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Effects of Zinc and Nutritional Status on Clinical Outcomes in Head and Neck Cancer

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ABSTRACT

The head and neck cancer patient often presents with both protein malnutrition and trace element deficiencies. Zinc has been found to be deficient in many head and neck cancer patients. In this study, pretreatment zinc status and nutritional status (measured by the Prognostic Nutritional Index [PNI]) were correlated with clinical outcomes in 47 patients. The patients were followed-up for a median of 52 mo from the time of enrollment. Our results showed that the tumor size and overall stage correlated significantly to zinc status whereas no such correlation was seen with PNI, alcohol intake, or smoking in our subjects. The results also showed that impaired zinc status was associated with an increased number of treatment morbidities, unplanned hospitalizations, and treatment delays ($P < 0.05$). Nutritional status was not associated with any studied outcome variable. The disease-free interval was highest for the group which had both zinc-sufficient and nutrition-sufficient status. Although our data do not prove conclusively, they do suggest that impaired zinc status at presentation may contribute to treatment morbidity, and that for an optimal mean disease-free interval, a sufficient zinc and nutritional status is required. *Nutrition* 1998;14:489–495. ©Elsevier Science Inc. 1998

Key words: zinc, head and neck cancer, prognostic nutritional index, morbidity, treatment delays, stage

INTRODUCTION

Protein deficiency is common in patients with head and neck cancer and is usually the result of inadequate caloric intake due to local tumor effects, combined with the chronic effects of tobacco

and alcohol abuse. The significant influence of nutritional status on therapeutic outcomes including surgical morbidity, tolerance of therapy, and overall mortality is well recognized.^{1–4} These observations therefore encourage the careful pretreatment evaluation of

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all head and neck cancer patients to identify patients at greater risk for treatment morbidity. A number of different physical and laboratory assessment measures have been used to study the relationship between malnutrition and poor clinical outcomes.^{1,3-8} Among the tools used to assess nutritional well-being is the Prognostic Nutritional Index (PNI). Developed initially to identify gastrointestinal surgery patients at risk for complications, this predictive model utilizes laboratory and anthropometric measures in an equation of prognostic significance.⁹ The PNI has subsequently been applied to head and neck cancer patients.^{3,4}

Zinc deficiency has been also reported in a number of malignancies.¹⁰⁻¹³ Zinc is a ubiquitous trace metal required for the activity of over 300 metalloenzymes, including many involved in nucleic acid synthesis and cellular replication. Additionally, there are over 1400 zinc-finger proteins that participate in the genetic expression of many proteins.¹⁴ Deficiency of zinc may result in increased wound complications and cell-mediated immune dysfunctions in humans and increased rates of tumor development in experimental animals.¹⁴ Despite its potential role in cancer, only a few studies have assessed zinc levels in head and neck cancer patients.^{11,15-18} Studies correlating zinc status and treatment outcomes in these patients are even more rare.¹¹

The purpose of this study was to examine the prognostic value of the pretreatment zinc and protein nutrition status in predicting treatment morbidity and outcomes in a series of newly diagnosed head and neck cancer patients.

MATERIALS AND METHODS

Patient Population

All eligible patients with a newly diagnosed head and neck cancer presenting to the Detroit Medical Center, Wayne State University, Detroit, Michigan, USA, or the Veterans Administration Medical Center, Allen Park, Michigan, USA, between June 1987 and June 1995 were invited to participate in this study. Excluded were patients who had previous cancer treatment, severe comorbidity with life expectancy less than 9 mo, coexisting disease states such as cirrhosis or diabetes, or known metastatic disease beyond the cervical lymph nodes. Participation in the study did not influence the choice of treatment that was selected by the patient in conjunction with the multimodality head and neck oncology team. Sixty patients agreed to participate in the study. At enrollment, demographics, tumor site, and tumor stage, using the 1988 American Joint Committee on Cancer classification, were recorded. A tobacco and alcohol history was also determined for each participant. Tobacco use was quantified into pack-years and alcohol consumption was categorized as either heavy or moderate/rare use.

