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ORIGINAL ARTICLE

The Influence of Resection and Aneuploidy on Mortality in Oral Leukoplakia

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ABSTRACT

BACKGROUND

Although the standard treatment of oral leukoplakia ranges from watchful waiting to complete resection, the value of these approaches is unknown.

METHODS

We studied the relations among resection, ploidy status, and death from cancer in 103 patients with diploid dysplastic oral leukoplakia, 20 patients with tetraploid lesions, and 27 patients with aneuploid lesions. Data on cancer-specific mortality and treatment were obtained from the Cancer Registry of Norway, Statistics Norway, and chart reviews.

RESULTS

Primary oral carcinoma developed in 47 of the 150 patients with leukoplakia (31 percent) — 5 with diploid, 16 with tetraploid, and 26 with aneuploid leukoplakia — during a mean follow-up of 80 months (range, 4 to 237). The margin status of the initial leukoplakia resection had no relation to the development of oral cancer (P=0.95). Twenty-six of the 47 patients in whom cancer developed (4 with prior tetraploid and 22 with prior aneuploid lesions) had recurrences (55 percent); the recurrences were more frequently multiple and distant (within the oral cavity) among patients with aneuploid lesions than among those with tetraploid or diploid lesions. All 47 patients underwent a standard regimen of surgery and radiation, followed by chemotherapy in the 26 with recurrent cancer. Only patients with aneuploid leukoplakia died of oral cancer; the five-year rate of death from cancer was 72 percent. Aneuploidy-related first carcinomas were diagnosed at a more advanced stage than were carcinomas originating from diploid or tetraploid leukoplakia (P=0.03) and were more likely to be lethal regardless of the stage.

CONCLUSIONS

Complete resection of aneuploid leukoplakia does not reduce the high risk of aggressive carcinoma and death from oral cancer.

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The standard treatment of oral leukoplakia ranges from watchful waiting to complete resection.[1,2] There is little evidence, however, that resecting precursor lesions of oral leukoplakia prevents oral cancer.[3,4] Oral carcinogenesis is a complex, multifocal process of multiclonal field carcinogenesis and intraepithelial clonal spread.[5-8] The multifocal nature of the early process may reduce the efficacy of local treatment.[9-11]

The cancer-specific mortality among patients with oral carcinomas that develop from aneuploid oral erythroplakia, which is clinically more aggressive than the far more common oral leukoplakia,[12,13] is substantial.[14] We previously found that a carcinoma developed in 36 of 150 patients with oral leukoplakia (24 percent) during a follow-up that exceeded 10 years in some cases and that a carcinoma developed in approximately 70 percent of patients with aneuploid oral leukoplakia within 3 years.[15] In the current study, we determined the effect of resecting oral leukoplakia on the rates of primary cancer, new or subsequent cancer, and death from oral cancer. We also evaluated the topographic relation between leukoplakias and their related cancers.

METHODS

CLINICAL AND PATHOLOGICAL ASSESSMENT

We used the Systematized Nomenclature of Medicine (SNOMED) coding system to identify the sites of leukoplakia and carcinoma.[16] The status of the resection margins was determined after consensus had been reached by four pathologists who conducted independent evaluations. Cancers that occurred after treatment of the first cancer were defined as new or subsequent cancers, since we did not determine whether they represented a recurrence or a second primary cancer. Information regarding the treatment of patients during follow-up was obtained by chart review. Oral squamous-cell carcinomas were graded according to the criteria of the World Health Organization.[17] The criteria of the American Joint Committee on Cancer were used to determine the clinical stage.[18]

ASSESSMENT OF NEW CANCERS AND CANCER-SPECIFIC MORTALITY

We used the data base of the Cancer Registry of Norway to assess cancer-specific mortality. All patients included in the study provided written or oral informed consent that follow-up data could be used for research purposes. The basis of the registry, which was created in 1953, is mandatory reporting of all new cases of cancer in the population,[19] thus justifying its use for epidemiologic and clinical research. Annually, the registry receives approximately 80,000 reports consisting of clinical forms from hospitals; copies of cytology, biopsy, and autopsy reports from pathology laboratories; and records on the cause of death from Statistics Norway (formerly the Central Bureau of Statistics). These forms provide data on new cases and give additional information on previously registered patients with cancer, including death certificates specifying the cause of death. Reporting dysplastic lesions to the registry is mandatory, as is the concurrent reporting of aneuploid oral premalignant lesions. The completeness of the reporting of patients who were hospitalized with oral cancer, defined as the ratio of patients listed in the Cancer Registry of Norway to those in the hospital-based registries, has been estimated to be 99 percent.[19]

The nature of the data in the registry enables investigators to reevaluate pathologists' reports, assess the type and grade of cancers, and determine the status of resection margins, the number of relapses, and the stage of disease at the time of the initial diagnosis and at each relapse. The registry's data base is annually checked against Statistics Norway's files. Matching and updating procedures are automated and are based on the system of 11-digit personal identification numbers used in Norway, facilitating the assessment of new cancers and cancer-specific mortality.

