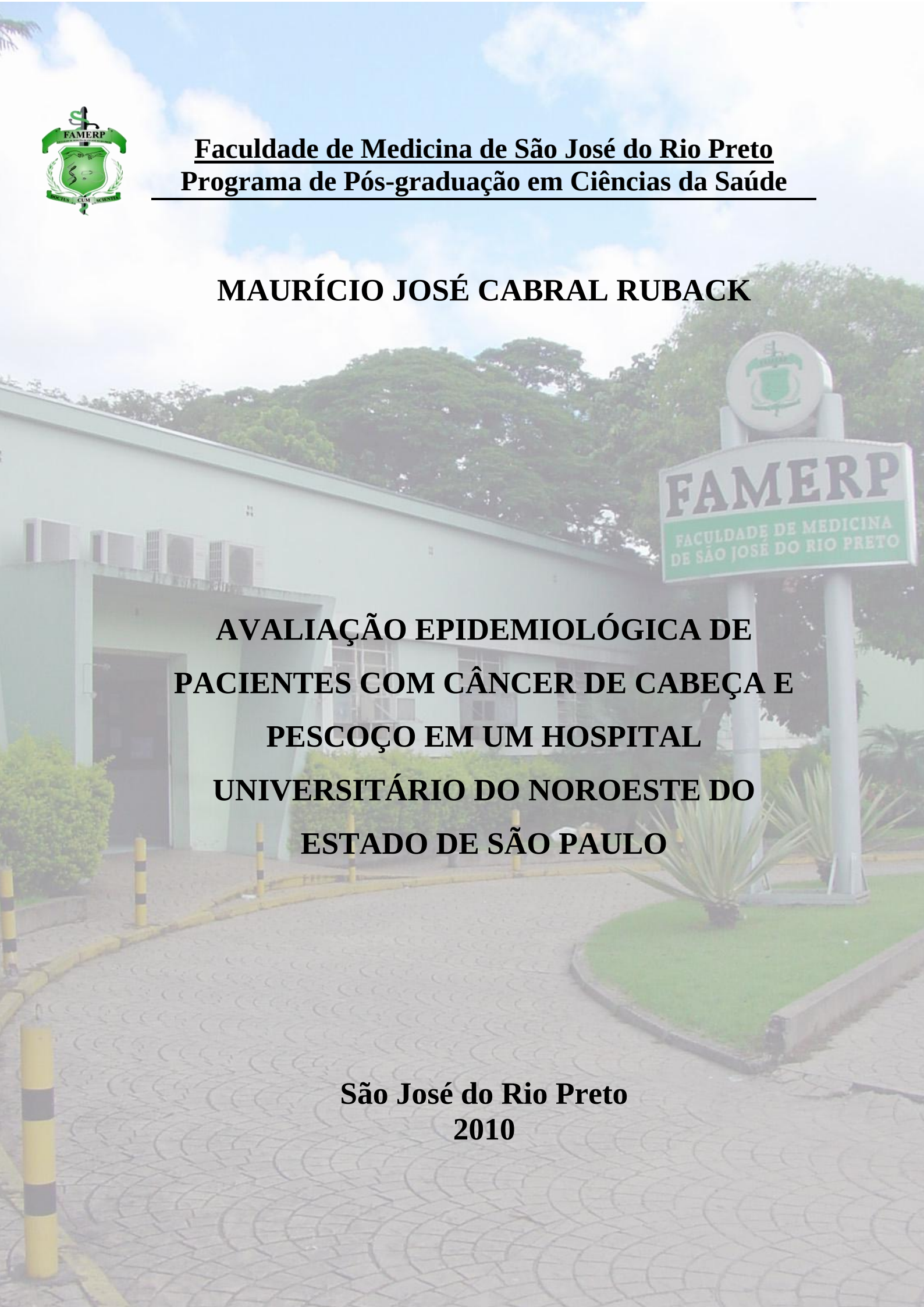
Faculdade de Medicina de São José do Rio Preto
Programa de Pós-graduação em Ciências da Saúde

MAURÍCIO JOSÉ CABRAL RUBACK



AVALIAÇÃO EPIDEMIOLÓGICA DE PACIENTES COM CÂNCER DE CABEÇA E PESCOÇO EM UM HOSPITAL UNIVERSITÁRIO DO NOROESTE DO ESTADO DE SÃO PAULO

São José do Rio Preto
2010

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Orientadora: Profa. Dra. Eny Maria Goloni Bertollo

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BANCA EXAMINADORA

DISSERTAÇÃO PARA OBTENÇÃO DO TÍTULO DE MESTRE

Presidente e Orientadora: Eny Maria Goloni Bertollo

1º Examinador: Mariangela Torreglosa Ruiz

2º Examinador: Atílio Maximino Fernandes

1º Suplente: José Vicente Tagliarini

2º Suplente: Érika Cristina Pavarino Bertelli

São José do Rio Preto, 13 /12 / 2010.

SUMÁRIO

Dedicatória

A minha esposa, por ter permanecido sempre ao meu lado, compartilhando momentos de alegria, tristeza e dúvidas, mas sempre com carinho e amor estendendo sua mão amiga em todos os momentos.

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Minha orientadora, quem sempre esteve ao meu lado, com muita paciência, carinho e incentivo. Pela compreensão e ajuda para superar obstáculos.

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Aqueles que sempre estavam disponíveis, não havendo negatórias, com dedicação exclusiva para o serviço de otorrinolaringologia e cirurgia de cabeça e pescoço da faculdade de medicina. Os quais torceram e vibram com esta etapa transposta.

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Membros da banca examinadora

Pela disponibilidade e colaboração.

Todos que de forma direta ou indireta contribuíram e permitiram que este percurso pudesse ser concluído

Epígrafe

Determinação, coragem e autoconfiança são fatores decisivos para o sucesso. Se estamos possuídos por uma inabalável determinação conseguiremos superá-los. Independentemente das circunstâncias, devemos ser sempre humildes, recatados e despidos de orgulho

Dalai Lama

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LISTA DE ABREVIATURAS E SÍMBOLOS

TNM	Classificação dos Tumores Malignos *(TNM classification)*
AJCC	*American Joint Committee on Cancer*
INCA	Instituto Nacional do Câncer *(Brazilian National Cancer Institute)*
RNA	Ácido ribonucleico
VEGF	Gene do fator de crescimento endotelial vascular (*Gene Vascular Endothelial Growth Factor*)
EGFR	Receptor de Fator de Crescimento Epidérmico *(Epidermal Growth Factor Receptor*
MMPs	Metaloproteínas (*Metalloproteins*)
GSTs	Glutatião S-transferases
DNA	Ácido desoxirribonucléico *(Desoxirribonucleic acid)*
HPV	Papiloma vírus humano
pRB	*Retinoblastoma tumor suppressor gene*
FAMERP	Faculdade de Medicina de São José do Rio Preto
FUNFARME	Fundação Faculdade Regional de Medicina de São José do Rio Preto
HNSCC	*Head and neck squamous cell carcinoma*
SUS	Sistema único de saúde
T	Tamanho do tumor
N	Envolvimento de linfonodos
M	Metástase à distância
UICC	*International Union of Cancer Control*
UPGEM	Unidade de Pesquisa em Genética e Biologia Molecular (*Genetics and Molecular Biology Research Unit*)

Resumo

Introdução: O serviço de cirurgia de cabeça e pescoço atende pacientes com tumores malignos do trato aéreo digestivo superior, de pele e tireóide. O tumor maligno de cabeça e pescoço é atualmente a quinta neoplasia mais comum de todo o mundo e apesar dos avanços em terapias convencionais, incluindo cirurgia, radioterapia e quimioterapia, a taxa de sobrevida não mudou nas ultimas três décadas. No Brasil, as estimativas revelam 14.120 casos novos de câncer de cavidade oral para 2010, sendo que 3.790 em mulheres e 10.330 em homens. **Objetivos:** Avaliar os parâmetros clínicos e epidemiológicos em pacientes com câncer atendidos no serviço de cirurgia de cabeça e pescoço em um Hospital Universitário da região noroeste do estado de São Paulo. **Casuística e Método:** Foram avaliados retrospectivamente prontuários médicos de 1.351 pacientes do serviço de cirurgia de cabeça e pescoço no período de janeiro de 2000 a maio de 2010. As variáveis analisadas foram: idade, gênero, cor da pele, hábitos tabagista e etilista, sítio primário, estadiamento, tipo histológico do tumor, tratamento, número de óbitos e atividade ocupacional dos pacientes atendidos no serviço de cirurgia de cabeça e pescoço. **Resultados:** Esta doença foi mais frequente em homens (79,70%), tabagistas (75,15%) e elitistas (58,25%). Os sítios primários mais freqüentes foram cavidade oral (29,65%) e laringe (24,12%). O carcinoma espinocelular foi o tipo histológico (84,92%) mais comum e 29,04% dos indivíduos tiveram a cirurgia como tratamento e 14,19% radioterapia. **Conclusões:** Este tipo de neoplasia é mais freqüente em homens tabagistas e etilistas. Os sítios primários mais acometidos nos pacientes do serviço são cavidade oral e laringe. A alta taxa de pacientes com estadios III e IV

indica uma procura tardia dos centros de tratamento, o que reflete a necessidade de campanhas de prevenção educativas para o diagnóstico precoce da doença.

Palavras-chave: serviço de cirurgia de cabeça e pescoço, câncer de cabeça e pescoço, epidemiologia.