Nutrition Status: PNI

Participants underwent a pretreatment laboratory and clinical assessment of baseline nutritional status to calculate the PNI. Prognostic Nutritional Index was calculated by using the formula: $PNI\% = 158\% - 16.6 (\text{serum albumin}) - 0.78 (\text{triceps skin-fold thickness [mm]}) - 0.2 (\text{serum transferrin}) - 5.8 (\text{delayed hypersensitivity score})$. Serum albumin was determined on an automated Olympus Au-5000 (Olympus, Melville, NY, USA) machine. Serum transferrin (mg/dL) was determined by turbidimetric analysis. The delayed hypersensitivity score was determined from the cutaneous response to intradermal trichophyton, mumps, and candida antigens at 48 h (nonreactive = 0, ≤ 5 mm induration = 1, and ≥ 5 mm induration = 2). Prognostic Nutritional Index scores $\geq 20\%$ were regarded as nutritionally deficient (NUTR⁻) and scores $< 20\%$ were classified as nutritionally sufficient (NUTR⁺).

Zinc Status

Zinc assay. Extreme precautions were taken to avoid contamination during preparation and assay of samples. All of the water used throughout the procedure was distilled (Barnstead) and passed through a continental water systems (Hazel Park, MI, USA) primary deionization unit and Millipore 0.2- μm post filter cartridge with final filtration through an ultrapore mixed-bed resin column (Barnstead Co., Division of Sybron Corp., Boston, MA, USA).

Plasma zinc. Plasma zinc was assayed by the direct dilution method. Working standards were prepared by dilution stock and intermediary standards with glycerol 5% v/v for zinc. Plasma dilutions (fivefold) were prepared with distilled, deionized water.

Isolation of cells and zinc assay. Lymphocytes, granulocytes, and platelets were separated simultaneously by using a modification of a previous method.¹⁴ The cells were isolated at room temperature by using a discontinuous Ficoll-Histopaque density centrifugation technique (Sigma Diagnostics, St. Louis, MO, USA). Extreme care was taken to remove erythrocytes from granulocytes and lymphocytes and to remove platelets from lymphocytes.

A 15-mL sample of blood was collected in a polystyrene centrifuge tube containing 300 μg of zinc-free and preservative-free heparin. The sample was centrifuged at 180g for 5 min, and platelet-rich plasma was removed and saved for zinc assay in the platelets. The residual blood sample was transferred to a 50-mL polypropylene centrifuge tube, and normal saline solution was added very slowly (along the side of the tube) to a total volume of 30 mL and then centrifuged at 180g for 5 min. This step of adding saline solution and centrifuging at 180g for 5 min was repeated once again. The supernatant was discarded, and normal saline solution was added to a total volume of 24 mL. The tube was capped and gently inverted several times.

Four 14-mL polypropylene tubes of a discontinuous gradient were prepared. The lower gradient was 3 mL Sigma Histopaque 1.119 and the upper gradient was 3 mL Sigma Histopaque 1.077. These gradients were carefully layered by using transfer pipettes (Saint-Amand Manufacturing Co., San Fernando, CA, USA) just before layering the diluted sample. The diluted blood (8 mL) was layered very gently with a transfer pipette over the gradient of 1.077 in each of the 4 tubes. The tube was capped and centrifuged at 280g for 20 min. The supernatant was removed down to the normal saline Histopaque 1.077 interface, and the cloudy layer of lymphocytes from the four tubes was transferred to a 14-mL polypropylene tube with a transfer pipette. For harvesting the granulocytes, the remaining Histopaque 1.077 down to the 1.077-1.119 interface was discarded, and the cloudy layer of granulocytes was transferred to two 14-mL polypropylene tubes. The lymphocyte and granulocyte tubes were filled with normal saline solution to a 13 mL volume. The tubes were then capped and mixed gently.

