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ORIGINAL ARTICLE

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Incidence and malignant transformation of glottic precursor lesions in Denmark

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ABSTRACT

Objectives: Glottic precursor lesion (GPL) is a well-known premalignant condition, but the existing knowledge of incidence and malignant potential is based on subpopulation studies. In this first, nationwide study we report data from all verified cases of GPL in Denmark during a 10-year period with focus on incidence and malignant transformation of GPL.

Methods: Patients were identified by a search for GPL in the time period from 01.01.2000 to 31.12.2009 using the Danish Pathology Data Base, Patobank, which is a nationwide source of all cyto- and histopathological data obtained in Denmark. Data were validated and supplemented by medical chart review.

Results: A 10-year national cohort of 965 patients (median age 60 years, male-female ratio 2:1) with histologically verified GPL was analyzed. The overall malignant transformation rate was 18.3% (mild dysplasia 7.7%, moderate dysplasia 19.8%, severe dysplasia 28.5%, and carcinoma *in situ* 40.3%) with a median progression time of 29 months. Eighty-eight percent of patients were active or former smokers. A significantly larger proportion of male patients (24.1%) experienced malignant transformation compared to females (6.6%) ($p < .001$).

Conclusion: This nationwide population-based study of GPL patients confirmed a stable incidence of GPL in Denmark from January 2000 to December 2009 and a considerable malignant potential, correlated to the grading of GPL according to the World Health Organization classification of laryngeal precursor lesions from 2005, WHOC2005. The recent update, WHOC2017, of low-grade versus high-grade lesions may thus contain less nuanced prognostic information than WHOC2005.

Level of evidence: 2b retrospective cohort study

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Introduction

A glottic precursor lesion (GPL) is defined as specific architectural and cytological changes in the mucosal epithelium considered precancerous [1]. GPL is the most common and the most challenging subgroup of laryngeal precursor lesions due to the opposing demands for both radical treatment and quality of voice. The World Health Organization classification from 2005 (WHOC2005) [2] categorizes GPL into mild, moderate or severe dysplasia, and carcinoma *in situ* (CIS) and has been widely accepted in the Western world [3]. Transformation rates to malignancy varies according to the grade of GPL and are reported from 0% to 12% for mild dysplasia [4–9] and up to 63% for carcinoma *in situ* (CIS) [4,10,11]. The existing knowledge of incidence and malignant potential of GPL is based on studies of selected smaller subpopulations [12] and the grading, classification and treatment of GPL remains a matter of debate [13–15].

The uncertainty regarding the malignant potential has caused varying treatment strategies internationally and nationally [16] dependent on institutional or personal preferences [17] and, thus, probably put patients at risk of both under- and overtreatment [18,19]. Recently, the World Health Organization classification was revised (WHOC2017) [1], into a two-category grading of low and high grade lesions, in an effort to harmonize the various grading systems internationally used for laryngeal precursor lesions.

The aim of this study was to investigate the incidence, characteristics and malignant potential in a Danish national 10-year cohort.

Material and methods

This national population-based retrospective cohort study of GPL is based on tissue samples registered in the Danish Pathology Database, Patobank, which contains information of all cyto- and histopathological assessments performed in Denmark. Patobank is a real-time database with immediate data transfer from Danish departments of pathology. It is

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associated with the national civil registration number, assigned to all Danish residents, and is controlled by the Danish Data Protection Agency.

Data were retrieved by a computer-assisted search using the specific classification codes for Systematized Nomenclature of Medicine (SNOMED) for the locations vocal cords, glottis, and laryngeal commissures (SNOMED T24400, T24410, T24420, T24440, T24470, and TX2980) and for precancerous lesions, according to WHOC2005, dysplasia not otherwise specified (NOS), mild, moderate, severe dysplasia and carcinoma *in situ* (CIS) (SNOMED M74009, M74A09, M74B09, M74C09, M80102, and M80702/M807*2). The aim of this study was to investigate incidence and malignant transformation of GPL and therefore biopsies initially registered as carcinomas were not included.