STATISTICAL ANALYSIS

We used event charts to evaluate the history of each patient.[20] The Kaplan–Meier method was used to construct survival curves according to ploidy status.[21] The designated end point was death from oral squamous-cell carcinoma. Data on a patient were censored in the Kaplan–Meier estimate if the patient died of unrelated disease or was alive at the end of follow-up. The log-rank test was used to assess the prognostic value of ploidy status in relation to disease-free survival and cancer-specific survival. Differences in proportions were evaluated by means of the chi-square test or Fisher's exact test. All P values were calculated on the basis of two-sided tests, and P values of 0.05 or less were considered to indi-

cate statistical significance. SPSS statistical software (SPSS) and S-PLUS software (Insightful) were used for the calculations.

RESULTS

CHARACTERISTICS OF THE PATIENTS

The base-line characteristics of the patients, the number of biopsies, and the number of follow-up visits before carcinomas developed have been reported previously.[15] Table 1 summarizes the main clinical characteristics of the patients. All patients were routinely evaluated every six months. Indications for a biopsy at follow-up visits were the same for all patients and included the occurrence of new lesions or a change in the clinical appearance of a previously identified lesion. All cancers considered in this study were oral squamous-cell carcinomas.

DEVELOPMENT OF CARCINOMA FROM LEUKOPLAKIA

Figure 1A shows the course of events in all 150 patients according to ploidy status. All patients had at least three years of follow-up data that could be evaluated for the development of oral cancer. We previously reported that a carcinoma developed in 36 of 150 patients with oral leukoplakia during a follow-up period that extended to June 30, 2000, and that in some cases exceeded 10 years.[15] During the current three-year extension of that study, we found that a carcinoma developed in an additional 11 of the 150 patients, including 2 patients with initially diploid lesions in whom first new aneuploid lesions and then cancer subsequently developed. During a mean follow-up of 80 months (range, 4 to 237), oral carcinoma developed in 47 of 150 patients with dysplastic oral leukoplakia: 5 patients with diploid lesions, 16 patients with tetraploid lesions, and 26 patients with aneuploid lesions (Fig. 1A, 2, and 3B).

LEUKOPLAKIA RESECTION MARGINS

Among the 150 patients, 37 had positive margins after the initial resection of the leukoplakia and 113 had negative margins. The percentage of positive margins was similar among the diploid, tetraploid, and aneuploid groups (25 percent, 25 percent, and 22 percent, respectively). A carcinoma developed in 32 percent of the patients with negative resection margins (36 of 113), as compared with 30 percent of the patients with positive margins (11 of 37). The margin status of the initial leukoplakia resection had no relation to the development of oral cancer (P=0.95 by the log-rank test) (Fig. 3A).

TOPOGRAPHIC RELATIONS BETWEEN LEUKOPLAKIAS AND SUBSEQUENT CARCINOMAS

Cancer developed in the same SNOMED-coded location as the preceding leukoplakia in 79 percent of patients with oral cancer (37 of 47) (Fig. 4).[16] With respect to the ploidy status, cancer developed in the same location as the preceding leukoplakia in all 5 patients with diploid lesions (3 carcinomas in the buccal mucosa and 2 in the floor of the mouth) (Fig. 4A), in 13 of 16 patients with tetraploid lesions (10 of 11 carcinomas at the lateral border of the tongue and 3 of 5 carcinomas in the floor of the

Table 1. Characteristics of 150 Patients According to the Ploidy Status of Their Oral Leukoplakia.*

Characteristic	Patients with Diploid Lesions (N=103)	Patients with Tetraploid Lesions (N=20)	Patients with Aneuploid Lesions (N=27)
Mean age — yr	69.6±6.3	64.5±11.0	69.6±7.1
Male sex — no. (%)	58 (56)	10 (50)	15 (56)
Tobacco use — no. (%)			
Never	21 (20)	3 (15)	3 (11)
Former	15 (15)	3 (15)	6 (22)
Current	64 (62)	10 (50)	15 (55)
Cigarettes	45 (44)	7 (35)	12 (44)
Smokeless tobacco (snuff)	19 (18)	3 (15)	3 (11)
No information available	3 (3)	4 (20)	3 (11)

* Plus–minus values are means ±SD. Because of rounding, percentages may not total 100.