Abstract

Introduction: The head and neck surgery service assist patients with malignant tumors of upper aero digestive tract, skin and thyroid. Head and neck cancer is currently the fifth most worldwide common cancer and despite advances in conventional therapies, including surgery, radiotherapy and chemotherapy, the survival rate has not changed in the last three decades. In Brazil, estimatives shows 14.120 new cases of oral cavity cancer in 2010, with 3.790 women and 10.330 men. **Objectives**: To evaluate the clinical and epidemiological parameters in patients with cancer assisted by head and neck surgery service at the University Hospital of northwest region of São Paulo. **Casuistic and Methods:** Were retrospectively evaluated medical records of 1.351 patients of head and neck surgery service from january 2000 to may 2010. The variables analyzed were: age, gender, skin color, tobacco and alcohol consumption, primary site, staging and histologic type of tumor, treatment, number of deaths and occupational activity of patients assisted by head and neck surgery service. **Results:** The disease was more frequent in men (79.70%), smokers (75.15%) and etilist (58.25%). The most frequents sites were oral cavity (29.65%) and larynx (24.12%). The most common histological type was squamous cell carcinoma (84.92%) and 29.04% of individuals had as treatment surgical and 14,19 % radiotherapy **Conclusions:** This cancer type occurs more common in men smokers and etilists. The primary sites more incident for the patients service are oral cavity and larynx. The high rate of patients with stages III and IV indicates a late diagnosis by the treatment centers, which reflects the need for prevention education campaigns for early diagnosis of the disease.

Key words: head and neck surgery service, head and neck cancer, epidemiology.

1.INTRODUÇÃO

1. INTRODUÇÃO

O câncer de cabeça e pescoço, que compreende sítios anatômicos do trato aerodigestivo superior, representa a quinta causa de morte na população mundial, apresentando incidência de 500.000 novos casos por ano. [1,2] As regiões geográficas que apresentam maior incidência de câncer na cavidade oral, o sítio mais representativo de câncer de cabeça e pescoço, incluem a Melanesia (sub-região da Oceania, nordeste da Austrália), centro-sul da Ásia, região oeste e meridional da Europa e África meridional. [3]

No Brasil, o câncer de cavidade oral representa a nona causa de morte por câncer, sendo o quinto tipo de câncer mais comum entre os homens e o sétimo entre as mulheres.[4] A estimativa para câncer de cavidade oral na população brasileira para o ano de 2010 é de 10.330 casos novos para o gênero masculino e 3.790 para o gênero feminino, totalizando 14.120 casos novos.[4] Dados do Instituto Nacional do câncer (INCA) mostram que somente no estado de São Paulo, para o ano de 2010 são esperados 4.120 casos novos, destes 3.230 para o gênero masculino e 890 para o gênero feminino.[4]

A maioria dos tumores epiteliais é classificada como carcinoma de células escamosas de cabeça e pescoço (HNSCC – *head and neck squamous cell carcinoma*) e os sítios anatômicos que estão incluídos neste grupo compreendem a cavidade oral com ocorrência aproximada de 40%, laringe (25%) e faringe (15%). [2,5-7]

Os primeiros sintomas manifestados pelos indivíduos portadores de câncer da cabeça e pescoço podem incluir manchas brancas, dor, feridas de difícil cicatrização e escarro sanguinolento na cavidade oral; obstrução persistente assim como sangramento na cavidade nasal; disfagia na faringe; dores no pavilhão auricular e rouquidão

permanente na laringe. Todas as lesões podem resultar em nódulos cervicais. [8,9]

Cerca de dois terços dos pacientes com essa doença apresentam estadio avançado, geralmente envolvendo linfonodos regionais. A incidência de metástase a distância é relativamente pequena em tumores malignos de cabeça e pescoço quando comparada com doenças malignas de outras localidades.[10] O tratamento varia de acordo com o estadio da doença, e dados da literatura mostram que 60-65% dos pacientes com câncer de cabeça e pescoço em estadio inicial podem ser curados com cirurgia e / ou radioterapia. Pacientes com fase inicial (estadios I e II) da doença são tratados com uma única modalidade (cirurgia ou radioterapia), enquanto pacientes com doença mais avançada (estadios III e IV) necessitam de uma abordagem combinada, como a cirurgia e radioterapia ou quimioradioterapia.[11] Este tipo de tumor acomete em maior proporção indivíduos do gênero masculino e com idade avançada.[10,12]

Os principais fatores de risco já estabelecidos para esta doença são tabagismo e etilismo, que quando atuam em conjunto multiplicam o risco para câncer, especialmente câncer de cavidade oral e faringe.[13] Isso porque o cigarro possui aproximadamente 4.700 substâncias e destas pelo menos 50 são carcinogênicas. Já o consumo freqüente de bebida alcoólica impede que as células epiteliais formem a barreira de proteção contra agentes externos, permitindo assim a entrada facilitada dos agentes carcinógenos do cigarro, que formam adutos de DNA e que não são reconhecidos durante o processo de replicação do DNA. [14,15]

O estudo de Hashibe e colaboradores (2007) [13] mostrou que o consumo de álcool independente do fumo apresentou risco elevado para o câncer de orofaringe, hipofaringe e laringe em indivíduos que nunca fumaram. O consumo excessivo de

álcool pode também resultar em deficiências nutricionais devido às falhas na absorção intestinal e alterar vias metabólicas importantes, como por exemplo, a do metabolismo do folato envolvido nas reações de metilação celulares. Como conseqüência, a metilação de genes com um potencial papel na carcinogênese pode ser comprometida. [16]

Vários estudos também relatam uma associação entre má higiene bucal e mal estado dentário com o câncer oral. Experimentos sobre carcinogênese realizados em animais revelaram que danos repetidos na mucosa do sítio primário tumoral podem aumentar o processo de crescimento das células cancerígenas, além de reduzir o período de latência. São descritas situações onde o processo tumoral iniciou-se a partir de problemas dentários e próteses mal elaboradas, que podem levar ao surgimento de infecções com conseqüente liberação de mediadores inflamatórios, como as citocinas que podem favorecer o desenvolvimento do câncer. [6,17].

Fatores dentários e de higienização pessoal não são por si só denotados como fatores de risco; no entanto, na presença de outros fatores previamente estabelecidos, podem promover o processo de carcinogênese.[18] A perda de dentes também pode contribuir para o desenvolvimento do câncer oral, uma vez que leva a alteração da flora oral, favorece a redução de nitritos e nitratos e a produção de acetaldeído, que leva à formação de adutos de DNA. [15,17]

Estudos epidemiológicos também revelam uma forte associação do câncer de cabeça e pescoço com as infecções virais, destacando-se entre elas o papiloma vírus humano (HPV), que afeta células epiteliais e produz oncoproteínas virais (E6 e E7) que promovem a progressão tumoral pela inativação do produto de alguns genes supressores

de tumor, como o Tp53 (*tumor protein 53*) e o pRb (*retinoblastoma tumor suppressor gene*).[19,20]

Outros fatores que podem contribuir para a carcinogênese de cabeça e pescoço incluem a dieta, com redução do risco por meio da ingestão de frutas e vegetais, uma vez que esses alimentos possuem micronutrientes tais como vitaminas B, C e E, carotenóides, flavonódeis entre outros, com propriedades antioxidantes e anticarcinogênicas, diminuindo assim o risco de câncer oral. [21-24]

Um estudo realizado na Escócia em 2010 [25] relatou que indivíduos responsáveis por trabalhos manuais, indivíduos com condição socioeconômica escassa e indivíduos que não conseguiram terminar a escolaridade obrigatória (8 a 12 anos) apresentaram risco aumentado para o desenvolvimento da doença. Além disso, o estudo de Santos et al [26] (2009) realizado no Brasil, confirmou que indivíduos que atuam em atividades rurais e estão em constante exposição ao sol e em contato com substâncias carcinogênicas podem desenvolver o câncer de cavidade oral.

O câncer de pele também está relacionado com a exposição excessiva à radiação solar, atingindo dessa forma, e com maior frequência, as porções do corpo expostas ao sol (cabeça, pescoço e membros). Também influem no aparecimento dessas lesões fatores como idade, sexo, grupo étnico, hábito de fumar, abuso de álcool, distribuição geográfica, cicatriz antiga, agressão física persistente e exposição a agentes radioativos.[27]

Com características próprias, porém também atendidos no serviço de cirurgia de cabeça e pescoço, os tumores da glândula tireóide têm sua origem relacionada com deficiência de iodo, radioterapia externa na infância e adolescência, exposição à radiação ionizante e doença tireoidiana preexistente. [28]

OBJETIVOS

Considerando as evidências apresentadas, este estudo teve como objetivos:

Avaliar aspectos sócio-demográficos, fatores de risco e clínico-patológicos dos pacientes atendidos no serviço de cirurgia de cabeça e pescoço em um hospital de ensino na região noroeste do estado de São Paulo, no período de janeiro de 2000 a maio de 2010.

2. ARTIGOS CIENTÍFICOS

2. ARTIGOS CIENTÍFICOS

Os resultados estão apresentados em forma de artigo. No total estão apresentados 03 artigos, dois artigos publicados e um a ser submetido a publicação.

Artigo I:

Título: Epidemiologic evaluation of head and neck patients in a university hospital of Northwestern São Paulo State.