A total of 2518 histopathological records from 1534 patients diagnosed from 1.1.2000 to 31.12.2009 were retrieved from Patobank and data were extracted regarding the gender and age of the patient, number and the anatomical location of the tissue samples, any tissue samples classified with cancer, tissue samples performed prior to the year 2000, and number and diagnosis of subsequent tissue samples after primary diagnosis. Patients were excluded in case of previous or simultaneous laryngeal or hypopharyngeal cancer, cancer transformation within 3 months of the initial GPL, GPL prior to 01.01.2000, GPL solely on the ventricular folds or incorrect registration of the location of the lesions when validated by the medical chart. Sixteen cases of GPL restricted to the false vocal cords were registered as SNOMED T24400 (vocal cords) in Patobank, but excluded when location was revealed by review of information from the database. All primary cases of histologically verified GPL in Denmark in the period were thereby included for analysis. For details, see Figure 1. A total of 966 patients were included and subsequently divided in two groups according to geographical area respectively Eastern Denmark ($n = 421$) and Western Denmark ($n = 545$)) representing approximately 45% and 55% of the Danish population, respectively [20].

Initially, the medical charts were requested for all patients from Eastern Denmark of which 326 of 421 (77%) charts were accessible. Information from the medical charts regarding the extend and site of lesion as well as cancer transformation during follow-up were compared to the data retrieved from Patobank to validate the data from Patobank.

After validating the data from patients of Eastern Denmark, a sample of 93 patients from Western Denmark were randomly selected by national civil registration number and their medical charts requested for review to ensure validity also of the data from Western Denmark. Of these 93 medical charts 73 (78%) were accessible. One patient (1.4%) was excluded from the sample of Western Denmark as the medical chart revealed biopsy of leukoplakia on the ventricular fold and not the vocal fold.

Supplementary sociodemographic and clinical data were collected retrospectively from the 398 received medical charts regarding alcohol consumption, tobacco history, occupation, gastroesophgeal reflux disease (GERD), and the extend of the surgical procedure. The follow-up period was defined as the time from the initial diagnosis of GPL to the last update of data from Patobank on 2 October 2017. In case of death, the follow up was closed at the date of death. The data were processed in SPSS (SPSS inc. Released 2007, SPSS for Windows, Version 16.0. Chicago, IL, SPSS Inc.) and analyzed in Rstudio (Version 1.0.136 – © 2009-2016 RStudio Inc., Boston, MA) Summary statistics for demographic and clinical characteristics were determined. Odds ratios for malignant transformation were calculated using a 2×2 table for each subgroup of GPL with the odds for mild dysplasia as baseline. Confidence intervals were calculated using the Woolfs formula. For comparison of the malignant potential among the subgroups of GPL, logistic regression was performed with binary outcome (malignant transformation yes/