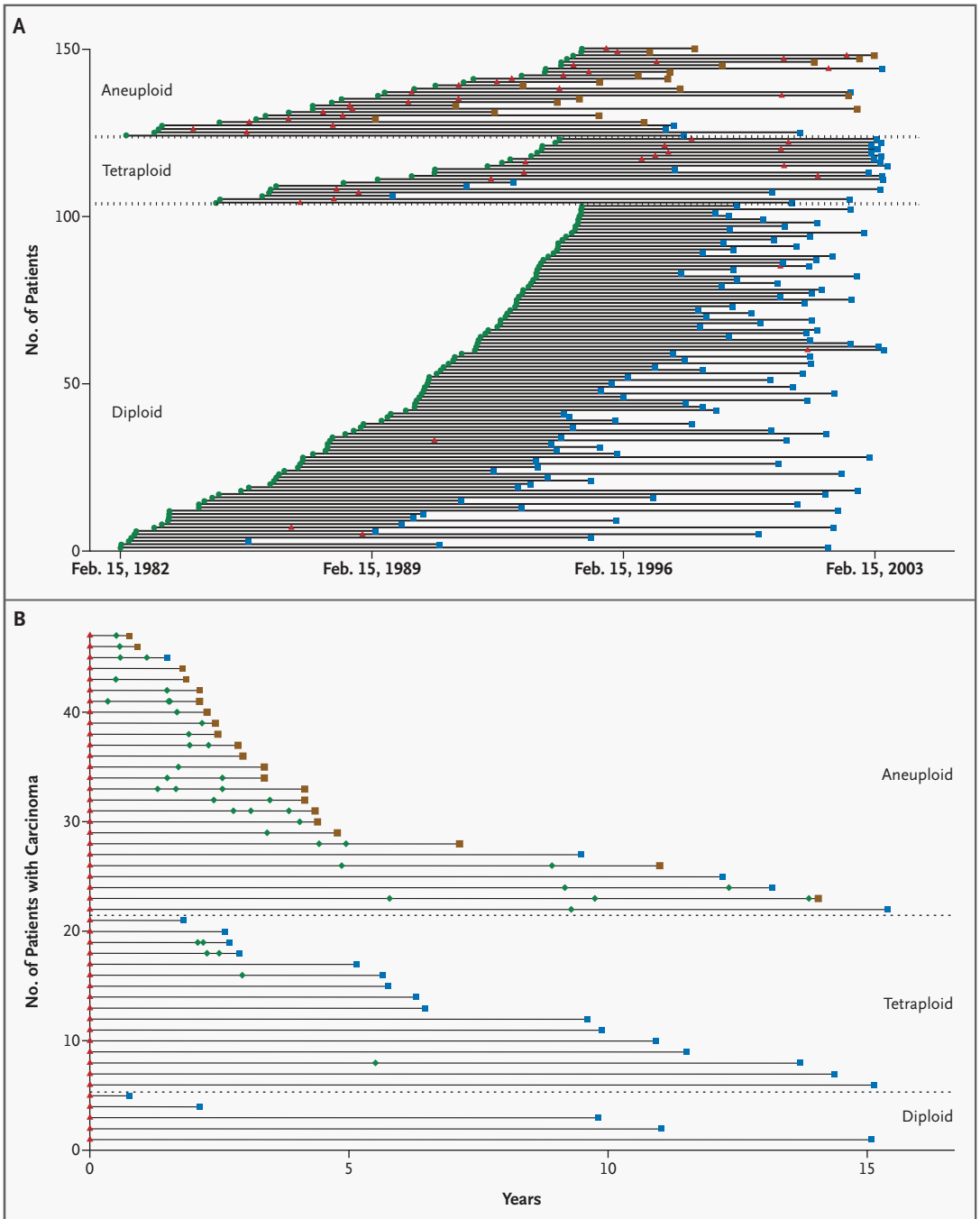

Figure 1. Course of Events in 150 Patients with Dysplastic Oral Leukoplakia from the Time of the First Biopsy (Panel A) and Course of Events from the Time of the Development of the First Cancer in the 47 Patients with Oral Cancers (Panel B), According to Ploidy Status.

