lek. Michał Żurek

Analiza kliniczno-epidemiologiczna patologii ślinianek w populacji Polski

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu

w dyscyplinie nauki medyczne

Promotor: dr hab. n. med. Anna Rzepakowska

Katedra i Klinika Otorynolaryngologii, Chirurgii Głowy i Szyi

Warszawskiego Uniwersytetu Medycznego

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3. Żurek, M., Fus, Ł., Niemczyk, K., & Rzepakowska, A. (2023). Salivary gland pathologies: evolution in classification and association with unique genetic alterations. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery, 280*(11), 4739–4750. https://doi.org/10.1007/s00405-023-08110-w
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Spis treści

Wykaz stosowanych skrótów

NFZ – Narodowy Fundusz Zdrowia

ICD-10 - Międzynarodowa Statystyczna Klasyfikacja Chorób i Problemów Zdrowotnych ICD-10

KRN – Krajowy Rejestr Nowotworów

WHO – Światowa Organizacja Zdrowia (ang. World Health Organization)

Streszczenie w języku polskim

Analiza kliniczno-epidemiologiczna patologii ślinianek w populacji Polski

Wstęp

Patologie gruczołów ślinowych to zróżnicowana grupa chorób o różnorodnym obrazie klinicznym i patomorfologicznym. Ta różnorodność stanowi wyzwanie diagnostyczne i terapeutyczne. Rozwój metod badawczych, szczególnie na poziomie molekularnym, pozwala na odkrywanie nowych podtypów znanych patologii, a prawidłowa klasyfikacja choroby pacjenta ma kluczowe znaczenie dla wyboru metody leczenia i określenia rokowania.

Na rokowanie pacjentów wpływają również czynniki demograficzne, kliniczne i patomorfologiczne. W niniejszym projekcie zostały poddane analizie dane kliniczne oraz epidemiologiczne pacjentów z patologiami gruczołów ślinowych z całej Polski zaraportowane do Narodowego Funduszu Zdrowia (NFZ) oraz Krajowego Rejestru Nowotworów (KRN).

Celem pracy jest wszechstronna analiza epidemiologii oraz cech demograficznych i klinicznych, w tym zaawansowania chorób ślinianek, sposobów ich leczenia oraz wpływu tych czynników na rokowanie w populacji polskiej w ostatnich dekadach. Wykonane w badaniu porównania są zestawione ze zmianami w klasyfikacjach patologii ślinianek oraz ich ewoluowaniem na przestrzeni ostatnich ponad 50 lat.

Publikacja 1

Żurek, M., Rzepakowska, A., Jasak, K., & Niemczyk, K. (2021). The Epidemiology of Salivary Glands Pathologies in Adult Population over 10 Years in Poland-Cohort Study. International journal of environmental research and public health, 19(1), 179. https://doi.org/10.3390/ijerph19010179

Artykuł prezentuje w sposób kompleksowy epidemiologię patologii gruczołów ślinowych wśród dorosłych pacjentów w Polsce w ciągu dekady. W tym celu przeprowadzono retrospektywną analizę rozpoznanych w Polsce w latach 2010-2019 patologii gruczołów ślinowych na podstawie bazy danych Narodowego Funduszu Zdrowia (NFZ). Patologie podzielono na trzy główne grupy: choroby nienowotworowe (w tym zapalne), nowotwory

łagodne oraz nowotwory złośliwe. Poszczególne rozpoznania zostały zidentyfikowane przy użyciu kodów Międzynarodowej Statystycznej Klasyfikacji Chorób i Problemów Zdrowotnych ICD-10 (ICD-10). Analizie poddano wskaźniki zapadalności i zachorowalności, dane demograficzne pacjentów oraz liczbę udzielonych świadczeń szpitalnych i ambulatoryjnych. W badanym okresie patologie gruczołów ślinowych zdiagnozowano u 230 589 pacjentów (85,5% stanowiły zmiany nienowotworowe, 11,53% łagodne i 2,93% złośliwe). Zapadalność dla wszystkich patologii wynosiła 59,94 pacjentów na 100 000 dorosłych mieszkańców Polski. Średnia zapadalność dla nowotworów złośliwych wynosiła 1,78/100 000 oraz zaobserwowano spadek zapadalności w tej grupie rozpoznań w analizowanym okresie. Z kolei w przypadku nowotworów łagodnych (średnia zapadalność - 6,91/100 000) odnotowano coroczny wzrost liczby zachorowań. Częstość występowania zmian nienowotworowych była dość stabilna (średnio: 51,25/100 000) w analizowanym przedziale czasowym. Najwięcej świadczeń medycznych w przeliczeniu na pacjenta zostało udzielonych w przypadku nowotworów złośliwych (średnio dwa pobyty w szpitalu i jedenaście wizyt ambulatoryjnych). Ponadto w badanym okresie zaobserwowano wzrost całkowitej liczby świadczeń medycznych związanych z patologiami ślinianek.

Publikacja 2

Żurek, M., Jasak, K., Jaros, K., Daniel, P., Niemczyk, K., & Rzepakowska, A. (2022). Clinico-Epidemiological Analysis of Most Prevalent Parotid Gland Carcinomas in Poland over a 20-Year Period. International journal of environmental research and public health, 19(16), 10247. https://doi.org/10.3390/ijerph191610247

W powyższej pracy przedstawiono wyniki dogłębnej analizy sześciu najczęściej występujących nowotworów złośliwych ślinianek przyusznych w Polsce. Do analizy wybrano następujące typy nowotworów złośliwych: rak śluzowo-naskórkowy, rak gruczołowo-torbielowaty, rak zrazikowokomórkowy, gruczolakorak, rak w gruczolaku wielopostaciowym i rak płaskonabłonkowy. W analizie ujęto 2 318 pacjentów ze złośliwymi nowotworami ślinianki przyusznej zgłoszonych do Krajowego Rejestru Nowotworów (KRN) w Polsce w ciągu 20 lat (1999-2018). Przeanalizowano charakterystykę demograficzną pacjentów, czynniki kliniczne i całkowite przeżycie. Średni wiek pacjentów wyniósł 61,33±16,1 lat. Większość stanowili mężczyźni (55%) i mieszkańcy miast (64%). Najczęściej rozpoznawany był rak płaskonabłonkowy (33,3%) i gruczolakorak (19,6%). Podstawową metodą leczenia była

resekcja chirurgiczna z uzupełniającą radioterapią (42,1%). Mediana czasu przeżycia od rozpoznania wyniosła średnio 5,6 roku. Najkorzystniejszą medianę całkowitego przeżycia stwierdzono u pacjentów z rakiem zrazikowokomórkowym (18,3 roku), najgorszą zaś w przypadku raka płaskonabłonkowego (1,58 roku). Średni czas przeżycia chorych z populacji polskiej okazał się krótszy dla pewnych grup nowotworów złośliwych w porównaniu z danymi z innych krajów. W podsumowaniu pracy zwrócono uwagę na możliwość poprawy metod diagnostycznych i konieczność weryfikacji standardów leczenia nowotworów złośliwych ślinianki przyusznej w Polsce w celu poprawy rokowania pacjentów.

Publikacja 3

Żurek, M., Fus, Ł., Niemczyk, K., & Rzepakowska, A. (2023). Salivary gland pathologies: evolution in classification and association with unique genetic alterations. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery, 280(11), 4739–4750. https://doi.org/10.1007/s00405-023-08110-w

W pracy poglądowej przedstawiono aktualnie obowiązującą klasyfikację patologii gruczołów ślinowych wg Klasyfikacji Nowotworów Światowej Organizacji Zdrowia z 2022 roku (5. edycja) oraz jej ewolucję od 1972 roku, zatem obejmującą również okres wykonywanych analiz epidemiologicznych. Wraz z rozwojem nowych metod diagnostycznych, opartych na zmianach genetycznych, najnowsza klasyfikacja zapewnia wgląd w molekularne podstawy patologii. Doprowadziło to do weryfikacji pewnych rozpoznań, wprowadzenia nowych jednostek i reklasyfikacji istniejących. W przyszłości zmiany genetyczne będą miały coraz większe znaczenie w identyfikacji patologii gruczołów ślinowych. Prawdopodobnie uzyskają one również znaczenie jako biomarkery prognostyczne i predykcyjne, a także będą mogły służyć jako cele dla terapii przeciwnowotworowych.

Podsumowanie

Patologie gruczołów ślinowych to różnorodna grupa chorób charakteryzująca się odmienną epidemiologią i charakterystyką kliniczną. W Polsce najczęściej rozpoznaje się zmiany

nienowotworowe, jednak należy zwrócić uwagę, że coraz częściej rozpoznawane są nowotworowe zmiany łagodne ślinianek. Nowotwory złośliwe, choć rzadkie, wiążą się jednak z największą liczbą świadczeń medycznych, a rokowanie zależy od wielu czynników, głównie od rozpoznania histopatologicznego. Najczęstszymi rozpoznaniami histopatologicznymi są rak płaskonabłonkowy i gruczolakorak. Najlepsze rokowanie dotyczy raka zrazikowokomórkowego, a najgorsze raka płaskonabłonkowego. Należy zwrócić uwagę, że dzięki ewolucji klasyfikacji coraz dokładniej można określić rokowanie pacjenta i zaplanować leczenie. Najnowsza Klasyfikacja Nowotworów Światowej Organizacji Zdrowia z 2022 roku wprowadziła kolejne nowe zmiany w zakresie diagnostyki patologii ślinianek, głównie w oparciu o najnowsze odkrycia genetyczne.

Streszczenie w języku angielskim

Clinical-epidemiological analysis of salivary gland pathologies in the Polish population

Introduction

Pathologies of the salivary glands are a diverse group of diseases with a variety of clinical and pathomorphological presentations. This diversity poses diagnostic and therapeutic challenge. The development of research methods, especially at the molecular level, allows the discovery of new subtypes of known pathologies, and the correct classification of a patient's disease is crucial for the choice of treatment and determination of prognosis.

Patient prognosis is also influenced by demographic, clinical and pathological factors. In this project, clinical and epidemiological data of patients with salivary gland pathologies from all over Poland reported to the National Health Fund (NHF) and the National Cancer Registry (NCR) were analyzed.

The aim of the study was the comprehensive analysis of the epidemiology, demographic and clinical characteristics, including the advancement of salivary gland diseases, methods of their treatment and the impact of these factors on the prognosis in the Polish population in recent decades. The performed comparisons were confronted with changes in the classifications of salivary gland pathologies and their evolution over the last 50 years.

Manuscript 1

Żurek, M., Rzepakowska, A., Jasak, K., & Niemczyk, K. (2021). The Epidemiology of Salivary Glands Pathologies in Adult Population over 10 Years in Poland-Cohort Study. International journal of environmental research and public health, 19(1), 179. https://doi.org/10.3390/ijerph19010179

The article comprehensively presents the epidemiology of salivary gland pathologies among adult patients in Poland over a decade. For this purpose, a retrospective analysis of salivary gland pathologies diagnosed in Poland in 2010-2019 was carried out on the basis of the National Health Fund (NHF) database. Pathologies were divided into three main groups: non-cancerous diseases (including inflammatory), benign neoplasms and malignant neoplasms. Individual

diagnoses were identified using International Statistical Classification of Diseases and Health Problems ICD-10 (ICD-10) codes. Incidence and morbidity rates, patient demographics and the number of inpatient and outpatient services were analyzed. During the study period, salivary gland pathologies were diagnosed in 230,589 patients (85.5% were non-cancerous lesions, 11.53% benign and 2.93% malignant). The incidence of all pathologies was 59.94 patients / 100,000 adult Polish residents. The average incidence for malignant neoplasms was 1.78/100,000 and a decrease in incidence was observed during the analyzed period. On the other hand, for benign neoplasms (average incidence - 6.91/100,000) there was an annual increase in the new number of cases. The incidence of non-cancerous lesions was fairly stable (average: 51.25/100,000) during the analyzed period. The largest number of medical services per patient was provided for malignant tumors (an average of two hospital stays and eleven outpatient visits). In addition, the number of medical services related to salivary gland pathologies increased during the period under review.

Manuscript 2

Żurek, M., Jasak, K., Jaros, K., Daniel, P., Niemczyk, K., & Rzepakowska, A. (2022). Clinico-Epidemiological Analysis of Most Prevalent Parotid Gland Carcinomas in Poland over a 20-Year Period. International journal of environmental research and public health, 19(16), 10247. https://doi.org/10.3390/ijerph191610247

The above paper presents the results of a comprehensive analysis of the six most common malignant tumors of the parotid glands in Poland. The following types of malignant neoplasms were selected for analysis: mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, adenocarcinoma, carcinoma ex pleomorphic adenoma and squamous cell carcinoma. The analysis included 2,318 patients with malignant parotid gland tumors reported to the National Cancer Registry (NCR) in Poland over a 20-year period (1999-2018). Patients' demographic characteristics, clinical factors and overall survival were analyzed. The mean age of patients was 61.33±16.1 years. The majority were men (55%) and urban residents (64%). The most common diagnoses were squamous cell carcinoma (33.3%) and adenocarcinoma (19.6%). The most common treatment was surgical resection with adjuvant radiotherapy (42.1%). The median survival time from diagnosis was 5.6 years. The most favorable median overall survival was found for patients with acinic cell carcinoma (18.30 years), and the worst for squamous cell carcinoma (1.58 years). The average survival time of patients from the Polish

population turned out to be shorter compared to data from other countries. In the summary of the work, attention was drawn to an important aspect of improving diagnostic methods and the need to verify the standards of treatment of malignant tumors of the parotid gland in Poland in order to improve patient prognosis.

Manuscript 3

Żurek, M., Fus, Ł., Niemczyk, K., & Rzepakowska, A. (2023). Salivary gland pathologies: evolution in classification and association with unique genetic alterations. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery, 280(11), 4739–4750. https://doi.org/10.1007/s00405-023-08110-w

This review presents the current classification of salivary gland pathologies according to the World Health Organization (WHO) Classification (5th edition) and its evolution since 1972. With the development of new diagnostic methods based on genetic alterations, the latest classification provides insight into the molecular bases of pathologies. This has led to the evolution of diagnoses, especially within the malignant pathologies, the introduction of new entities and the reclassification of existing ones. In the future, genetic alterations will become increasingly important in identifying salivary gland pathology. They are also likely to gain prominence as prognostic and predictive biomarkers, and could serve as targets for anti-cancer therapies.

Summary

Pathologies of the salivary glands are a diverse group of diseases with different epidemiology and clinical characteristics. In Poland, non-cancerous lesions are most often diagnosed, but it should be noted that a substantial increase of benign salivary gland lesions was observed in the recent decade. Malignant neoplasms, although rare, require the greatest number of medical services, and the prognosis depends on many factors, mainly the histopathological diagnosis. The most common histopathological diagnoses are squamous cell carcinoma and adenocarcinoma. The best prognosis is for acinic cell carcinoma and the worst for squamous

cell carcinoma. It should be noted that thanks to the evolution of the classification of lesions, it is increasingly possible to determine a patient's prognosis and propose optimal treatment. The latest World Health Organization Cancer Classification from 2022 has introduced many changes in the diagnosis of salivary gland pathologies, mainly based on the latest genetic discoveries.

Analiza kliniczno-epidemiologiczna patologii ślinianek w populacji Polski

Wstęp

Patologie gruczołów ślinowych to niejednorodna grupa chorób o zróżnicowanych objawach klinicznych i różnorodnym obrazie patomorfologicznym. Ta różnorodność stanowi wyzwanie diagnostyczne i terapeutyczne.

Zmiany zapalne ślinianek, zwłaszcza o przebiegu ostrym lub podostrym, wiążą się z dolegliwościami bólowymi u pacjentów oraz nagłym obrzękiem okolicy gruczołu, ale rokowanie w tych schorzeniach jest korzystne. Szacuje się, że częstość występowania zmian zapalnych ślinianek w populacji wynosi około 1,2%, przy czym w dużym odsetku przypadków choroba przebiega bezobjawowo lub z niewielkimi objawami. Szacuje się, że za połowę patologii zapalnych odpowiadają zmiany związane z kamicą ślinianek.

Guzy ślinianek są bardziej poważnymi rokowniczo patologiami. Szacuje się, że stanowią one od 3 do 10% wszystkich nowotworów głowy i szyi, a w Europie odsetek ten wynosi 8,5%. Guzy są w większości łagodnymi zmianami, tylko mniej niż 20% z nich ma charakter złośliwy. Częstość występowania wszystkich guzów ślinianek zależy od wieku i populacji. Na podstawie wyników badań zapadalność wynosi 0,4-13,5/100 000 mieszkańców.

Prezentowany cykl publikacji stanowiących moją rozprawę doktorską jest pierwszą w Polsce, kompleksową, ogólnokrajową analizą epidemiologiczną i kliniczną patologii gruczołów ślinowych. Poddano przeglądowi dane kliniczne i epidemiologiczne pacjentów z patologiami gruczołów ślinowych z całej Polski zaraportowane do Narodowego Funduszu Zdrowia (NFZ) oraz Krajowego Rejestru Nowotworów (KRN).