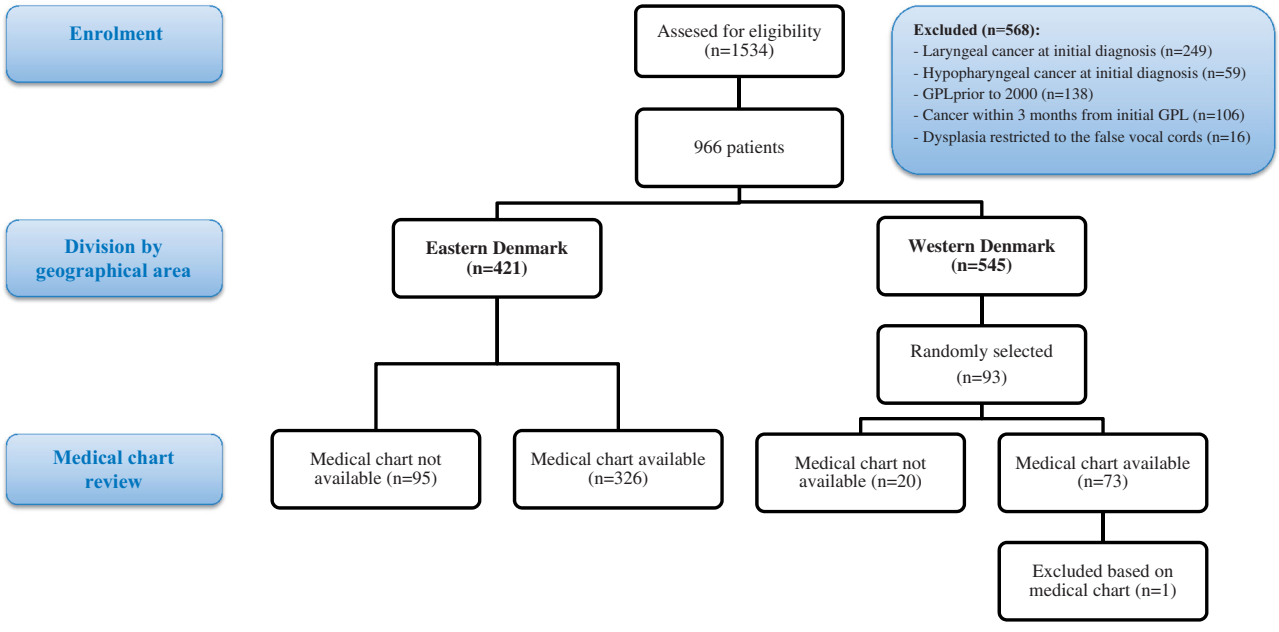

Figure 1. Patient selection flowchart. GPL: glottic precursor lesion.

no) based on the information retrieved from Patobank. Gender was included as a variable. Statistical methods and results were conferred with statisticians at the Faculty of Social Science, University of Copenhagen.

Results

A cohort of 965 patients (median age 60 years, male-female ratio 2:1) with histologically verified GPL was analyzed. Patient characteristics are summarized in Table 1. Data were provided from all the 23 departments of Otorhinolaryngology in Denmark at the time, including four University Hospitals (33.9% of patients) and a few private clinics (1.8% of patients).

Data regarding tobacco use were available in 388 (97%) of the 398 reviewed medical charts and revealed that eighty-eight percent of the patients were active or former smokers. Calculation of pack-years was possible for 152 of those patients with a median 41 pack-years (mean 44, range 4–125).

The median follow-up time was 144 months (mean 155.3, range 93–204). After the initial diagnosis of GPL, subsequent tissue sampling was performed in 59% of the patients due to clinically suspected persistence/recurrence of GPL. The number of subsequent tissue samples correlated positively to the severity of the initial histopathological diagnosis (Table 2).

Table 1. Patient characteristics.

	Females	Males	Total
Gender (*n*, % of total)	318 (33%)	647(67%)	965
Age (years)			
<40	29	42	71
40 < 50	57	63	120
50 < 60	102	178	280
60 < 70	69	208	277
70 < 80	46	124	170
≥80	15	32	47
Mean	57.0	60.7	59.4
Median	57	61	60
Tobacco			
History known	114	274	388
Active	87 (76%)	156 (57%)	243
Former	10 (9%)	86 (31%)	96
Never	17 (15%)	32 (12%)	49
Packyears (mean/med)	41.0/35	45.4/42	44.0/41

Tobacco history was based on information available in 388 (97%) of the 398 reviewed patient medical charts. Packyears was registered for 156 of the 388 patients with known tobacco history (1 packyear is equivalent to smoking twenty cigarettes a day for 1 year).

The mean annual national incidence of GPL was 95.6 (range 73–117 patients per year). According to the national institute of statistics, Statistics Denmark [21], the average population for adults (above or 18 years of age) was 4.216.714 inhabitants with a population growth of 0.26% from 2000 to 2009. This corresponds to a mean incidence of GPL for adults of 2.3/100,000 inhabitants a year (Figure 2). Three patients below 18 years of age were omitted from these calculations. The highest incidence of GPL of 7.7/100,000 a year was found for patients aged 50-69 years.