Autores: Larissa de Melo Alvarenga, Mariangela Torreglosa Ruiz, Érika Cristina Pavarino-Bertelli, **Maurício José Cabral Ruback**, José Victor Maniglia, Eny Maria Goloni-Bertollo

Periódico: Rev Bras Otorrinolaringol 2008;74(1):68-73.

Artigo II

Título: Epidemiologia e biomarcadores em câncer de cabeça e pescoço.

Autores: Mariangela T. Ruiz; Érika Pavarino-Bertelli; José Victor Maniglia; **Maurício J.C. Ruback**; Eny M.Goloni-Bertollo.

Periódico: Arq Ciênc Saúde 2006 jan-mar;13(1):34-8

Artigo III

Título: Caracterização clínica e epidemiológica de pacientes do serviço de cirurgia de cabeça e pescoço de um hospital universitário do Estado de São Paulo.

Autores: Maurício José Cabral Ruback, Gustavo Henrique Marucci; Lidia Maria Rebolho Batista da Silva; Ana Lívia Silva Galbiatti, Mariangela Torreglosa Ruiz,; Anelise Russo, Luis Sérgio Raposo, José Victor Maníglia, Érika Cristina Pavarino-Bertelli, Eny Maria Goloni-Bertollo.

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ARTIGO CIENTÍFICO 1

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ORIGINAL ARTICLE

Epidemiologic evaluation of head and neck patients in a university hospital of Northwestern São Paulo State

Larissa de Melo Alvarenga[1], Mariangela Torreglosa Ruiz[2], Érika Cristina Pavarino-Bertelli[3], Maurício José Cabral Ruback[4], José Victor Maniglia[5], Eny Maria Goloni-Bertollo[6]

Keywords: epidemiology, and neck neoplasia, tobacco and alcohol.

Summary

Head and neck cancer accounts for nearly 200.000 new cases worldwide. A mean of 13.470 new cases of cancer in the oral cavity for 100.000 inhabitants is observed in Brazil. **Aim:** To analyze clinical and epidemiological aspects in patients consulted in the Otorhinolaryngology and Head and Neck Surgery ward in a University hospital of Northwestern São Paulo, Brazil. **Materials and Methods:** A total of 427 patients consulted in the hospital in the period from 2000 to 2005 were investigated. The variables analyzed included: age, gender, occupation, skin color, tobacco and alcohol consumption, primary site of the tumor, clinical staging, degree of histological differentiation and outcome. The data was analyzed by descriptive and exploratory statistics. **Results:** Prevalence was found among men (86%), white color (90%), smokers (83.37%), and alcoholics (65.80%); the average age was 61 years, 24.25% of men were farmers and 60% of women, housekeepers. Primary site of tumor was usually in the oral cavity (35.37%), with histological squamous cell. The incidence of deaths was 164. **Conclusion:** This study has provided the profile of the patients assisted in this hospital; moreover, it has contributed to outline further programs for preventing this disease.

[1] Undergraduate Nurse.
[2] Master's degree in Biological Science, Biologist - Sao Jose do Rio Preto Medical School.
[3] Doctorate in Biological Science, Adjunct Professor of Genetics - Sao Jose do Rio Preto Medical School.
[4] Physician, Otorhinolaryngology and Head & Neck Surgery Specialist.
[5] Associate Professor (livre-docente habilitation) of Otorhinolaryngology and Head & Neck Surgery.
[6] Associate Professor (livre-docente habilitation) of Human and Medical Genetics, Associate Professor (livre-docente) of the Genetics Discipline, Sao Jose do Rio Preto Medical School.
Address for correspondence: Faculdade de Medicina de Sao Jose do Rio Preto - FAMERP UPGEM - Unidade de Pesquisa em Genética e Biologia Molecular. Av. Brigadeiro Faria Lima 5416 Bloco U-6 São José do Rio Preto SP 15.090-000.
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INTRODUCTION

Head and neck cancer is a collective term based on anatomical and topographic definitions for describing malignant tumors of the upper aerodigestive tract. This anatomical region comprises the oral cavity, the pharynx and the larynx. "Oral cancer" is one of the major subgroups of head and neck carcinomas; it involves the mucosa of the mouth (lips, base of tongue, tongue, floor of the mouth and the hard palate) and pharynx (oropharynx, hypopharynx and nasopharynx). About 40% of head and neck cancers occur in the oral cavity, 15% occur in the pharynx, 25% occur in the larynx and the remaining tumors occur in other sites (salivary glands and thyroid)[1]. The most frequent histological type, occurring in over 90% of cases, is the squamous cell carcinoma.[2]

This disease is responsible for many deaths worldwide; it is the sixth cause of death by cancer. Each year approximately 200 thousand new cases of head and neck cancer are diagnosed worldwide.[3] In Brazil, estimates indicate that there will be approximately 13,470 new cases of oral cavity cancer for each 100 thousand persons in 2008 (10,060 estimated in males and 3,410 estimated cases in females).4 The incidence of mouth cancer in Brazil is 2% of all cancers, one of the highest in the world, and significant in Latin America.[5] The estimated mortality rate is approximately 12,300 deaths per year;[6] the survival rate is 40 to 50% for diagnosed patients.[7,8]

Epidemiological evidence shows that the incidence of head and neck cancer increases with age. In Europe, 98% of the patients are aged over 40 years.1 This type of tumor is rare in young patients, involving only 4 to 6% of persons aged below 40 years, although this incidence has increased in a number of countries,[9] The carcinogenetic mechanisms in this age group are still little known.[1,8,10]

Smoking and alcohol drinking are well-established risk factors for head and neck cancer.[11] Although this form of cancer affects mostly males, there has been a significant increase in the incidence in females, probably reflecting changes in smoking and drinking habits.[12]

The aim of this paper was to describe the social and demographic profile of head and neck cancer patients at a university hospital, and to identify the risk factors (smoking and alcohol drinking) to support disease prevention programs.

SERIES AND METHOD

The Research Ethics Committee of our institution approved the research project (protocol 5566/2005).

A retrospective study was done of the medical files of head and neck cancer patients of the hospital Otorhinolaryngology Unit comprising six years between 2000 and 2005.

Variables were age, sex, occupation, skin color, smoking and alcohol drinking habits, primary tumor site, clinical staging, histological differentiation, treatment and patient mortality.

Tumors were classified according to the anatomical site in the mouth, the pharynx and the larynx. The oral cavity was divided into the lips, the anterior 2/3 of the tongue, the palate, the oral mucosa, the gingiva, the retromolar trigone and the hard palate. The pharynx was divided into the following three separate regions: the oropharynx (soft palate and uvula, the tonsils, and the lateral and posterior walls), the hypopharynx (piriform sinuses, hypopharyngeal wall, the postcricoid region and non-postcricoid areas), and the nasopharynx (lateral walls, choanae). The larynx is subdivided into the supraglottis, the glottis and the subglottis.[13]

Tumor staging (TNM) was done according to the guidelines of the American Joint Committee on Cancer (AJCC).14,15 Initially, the files of 427 patients were analyzed, but only 372 were TNM-staged.

Data were compiled in the software Microsoft Excel and analyzed by exploratory descriptive statistics.

RESULTS

Data were collected from 427 patients seen between 2000 and 2005.

There were 367 male patients (86%) and 60 female patients (14%). Age ranged from 30 to 94 years (mean - 61.77 years; standard deviation - 11.44 years). Table 1 shows the age distribution of patients for each age group. Skin color was subdivided into two types (white and non-white). Non-white subjects were those with black, brown and oriental skin colors. In this study 90% of the subjects were white.

Table 1. Age distribution of head and neck cancer patients.

Age group	Number of patients (%)
30 a 40	9 (2,11)
41 a 50	66 (15,45)
51 a 60	121 (28,34)
61 a 70	127 (29,75)
71 a 80	82 (19,2)
81 a 90	20 (4,68)
> 90	2 (0,47)

The most frequent professional occupation in males was a rural activity (grower - 24.25%), followed by bricklayer (13.9%) and driver (11.17%). The most frequent occupation for females was housewife (60%) and rural activities (grower - 8.3%). Retirement with no specification

as to the previous occupation was reported by 8.17% of males and 15% of females (Table 2 and 3).

Smoking was a habit in 83.37% of the sample; 65.8% reported using alcoholic beverages; 55.27% of the sample reported having both habits; and 6.18% reported having neither habit. Quantities consumed were not documented.

Table 2. Occupation of male head and neck cancer patients.

Occupation of males	Number of patients (%)
Grower	89 (24,25)
Bricklayer	51 (13,9)
Driver	41 (11,17)
Retired	30 (8,17)
Shopkeeper	16 (4,36)
Non-specialized services	13 (3,55)
Carpenter	11 (3)
Painter	9 (2,45)
Guard	9 (2,45)
Other	98 (26,7)

Table 3. Occupation of female head and neck cancer patients.

Occupation of females	Number of patients (%)
Housewife	36 (60)
Retired	9 (15)
Grower	5 (8,3)
Other	10 (16,7)

Table 4 shows the primary tumor sites in 427 patients. The oral cavity had the highest rate, 35.37% (151 of the 427 cases).

Tables 5, 6 and 7 present tumor staging according to the malignant tumor classification (TNM) and their frequency in the primary tumor sites. This information was not reported in the files in 55 cases.

Table 4. Primary anatomical site in head and neck cancer patients.