Pierwsza praca prezentowanego cyklu (*Żurek, M., Rzepakowska, A., Jasak, K., & Niemczyk, K. (2021). The Epidemiology of Salivary Glands Pathologies in Adult Population over 10 Years in Poland-Cohort Study. International journal of environmental research and public health, 19(1), 179. https://doi.org/10.3390/ijerph19010179*) przedstawia retrospektywną analizę wszystkich chorób gruczołów ślinowych zdiagnozowanych w Polsce w latach 2010–2019 na podstawie danych NFZ. Zestawienia obejmowały zapadalność i chorobowość, dane demograficzne pacjentów oraz liczbę świadczonych usług szpitalnych i ambulatoryjnych.

W drugiej pracy prezentowanego cyklu (*Żurek, M., Jasak, K., Jaros, K., Daniel, P., Niemczyk, K., & Rzepakowska, A. (2022). Clinico-Epidemiological Analysis of Most Prevalent Parotid Gland Carcinomas in Poland over a 20-Year Period. International journal of environmental research and public health, 19(16), 10247. https://doi.org/10.3390/ijerph191610247*) przedstawiono porównanie wyników epidemiologicznych i klinicznych dla sześciu najczęściej występujących nowotworów złośliwych ślinianek przyusznych w Polsce. W tym celu wykorzystano dane KRN dotyczące nowotworów złośliwych ślinianek zaraportowanych w latach 1999-2018. Określono czas przeżycia pacjentów z poszczególnymi typami nowotworów. Przeanalizowano również cechy kliniczne oraz zastosowane metody leczenia, a także ich wpływ na rokowanie.

Trzecia praca prezentowanego cyklu (*Żurek, M., Fus, Ł., Niemczyk, K., & Rzepakowska, A. (2023). Salivary gland pathologies: evolution in classification and association with unique genetic alterations. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery, 280(11), 4739–4750. https://doi.org/10.1007/s00405-023-08110-w*) przedstawia problemy związane z klasyfikacją patologii gruczołów ślinowych na przestrzeni lat. Odnosząc się do aktualnie obowiązującej klasyfikacji patologii gruczołów ślinowych według Klasyfikacji Nowotworów Światowej Organizacji Zdrowia z 2022 roku, zaprezentowano ewolucję rozpoznań w poszczególnych grupach patologicznych od 1972 roku. Zwrócono szczególną uwagę na zaprezentowanie uzasadnień autorów klasyfikacji dla wprowadzanych kolejno zmian. Część patologii w najnowszej klasyfikacji opiera się na molekularnych aspektach, które przedstawiono sumarycznie w treści pracy. Analiza genetyczna zmian uzasadnia wprowadzenie nowych jednostek chorobowych i zmianę klasyfikacji już istniejących.

Dokładna analiza epidemiologii oraz trendów w zapadalności i chorobowości pozwala na lepszy wgląd w problematykę chorób ślinianek. Najnowsze metody diagnostyczne pozwalają ponadto na precyzyjniejsze określenie podstaw molekularnych chorób gruczołów ślinowych oraz zaplanowanie optymalnej terapii i poprawę efektów leczenia. Dodatkowo wzbogacenie analiz o dane demograficzne i kliniczne pozwala dokładnej określić czynniki wpływające na rokowanie pacjentów.

Założenia i cel pracy

1. Analiza wskaźników epidemiologicznych chorób gruczołów ślinowych w Polsce, a także określenie obciążenia systemu ochrony zdrowia w związku z patologiami gruczołów ślinowych.
2. Ocena wpływu czynników demograficznych i klinicznych na rokowanie pacjentów z nowotworami złośliwymi ślinianek przyusznych w Polsce.
3. Przedstawienie problematyki klasyfikacji patologii gruczołów ślinowych, w tym ewolucji systemu rozpoznań patomorfologicznych dla zmian w śliniankach oraz wskazanie dalszych kierunków rozwoju diagnostyki.

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Article

The Epidemiology of Salivary Glands Pathologies in Adult Population over 10 Years in Poland—Cohort Study

Michał Żurek [1,2,*], Anna Rzepakowska [1,*], Kamil Jasak [3] and Kazimierz Niemczyk [1]

[1] Department of Otorhinolaryngology Head and Neck Surgery, Medical University of Warsaw, 1a Banacha Str., 02-097 Warsaw, Poland; kniemczyk@wum.edu.pl
[2] Doctoral School, Medical University of Warsaw, 61 Żwirki i Wigury Str., 02-091 Warsaw, Poland
[3] Students Scientific Research Group at the Department of Otorhinolaryngology Head and Neck Surgery, Medical University of Warsaw, 1a Banacha Str., 02-097 Warsaw, Poland; s071767@student.wum.edu.pl
* Correspondence: mzurek@wum.edu.pl (M.Ż.); arzepakowska@wum.edu.pl (A.R.); Tel.: +48-780092703 (M.Ż.); +48-225992716 (A.R.)

Abstract: Background: The aim of this study was a comprehensive analysis of the incidence of different salivary gland pathologies in the adult population of Poland. Methods: A retrospective analysis of salivary gland pathologies diagnosed in Poland in 2010–2019 based on the National Health Fund (NHF) database was performed. Non-neoplastic diseases, and benign and malignant lesions were identified using ICD-10 codes. Demographic characteristics, incidence rates, and the number of inpatient and outpatient medical services were analyzed. Results: Salivary gland pathologies were diagnosed in 230,589 patients over 10 years (85.5% were non-neoplastic lesions, 11.53% benign and 2.93% malignant neoplasms). Incidence rate for all pathologies was 59.94/100,000. The mean incidence for malignant neoplasms was 1.78, and decreasing trend was observed over the analyzed period. Contrarily, for benign neoplasms (mean incidence—6.91), an increase in numbers was noted annually. The incidence for non-malignant lesions was quite stable (mean: 51.25) over the time. The highest number of medical services per patient concerned malignant neoplasms (on average, two hospital stays, and eleven outpatient consultations). Conclusions: An increase of benign salivary gland tumors, and a decrease of malignant neoplasms was observed during the studied period. The number of medical services related to salivary gland pathologies increased during the period under study.

Keywords: salivary gland pathologies; epidemiology; Poland; incidence rate

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1. Introduction

Salivary gland pathologies are a heterogeneous group of diseases with diverse clinical manifestations, and a heterogeneous pathomorphological image. In clinical practice, effective diagnosis and early treatment of patients with neoplastic lesions are the most important ways to achieve a good therapeutic effect. Inflammatory lesions of the salivary glands, especially of the acute or subacute course, are associated with more severe pain in patients, but the prognosis is favorable. Unfortunately, a number of inflammatory and reactive lesions of the salivary glands may mimic neoplastic disease, so in most patients, imaging diagnosis, including ultrasonography and magnetic resonance imaging or computed tomography, must be routinely performed. Salivary gland tumors account for 3 to 10% of all head and neck cancers [1–4]; in Europe, this percentage is 8.5% [5]. Most of the proliferative lesions in the salivary glands are benign, and only less than 20% are malignant [6]. According to published data, the incidence is 0.4–13.5 per 100,000 inhabitants [1,2,5,7]. The incidence of salivary gland tumors depends on age and geographical area. The average incidence increases from 0.15 for patients under 25 years of age, to 1.2 for those in age range of 25–64 years, up to as high as 4.3 per 100,000 in the population over 65 years [5]. The highest incidence of salivary gland cancer occurs in European and North American populations compared to other continents' inhabitants [4].

Most of the available epidemiological studies on the pathology of the salivary glands focus selectively on the group of neoplastic diseases, with the largest number of studies analyzing the occurrence of malignant lesions [1–5]. Among the publications, only few are cohort studies; observations from one or several research centers predominate. Pathologies of salivary glands of inflammatory etiology are less frequently described in the literature, and the epidemiology of this type of lesions is scarcely analyzed in comparison to neoplasms. It is estimated that the prevalence of inflammatory lesions of the salivary glands in the population is about 1.2%, but in most cases, the disease is asymptomatic or scantly symptomatic [8]. Inflammatory changes associated with salivary gland stones are responsible for up to half of such pathologies [9].

In the present study, we performed a comprehensive analysis of the incidence of different types of salivary gland pathologies, including non-neoplastic lesions, and benign and malignant neoplasms in the adult patient population in Poland over the period from 2010 to 2019. The aim of the study was to comprehensively evaluate the epidemiology of different types of salivary gland pathologies, and the trends in incidence and prevalence.

2. Materials and Methods

The research project is a retrospective analysis of data from the National Health Fund (NHF) [10]. In Poland, health care is based on insurance, and supplied by the NHF, a publicly funded health-care system. The system is free for all insured citizens, employees, registered unemployed persons, and spouses or children of an insured person. The NHF database includes primary, outpatient, and inpatient care, so the data in the analyses refer to all patients in Poland receiving healthcare financed from public funds. The information in NHF databases include medical data and demographic characteristics of the patients, in particular, gender, age, and place of residence. Diagnoses are coded according to the International Statistical Classification of Diseases and Related Health Problems ICD-10 (ICD-10). The research group was defined as patients diagnosed with salivary gland pathologies between 2010 and 2019. Salivary gland pathologies are defined by the following ICD-10 codes, and divided into the following three groups (Table 1):

- Malignant neoplasms: C07, C08, C08.0, C08.1, C08.8, C08.9
- Benign neoplasms: D11, D11.0, D11.7, D11.9
- Non-neoplastic diseases: K11.0, K11.1, K11.2, K11.3, K11.4, K11.5, K11.6, K11.7, K11.8, K11.9

Table 1. Analyzed codes of salivary gland diagnosis according to the ICD-10 classification, with descriptions and division into three types of pathologies: malignant, benign, and non-neoplastic.

ICD-10 Code	Description	Group of Pathologies
C07	Malignant neoplasm of parotid gland	Malignant neoplasms
C08	Malignant neoplasm of other and unspecified major salivary glands	
C08.0	Submandibular gland	
C08.1	Sublingual gland	
C08.8	Overlapping lesion of major salivary glands	
C08.9	Major salivary gland, unspecified	
D11	Benign neoplasm of major salivary glands	Benign neoplasms
D11.0	Parotid gland	
D11.7	Other major salivary glands	
D11.9	Major salivary gland, unspecified	

Table 1. *Cont.*

ICD-10 Code	Description	Group of Pathologies
K11	Diseases of salivary glands	Non-neoplastic
K11.0	Atrophy of salivary gland	
K11.1	Hypertrophy of salivary gland	
K11.2	Sialadenitis	
K11.3	Abscess of salivary gland	
K11.4	Fistula of salivary gland	
K11.5	Sialolithiasis	
K11.6	Mucocele of salivary gland	
K11.7	Disturbances of salivary secretion	
K11.8	Other diseases of the salivary glands	
K11.9	Disease of salivary gland, unspecified	

For each salivary gland pathology group, the mean age of patients at the diagnosis with standard deviation, and the percentage of males and females were calculated. The incidence of each salivary gland pathology group was calculated by dividing the number of new patients by 100,000 adult citizens. Data on the number of adults in Poland are from Statistics Poland [11], and include all citizens over 18 years of age, regardless of their insurance status with the NHF. The number of outpatient consultations and hospital stays for patients with salivary gland diseases was also analyzed. The last section of the study presents a map of the provinces with the number of treated patients per 100,000 inhabitants for different types of lesions.

3. Results

In the analyzed period, pathologies of salivary glands were diagnosed in 230,589 patients. The percentages amounted to 85.5% for non-neoplastic lesions, 11.53% for benign tumors, and 2.93% for malignant neoplasms.

3.1. Incidence Rates and Characteristics of Patients

The incidence rate for all types of salivary gland pathologies was 59.94/100,000, including malignant neoplasms—1.78, benign neoplasms—6.91, and non-malignant lesions—51.25 (Table 2). Over the 10 years, there was a decrease in the incidence of malignant neoplasms (from 2.198 in 2009, to 1.449 in 2019; the absolute number of new patients decreased on average by 4.57% per year). The downward trend was also observed for incidence of non-malignant pathologies (from 54.514 in 2009, to 46.091 in 2019; 1.89% decrease in new patients each year), whereas the number of non-malignant neoplasms gradually increased (from 5.398 in 2009, to 8.137 in 2019; average annual increase in new patients of 4.62%). The incidence rates and demographic characteristics of the studied group are presented in Figure 1 and Table 2.

Table 2. Structure of new cases of salivary gland pathologies between 2010 and 2019 in Poland.

Salivary Gland Pathologies		2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Total	Percentage of Incidence
Number of new cases according to type of pathology													
Non-neoplastic lesions		21,004	19,632	19,128	20,559	21,280	19,718	20,399	19,714	18,019	17,691	197,144	85.50%
Benign neoplasms		2080	2273	2244	2634	2812	3110	2579	2791	2955	3123	26,601	11.53%
Malignant neoplasms		847	807	812	778	732	737	557	533	485	556	6844	2.97%
Incidence per 100,000 adult inhabitants													
Non-neoplastic lesions		54.514	50.941	49.64	53.406	55.303	51.299	53.077	51.294	46.911	46.091	51.25	
Benign neoplasms		5.398	5.898	5.824	6.842	7.308	8.091	6.71	7.262	7.693	8.137	6.915	
Malignant neoplasms		2.198	2.094	2.107	2.021	1.902	1.917	1.449	1.387	1.263	1.449	1.779	
All pathologies of the salivary glands		62.11	58.933	57.571	62.269	64.514	61.308	61.236	59.942	55.867	55.676	59.944	
Age of patients according to the type of pathology (mean age ± SD)													
Non-neoplastic lesions		48.19 ± 20.48	49 ± 24.74	49.11 ± 20.54	49.89 ± 20.29	50.22 ± 20.47	50.21 ± 20.71	50.92 ± 20.67	51.19 ± 20.57	51.59 ± 20.98	51.93 ± 21.09	50.23 ± 21.05	
Benign neoplasms		52.77 ± 17.09	54.09 ± 17.42	54.1 ± 17.5	54.61 ± 17.19	54.81 ± 17.51	55.91 ± 17.01	56.32 ± 17.26	55.98 ± 16.85	57.25 ± 16.84	56.86 ± 16.81	55.27 ± 17.15	
Malignant neoplasms		61.04 ± 16.39	61.23 ± 15.92	60.42 ± 15.97	60.15 ± 16.95	63.38 ± 16.91	63.06 ± 15.77	63.07 ± 15.8	62.28 ± 16.96	64.5 ± 14.97	62.84 ± 16.97	62.2 ± 16.26	
Gender structure of patients according to type of pathology													
Non-neoplastic lesions	Men (%)	38.73%	38.98%	38.31%	38.80%	38.53%	38.50%	38.93%	39.53%	38.73%	38.92%	38.80%	
	Women (%)	61.27%	61.02%	61.69%	61.20%	61.47%	61.50%	61.07%	60.47%	61.27%	61.08%	61.20%	
Benign neoplasms	Men (%)	43.32%	44.21%	44.83%	45.32%	43.81%	45.98%	45.72%	45.90%	44.20%	46.30%	44.98%	
	Women (%)	56.68%	55.79%	55.17%	54.48%	56.19%	54.02%	54.28%	54.10%	55.80%	53.70%	53.02%	
Malignant neoplasms	Men (%)	58.44%	55.27%	54.93%	60.93%	53.69%	54.55%	55.30%	54.60%	59.38%	59.89%	56.70%	
	Women (%)	41.56%	44.73%	45.07%	39.07%	46.31%	45.45%	44.70%	45.40%	40.62%	40.11%	43.30%	

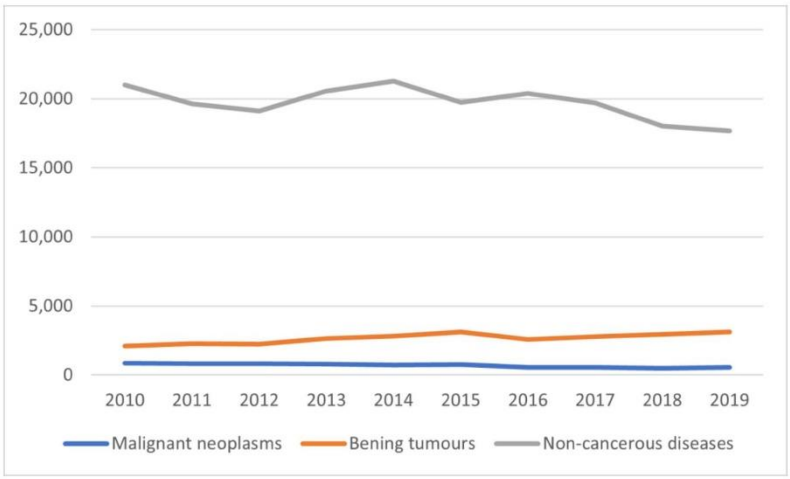

Figure 1. Overview of new salivary gland pathologies diagnosed in 2010–2019 in Poland.

Overall, the mean age was highest in the group of patients with malignant salivary gland tumors—62.2 years. Moreover, the progressive increase of the mean age for this patient category was observed, on average by 0.34 per year. A slight predominance of incidence in males (56.70%) was found in this group. Patients with benign salivary gland tumors were younger, with an average age of 55.27 years at the time of the diagnosis. Also, in this group, an increase in the mean age value was observed, with an average of 0.45 per year. The incidence was predominant in women—55.02%, but over the study period, the percentage advantage decreased by 2.88%. The lowest mean age was found for non-neoplastic salivary gland pathologies—50.23 years, but the standard deviation was the highest in this group of patients (±21.05 years). The vast majority of patients in this group were women (61.2%), and this proportion did not change over the study period.