A total of 177 patients (18.3%) were diagnosed with glottic cancer during follow-up, with a median transformation time of 29 months (mean 41, range 3–172 months) from the initial diagnosis of GPL. Progression to cancer occurred within 120 months in 95.5% of cancer cases, within 60 months in 75% of cases and within 24 months for 46% of cases. The transformation rates and corresponding transformation times for subgroups of GPL are shown in Tables 3 and

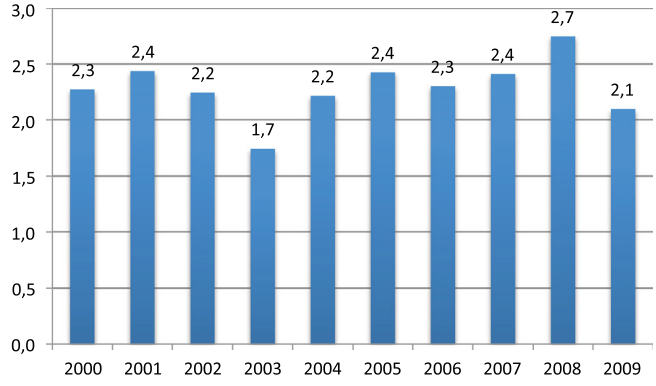

Figure 2. Annual national incidence for adults (above or at 18 years of age) of glottic precursor lesions in Denmark 2000–2009 (per 100,000 inhabitants). Three patients below 18 years of age were omitted from these calculations.

Table 3. Distribution of glottic precursor lesions at initial diagnosis graded according to World Health Organization Classification 2005 and Malignant Transformation.

		Malignant transformation					
Initial diagnosis	*n*	No	Yes	Odds	Odds ratio	CI 2.5%	CI 97.5%
Dysplasia, NOS	114	92	22 (19.3%)				
Mild dysplasia	365	337	28 (7.7%)	0.083	1		
Moderate dysplasia	237	190	47 (19.8%)	0.247	2.977	1.817	4.961
Severe dysplasia	172	123	49 (28.5%)	0.398	4.795	2.905	8.054
Carcinoma in situ	77	46	31 (40.3%)	0.674	8.111	4.479	14.830
Total	965	788	177 (18.3%)				

NOS: dysplasia not otherwise specified is not included in the statistics but the data for overall transformation. Mild dysplasia is the baseline for comparison.

Table 2. Number of subsequently obtained tissue samples during follow-up based on the initial diagnosis of glottic precursor lesion.

		Number of subsequent tissue samples after initial diagnosis		
Initial diagnosis	*n*	0	1–2	>2
Dysplasia, NOS	114	51 (45%)	34 (30%)	29 (25%)
Mild dysplasia	365	214 (59%)	92 (25%)	59 (16%)
Moderate dysplasia	237	94 (40%)	74 (31%)	69 (29%)
Severe dysplasia	172	34 (20%)	68 (40%)	70 (41%)
Carcinoma in situ	77	9 (12%)	29 (38%)	39 (51%)
Total	965	402 (42%)	297 (31%)	266 (28%)

NOS: dysplasia not otherwise specified.

Table 4. Distribution of glottic precursor lesions and transformation to cancer of based on gender.