Anatomical site	Number of patients (%)
Oral cavity	151 (35,37)
Larynx	133 (31,15)
Oropharynx	69 (16,15)
Hypopharynx	36 (8,43)
Nasopharynx 8	8 (1,88)
Unknown primary site	30 (7,02)

Table 5. Distribution of primary tumor anatomical sites according to the TNM classification (category T).

Category	Anatomical site	Number of patients (%)
T1	Oral cavity	26 (38)
	Larynx	26 (38)
	Oropharynx	9 (13)
	Hypopharynx	4 (6)
	Nasopharynx	3 (4)
T2	Oral cavity	39 (48)
	Larynx	27 (33)
	Oropharynx	11 (14)
	Hypopharynx	2 (2)
	Unknown primary site	2 (2)
T3	Oral cavity	32 (30)
	Larynx	38 (36)
	Oropharynx	17 (16)
	Hypopharynx	15 (14)
	Nasopharynx	2 (2)
	Unknown primary site	3 (3)
T4	Oral cavity	39 (41)
	Larynx	23 (24)
	Oropharynx	21 (22)
	Hypopharynx	10 (11)
	Nasopharynx	1 (1)
	Unknown primary site	1 (1)
Tx	Larynx	2 (9,5)
	Nasopharynx	1 (4,75)
	Unknown primary site	18 (85,75)

There was a predominance of squamous cell carcinomas (SCC), which was present in 96.7% of cases. Other histological types were also found, such as non-Hodgkin's lymphoma, undifferentiated carcinomas and others (Table 8).

Indications for radiotherapy or surgery generally balanced out for T1 and T2 tumors; most of the T3 and T4 tumors, however, required multimode treatment, usually surgery and adjuvant radiotherapy. On the other hand, other factors may have influenced somewhat the choice of treatment, such as age, professional voice users, uncontrolled smoking or alcohol drinking, as well as social and economic factors that might have required short-term solutions. At our unit treatment includes surgery, chemotherapy and radiotherapy. Most of the patients underwent surgery associated with radiotherapy (33.25%).

There were 164 deaths out of 427 cases; lack of information in the charts precluded a survey of the causes of death in most patients.

Table 6. Distribution of primary tumor anatomical sites according to the TNM classification (category N).

Category	Anatomical site	Number of patients (%)
N0	Oral cavity	94 (40)
	Larynx	87 (37)
	Oropharynx	31 (13)
	Hypopharynx	15 (6)
	Nasopharynx	4 (2)
	Unknown primary site	2 (1)
N1	Oral cavity	25 (42)
	Larynx	13 (22)
	Oropharynx	13 (22)
	Hypopharynx	6 (10)
	Unknown primary site	3 (5)
N2	Oral cavity	12 (23)
	Larynx	9 (17)
	Oropharynx	12 (23)
	Hypopharynx	7 (13)
	Nasopharynx	3 (6)
	Unknown primary site	9 (17)
N3	Oral cavity	5 (21)
	Larynx	6 (25)
	Oropharynx	2 (8)
	Hypopharynx	3 (13)
	Unknown primary site	8 (33)
Nx	Larynx	1 (33)
	Unknown primary site	2 (67)

Table 7. Distribution of primary tumor anatomical sites according to the TNM classification (category M).

Category	Anatomical site	Number of patients (%)
M0	Oral cavity	120 (36)
	Larynx	111 (33)
	Oropharynx	54 (16)
	Hypopharynx	23 (7)
	Nasopharynx	6 (2)
	Unknown primary site	19 (6)
M1	Oral cavity	1 (25)
	Larynx	1 (25)
	Unknown primary site	2 (50)
Mx	Oral cavity	15 (43)
	Larynx	4 (11)
	Oropharynx	4 (11)
	Hypopharynx	8 (23)
	Nasopharynx	1 (3)
	Unknown primary site	3 (9)

Table 8. Histological differentiation of head and neck cancer patients.

Histological differentiation	Number of patients (%)
Squamous cell carcinoma (SCC)	413 (96,7)
Non-Hodgkin's lymphoma	3 (0,69)
Undifferentiated carcinoma	3 (0,69)
Other *	8 (1,92)

* adenocarcinoma, cystic adenoid carcinoma, clear cell carcinoma, mucoepithelioid carcinoma, poorly differentiated carcinoma.

DISCUSSION

Most of the subjects in our sample were aged between 51 and 70 years, which is similar to the data reported by the Head & Neck Unit of the Oncology Center, Oswaldo Cruz University Hospital, in the state of Pernambuco; their data shows that 55.82% of these tumors occur in this age group.[16]

Our finding that there is a higher incidence of head and neck tumors in males is similar to existing reports in the literature.[2] Head and neck tumors are relatively rare in females,[17] particularly in developing countries, where males predominate.[18] In recent years there has been a significant increase in the incidence of head and neck tumors in females, probably due to changes in smoking and alcohol drinking habits.[12] There were more rural workers among males, and more housewives among females. A survey undertaken at the Head & Neck Surgery Unit of the Heliopolis Hospital in the state of Sao Paulo revealed that the most frequent occupation among males was that of bricklayer, with rural activities in sixth place; the most frequent occupation for females was that of housewife, followed by rural activities.[19] It should be noted that rural work exposes individuals constantly to the sun and to carcinogens, which helps promote cancer development.[19,20] Another study done at the same hospital showed that about 85% of male and female patients were white.[19] White was also the predominant skin color in our sample (90%).

Most of our patients were smokers (83.37%) and alcohol drinkers (65.8%), which strengthens the association between alcohol drinking and smoking and head and neck cancers.1 Many studies have shown a consistent relation between tobacco and alcohol, and cancer of the larynx and oral cavity.[1,21-23]

The most frequent tumor site in our series was the oral cavity (35.37%), followed by the larynx (31.15%). Epidemiological studies have also reported that 40% of head and neck cancers occur in in the oral cavity.[1] This

finding appears to reflect smoking and alcohol drinking habits, which may increase two or threefold the risk of these diseases in the oral cavity.[9,11]

The TNM classification of our series revealed that 25% of the cases were T3, 35.65% of the cases had lymph node involvement, and 2% presented metastases, showing that advanced disease was present upon the diagnosis. The literature reports that a high frequency of head and neck cancer cases are diagnosed at an advanced stage,24 as we ourselves also demonstrated. A Brazilian study, taking place in a developing country, shows statistically significant differences in these features compared to the findings of studies about patients from institutions in developed countries.[17]

The most representative histological type was the squamous cell carcinoma (96.7% of cases). Another study done in the state of Pernambuco has reported this type as the most frequent.[16] The literature shows that over 90% of the cases of head and neck cancer are squamous cell carcinoma.[22]

Open surgery and external radiotherapy are fundamental approaches to treat carcinomas.[25] Radiotherapy associated with surgery was the predominant approach in our series (33.25%), followed by radiotherapy only (28.10%). In another study, 528 out of 1,010 cases underwent surgery, 335 were treated by both surgery and radiotherapy, and 67 were treated by surgery, radiotherapy and chemotherapy.25 In our sample only 23 cases were treated with surgery associated with chemotherapy.

There were 164 deaths (38.4%) between 2000 and 2005. Head and neck cancer is characterized by local aggressiveness and by a high recurrence rate of secondary tumors with a high mortality rate.[10]

High-risk populations should be targeted for educational and surveillance programs. These programs and measures can attenuate the unfavorable outcomes in patients with mouth cancer, and decrease the risk of developing secondary tumors.

CONCLUSION

The analysis of 427 patients seen at a university hospital between 2000 and 2005 is in agreement with data reported in the literature showing that head and neck cancer is more frequent in male smokers aged over 40 years. Medical data reveal that the primary site in most of the patients is the oral cavity. Identifying the risk factors for these patients may enable strategies for implementing prevention programs against this disease.

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ARTIGO CIENTÍFICO 2

ARTIGO DE ATUALIZAÇÃO

Epidemiologia e biomarcadores em câncer de cabeça e pescoço.

Head and neck cancer epidemiology and biomarkers.

Mariangela T. Ruiz[1]; Érika Pavarino-Bertelli[2]; José Victor Maniglia[3]; Maurício J.C. Ruback[4]; Eny M.Goloni-Bertollo[5].

[1] Doutoranda em Ciências da Saúde*; [2]Doutora em Genética*; [3]Livre Docente em Otorrinolaringologia e Cirurgia de Cabeça e Pescoço**; [4]Mestrando em Ciências da Saúde**; [5]Livre Docente em Genética Humana e Médica* .

* Unidade de Pesquisa em Genética e Biologia Molecular – UPGEM- Departamento de Biologia Molecular – Faculdade de Medicina de São José do Rio Preto – FAMERP

**Departamento de Otorrinolaringologia e Cirurgia de Cabeça e Pescoço Faculdade de Medicina de São José do Rio Preto – FAMERP

Resumo O presente artigo é uma revisão com o objetivo de atualizar os aspectos epidemiológicos e marcadores moleculares em câncer de cabeça e pescoço com ênfase nos fatores de riscos desta doença, na prevalência e nas novas descobertas de marcadores moleculares. Para isso foi realizado um levantamento bibliográfico para a obtenção destes dados. O câncer de cabeça e pescoço é responsável por uma grande incidência de óbitos e apresenta uma freqüência de aproximadamente 200.000 casos novos por ano. O tabagismo e o consumo de álcool são os principais fatores etiológicos dessa doença. A análise de marcadores moleculares é útil para a compreensão da fisiologia, diagnóstico, prognóstico, seleção de tratamentos e prevenção desta doença.

