to the consumption of resources in acute care and the exhaustion of the healthcare workers, as well as on the mental health of patients[444]. The aftermath also led to a backlog of patients with symptoms that needed assessment, creating further stress on an already overloaded health system.

Many of the strategies used to manage cancer care during the pandemic, such as remote consultations, are not new[445], and the remote assessment of patients during the pandemic either via telephone consultations or telemedicine became in many cases the norm[446, 447]. The use of teleconsultation, used in conjunction with risk stratification, has the potential to provide a viable and effective adjunct in the initial assessment and management of new suspected head and neck cancer patients[448]. Although it should be considered as part of the inherent re-shaping of clinical service delivery following the ongoing pandemic[447, 449]; in the short term, it will not be an alternative to a thorough clinical examination with the current technology, due to the complexity of the anatomy of the oral cavity, that makes it difficult to obtain pictures, and requires retraction for correct visualization[450].

The real impact of the pandemic in terms of mortality is still unknown. Excess mortality is an important measure of the scale of the COVID-19 pandemic. It includes both deaths caused directly by the pandemic, and deaths caused by the unintended consequences of containment such as delays to accessing care or postponements of healthcare provision in the population. A few studies have anticipated an excess of mortality linked to a COVID-19 associated disruption of the cancer [451, 452], but these projections are made from data collected before the pandemic and such perturbations in cancer care may contribute, over a 1-year time horizon, to substantial excess mortality

among people with cancer and multimorbidity[453]. Diagnostic delay in head and neck cancer increased mortality and favoured diagnosis at advanced stages, whilst treatment delay negatively impacted survival rates[454]. The former has been confirmed by a tree-fold increase in the number of advanced head and neck cancers observed during April-May 2020 compared to the same period of 2019[455].

In the near future, early diagnosis could be aided by computer assisted diagnosis. The use of predictive models developed through machine learning could help predict the progression of intraoral lesions to malignancy[456–460], and assist the clinician during the screening process[461].These models still require further development as they are not yet streamlined enough for clinical application. As the capabilities of machine learning further develop they could even aid the clinician in making informed therapeutic decisions and tailoring treatments appropiately, as they may identify characteristics that would indicate if a particular patient would benefit from adjuvant therapy[462, 463].

Some research groups[464] have tried to predict malignant transformation in oral epithelial dysplasia using infrared absorbance spectra. The premise is that OSCC is often preceded by a spectrum of clinical changes, collectively termed potentially pre-malignant oral dysplasia (leukoplakia, erythroplakia and leukoerythroplakia) which are graded graded as mild, moderate or severe based on various architectural and cytological changes. On the other hand, Fourier transform infrared micro-spectroscopy (FTIR-MS) utilizes infrared light over a broad spectral range to assess the overall chemical profile of a sample. Molecules which vibrate at frequencies corresponding to the wavelengths applied will absorb the radiation at those wavelengths, resulting in an absorption spectrum characteristic of the chemical characteristics that are present. This technology has been used in biomedical research, with a particular focus on its application

to the investigation of cancerous tissues, and it could be useful in the identification of lesions that could progress to OSCC[465]. In the future, FTIR-MS could be applied in a timely and cost-effective manner to multiple small samples obtained from the same field in order to ensure correct assessment of the potential malignant change of the lesion.

From the clinician standpoint, we are interested in providing the best available care to our patients in order to ensure the most favourable outcomes. In order to continuously improve patient care and ensure early diagnosis and treatment of OSCC, not only do we need to encourage research in basic science with the aim of developing predictive models, machine learning and technologies that can ascertain the likelihood of malignant progression of apparently innocent lesions; we must also consider what we can improve from the clinical standpoint. The establishment of fast-tracks referral systems has been useful in diminishing the time between referral and the beginning of cancer treatment. Refining and updating referral guidelines is also necessary to clarify the roles of GDPs and GPs in the patient referral pathway, as is the implementation of new interventions aimed at reducing the prereferral interval of patients with oral cancer. We should work on increasing the patient´s awareness of oral cancer and provide ongoing education for primary care clinicians on this topic. We could consider the implementation of oral screening programs that could even take place at the same time as a yearly or six-monthly scheduled dental check-up. Equal access to healthcare for all the different sectors of the population should be ensured, and certain interventions should be aimed at those groups who may be high-risk due to their sociodemographic characteristics. It is clear that some of these interventions have to be implemented in the wider framework of the healthcare system. However, other interventions can be implemented by clinicians in their daily practice, equally contributing to change and improvement in patient care.

Without looking any further, a seemingly small action, such as the effortless adoption of the theoretical framework proposed by the Aarhus statement at the time of clinical documentation, could induce change. This framework, which provides clear and well-defined criteria for key events in the patient´s pathway, will enable us to assess the outcome of our interventions, and compare future and past results with more accuracy than we ever have up to now.