	Distribution of GPL				Malignant transformation				Months to malignant transformation	
Initial diagnosis	Total ($n = 965$)	Women ($n = 318$)[a]	Men ($n = 647$)[a]	p Value (Gender diff)	Total ($n = 177$)[b]	Women ($n = 21$)[c]	Men ($n = 156$)[c]	p Value (Gender diff)	Median	Mean
Dysplasia, NOS	114 (11.8%)	36 (11.3%)	78 (12.1%)	n.s	22 (19.3%)	3 (8.3%)	19 (24.4%)		36.3	41.7
Mild dysplasia	365 (37.8%)	152 (47.8%)	213 (32.9%)	<.01	28 (7.7%)	3 (2.0%)	25(11.8%)	<.001	34	48.5
Moderate dysplasia	237 (24.6%)	73 (23.0 %)	164 (25.3%)	<.01	47 (19.8%)	4 (5.5%)	43(26.2%)	<.001	34	43.3
Severe dysplasia	172 (17.8%)	44 (13.8%)	128 (19.8%)	<.001	49 (28.5%)	8 (18.2%)	41 (32.0%)	<.001	26	36.3
CIS	77 (8.0 %)	13 (4.0%)	64 (9.9%)	<.001	31 (40.3%)	3 (23.1%)	28 (43.8%)	<.001	16	38.0
Overall					177 (18.3%)	21 (6.6%)	156 (24.1%)		29	40.8

CIS: carcinoma *in situ*; NOS: dysplasia not otherwise specified; n.s.: not significant.
[a]Percentages of subgroup of glottic precursor lesion among 318 women resp. 647 men.
[b]Percentages of malignant transformation in the specific histological subgroup.
[c]Percentages of malignant transformation in the specific histological subgroup among women resp. men.

4. There was no substantial difference in cancer transformation or grade of GPL when separating the data by geographical area (data not shown elsewhere).

There was a considerable gender difference in the distribution of GPL, thus a significantly larger proportions of males were diagnosed with severe dysplasia or CIS and smaller proportions with mild dysplasia. For details, see Table 4. The overall malignant transformation rate for males was 24.1% and for females 6.6% with significant differences between all of the histopathological subgroups.

Details regarding the patient's occupation, extend of the surgical procedure, alcohol intake, and GERD were unfortunately very inconsistently reported in the medical charts and therefore not analyzed further.

Discussion

To our knowledge, this is the first report of a nationwide cohort of GPL. We confirmed a stable incidence of GPL in Denmark between 2000 and 2009 and a considerable malignant potential positively correlated to the severity of GPL, with an overall malignant transformation rate of 18.3% comparable to previous studies reporting transformation rates of 15–19% [9,16]. The incidence of GPL in Denmark was highest in patients aged 50–69 years (7.7/100,000 inhabitants per year). The rates of malignant transformation in our cohort were evenly proportional to the severity of GPL. Thus, we found that the histological classification according to WHOC2005 [2] was an important prognostic factor as reported in other studies [12].

The recently updated WHOC2017 [1] separates laryngeal precursor lesions into only two categories. The former categories of "hyperplasia" (no atypia or architectural disturbances), "mild dysplasia" (architectural disturbances and limited atypia in the lower third of the epithelium) and those of "moderate dysplasia" that only involve the lower half of the epithelium (WHOC2005 moderate dysplasia comprises architectural disturbances and limited atypia into the middle third of the epithelium), are fused into "low-grade dysplasia, LGD." The "high-grade dysplasia, HGD" comprises the former categories of carcinoma *in situ*, severe dysplasia, and those of moderate dysplasia that involves more than the lower half of the epithelial thickness. An unfortunate error in the latest edition of the reference book on WHOC2017 [1] may cause confusion, as one table (Table 3.02, page 91) defines LGD as a spectrum of morphological changes restricted to the lower half of the epithelium, whereas another table (Table 3.03, page 92) restricts LGD only to the lower one-third. This error has recently been recognized by the authors of the reference book, and it was emphasized that LGD is correctly restricted to the lower epithelial half, as in Table 3.02 [22,23,24].

We found a considerable proportion of malignant transformation of mild dysplasia (7.7%) in accordance with previous studies reporting malignant transformations in up to 12% of lesions with mild dysplasia [4–9,16,25,26] whereas moderate dysplasia carries a risk of malignant transformation of 4–24% [26], in our study 19.8%. Squamous hyperplasia has very limited or no malignant potential (0–4.1%) [26,27]. We did not investigate this subgroup in our study, as it was not classified as dysplasia in WHOC 2005.