The comprehensive analysis of newly diagnosed salivary glands pathologies with respect to all analyzed ICD 10 codes is summarized in Supplementary Materials Table S1, allowing the comparison of diseases incidence within major salivary glands, and some differentiation of the diagnosis for non-neoplastic lesions.

In terms of location, malignant neoplasms predominated in the parotid gland—C07 (4469 of 6844 total patients, 65.30%), and the number of new cases for this location decreased on average by 4.13% each year. Among non-malignant neoplasms, parotid lesions (D11.0) also had the highest share (12,259 of 26,601 patients, 46.08%). An average annual increase in the number of new lesions in this location of 10.32% was observed. A similar trend was also observed for benign tumors of the sublingual and submandibular salivary glands (D11.7 and D11.9), and a mean increase in the number of patients by 7.61% was calculated. For non-neoplastic pathologies, the most common diagnosis was general salivary gland diseases—K11 (128,845 patients, 65.36%), followed by salivary gland inflammation—K11.2 (24,302 patients, 12.33%), and sialolithiasis—K11.5 (12,265 patients, 6.22%). There was also an increase in the number of diagnoses for salivary gland inflammation and sialolithiasis, which annually reached on average 7.21% and 6.41%, respectively.

3.2. *Outpatient and Inpatient Care*

Data on outpatient and inpatient services related to salivary gland pathologies are presented in Table 3 and Figure 2. The number of outpatient services related to non-malignant salivary gland pathologies changed little between 2010 and 2019 (from 38,217 to 44,267), whereas a higher than 2.6-fold increase was noted for hospital stays in this group

of patients (from 5786 to 15,073). On average, each patient with such pathology had two visits at the outpatient clinic, and every second patient was admitted to hospital for this reason. In the case of benign salivary gland tumors, the number of outpatient consultations increased 2.3-fold (from 6411 to 14,803), and the average patient with a benign tumor had four outpatient consultations. The number of inpatient stays for benign tumors also increased from 1800 to 5076 (a 2.8-fold increase). Patients with malignant neoplasms required the highest number of outpatient consultations and hospital stays, respectively: 11 outpatient services per patient, and more than 2 hospital stays. There was a small increase in outpatient visits in this group (about a 1.3-fold rise), whereas the number of hospital stays increased from 911 in 2013, to 2197 in 2019.

Table 3. Number of inpatient and outpatient services among patients with non-neoplastic, benign, and malignant salivary gland lesions in 2010–2019 in Poland (SD—standard deviation).

Salivary Gland Pathologies	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Total	Average Number of Services per Patient (± SD)
Number of outpatient consultations												
Non-neoplastic lesions	39,765	37,808	38,217	42,616	44,267	42,634	43,050	42,366	39,023	39,249	408,995	2.07 ± 0.11
Benign neoplasms	6411	7506	7880	9445	10,361	11,426	11,951	13,237	13,435	14,803	106,455	4 ± 0.64
Malignant neoplasms	6684	6280	6666	7491	7599	7823	8271	8253	8212	8612	75,891	11.09 ± 3.58
Number of hospital stays												
Non-neoplastic lesions	5786	5781	6012	6390	7437	11,786	12,807	14,121	15,253	15,073	100,446	0.51 ± 0.24
Benign neoplasms	1800	1734	1808	1844	2180	2612	3104	3080	4153	5076	27,391	1.03 ± 0.31
Malignant neoplasms	1933	1836	1197	911	1233	1162	1589	1596	1721	2191	15,369	2.25 ± 0.93

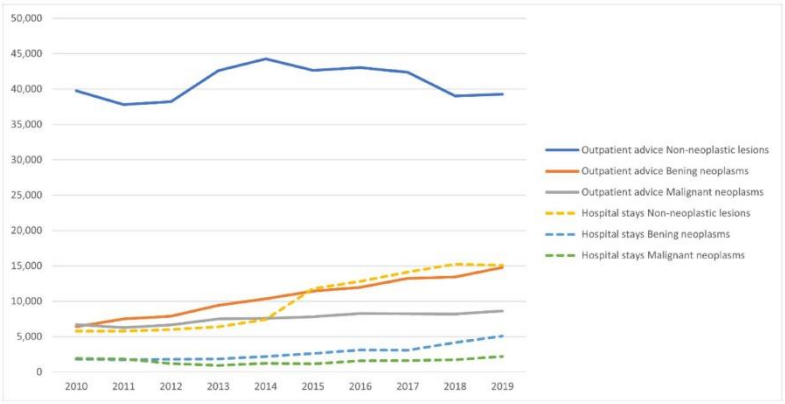

Figure 2. Number of medical services related to salivary gland pathologies in Poland between 2010 and 2019.

3.3. Regional Prevalence

Figure 3 presents the mean prevalence (per 100,000 inhabitants) of salivary gland pathologies in the analyzed period divided into voivodeships in Poland. Territorial variation of prevalence was observed for all types of lesions. In cases of non-neoplastic pathologies and benign neoplasms, the highest prevalence was observed in the Greater Poland Voivodeship. The highest prevalence of malignant salivary gland tumors was observed in the Lower Silesian region. It is worth noticing that the prevalence of salivary gland benign lesions varies greatly, from 2.51 for the Lublin Voivodeship, to 11.76 for the Greater Poland Voivodeship (Figure 3B).

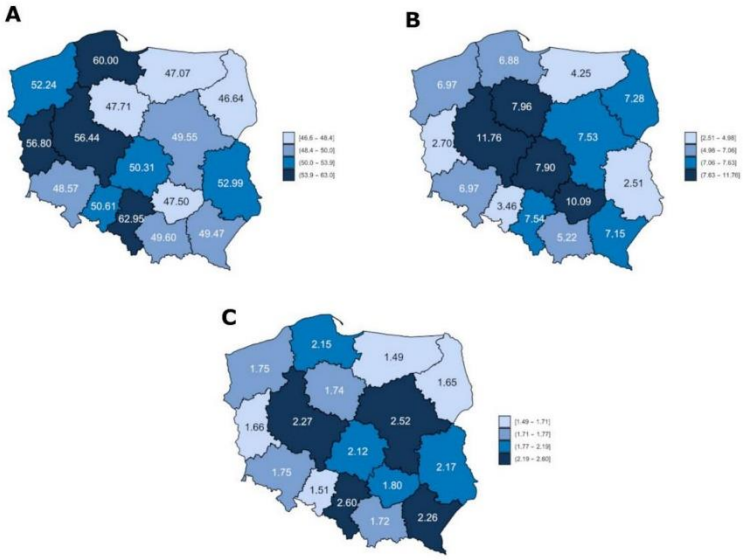

Figure 3. Prevalence of salivary gland pathologies by voivodeships in Poland in 2010–2019 per 100,000 inhabitants. (**A**)—Prevalence of non-neoplastic salivary gland diseases; (**B**)—Prevalence of benign salivary gland neoplasms; (**C**)—Prevalence of malignant salivary gland neoplasms.

4. Discussion

The presented epidemiological analysis of salivary gland pathologies among adult Poles presents extensive and comprehensive data from the last decade, which may be used in the prognosis and planning of medical services, and constitute a basis for further research on the observed variability of incidence depending on the region of the country.

In terms of gender predisposition, our analysis is consistent with the results of earlier, smaller population-based studies conducted by other Polish authors: women constituted about 55.7–56.5% of patients with benign salivary gland tumors, and 47.6–49% of patients with malignant tumors [12,13]. Data from other countries are more varied, and the percentage of women among patients with malignant lesions of the salivary glands ranges from 46% to 52% [2,14–18].

On the basis of performed analyses concerning the mean age of incidence of particular salivary gland pathologies, differences were observed depending on the type of lesions, and over the years in the analyzed period. Other Polish studies report the mean age of patients with benign salivary gland lesions in the range 50.1–52.63 years, and with malignant lesions in the range of 59.4–65.1 years [12,13]. However, this study included patients from earlier years, and as suggested by the results of the current analysis, there was an annual increase in the mean age of onset for benign and malignant pathologies observed. The variation in the mean age of onset also shows marked differences between countries. The studies report the mean age of patients with malignant lesions of the salivary glands between 51–62 years [2,14–16,19].

The incidence of salivary gland pathologies shows differences in the examined period; however, the average values are similar to those reported in other countries. Bradley et al. [7], in a study from Great Britain, reported similar incidence values of 6.2–7.2 for benign, and 0.83–1.38 for malignant neoplasms per 100,000 inhabitants. The incidence of salivary gland malignancies varies from 0.5 to 2 per 100,000 inhabitants, with the highest value for Croatia, and the lowest for Japan [16,19–21]. It is worth noting that the changes in incidence rates depend on the nature of the lesion, with an increasing trend for benign

salivary gland tumors (from 5.4 to 8.2), and a decreasing trend for malignant tumors (from 2.2 to 1.4) between 2010 and 2019. A similar incidence trend for benign salivary gland tumors was observed in the work of Stryjewska-Makuch et al. [3]. In turn, these results differ from those presented in the Danish study by Westergaard-Nielsen et al. [19], where an annual increase in the incidence of salivary gland malignancies was observed, but the analysis included earlier years, from 1990 to 2015. A similar increase in the incidence of malignancies was reported in the United States at the turn of the century between 1973 and 2009 [22].

The observed reverse trends in the incidence of benign and malignant salivary gland tumors in the analyzed study can be explained with more widespread and available imaging diagnosis, especially the ultrasounds in recent decades. Therefore, the benign salivary gland pathologies are identified and treated earlier, and the group of benign lesions with the potential for malignant transformation has been currently reduced.

In the analyzed material, neoplastic pathologies of salivary glands were most frequently located in the parotid glands. Malignant tumors of the parotid gland constituted 65.3% of all diagnoses in this group. Analyzing all parotid neoplasms, benign lesions constituted 73.28%, and malignant ones constituted 26.72%. In previously presented studies from different centers in Poland, similar percentages of malignant lesions were observed [12,13], although in some studies, due to lower heterogeneity or a more specialized center profile, the percentages of parotid gland involvement for malignant neoplasms were overestimated, even up to 79.6% [23]. In a study from Israel, salivary gland malignancies initially occupied the parotid glands in 55% of cases. Similarly, in a population-based study from Denmark, the localization of malignant neoplasm in the parotid gland was reported in 51.8–52.5% of cases, and in a study from Sweden, this percentage was 57.5% [24]. In contrast, a study by Tian et al. [18] from China reported only 34.12% of malignant tumors in the parotid gland.

The strength of the following study is the analysis of medical services related to salivary gland pathologies. The highest number of services per patient concerns those with malignant neoplasms (an average of 11 outpatient specialist care visits per patient, and more than 2 hospital visits). At the same time, there has been an annual increase in outpatient visits for this group of patients between 2010 and 2019, indicating improved care for oncological patients. For benign salivary gland tumors, there has also been an increase in outpatient services (2.3-fold), as well as inpatient services (2.8-fold). Inpatient treatment is also increasing among patients with non-malignant salivary gland lesions (2.6-fold increase), which may be related to more favorable billing for surgical procedures such as sialoendoscopy during the hospitalization. The upward trend in the number of outpatient services may result from the release of limits on services, and from an increase in health awareness in the population. The increase in the number of inpatient services, especially in the case of non-cancer diseases, is also associated with the development of diagnostic and treatment methods, such as sialoendoscopy, which are preferably carried out in hospital conditions. Comparison of the frequency and structure of services with other countries would be an interesting aspect and a pretext for the assessment of the effectiveness; unfortunately, there was no publication presenting such data found.

Another very interesting observation from the study is large regional variation in the prevalence of salivary gland pathology in individual provinces in Poland. On the one hand, the highest rates were noted in provinces with the leading clinical head and neck surgery centers that have extensive experience with complex salivary gland pathologies. Unfortunately, these areas are also highly urbanized and industrialized on a national scale, which may be a factor of exposure for the inhabitants. Similar observations regarding the large regional variation in the prevalence of salivary gland malignancies were presented in the study by Kordzińska-Cisek et al. [4].

The presented analysis has some limitations related to the lack of clinical data, complete histopathological diagnoses, and stage of malignant lesions, which are not reported to the NHF, and thus, could not be included in the study. The reason for these limitations is

primarily the fact that the data in NHF database are mainly recorded for administrative purposes, not for research.

5. Conclusions

The analysis revealed an increasing trend in the incidence of benign salivary gland neoplasm, and a decrease in malignant pathologies over the recent decade in the Polish population. The number of services for patients with benign salivary gland neoplasms has increased in the period under review, and further increases should be expected. Although there was an observed decrease in the number of malignant neoplasms, there was also an increase in the number of outpatient services noted in this group. At the same time, the number of non-malignant salivary gland diseases is decreasing from year to year, but the number of hospital stays associated with these pathologies is increasing. The geographical variation in prevalence, and the presented trends of incidence require reorganization in the health care system to afford optimal medical care in the upcoming years.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/ijerph19010179/s1, Table S1: The detailed number of newly diagnosed salivary glands pathologies with respect to all analyzed ICD-10 codes between 2010 and 2019 in Poland.

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Institutional Review Board Statement: The study followed the tenets of the Declaration of Helsinki for research involving human subjects. The study protocol was approved by the Polish Ministry of Health, which is authorized under Polish law to process National Health Fund data.

Informed Consent Statement: Patient consent was waived due to the law of the Republic of Poland which entitles the Polish Ministry of Health to process the National Health Fund data.

Data Availability Statement: The National Health Fund Registry data are available at http://www.nfz.gov.pl (accessed on 30 June 2021).

Conflicts of Interest: The authors declare no conflict of interest.

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Supplementary Materials

Table S1. The detailed number of newly diagnosed salivary glands pathologies with respect to all analyzed ICD 10 codes between 2010 and 2019 in Poland.

ICD-10	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Total
Malignant neoplasms											
C07	535	554	555	534	485	474	341	326	299	366	4469
C08	215	158	135	129	138	119	106	74	82	92	1248
C08.0	54	45	62	62	60	80	54	61	49	51	578
C08.1	4	2	5	4	7	4	5	4	1	6	42
C08.8	8	16	24	23	17	26	16	27	27	18	202
C08.9	31	32	31	26	25	34	35	41	27	23	305
Benign neoplasms											
D11	1235	1271	1189	1275	1328	1362	957	1074	1001	1184	11876
D11.0	685	787	848	1147	1240	1487	1338	1445	1624	1658	12259
D11.7	77	105	118	139	128	159	177	172	213	149	1437
D11.9	83	110	89	73	116	102	107	100	117	132	1029
Noncancerous diseases											
K11	16920	14748	12697	13518	13810	12534	12118	11666	10535	10299	128845
K11.0	564	503	601	576	548	359	349	276	239	214	4229
K11.1	128	197	250	223	252	223	202	188	164	150	1977
K11.2	1391	1710	2304	2470	2626	2567	3007	2880	2745	2602	24302
K11.3	104	98	112	120	115	134	121	116	124	105	1149
K11.4	28	30	30	31	27	31	30	26	17	18	268
K11.5	737	959	1141	1300	1370	1313	1481	1387	1288	1289	12265
K11.6	269	270	308	292	366	426	383	375	354	373	3416
K11.7	44	56	75	121	153	133	125	137	153	239	1236
K11.8	463	613	954	1139	1190	1234	1533	1528	1346	1319	11319
K11.9	356	448	656	769	823	764	1050	1135	1054	1083	8138
Total	25941	24723	24196	25984	26838	25580	25551	25055	23477	23389	230589

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Article

Clinico-Epidemiological Analysis of Most Prevalent Parotid Gland Carcinomas in Poland over a 20-Year Period

Michał Żurek [1,2,3,*], Kamil Jasak [4], Karolina Jaros [4], Piotr Daniel [4], Kazimierz Niemczyk [1] and Anna Rzepakowska [1,*]

[1] Department of Otorhinolaryngology Head and Neck Surgery, Medical University of Warsaw, 1a Banacha Str., 02-097 Warsaw, Poland
[2] Doctoral School, Medical University of Warsaw, 61 Żwirki i Wigury Str., 02-091 Warsaw, Poland
[3] Department of Analyses and Strategies, Ministry of Health, Miodowa 15 Str., 00-952 Warsaw, Poland
[4] Students Scientific Research Group at the Department of Otorhinolaryngology Head and Neck Surgery, Medical University of Warsaw, 1a Banacha Str., 02-097 Warsaw, Poland
* Correspondence: mzurek@wum.edu.pl (M.Ż.); arzepakowska@wum.edu.pl (A.R.); Tel.: +48-225992716 (M.Ż.); +48-225992716 (A.R.)