Conclusions

6. CONCLUSIONS

1. Specialist time interval is a short time interval in oral cancer diagnosis, imposing a limited time burden in the context of the whole interval until diagnosis. This interval is fundamentally conditioned by tumoral extension, however other patient or tumour characteristics do not seem to be associated with the length of this interval. There seems to be room for improvement and a possible target for future interventions would be to shorten specialist time interval particularly for patients at early stages after their disease has been disclosed.

2. The hospital interval is relevant in the pathway to treatment of the patient with oral cancer, representing a quarter of the total length of the overall interval. Even though tumoral extension is frequently associated with an increased mortality, our results show a counterintuitive association where patients with short hospital intervals had significantly higher mortality, due to the waiting time paradox. The presence of this important clinical bias, confounding by indication, could condition survival of patients diagnosed at early stages, as they constitute the most sensitive population in regards to delays in the treatment of oral cancer.

3. The median of the overall interval is greater than 2.5 months. This interval and the mortality attributed to oral cancer showed a U-shaped association, where patients with short overall intervals

-patients with shorter recurrence times and presence of vascular infiltration- and those with long overall intervals had higher mortality than those with medium overall intervals. The highest mortality rates are linked to the shortest and longest time intervals and this non-monotonic association between time interval and mortality may induce an underestimation of the association when time intervals are considered dichotomously. In order to diminish the overall time interval, efforts focused on the contributing factors in the patient's pathway to treatment should be implemented, as well as interventions aimed at increasing both the awareness among the general population and the diagnostic capabilities among primary care clinicians while decreasing hospital pre-treatment times simultaneously.

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Appendix

8. APPENDIX

8.1. ABBREVIATIONS

ACE 27	Adult Comorbidity Evaluation 27
AIC	Akaike Information Criterion
AJCC	American Joint Committee on Cancer
CAEI	Comité Autnómico de Ética en la Investigación
CHUAC	Complejo Hospitalario Universitario A Coruña
CCI	Charlson Comorbidity Index
GLOBOCAN	Global Cancer Observatory
CWG	Consensus Work Group
DOI	Depth of Invasion
DSS	Disease-Specific Survival
EGFR	Epidermal Growth Factor
ENE	Extranodal Extension
HNC	Head and Neck Cancer

HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human Papilloma Virus
IARC	International Agency for the Research on Cancer
NCCN	National Comprehensive Cancer Network
OPMD	Oral Potentially Malignant Disorders
OS	Overall survival
OSCC	Oral Squamous Cell Carcinoma
SERGAS	Servicio Galego de Saúde
STI	Specialist Time Interval
UICC	Union for International Cancer Control

8.2. CAEI AUTHORIZATION

XUNTA DE GALICIA
CONSELLERÍA DE SANIDADE
Secretaría Xeral

Comité Autonómico de Ética de la Investigación de Galicia
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DICTAMEN DEL COMITÉ AUTONÓMICO DE ÉTICA DE LA INVESTIGACIÓN DE GALICIA

Paula M. López Vázquez, Secretaria del Comité Autonómico de Ética de la Investigación de Galicia

CERTIFICA:

Que este Comité evaluó en su reunión del día 27/03/2014 el estudio:

Título: Factores pronósticos e influenciade la demora diagnóstica en la recidiva y la supervivencia en carcinoma epidermoide oral
Promotor: Ana Otero Rico
Código del Promotor: PDSR-SCC
Código de Registro CAEI de Galicia: 2014/097

Y, tomando en consideración las siguientes cuestiones:

- La pertinencia del estudio, teniendo en cuenta el conocimiento disponible, así como los requisitos legales aplicables, y en particular la Ley 14/2007, de investigación biomédica, el Real Decreto 1716/2011, de 18 de noviembre, por el que se establecen los requisitos básicos de autorización y funcionamiento de los biobancos con fines de investigación biomédica y del tratamiento de las muestras biológicas de origen humano, y se regula el funcionamiento y organización del Registro Nacional de Biobancos para investigación biomédica, la ORDEN SAS/3470/2009, de 16 de diciembre, por la que se publican las Directrices sobre estudios Posautorización de Tipo Observacional para medicamentos de uso humano, y el la Circular nº 07 / 2004, investigaciones clínicas con productos sanitarios.
- La idoneidad del protocolo en relación con los objetivos del estudio, justificación de los riesgos y molestias previsibles para el sujeto, así como los beneficios esperados.
- Los principios éticos de la Declaración de Helsinki vigente.
- Los Procedimientos Normalizados de Trabajo del CEIC de Galicia

Emite un **INFORME FAVORABLE** para la realización del estudio por el/la investigador/a del centro:

Centros	Investigadores Principales
C.H. Universitario de A Coruña	Ana Otero Rico

NOTA: Incluir consentimiento oral ante testigos

En Santiago de Compostela, a 31 de marzo de 2014
La Secretaria

Paula M. López Vázquez

8.3. CONFLICT OF INTERESTS

CENTRO INTERNACIONAL DE ESTUDOS
DE DOUTORAMENTO E AVANZADOS
DA USC (CIEDUS)

Conflict of interests

I declare that there are no competing interests with the subject matter or materials discussed in this thesis.

