IMPORTÂNCIA DE SINTOMAS, COMORBIDADES E OUTRAS CARACTERÍSTICAS CLÍNICAS NO PROGNÓSTICO E NO RISCO DE COMPLICAÇÕES PERIOPERATÓRIAS EM PACIENTES COM CARCINOMA ESPINOCELULAR DE BOCA E OROFARINGE

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RESUMO

Ribeiro KCB. **Importância de sintomas, comorbidades e outras características clínicas no prognóstico e no risco de complicações perioperatórias em pacientes com carcinoma espinocelular de boca e orofaringe**. São Paulo; 2001. [Tese de Doutorado – Fundação Antônio Prudente].

Objetivo. Os objetivos deste estudo foram: avaliar a importância de fatores clínicos na predição de complicações perioperatórias e óbito em pacientes com carcinoma espinocelular de boca e orofaringe e gerar melhores estimativas do prognóstico, através da combinação de fatores relacionados ao tumor e ao pacientes, em um novo estadiamento por severidade clínica ampliado (ESCA). **Métodos.** O estudo consistiu em uma coorte retrospectiva de 530 pacientes com carcinoma espinocelular de boca e orofaringe, admitidos no Centro de Tratamento e Pesquisa Hospital do Câncer A. C. Camargo, no período de Janeiro de 1990 a Dezembro de 1997, e submetidos a tratamento cirúrgico. **Resultados.** A sobrevida global em 5 anos foi 45,7%. O modelo dos riscos proporcionais de Cox identificou na análise univariada 15 variáveis com impacto no prognóstico: consumo diário de álcool, tabagismo, sexo, caroço no pescoço, otalgia, dor, disfagia, emagrecimento, sangramento oral, odinofagia, índice de massa corpórea (IMC), comorbidades, risco cirúrgico, hematócrito e contagem total de linfócitos. As taxas de sobrevida de acordo com o ESCA foram: 76,7% (estádio 1), 64,4% (estádio 2), 44,7% (estádio 3) e 25,5% (estádio 4) (χ^2=64,16, p<0,001). Na análise univariada as complicações perioperatórias estavam associadas com as seguintes variáveis: APACHE II, duração

da cirurgia, estádio clínico TNM, ESCA, esvaziamento cervical, tipo de reconstrução, transfusão de sangue intraoperatória, estadia na UTI, risco cirúrgico (ASA) e índice POSSUM. Somente o escore APACHE II, o esvaziamento cervical, o índice POSSUM e o tipo de reconstrução foram identificados como fatores de risco independentes para a ocorrência de complicações perioperatórias. O modelo prognóstico final incluiu o desenvolvimento de complicações perioperatórias locais e sistêmicas, tipo de reconstrução, escore APACHE II e o ESCA. **Conclusões.** Este estudo demonstra que as variáveis clínicas têm impacto na morbidade e na mortalidade de pacientes com câncer de boca e orofaringe tratados cirurgicamente. As complicações perioperatórias locais e sistêmicas podem piorar o prognóstico. A uniformidade dos resultados confirma que as estimativas de sobrevida podem ser melhoradas pela adição de características clínicas dos pacientes à classificação TNM, criando um sistema de estadiamento mais preciso na determinação do prognóstico.

Descritores: Neoplasias de cabeça e pescoço. Neoplasias bucais/sintomas. Neoplasias de orofaringe/sintomas. Carcinoma de células escamosas. Comorbidades. Complicações perioperatórias. APACHE. Neoplasias/estadiamento. Prognóstico.

SUMMARY

Ribeiro KCB. **Importância de sintomas, comorbidades e outras características clínicas no prognóstico e no risco de complicações perioperatórias em pacientes com carcinoma espinocelular de boca e orofaringe** [Importance of symptoms, comorbidities and other clinical characteristics on the prognosis and risk of perioperative complications in patients with oral and oropharyngeal squamous cell carcinoma]. São Paulo (BR); 2001. [Tese de Doutorado – Fundação Antônio Prudente].

Objective. To evaluate the importance of clinical factors in the prediction of perioperative complications and death in patients with oral and oropharyngeal carcinomas and to develop a better estimate of the prognosis by combining patient and tumor related factors in a new extended clinical severity staging system (ECSS). **Methods.** 530 patients with oral or oropharyngeal carcinomas admitted at the hospital from 1990 to 1997, and submitted to surgical treatment were studied. Logistic regression was utilized to identify risk factors for perioperative complications. Clinical characteristics that have a significant impact on 5-year overall survival created the functional severity index, which was combined with TNM stage to create the ECSS. **Results.** The 5-year overall survival rate was 45.7%. The Cox proportional hazards regression model identified, in an univariate analysis, 15 variables with impact on prognosis: daily alcohol consumption, smoking, gender, neck lump, earache, pain, dysphagia, weight loss, oral bleeding, odynophagia, body mass index, NCI comorbidity index, surgical risk ASA, hematocrit and total

lymphocytes count. Survival rates according to the ECSS were: 76.7% (stage 1), 64.4% (stage 2), 44.7% (stage 3), and 25.5% (stage 4) (χ^2=64,16, p<0.001). Perioperative complications were associated in an univariate analysis with the following variables: APACHE II, operative time, TNM clinical stage, ECSS, neck dissection, type of reconstruction, intraoperative blood transfusion, ICU staying, ASA surgical risk, POSSUM index. In the multiple analysis, only APACHE II score, neck dissection, POSSUM index and type of reconstruction were identified as independent risk factors for perioperative complications. The final prognostic model included the development of local plus systemic complications, ECSS, type of reconstruction and APACHE II score. **Conclusions:** This study demonstrates that clinical variables have predictive effect on morbidity and mortality of patients with oral and oropharyngeal cancer surgically treated. Local plus systemic perioperative complications can adversely affect the prognosis. The uniformity of results confirms that survival estimates can be enhanced by the addition of clinical characteristics to the TNM classification, creating a more accurate system in the estimation of prognosis.

Descriptors: Head and neck neoplasms. Mouth neoplasms/symptoms. Oropharynx neoplasms/symptoms. Squamous cell carcinoma. Comorbidities. Perioperative complications. APACHE. Neoplasms/staging. Prognosis.