Abstract: (1) Background: Malignant tumours of the salivary glands have different clinical and histopathological characteristics. They most commonly involve the parotid gland. Histopathologically, the most common are mucoepidermoid carcinoma (MEC), adenoid cystic carcinoma (AdCC), acinic cell carcinoma (AcCC), adenocarcinoma, carcinoma in pleomorphic adenoma (CPA), and squamous cell carcinoma (SCC). (2) Methods: We analysed 2318 patients with malignant parotid gland tumours reported to the National Cancer Registry (NCR) in Poland over 20 years (1999–2018). The demographic characteristics of patients, clinical factors, and overall survival (OS) were analysed. (3) Results: The average age was 61.33 ± 16.1 years. The majority were males (55%) and urban citizens (64%). High percentage of carcinomas was diagnosed in locoregional (33.7%) and systemic (10.4%) stadium. The most prevalent diagnoses were SCC (33.3%) and adenocarcinoma (19.6%). Surgical resection with adjuvant RT (42.1%) was the most common treatment. The OS analysis showed a median survival time of 5.6 years. The most favorable median OS was found in patients with AcCC (18.30 years), the worst for SCC (1.58 years). (4) Conclusion: AcCC has the best prognosis and SCC the worst. Tumour stadium, treatment, and demographic factors affect prognosis. Improvements in diagnosis and re-evaluation of treatment standards are necessary to enhance the outcome of patients with parotid gland cancers in Poland.

Keywords: parotid gland cancer; mucoepidermoid carcinoma; adenoid cystic carcinoma; acinic cell carcinoma; adenocarcinoma; carcinoma in pleomorphic adenoma; squamous cell carcinoma; overall survival; clinico-epidemiological analysis

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1. Introduction

Salivary gland tumours are heterogeneous lesions with complex clinicopathological characteristics. They constitute 3–10% of all head and neck cancers [1–3], in Europe the percentage amounts to 8.5% [4]. Tumours are mostly benign, only less than 20% of them are malignant [3,5]. The incidence rate of malignant neoplasms of the salivary glands depends on age and population, in most studies it amounts to 0.5–2/100,000 inhabitants [6–8], in Poland average incidence rate over last decade amounts to 1.78 [9]. The most common tumor location of salivary gland malignancies is the parotid gland, with a relative frequency of 58–69% [9–11]. Analyzing all lesions of parotid glands, malignant tumors comprise 15–32% of parotid tumors [8]. These data indicate the importance of parotid glands in the analysis of head and neck cancers, and therefore parotid gland carcinomas are the focus of this article.

The World Health Organization Classification of Head and Neck Tumours distinguishes 24 histopathological types of malignant epithelial tumours of salivary glands [12]. The most prevalent are mucoepidermoid carcinoma (MEC), adenoid cystic carcinoma (AdCC), acinic cell carcinoma (AcCC), and adenocarcinoma. Carcinoma ex pleomorphic adenoma (CPA) and squamous cell carcinoma (SCC) are less commonly diagnosed [8,13,14].

The risk factors of salivary gland cancers are still undefined. Some studies suggest that the history of head and neck cancer, radiotherapy, and some occupations were associated with an increased risk of salivary gland cancers [15,16]. A diet rich in fruit and vegetables and low in foods high in cholesterol may be effective in preventing salivary gland cancer [17]. The role of alcohol consumption and smoking in development of salivary gland cancer is still questionable [15,18,19].

Surgical resection represents the treatment of choice in malignant tumors of the salivary glands [20–23]. The method of surgery depends on the clinical characteristics of carcinoma. The role of elective neck dissection in every salivary gland carcinoma is still controversial, but it is recommended in patients with high-grade histology or T3/T4 tumors [21,23]. It is also recommended to supplement the resection with adjuvant radiotherapy (RT) in high grade or large tumors or in cases where there were incomplete or close resection margins [20–24]. Some authors recommend also adjuvant chemotherapy (CT) or radiochemotherapy (RCT) [22]. In the case of recurrent and inoperable tumors, it is recommended to consider palliative therapy including RT and/or CT [20].

The choice of appropriate treatment has a direct impact on patient prognosis, but it is not the only prognostic factor. Findings indicate clinical factors such as histopathological type and grade of lesion, advanced tumor stage, facial nerve involvement, vascular invasion, lymph node metastasis, and distant metastasis, negatively affect prognosis [14,25–35]. In addition, demographic factors such as gender or age are also factors that affect prognosis [14,26,31,34,36]. Assessing survival and risk of recurrence is extremely important for both clinicians and patients.

Epidemiological studies of the salivary glands pathologies are mainly focused on patients from one or few research centers. Our study covered patients from all over the country registered in The National Cancer Registry (NCR) over 20 years (1999–2018). This gives a comprehensive picture of specified types of carcinomas and applied treatment methods.

The aim of this study was to find out the relative frequency and clinical advancement of the selected, most often histological types of parotid gland cancers and to compare treatment modalities and determine overall survival and define risk factors for death in the Polish population between 1999 and 2018.

2. Materials and Methods

The study design was a nationwide and retrospective survey according to National Health Fund (NHF) and National Cancer Registry (NCR) databases [37,38]. The data concerns all patients who were diagnosed with parotid gland carcinoma in Poland between January 1999 and December 2018. The information includes medical data and demographical features, notably age of patients in moment of the diagnosis, area code, and sex of patients. Medical variables are histopathological diagnosis, disease stadium, treatment method, and survival time.

The diagnoses are coded according to the International Classification of Diseases, 10th Revision (ICD-10) and the International Classification of Diseases for Oncology, 3rd Revision (ICD-O-3). During the study period each patient reported in databases with a confirmed primary diagnosis of parotid gland pathologies was retrospectively identified with ICD-10 codes C07 (with all extensions). The histopathological diagnoses were defined using ICD-O-3 codes:

- 8200/3 for adenoid cystic carcinoma (AdCC)
- 8430/3 for mucoepidermoid carcinoma (MEC)
- 8525/3, 8140/3 and 8147/3 for adenocarcinoma
- 8070/3, 8071/3, 8072/3 and 8073/3 for squamous cell carcinoma (SCC)

- 8550/3 for acinar cell carcinoma (AcCC)
- 6940/3 and 8914/3 for carcinoma in pleomorphic adenoma (CPA)

The treatment methods were identified in NCR database. All therapies are divided into the following groups: only surgery, only radiotherapy, surgery + radiotherapy, surgery + chemotherapy + radiotherapy, and other therapies. Other therapies included: chemoradiotherapy, immunotherapy, and other undefined therapies.

Cancer stadium is a simplified staging according to the clinical stage of disease in NCR reports. It is based on the TNM scale and consists of four levels: in situ, regional, loco-regional, and systemic stadium. Regional stage refers to T1–4 N0 M0, loco-regional to T1–4 N1–3 M0, and systemic stage to T1–4 N1–3 M1.

The information about deaths and population were obtained from Statistics Poland [39]. Patient deaths were reviewed until 31 December 2021.

A statistical analysis was performed for some demographic and clinical factors in the specified period. The following time intervals were created—from 1999 to 2003, from 2004 to 2008, from 2009 to 2013, and from 2014 to 2018. The same factors were also analysed in the specified parotid gland malignancy groups.

The next part of the study included survival analysis conducted in all patients diagnosed with selected types of parotid gland cancer during the period 1999–2018. The Kaplan–Meier curves were used to present the overall patient survival and log-rank tests were used to compare the groups depending on the selected variables (p values < 0.05 were considered statistically significant).

All statistical analyses were performed using R statistical software V. 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

The study was consistent with the assumptions of the Declaration of Helsinki for human research. Demographic characteristics including age, gender, and place of residence were recorded anonymously. Conducting the research did not require the consent of the ethics committee due to the full anonymization of used data.

3. Results

Between 1999 and 2018, 2318 patients with specified parotid gland malignancies were registered. The number of patients significantly increased during the study period ($p = 0.027$). The average age of patients was 61.3 ± 16.1 years. The majority were males (55%) and urban citizens (64%). No statistically significant trend was observed for demographic data (Table 1).

Table 1. Characteristics of patients diagnosed with parotid cancers in NCR in 1999–2018.

Years	1999–2003	2004–2008	2009–2013	2014–2018	All	p-Value
Total number of selected parotid gland cancers	460	548	644	666	2318	0.027
Demographic characteristics						
Mean age ± SD	57.9 ± 15.2	60.4 ± 16.5	63.1 ± 15.7	62.8 ± 16.4	61.3 ± 16.1	0.075
Women (%)	209 (45.4%)	248 (45.3%)	274 (42.6%)	313 (47%)	1044 (45%)	0.442
Men (%)	251 (54.6%)	300 (54.7%)	370 (57.4%)	353 (53%)	1274 (55%)	
Urban citizens (%)	311 (67.6%)	340 (62%)	404 (62.7%)	430 (64.6%)	1485 (64%)	0.256
Rural citizens (%)	149 (32.4%)	208 (38%)	240 (37.3%)	236 (35.4%)	833 (36%)	
Histopathological diagnosis						
Adenoid cystic carcinoma	63 (13.7%)	62 (11.3%)	75 (11.7%)	62 (9.3%)	262 (11.3%)	0.148
Mucoepidermoid carcinoma	57 (12.4%)	87 (15.9%)	93 (14.4%)	81 (12.2%)	318 (13.7%)	0.214
Adenocarcinoma	104 (22.6%)	118 (21.5%)	104 (16.2%)	128 (19.2%)	454 (19.6%)	0.031
Squamous cell carcinoma	131 (28.5%)	168 (30.7%)	244 (37.9%)	229 (34.4%)	772 (33.3%)	0.005
Acinar cell carcinoma	30 (6.5%)	45 (8.2%)	59 (9.2%)	66 (9.9%)	200 (8.6%)	0.228
Carcinoma in pleomorphic adenoma	75 (16.3%)	68 (12.4%)	69 (10.7%)	100 (15%)	312 (13.5%)	0.026
Clinical stage						
Regional	264 (57.4%)	308 (56.2%)	342 (53.1%)	384 (57.7%)	1298 (56%)	0.347
Locoregional	156 (33.9%)	181 (33%)	231 (35.9%)	212 (31.8%)	780 (33.6%)	0.472
Systemic	40 (8.7%)	59 (10.8%)	71 (11%)	70 (10.5%)	240 (10.4%)	0.616

Table 1. *Cont.*

Years	1999–2003	2004–2008	2009–2013	2014–2018	All	*p*-Value
			Therapy			
Only surgery	107 (23.3%)	127 (23.2%)	162 (25.2%)	219 (32.9%)	615 (26.5%)	<0.001
Only radiotherapy	32 (7%)	48 (8.8%)	91 (14.1%)	95 (14.3%)	266 (11.5%)	<0.001
Surgery + radiotherapy	243 (52.8%)	274 (50%)	259 (40.2%)	200 (30%)	976 (42.1%)	<0.001
Surgery + chemotherapy + radiotherapy	37 (8%)	38 (6.9%)	51 (7.9%)	28 (4.2%)	154 (6.6%)	0.022
Others	41 (8.9%)	61 (11.1%)	81 (12.6%)	124 (18.6%)	307 (13.2%)	<0.001

Histopathologically, SCC constituted the largest group of malignancies (33.3%). This was followed by adenocarcinoma (19.6%), MEC (13.7%), and CPA (13.5%). AcCC accounted for the smallest histopathological group (8.6%). Analysis of the proportion of patients with SCC and CPA revealed a statistically significant increasing trend over the study period ($p = 0.005$, $p = 0.026$, respectively). The decreasing trend concerns patients with adenocarcinoma ($p = 0.031$). The mean age of patients at diagnosis date was the highest for SCC (67.6 ± 13.4) and the lowest for AcCC (54.1 ± 19.3). For AcCC, AdCC, and CPA, the majority of patients were female (64%, 59.6%, and 58.7% respectively). Regardless of the diagnosis, patients were predominantly urban residents (from 60.5% to 73.9%). The vast majority were regional stage tumours (56%), locoregional spread affected 33.7% of patients, and systemic spread 10.4%. The largest percentage of advanced stages was identified for SCC (47.4% patients for locoregional advancement and 13.1% for systemic) (Table 2).

Table 2. Characteristic of different histopathological types of parotid cancers.

Histopathology	Adenoid Cystic Carcinoma	Mucoepidermoid Carcinoma	Adenocarcinoma	Squamous Cell Carcinoma	Acinar Cell Carcinoma	Carcinoma in Pleomorphic Adenoma	All
All patients	262	318	454	772	200	312	2318
			Demographic characteristics				
Mean age ± SD	56.34 ± 15.9	56.4 ± 18.6	62.9 ± 13.3	67.6 ± 13.4	54.1 ± 19.3	57.4 ± 15.3	61.3 ± 16.1
Women	155 (59.2%)	146 (45.9%)	184 (40.5%)	248 (32.1%)	128 (64%)	183 (58.7%)	1044 (45%)
Men	107 (40.8%)	172 (54.1%)	270 (59.5%)	524 (67.9%)	72 (36%)	129 (41.3%)	1274 (55%)
Urban citizens	192 (73.9%)	205 (64.5%)	295 (65%)	470 (60.9%)	121 (60.5%)	202 (64.7%)	1485 (64.1%)
Rural citizens	70 (26.1%)	113 (35.5%)	159 (35%)	302 (39.1%)	79 (39.5%)	110 (35.3%)	833 (35.9%)
			Clinical stage				
Regional	174 (66.4%)	190 (59.8%)	236 (52%)	305 (39.5%)	157 (78.5%)	236 (75.6%)	1298 (56%)
Locoregional	57 (21.8%)	113 (35.5%)	148 (32.6%)	366 (47.4%)	36 (18%)	60 (19.2%)	780 (33.8%)
Systemic	31 (11.8%)	15 (4.7%)	70 (15.4%)	101 (13.1%)	7 (3.5%)	13 (4.2%)	237 (10.2%)
			Therapy				
Only surgery	66 (25.4%)	91 (28.6%)	92 (20.3%)	142 (18.4%)	76 (38%)	148 (47.4%)	615 (26.5%)
Only RT	21 (8.1%)	30 (9.4%)	48 (10.6%)	139 (18%)	8 (4%)	20 (6.4%)	266 (11.5%)
Surgery + RT	138 (53.1%)	159 (50%)	209 (46%)	263 (34.1%)	104 (52%)	103 (33%)	976 (42.1%)
Surgery + RCT	19 (7.3%)	21 (6.6%)	33 (7.3%)	63 (8.2%)	5 (2.5%)	13 (4.2%)	154 (6.6%)
Others	18 (3.9%)	17 (3.1%)	72 (11.2%)	165 (24.8%)	7 (0.3%)	28 (1.2%)	307 (13.2%)

The most prevalent therapy for malignant parotid gland tumours was surgical resection with adjuvant RT (42.1%) and surgery alone (26.5%), and the least common was resection with RCT (6.6%). The type of therapy depended on the histopathological type and tumour stage (Figure 1). The fraction of patients treated with surgery alone and RT alone increased significantly (for both $p < 0.001$). However, the proportion of patients treated with surgery followed by RT or RCT decreased ($p < 0.001$, $p = 0.022$, respectively). Palliative therapies (defined as radiotherapy alone or other therapies) also showed an increasing trend ($p < 0.001$).

The OS analysis (Table 3) of selected parotid gland cancers showed a mean survival time of 5.6 years. The most favorable mean overall survival was found in patients with AcCC (18.3 years), CPA (17.4 years), and AdCC (14.9 years). More than 42% of patients survived 20 years or more. The shortest OS was for SCC with an average of 1.6 years; only 27.6% of patients survived 5 years. OS also decreases with tumour stadium (average 13.5 years OS for regional stage, 2.2 years for locoregional, and 1 for systemic). The therapy

with the most favorable prognosis was surgery alone (average 15.1 years of OS) and surgery with radiotherapy (9.2 years of OS). The other therapies were associated with a worse prognosis.

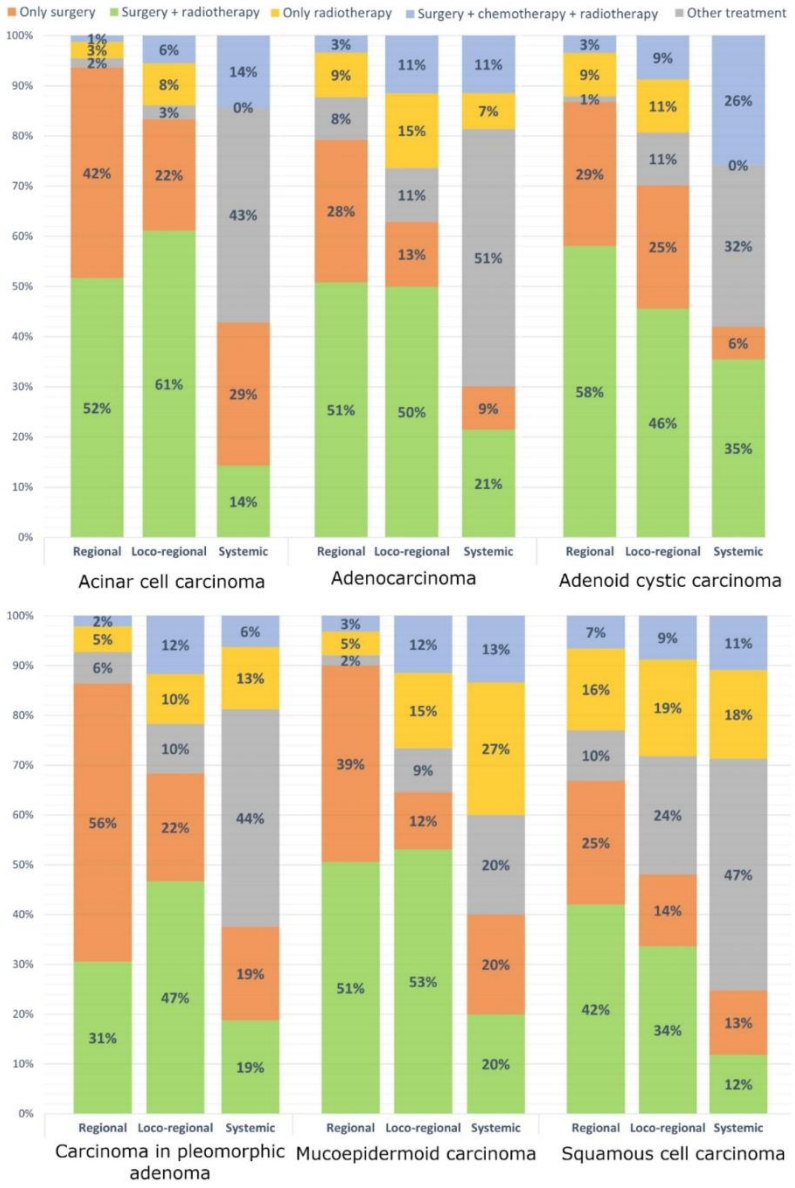

Figure 1. Frequency of treatment modalities stratified by stadium and histology of the cancer.

