

Aggressive elimination of precancerous lesions of the vocal cords to avoid risk of cancer

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ABSTRACT

INTRODUCTION: Several studies show that early histological classification and excision of precancerous lesions of the vocal cords reduces the risk of cancer development. National Danish guidelines have not been established. The purpose of this study was to describe a Danish series of patients with precancerous lesions of the vocal cords and to estimate the risk of malignant transformation.

MATERIAL AND METHODS: This was a retrospective cohort study, including a total of 101 patients with histologically verified precancerous lesions of the vocal cords who were treated from 1997 to 2007 at Odense University Hospital (OUH).

RESULTS: Among the 101 patients, 18 (18%) were diagnosed with mild dysplasia, 16 (16%) with moderate dysplasia, 35 (35%) with severe dysplasia and 32 (32%) with carcinoma in situ (CIS) at the initial examination at OUH. Fifteen patients (15%), all males, developed invasive cancer. Among these, one patient was initially diagnosed with mild dysplasia, one with moderate dysplasia, seven with severe dysplasia and six with CIS. In 11 of the 15 patients (73%), cancer occurred within one year from the time of diagnosis of the precancerous lesion, whereas four cancers occurred years later.

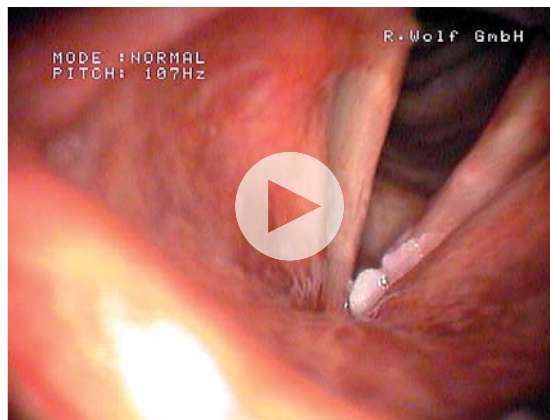
CONCLUSION: The malignant transformation rate is comparable with other recent series. A strategy with elimination of all visible pathology is preferable.

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The majority of vocal cord cancers are squamous cell carcinomas. The development might be a multistep process from dysplasia through carcinoma in situ (CIS) to manifest cancer [1]. According to the literature, malignant transformation rates vary from 6% to 22%, and they increase with the severity of the precancerous lesion [2-5]. The principal risk factor is tobacco smoking, particularly in association with heavy alcohol intake [6, 7].

The literature indicates that early histological diagnosis and surgical treatment (cold steel or laser) of the precancerous tissue may reduce the risk of cancer development [2, 3, 8]. However, no international or Danish guidelines for the management of laryngeal precancerous lesions have been established, and uncertainty



Videostroboscopy showing hyperkeratosis and mild dysplasia.

about the right strategy may exist. Some make a simple nipple biopsy and observe; others perform a complete removal of pathological tissue, often by laser evaporation. Generally, there is a tendency towards an expectant attitude when the grade of dysplasia is mild and towards a more active strategy as the grade of the precancerous lesion increases. Whether laser ablation is part of the treatment does not seem to depend on the grade of dysplasia, but rather to be a matter of personal preferences [8-11].

The aim of this study is to describe a series of patients with precancerous lesions of the vocal cords and to estimate the risk of malignant transformation.

MATERIAL AND METHODS

Based on a search of the local patient database and the local pathology register, a total of 195 patients with a neoplastic lesion of the vocal cords diagnosed from January 1997 to December 2007 were identified. All patient- and pathology reports were reviewed, and patients not treated at the Department of ENT Head & Neck Surgery, Odense University Hospital (OUH) (n = 3), patients with previous or simultaneous laryngeal cancer (including microinvasive carcinoma) (n = 83), and patients who had previously received laryngeal radiotherapy (n = 8) were excluded. This left a total of 101 patients with histologically verified dysplasia of grade 1-3 or CIS on the vocal cords eligible for analysis.