ÍNDICE

1 INTRODUÇÃO

A cada ano, aproximadamente 30.000 casos novos de câncer de boca e orofaringe são diagnosticados nos Estados Unidos, o que representa quase 3% de todas as neoplasias malignas no sexo masculino (GREENLEE et al. 2001). No Brasil, foi estimada para este ano a ocorrência de 10.565 casos novos de câncer de boca (MINISTÉRIO DA SAÚDE 2001). O diagnóstico precoce é a melhor oportunidade para a realização de um tratamento eficaz, com resultados satisfatórios tanto estética como funcionalmente. A cirurgia e a radioterapia são as principais modalidades de tratamento e o planejamento terapêutico depende de fatores relacionados ao tumor, ao paciente e à experiência institucional (BYERS 1995). A extensão anatômica da doença, descrita pela classificação TNM, é o fator prognóstico mais importante.

As características clínicas dos pacientes, tais como a severidade dos sintomas relacionados ao câncer e as comorbidades médicas (definidas como doenças concomitantes não associadas à doença em estudo), são importantes na escolha do tratamento, no risco das complicações perioperatórias e no prognóstico de diversos tipos de câncer (FEINSTEIN 1970; FEINSTEIN et al. 1975, 1977; WELLS et al. 1984; CLEMENS et al. 1986; FEINSTEIN e WELLS 1990; PICCIRILLO et al. 1994; SINGH et al. 1999; PICCIRILLO 2000). A adição destes fatores à tradicional classificação TNM permitiu a criação de novos sistemas de estadiamento, superiores como estimadores da sobrevida quando comparados ao TNM isoladamente (FEINSTEIN et al. 1977; WELLS et al. 1984; CLEMENS et al. 1986; PUGLIANO et al. 1997, 1999b; RIBEIRO et al. 2000).

Avanços recentes nas técnicas anestésicas e cirúrgicas, incluindo a reconstrução microcirúrgica do defeito resultante, têm permitido procedimentos oncológicos mais radicais para o tratamento do câncer de cabeça e pescoço em estádios avançados. No entanto, a intenção curativa pode ser limitada pelo risco de complicações operatórias, que podem ser até fatais (SINGH et al. 1999). As complicações perioperatórias aumentam o tempo de internação e a necessidade de outros procedimentos diagnósticos e terapêuticos, com um conseqüente incremento dos custos hospitalares (DURAZZO et al. 1999).

As complicações perioperatórias podem ser definidas como outras doenças que ocorrem até 30 dias após a cirurgia e podem alterar o quadro clínico do paciente, gerando a necessidade de intervenções terapêuticas, medicamentosas ou não. Estas complicações podem ser cardíacas, pulmonares, vasculares, renais, metabólicas e infecciosas (DURAZZO et al. 1999).

Não existem protocolos de avaliação perioperatória específicos para cada tipo de intervenção cirúrgica. Os resultados apresentados são baseados em estudos que incluem todos os tipos de cirurgias, sendo que as cirurgias vasculares apresentam os maiores índices de complicações cardiovasculares (DURAZZO et al. 1999).

O pronto reconhecimento de fatores de risco para complicações, baseado nas características clínicas pré-operatórias dos pacientes com câncer de boca e na identificação dos riscos relacionados ao procedimento cirúrgico, pode auxiliar no planejamento terapêutico e no estabelecimento das medidas adequadas para prevenir complicações graves (SINGH et al. 1998).

Deste modo, como já afirmado por outros autores (BURKE e HENSON 1993), é necessária a criação de um novo sistema de estadiamento que contenha as

variáveis da classificação TNM, assim como novos fatores preditivos, para melhorar a acurácia na determinação do risco de complicações perioperatórias e do prognóstico.

2 OBJETIVOS

- Determinar os fatores de risco para o desenvolvimento de complicações perioperatórias em pacientes portadores de carcinoma espinocelular de boca e orofaringe, submetidos a tratamento cirúrgico com intenção curativa, e o valor prognóstico destas complicações neste grupo de pacientes;
- Avaliar a validade do sistema de estadiamento por severidade clínica na predição de recorrência, sobrevida livre de doença e sobrevida global a 5 anos, nos pacientes portadores de carcinoma espinocelular de boca e orofaringe submetidos a tratamento cirúrgico.

3 ARTIGOS CIENTÍFICOS

3.1 Risk factors for postoperative complications in oral cancer and their prognostic implications

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ABSTRACT

Introduction: The surgical treatment of head and neck cancer can be limited by the risk of postoperative complications. Early identification of risk factors based on clinical characteristics may help on the therapeutic planning.

Objectives: This study was designed to identify risk factors for these complications and to evaluate their prognostic significance.

Methods: The medical records of 110 patients with oral squamous cell carcinoma admitted from January 1, 1990, to December 31, 1994, who underwent radical surgery were reviewed. Data collected included demographic information, comorbidities, extended clinical severity stage, treatment, complications and survival. The χ^2 test was used to verify association between the variables. Survival analysis was performed with the Kaplan-Meier method. Logistic and Cox proportional hazards regression were used to build models with independent predictive factors for the risk of complications and death, respectively.

Results: The overall complication rate was 50%. Dehiscence and infection rates were 20.9% and 22.7%, respectively. The death rate was 3.6%. Forty-seven patients (42.7%) were electively referred to the intensive care unit (ICU). The occurrence of postoperative complications was associated with extended clinical severity stage (p=.02), type of surgery (p=.03), ICU (p=.03), type of reconstruction (p=.02), Functional Severity Index (p=.03), neck dissection (p=.002), and APACHE II (Acute Physiology and Chronic Health Evaluation II) (p=.008). The number of complications was significantly correlated with the length of hospital stay (r= 0.24, p=.01) and with the Functional Severity Index (r=0.19, p=.04). Five-year overall

survival was affected by the type of complications (none, 41.7%; local, 34.1%; and local plus systemic, 0% [p<.001]), ICU (no, 46.3%; yes, 20.7% [p=.001]), and extended clinical severity stage (stage 1, 75.6%; stage 2, 50%; stage 3, 28.6%; stage 4, 10.2% [p<.001]). In a multivariate analysis bilateral neck dissection (relative risk=3.57, p=.01) and an APACHE II score greater than 10 (relative risk=3.86, p=.02) were independent risk factors for complications. The predictive prognostic model consisted of the following: staying at ICU (hazard ratio=1.83), local plus systemic complications (hazard ratio=6.27) and extended clinical severity stage (stage 3, hazard ratio=3.57; stage 4, hazard ratio=6.34).

Conclusions: Bilateral neck dissection and the APACHE II score were identified as risk factors for postoperative complications in oral cancer, which also increase the length of hospital stay. The occurrence of systemic complications, advanced extended clinical severity stage, and staying at ICU adversely affect the prognosis. Therefore, the prompt recognition of the adverse risk factors for postoperative complications may guide proactive interventions that may improve survival and achieve cost-effectiveness.