Table 3. OS of patients with parotid cancers stratified by histology, stadium, and therapy.

OS	Median (Years)	1-Year (%)	5-Years (%)	10-Years (%)	20-Years (%)
All analysed parotid gland cancers	5.6	80%	51.7%	41.1%	28.1%
Histopathological diagnosis					
Acinar cell carcinoma	18.3	97%	81.1%	72.6%	47.3%
Adenocarcinoma	4.5	81.3%	48.7%	35.9%	23.6%
Adenoid cystic carcinoma	14.9	91.6%	75%	58.4%	42.7%
Carcinoma in pleomorphic adenoma	17.4	88.1%	69.6%	60.7%	42.2%
Mucoepidermoid carcinoma	10.9	85.8%	58.9%	51.2%	40.2%
Squamous cell carcinoma	1.6	65.2%	27.6%	18.5%	10.3%
Clinical stage					
Regional	13.5	90.8%	69.3%	57.5%	41.8%
Locoregional	2.21	71.4%	34%	24.1%	13.5%
Systemic	1	49.6%	14%	9.4%	2.3%
Therapy					
Only surgery	15.1	86.8%	69.6%	57.5%	43.5%
Only radiotherapy	1.3	59%	26%	18.7%	16.9%
Surgery + radiotherapy	9.2	89.2%	60.5%	49.2%	31.7%
Surgery + chemotherapy + radiotherapy	2.5	83.8%	28.4%	15.2%	7.8%
Other treatment	1.2	53.1%	21.8%	14.8%	10.5%

The Kaplan–Meier curves presenting OS in patients with parotid cancers were stratified by demographic factors, stadium, histology, and treatment modality (Figures 2–4).

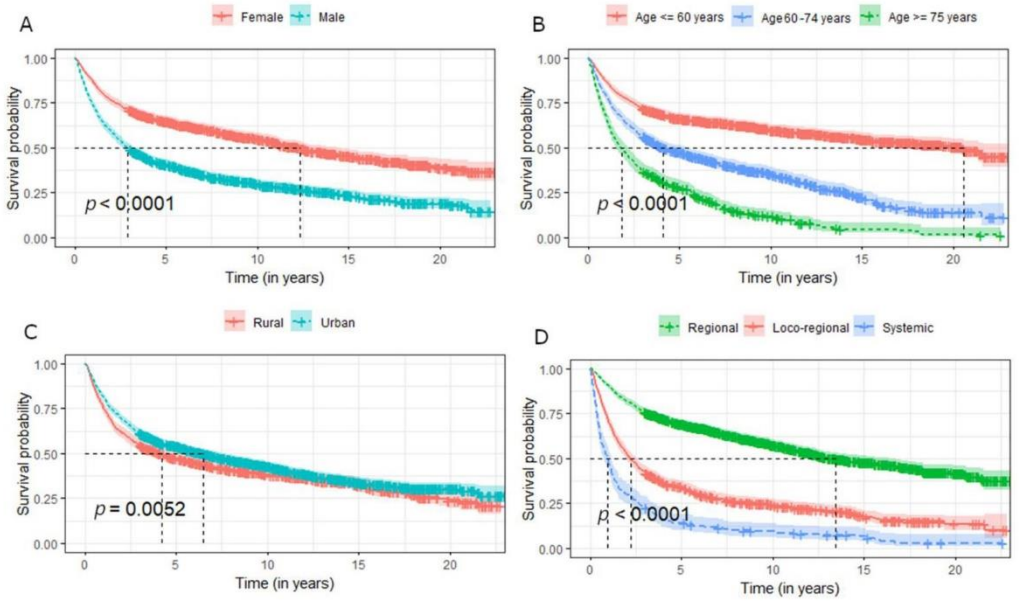

Figure 2. Survival of patients with parotid cancers stratified by demographic factors and stadium of the cancer: (**A**) sex, (**B**) group of age, (**C**) place of residence, (**D**) stadium.

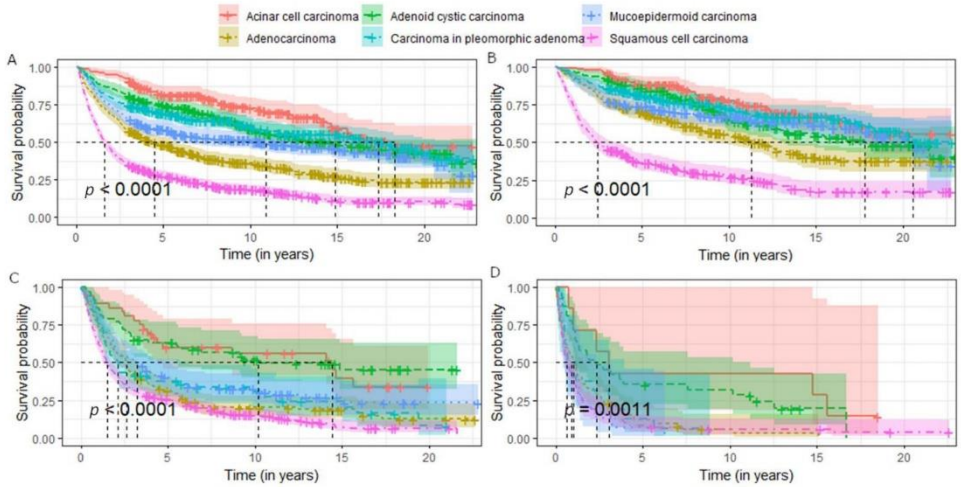

Figure 3. Survival of patients with specified parotid gland cancers stratified by stadium of advancement: (**A**) all cancers, (**B**)regional stadium, (**C**) locoregional stadium, (**D**) systemic stadium.

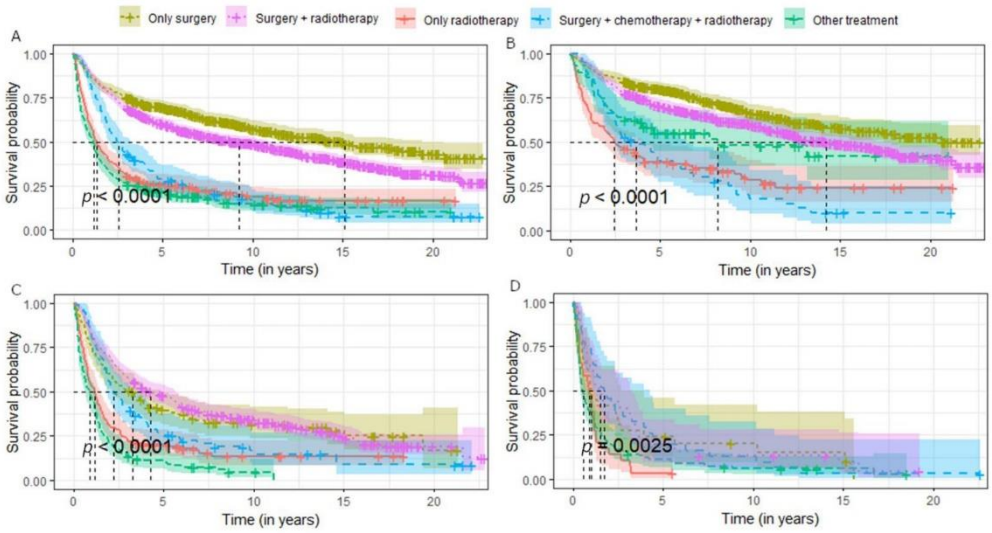

Figure 4. Survival of patients with parotid gland cancers stratified by treatment methods and stadium of the cancer: (**A**) all cancers, (**B**) regional stadium, (**C**) locoregional stadium, (**D**) systemic stadium.

4. Discussion

Salivary gland malignancies are a heterogeneous group of pathologies that vary significantly in terms of prognosis depending on the histopathological nature of the lesion. There have been several retrospective cohort studies so far [10,14,29,40–43], but none of them explored the issue in such a comprehensive way. To our knowledge, this is the only study that comprehensively assesses prognosis and risk factors in the six most common histopathological types of salivary gland malignancies. It is also one of the largest studies in terms of number of patients.

4.1. Epidemiological Characteristics of Patients

AcCC represented the youngest group among all tumours and the vast majority were women, which is consistent with literature data [31,42,44,45]. The demographic characteristics of patients with AdCC are consistent with other results in the literature, especially the gender ratio is consistent regardless of the centre or country studied (percentage of female patients between 59% and 67%) [46–49]. A systematic review including 13 articles and 263 patients with AdCC identified a mean patient age of 55.26 years and a female percentage of 56.5% [50]. CPA is a rare malignant tumour of the salivary glands. It represents 3–15% of all malignant salivary gland carcinomas [51], as in our study. The majority of studies report a higher incidence among men [33,51–53]. The range of patients mean age is from 57 to 62.1 years [33,51–54], which is consistent with our results. MEC is considered one of the most common salivary gland malignancies [11,41,55], however, in this study, MEC represents only 13.7% of all malignancies. Data from other studies confirm the average age of patients with MEC [41,55], but women appear to be more commonly affected than men [11,41,55–57], which is inconsistent with the above results. Adenocarcinoma is estimated also as one of the most common malignancies of the salivary glands and accounts for approximately 13–17% of all salivary carcinomas [58,59]. According to the literature, salivary gland adenocarcinoma more commonly affects men, with an average age range of 57.5–67 years [43,58–60]; our results confirm the literature data. Parotid gland SCC is thought to be more often metastatic cutaneous SCC rather than primary disease [40,61,62]. Generally it is thought to be a rare type among primary parotid pathology, however, it is considered highly malicious [61,63,64], but some epidemiological studies confirm the significant share of SCC among malignancies of parotid gland, especially when only metastases are analysed [65–68]. In the study of Mayer et al. [67], SCC accounted for 35.4% of all parotid malignancies, a very similar result to the above analysis. However, it should be emphasised that the vast majority of parotid SCCs are metastases from other sites, and they account for up to 86% of all salivary SCC [65,68]. The methodology of the study precludes the identification of primary and metastatic carcinomas, so the results reported concern both types of lesions (see "Limitations"). Epidemiological data indicate an approximately over 2-fold higher incidence among men [25,40,61,62,69]. The average age of patients is 64–73 years [40,61,69]. SCC is often diagnosed at the advanced stage with involvement of lymph nodes or with distant metastases [25,64]. The above results are consistent with those we presented.

In conclusion, the results are largely consistent with reports from other countries, demonstrating the lack of regional differences in demographic characteristics of patients with parotid gland malignancies. This allows us to conclude that geographical factors and related cultural differences do not influence the epidemiological depiction of parotid carcinomas.

4.2. Clinical Characteristics of Patients

AcCC is considered a slow-growing tumour and less aggressive than other malignancies [30,31,45,70], as confirmed by the above results. CPA is a rare and aggressive parotid carcinoma, and can develop de novo or based on pleomorphic adenoma. It is poorly understood and the clinical picture of the lesion cannot be briefly characterised; the exact factors for less or more aggressive course of CPA are not known [51,71,72]. Due to the high clinical variability at the time of diagnosis, the discrepancy in prognosis is so high. In the case of the present study, the majority of patients were in the early stages at the time of diagnosis, which should be considered as a coincidence or success of an effective diagnosis. For AdCC, the proportions in stages are similar to the average for all malignancies. Although these tumors have a slow growth rate, they are characterised by extensive local infiltration and a high risk of recurrence [47,49,73]. MEC is one of the most common major salivary malignancies [11,41,57]. Descriptions of MEC in the literature indicate a large variety of biological behavior and clinical course because of cellular heterogeneity. MEC can reoccur and metastasize to regional lymph nodes or distant sites [11,41,55,57],

although in our study the vast majority of patients were diagnosed at the regional stadium of the disease. Adenocarcinoma (especially high-grade adenocarcinoma) presents aggressive features such as perineural invasion, positive margins, advanced T status, or lymph node involvement at the time of diagnosis [58,59]. Therefore, diagnosis is often made at an advanced stage, as confirmed by the results of our study. The higher frequency of diagnoses in advanced stage of cancer is also confirmed by Zhan et al. [43]. SCC of parotid glands are thought to be invasions from adjacent SCC of head and neck or distant metastases rather than de novo neoplasms; SCC arising de novo from the parotid gland comprise from 0.3 to 6.9% of primary salivary gland neoplasms [25,61,64]. Both primary parotid and metastatic SCC are aggressive with high malignant potential and the prognosis is relatively unfavorable [25,40,63,69]. Parotid SCC are usually diagnosed at an advanced stage with involvement of facial nerve and cervical metastases [25,62]. In our study, the data precludes to distinguish primary lesions from metastases, but still, the frequent diagnosis at an advanced stage and the poor prognosis are confirmed.

4.3. Treatment Modalities

The choice of therapy in malignancies of parotid glands depends mainly on the advancement of the disease and histopathological type of the lesion. According to NCCN Guidelines Version 2.2022 [24], surgery with complete resection of a tumour is the treatment of choice if there are no contraindications. In addition, postoperative RT should be considered in all cases of AdCC and for other malignancies when certain conditions are identified. RT is also recommended in most cases of recurrent lesions. New analyses highlight the role of RT in the treatment of salivary gland malignancies and indicate better OS in certain histopathological types of tumors [74].

Analysis of the treatment modalities in Poland shows a definite advantage of surgical treatment with RT in regional and locoregional stadium. Only for CPA at the initial stadium, the majority of patients (58%) were treated with surgery alone. NCCN guidelines do not indicate the need for specific treatment regimen in the case of CPA, however, some studies suggests that surgery followed by postoperative RT should be considered the standard of care [53,75]. The lack of an accurate clinical picture of the patients enrolled in the NCR database precludes to objectively assess the results presented; however, it is important to emphasise the current discrepancies in the results of efficacy of treatment modalities and to recommend the need for an individual approach and consideration of postoperative RT in each case.

A major deviation from current standards concerns patients with AdCC treated surgically without adjuvant RT. The current Polish recommendations are based on NCCN standards, but differ slightly from them. First of all, in the context of AdCC, surgical resection with postoperative RT is recommended when the lesion size exceeds 2 cm. This discrepancy may be one reason for such a high number of AdCC resections without RT. The majority of studies recommend surgery and postoperative RT for each primary AdCC, such treatment results in excellent outcomes with a low rate of late toxicity and preservation of a good quality of life [22,47,76].

The biggest deviation from the average treatment scheme concerns SCC. The overall analysis indicates the frequent use of palliative treatment methods. As stated in the previous paragraph, most parotid SCC lesions are invasions from adjacent cancers or distant metastases. In such cases, the use of palliative therapy is common. However, it is worth looking at the rather high percentage of RT alone. Studies on parotid SCC, however, show no benefit in the use of RT alone [40,62], even compared to no treatment at all [61]. It is therefore important to consider the precise indications for this type of treatment and the resulting benefits and disadvantages to the patient's quality of life, especially with RT alone being so frequently chosen as a therapy.

Analysis of OS according to the performed therapy gives some unambiguous conclusions. Depending on the period analysed, the best prognostic therapy is surgery alone or surgery with adjuvant RT. Within 1 year from the diagnosis of the neoplasm, more patients

survived when treated with surgery with RT comparing surgery alone, but in subsequent years this trend changes in favor of radical surgery. However, the results must be stratified by tumour stage in order to draw correct conclusions. In the regional stadium, average survival is better for surgical treatment alone, but in the loco-regional stage, surgery with adjuvant RT has a better prognosis for the first 10 years (Figure 4). The results are supported by other studies showing a lack of benefit of post-operative radiotherapy in early stages of salivary gland cancers [19,46].

4.4. Overal Survival

Other studies have reported higher 5-year OS than in our analysis (between 55 and 84.6%) but comparable 10-year OS (between 32 and 74.7%) [10,29,32,34,35]. The prognosis of OS for patients with parotid cancers depends on many factors. The major one is histopathologic type of the tumor.

AcCC is one with the most favourable prognosis. Positive results are confirmed in other studies, with 5- and 10-year survival rates ranging from 85 to 93% and from 79 to 88%, respectively [19,47,49–51].