Each symbol represents one event: green circles indicate the diagnosis of leukoplakia; red triangles the diagnosis of a first cancer; green diamonds the diagnoses of a second, third, or fourth cancer; blue squares the time of the last follow-up visit; and brown squares, the time of death.

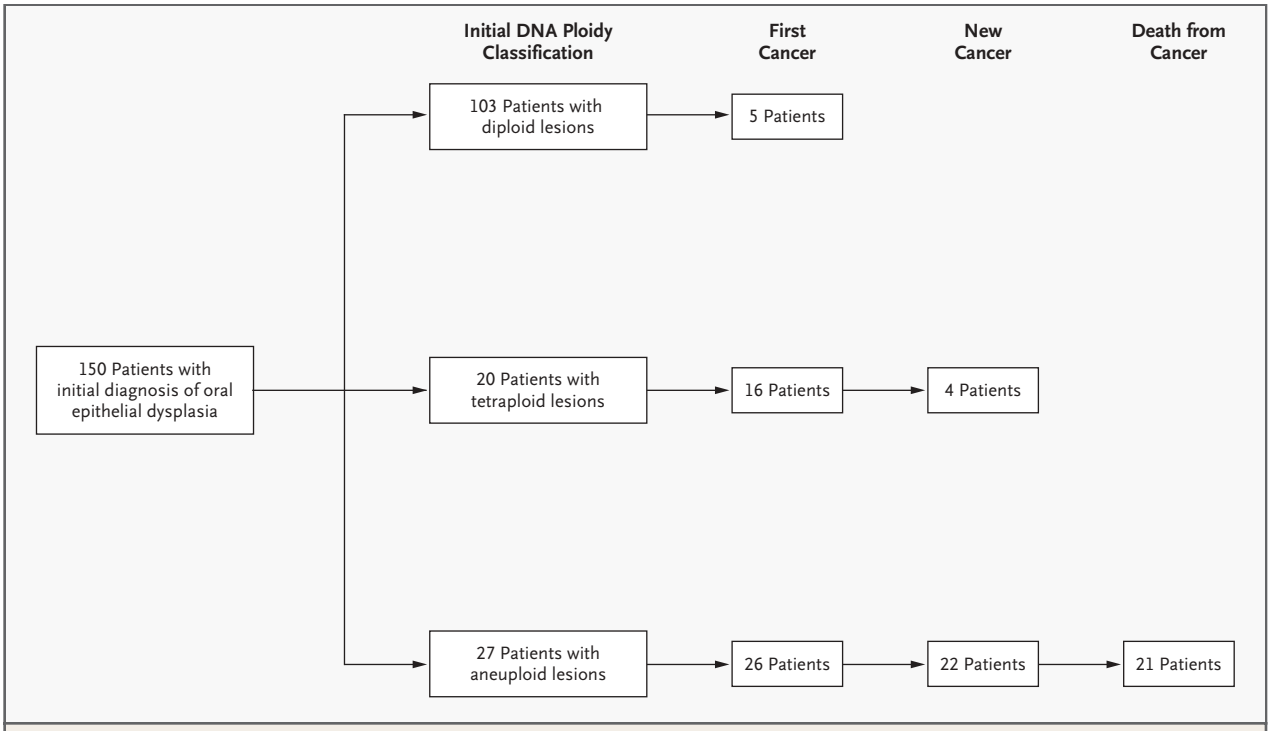

Figure 2. Clinical Course of Oral Leukoplakia, According to the Presence (Aneuploidy and Tetraploidy) or Absence (Diploidy) of Markers of Genomic Instability.

Initially, 105 patients were classified as having diploid oral leukoplakia, and 25 patients were classified as having aneuploid lesions. During follow-up but before the development of carcinoma, aneuploid lesions were diagnosed in two patients who initially had diploid lesions. Thus, 103 patients with diploid lesions, 20 patients with tetraploid lesions, and 27 patients with aneuploid leukoplakia were included in the analysis.

mouth) (Fig. 4B), and in 19 of 26 patients with aneuploid lesions (13 of 15 carcinomas in the floor of the mouth and 6 of 11 carcinomas in the lateral border of the tongue) (Fig. 4C). Twenty-one percent of the oral carcinomas (10 of 47) developed in a location different from that of the preceding leukoplakia (Fig. 4D). The mean distance between these carcinomas and the prior leukoplakias was 4.5 cm, with a range of 3.0 to 8.5 cm.