The rest of the procedures for final isolation of lymphocytes, granulocytes, and platelets were similar to those published earlier.^{13,15}

Zinc assays in lymphocytes, granulocytes, and platelets. Baseline zinc levels were determined for subjects in the study. Prior to 1992 in 20 subjects, zinc status was assessed using plasma zinc levels determined by flame atomic absorption spectrophotometry (Perkin Elmer, Norwalk, CT, USA). Levels $\leq 80 \mu\text{g/dL}$ were classified as impaired zinc status (ZINC⁻). Beginning in 1992, cellular zinc assays became available and were used to determine zinc status in 32 subjects. Cellular zinc concentrations were analyzed from freshly isolated peripheral blood lymphocytes and granulocytes using a Varian SpectraAA-40 flameless atomic ab-

TABLE I.

DISTRIBUTION OF PATIENTS BY ZINC AND NUTRITIONAL STATUS*		
	NUTR ⁻ (%)	NUTR ⁺ (%)
ZINC ⁻	17 (36.1)	14 (29.8)
ZINC ⁺	10 (21.3)	6 (12.1)

* $P = 0.60$.

NUTR⁻, nutritionally deficient; NUTR⁺, nutritionally sufficient; ZINC⁻, impaired zinc status; ZINC⁺, zinc sufficient.

sorption spectrophotometer with a Zeeman background corrector (Varian Instruments, Palo Alto, CA, USA).^{14,15} All samples were analyzed against Bovine Liver Standard (National Bureau of Standards, Washington, DC, USA) and three internal standards of pooled lymphocytes. Based on previous studies in an experimental human model of zinc deficiency,¹⁹ subjects were defined as impaired zinc status (ZINC⁻) if their lymphocyte zinc was $\leq 50 \mu\text{g}/10^{10}$ cells and granulocyte zinc was $\leq 42 \mu\text{g}/10^{10}$ cells. Subjects with cellular zinc levels exceeding these criteria were classified as zinc sufficient (ZINC⁺).

DATA COLLECTION

To obtain the study database, available inpatient and outpatient hospital records, otolaryngology-head and neck surgery clinic charts, and radiation oncology clinic charts were reviewed. The patients in this study were followed up for a median of 52 mo (range; 16–98 mo) from the time of enrollment.

Operative Morbidity Measures

For patients undergoing a surgical resection, hospital records were reviewed to determine the presence of a wound infection or fistula. For this study, *wound infection* included only those who had purulent drainage spontaneously or by incision and drainage clearly documented in the chart. Additionally, the number of postoperative days and febrile postoperative days ($T_{\text{max}} > 38^{\circ}\text{C}$) were recorded as indirect indicators of postoperative complications. Any medical or surgical complication identified that extended the postoperative course was defined as a postoperative morbidity.

Treatment Morbidity Measures

Available medical records were reviewed to identify any disease morbidities occurring within 12 mo of treatment. In the case of disease recurrence, only morbidities occurring before the documentation of recurrence were included. For this study, a treatment morbidity was defined as any documented medical or surgical complication that necessitated hospitalization, surgical intervention, or delays in completing the planned treatment. Unplanned hospital days were defined as days spent in the hospital or hospital emergency room beyond the planned cancer treatment. For unplanned hospitalizations, and in instances where planned hospitalizations were extended because of complications, the number of unplanned days was determined by review of the daily progress notes. Treatment delays were defined as unplanned breaks or pauses in the course of treatment. The number of delay days was determined from clinic charts and treatment records. Patient weights at enrollment, 6, and 12 mo were measured to determine weight changes. The disease-free interval was also determined for each patient based on the completion of primary therapy.