Satisfactory prognosis concerns patients with AdCC, which is consistent with other studies with 5-year OS ranging from 67% to 92.5%, and 10-year OS from 25.6% to 65% [22,46,47,50,73,77,78].

The OS of CPA indicates a relatively good prognosis. The presented results are better than in other studies (range 25–68.5%) [33,51,53,54,71,72], but worse than in the study of Zbären et al. [79] who noted 5-year OS of 76%.

Results of OS for MEC are completely unsatisfactory compared to those reported in the literature. In the study by Boahene et al. [55], the 5- and 10-year OS were 96.6% and 97.4%, respectively, and in the study by Chan et al. [11] 93.6% and 67.4%, respectively. In the US, the 5-year OS was determined as 75.2% [41].

Poor prognosis concerns patients with adenocarcinoma, which was confirmed by other studies; 5-year OS was estimated at 43–62.2% [43,58–60,72]; and 10-year OS was only 20.7% [58].

SCC is one of the cancers with the worst prognosis. The 5-year survival is estimated at 25–31% [63,64], which is consistent with the results of the above analysis.

In the case of AcCC and MEC, the prognosis is generally worse than in other studies. The reason for differences in MEC may be due to the rather high proportion of patients with advanced stage of the disease compared to proportions from the cited studies. In the case of AcCC, most of the reported cancers were in regional stadium, so there is no clear justification for the difference.

Presented outcomes analysis shows that there is a potential to improve the prognosis of patients with parotid gland cancers in Poland both through more effective and earlier initiated diagnostics and application of more comprehensive treatment modalities.

4.5. Limitations

This study analyses cases registered in the NCR database. This is a nationwide database, but due to the dispersed nature of the reporting, we have no assurance of the reliability and completeness of the data and the results may be subject to error, which is beyond the control of the authors. The NCR database contains specific clinical data with varying degrees of detail. In the above analysis, we could differentiate regional, local, or distant disease. More detailed data on the TNM classification or clinical stage were highly incomplete, which precluded an accurate statistical analysis. The lack of clinical data on individual patients is a significant limitation of the study, the reason is the specific data encoding profile in the NCR and NHF databases and the authors of the project have no influence on the issue.

The evaluation of parotid SCC in the study group requires separate comment. The significant proportion of this type of cancer is probably due to the presence of metastatic lesions in the salivary glands. The data provided did not include information on other

types of cancer, so we cannot identify which patients have SCC as a primary cancer or as a metastasis. This is a significant limitation in the clinical interpretation of the results. However, it should be noted that primary parotid SCC is a diagnosis by exclusion, and with this histopathological diagnosis, it should be assumed that the lesion is a metastasis and the primary cancer should be sought.

5. Conclusions

Over the 20 years there were no observed changes in the age, sex, and inhabitant of patients with the analysed malignant parotid gland neoplasms. The results of demographic analyses are largely consistent with reports from other countries, demonstrating the lack of regional differences in demographic characteristics of patients with parotid gland malignancies. Treatment modalities for malignancies of parotid glands do not follow NCCN standards in every case; the high proportion of patients treated with RT alone remains controversial and requires detailed reevaluation regarding presented poor survival outcomes for this modality. SCC constituted the largest group of malignancies (33.3%), followed by adenocarcinoma (19.6%) and MEC (13.7%). SCC include primary or metastatic tumours, thereby results in this group concern a heterogeneous group of patients. The best performing malignancy among those analysed is AcCC, and the worst is SCC. Tumour stadium seems to have the crucial role when assessing prognosis.

Presented analysis shows potential directions to improve the outcomes in patients with parotid gland cancers in Poland.

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Abbreviations

AcCC	acinic cell carcinoma
AdCC	adenoid cystic carcinoma
CPA	carcinoma in pleomorphic adenoma
CT	chemotherapy
MEC	mucoepidermoid carcinoma
NCR	National Cancer Registry
NHF	National Health Fund
OS	overall survival
RCT	radiochemotherapy
RT	radiotherapy
SCC	squamous cell carcinoma

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REVIEW ARTICLE

Salivary gland pathologies: evolution in classification and association with unique genetic alterations

Michał Żurek[1,2] · Łukasz Fus[3] · Kazimierz Niemczyk[1] · Anna Rzepakowska[1]

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Abstract

Purpose The correct classification of salivary gland pathologies is crucial for choosing a treatment method and determining the prognosis. Better outcomes are now achievable thanks to the introduction of new therapy approaches, such as targeted therapies for malignant salivary gland tumors. To apply these in clinical routine, a clear classification of the lesions is required.

Methods The following review examines all changes from the first World Health Organization (WHO) Classification of salivary gland pathologies from 1972 to fifth edition from 2022. Possible developments in the diagnosis and classification of salivary gland pathology are also presented.

Results The current WHO classification is the fifth edition. With the development of new diagnostic methods, based on genetic alterations, it provides insight into the molecular basis of lesions. This has resulted in the evolution of classification, introduction of new entities and reclassification of existing ones.

Conclusions Genetic alterations will become increasingly more significant in the identification of salivary gland pathologies in the future. These alterations will be helpful as prognostic and predictive biomarkers, and may also serve as targets for anti-cancer therapies.

Keywords Salivary gland pathologies · Salivary gland tumours · Salivary gland cancers · Classification · Genetic alterations

Abbreviations

WHO	World Health Organisation
IPMN	Intraductal papillary mucinous neoplasm
SCC	Squamous cell carcinoma
MALT	Mucosa-associated lymphoid tissue
FNA	Fine needle aspiration
DCE	Dynamic contrast-enhanced
MRI	Magnetic resonance imaging
CT	Computed tomography
CNB	Core-needle biopsy
ORR	Objective response rate
DCR	Disease control rate
AR	Androgen receptor
ADT	Androgen-deprivation therapy
SWE	Shear wave elastography
CEUS	Contrast enhanced ultrasonography

✉ Michał Żurek
michal.zurek@wum.edu.pl

[1] Department of Otorhinolaryngology Head and Neck Surgery, Medical University of Warsaw, 1a Banacha Str, 02-097 Warsaw, Poland

[2] Doctoral School, Medical University of Warsaw, 61 Żwirki I Wigury Str, 02-091 Warsaw, Poland

[3] Department of Pathology, Medical University of Warsaw, 7 Pawińskiego Str, 02-004 Warsaw, Poland

Introduction

Salivary gland pathologies are a range of diverse diseases, therefore, classification is challenging. Moreover, developments in diagnostic methods, particularly at the molecular level, are allowing the discovery of novel subtypes of known diseases, that restrict the proper classification.

The first edition of the WHO Histologic Classification of Salivary Gland Tumours [1] was published in 1972 and included 11 different pathologies divided into three main categories (epithelial tumours, non-epithelial tumours and unclassified tumours). This classification remained in force for almost 20 years until the introduction of the second edition of the WHO Histologic Classification of Salivary

Gland Tumours in 1991 [2]. There were 31 pathologies, which were divided into the following categories: carcinomas, adenomas, non-epithelial tumours, malignant lymphomas, secondary tumours and unclassified tumours. Further development of research and improved availability of modern diagnostic methods led to the reclassification of salivary gland diseases in 2005. The third edition of the WHO Classification [3] included 39 pathologies divided into categories: malignant epithelial tumours, benign epithelial tumours, soft-tissue tumours, haematolymphoid tumours and secondary tumours. This classification was in force for 12 years until the fourth edition of the Blue Book was introduced in 2017 [4]. It presented salivary gland lesions in a new perspective, with an emphasis on genetic alterations. Also, new was the proposition of the category 'non-neoplastic epithelial lesions'. In addition, a distinction was made between malignant epithelial tumours, benign epithelial tumours, benign soft tissue tumours and haematolymphoid tumours (a total of 39 pathologies). This was the shortest-lived classification, as only 5 years later, in 2022, the fifth edition of the WHO Classification [5] was introduced. Many key rearrangements in the classification were incorporated. The latest edition also highlights 39 salivary gland pathologies, which are divided into four categories: non-neoplastic epithelial lesions, malignant and benign epithelial tumours and mesenchymal tumours specific to the salivary glands.

The correct classification of a patient's disease is crucial for choosing a treatment method and determining the prognosis. In the future, the development of modern treatment methods, including targeted therapies in management of malignant salivary glands tumours [6], would provide better treatment outcomes. Worldwide and routine application of such methods in everyday clinical practice will be possible with the accurate and practical classification based on biological and prognostic factors of the lesions for precise identification of patients eligible for a specific therapy.

Carcinomas/malignant epithelial tumours

The first edition of the WHO classification of salivary gland diseases distinguished five carcinomas and two tumours (the malignant nature of these was not specified at the time). In subsequent editions, the number of distinguished malignant salivary gland lesions increased. The 1991 classification proposed 18 primary carcinomas. The next edition from 2005 distinguished 24 malignant epithelial tumours. Contrary, the number of malignant epithelial tumours was reduced to 20 types of carcinomas in 2017 and in the following classification from 2022, 21 different malignant salivary gland pathologies were identified. The changes in classifications are shown in Fig. 1.

Some diagnoses have remained the same since 1972. These include adenoid cystic carcinoma and carcinoma in pleomorphic adenoma (or carcinoma ex pleomorphic adenoma). Mucoepidermoid and acinic cell carcinomas were initially classified as tumours of uncertain malignancy, but were recognized as malignant lesions in the second edition of the classification. Although there has not been a reclassification of these lesions over the years, it should be emphasized that the definitions of individual diagnoses have been updated. The first two editions of the Blue Book based the classification on histological features seen with conventional light microscopy. Immunocytochemistry was limited to specific cases [7]. From 2005, immunohistochemical markers started to be introduced into the definitions. In the fourth edition, the importance of translocations and gene fusions was raised. Molecular alterations were included, among others, in definitions of mucoepidermoid and adenoid cystic carcinoma in the latest edition of the Blue Book [5]. The key molecular alterations of salivary gland malignancies are presented in Table 1.

Essential modifications have occurred in the classification of adenocarcinomas. The first edition of the WHO classification [1] did not distinguish subtypes of this carcinoma at all. In the second edition [2], it was divided into five distinct types. and in the subsequent 2005 edition [3] into 7 adenocarcinoma subtypes. The next classification from 2017 [4] was simplified to four types of adenocarcinomas These changes have given more freedom to pathomorphologists. The grade of the tumours was no longer included in the classification. At the same time, low-grade cribriform cystadenocarcinoma was reclassified into intraductal carcinoma. The latest, fifth WHO classification [5] introduces three new entities—microsecretory adenocarcinoma, sclerosing microcystic adenocarcinoma and mucinous adenocarcinoma.

Despite the development of diagnostic methods and increasingly precise requirements for classifying lesions into a specific type of carcinoma, there are still some difficulties in distinguishing between certain pathologies. Some of these are discussed in the following paragraphs.

An example is the relation between intraductal papillary mucinous neoplasm (IPMN) and mucinous adenocarcinoma. Mucinous adenocarcinoma (regardless of subtype) is characterized by a recurrent AKT1 p.E17K mutation [8, 9]. The same mutation is present in IPMN and the histopathological features resemble mucinous adenocarcinoma [10]. The relationship between the two lesions remains controversial. IPMN can be considered as a separate lesion, precursor or subtype of mucinous adenocarcinoma [5].

Intraductal carcinoma is characterized by proliferations entirely or predominantly intraductal. Some scientific reports state that invasive growth can appear in intraductal carcinoma, so it is not truly in-situ neoplasm and the name "intraductal" may not be correct [11–13].

Fig. 1 Changes in classifications of salivary gland malignancies

Oncocytic appearance is common in different salivary gland tumours. Lesions consisting entirely of oncocytes have been classified as oncocytic carcinoma. However, some studies at the molecular level indicate that these lesions should rather be classified as an oncocytic subtype of other carcinomas. To date, neither we have real evidence that purely oncocytic carcinoma exists, nor there have been discovered characteristic genetic alterations for this type of cancer [11, 14–16].

The distinction between primary and secondary squamous cell carcinoma (SCC) of salivary gland still remains a diagnostic challenge. The majority of cases are metastatic tumours [17]. The diagnosis of primary SCC remains a diagnosis of exclusion. The radiological examinations are necessary to identify the site of origin, because

Table 1 Selected genetic alterations in salivary gland malignancies [11, 14, 20]

Tumour type	Gene	Mechanism	Prevalence
Acinic cell carcinoma	NR4A3	Fusion/activation	86%
Adenoid cystic carcinoma	MYB	Fusion/activation/amplification	80%
	MYBL1	Fusion/activation/amplification	10%
	NOTCH	Mutation	14%
Basal cell adenocarcinoma	CYLD	Mutation	29%
Carcinoma ex pleomorphic adenoma	PLAG1	Fusion/amplification	73%
	HMGA2	Fusion/amplification	14%
	TP53	Mutation	60%
Epithelial-myoepithelial carcinoma	HRAS	Mutation	78%
Hyalinizing clear cell carcinoma	EWSR1-ATF1	Fusion	93%
Intraductal carcinoma			
Intercalated duct subtype	NCOA4-RET	Fusion	47%
Apocrine subtype	PIK3CA HRAS	Mutation Mutation	High High
Salivary duct carcinoma	HER2	Amplification	31%
	FGFR1	Amplification	10%
	TP53	Mutation	56%
	PIK3CA	Mutation	33%
	HRAS	Mutation	33%
	AR	Copy gain	35%
	PTEN	Loss	38%
	CDKN2A	Loss	10%
Microsecretory adenocarcinoma	MEF2C-SS18	Fusion	> 90%
Mucinous adenocarcinoma	AKT1 E17K	Mutation	100%
	TP53	Mutation	88%
Mucoepidermoid carcinoma	CRTC1-MAML2	Fusion	40–90%
	CRTC3-MAML2	Fusion	6%
	CDKN2A	Deletion	25%
Myoepithelial carcinoma	PLAG1	Fusion	38%
	EWSR1	Rearrangement	13%
Polymorphous adenocarcinoma			
Classic subtype	PRKD1	Mutation	73%
Cribriform subtype	PRKD1	Fusion	38%
	PRKD2	Fusion	14%
	PRKD3	Fusion	19%
Sebaceous adenocarcinoma	MSH2	Loss	10%
Secretory carcinoma	ETV6-NTRK3	Fusion	> 90%
	ETV6-RET	Fusion	2–5%

it is often not obvious at the time of presentation. It is difficult to differentiate between primary and secondary SCC on histopathology exam [18]. Both are characterized by keratinization. Primary SCCs exhibit a desmoplastic reaction and peritumoral inflammation compared to metastatic SCCs, as well as a serrated margin and less central necrosis [19]. However, these findings are non-specific. Till now, no characteristic biomarkers or genetic alterations specific to primary SCC have been discovered.

Adenomas/benign epithelial tumours

The first edition of the WHO classification of head and neck tumours [1] distinguished two benign salivary gland tumours—pleomorphic and monomorphic adenomas (with subtypes adenolymphoma, oxyphilic adenoma and other types). Subsequent classifications included many more benign lesions—9 in the second [2], 10 in the third [3], 11 in the fourth [4], and 15 in the fifth [5]. The breakthrough between the first and second editions of the Blue Book was due to the increased recognition of benign lesions and

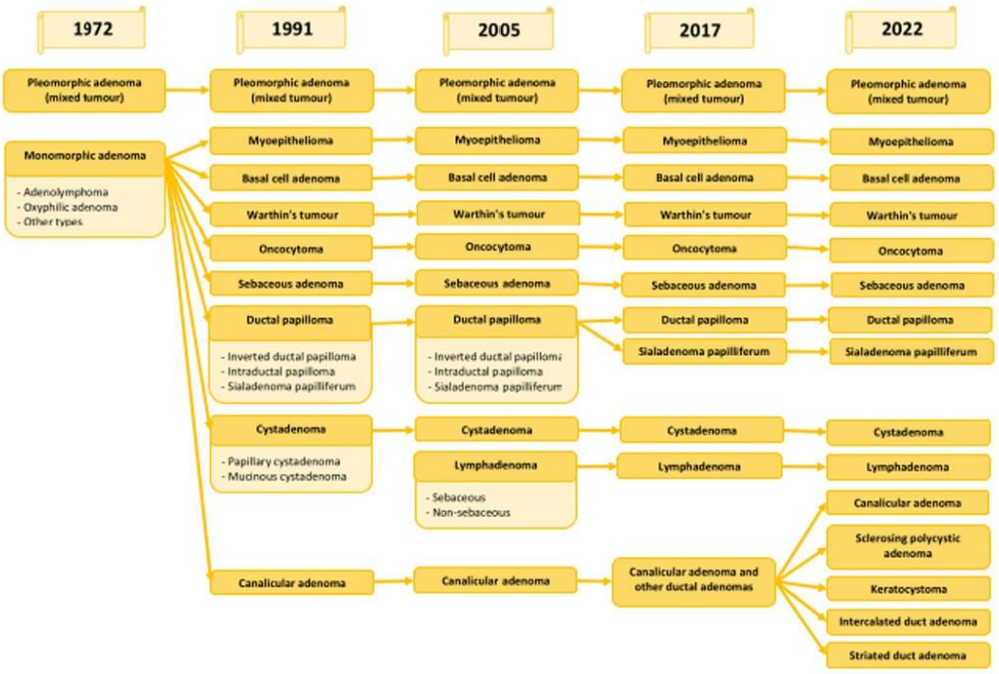

Fig. 2 Changes in classifications of salivary benign epithelial tumours

Table 2 Key genetic alterations in salivary benign tumours [11, 20]

Benign epithelial tumours	Gene	Mechanism	Prevalence
Basal cell adenoma	CTNNB1	Mutation	37–80%
	AXIN1	Mutation	~36%
Myoepithelioma	PLAG1	Fusion	~40%
Pleomorphic adenoma	PLAG1	Fusion/amplification	>50%
	HMGA2	Fusion/amplification	~15%
Sialadenoma papilliferum	BRAF V600E	Mutation	50–100%

distinct morphological features of monomorphic adenomas, so it was decided to separate the lesions for identification purposes (Fig. 2).