CLINICAL COURSE OF PATIENTS IN WHOM A CARCINOMA DEVELOPED

Figure 1B shows the clinical course for the 47 patients in whom a carcinoma developed. The date of the first oral cancer was set as time 0, and the time to subsequent cancers, the last follow-up visit, or death was plotted. Among these 47 patients, 26 (55 percent) had a subsequent cancer. Of the five patients with carcinomas that arose from diploid leukoplakia, none had a subsequent cancer (Fig. 2). A subsequent cancer developed in 4 of 16 patients with tetraploid oral leukoplakia. Two of these patients had one new cancer, and two had two new cancers of the oral cavity. In all four patients, the initial tumors were at the lateral border of the tongue and the subsequent carcinomas developed in a similar site. None died from their cancer during a mean follow-up of 63 months (range, 32 to 128). Of 26 patients in whom oral carcinoma developed from aneuploid leukoplakia, 22 (85 percent) had subsequent or new cancers (total number of cancers, 37) (Fig. 1B and 2), and in 8 of these 22 patients (36 percent) the new oral cancers developed at sites that differed from those of the previous cancer.

The percentages of new cancers in the three ploidy groups were strikingly different: 0 percent in the diploid group (0 of 5 patients), 25 percent in the tetraploid group (4 of 16), and 85 percent in the aneuploid group (22 of 26) ($P<0.001$ by Fisher's exact test). The time to the development of a new cancer also differed significantly among the three ploidy groups (Fig. 3C) ($P<0.001$ by the log-rank test).

The clinical stage of the first carcinomas arising from oral leukoplakia was significantly associated