With recognition of the thorough work regarding the establishment of WHOC2017, we find that the results in our study encourages further discussion whether the term "Low grade" is justified and especially if it can be interpreted as "Low risk."

Further, the options for stratified prognostication and intervention may be hampered with the implementation of WHOC2017 illustrated by the considerable differences in malignant potential for the four WHOC2005 categories of GPL reported here and in previous papers [12,16,28]. The WHOC2017 undoubtedly has important prognostic value and reflects significant difference in malignant potential of LGD and HGD. A cohort of 1444 patients from Slovenia was graded according to the amended Ljubljana classification on which the WHOC2017 is based, and malignant transformation was reported in 19/1204 (1.6%) of LGD over a period of 2–15 years as opposed to 30/240 (12.5%) of HGD over a period of 2–26 years ($p = .0001$) [1,27,29].

Based on the diagnostic criteria and corresponding malignant potential mentioned above, we do, however, find that the WHOC2017 pooling of squamous hyperplasia, mild

dysplasia and partly moderate dysplasia into LGD raises some questions, as the malignant potential varies considerably within the group of LGD.

The inclusion of lesions (hyperplasia) with very low or no malignant potential will inevitably lower the overall rate of malignant transformation in the group of LGD. Thus, we are concerned that the risk of malignancy and need for treatment and follow-up may be underestimated, for a proportion of future patients diagnosed with LGD, who earlier would have been diagnosed "mild" or even "moderate" dysplasia.

In recognition of the thorough work behind the establishment of the WHOC2017, and its undeniable prognostic value, we suggest future research continue to strive to develop nuanced and applicable diagnostic criteria for laryngeal precursor lesions.

Patients who were diagnosed with dysplasia NOS ($n = 114$, 11.8%) were included for assessment of incidence. Histological grades of GPL may be difficult to distinguish by both the WHOC2005 and WHOC2017 [1] with substantial intra- and interobserver variability [22,30]. Intra- and interobserver variability is suspected to be uniformly distributed across the different grades of GPL, but in our study, the NOS diagnose was predominantly, though not exclusively, caused by difficulties in separating mild from moderate dysplasia. The heterogeneity of the subgroup made it unsuitable for detailed analysis.

In 2012, a national guideline for management of GPL was proposed by The Danish Glottic Study Group, an established collaboration of Danish health care professionals, as the DANGLOT protocol [31]. Surgical endoscopic cordectomy type I-III, according to the European Laryngological Society nomenclature [32] was proposed as the primary choice of treatment for suspected GPL to ensure complete removal of GPL and avoid progression to cancer. Up to this point, the watchful waiting approach after initial simple biopsy was not uncommon neither in Denmark nor in other countries [17,33]. We found that 59% of patients had subsequent tissue samples performed after the initial diagnosis due to clinically suspicion of recurrent GPL or malignant transformation, which could suggest an incomplete surgical removal of the initial lesion. The available information from Patobank and the medical charts did, however, not reveal details enough to disprove or confirm this thesis and neither do we know whether patients continued smoking after the initial diagnosis.

Our data showed no linear correlation between time to cancer transformation and initial severity of GPL. However, a difference in mean and median, though not significant, was found as shown in Table 4. It is noticeable that 25.4% of those patients who developed cancer did so after more than 60 months, as the recommended follow up period in Denmark is 5 years from the latest recurrence of GPL. According to literature the mean time to cancer transformation varies from 29 to 173 months for mild dysplasia, 22 to 56 months for moderate dysplasia, 25 to 132 months for severe dysplasia, and from 10 to 192 months for CIS [12,28].