STATISTICAL ANALYSIS

Both enrollment data, including demographics, tumor site and stage, smoking and alcohol behavior, and treatment data, including treatment modality, febrile days, wound infection, fistula, postoperative morbidity, treatment morbidity, unplanned hospital days, treatment delays (delay days), 6 and 12 mo weight change, and disease-free interval, were compared for the zinc and protein nutrition deficient and sufficient groups. Oral cavity and oropharynx sites were combined and hypopharyngeal and laryngeal sites were combined for statistical analysis. In the analysis of disease stage, early stage I and stage II tumors were combined so that three groups; early (stage I and II), stage III, and stage IV, were used. A univariate analysis using the *t* test or Wilcoxon nonparametric test was employed for continuous variables, and a chi-square or Fisher's exact test was employed for discrete variables. Mantel-Haenzel test was applied when adjusting for nutrition effect. For all, statistical analysis results were considered to be significant at $\alpha = 0.05$. In order to investigate the relationships of the study variables such as zinc status, nutritional status, site, and stage with outcomes, a multiway analysis of variance was used. This analysis was, however, somewhat limited because of our small sample size.

TABLE II.

PATIENT DEMOGRAPHICS AT ENROLLMENT						
Enrollment data	ZINC ⁻ ($n = 34$)	ZINC ⁺ ($n = 18$)	<i>P</i>	NUTR ⁻ ($n = 27$)	NUTR ⁺ ($n = 20$)	<i>P</i>
Age (y)*	59 \pm 11	58 \pm 10	0.95	57 \pm 10	61 \pm 10	0.10
Gender (% males)	73.5	83.3	0.50	81.5	75.0	0.70
Tobacco (pack years)*	55 \pm 44	46 \pm 37	0.49	53 \pm 44	47 \pm 42	0.61
Alcohol (% heavy)†	67.6	73.7	0.65	70.4	57.9	0.38

* Mean \pm standard deviation.

† Alcohol-heavy drinkers were defined as those who drank more than one drink daily, and rare/occasional drinkers who either abstained or had a drink only on rare occasions or who drank one to five drinks weekly.

ZINC⁻, impaired zinc status; ZINC⁺, zinc sufficient; NUTR⁻, nutritionally deficient; NUTR⁺, nutritionally sufficient.

TABLE III.

ZINC CONCENTRATION IN ZINC ⁻ AND ZINC ⁺ HEAD AND NECK CANCER SUBJECTS (MEAN ± SD)*			
	Plasma zinc μmol/L	Lymphocyte zinc μg/10 ¹⁰ cells	Granulocyte zinc μg/10 ¹⁰ cells
ZINC ⁻	14.80 ± 2.92	47.03 ± 5.55	39.78 ± 4.59
ZINC ⁺	14.80 ± 2.50	54.80 ± 2.67	45.19 ± 4.84

* The cancer subjects at enrollment were divided into ZINC⁻ and ZINC⁺ groups according to the criteria previously developed in our laboratory. Lymphocyte and granulocyte zinc concentration less than 50 μg/10¹⁰ cells and 42.3 μg/10¹⁰ cells were considered to be indicative of impaired zinc status.

ZINC⁻, impaired zinc status; ZINC⁺, zinc sufficient.

RESULTS

Morbidity data were available in 60 patients; of these, complete nutritional data were available for 47 and zinc data available

for 52. The classification of patients by protein nutrition and zinc status is shown in Table I. Age, gender, and social habits were all similar between the groups (Table II). Tables III and IV present zinc data and body weight and body mass index (BMI) data, respectively.