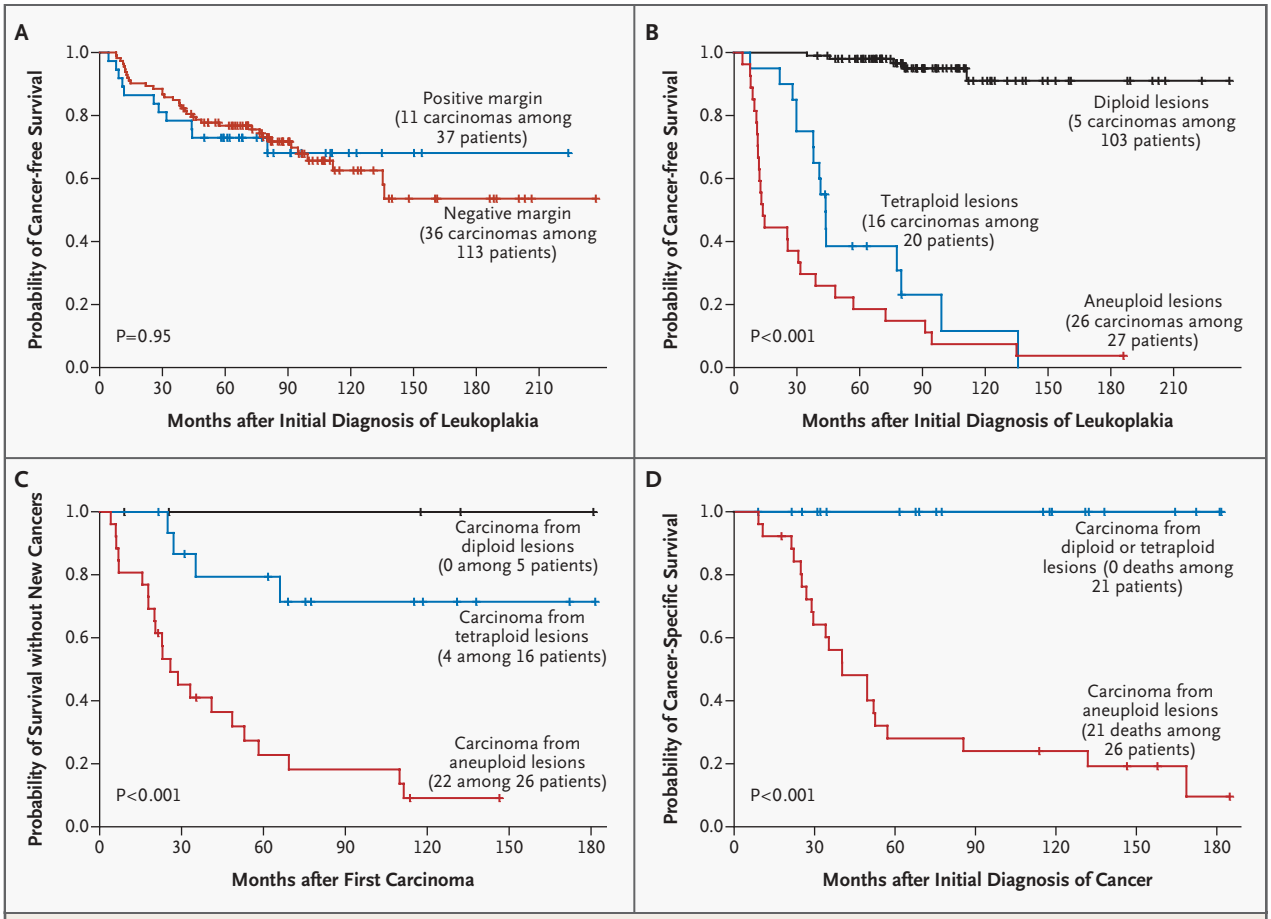

Figure 3. Kaplan–Meier Estimates of Cancer-free Survival According to the Margin Status after Resection of Leukoplakia (Panel A) and the Leukoplakia Ploidy Status (Panel B) among All 150 Patients and Estimates of Survival Free from New Cancers (Panel C) and Overall Survival (Panel D) among the 47 Patients with Primary Oral Cancer, According to the Ploidy Status of the Prior Leukoplakia.
Tick marks indicate censored data.

with ploidy status. Among the carcinomas that arose from diploid or tetraploid lesions, 14 percent were in clinical stage I, 48 percent were in stage II, 38 percent were in stage III, and 0 percent were in stage IV, as compared with values of 4 percent, 19 percent, 65 percent, and 12 percent, respectively, for carcinomas that arose from aneuploid lesions (Table 2) (P=0.03).

CANCER TREATMENT

Among the 47 patients with a carcinoma arising from oral leukoplakia, all but 1 had negative resection margins. A total of 12 patients had unilateral lymph-node metastasis and underwent neck dissection. One patient had distant metastasis to the lung and was not treated with definitive surgery. Hence, 45 of 47 patients were considered to have negative resection margins after the initial treatment of their carcinoma. All patients who underwent resection received postoperative radiotherapy (50 Gy, given in 25 fractionated doses, with daily doses of 2 Gy given five days a week). Twelve patients with lymph-node metastasis also received radiation to the neck nodes at levels III and IV by means of a separate anterior portal in the lower portion of the neck. All 12 patients received one of three regimens of chemotherapy at the time of recurrence: 50 mg of methotrexate per square meter of body-surface area every three weeks (4 patients), 100 mg of docetaxel per square meter every three weeks (1 patient), or 100 mg of cisplatin per square meter in combination with 100 mg of fluorouracil per square meter (for five days) every three weeks (7 patients). Treatment did not vary according to ploidy status.