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Figures 5 and 6 presented in this work were made by the author of the thesis.

8.4. AUTHOR CONTRIBUTIONS

Contribution	**1st Publication** Oral Dis. 2018	**2nd Publication** PLoS One. 2019	**3rd Publication** Oral Oncol. 2020
Conceptualization	+	+	+
Formal analysis	+	+	+
Methodology	+	+	+
Data collection	+	+	+
Data curation	+	+	+
Resources	+	+	+
Supervision	+	+	+
Validation	+	+	+
Visualization	+	+	+
Writing- original draft	+	+	+
Writing- review & editing	+	+	+
Preparation of final documentation	+	+	+

8.5. COPYRIGHT AUTHORIZATION

FIGURE 1

Olesen F, Hansen RP, Vedsted P. Delay in diagnosis: the experience in Denmark. Br J Cancer. 2009 Dec 3;101 Suppl 2:S5-8.

Br J Cancer. 2009 Dec 3; 101(Suppl 2): S5–S8.
Published online 2009 Dec 3. doi: 10.1038/sj.bjc.6605383
PMCID: PMC2790711
PMID: 19956163

Delay in diagnosis: the experience in Denmark

F Olesen,[1,*] R P Hansen,[1] and P Vedsted[1]

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FIGURE 2

Walter F, Webster A, Scott S, Emery J. The Andersen Model of Total Patient Delay: a systematic review of its application in cancer diagnosis. J Health Serv Res Policy. 2012 Apr;17(2):110–8.

J Health Serv Res Policy. 2012 Apr; 17(2): 110–118. PMCID: PMC3336942
doi: 10.1258/jhsrp.2011.010113 PMID: 22008712

The Andersen Model of Total Patient Delay: a systematic review of its application in cancer diagnosis

Fiona Walter,[1,2] Andrew Webster,[2] Suzanne Scott,[3] and Jon Emery[2,1]

FIGURE 3

Andersen BL, Cacioppo JT. Delay in seeking a cancer diagnosis: delay stages and psychophysiological comparison processes. Br J Soc Psychol. 1995 Mar;34 (Pt 1):33–52.

FIGURE 4

Varela-Centelles P, López-Cedrún JL, Fernández-Sanromán J, Seoane-Romero JM, Santos de Melo N, Álvarez-Nóvoa P, et al. Key points and time intervals for early diagnosis in symptomatic oral cancer: a systematic review. Int J Oral Maxillofac Surg. 2017 Jan;46(1):1–10.

1ST ARTICLE

Seoane J, Otero-Rico A, López-Cedrún JL, Varela-Centelles P. Shorter specialist time intervals are associated with advanced stage on symptomatic oral cancer. Oral Dis. 2018 Mar;24(1-2):112-114. doi: 10.1111/odi.12754. PMID: 29480638.

Journal: Oral Diseases

Impact factor: 2.310

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Position:21/92

Link to the article:
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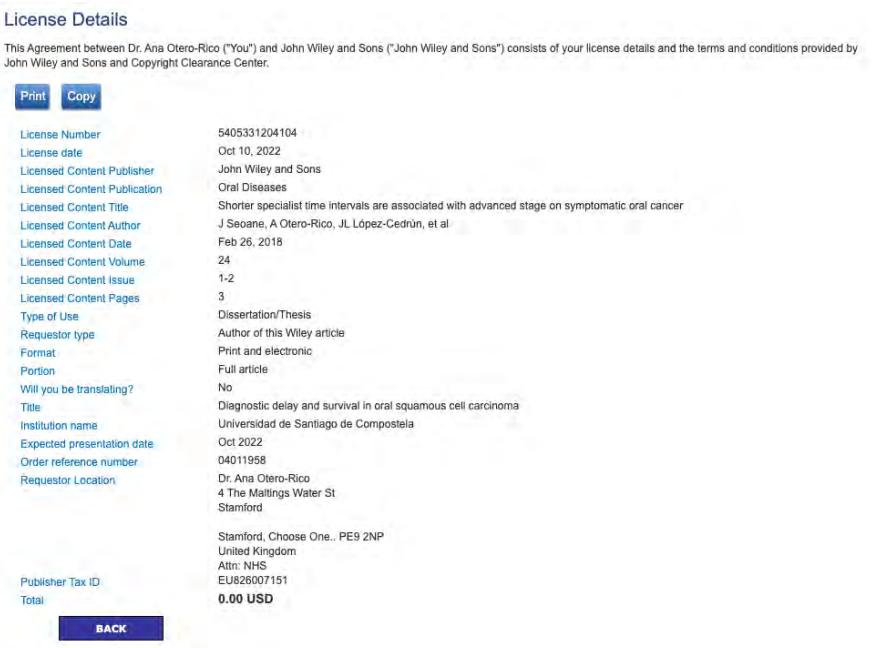