The overall age distribution and tobacco history of our cohort did not differ considerably from results reported in other studies [7,34] nor did the proportion of active smokers [16,35], whereas the proportion of females (33%) was higher than in most previous studies in which male-female ratios of 3:1 more often are reported [28,35]. Furthermore, the proportion of active smokers was larger for women than for men. This correlates to the fact that in Denmark the proportion of smokers has not decreased so much among women as among men or among women in neighboring countries in the recent decades [36]. Somehow contradictory to this, we found that almost half (48%) of the females in our cohort had only mild dysplasia compared to 33% of the males ($p = .003$), whereas a cumulative of 18% of the females and 30% of the males had severe dysplasia ($p < .001$) or CIS ($p < .001$) initially. Males were also significantly more prone to develop cancer than females in all subgroups as well as overall (24.1% and 6.6%, respectively) as shown in Table 4. This surprisingly large difference in malignant transformation between the sexes has only rarely been reported, but was suggested by Rohde et al. [16] who reported an overall transformation rate of 15% among 101 patients (18 mild dysplasia, 16 moderate dysplasia, 35 severe dysplasia, and 32 CIS); 15 of 82 males (18.3%) developed cancer, but none of the 19 included women. Several factors may contribute to the more frequent finding of the severe subtypes of GPL and the more frequent malignant transformation among males. A likely explanation may be a larger tobacco consumption among male smokers [37], but the more frequent male malignant transformation in all subgroups of GPL probably cannot be explained solely by a larger tobacco consumption. A possible causality is the larger alcohol consumption by males than females [38] as alcohol is known to have synergistic carcinogenic effect when combined with tobacco [1]. Furthermore, aspects like gender differences in patient compliance to follow-up, treatment delay [36] and ability to stop smoking after initial diagnosis may be considered, but is outside the scope of our study.

The gender difference in malignant transformation ought further investigation but might suggest for a longer and closer follow up for males and perhaps even more encouragement and support for smoking cessation.

Glottic cancer is the most common form of laryngeal cancer [39]. The annual number of cases diagnosed with glottic cancer in Denmark in the period 2000–2009 was approximately 139 and the corresponding incidence 2.6 per 100,000 persons [40]. With only around 95 annual new cases of GPL in Denmark, of which approximately 17–18 per year transforms into cancer, it seems as if only a limited fraction of all new patients with glottic cancer in those years have had biopsy proven GPL prior to the cancer diagnosis. However, since we excluded patients for whom the initial biopsy revealed cancer, further analysis of that cohort is outside the scope of our study and we cannot comment on possible patients delay or the extent of benign (non-GPL) biopsies prior to the cancer diagnosis.

Limitations and strengths

Our data were based on histological assessments by several Danish pathologists during 10 years. One, therefore, might

expect a large inconsistency in data. However this did not seem to be the case as there was no substantial difference in data when separated by geographical area (data not shown elsewhere). The study was, however, limited by the fact that some medical charts were unaccessible for review and the requested data on smoking status after primary diagnosis, details concerning tobacco and alcohol consumption, GERD and information regarding the extend of the surgical procedure performed were largely unavailable.

To our knowledge, this study is one of the largest published cohort studies of GPL and the first nationwide study conducted in the field. The Patobank database ultimately proved valid and is to be considered a highly reliable source of information.

Future perspectives

The recently introduced DANGLOT protocol [31] favoring cordectomy, and, thus, the intended removal of all neoplastic tissue in the initial procedure is expected to minimize the risk of repetitive tissue samples and prevent partial biopsies that lead to a risk of underestimating severity. The treatment of GPL is now centralized to the five oncologic centers in Denmark to ensure a higher level of experience among those responsible for diagnosis and treatment and provide uniform management of Danish patients. Hopefully, in time, these initiatives will reduce the incidence of recurrent GPL and transformation to glottic cancer.

Conclusion

This national population-based study of GPL patients confirmed a stable incidence of GPL in Denmark from January 2000 until December 2009 and a considerable malignant potential positively correlated to the severity of GPL. With recognition of the thorough work regarding the establishment of the WHOC2017, the results provided by this study encourages further discussion and suggests that the new classification may contain less nuanced prognostic information than the WHOC2005.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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