Palavras-chave Epidemiologia; Neoplasias de Cabeça e Pescoço; Marcadores Biológicos; Genética; Tabagismo; Alcoolismo.

Abstract This study is a review aiming to update the epidemiological aspects and molecular markers of head and neck cancer, focusing the risks factors, the prevalence and the new findings of molecular markers of this disease. A literature review was made to obtain these data. Head and neck cancer accounts for a great incidence of deaths, and its frequency is approximately 200.000 new cases a year. Smoking and alcohol consumption are the main etiological factors of this disease. The analysis of molecular markers is useful to understand the physiology, diagnosis, prognosis, treatment choices and prevention of this disease.

Keywords Epidemiology; Head and Neck Neoplasms; Biological Markers; Genetics; Smoking; Alcoholism.

Aspectos epidemiológicos

O câncer de cabeça e pescoço é responsável por uma grande incidência de óbitos em todo o mundo, constituindo a 6ª causa de morte por câncer. Segundo dados do Instituto Nacional do Câncer (INCA), no Estado de São Paulo, as estimativas de câncer na cavidade oral, para o ano 2006, mostram um total de 13.470 novos casos por 100.000 habitantes, com taxas de 10.060 para o sexo masculino e 3.410 para o sexo feminino[1].

A incidência do câncer de cabeça e pescoço aumenta com a idade. Na Europa, 98% dos pacientes têm idade superior a 40 anos de idade[2] e apenas 4 a 6% são indivíduos mais jovens. Entretanto, a incidência nesta faixa etária tem aumentado em vários países[3] e os mecanismos envolvidos na tumorigênese de pacientes jovens são pouco conhecidos [4,5, 6].

O tipo histológico mais freqüente, presente em mais de 90% dos casos[7], é o carcinoma de células escamosas com ocorrência aproximada de 40% na cavidade oral, 15% na faringe e 25% na laringe. O restante nos demais sítios remanescentes, como por exemplo as glândulas salivares. Outros tumores da região da cabeça e pescoço, tais como, cérebro, tireóide e face não são convencionalmente inclusos no termo "câncer de cabeça e pescoço"[2].

O câncer de cabeça e pescoço é caracterizado pela agressividade de local e pelo risco de ocorrência de tumores secundários. O risco para o desenvolvimento de tumores secundários está estimado em 20% correspondendo a uma taxa anual é de 4-6%[8], geralmente maior em mulheres quando comparadas aos homens[9]. Os pacientes em tratamento apresentam risco para neoplasmas adicionais principalmente no trato aerodigestivo. A taxa de mortalidade é estimada em, aproximadamente, 12.300 mortes por ano[10] e a de sobrevida é de apenas 40 a 50% no mundo[11,12].

Evidências epidemiológicas sugerem que muitos fatores diferentes podem estar associados com o aumento da probabilidade de ocorrência destes cânceres. Vários estudos têm mostrado uma relação consistente do fumo com câncer de laringe e da cavidade oral. Na União Européia estima-se que aproximadamente 60% do câncer oral em homens e 30% em mulheres seriam atribuídos somente ao cigarro[2].

Além do fumo, o consumo de álcool também é um fator de risco

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Não há conflito de interesse

bem estabelecido para o câncer de cabeça e pescoço. Estes fatores de risco isolados podem aumentar de duas a três vezes o risco para esta doença; para a cavidade oral e laringe o risco aumenta mais de 15 vezes quando o consumo de álcool e cigarro estão combinados [3,4,13,14,15,16,17].

Embora os homens sejam mais afetados que as mulheres, nos últimos anos, observou-se um aumento notável na incidência entre mulheres, o que parece refletir a alteração de hábitos tabagistas e etilistas neste grupo[18].

Uma pobre higiene bucal pode agir sinergisticamente com o álcool que nessas condições, aumenta a produção de acetaldeído na saliva, um metabólito do etanol que contribui para o desenvolvimento do câncer[2].

Em relação à dieta, as deficiências de micronutrientes parecem estar associadas com um risco aumentado deste tipo de neoplasia, entretanto essas evidências são inconsistentes. Paralelamente, há evidência de que uma dieta rica em vegetais (particularmente em carotenos) e frutas provavelmente diminui o risco[2,19]. Por outro lado, uma história familial positiva aumenta em 3,5 vezes a probabilidade empírica do desenvolvimento do câncer de cabeça e pescoço [20].

Variações geográficas ou regionais indicam que o estilo de vida sociocultural de uma população pode refletir a apresentação clínica e as características do tumor. Um estudo realizado no Brasil, país em desenvolvimento, revela diferenças estatisticamente significantes dessas características quando comparado àquelas de pacientes provenientes de uma instituição de país desenvolvido (Estados Unidos)[21].

Marcadores moleculares

Os avanços na compreensão da biologia molecular do câncer de cabeça e pescoço têm aberto novas direções na ciência. O aumento das pesquisas está sendo direcionado para o desenvolvimento de terapias com alvos moleculares ou marcadores moleculares que são úteis na predição dos tratamentos ou na seleção de pacientes para terapias moleculares específicas baseadas nas características dos tumores [22].

Cada passo da progressão da doença é seguido por alterações cromossômicas resultantes tanto da perda como do ganho de material genético e, conseqüentemente perda ou ganho de função celular. Os resultados fenotípicos dessas alterações estão descritos em diferentes níveis do desenvolvimento do câncer: crescimento e supressão do tumor, angiogênese e invasão, potencial metastático, resposta imune. A maioria das alterações genéticas que ocorrem durante este processo ainda não é conhecida ou não está totalmente compreendida[23]. O Quadro 1 mostra algumas alterações moleculares mais freqüentes em câncer de cabeça e pescoço.

Marcadores moleculares, tais como *EGFR*, *CICLINA DL*, *FAS/FASL*, proteína *p27*, *VEGF*, e metaloproteínases têm auxiliado no prognóstico de tumores de cabeça e pescoço.

Os fatores de crescimento e seus receptores de membrana desempenham papéis importantes na proliferação celular, sobrevida, adesão, migração e diferenciação[25]. O gene EGFR *(Epidermal Growth Factor Receptor)* possui expressão elevada em câncer de cabeça e pescoço, e está relacionado com um mau prognóstico para a doença. A ativação do gene EGFR estimula o crescimento e proliferação, angiogênese, invasão, metástase e inibição da apoptose. É amplamente expresso por vários tipos celulares, incluindo linhagens epiteliais e mesenquimais[26, 27].

Em câncer de cabeça e pescoço, é encontrada expressão elevada do RNA mensageiro em 92% a 87% dos tumores, e está aumentada 69 vezes em 92% dos tumores quando comparados à mucosa normal [22,28,29, 30].

O gene da ciclina D1 (*CCDN1*) localizado em 11q13, é expresso em células epiteliais na transição G1-S do ciclo celular. Em alguns tipos celulares induz a apoptose [31]. A atividade da ciclina D1 pode ser inibida por vários genes supressores de tumor incluindo as proteínas p16 (gene *CDKN2A - Cyclin-dependent kinase inhibitor 2A*), p21 (gene *WAF1/CIP1- cyclin-dependent kinase inhibitor 1A*) e p27 (gene *KIP1- cyclin-dependent kinase inhibitor 1B*) . Vários estudos mostram que a amplificação ou expressão elevada foram associadas com a doença em estágios avançados, expansão precoce de nódulos, pobre resposta à quimioterapia e redução da sobrevida[20, 30, 32].

A amplificação da região 11q13 que contém os oncogenes *INT-2* (*FGF-3*), *HST-1* (*FGF-4*), *CICLINA D1* (*PRAD-1, BCL-1*) e *EMS-1* foi correlacionada com carcinomas invasivos e está presente em 30-50% dos tumores[30].

O gene *FAS* (*TNF RECEPTOR SUPERFAMILY MEMBER*) também conhecido como *TNFSF6*, *CD95*, ou *APO-1* é um receptor de superfície celular que desempenha um papel central na sinalização da apoptose em vários tipos celulares. Este receptor interage com seu ligante natural *FASL* (também conhecido como *CD95L*), um membro da superfamília de fatores de necrose tumoral. A diminuição da expressão de *FAS* e/ou o aumento da expressão de *FASL* favorece a transformação maligna e progressão do tumor. Mutações em linhagens somáticas e germinativas do gene *FAS* e também do gene *FASL* estão associadas com um risco aumentado de câncer [33, 34, 35].

A proteína p16, codificada pelo gene supressor de tumor *CDKN2A* (*Cyclin-dependent kinase inhibitor 2A*), localizado em 9p21, pertence a família dos inibidores de quinase dependentes de ciclina, que incluem as proteínas p15 (gene *INK4B - cyclin-dependent kinase inhibitor 2B*), p21 e p27. Estes genes regulam a fase G1 do ciclo celular de uma maneira negativa. A proteína p16 se liga a CDK4 (*cyclin-dependent kinase-4)* e CDK6 (*cyclin-dependent kinase-6)*, inibindo sua associação com a ciclina D1. A inibição da atividade do complexo ciclina D1/CDK4/6 interrompe a fosforilação da proteína Rb (retinoblastoma) e a liberação do fator de transrição E2F, o que leva à inibição do ciclo celular na fase de transição G1-S. Alterações genéticas em p16 podem conferir vantagens para o crescimento celular contribuindo com o processo tumorigênico [36]. Estudos mostram que a proteína p16 alterada está associada com baixa sobrevida, aumento de recorrências, progressão tumoral, e metástase nodular em muitos estudos [32]. Entretanto, os resultados relacionados ao prognóstico, utilizando a proteína p16 como marcador em câncer de cabeça e pescoço são conflitantes e, portanto, o papel dessa proteína na carcinogênese ainda não está claramente estabelecido[37].