Introduction

Approximately 30000 new cases of oral cavity and pharyngeal cancer are diagnosed annually in the United States, with almost 58% being located in the tongue and other parts of mouth (GREENLEE et al. 2000). In Brazil 10980 new cases of mouth cancer were estimated for the year 2000 (MINISTÉRIO DA SAÚDE 2000). The main goal of the treatment is the eradication of the cancer through control of the primary lesion and regional metastasis, with restoration of form and function (CUNNINGHAM et al. 1986). The anatomical extension of the disease, evaluated by the TNM system, is the most important prognostic factor (HERMANEK e SOBIN 1992). However, the unpredictable clinical evolution of some patients has led to the searching of other prognostic markers such as surgical margins (LOREE e STRONG 1990), histopathological features (WOOLGAR e SCOTT 1995; ASAKAGE et al. 1998), molecular abnormalities (SHIN et al. 1996) and comorbidities (PUGLIANO et al. 1997; SINGH et al. 1998; PUGLIANO et al. 1999b; RIBEIRO et al. 2000). Recent advances in the anesthetic and cancer ablative techniques, as well as microvascular reconstruction of the resultant defect allowed more radical oncological procedures for advanced head and neck cancer (SINGH et al. 1999). Nevertheless, the curative intent can be limited by the hazard of life-threatening postoperative complications. The prompt recognition of risk factors for complications based on preoperative clinical characteristics of the patient with oral cancer plus the identification of the risks associated with the surgical procedure itself can help determine the appropriate therapeutic planning to prevent severe complications (SINGH et al. 1998). The objectives of this article are to identify the risk factors

associated with the development of postoperative complications and to establish their prognostic significance on the survival of patients with oral cancer.

Patients and Methods

We reviewed 247 medical records of patients with squamous cell carcinoma of the oral tongue or floor of the mouth, admitted to the Centro de Tratamento e Pesquisa Hospital do Câncer A. C. Camargo, São Paulo, Brazil, from January 1, 1990, to December 31, 1994. The following criteria were used for inclusion in the study: a histologically confirmed diagnosis; absence of previous oncological treatment for this primary tumor; complete clinical evaluation allowing APACHE II (Acute Physiology and Chronic Health Evaluation II), American Society of Anesthesiologists, National Cancer Institute and Functional Severity Index (FSI) classifications; absence of distant metastasis at diagnosis; and surgical treatment with a curative purpose, exclusive or as part of a multidisciplinary approach. A total of 110 patients met the criteria for inclusion in the study.

Data collection from the medical records was performed using a specially designed form. These data included demographic information, smoking status, alcoholism status, TNM staging (Union Internationale Contre le Cancer or American Joint Committee on Cancer classification) (HERMANEK e SOBIN 1992), tumor site, surgical risk (American Society of Anesthesiology Scale), type of surgery and neck dissection, type of reconstruction, comorbidities according to National Cancer Institute classification (YANCIK et al. 1998), FSI (RIBEIRO et al. 2000), extended clinical severity stage (ECSS) (RIBEIRO et al. 2000), APACHE II score (KNAUS et al. 1985), length of stay in an intensive care unit (ICU), and nosocomial and

postoperative complications. Outcomes measures included development of complications in the immediate postoperative period (until 30 days) and 5-year overall survival. Patients were followed up from the date of diagnosis to the date of last objective evaluation or death. Only 4.5% of the patients were lost to follow-up.

The FSI was created through the identification of 9 variables that influenced prognosis based on the following Cox proportional hazards regression model: daily alcohol consumption, neck lump, dysphagia, weight loss, hematocrit of 0.35 or lower, age older than 50 years, National Cancer Institute comorbidity index level 2 (>3 comorbidities), earache, and oral cavity bleeding. The FSI was built through the multiplication of the values of the hazard ratio (HR) for each patient. When the condition was absent, we gave the value of 1 for that category. The score ranged from 1 to 258.23, and the results allowed for grouping patients into 3 categories, based on the percentiles 30 and 60: high (score $\geq$ 8.7), intermediate (score > 3.8 and <8.7), and low (score $\leq$ 3.8) grade of functional commitment. Consolidation of the FSI categories with the TNM system created the extended clinical severity staging system (ECSS), consisting of 4 stages: (1 [best] to 4 [worst]) (RIBEIRO et al. 2000).

The APACHE II classification is a revised version of the APACHE prototype system. It includes 12 physiologic measures (temperature; mean arterial pressure; heart rate; respiratory rate; oxygenation; levels of arterial sodium, serum potassium, and serum creatinine; hematocrit, white cell blood count, and Glasgow Coma Scale score), age, and severe chronic health problems. The physiologic score is determined from the worst value, e.g., the lowest hematocrit or the highest respiratory rate, during the initial 24 hours after admission to the ICU (KNAUS et al. 1985). In our

study we also applied APACHE II for patients not referred to the ICU, based on findings of the first 24 hours of the postoperative period.

Patients were electively referred to the ICU based on 1 of the following criteria: expected operative time longer than 6 hours and/or the presence of a comorbidity diagnosed preoperatively, such as coronary insufficiency or advanced chronic obstructive pulmonary disease, requiring strict cardiopulmonary monitoring.

Wound infection was recorded only for patients who present suppurative drainage and/or who develop a mucocutaneous fistula (ROBBINS et al. 1990). Wounds noted to have erythema or erythema and edema may be considered as infected in the presence of fever, based on an evaluation performed by the surgeon.

The information contained in the forms was entered in a database (DBase for Windows; Borland International, Scotts Valley, Calif). Periodically, revisions were made to verify the internal consistency of the data. For statistical analysis, commercially available software (Statistical Product and Service Solutions for Windows, release 7.5; SPSS Inc, Chicago, Ill) was used. Descriptive statistics were used as a preliminary analysis of the relationship between the baseline variables and outcome events. The *t* test was used to compare means. The Pearson coefficient was used to confirm correlation between the continuous variables; the χ^2 test was used to verify association between categorical variables. Survival analysis was performed using the Kaplan-Meier method (with the log-rank test value being used to compare groups). Logistic regression was used to find risk factors for postoperative complications and the Cox proportional hazards regression model was chosen to identify independent prognostic factors. For all statistical tests α=.05.