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BACK

2ND ARTICLE

Lopez-Cedrún JL, Otero-Rico A, Vázquez-Mahía I, Seoane J, García-Caballero L, Seoane-Romero JM, Varela-Centelles P. Association between hospital interval and survival in patients with oral cancer: A waiting time paradox. PLoS One. 2019 Oct 25;14(10):e0224067. doi: 10.1371/journal.pone.0224067. PMID: 31652279.

Journal: PLoS One

Impact factor: 2.740

Quartile: Q2

Position: 27/71

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PLoS One. 2019; 14(10): e0224067.
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PMCID: PMC6814211
PMID: 31652279

Association between hospital interval and survival in patients with oral cancer: A waiting time paradox

José Luis Lopez-Cedrún, Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing – review & editing,[#1] Ana Otero-Rico, Conceptualization, Data curation, Formal analysis, Investigation, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing,[#1] Inés Vázquez-Mahía, Conceptualization, Data curation, Investigation, Resources, Validation, Writing – review & editing,[#1] Juan Seoane, Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing,[#2] Lucía García-Caballero, Formal analysis, Methodology, Resources, Validation, Writing – review & editing,[2,‡] Juan Manuel Seoane-Romero, Formal analysis, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing,[3,‡*] and Pablo Varela-Centelles, Formal analysis, Funding acquisition, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing[4,‡]

Jason Chia-Hsun Hsieh, Editor

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3RD ARTICLE

Lopez-Cedrún JL, Varela-Centelles P, Otero-Rico A, Vázquez-Mahía I, Seoane J, Castelo-Baz P, Seoane-Romero J. Overall time interval ("Total diagnostic delay") and mortality in symptomatic oral cancer: A U-shaped association. Oral Oncol. 2020 May;104:104626. doi: 10.1016/j.oraloncology.2020.104626. Epub 2020 Mar 5. PMID: 32146387.

Journal: Oral Oncology

Impact factor: 5.337

Quartile: Q1

Position: 7/92

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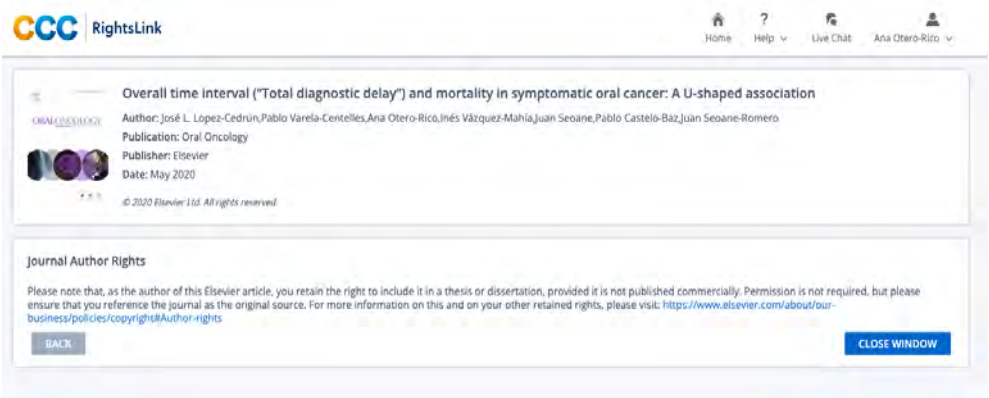

The aim of this thesis was to identify the magnitude of the time intervals that define the pathway of the oral cancer patient from the beginning of the symptoms until diagnosis and treatment, and to evaluate their impact on patients´survival. For this purpose, we designed an observational survival study, with an ambispective component. In our study, the hospital interval was a relevant interval in the oral cancer patients´pathway to treatment, representing a fourth of the overall interval, and showing a counterintuitive association, where those patients with short hospital intervals had significantly higher mortality, due to the waiting time paradox. Also, the overall time interval has shown a non-monotonic association with oral cancer mortality.