Data were registered concerning histology accord-

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ing to the WHO classification [12], glottic spread, type of intervention (surgical excision and/or laser evaporation), histological progression, result of stroboscopic evaluation, number of treatments and smoking status.

During the study period, the departmental recommendation was complete surgical removal of pathological tissue, regardless of the grade of dysplasia. The use of laser was optional. As a standard, patients were offered a five-year follow-up course with three-month intervals the first two years and six-month intervals the last three years.

Data were processed in the medical database and the analysis programme Medlog. Descriptive statistics and the Kaplan Meier method were used.

Trial registration: not relevant.

RESULTS

Of the 101 patients, 82 (81%) were males and 19 (19%) were females. Their median age was 66 years at the time of diagnosis (range 26 to 86 years). A total of 65% of the patients were smokers or had quit smoking within two months before diagnosis. Fifty-four (83%) of these had smoked more than 20 pack years.

Ninety-one of the 101 patients (90%) were treated with complete removal of visible pathological tissue, among these 72 (79%) with laser evaporation, regardless of the grade of dysplasia. Five patients (5%) were managed with a simple nipple biopsy and subsequent observation. The treatment was unknown for five patients (5%).

Histological examination at the time of the initial procedure performed at the OUH (WHO [12]) showed mild dysplasia in 18 patients (18%), moderate dysplasia in 16 (16%), severe dysplasia in 35 (35%) and CIS in 32 patients (32%).

In 15 of the 101 patients (15%), the precancerous lesion progressed to invasive glottic carcinoma. Among these, one patient was initially diagnosed with mild dysplasia, one with moderate dysplasia, seven with severe

dysplasia and six with CIS. **Table 1** shows the percentage of patients from each group who developed cancer. All of these 15 patients were males.

In four patients, cancer occurred after one year or more, whereas in 11 of the 15 patients (73%), cancer occurred within one year from the time of diagnosis of the precancerous lesion.

The difference in malignant transformation rate, i.e. development of invasive cancer, for mild and moderate dysplasia compared with severe dysplasia and CIS was not statistically significant.

The follow-up time ranged from one month to 11 years with an average of 36 months.

Among the 101 patients, 69 (68%) had a recurrence; thus 30 (30%) were treated more than once and 39 (39%) were treated three times or more. Among these, 62 (90%) were treated with complete removal of pathological tissue, including 54 (87%) with laser evaporation, regardless of the grade of dysplasia. Four (6%) were managed with a simple nipple biopsy and subsequent observation. Finally, the treatment was unknown for two patients (3%).

DISCUSSION

The 4:1 male-to-female ratio in the present series is similar to that of other reports, e.g. 4:1 found by Gallo et al [3], 3:1 by Minni et al [13] and 3:1 by Ricci et al [2].

All of the 15 (15%) patients who developed invasive cancer were male, which indicates that sex may be a risk factor for cancer development. However, the difference was not statistically significant, probably because of the relatively small number of patients.

The median age of 66 years is relatively high compared with the age of patients reported by Plch et al [8] (52 years), Minni et al [13] (54 years) and Ricci et al [2] (53 years). The reason may be a longer time interval from symptom to initial diagnosis in our series. However, the regional referral pattern might also be part of the explanation since patients with severe dysplasia or CIS are more often referred to our university hospital department than are other dysplasias.

65% (95% confidence interval: 55-74%) of the patients were smokers or had quit smoking within two months before diagnosis, which is lower than the 84% and 76%, reported by Minni et al [13] and Ricci et al [2], respectively. In our study, ongoing or recent smoking seems without significant influence on the risk of malignant transformation. Since our study was retrospective, the information about tobacco load is uncertain, and we therefore consider it of minimal scientific value. We absolutely recommend tobacco smoking cessation.