Results

The cohort of 110 patients included 93 men (84.5%) and 17 women (15.5%); 93 patients were white and 17 belong to other ethnic groups. The patients' ages ranged from 31 to 80 years (mean age, 57.5 years). Fifty-nine patients had tumors in the tongue; 51 had tumors in the floor of the mouth. Eighty-two patients (75.6%) were daily drinkers of alcohol, while there was an equal division between patients who never drank alcohol and social drinkers (12.7% in each group). One hundred patients (90.9%) were tobacco users and 10 (9.1%) had never smoked. Pain was the most frequently reported symptom (affecting 69 patients [62.7%]) followed by weight loss (affecting 46 patients [41.8%]). Earache, odynophagia, and oral cavity bleeding affected only 19 patients (17.3%) who had symptoms. According to the comorbidity National Cancer Institute index (YANCIK et al. 1998), 64 patients (58.1%) were classified as level 1 (0-3 comorbidities) and the remaining 46 patients (41.9%) were classified as being at level 2 (> 3 comorbidities). Patients´ distribution according to FSI, ECSS, and TNM is given in Table 1.

Sixty-four patients (58.2%) did not have lymph node involvement (N0). Clinical neck metastasis was detected in 46 patients (41.8%) with the following distribution: N1, 11 patients (36.7%); N2a, 1 patient (0.9%); N2b, 12 patients (10.9%); N2c, 10 patients (9.1%); N3, 3 patients (2.7%). Among patients classified as having TNM stage IV, 13 (11.8%) had bilateral neck involvement. All patients underwent surgery as the primary treatment; 69 received irradiation as adjuvant therapy. They underwent the following types of surgery: partial glossectomy or pelvectomy (17 patients), pelviglossectomy or pelviglossomandibulectomy (80 patients), and hemiglossectomy or total glossectomy (13 patients). Forty-four

patients (40%) underwent marginal or sectional mandibulectomy. Neck dissection was performed in 97 patients (88.2%), with 57 (51.8%) unilateral surgical procedures and 40 (36.4%) bilateral surgical procedures. Supraomohyoid, classic radical, or a modified radical neck dissection was performed unilaterally in 22 patients (20%), 20 (18.2%), and 15 (13.6%), respectively. Among those who had bilateral neck dissections, the combination of radical neck dissection and contralateral supraomohyoid was performed in 19 patients (17.3%) and bilateral supraomohyoid neck dissection was the therapy used in 12 patients (10.9%). Simultaneous bilateral comprehensive neck dissection or bilateral modified radical neck dissection was performed in 5 (4.5%) and 4 (3.6%) patients, respectively. The surgical defect was closed primarily in 50 patients (45.5%). A tongue flap was used in 29 patients (26.3%), pectoralis major myocutaneous flap in 24 (21.8%), a microvascular flap in 4 (3.6%), and other myocutaneous flaps in 3 (2.7%).

Surgical procedure included a tracheostomy in 96 patients (87.3%). No significant statistical association was noted between tracheostomy and chest infection (p=.49).

Operative time varied from 25 to 810 minutes (mean±SD=334.8±164.2 minutes). Twenty-nine (67.4%) of 43 patients with operative times longer than 6 hours developed postoperative complications in contrast to 26 (39.4%) of 66 with operative times shorter than 6 hours (p=.004). A higher rate of systemic complications (14%) between patients with operative times longer than 6 hours (p=.03) as well as more frequent occurrence of wound infection (39.5%) (p=0.001) were observed.

All but 1 patient received prophylactic antibiotic agents starting in the operating room, immediately before surgery, for a period that varied from 24 to 288 hours (median time, 72 hours). Fifty-four patients (49.1%) received a combination of 4g/d of cephalothin sodium plus 4g/d of chloramphenicol succinate, 45 patients received 1.8 g/d of clindamycin phosphate (40.9%), and 10 patients (9.1%) received other types of antibiotic agents. There was no association between the type of antibiotic used and postoperative complications (p=.63). We also could not observe a statistically significant difference between the mean period of antibiotic therapy in the group that had postoperative complications (97.3 hours) and the group without postoperative complications (95.1 hours) (p=.86). There was no difference in the frequency of postoperative complications comparing patients receiving antibiotic therapy up to 24 hours and patients receiving antibiotic therapy for longer than 24 hours (p=.82).

Forty-seven patients (42.7%) were electively referred to the ICU. The length of stay in the ICU varied from 1 to 13 days (mean length of ICU stay, 2 days). The APACHE II score was 10 or fewer in 76 patients (69.1%) and higher than 10 in 34 patients. The length of hospital stay ranged from 2 to 54 days (mean length of hospital stay, 9 days).

The overall complication rate was 50%. Postoperative complications are listed in Table 2.

The occurrence of postoperative complications was associated with neck dissection (p=.002), APACHE II score (p=.008), type of reconstruction (p=.02), ECSS (p=.02), type of surgery (p=.03), FSI (p=.03), tracheostomy (p=.004), operative time (p=.004), and staying in the ICU (p=.03). The number of

complications was significantly correlated with the length of hospital stay (r=0.24, p=.01) and FSI (r=0.19, p=.04). In a multivariate analysis bilateral neck dissection (relative risk [RR]=3.57, p=.01) and an APACHE II score higher than 10 (RR=3.86, p=.02) were independent risk factors for complications.

Five-year overall survival was affected by the type of complications (none, 41.7%; local, 34.1%; and local plus systemic, 0%; p<.001) (Figure 1), staying in the ICU (no, 46.3%; yes, 20.7%; p=.001) (Figure 2), and ECSS (stage 1: 75.6%; stage 2, 50%; stage 3, 28.6%; stage 4, 10.2%; p<.001). The predictive prognostic model was composed by staying in the ICU (HR=1.83), local plus systemic complications (HR=6.27), and ECSS (stage 3, HR=3.57; and stage 4, HR=6.34).

Discussion

A surgical complication has been defined as a development, which is generally to the patient's detriment, arising at the time of operation or during the postoperative period (SHAHEEN 1984). Complications after major surgery for patients with oral cancer increase treatment costs, delay adjuvant treatment, augment late sequelae, affect quality of life, and can also cause a patient's death, if not diagnosed and promptly treated (EVANS 1989). During the last few years, advances in surgical techniques, the introduction of new antibiotic agents, a better understanding of fluid balance physiology, improved methods for blood transfusions, developments in anesthetic techniques, and the establishment of ICUs improved the safety of major head and neck oncological surgery decreasing the risk and severity of complications (KOWALSKI et al. 1994a). Although the indications of surgical treatment are standardized in most institutions, the rates of complications are still

high and the identification of risk factors associated with them can reduce morbidity and possibly improve survival in patients with oral cancer, thus achieving cost-effectiveness (YODER et al. 1979; PELCZAR et al. 1993; GIROD et al. 1995).