A proteína VEGF (gene *vascular endothelial growth factor*) foi relacionada à agressividade [38, 39], invasão e metástase de tumores sólidos. Desempenha um papel crítico na angiogênse, essencial para o crescimento tumoral e ocorrência de metástase. Induz a proliferação, migração e sobrevida das células endotelias durante o crescimento tumoral pela ligação às quinases receptoras de tirosinas específicas. Vários estudos mostram o valor prognóstico de *VEGF* e seu papel na promoção da invasão e no comportamento agressivo de tumores de cabeça e pescoço [40,41,42].

As metaloproteínas (MMPs) são enzimas proteolíticas dependentes de zinco que degradam a maioria dos componentes da

Quadro 1. Alterações moleculares em câncer de cabeça e pescoço*

Cromossomo	Cromossomo	Alteração	Freqüência (%)	Genes associados	Significado
3q11-qter	3q11-qter	Ganho	37-71	AIS (p40/73)	Carcinogênese e fenótipo transformado
7p12-p22	7p12-p22	Ganho	34-47	EGFR	Crescimento e fenótipo agressivo
8q13-q24.3	8q13-q24.3	Ganho	27-50	MYC, PTK2	Adesão e regulação do crescimento
11q13	11q13	Ganho	39-61	CICLINA D1, EMS, FGF3, FGF4	Progressão do ciclo celular, migração, regulação do crescimento
20q12-q13.2	20q12-q13.2	Ganho	33-48	BCAS1, ZNF217	Fenótipo agressivo
3p12-p24	3p12-p24	Perda	53-72	FHIT	Supressão de tumor
8pter-p21	8pter-p21	Perda	62-43	Desconhecidos	Suposta supressão tumoral
9p21-p24	9p21-p24	Perda	39-67	Proteínas p16, p15, p18, p19	Progressão do ciclo celular, senescência
18q	18q	Perda	58-59	DCC, DPC4, MADR2, P15, SCCA1, SCCA2, PAI2, PAII3	Pobre prognóstico
17p13	17p13	Perda ou mutação	55	TP53	Regulação do ciclo celular, apoptose

* Adaptado de Le & Giaccia, 2003 [24].

matriz extracelular incluindo colágeno, elastina e fibronectina. A degradação da matriz de colágeno é importante para a invasão de tecidos subjacentes e metástases[43]. Várias MMPs possuem expressão elevada em câncer de cabeça e pescoço incluindo MMP-2 [44], MMP-8 [45], MMP-9 [46] e MMP-13 [47]. MMP-2 e MMP-9 e desempenham um papel importante na carcinogênese de cabeça e pescoço por degradar o colágeno tipo IV, o principal componente da membrana basal. Alguns estudos mostram uma correlação significante entre a expressão de MMP-9 e baixa sobrevida em pacientes com câncer de cabeça e pescoço[37].

O gene *TP53* (*tumor protein p53*), mapeado em 17q13, está envolvido em muitas funções celulares, incluindo a manutenção da estabilidade genômica, progressão do ciclo celular, diferenciação celular, reparo a danos no DNA e apoptose. A produção da proteína é aumentada na célula em resposta a danos no DNA, induzindo a parada do ciclo celular na transição G1/S. Se o dano não for reparado, p53 leva a célula à apoptose. Na presença de mutações deste gene, o produto gênico é freqüentemente presente em altas concentrações. No câncer de cabeça e pescoço, são relatadas mutações em 33 a 59% dos casos, perdas alélicas em 38% e expressão aumentada da proteína em 37 a 76% [32,47].

A detecção de mutações da p53 nas margens cirúrgicas ou nos nódulos linfáticos cervicais considerados histologicamente livres da doença, pode auxiliar na localização das células cancerígenas persistentes, no sangue ou na medula óssea, na ausência de doença clínica, radiológica e histopatológica. Isto poderia teoricamente evidenciar a necessidade de uma terapia adjuvante[23]. A expressão elevada da proteína p53 nos tumores primários é considerada um sinal preditivo de sobrevida reduzida em função de sua associação com a recorrência de tumores primários e secundários[20].

A expressão elevada de *C-ERBB-2*(*HER-2*), gene codificador do receptor para o fator de crescimento epidérmico, localizado no cromossomo17, observada em 75% dos pacientes com câncer de cabeça e pescoço, também foi correlacionada à baixa sobrevida. Expressão diferencial de outros genes como aqueles relacionados com a matriz extracelular, adesão, motilidade, inflamação e inibição da protease tem contribuído para o desenvolvimento de carcinomas oral e faríngeano metastáticos e não-metastáticos [48]. A análise dos padrões de metilação (hipometilação e hipermetilação) de genes específicos também pode ser utilizada para diagnóstico precoce[24,29].

Genes que codificam enzimas envolvidas na biotransformação de carcinógenos têm sido associados ao desenvolvimento do câncer de cabeça e pescoço. Dois genes em particular, *GSTT1* e *GSTM1*, que codificam enzimas pertencentes à família das glutatião S-transferases (GSTs), parecem relevantes para a suscetibilidade ao carcinoma espinocelular de cabeça e pescoço, pois atuam na detoxificação de metabólitos reativos de substâncias carcinógenas da fumaça do tabaco[49]. Os estudos dos polimorfismos *GSTT1* e *GSTM1* realizados em carcinomas de cabeça e pescoço são contraditórios. Vários autores demonstram uma associação com o genótipo nulo [-] *GSTM1* [50, 51, 52, 53, 54, 55] enquanto outros não [56, 57, 58, 59, 60] Para o genótipo nulo [-] GSTT1 também foi demonstrada uma relação em alguns casos [51, 52] e ausência da mesma em outros [56, 57, 59, 60]. Desse modo, a variabilidade individual em genes relacionados aos processos de ativação e detoxificação metabólica parece crucial na suscetibilidade ao câncer de cabeça e pescoço.

Considerações finais

A detecção de alterações moleculares pode auxiliar no diagnóstico e no tratamento do câncer de cabeça e pescoço, o que tem estimulado a busca de biomarcadores com aplicações clínicas potenciais. A era da genômica e da proteômica, com o desvendamento do genoma humano tem melhorado significativamente a compreensão da fisiologia dos tumores sólidos resultando na rápida identificação de novos alvos moleculares para o diagnóstico, prevenção e tratamento do câncer de cabeça e pescoço[24]

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ARTIGO CIENTÍFICO 3

Head & Neck

Head and Neck

CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS OF PATIENTS OF THE HEAD AND NECK SURGERY DEPARTMENT IN A UNIVERSITY HOSPITAL OF NORTHWEST STATE OF SAO PAULO.

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CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS OF PATIENTS OF THE HEAD AND NECK SURGERY DEPARTMENT IN A UNIVERSITY HOSPITAL OF NORTHWEST STATE OF SAO PAULO.

Authors: Maurício José Cabral Ruback[1] (MD), Ana Lívia Silva Galbiatti[1](MD), Lidia Maria Rebolho Batista da Silva[1](MD), Gustavo Henrique Marucci[1], Mariangela Torreglosa Ruiz[1](PhD), Anelise Russo[1], Luis Sérgio Raposo[2](MD), José Victor Maníglia[2](PhD), Érika Cristina Pavarino-Bertelli[1](PhD), Eny Maria Goloni-Bertollo[1](PhD).

[1]Genetics and Molecular Biology Research Unit (UPGEM), Department of Molecular Biology, São José do Rio Preto Medical School (FAMERP), São José do Rio Preto, São Paulo, Brazil.
[2]Otorhinolaryngology and Head and Neck Surgery Department, São José do Rio Preto Medical School (FAMERP), São José do Rio Preto, São Paulo, Brazil.

Address for correspondence:

Profa. Dra. Eny Maria Goloni-Bertollo, UPGEM, FAMERP (bloco U6)
Avenida Brigadeiro Faria Lima, n.° 5416
São José do Rio Preto – SP, Brazil.
CEP: 15.090-000
Phone: +55 17 3201-5720
Fax: +55 17 3201-5708
E-mail: eny.goloni@famerp.br

ABSTRACT

BACKGROUND: Head and neck cancer is located in upper aerodigestive tract, and accounts for nearly 650,000 new cases worldwide. Squamous cell carcinoma is the most frequent histological type, and the main risk factors are tobacco and alcoholism. PATIENTS AND METHODS: A total of 995 patients from a head and neck surgery department were evaluated. The variables analyzed included: age, gender, skin color, tobacco and alcohol consumption, primary site, histological tumor type, stage, treatment and number of deaths. RESULTS: This disease was more frequent among men (79.70%), smokers (75.15%) and alcohol consumers (58.25%). The most represented results were oral cavity (29.65%) and larynx (24.12%) for primary site, squamous cell carcinoma (84.92%) for histological type, surgery (29.04%) and radiotherapy (14.19%) for patient treatment. CONCLUSION: Tumors in patients treated by the head and neck surgery department occur mainly in males, tabagists and etilists, with the oral cavity and larynx having the highest incidence.

Keywords: Epidemiology, cancer, head and neck surgery department, alcohol and tobacco.