The present study confirms that precancerous lesions of the vocal cords may develop into invasive cancer. Furthermore, the present series indicates a trend

TABLE 1

Malignant transformation rate in selected publications. The values are n/N (%; 95% confidence interval).

Reference	LIN 1/mild dysplasia	LIN2/moderate dysplasia	LIN3/severe dysplasia and CIS	Total
Blackwell et al, 1995 [5]	3/26 (12; 0-24)	5/15 (33; 9-57)	5/18 (28; 7-49)	13/59 (22; 11-33)
Gallo et al, 2001 [3]	4/56 (7; 0.3-14)	6/28 (21; 6-36)	3/32 (9; 0-19)	13/116 (11; 5-17)
Ricci et al, 2003 [2]	2/46 (4; 0-10)	5/42 (12; 2-22)	3/23 (13; 0-27)	10/111 (9; 4-14)
Isenberg et al, 2008 [4] ^a	2/38 (5; 0-14)	2/38 (5; 0-14)	2/31 (6; 0-14)	4/69 (6; 0.4-12)
Present study 2010 ^b	1/18 (6; 0-16)	1/16 (6; 0-18)	13/67 (19; 10-29)	15/101 (15; 8-22)

CIS = carcinoma in situ; LIN = laryngeal intraepithelial neoplasia.

a) Mild and moderate dysplasia have been pooled.

b) Includes cancer-associated precancerous lesions.

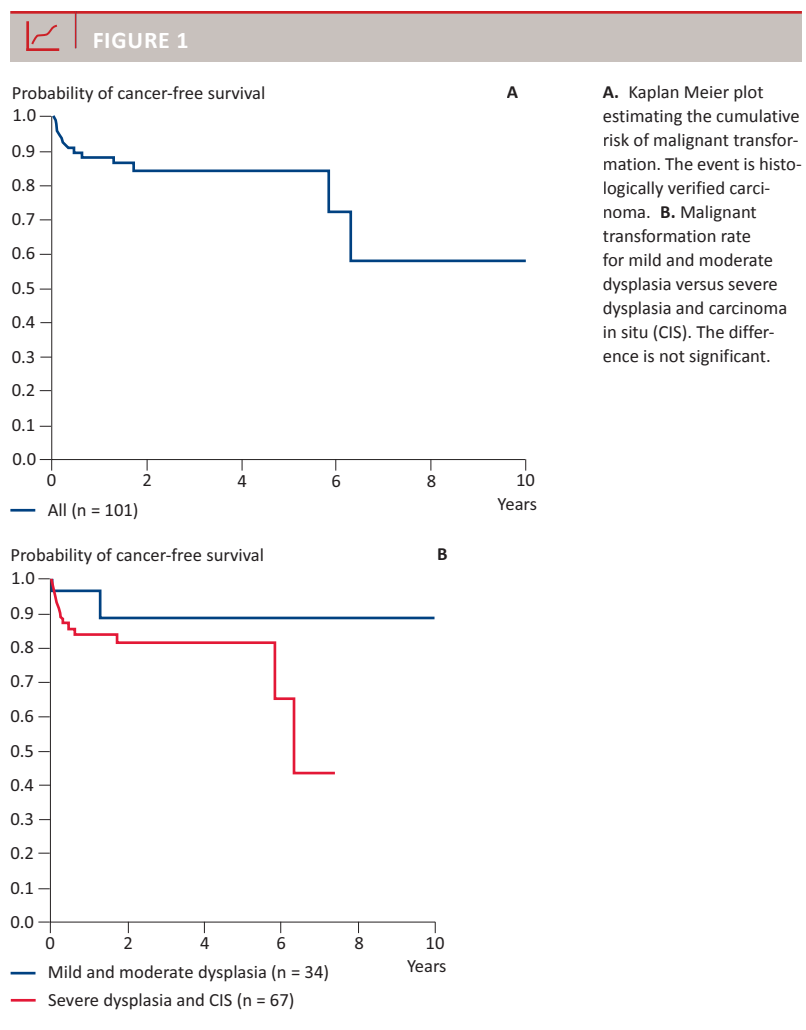
towards an increasing transformation rate with growing severity of dysplasia, even though this is absolutely not significant. 6% of the patients classified as having a mild or moderate dysplasia developed invasive carcinoma. Of the patients classified as having severe dysplasia or CIS, the malignant transformation rate was 20% and 19%, respectively.