We have reported our data correlating zinc and protein status with several baseline variables.²⁰ In Table V we briefly summarize the effects of zinc and nutritional status on tumor size and stage of cancer in our subjects. A strong association was found between tumor size and advancing stage and zinc status: in 76.4% of the ZINC⁺ cancer patients the tumor size was T1 and T2, whereas only in 27.6% of the ZINC⁻ cancer patients the tumor size was T1 and T2 ($P = 0.002$). After adjusting for the effect of nutrition, the tumor size was significantly associated with zinc status ($P = 0.003$). In stage IV patients, 66.6% had impaired zinc status, whereas in the ZINC⁺ group only 29.4% of the patients were stage IV ($P = 0.04$). After adjusting for the effect of nutrition, the stage was significantly associated with zinc status ($P = 0.01$). Among patients with oral cavity and oropharyngeal primary tumors, 75% were nutritionally deficient, whereas among patients with laryngeal or hypopharyngeal tumors only 38% were nutri-

TABLE IV.

BODY WEIGHT AND BODY MASS INDEX OF CONTROLS AND HEAD AND NECK CANCER PATIENTS						
Parameter	Group*	<i>n</i>	Mean comparison	± Standard deviation	ANOVA <i>P</i> value	Duncan's multiple range comparison
Percent of ideal body weight	1	25	125.61	21.08		
	2	32	102.30	25.31	0.030	2 < 1
	3	34	102.21	15.13		3 < 1
Body mass index	1	25	26.92	5.02		
	2	32	23.44	5.56	0.020	2 < 1
	3	34	23.77	4.32		3 < 1

* In group 1, normal zinc-sufficient volunteers were of both sexes, mixed races, and were 25 to 50 years old. They were primarily employees of the Detroit Medical Center. group 2 consisted of ZINC⁻ head and neck cancer subjects and group 3 consisted of ZINC⁺ head and neck cancer subjects. ANOVA, analysis of variance.

TABLE V.

EFFECT OF ZINC AND NUTRITION STATUS ON TUMOR SIZE AND STAGE*							
Specific nutrient variable	ZINC ⁻ (%) (<i>n</i> = 34)	ZINC ⁺ (%) (<i>n</i> = 18)	ANOVA (<i>P</i>)	NUTR ⁻ (%) (<i>n</i> = 27)	NUTR ⁺ (%) (<i>n</i> = 20)	ANOVA (<i>P</i>)	Effect of zinc status adjusted for nutrition (<i>P</i>)
Tumor size (%)							
T1 and T2	27.6	76.4	0.002	50.0	50.0	1.00	0.003
T3 and T4	72.4	23.6	—	50.0	50.0	—	—
Stages (%)							
I & II	16.7	35.3	0.04	17.4	36.8	0.24	0.01
III	16.7	35.3	—	21.7	26.4	—	—
IV	66.6	29.4	—	60.9	36.8	—	—
Site (%)							
OC/OP	67.7	53.6	0.50	75.0	44.4	0.05	0.30
HP/LNX	32.3	43.7	—	25.0	55.6	—	—

* Nutrition status was defined by Prognostic Nutrition Index.

NUTR⁻, nutritionally deficient; NUTR⁺, nutritionally sufficient; ZINC⁻, impaired zinc status; ZINC⁺, zinc sufficient; ANOVA, analysis of variance; OC/OP, oral cavity and oropharynx; HP/LNX, hypopharynx and larynx.

TABLE VI.

COMPLICATIONS AND MORBIDITIES DURING TREATMENT	
Complication	Number (%)
Infectious (non-pulmonary)	21 (27)
Infectious (pulmonary)	18 (23)
Dehydration*	14 (18)
Cardiac	7 (9)
Hematopoietic	5 (6)
Renal†	5 (6)
Gastrointestinal	5 (6)
Vascular	2 (3)
Neurologic	1 (1)

* Dehydration was defined by inadequate enteral intake requiring admission for intravenous hydration.

† Included acute tubular necrosis and acute and chronic renal failures.

tionally deficient ($P = 0.05$). Zinc status did not correlate with site of tumor.

The treatment modalities employed were evaluated and found to be similar for patients in all of the zinc and nutrition groups. Surgical resections were performed in 63% of patients. Ninety-two percent of patients received radiotherapy and 57% of patients had chemotherapy.