Introduction

Head and neck cancer is not a specific entity, but rather a broad category of diverse tumor types arising from various anatomic structures including the craniofacial bones, soft tissues, salivary glands, skin, and mucosal membranes.[1]

Although the head and neck surgery department treats patients with malignant tumors of the upper aero digestive tract, skin and thyroid, the term "head and neck cancer" is used only for the group of neoplasms located in the upper aero digestive tract, with approximately 40% occurring in the oral cavity, 15% in the pharynx, 25% in larynx and 20% in other anatomic sites.[2,3] Approximately 95% of these tumors have squamous cell carcinoma as the primary histological type.[4]

Head and neck cancer is the fifth most common cancer worldwide among all neoplasias.[4] The overall survival rate for this cancer is variable, depending on the primary site and disease stage. For oral cavity cancer, the overall survival rate is 50% over five years.[5] For other sites (pharynx and larynx), the rate is above 50% for early stage disease (T1-T2, N0) and generally below 50% in advanced stage (T3-T4, N0, T3-T4, N +, or any T, N2-N3). [6] In 2008, 6,214 deaths were observed in Brazil as a result of this disease.[7]

Oral cavity cancer, the most representative site of the disease, has a high frequency in Southeast Asia and India, due to the habit within such regions of chewing tobacco leaf and betel nut, a stimulant commonly used among indians.[8] In the United States, about 21,000 new cases of oral cancer are diagnosed each year and it is estimated that more than 650,000 new cases of head and neck cancer are diagnosed each year worldwide, two-thirds of them in developed countries.[6]

The estimated new cases of oral cavity cancer for 2010 is 14,120 and 4,120 for Brazil and Sao Paulo State, respectively.[7] The preliminary search conducted by our

group in a period of five years, in a reference hospital in the northwestern state of Sao Paulo showed 427 patients diagnosed with head and neck cancer.[10]

This tumor type occurs mainly in male subjects, and its occurrence increases with age.[11] In the last decade, there has been a significant increase in this cancer in younger individuals, possibly due to increased infections by human papilloma virus (HPV) .[6,12,13]

The development of head and neck cancer is the result of the interaction of both environmental factors and genetic inheritance, and is therefore, multifactorial. Tobacco use associated with alcohol consumption is a well-established risk factor for the head and neck cancer.[14] Alcohol can act as a solvent for some tobacco carcinogens, increasing cellular uptake of these. According Maruri and Forastiere (2008),[6] the consumption of tobacco associated with alcohol consumption increases head and neck cancer risk by a rate of 40 times.

A significant proportion of head and neck tumors is a result of infection by some HPV types. These virus affect cells and produce viral oncoproteins (E6 and E7) that promote tumor progression by inactivating the product of some tumor suppressor genes such as Tp53 (tumor protein 53) and pRb (retinoblastoma tumor suppressor gene)[13]. Other factors that may contribute to head and neck carcinogenesis include diet, with risk reduced by fruit and vegetable consumption, and increased risk by [15] inadequate oral hygiene, leading to chronic infections by bacteria responsible for the pathogenesis of this tumor type, and[16] body mass, which can modulate toxin and carcinogenic metabolism. [17]

Occupational activity also appears to be associated with development of head and neck cancer. The study by Conway et al. (2010) [18] showed that manual occupational activities, low income, low occupational-social class, low educational attainment and

unemployment correlate with increased risk for disease development. The individuals who work in rural activities are in constant exposure to sunlight and in contact with carcinogenic substances that contribute to the development of oral cavity cancer.[19]

Skin cancer is also associated with excessive exposure to solar radiation and occurs more frequently in the portions of the body exposed to the sun (head, neck and limbs). Also influencing the appearance of these lesions are factors such as age, sex, ethnicity, smoking, alcohol abuse, geographical distribution, old scars, persistent physical aggression and exposure to radioactives.[20]

Thyroid gland tumors, with their own unique characteristics, but also treated in the head and neck surgery department, have an origin related to iodine deficiency, external beam radiotherapy in childhood and adolescence, exposure to ionizing radiation and pre-existing thyroid disease.[21]

This study aimed to describe the socio-demographic aspects and clinical-pathology of patients in head and neck surgery department treated at a university hospital in the northwestern state of Sao Paulo, from January 2000 to May 2010.

Patients and methods

We retrospectively evaluated medical records of 1,351 cancer patients treated at the Otolaryngology and Head and Neck department of a university hospital in the northwestern state of Sao Paulo, from January 2000 to May 2010.

The variables analyzed were age, gender, skin color, tobacco and alcohol consumption, primary site, histological type, staging, treatment, death and occupational therapy of patients with the upper aero digestive tract, skin and thyroid cancer. Individuals who smoked more than 100 cigarettes in their lifetime were considered

smokers, and individuals who consumed at least four drinks per week were considered alcohol drinkers. [22.23].

Tumors of the upper aero digestive tract were classified according to the anatomical site in the oral cavity, pharynx, larynx, nasal cavity, salivary glands and unknown primary site. Skin tumors and thyroid cases were also included.

Clinical staging of patients was performed according to the International Union Against Cancer based on the classification of malignant tumors (TNM) .[24] According to these standards, for the classification stage, T represents the tumor size, and tumors classified as Tx and T0 indicate primary indefinite tumor and no signs of primary tumor, respectively. N1, N2 and N3 indicate the existence of lymph nodes and N0 the absence of them. Tumors classified as Nx indicate undetermined lymph node status. Metastasis is represented by M1 and M0 for absence. In cases of failure to diagnose the presence or absence of metastasis, tumors were classified as Mx.

The occupations of patients were classified in such sectors as agriculture, construction, domestic service, driver, commercial, administrative, surveillance, metalwork, tapestries and aesthetics.

Data were analyzed using descriptive statistics, using the software Excel (version 2007).

Results

We analyzed records of 1,351 patients, of whom it was possible to obtain the most comprehensive information in hospital records of 995 cases, except for tumor staging and treatment, which were obtained for 785 and 909 cases, respectively.

A substantial majority of the cases were males (79.68%) and the mean age of patients was 60.48 years. Of the total patients, 747 were smokers (75.15%), 579 were

etilists (58.25%) and 547 (54.00%) were both. For skin color classification, the subjects were divided into white and nonwhite, according to medical records, and was found a 90.04% frequency of patients with white skin. The oral cavity was the primary site of occurrence (29.65%), followed by the larynx and pharynx (24.12% and 18.29%, respectively). The thyroid gland tumors corresponded to 5.43%, while skin tumors accounted for 6.83% of patients. In 110 patients, it was not possible to identify the primary site (Table 1). The predominant histological type was squamous cell carcinoma, representing 84.92% of cases, followed by basal cell carcinoma (6.03%) and papillary carcinoma (5.22%). Other types of malignant tumors such as adenocarcinoma, melanoma, sarcoma, chondrosarcoma, fibrosarcoma and follicular carcinoma accounted for 3.08% (Table 2).

The tumor stage (TNM) in relation to primary sites and the main methods of treatment made by patients are described in Tables 3 and 4, respectively.

Regarding the occupation of the patients, the main activity was related to agriculture represented by 207 patients (20.82%) (Table 5).

Discussion

In the present study, the mean age of patients, regardless of gender, was 60.48 years, similar to that observed in Brazilian[25] and American[26] populations. Although the frequency of patients with head and neck cancer is higher in individuals with advanced age, an increasing number of cases, especially for oral cavity and oropharynx cancer in young people has been observed and associated with HPV 16 infection,[13] an etiological agent related to carcinogenesis of this tumor type.[12]

Head and neck cancer affects mostly males [10, 27-29]. Likewise, in the present study, 79.68% of individuals affected by this type of cancer were males. Despite the low

incidence of malignancies in women, an increase in number of cases is expected as a result of increased tobacco and alcohol consumption in the female population.[30]

In the present study, a prevalence of white individuals (90.04%) was observed, similar to findings in a study conducted recently in southern states of Brazil[31]and Midwest United States.[32] However, Hayat et al (2007)[33] observed a higher prevalence of head and neck cancer in African-American descendents from different areas of the United States. The ethnic differences in the distribution found in patients with head and neck cancer in different studies are mainly due to population composition where the research was done. Our study was conducted in northwestern São Paulo State, predominantly colonized by Europeans, comprising a high percentage of white-skinned people in the population.

Tobacco consumption was 75.15%; alcohol consumption was 58.25%; and both were 54.00% among the patients studied. The association between alcohol and tobacco with head and neck cancer is well established and has been reported in several studies [14, 27, 34]. An association between experiencing passive smoking for over 15 years and the development of head and neck cancer has been reported, independent of alcohol consumption. [35]

Squamous cell carcinoma was the most common histological type, representing 84.82% of cases, with a frequency close to that observed in the literature, which is approximately 90%[5]. In relation to primary site of tumor, oral cavity was the most representative (29. 65%), followed by larynx (24.12%) and pharynx (18.29%). The incidence of oral cancer worldwide is highest compared to other anatomical sites and is more common in individuals with low income, low occupational social class, low educational attainment.[36] Although it was not possible to obtain all information in our

study , most patients treated in the hospital were from public health system, which assists low-income patients.