In our study the overall complication rate was 50%, similar to other reports in the literature (KOWALSKI et al. 1994a; GIROD et al. 1995). Infection was also the most frequent (22.7%) among local and systemic complications, again in agreement with the literature (ROBBINS et al. 1990; GRANDIS et al. 1992; GIROD et al. 1995). Many recent studies have addressed the issue of identifying patients at high risk for developing a wound infection following head and neck oncological surgery (BECKER 1986; BROWN et al. 1987; COLE et al. 1987). Advanced stage of tumor (ROBBINS et al. 1990), type of reconstruction (ROBBINS et al. 1990), preoperative radiotherapy (YODER et al. 1979), nutritional status (ROBBINS et al. 1990), comorbidities (ROBBINS et al. 1990), duration of surgery (ROBBINS et al. 1990), classification of procedure (ROBBINS et al. 1990), antibiotic prophylaxis (ROBBINS et al. 1990), and alcohol consumption (ROBBINS et al. 1990) have been significantly related to the probability of postoperative wound infection. Robbins et al did also note that the use of blood replacement, surgical drains, and nasogastric tubes were significant predictors of wound infection even when it was hypothesized that this finding was essentially related to the extent and duration of surgery (ROBBINS et al. 1990). The prognostic significance of postoperative wound infection on head and neck cancer is still controversial.

The variations in type and duration of antibiotic agents that were noted in our study can be explained by the lack of a standardized regimen in the study period. The benefit of prophylactic antibiotic therapy has been clearly proven, whereas the best

regimen and length of time the antibiotic agents are administered remains controversial (BRAND et al. 1982; FEE et al. 1984; BECKER 1986; COLE et al. 1987). Some authors reported that there was no statistically significant difference in the rate of wound infection noted in patients receiving distinct types of antibiotic agents (JOHNSON et al. 1992) that was also noted in our study. However, another study showed that the rate of wound infection was significantly lower in patients receiving prophylaxis with a combined regimen of metronidazole and cefazolin vs cefazolin alone (ROBBINS et al. 1990).

Our incidence of chylous fistula is similar to other series (SMITS et al. 1972; MYERS e DINERMAN 1975; CRUMLEY e SMITH 1976; YODER et al.1979). Our rate of hematoma (3.7%) is higher than the 1% and 1.9% incidence reported by Gall et al (GALL et al. 1977) and Yoder et al (YODER et al. 1979), respectively, but is lower than the 4.2% rate described by Johnson and Cummings (JOHNSON e CUMMINGS 1978).

In our series, a low rate of pneumonia was detected, whereas in other studies it ranged from 7% to 15% (JOYCE e MCQUARRIE 1976; PELCZAR et al. 1993; WEBER et al. 1993; MCCULLOCH et al. 1997). Several aspects of the head and neck surgery make pneumonia a frequent complication irrespective of the underlying functional class or medical condition. Probably, the intensive pulmonary care and the few patients who underwent hemiglossectomy or total glossectomy with risk for aspiration have contributed to the low rate of pneumonia in our patients.

Reported postoperative complication rates associated with tracheostomy vary considerably (CHEW e CANTRELL 1972) and the chest infection is the commonest problem detected, achieving rates up to 20% (CASTLING et al. 1994). Although

tracheostomy was associated with postoperative complications in our study, this correlation with chest infection was unconfirmed.

The mortality rate (3.6%) is comparable to other studies (CUMMINGS et al 1977; GALL et al. 1977; PELCZAR et al. 1993; KOWALSKI et al. 1994a). The causes of postoperative death in our study were arterial rupture, hypovolemic shock, respiratory distress, and sudden death.

To our knowledge, no report analyzed the influence of the number of complications on the length of hospital stay for head and neck cancer until this article. However, some authors reported a strong correlation between wound infection and prolonged hospital stay (PELCZAR et al. 1993).

Clinical conditions can adversely affect the rate of complications in head and neck cancer surgery (YODER et al. 1979; ROBBINS et al. 1990; PELCZAR et al. 1993; WEBER et al. 1993; VAN BOKHORST-DE VAN DER SCHUEREN et al. 1997). Such factors have been studied recently (SINGH et al. 1998, 1999; MCCULLOCH et al. 1997), with predictive value in determining the risk of complications in surgically treated patients with oral cancer.

The choice of a neck dissection is based on the primary site as well as the number, size, and location of positive lymph nodes. In addition, the results and morbidity associated with each type of neck dissection must be considered. A selective neck dissection is often recommended for patients with cancer of the oral tongue who have a clinically N0 neck. Comprehensive neck dissection is required in the presence of palpable cervical metastases. Bilateral radical neck dissection has been used for many years for the treatment of proved or suspected bilateral metastatic disease, carrying significant morbidity and mortality rates

(BALLANTYNE e JACKSON 1982). Our mortality rate for patients who underwent this procedure (7.5%) is similar to other rates described in the literature (RAZACK et al. 1980; BALLANTYNE e JACKSON 1982), but it is higher than 2.1% reported in a series of 193 bilateral radical neck dissection from our institution (MAGRIN e KOWALSKI 2000).

The APACHE II scoring system is primarily intended for patients in ICUs, but attempts have been made to use this score in patients with severe trauma (RUTLEDGE et al. 1993), abdominal sepsis (BOHNEN et al. 1994), postoperative enterocutaneous fistulas (ALTOMARE et al. 1990), and acute pancreatitis (FAN et al. 1993). The prognostic value of APACHE II has been shown in patients having major general surgery with indications that included colorectal cancer, breast cancer, gastric cancer, ovarian cancer, lymphoma and pancreatic cancer (GOFFI et al. 1999), but we could not find in the literature any study emphasizing the relation between APACHE II score and postoperative complications in patients with head and neck cancer.