Operative Morbidity Measures

Operative morbidity measures include the number of postoperative days, wound infection, fistule, and postoperative morbidity. Overall complication rates were found to be typical of head and neck surgery patients. None of these measures were statistically different between either the two zinc or two protein nutrition groups. This is probably due to the low frequency of fistulas and the smaller number of patients evaluated. Fistulas occurred exclusively in patients with ZINC⁻ or nutrition deficiency.

Treatment Morbidity Measures

A total of 78 treatment morbidities were identified in this study. The morbidities identified (Table VI) show pulmonary infectious (23%) and non-pulmonary infectious (27%) complications to be the most common. The results of the analysis of treatment morbidities are shown in Table VII. There were no

statistically significant differences in outcomes by nutritional status. Analysis according to zinc status showed the overall incidence of treatment morbidity was similar in both zinc groups; however the mean number of treatment morbidities in the ZINC⁻ group was significantly higher than the morbidities seen in ZINC⁺ patients ($P = 0.03$). The ZINC⁻ group also had significantly more unplanned hospital days ($P = 0.02$) and treatment delays ($P = 0.049$) than the ZINC⁺ patients. Weight loss for nearly all patients was substantial; however, neither the 6 or 12 mo differences were significant.

Figure 1 shows the effects of zinc and nutritional status on mean disease-free interval (months). ZINC⁺ and NUTR⁺ cancer patients had a significantly increased disease-free interval ($P = 0.01$).

DISCUSSION

The profound negative influence of malnutrition on cancer treatment is well recognized, with nutritional deficiencies impacting on all modalities of treatment. It therefore becomes critical to assess the nutritional status of patients before therapy and identify those at greater risk for morbidity. Given the presence of local tumor effects coupled with years of tobacco and alcohol abuse, the high incidence of nutritional deficiency in the head and neck patient is not surprising. This study identified malnutrition in 57% of subjects using the defined cutoff of PNI > 20%. Hooley et al.³ noted a 50% prevalence, and Goodwin and Torres¹ noted a 64% prevalence of malnutrition in head and neck patients using identical criteria. By comparison, other studies have used alternate strategies to assess nutritional status and report malnutrition in a range of 38–59%.^{4–8}

Although the existing data concerning malnutrition and head and neck cancer are numerous, the data regarding the prevalence of ZINC⁻ in patients with head and neck cancer are limited. Most studies have shown decreases in the mean plasma and serum zinc levels of head and neck cancer patients compared with normal controls,^{11,15,17,18} whereas others failed to demonstrate a significant difference.¹⁶ It is important to note that these studies all used serum or plasma measures that can be inaccurate indicators of true zinc status, and none reported a “prevalence” of impaired zinc status based on normal values.¹⁹ Our current study shows a 65% overall prevalence of ZINC⁻ at diagnosis using predominantly cellular zinc criteria.

In most hypercatabolic disease states, zinc deficiency often accompanies protein malnutrition.¹⁴ Limited studies in head and neck cancer patients showed that low serum zinc correlated directly with a decrease in serum albumin.¹⁸ Interestingly, however,

TABLE VII.

TREATMENT MORBIDITY MEASURES BY ZINC AND NUTRITION STATUS						
Morbidity measure	ZINC ⁻	ZINC ⁺	<i>P</i>	NUTR ⁻	NUTR ⁺	<i>P</i>
Treatment morbidity	19/31 (61%)	6/16 (38%)	0.12	13/24 (54%)	10/18 (56%)	0.93
Unplanned hospital days*	22 ± 32	1.5 ± 2.9	0.02†	20 ± 34	14 ± 23	0.51
Mean no. of morbidities*	1.8 ± 2.2	0.5 ± 0.7	0.03†	1.7 ± 2.4	1.2 ± 1.4	0.34
Treatment delays	7/32 (22%)	0/15 (0%)	0.049†	4/24 (17%)	2/19 (11%)	0.56
Delay days*	6.4 ± 22	0 ± 0	0.11	7.9 ± 25.7	0.7 ± 2.1	0.21
6 mo weight change (kg)*	-8.2 ± 9.5	-5.9 ± 5.5	0.47	-7.7 ± 6.4	-6.4 ± 11.4	0.66
12 mo weight change (kg)*	-10.9 ± 9.1	-7.3 ± 7.7	0.29	-18.2 ± 8.2	-8.6 ± 8.6	0.88

* Mean ± standard deviation.