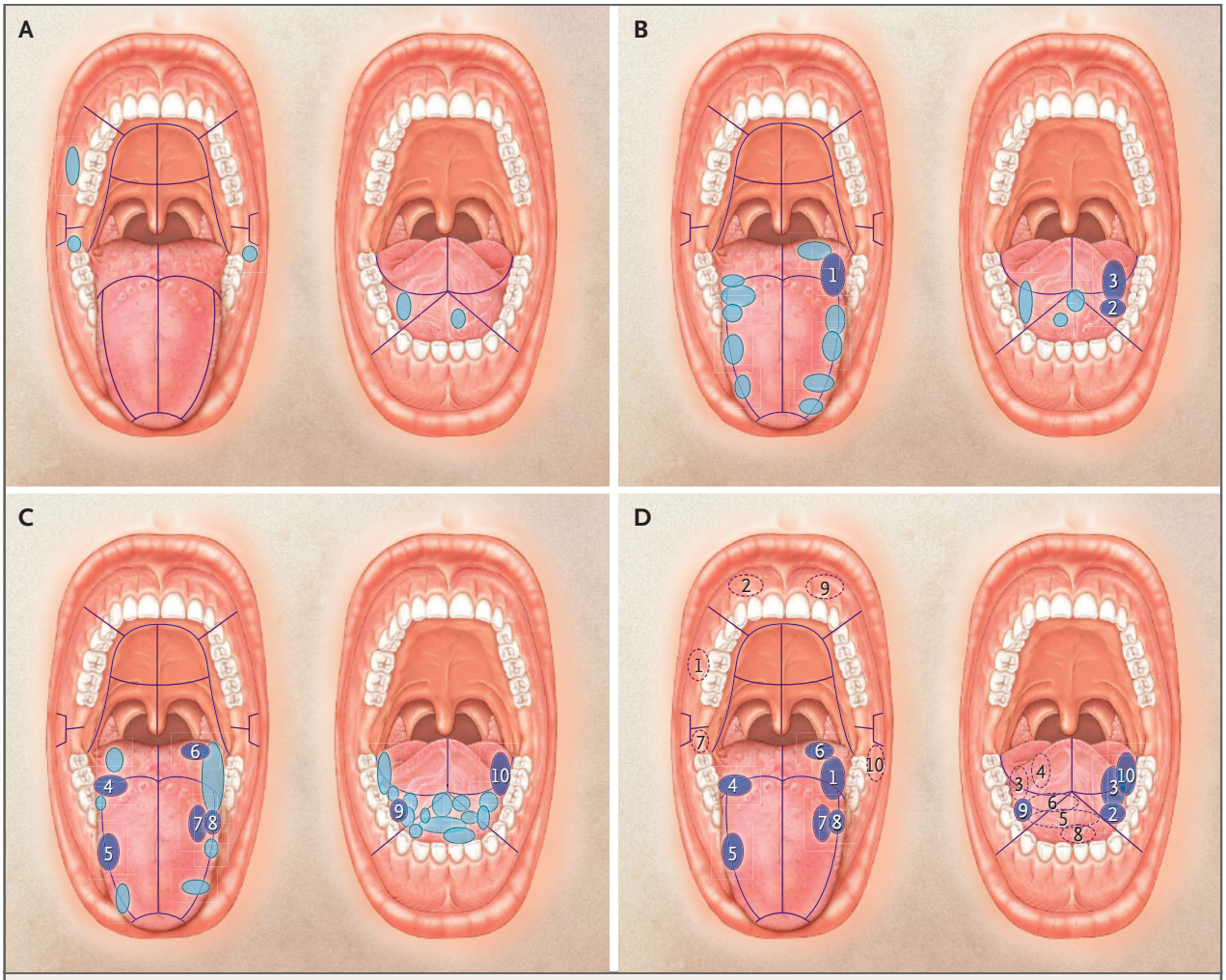

Figure 4. Topographic Relations between Oral Leukoplakias and Subsequent Oral Carcinomas.

The drawing on the left side of each panel shows the maxilla, hard and soft palate, upper part of the buccal mucosa, and tongue. The drawing on the right side of each panel shows the floor of the mouth, lower part of the buccal mucosa, and mandible. Panel A shows where diploid oral leukoplakia developed into a primary carcinoma at the same location in five patients (light-blue ellipses or circles). Panel B shows the locations of primary oral carcinoma that developed from tetraploid leukoplakia in 16 patients. The location of the carcinoma was the same as that of the preceding leukoplakia in 13 patients (light-blue ellipses or circles) and different in 3 (dark-blue ellipses, numbered 1, 2, and 3). Panel C shows the individual locations of primary oral carcinoma that developed from aneuploid leukoplakia in 26 patients. The location of the carcinoma was the same as that of the preceding leukoplakia in 19 patients (light-blue ellipses or circles) and different in 7 (dark-blue ellipses, numbered 4 through 10). Panel D shows the topographic relations between the primary carcinomas (dark-blue ellipses, numbered as in Panels B and C) that developed in locations that differed from those of the preceding leukoplakias (dotted-line ellipses) in the 10 patients with such lesions represented in Panels B and C. The numbering of the leukoplakias corresponds to that of the carcinomas that arose from them.

CANCER-SPECIFIC MORTALITY

Of the 47 patients in whom oral cancer developed, only 1 (who had had a diploid leukoplakia) died of a cause unrelated to cancer — trauma 11 years after the initial diagnosis of oral cancer. The overall cancer-specific mortality rate was 45 percent (21 of 47 patients died) during a mean observation period of 76 months (range, 9 to 185) after the first cancer. As expected, a more advanced stage (stage III or IV) at diagnosis was associated with poor survival ($P=0.03$). Aneuploid lesions, as compared with diploid or tetraploid lesions, were also significantly associated with poor survival ($P<0.001$) (Fig. 3C). The five-year mortality rate for the aneuploid group was 72 percent (95 percent confidence interval, 49 to 85) (Fig. 3D). Although patients with stage III or IV

Table 2. Clinical Stage of First Carcinomas That Arose from Oral Leukoplakia, According to Ploidy Status.*

Clinical Stage	Diploid Leukoplakia (N=5)	Tetraploid Leukoplakia (N=16)	Aneuploid Leukoplakia (N=26)
		number of patients	
Stage I	0	3	1
Stage II	2	8	5
Stage III	3	5	17
T3N0M0	1	3	5
T1N1M0	2	0	6
T2N1M0	0	2	4
T3N1M0	0	0	2
Stage IV	0	0	3