Similarly to the malignant lesions, the involvement of genetic differences is also emphasized among benign lesions. Although still none of the benign salivary gland lesions is defined by genetic alterations, specific molecular changes have been identified and may provide an aid to classification and serve as potential biomarkers in the future. The most important genetic alterations in benign salivary gland lesions are shown in Table 2.

Although the classification of benign salivary gland lesions does not pose as many problems as in case of malignancies, the relationship between pleomorphic adenoma and metastasizing pleomorphic adenoma has caused controversy over the last few classifications. Pleomorphic adenoma, also called benign mixed tumour, is found mostly in the parotid gland in third to sixth decade of life, and occurs more frequently in women [21, 22]. It is the most prevalent lesion among salivary gland benign tumours (up to two-thirds of all adenomas) [23, 24], but it is worth noting that recent studies indicate that this lesion is becoming rarer compared to Warthin's tumour, the incidence of which has been increasing recently [25–27], particularly affecting Europe [28]. Pleomorphic adenoma progresses slowly, but can undergo malignant transformation to carcinoma

ex-pleomorphic adenoma [29]; rarely can metastasise without the transformation and is called metastasizing pleomorphic adenoma [30]. Metastasizing pleomorphic adenoma is histologically indistinguishable from pleomorphic adenoma [31]. The term was introduced in the third edition of Blue Book as malignant carcinoma, but subsequent classifications have dropped the distinction of this change as a separate entity. The most common genetic alterations in pleomorphic adenomas are PLAG1 and HMGA2 fusions or amplifications [11, 32].

The merit of genetic studies is the manifestation of the neoplastic features of sclerosing polycystic adenoma. This lesion was first introduced in the fourth edition of the WHO classification in the non-neoplastic epithelial lesion category [4]. However, several studies have shown recurrent mutations in the PI3 kinase pathway (primarily PIK3CA mutation), which confirm its neoplastic nature [33–36]. As a result of these findings, the latest classification of salivary gland lesions includes sclerosing polycystic adenoma to benign epithelial tumours [5].

Others

Other lesions described in the WHO classification included secondary and unclassified tumours, soft tissue tumours, lymphomas and non-neoplastic epithelial lesions.

Non-epithelial tumours were classified since the first edition of the Blue Book [1]. Starting from the third edition in 2005, the name of this group of lesions has been changed to soft tissue tumours and one subtype, haemangioma, has been distinguished [3]. In 2017, lipoma/sialolipoma and nodular fasciitis were added to this category [4]. However, these lesions were omitted from the latest classification [5]. The reason is that they do not occur exclusively or predominantly in salivary glands [11].

Hematolymphoid tumours were firstly added to classification in second edition, and described as malignant lymphomas [2]. There are distinguished lymphomas as part of systemic disease and as separate salivary gland manifestations. The lymphomas were classified using the same terminology as is applied to lymphoid lesions [37]. In the next edition, the name was changed to haematolymphoid tumours and three types of lesions were distinguished [3]. In 2017, this category was restricted to a single diagnosis [4]. The lymphoid tissue is a part of mucosa-associated lymphoid tissue and the extranodal marginal-zone B-cell lymphoma is the most common primary non-Hodgkin's lymphoma of the salivary glands [38]. In the latest edition of the Blue Book, these changes have been deleted from the classification [5].

For the first time in the fourth edition of the Blue Book, a category of non-neoplastic epithelial lesions was introduced [4]. The main diagnosis in this group is sclerosing polycystic adenosis. Lesions of this type had been known since 1996 [39], and the need to add this diagnosis to the classification had already been postulated several years before the fourth edition [40]. Other diagnoses in this category included nodular oncocytic hyperplasia, lymphoepithelial sialadenitis and intercalated duct hyperplasia. In 2022, non-neoplastic epithelial lesions were limited to two diagnoses: nodular oncocytic hyperplasia and lymphoepithelial sialadenitis [5]. Sclerosing polycystic adenosis has been renamed to sclerosing polycystic adenoma and added to the category benign epithelial tumours [11].

A summary of the changes in the classifications described above is shown in Fig. 3.

Therapeutic and prognostic implications of correct diagnosis

Proper diagnosis of salivary gland pathology allows us to make the right therapeutic decision and determine the patient's prognosis. The most common treatment for salivary gland tumours is surgical resection, and the extent of surgery is determined mainly by anatomical and clinical criteria, but for some lesions an accurate diagnosis should influence therapeutic decisions. In the case of pleomorphic adenoma, the risk of tumour recurrence is about 2–3% and is highest in the myxoid subtype, as well as in the presence of thickness and incompleteness of the tumour capsule, pseudopodia, and satellite nodules [41, 42]. For this reason, more extended surgical techniques are preferred for the treatment of pleomorphic adenoma. Another criterion for extended surgical treatment is recurrence [42, 43].

Accurate differentiation of lesions is also important in planning treatment of canalicular adenomas, which have been divided into five different diagnoses in the latest classification of pathology [5]. Currently lesions classified as canalicular adenomas occur mainly in the upper lip [44], but other lesions are predominantly recognized in the parotid glands. For intercalated duct adenoma, striated duct adenoma and keratocystoma, the prognosis is the best, and no recurrence of the lesions has been described to date [5]. However, in the case of sclerosing polycystic adenoma, there is a risk of recurrence [45] and even malignant transformation of the lesions [40, 46], which should prompt expanded resection technique and more frequent postoperative follow-up. Until 2022, the aforementioned pathologies were not differentiated, which, as indicated above, may be misleading in the treatment and prognosis of patients.

The biggest differences in patient prognosis and treatment standards are seen when comparing different types of malignancies. If there are no contraindications, surgery with total tumour excision is the treatment of choice, according

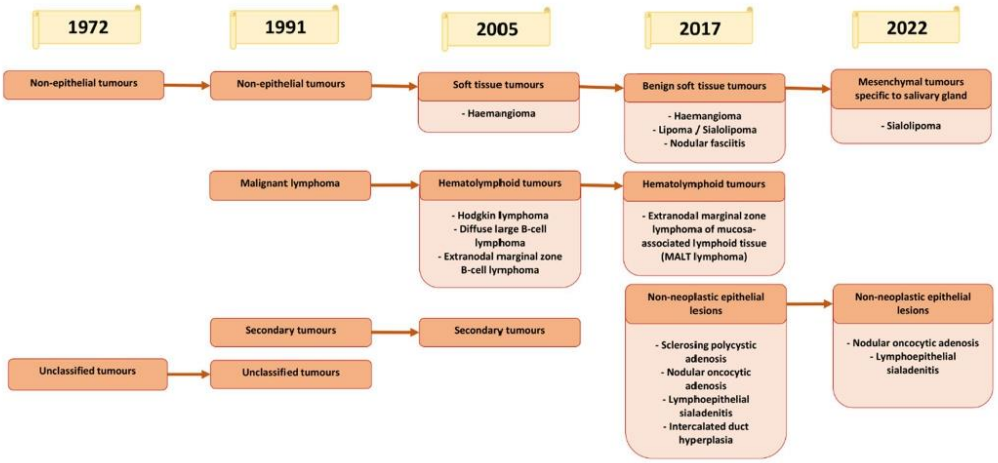

Fig. 3 Changes in classifications of other salivary gland entities

to NCCN Guidelines [47]. Postoperative radiotherapy (RT) should also be considered in all adenoid cystic carcinomas as well as for other malignancies when specific circumstances are found. In most cases of recurrences, RT is also recommended. Recent studies emphasize the role of RT in the management of malignancies of the salivary glands and show improved overall survival in specific subtypes—adenoid cystic carcinoma, adenocarcinoma, high-grade mucoepidermoid carcinoma, and carcinoma ex pleomorphic adenoma [48, 49]. Studies show 5- and 10-year survival rates with different salivary gland malignancies at 52–85% and 32–75%, respectively [49–53]. The best prognosis is for acinic and adenoid cell carcinoma, and the worst for adenocarcinoma and squamous cell carcinoma, with differences in 5-year survival reaching up to 68% [49].

Changes in the latest WHO classification [5] allow a more accurate determination of patient prognosis for less common malignancies. The introduced diagnoses—mucinous adenocarcinoma, sclerosing microcystic adenocarcinoma and microsecretory adenocarcinoma—are mainly located in the intraoral minor salivary glands, and their clinical features include painless mass or swelling [54, 55]. Only in case of mucinous adenocarcinoma recurrence, local and distant metastases are common [54, 56], which should prompt appropriate diagnostic and therapeutic decisions.

The uncovered specific molecular characterization of salivary gland cancers subtypes provides potential for exact definition and diagnosis but also perspectives for development of personalized therapeutic strategies. The described genetic alterations are oftentimes targetable, thus recurrent and metastatic cancers patients are already encouraged to participate in clinical trials. Patients with adenoid cystic carcinoma and MYB overexpression are included in the ongoing MYPHISMO trial with novel vaccination approach, used synergistically with programmed cell death protein 1 (PD-1) inhibitors [57]. In turn, 12 patients with adenoid cystic carcinoma and confirmed activating NOTCH1 mutations were targeted with monoclonal antibody, brontictuzumab, and the phase I study resulted in an objective response rate (ORR) of 17% [58]. The phase II clinical trial ACCURACY evaluated the inhibitor AL101 in patients with recurrent and metastatic adenoid cystic carcinoma and activating NOTCH 1–4 mutations and resulted in the ORR of 15% and disease control rate (DCR) of 65%, determining the inhibitor as promising neoadjuvant setting [59]. Recent studies confirmed detection of prostate-specific membrane antigen (PSMA)-ligand in 93% of adenoid cystic carcinomas, opening perspectives for efficient therapy with ^{177} Lutetium PSMA [60]. In vitro studies with mucoepidermoid cancer models positive for CRTC1-MAML2-positive present sensitivity to EGFR inhibitors, such as erlotinib, gefitinib, or cetuximab, that in the future can be an attractive therapeutic option. The salivary duct carcinoma characterize in high overexpression (78–96%) of androgen receptor (AR) [61] and the treatment has been already supported with androgen-deprivation therapy (ADT; with goserelin). The phase II one-arm study on combined androgen blockade with leuprorelin and bicalutamide in patients with recurrent or metastatic salivary gland cancer proved the ORR of 42% and DCR of 86% with 30.5 months of median overall survival (OS) [62]. Adenocarcinoma is another type with

relatively increased load of genetic alterations. AR positive adenocarcinomas were similarly to salivary duct carcinoma targeted with ADT therapy in clinical trials, while HER2 amplified tumours demonstrated enhanced sensitivity to T-DM1 therapy [63].

The rare incidence of other salivary gland cancers subtypes and even the lower rate of metastatic and recurrent cases are so far not conducive to inclusion in clinical trials on systemic therapies.

Potential developments and trends in salivary gland pathology classification

Initial classifications of salivary gland pathologies focussed on conventional histopathological examination. The second edition of the WHO classification [2] recommended selected immunocytochemical tests—amylase, S-100 protein, actin, myosin, cytokeratin, leukocyte common antigen, carcinoembryonic antigen and thyreoglobulin—for identifying lesions in addition to basic staining. At the time, cytophotometry was an additional test to help differentiate between selected tumour types [7].

A decisive direction in the development of diagnosis and identification of pathologies was introduced in the fourth version of the Blue Book [4], when emphasis was placed on genetic alterations in tumour cells [64]. The new paradigm of genomic alterations is featured heavily for adenoid cystic carcinoma, mucoepidermoid carcinoma, secretory carcinoma, and pleomorphic adenoma [32]. The current edition of the WHO classification introduced commonly reported genetic alterations into the definition of certain cancer types: mucoepidermoid carcinoma, adenoid cystic carcinoma, secretory carcinoma, polymorphous adenocarcinoma, hyalinizing clear cell carcinoma, mucinous adenocarcinoma, and microsecretory adenocarcinoma [5, 11]. The most important genetic variations included in the WHO classification are shown in Tables 1 and 2. Although, the number of salivary gland carcinomas without known molecular alterations has shrunk in last years, there are still a few lesions that remain mysteries. These are basal cell adenocarcinoma, epithelial–myoepithelial carcinoma, sialoblastoma, sclerosing microcystic carcinoma, and sebaceous adenocarcinoma [15]. The reason for these unsolved problems is the rare occurrence of these tumours. However, it is likely that the forthcoming research will soon help to understand the cytopathophysiology of these lesions.

Increasing numbers of researchers are highlighting the importance of genetic alterations as biomarkers of salivary gland pathology. It has been suggested that the genetic changes have also prognostic and predictive potential [14, 65]. Alterations at the genetic level result in changes to the tumour microenvironment. This represents a potential focus for targeted therapies and offers many promising results. Combination of immunotherapies with the antineoplastic agents constitutes a promising approach for the future [66]. Many therapies are still in the early preclinical phase and most of them are described in the review by Mueller et al. [6]. The most potential immunohistochemical biomarkers for underlying molecular changes are presented in Table 3.

Recently, the importance of fine needle aspiration (FNA) cytology in the diagnosis of salivary gland lesions has increased [11]. Although it is a well-known examination that has been used for years [67], only with the introduction of an international standardized FNA assessment system—the Milan system [68]—there has been a return to the widespread use of this test in routine diagnosis of salivary gland lesions. Recently there have been an increasing number of reports of the very high sensitivity and specificity of FNA examination assessed by the Milan system [69, 70]. FNA has the advantage of safety, simplicity of technique and low cost. It is commonly used as an initial diagnostic method. Sometimes, however, non-diagnostic results are reported due to insufficient aspiration or inherent limitations in distinguishing between benign and malignant cytology results [71]. While FNA is cytological, in core-needle biopsy (CNB) a small piece of tissue is taken intact, making it possible to diagnose and stage malignant and benign tumours by examining the histological architecture of the tissue and all its components [72]. In comparison studies, CNB yields significantly fewer non-diagnostic results and has higher sensitivity and specificity than FNA for differentiating malignant and benign salivary gland tumours [71–73]. However, it is known that the risk of complications such as bleeding, pain or tumour seeding is higher for CNB than for FNA [71]. Some authors suggest that the safety profile of CNB conducted by experienced staff and using good-quality equipment is excellent and CNB should be considered the technique of choice when a nodule is detected in the parotid glands [72, 74]. Comparing the development potential of the two methods, it is reasonable to suspect that due to its advantages, FNA will be fostered, but until it achieves comparable sensitivity and specificity results, CNB remains the standard for preoperative testing.

So far none of the WHO classification of salivary gland pathologies includes imaging findings in the diagnosis of the lesions. Radiological examinations are also under constant development, and the utility of new techniques in the diagnosis of salivary gland proliferative lesions has been confirmed in recent studies. The recent significant progress in improving ultrasound imaging with the introduction of new technological solutions as shear wave elastography (SWE) and contrast enhanced ultrasonography (CEUS) influence the preoperative diagnostic workup in salivary gland pathologies. The studies published so far confirm the increased value of SWE versus classic ultrasound in differentiating

Table 3 Potential biomarkers in salivary gland tumours [11, 14]

Tumour type	Gene rearranged or mutated	Frequencies	Ancillary IHC
Acinic cell carcinoma	NR4A3	~85%	NR4A3
Adenoid cystic carcinoma	MYB	29–86%	Myb
	NOTCH1	~14%	NICD
Mucoepidermoid carcinoma	CRTC1	40–90%	Areg
Salivary duct carcinoma	AR	40–70%	AR
	ERBB2 (HER2)	29–35%	Her2
Secretory carcinoma	NTRK (primarily ETV3-NTRK3 fusion)	> 90%	Pan-Trk
Basal cell adenoma	CTNNB1	37–80%	β-Catenin, LEF-1
Pleomorphic adenoma and carcinoma ex pleomorphic adenoma	PLAG1	> 50%	Plag1
	HMGA2	10–20%	Hmga2

between the most common benign lesions, polymorphic adenoma and adenolymphoma [75, 76]. Although the amount of studies evaluating the value of CEUS in salivary gland tumours is still low, the presented results are very promising. It has been proven that the mean washout time of the contrast is significantly higher in malignant lesions, while the time to peak enhancement is significantly longer in pleomorphic adenoma than adenolymphoma [77]. Wei et al. [78] proved high combined efficacy of CEUS and Doppler ultrasound in diagnosis of a malignant tumour with the sensitivity of 92.3%, specificity of 86.9% and negative predictive value of 98.5%.