There is little information available about the level of utilization of the ICU by patients with head and neck cancer (DOWNEY et al. 1999; GODDEN et al.1999). Some centers prefer not admitting patients with cancer to an ICU (SCULIER e MARKIEWICZ 1995) while other centers admit all patients to an ICU after head and neck procedures (MUAKKASSA et al. 1990). Ryan and Hochman (RYAN e HOCHMAN 2000) could not find complications associated with early hospital discharge. Inversely to the expected, staying in an ICU for at least 3 days is encouraged for better monitoring of the patient's condition. In a retrospective study, 37 (1.5%) of 2346 patients undergoing head and neck surgical procedures required

admission to the ICU, since this access is extraordinary and reserved for patients requiring cardiopulmonary assistance or monitoring (DOWNEY et al. 1999). Another study comparing patients who had had major head and neck oncological resections and who were nursed postoperatively on a general ward with those who were referred to an ICU contrasts with the findings in our study that did not find differences in general morbidity (20% versus 27%) (GODDEN et al. 1999). This observation is in partial agreement with our findings, since it was noted that a statistically significant higher rate of postoperative complications were found in patients referred to the ICU. In this series, the advanced ECSS (stages 3 and 4), the type of surgery, and the surgical reconstruction (microvascular or myocutaneous flap) determined the necessity of the ICU. Characteristically, the patients who required ICU monitoring were those at high risk for complications (local and local plus systemic). Therefore, the use of this variable as a prognostic marker could not be reliable because it would be just a reflex of the severity of the disease. Moreover, excluding ICU from the predictive model of death, type of reconstruction emerges as a prognostic factor. This finding is in accord with the extension of surgery criteria used for ICU referral. The indication for admittance to the ICU for patients with oral cancer in our study was adequate and was supported by the lower inpatient postoperative death rates.

Some authors reported the negative influence of advanced comorbidities on survival of patients with head and neck cancer (PUGLIANO et al. 1997; SINGH et al. 1998; PUGLIANO et al. 1999b) corroborating our findings, probably by alterations on biological interaction between tumor and host. Prediction of outcome is important in disease stratification and subsequent decision-making process

(GOFFI et al. 1999). The identification of risk factors for postoperative complications may assist the surgeon in classifying patients into groups with distinct probabilities of postoperative morbidity and mortality, and the prevention of complications can turn to a better prognosis.

Table 1 Patients´ distribution according FSI, ECSS and TNM

Variables	n (%)
Clinical Stage TNM	
I	14 (12.7)
II	20 (18.2)
III	30 (27.3)
IV	46 (41.8)
FSI	
Low	33 (30.0)
Intermediate	35 (31.8)
High	42 (38.2)
ECSS	
1	30 (27.3)
2	14 (12.7)
3	14 (12.7)
4	52 (47.3)

Table 2 Frequency of postoperative complications according to the type

Complications	n (%)
Infection	25 (22.7%)
Dehiscence	23 (20.9%)
Flap necrosis	23 (20.9%)
Fistula	10 (9.1%)
Seroma	7 (6.4%)
Pneumonia	5 (4.5%)
Death	4 (3.6%)
Bleeding	4 (3.6%)
Hematoma	3 (2.7%)
Chyle fistula	2 (1.8%)
Sepsis	2 (1.8%)

Figure 1 Five-year overall survival according to the type of complications

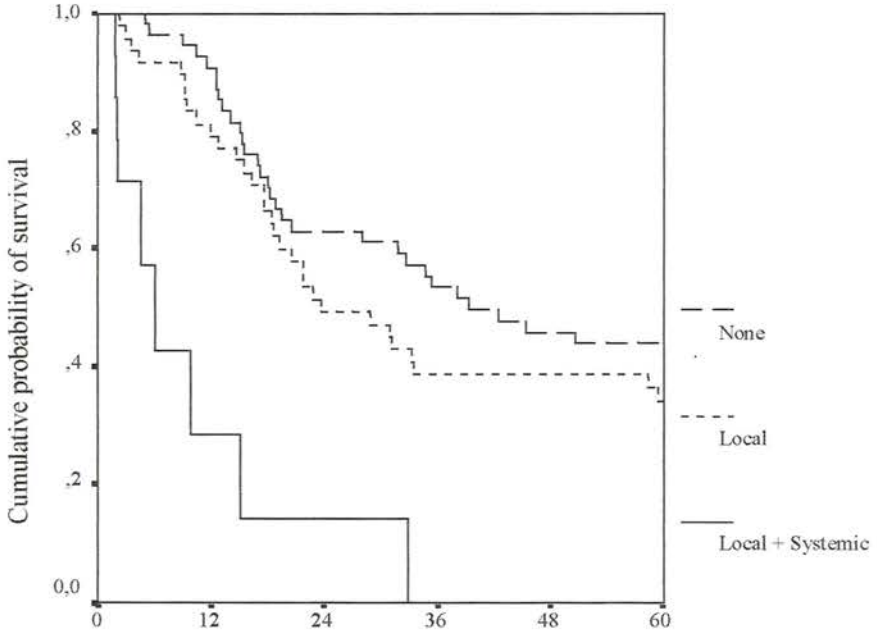
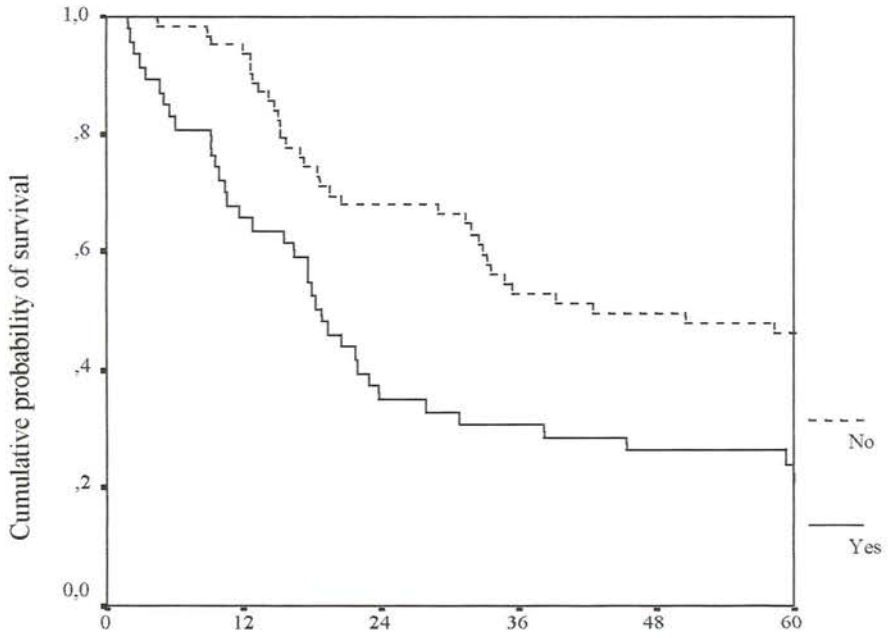


Figure 2 Five-year overall survival according to the staying at ICU



3.2 Effect of perioperative complications and clinical characteristics on survival of patients with oral or oropharyngeal carcinomas

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ABSTRACT

Objective: To establish the value of clinical factors in the prediction of perioperative complications and death in patients with oral and oropharyngeal carcinomas and to develop a better estimate of the prognosis by combining patient and tumor factors in a new extended clinical severity staging system (ECSS).