* The criteria of the American Joint Committee on Cancer were used to determine the clinical stage.[18] T denotes tumor, N node, and M metastasis.

cancer were more likely to die of cancer than those with stage I or II, only patients whose carcinomas arose from aneuploid leukoplakia (21 of 26, or 81 percent) died from their cancer during a follow-up of 62 months (range, 9 to 185) (Fig. 2 and 3D). The histologic grade did not have a prognostic influence in this study. Thirteen patients had histologic grade I disease at diagnosis, 16 had grade II, and 18 had grade III. Among these patients, 7 (54 percent), 11 (69 percent), and 8 (44 percent), respectively, had new cases of cancer, which resulted in rates of death from cancer of 38 percent (5 of 13 patients with grade I disease died), 56 percent (9 of 16 with grade II), and 39 percent (7 of 18 with grade III).

DISCUSSION

Our results show that the complete resection of oral leukoplakia does not prevent carcinoma and that oral carcinoma arising from aneuploid leukoplakia has aggressive clinical behavior despite the use of standard treatment. We previously reported that oral erythroplakia with aneuploidy, which is rare and aggressive, is associated with a high risk of death,[14] and we have now determined the risk of death from cancer associated with oral leukoplakia, a far more common premalignant lesion. The patients with aneuploid leukoplakia had a rate of primary cancer of 96 percent, a rate of new or subsequent cancer of 81 percent, and a rate of death from cancer of 78 percent during the study.

The status of the margins of the initial resection of leukoplakia did not affect the risk of cancer in our study. The percentage of patients with positive margins was approximately the same in the group with a poor prognosis (as defined by tetraploidy or aneuploidy) and the group with a more favorable prognosis (as defined by diploidy). We could not assess the margin status of the resection of the first carcinoma as an independent prognostic factor because all but two tumors had negative resection margins. The histologic grade of carcinomas according to the criteria of the World Health Organization did not have a prognostic effect, which corroborates previous findings.[22]

The high overall rate of primary cancer in the same oral location as the prior dysplastic leukoplakia (79 percent) provides topographic evidence of the presence of clonal alterations at histologically negative resection margins.[23] The fact that 10 patients had cancer and prior leukoplakia in different locations suggests that the cancer either was genetically distinct from the resected leukoplakia or resulted from the lateral clonal spread of the leukoplakia.[5,7]

Several of our results suggest that aneuploidy is associated with a biologically more aggressive cancer. Subsequent cancers were more frequently multiple and distant (within the oral cavity) in patients with aneuploid lesions than in those with tetraploid lesions (no subsequent cancers occurred among patients with diploid lesions). The stage of cancer was more advanced in association with aneuploid leukoplakia than with diploid or tetraploid leukoplakia. Since routine treatment and follow-up of all patients with dysplastic leukoplakia were the same regardless of ploidy status,[15] the association between the ploidy status and the clinical stage of first carcinomas was probably due to the more aggressive behavior of the tumor in the aneuploid group. The more advanced stage could explain, in part, the poorer survival among the patients with aneuploid lesions than among those with diploid or tetraploid lesions. Furthermore, only patients with aneuploid lesions died of cancer, suggesting that the aneuploidy-related cancers were more lethal than were diploidy- or tetraploidy-related cancers of the same stage.

The development of oral cancer is related to exposure to tobacco[24-27] and involves field carcinogenesis and multifocal lesions.[5,8,28-31] New cancers in patients with primary oral cancers arise through a complex process of recurrence and the development of second primary cancers.[30,31] This process

involves the independent development of malignant clones as well as lateral spread of premalignant and malignant cells within the epithelium.[5,7,28] Previous studies have shown that other biomarkers of genomic instability, such as chromosomal polysomy and microsatellite alterations, can predict the likelihood of malignant transformation of oral premalignant lesions.[32] Future studies may provide mechanistic insights into the aggressive behavior of these lesions.

We identified a subgroup of patients with oral leukoplakia, as defined by aneuploidy, a marker of genomic instability, who are at extremely high risk for biologically aggressive carcinomas despite undergoing complete resection. Therefore, aneuploid leukoplakia is tantamount to carcinoma. The failure of current treatment for aneuploid oral leukoplakia to avert cancer shows that patients with such aggressive, high-risk lesions have an unmet medical need. These patients urgently need new, effective treatments and preventive therapies, such as those involving molecular targets, which in this setting would be equivalent to cancer therapy.[33,34]

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