† $P < 0.05$.

ZINC⁻, impaired zinc status; ZINC⁺, zinc sufficient; NUTR⁻, nutritionally deficient; NUTR⁺, nutritionally sufficient.

Mean Disease Free Interval

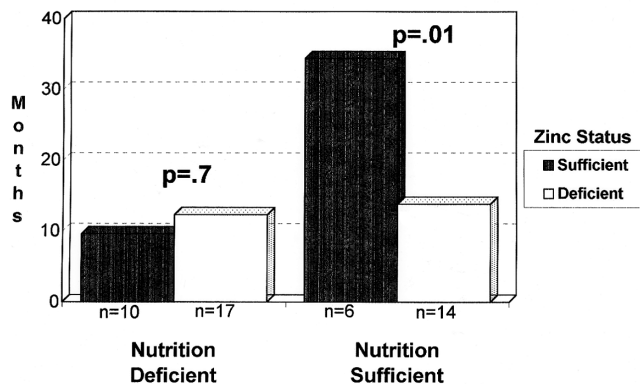


FIG. 1. The disease-free interval for the 47 study patients (median follow-up: 52 mo; range: 16–98 mo) based on zinc status and nutritional status is shown here. These data demonstrate an interaction between the zinc status and nutrition status with maximum disease-free interval observed in those patients with both normal zinc and nutrition status ($P = 0.01$).

this current study found no correlation between zinc status and nutritional status. Impaired zinc status was identified in 63% of malnourished patients and also in 70% of patients with normal nutrition. These observations indicate that impaired zinc status can exist independent of protein deficiency in the head and neck cancer patient and further support the use of cellular zinc criteria for evaluating zinc status.

The influence of both protein nutrition and elemental zinc on wound healing and postoperative complications has been well established. Hooley et al.³ found 86% of major postoperative complications occurred in patients with a PNI > 20%. Goodwin and Torres,¹ in a series of advanced stage III and IV and recurrent cancers, reported major complications in 89% of resections where the PNI > 40% and suggested such complication rates make surgery in these patients prohibitive. In our study, postoperative wound infection and fistulas were infrequent irrespective of nutrition or zinc status. We suggest that given the low overall incidence of these complications seen in our study, a larger sample size would be required before any statistical differences could be appreciated. It could similarly be expected that febrile postoperative days and total postoperative days, both indirect measures of postoperative complications, would not show any differences according to the zinc or nutritional status. Nonetheless, the twofold increased rate of postoperative morbidity and the 100% association of fistula seen in the deficient groups of our series support a role for both zinc and protein nutrition in postoperative healing.

In addition to predicting surgical complications, a pretreatment nutritional assessment can also alert the clinician to potential treatment morbidity from chemotherapy or radiotherapy. Previous studies have used nutrition status measures to predict tolerance of both cytotoxic agents and radiation.^{1,2,21} Goodwin and Torres¹ noted major iatrogenic complications at a much higher frequency in patients with a PNI > 39%. Our series however, does not show the PNI to be predictive of treatment complications as measured by treatment morbidities, unplanned hospitalizations, or treatment delays using a lower level of PNI to determine protein malnutrition.