Patients and Methods: 530 patients with oral or oropharyngeal carcinomas admitted at the hospital from 1990 to 1997, and submitted to surgical treatment were studied. Logistic regression was utilized to identify risk factors for perioperative complications. Clinical characteristics that had a significant impact on 5-year overall survival were used to create the Functional Severity Index (FSI), which was combined to the TNM stage to create the ECSS.

Results: The 5-year overall survival rate was 45.7%. The Cox proportional hazards regression model identified, in an univariate analysis, 15 variables with impact on prognosis: daily alcohol consumption, smoking, gender, neck lump, earache, pain, dysphagia, weight loss, oral bleeding, odynophagia, body mass index (BMI), NCI comorbidity index, surgical risk according the American Society of Anesthesiologists (ASA), hematocrit and total lymphocytes count. Survival rates according to the ECSS were: 76.7% (stage 1), 64.4% (stage 2), 44.7% (stage 3), and 25.5% (stage 4) (χ^2=64.16, $p<0.001$). Perioperative complications were associated in an univariate analysis with the following variables: APACHE II, operative time, TNM clinical stage, ECSS, neck dissection, type of reconstruction, intraoperative blood transfusion, ICU staying, ASA surgical risk, POSSUM index. In the multiple analysis, only APACHE II score, neck dissection, POSSUM index and type of

reconstruction were identified as independent risk factors for perioperative complications. The final prognostic model included the development of local plus systemic complications, ECSS, type of reconstruction, and APACHE II score.

Conclusions: This study demonstrates that clinical variables have predictive effect on morbidity and mortality of patients with oral and oropharyngeal cancer surgically treated. Local plus systemic perioperative complications can adversely affect the prognosis. The uniformity of results confirms that survival estimates can be enhanced by the addition of clinical characteristics to the TNM classification, creating a more accurate system for the estimation of prognosis.

Introduction

Oral and oropharyngeal cancers are predominant in the elderly. Surgery and radiotherapy are the primary therapeutic procedures, and the choice of therapy depends on factors related to the tumor, patient, and institutional experience (BYERS 1995). Anatomical extension of the disease, described through TNM staging system (SOBIN e WITTEKIND 1997), has long been accepted as one of the most important prognostic factors. However, recent reports suggest that symptoms, comorbidities and other clinical characteristics of the patients are important for therapeutic planning and for determining the risk of complications (DE MELO et al. 2001) and the prognosis of several types of cancer (FEINSTEIN et al. 1975; FEINSTEIN et al. 1977; WELLS et al. 1984; CLEMENS et al. 1986; FEINSTEIN e WELLS 1990; PICCIRILLO et al. 1994; SATARIANO e RAGLAND 1994). The addition of these factors to the TNM classification permitted the creation of new staging systems, superior in the prediction of survival when compared with the TNM staging system alone (FEINSTEIN et al. 1977; WELLS et al. 1984; CLEMENS et al. 1986; PUGLIANO et al. 1997, 1999b; RIBEIRO et al. 2000).

Recent advances in the anesthetic and surgical techniques, including microvascular reconstruction, have allowed more radical oncological procedures for advanced head and neck cancer. However, the curative intent can be limited by the hazard of life-threatening perioperative complications. The occurrence of perioperative complications increases the length of hospital stay and the necessity of other diagnostic and therapeutic procedures, with a subsequent increase in the hospital costs (DURAZZO et al. 1999). Local plus systemic complications, along

with an advanced clinical severity stage of the disease are responsible for a worse prognosis in patients with oral cancer (DE MELO et al. 2001).

There are no preoperative scoring systems directed to particular types of surgery, and reported results are based on studies including all types of surgical procedures (DURAZZO et al. 1999). Accurate staging and prediction of perioperative complications are of paramount importance for treatment planning of elderly or chronically ill patients with a wide variety of pathophysiologic alterations, because they require continuous medical assistance and high technologic support. However, the assessment of the results of providing such care is limited and imprecise. Furthermore, a severity of disease classification system is essential to estimate the pretreatment risk of death, the appropriate indication of surgical treatments, and the prediction of outcome (WAGNER et al. 1983).

The objectives of this article are to evaluate the importance of clinical factors in the prediction of perioperative complications and survival in patients with oral cavity and oropharyngeal cancer and to develop a more accurate estimate of the prognosis by combining patient and tumor related factors in a new staging system.

Patients and Methods

Five hundred thirty medical records of patients with squamous cell carcinoma of oral cavity and oropharynx, admitted to the Centro de Tratamento e Pesquisa Hospital do Câncer A. C. Camargo, São Paulo, Brazil, from January 1, 1990, to December 31, 1997, were reviewed. The following criteria were used for inclusion in the study: a histologically confirmed diagnosis; absence of previous oncological

treatment for this primary tumor; no distant metastasis and surgical treatment with a curative purpose, exclusive or as a part of a multidisciplinary approach.

Data collection from the medical records was performed using a specially designed form. These data included demographic information, hematocrit, hemoglobin, body mass index (BMI), smoking status, alcoholism status, TNM staging (Union Internationale Contre le Cancer or American Joint Committee on Cancer classification) (SOBIN e WITTEKIND 1997), tumor site, surgical risk according to the American Society of Anesthesiology (ASA) (SAKLAD 1941), type of surgery and neck dissection, type of reconstruction, blood transfusion, comorbidities according to National Cancer Institute classification (YANCIK et al. 1998), Charlson comorbidity index (CHARLSON et al. 1987), Functional Severity Index (FSI) (RIBEIRO et al. 2000), extended clinical severity stage (ECSS) (RIBEIRO et al. 2000), Acute Physiology and Chronic Health Evaluation II (APACHE II) score (KNAUS et al. 1985), Physiological and Operative Severity Score for Enumeration of Mortality and Morbidity (POSSUM) index (COPELAND et al. 1991), length of stay in an Intensive Care Unit (ICU), length of hospital stay and perioperative complications. Outcomes measures included development of complications in the immediate postoperative period (until 30 days) and 5-year overall survival. Patients were followed from the date of diagnosis to the date of last objective evaluation or death. Only 9.1% of the patients were lost to follow-up.