Surgical procedure and radiotherapy were performed in 29.04% and 14.19% of patients, respectively. The use of surgical practice followed by radiotherapy is a common practice in the treatment of head and neck squamous cell carcinoma, especially in early stages of the disease (I or II) with a high percentage of cure.[37] In this study, both treatment procedures were used in 29.92% of cases. In advanced stages (III or IV), chemotherapy is usually used in conjunction with other forms of treatment, promoting, especially in conjunction with radiotherapy, increased locoregional control in many cases.[37] Among the patients analyzed in this study, 13.86% underwent surgical, radiotherapy and chemotherapy procedures.

Patients with skin tumors in our study underwent surgery, which has cure rates above 95% when treated early and properly.[20]

Regarding thyroid gland tumors, our results indicate the prevalence of surgery associated with iodine therapy as an optional treatment. The use of less conservative surgery and the exploration of lymph nodes, as well as the use of adjuvant iodine therapy seems to determine a more favorable prognosis for patients with thyroid cancer.[38]

In the analysis of the tumor stage, a high proportion of tumors classified as T3 and T4 were observed. These data reveal a significant number of patients diagnosed in advanced stages of disease and demonstrated the difficulty in obtaining an early diagnosis, since symptoms rarely appear in the early stages. According to the literature, on average, 40% of patients with oral cancer are diagnosed in advanced stages.[39]

In Brazil, some studies reported less than 50% of patients receive an early diagnosis[40,41]. Nearly two-thirds of patients with head and neck cancer have an

advanced stage of the disease, usually involving regional lymph nodes. The incidence of distant metastases is relatively small in malignant tumors of head and neck cancer compared with other regions.[42] Approximately one-third of patients of this study had lymph node involvement and only 1% of metastasis.

During the study period, 265 patients died. The high mortality rate for this tumor type remains virtually constant over past decades.[11] Nevertheless Zigon et al (2010)[28] observed an increase in the relative rate of five-year survival for head and neck cancers study in the European population. In another study in the Brazilian population, we observed a significant increase in survival rate over five years for oral and oropharyngeal cancer, ranging from 28.7% in patients treated in the 1950s to 43.2% in the 1990s.[41]

In relation to occupational activities performed by study subjects, the most frequent were those related to agriculture (20.82%) and construction (19.01%), which is consistent with Conway et al.[36] who showed a correlation between higher rates of head and neck cancer and individuals who practice manual occupational activities and have a low occupational social class.

Sartor et al.[43] also showed an association between laryngeal cancer and exposure to respirable-free crystalline silica. In this study, we found a risk twice as high for exposed individuals, such as those working in construction, compared to unexposed individuals.

Recent research in molecular biology has broadened our understanding of the etiology of these tumors. The combination of prognostic factors and molecular parameters could be beneficial for patients with the application of new therapeutic strategies. Such advances in studies of molecular markers may also improve the

diagnosis in early stages of the disease, which would not be possible by traditional clinical methods[27,44].

Conclusion

Malignant tumors that affect patients treated by head and neck surgery department of a university hospital in northwestern São Paulo State are more frequent in subjects from regions with low socioeconomic development, and limited access to education. The incidence of this disease in this specific population affects mostly male patients in their sixties, smokers and etilists, with the oral cavity and larynx being the regions most affected. The high rate of patients with stage III and IV indicates a late demand in treatment centers, which reflects the need for prevention education campaigns for early diagnosis of the disease.

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Table 1. Distribution of cases according to demographic characteristics and sites of tumor.

Variables	Number of patients (%)
Gender	
Male	793 (79.70)
Female	202 (20.30)
Skin color	
White	895 (90.04)
Non-white	99 (9.96)
Tobacco use	
Tobacco users	747 (75.15)
Non tobacco users	247 (24.85)
Alcohol use	
Etilists	579 (58.25)
Non-etilists	415 (41.75)
Tobacco and alcohol use	547 (54.00)
Tumor sites	
Oral cavity	295 (29.65)
Larynx	240 (24.12)
Pharynx	182 (18.29)
Skin	68 (6.83)
Thyroid	54 (5.43)
Nasal cavity	16 (1.61)
Other sites	30 (3.01)
Unknown primary site	110 (11.06)

DP = standard deviation

Table 2. Most frequent histological types in patients attending a head and neck surgery department.

Histological types	Number of patients (%)
Squamous cell carcinoma	845 (84.92)
Basal cell carcinoma	60 (6.03)
Papillary carcinoma	52 (5.22)
Other	38 (3.83)

Table 3. Case distribuition by clinical-histopathological characteristics.

	Tumoral Staging					
Category	T1 e T2 n (%)	T3 e T4 n (%)	N0 n (%)	N1, N2 e N3 n (%)	M0 n (%)	M1 n (%)
Oral Cavity	169 (40.14)	102 (31.19)	202 (37.75)	69 (25.46)	249 (33.73)	2 (28.57)
Larynx	105 (24.94)	114 (34.86)	160 (29.90)	64 (23.62)	208 (28.18)	-----
Pharynx	66 (15.68)	98 (27.97)	89 (16.60)	78 (28.78)	141 (19.10)	2 (28.57)
Skin	39 (9.26)	1 (0.31)	41 (7.66)	-----	41 (5.55)	-----
Thyroid	24 (5.70)	7 (2.14)	23 (4.29)	5 (1.85)	28 (3.79)	-----
Nasal Cavity	5 (1.19)	3 (0.92)	7 (1.13)	1 (0.37)	8 (1.08)	-----
Other Sites	13 (3.09)	2 (0.61)	13 (2.49)	3 (1.11)	15 (2.03)	-----
Unknown Site	0 (0)	0 (0)	0 (0)	51 (18.82)	48 (6.54)	3 (42.86)

Table 4. Treatment forms of patients attending the head and neck surgery department.

Treatment	Number of Patients (%)
Surgery	264 (29.04)
Radiotherapy	129 (14.19)
Chemotherapy	18 (1.98)
Iodotherapy	1 (0.11)
Surgery and Iodotherapy	23 (2.53)
Surgery and Radiotherapy	272 (29.92)
Surgery and Chemotherapy	17 (1.87)
Radiotherapy and Chemotherapy	59 (6.49)
Surgery, Radiotherapy and Chemotherapy	126 (13.86)

Table 5. Occupation of patients attending the head and neck surgery department.

Ocupacional activities	Number of patients (%)
Farming	207 (20.82)
Civil construction	189 (19.01)
Domestic services	175 (17.60)
Driver	89 (8.95)
Commercial	82 (8.25)
Administrative	43 (4.32)
Vigilance	26 (2.61)
Metallurgy	21 (2.11)
Tapestry	9 (0.90)
Aesthetics	5 (0.50)
Other*	149 (14.89)

* Less than 1% in each profession

3.CONCLUSÕES

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Tumores malignos que acometem os pacientes atendidos pelo serviço de cirurgia de cabeça e pescoço do hospital universitário do Noroeste do Estado do São Paulo são mais frequentes em indivíduos provenientes de regiões com baixo desenvolvimento socioeconômico e limitado acesso à educação. A incidência desta doença nesta população específica acomete em sua maioria um perfil de pacientes do gênero masculino, na sexta década de vida, tabagistas e etilistas, tendo a cavidade oral e a laringe como regiões de maior incidência. A alta taxa de pacientes com estádios III e IV indica uma procura tardia dos centros de tratamento, o que reflete a necessidade de campanhas de prevenção educativas para o diagnóstico precoce da doença.

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5.ANEXOS

FACULDADE DE MEDICINA DE SÃO JOSÉ DO RIO PRETO
Autarquia Estadual - Lei nº 8899 de 27/09/94
(Reconhecida pelo Decreto Federal nº 74.179 de 14/06/74)

COMITÊ DE ÉTICA EM PESQUISA

O Comitê de Ética em Pesquisa da Faculdade de Medicina de São José do Rio Preto tomou ciência e aprovou a ampliação da metodologia datada de 11 de novembro de 2005, referente ao protocolo n.º *5566/2005* sob a responsabilidade de Maurício José Cabral Ruback, com o título "Câncer de cabeça e pescoço: um levantamento epidemiológico do Hospital de Base/FAMERP de SãoJosé do Rio Preto".

São José do Rio Preto, 19 de dezembro de 2005.

Prof. Dr. José Paulo Cipullo
Vice- Coordenador do CEP/FAMERP

Av. Brigadeiro Faria Lima 5416 - 15090-000 São José do Rio Preto SP - Brasil
Tel. (17) 210-5700 - Fax (17) 227-6201 - www.famerp.br

FACULDADE DE MEDICINA DE SÃO JOSÉ DO RIO PRETO
Autarquia Estadual - Lei n.° 8899 de 27/09/94
(Reconhecida pelo Decreto Federal n.° 74.179 de 14/06/74)

COMITÊ DE ÉTICA EM PESQUISA

O Comitê de Ética em Pesquisa em Seres Humanos da Faculdade de Medicina de São José do Rio Preto tomou ciência e autorizou a **dispensa do Termo de Consentimento Livre e Esclarecido conforme solicitação datado de 03/07/2008**, referente ao protocolo n.° **5566/2005** sob a responsabilidade de **Maurício José Cabral Ruback**, com o título "Câncer de cabeça e pescoço: um levantamento epidemiológico do Hospital de Base/FAMERP de São José do Rio Preto".

São José do Rio Preto, 08 de julho de 2008.

Prof. Dr. Antonio Carlos Pires
Coordenador do CEP/FAMERP

Av. Brigadeiro Faria Lima, 5416 - 15090-000 - São José do Rio Preto - SP - Brasil
Tel. (17) 3201-5700 - Fax (17) 3229-1777 - www.famerp.br