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) could be useful for recognizing the principal types of salivary gland tumours. The study of Mungai et al. [79] affirms DCE-MRI as very valuable biomarker for differentiating benign from malignant tumour. Similarly, Zhang et al. [80] used Haralick texture analysis on computed tomography (CT) imaging of mucoepidermoid carcinomas of salivary glands to determine the tumour phenotype with 89% sensitivity. It is likely that the radiomic biomarkers in the identification of salivary gland lesions will be one of the development pathways for the diagnosis and classification of this type of pathology. The level of advanced capabilities for radiological evaluation and the development of new imaging techniques is a topic too vast for thorough discussion in this article. We point out, however, that the undeniable advantage of imaging examinations is their widespread accessibility in daily clinical work. Perhaps this will become an alternative to expensive genetic testing in the future.

Another perspective for the development of salivary pathology diagnostics is artificial intelligence. The first paper on using machine learning to evaluate salivary gland lesions was published in 2010. Siebers et al. [81] evaluated 10 parameters based on ultrasound of parotid glands of 138 patients differentiating lesions into benign and malignant. They obtained area under receiver operating characteristic curve (AUC) score of 0.91. In the following years, more and more papers addressing this topic were published, and in recent years the topic has become extremely popular, and dozens of original papers and reviews on artificial intelligence in the evaluation of salivary gland tumours are published every year. There is considerable hope for results using machine learning to evaluate ultrasound, CT and MRI images of salivary gland pathology. Wang et al. [82] and then Zhang et al. [83] proved the greater effectiveness of artificial intelligence in distinguishing benign from malignant parotid lesions based on ultrasound compared to experienced clinicians.

Some studies used machine learning to distinguish benign and malignant lesions of the parotid glands based on CT scans [85–87] and MRI images [84, 88, 89] obtaining great effectiveness. Yu et al. [87] developed a deep learning-assisted diagnosis models based on CT images that significantly improved the accuracy of diagnoses of benign and malignant lesions made by experienced radiologists (AUC by 0.128 and sensitivity by 0.194). Chang et al. [90] used deep learning to distinguish Warthin's tumour, pleomorphic adenoma and malignancies of the parotid glands. Not only did the method proposed by the researchers achieve high results (accuracy: 0.71–0.81), but it also detects pathologies on its own and the radiologist does not need to mark the suspicious area on the MRI image, which gives extremely high potential for using the algorithm in clinical practice. Unfortunately, the methodology needs to be improved due to its low sensitivity for detecting malignant lesions (0.33). The number of ongoing research on artificial intelligence models is growing continuously, and the quality of the models is improving. This is a sure direction for the development of diagnostics, and artificial intelligence assisted diagnosis models will certainly become a standard in daily clinical practice in the future.

Conclusions

Correct diagnosis of salivary gland lesion is essential in determining the treatment and prognosis of the patient. Over the last 50 years, there have been many changes in the classification of salivary gland pathologies and the definitions of several lesions known for years have been updated. The most recent changes concern predominantly genetic studies results, which are increasingly being used in lesion classification. In the future, the importance of genetic alterations in the diagnosis of salivary gland pathology will increase even more. These alterations will also be helpful as prognostic and predictive biomarkers, and may also serve as targets for anti-cancer therapies.

Declarations

Conflict of interest The authors declare no conflict of interest. There are no relevant financial or non-financial competing interests to report.

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Podsumowanie i wnioski (łączące wyniki zawarte w cyklu publikacji)

Patologie gruczołów ślinowych stanowią zróżnicowaną grupę chorób o różnej epidemiologii i obrazie klinicznym. W Polsce najczęściej diagnozuje się zmiany nienowotworowe gruczołów ślinowych. Analiza wykazała rosnący trend zapadalności na łagodne nowotwory ślinianek oraz spadek zapadalności na nowotwory złośliwe w ciągu ostatniej dekady w polskiej populacji. Liczba świadczeń dla pacjentów z łagodnymi nowotworami ślinianek wzrosła w analizowanym okresie i należy spodziewać się dalszego wzrostu. Pomimo zaobserwowanego spadku liczby nowotworów złośliwych, odnotowano również wzrost liczby świadczeń ambulatoryjnych w tej grupie. Jednocześnie systematycznie spada liczba rozpoznań niezłośliwych chorób gruczołów ślinowych. W tej grupie zasobserwowano wzrost liczby pobytów w szpitalu, co może wiązać się z lepszą dostępnością do nowoczesnych metod diagnostycznych i leczniczych, w tym metod sialendoskopii. Geograficzne zróżnicowanie chorobowości oraz przedstawione trendy zapadalności mogą być wskazówkami dla ewentualnych potrzeb reorganizacji systemu opieki zdrowotnej w celu zapewnienia optymalnej opieki medycznej w nadchodzących latach.

Rokowanie w przypadku nowotworów złośliwych ślinianek zależy od wielu czynników, głównie od rozpoznania histopatologicznego, ale także od czynników demograficznych, zaawansowania choroby czy wybranej metody leczenia. Na przestrzeni dwóch dekad nie zaobserwowano zmian w wieku, płci i miejscu zamieszkania pacjentów z analizowanymi nowotworami złośliwymi ślinianki przyusznej. Wyniki analiz demograficznych są w dużej mierze spójne z doniesieniami z innych krajów, wykazując brak regionalnych różnic w charakterystyce demograficznej pacjentów. Na podstawie wykonanych zestawień wydaje się, że metody leczenia nowotworów złośliwych ślinianek przyusznych odbiegają od wytycznych National Comprehensive Cancer Network w pewnym odsetku pacjentów leczonych w Polsce. Dotyczy to grupy chorych poddanych pierwotnemu leczeniu radioterapią. Wymaga to weryfikacji w odniesieniu do przedstawionych niezadowalających wyników czasu przeżycia dla tej metody leczenia. Najczęściej wśród nowotworów złośliwych rozpoznawano raka płaskonabłonkowego (33,3%), a następnie gruczolakoraka (19,6%) i raka śluzowo-naskórkowego (13,7%). Należy podkreślić, że raki płaskonabłonkowe ślinianek obejmują nowotwory pierwotne oraz przerzutowe, co sprawia, że przedstawione wyniki dotyczą niejednorodnej grupy pacjentów. Najlepiej rokującym nowotworem złośliwym wśród analizowanych jest rak zrazikowo-komórkowy, a najgorzej rak płaskonabłonkowy. Ponadto

stadium guza ma również kluczową rolę w ocenie rokowania. Przedstawiona analiza wskazuje potencjalne kierunki poprawy rokowania u chorych na raka ślinianki przyusznej w Polsce.

Dzięki postępom technologii diagnostycznych weryfikacji podlegają rozpoznania patologii gruczołów ślinowych. Zmiany te pozwalają na dokładniejsze określenie rokowania pacjenta i zaplanowanie leczenia. W ciągu ostatnich 50 lat nastąpiło wiele zmian w klasyfikacji patologii ślinianek, a definicje kilku znanych od lat zmian zostały zaktualizowane. Najnowsza klasyfikacja nowotworów Światowej Organizacji Zdrowia z roku 2022 przyniosła wiele zmian w diagnostyce patologii gruczołów ślinowych, głównie w oparciu o odkrycia genetyczne. Wydaje się, że odkrycia genetyczne będą miały coraz większe znaczenie w diagnostyce patologii gruczołów ślinowych. Zmiany te będą również pomocne jako biomarkery prognostyczne i predykcyjne, a także mogą służyć jako cele dla terapii przeciwnowotworowych.

Zaprezentowany cykl publikacji w sposób wszechstronny i kompleksowy przedstawia problematykę patologii gruczołów ślinowych, zarówno w dziedzinie epidemiologii, ale również w zakresie diagnostyki, klasyfikacji, leczenia i oceny rokowania u pacjentów z chorobami ślinianek. Analizy kohortowe na tak dużej populacji dają wgląd w kształtowanie trendów zapadalności i chorobowości na patologie gruczołów ślinowych, co umożliwia wyciąganie wniosków w zakresie organizacji pracy oddziałów specjalistycznych oraz całego systemu ochrony zdrowia w zakresie otorynolaryngologii.

Opinia Komisji Bioetycznej lub Etycznej

Komisja Bioetyczna
przy Warszawskim Uniwersytecie Medycznym

Tel.: 022/ 57 - 20 -303
Fax: 022/ 57 - 20 -165

ul. Żwirki i Wigury nr 61
02-091 Warszawa

e-mail: komisja.bioetyczna@wum.edu.pl
www.komisja-bioetyczna.wum.edu.pl

Warszawa, dnia 04 października 2021r.

AKBE/178 / 2021

Dr n.med. Anna Rzepakowska
Katedra i Klinika Otolaryngologii,
Chirurgii Głowy i Szyi
ul. Banacha 1a
02-097 Warszawa

OŚWIADCZENIE

Niniejszym oświadczam, że Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym w dniu 04 października 2021 r. przyjęła do wiadomości informację na temat badania pt.:"Epidemiologia patologii gruczołów ślinowych leczonych chirurgicznie :10-letnie badanie kohortowe z jednego ośrodka."
Przedstawione badanie nie stanowi eksperymentu medycznego w rozumieniu art. 21 ust. 1 ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty(Dz.U. z 2018 r. poz. 617) i nie wymaga uzyskania opinii Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym, o której mowa w art. 29 ust.1 ww. ustawy.

Przewodnicząca Komisji Bioetycznej

Prof. dr hab. n. med. Magdalena Kuźma –Kozakiewicz

Oświadczenia wszystkich współautorów publikacji określające indywidualny wkład każdego z nich w ich powstanie.

Warszawa, 04.04.24
(miejscowość, data)

KAMIL PASAK
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „The Epidemiology of Salivary Glands Pathologies in Adult Population over 10 Years in Poland — Cohort Study" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: interpretacja wyników badań, przygotowanie bibliografii, wkład w przygotowanie manuskryptu

Mój udział procentowy w przygotowaniu publikacji określam jako 8 %.

Wkład lek. Michała Żurka w powstawanie publikacji określam jako 76 %,
obejmował on: konceptualizację badań, zebranie materiałów badawczych, wykonanie analiz, interpretacja wyników, wizualizacja wyników, przygotowanie manuskryptu, nadzorowanie prac zespołu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Michała Żurka

Kamil Pasak
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 03.04.2024
(miejscowość, data)

prof. dr hab. n. med. Kazimierz Niemczyk
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „The Epidemiology of Salivary Glands Pathologies in Adult Population over 10 Years in Poland — Cohort Study" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: nadzór merytoryczny nad pracami zespołu

Mój udział procentowy w przygotowaniu publikacji określam jako 2 %.

Wkład lek. Michała Żurka w powstawanie publikacji określam jako 76 %,
obejmował on: konceptualizację badań, zebranie materiałów badawczych, wykonanie analiz, interpretacja wyników, wizualizacja wyników, przygotowanie manuskryptu, nadzorowanie prac zespołu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Michała Żurka

Katedry i Kl... Otolaryngologii,
Chir... Głowy i Szyi
prof. dr hab. n. med. Kazimierz Niemczyk

(podpis oświadczającego)

WARSZAWA 03.04.2024
(miejscowość, data)

ANNA DZIEPAKOWSKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „The Epidemiology of Salivary Glands Pathologies in Adult Population over 10 Years in Poland — Cohort Study" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: konceptualizacja badań, interpretacja wyników, przygotowanie manuskryptu, nadzór merytoryczny

Mój udział procentowy w przygotowaniu publikacji określam jako 14 %.

Wkład lek. Michała Żurka w powstawanie publikacji określam jako 76 %,
obejmował on: konceptualizację badań, zebranie materiałów badawczych, wykonanie analiz, interpretacja wyników, wizualizacja wyników, przygotowanie manuskryptu, nadzorowanie prac zespołu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Michała Żurka

Anna Dziepakowska
(podpis oświadczającego)

Warszawa, 05.07, 2024
(miejscowość, data)

Pist, Daniel
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Clinico-Epidemiological Analysis of Most Prevalent Parotid Gland Carcinomas in Poland over a 20-Year Period" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: przygotowanie bibliografii oraz pisanie manuskrytpu.

Mój udział procentowy w przygotowaniu publikacji określam jako 4 %.

Wkład lek. Michała Żurka w powstawanie publikacji określam jako 76 %,
obejmował on: konceptualizację badań, zebranie materiałów badawczych, wykonanie analiz, interpretacja wyników, wizualizacja wyników, przygotowanie manuskryptu, nadzorowanie prac zespołu

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Michała Żurka

(podpis oświadczającego)

Warszawa, 04.04.2021
(miejscowość, data)

Karolina Jaros
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Clinico-Epidemiological Analysis of Most Prevalent Parotid Gland Carcinomas in Poland over a 20-Year Period" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: przygotowanie bibliografii oraz pisanie manuskrytpu.

Mój udział procentowy w przygotowaniu publikacji określam jako 4 %.

Wkład lek. Michała Żurka w powstawanie publikacji określam jako 76 %,
obejmował on: konceptualizację badań, zebranie materiałów badawczych, wykonanie analiz, interpretacja wyników, wizualizacja wyników, przygotowanie manuskryptu, nadzorowanie prac zespołu

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Michała Żurka

Karolina Jaros
(podpis oświadczającego)

Warszawa, 04.04.24
(miejscowość, data)

KAMIL JASAK
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Clinico-Epidemiological Analysis of Most Prevalent Parotid Gland Carcinomas in Poland over a 20-Year Period" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: przygotowanie bibliografii oraz pisanie manuskrytpu.

Mój udział procentowy w przygotowaniu publikacji określam jako 4 %.

Wkład lek. Michała Żurka w powstawanie publikacji określam jako 76 %,
obejmował on: konceptualizację badań, zebranie materiałów badawczych, wykonanie analiz, interpretacja wyników, wizualizacja wyników, przygotowanie manuskryptu, nadzorowanie prac zespołu

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Michała Żurka

Kamil Jasak
(podpis oświadczającego)

Warszawa, 03.04.2024
(miejscowość, data)

prof. dr hab. n. med. Katarzyna Niemczyk
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Clinico-Epidemiological Analysis of Most Prevalent Parotid Gland Carcinomas in Poland over a 20-Year Period" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: nadzór merytoryczny nad pracami zespołu.

Mój udział procentowy w przygotowaniu publikacji określam jako 2 %.

Wkład lek. Michała Żurka w powstawanie publikacji określam jako 76 %,
obejmował on: konceptualizację badań, zebranie materiałów badawczych, wykonanie analiz, interpretacja wyników, wizualizacja wyników, przygotowanie manuskryptu, nadzorowanie prac zespołu

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Michała Żurka

Kierownik
Katedry i Kliniki Otorynolaryngologii,
Chirurgii Głowy i Szyi
prof. dr hab. n. med. Katarzyna Niemczyk
(podpis oświadczającego)

Warszawa 03.04.2024
(miejscowość, data)

ANNA RZEPAKOWSKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Clinico-Epidemiological Analysis of Most Prevalent Parotid Gland Carcinomas in Poland over a 20-Year Period" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: konceptualizacja badań, wybór metod statystycznych do analiz, interpretacja wyników, pisanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określam jako 10 %.

Wkład lek. Michała Żurka w powstawanie publikacji określam jako 76 %,
obejmował on: konceptualizację badań, zebranie materiałów badawczych, wykonanie analiz, interpretacja wyników, wizualizacja wyników, przygotowanie manuskryptu, nadzorowanie prac zespołu

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Michała Żurka

Anna Rzepakowska
(podpis oświadczającego)

Warszawa, 03.04.2024
(miejscowość, data)

prof. dr hab. n. med. Kazimierz Niemczyk
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Salivary gland pathologies: evolution in classifcation and association with unique genetic alterations" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: nadzór merytoryczny nad treścią artykułu i pracą zespołu.

Mój udział procentowy w przygotowaniu publikacji określam jako 2 %.

Wkład lek. Michała Żurka w powstawanie publikacji określam jako 90 %,
obejmował on: konceptualizację badań, zebranie materiałów badawczych i bibliografii, przygotowanie manuskryptu, nadzorowanie prac zespołu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Michała Żurka

Katedry i Kl... Otolaryngologii,
Chiru... Głowy i Szyi
prof. dr hab. ...

(podpis oświadczającego)

Warszawa, 18.04.24
(miejscowość, data)

ŁUKASZ FUS
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Salivary gland pathologies: evolution in classifcation and association with unique genetic alterations" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: zebranie literatury i nadzór merytoryczny nad treścią artykułu.

Mój udział procentowy w przygotowaniu publikacji określam jako 2 %.

Wkład lek. Michała Żurka w powstawanie publikacji określam jako 90 %,
obejmował on: konceptualizację badań, zebranie materiałów badawczych i bibliografii, przygotowanie manuskryptu, nadzorowanie prac zespołu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Michała Żurka

Łukasz Fus
(podpis oświadczającego)

Hajnówka 03.05.2024
(miejscowość, data)

ANNA RZEPAKOWSKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Salivary gland pathologies: evolution in classifcation and association with unique genetic alterations" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: konceptualizacja badań oraz pisanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określam jako 6 %.

Wkład lek. Michała Żurka w powstawanie publikacji określam jako 90 %,
obejmował on: konceptualizację badań, zebranie materiałów badawczych i bibliografii, przygotowanie manuskryptu, nadzorowanie prac zespołu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Michała Żurka

Anna Rzepakowska
(podpis oświadczającego)