Our results indicate that baseline zinc status appears to predict treatment complications. We found statistically fewer number of treatment morbidities, unplanned hospitalizations, and treatment delays in the ZINC⁺ group than in the ZINC⁻ group. Although there

are no previous studies for comparison, our findings suggest that patients with adequate levels of zinc can better tolerate treatment. Given that the complications of treatment seen in this study were primarily infectious, the important role of zinc in cell-mediated and humoral immunity can explain our findings. We have recently reported that cytokines produced by T helper 1 (TH1) cells were particularly sensitive to zinc status, inasmuch as the production of interleukin-2 (IL-2) and interferon- γ were decreased in zinc deficient head and neck cancer patients. T helper 2 (TH2) cytokines (IL-4, IL-5, and IL-6), however, were not affected.^{22,23} Natural killer cell lytic activity was also decreased in zinc deficient head and neck cancer patients.^{22,23} Thus an imbalance between the functions of TH1 and TH2 cells may be responsible for cell-mediated immune disorders in head and neck cancer patients. The increased protection against infections that zinc affords these immunocompromised patients may in part explain the reductions in morbidities, delays, and hospitalizations that we observed.

A number of previous studies have demonstrated an inverse and sometimes dramatic relationship between malnutrition and both disease-free intervals and survival for head and neck cancer patients.^{1,4} As a prognostic tool, zinc also may have value in predicting disease-free interval and survival. Studies in acute nonlymphocytic leukemia and lung cancer have shown that the serum zinc levels correlate with response to treatment and overall survival.^{12,13} Observations in head and neck cancer patients are limited. Abdulla et al.¹¹ found significantly lower plasma zinc levels in patients who did not respond to therapy and died within 12 mo compared with the levels of patients who went on to disease remission. Our results showed that ZINC⁺ and NUTR⁺ cancer patients had a significantly increased disease-free interval.

We realize that a univariate analysis of outcome variables based on only zinc status and protein nutrition is insufficient for making a definitive conclusion on the role of zinc on morbidities and survival, inasmuch as it is well known that the stage of the disease also profoundly affects morbidities and survival in head and neck cancer patients. Unfortunately, because of small sample size and missing data mainly due to problems with patient compliance, a multiway ANOVA was not successful. Clearly further research must be carried out in order to document the effect of zinc supplementation in ZINC⁻ patients with squamous cell carcinoma of head and neck on clinical morbidities and disease-free interval.

It should be noted that in our study, the tumor size and stage of the disease correlated significantly to ZINC⁻, whereas no such correlation was seen with PNI, alcohol intake, or smoking in our subjects²⁰ (Table III). One may suggest that the correlation between ZINC⁻ and advanced stage disease was due to local and systemic tumor effects influencing dietary intake and increased catabolism. However, one would then expect to see also a similar relationship between disease state and protein nutrition, which was not the case in our study. Furthermore, our subjects when first seen presented no evidence for increased catabolism, their body weight was stable, and their food intake was not decreased.²⁰ Whether or not zinc and nutrition have an effect on disease-free interval independent of stage of the cancer needs to be examined in a larger study sample.

The potential pathways through which zinc could influence squamous cell cancers of the head and neck are many and the exact mechanisms are under debate. Its role in nucleic acid synthesis, its influence on the production of free radical scavenger metallothionein, and its role in T-cell cytolytic activity are all key sites where zinc deficiency could lead to progression or recurrence of malignancy.¹⁴ Given the potential role of zinc deficiency in squamous cell cancer, the value of supplementation in patients at risk for primary or recurrent cancer deserves consideration. Ani-

mal studies have demonstrated the ability of zinc to slow the progression of induced tumors¹⁴ and preliminary studies in humans also show administration of zinc and other micronutrients to have therapeutic effects in patients with cancerous and precancerous lesions.²⁴ These results are encouraging but further research in this area is needed.

In summary, our study shows pretreatment ZINC⁻ in head and neck cancer patients to correlate with disease stage, treatment morbidity, unplanned hospitalizations, and delays in treatment. Our results support the importance of pretreatment nutritional evaluation of these patients with special attention to micronutrients.

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