Comparing the present data with those reported by others is complicated since there are several systems of histological classification. We used the WHO classification. However, the most popular classification system in recent literature is laryngeal intraepithelial neoplasia (LIN) introduced by Friedmann et al in 1986 [14]. The LIN classification system corresponds to that applied in dysplastic lesions of the uterine cervix. Staging thus distinguishes between keratosis without dysplasia (KWD), keratosis with mild dysplasia (LIN 1), keratosis with moderate dysplasia (LIN 2), and keratosis with severe dysplasia or carcinoma in situ (LIN 3) [3]. Arguments for applying LIN include the fact that lesions characterized as KWD have been shown to be associated with an increased risk of invasive carcinoma development [4], and that the prognosis for severe dysplasia and CIS are similar [15]. The WHO and LIN classification systems are comparable despite their differences. Table I shows the data reported in the latest literature. KWD is left out of the comparison as it does not form part of the WHO classification.

When discussing transformation rates, the term cancer-associated precancerous lesion is essential.

Part of the existing literature excludes cases in which invasive carcinoma is diagnosed shortly after the initial biopsy. The argument for doing so is that an initial biopsy showing only a precancerous histology may not be representative of the whole lesion. Most of the authors who use this terminology have not defined a time frame, which is problematic as it causes selection bias [2]. According to a study by Kroghdahl [15], the epithelial lesion is considered a cancer-associated dysplasia if mild or moderate dysplasia develops into carcinoma within two years; or if severe dysplasia or CIS develop into carcinoma within one year.

As shown in **Figure 1**, most malignant transformations are diagnosed within one or two years and could, according to Kroghdahl, be considered cancer-associated precancerous lesions. In fact, 11 of the 15 patients (73%) who developed invasive carcinoma in this study could be classified as such. If these events were withdrawn from the material, the cancer-free survival time would increase significantly. The reason why our material contains cancer-associated precancerous lesions could be that the primary treatment strategy was biopsy and laser evaporation of the visible lesion. As we chose evaporation, we did not achieve histological evaluation



of the whole lesion, and a focus of carcinoma may have been missed in the treatment which may, in the long term, develop into clinical significant laryngeal carcinoma. Another explanation may be that the carcinoma had developed in an area outside the initially visible lesion. Complete epithelial resection with histological evaluation of the whole lesion may improve the results and should be considered the preferred strategy [15].

Table 1 shows malignant transformation rates ranging from 6% to 22%; these rates increase with the severity of the precancerous lesion. The in- or exclusion of cancer-associated precancerous lesions strongly influences the results. Other reasons for the differences in transformation rate may be related to the type of treatment as well as the duration of the follow-up. Transformation may occur even ten years after the initial diagnosis [2].

Compared with the literature, our series had more severe dysplasia and CIS, i.e. 35% and 32%, respectively (66% LIN3). Pich et al, Gallo et al and Ricci et al had 11%, 28%, 21% LIN3s, respectively. The reason for this may

be that patients with severe dysplasia and CIS who are diagnosed at other hospitals in the Region of Southern Denmark were referred to our university department. In this way, a selection of severe dysplasia and CIS occurred.

In conclusion, our malignant transformation rate, which was based on a treatment strategy including biopsy and laser evaporation of all visible pathological tissue, is comparable with that seen in other recent series. This strategy is definitely superior to nipple biopsy and observation described in literature.

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CONFLICTS OF INTEREST: none

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