The APACHE II classification is a revised version of a prototype system, APACHE (Acute Physiology and Chronic Health Evaluation). It includes 12 physiologic measures (temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, arterial pH, serum sodium, serum potassium, serum creatinine,

hematocrit, white blood count and Glasgow Coma Scale score), age and severe chronic health problems. The physiologic score is determined from the worst value, e.g., the lowest hematocrit or the highest respiratory rate, during the initial 24 hours after ICU admission (KNAUS et al. 1985) (Table 1). In our study we also applied APACHE II for patients not referred to the ICU, based on findings of the first 24 hours of the postoperative period.

POSSUM was developed by multivariant discriminant analysis to obtain a method of risk assessment. A 12-factor four-grade physiological score including age, cardiac status, pulse rate, systolic blood pressure, respiratory status, Glasgow Coma Scale score, serum concentrations of urea, potassium and sodium, haemoglobin concentration, white cell count and findings on eletrocardiography, was developed. This was combined with a six-factor operative score, which compensates for the type of surgical procedure and includes type and number of procedures, volume of blood loss, peritoneal contamination, presence and extent of malignancy, and timing of operation (COPELAND et al. 1991) (Table 2). In this study, the operative severity was: minor (pelvectomy, partial glossectomy, intraoral resection without neck dissection), moderate (total glossectomy, hemiglossectomy, pelviglossectomy, sectional pelviglossomandibulectomy, marginal pelviglossomandibulectomy, wide excision, classic or modified retromolar operation, inframesostructure resection, bucopharyngectomyany or any surgical procedure with unilateral neck dissection), major (any surgical procedure with myocutaneous flap reconstruction), and major plus (any surgical procedure with microvascular reconstruction). For both indexes, if an item was not evaluated and the patient did not have any disease that could be responsible for an abnormal result, the lowest score was assigned.

Patients were electively referred to the ICU based on 1 of the following criteria: expected operative time longer than 6 hours and/or the presence of a comorbidity diagnosed preoperatively, such as coronary insufficiency or advanced chronic obstructive pulmonary disease, requiring strict cardiopulmonary monitoring.

Wound infection was recorded only for patients who present suppurative drainage and/or who develop a mucocutaneous fistula (ROBBINS et al. 1990). Wounds noted to have erythema or erythema and edema may be considered as infected in the presence of fever, based on an evaluation performed by the surgeon.

The information contained in the forms was entered in a database (Dbase for Windows; Borland International, Scotts Valley, Calif). Periodically, revisions were made to verify the internal consistency of the data. For the statistical analysis, commercially available software (Statistical Product and Service Solutions for Windows, release 10.0; SPSS Inc, Chicago, IL) was used. Descriptive statistics was used as a preliminary analysis of the relation between the baseline variables and outcome events. The t test was used to compare means. Continuous variables were categorized to facilitate data analysis and presentation. Logistic regression was used to find independent risk factors for perioperative complications. Survival analysis was done using the Kaplan-Meier method (log-rank test was used to compare the curves), and the Cox proportional hazards model to estimate independent prognostic factors. For all statistical tests an alpha error equal to 5% was established.

Results

The cohort of 530 patients included 439 men (82.8%) and 91 women (17.2%); 446 were white (84.2%) and 84 (15.8%) belonged to other ethnic groups. The mean age was 57.3 years (ranging from 27 to 87 years). Tumors were located in the following sites: 34 base of the tongue (6.4%), 138 oral tongue (26.0%), 52 gums (9.8%), 129 floor of the mouth (24.3%), 14 palate (2.7%), 71 other parts of the mouth (13.5%), 84 tonsil (15.8%), and 8 oropharynx (1.5%), and. Most of the patients had advanced tumors (TNM clinical stage IV, 47.3%) and reported a wide variety of symptoms (Table 3).

All patients underwent surgery as the primary treatment and 330 patients were submitted to irradiation as adjuvant therapy. Four hundred seventy-eight patients also underwent neck dissection as a part of the initial treatment. Operative time ranged from 25 to 960 minutes (median=360 minutes). The majority of patients did not receive intraoperative blood transfusion (54.3%). Primary closure was employed for 217 patients (40.9%) and several types of reconstruction were utilized on remaining patients (Table 4). Two hundred forty-eight patients (46.7%) were electively referred to ICU after surgery during a period that varied from 1 to 20 days (median, 2 days). The length of hospital stay ranged from zero to seventy-one days (mean, 8 days). Patients who had perioperative complications had a significant higher length of hospital stay (mean, 11.9 days) than those who had not perioperative complications (mean, 7.1 days) ($p<0.001$).

The incidence of perioperative complications was 58.9%. Wound infection (32.5%) and dehiscence were the most frequent events (Table 5). Postoperative mortality rate was 2.6%.

Ninety-six percent of patients presented comorbidities, when classified according NCI index, compared to 39.1% obtained using Charlson comorbidity index. ASA classification provided the following results: ASA I (9.3%), ASA II (62.6%), ASA III (27.6%) and ASA IV (0.6%). The median POSSUM index was 27 (range 19-48) and APACHE II score varied from 0 to 23 (median, 7).

The Cox proportional hazards model identified, in an univariate analysis, 15 variables with impact on prognosis ($p \leq 0.10$): daily alcohol consumption (hazards ratio [HR], 1.5; p=0.003), smoking (HR=1.5; p=0.032), male gender (HR=1.4; p=0.035), neck lump (HR=1.5; p=0.002), earache (HR=1.5; p=0.005), pain (HR=1.5; p=0.002), dysphagia (HR=2.3; $p<0.001$), weight loss (HR=1.4, p=0.002), oral bleeding (HR=2.0; $p<0.001$), odynophagia (HR=1.4; p=0.015), body mass index (≤ 22.3) (HR=1.3; p=0.014), NCI comorbidity index > 2 (HR=1.4; p=0.008), surgical risk ASA III/IV (HR=1.5, p=0.003), hematocrit (<34.5) (HR=1.5; p=0.026) and total lymphocytes count ($\leq$ 1200) (HR=1.6; p=0.008). The functional severity index (FSI) was built through the multiplication of the values of the HR for each patient. When the condition was not present, we gave the value of 1 for that category. The score ranged from 1 to 199.37 (median=8.6), and the patients were grouped into 3 categories, based on the tercils: high (score >12.90), intermediate (score >6.14 and $\leq$12.90), and low (score $\leq$6.14) grade of functional impairment. Survival analysis confirmed a statistically significant difference between 5-year overall survival, among the 3 groups of the FSI, described as follows: low grade, 63.2%; intermediate

grade, 45.8%; and high grade, 22.8% (χ^2=52.53, p<0.001). Therefore, according to a method previously described (PUGLIANO et al. 1997), the next step was the conjunction of the FSI with the TNM staging system. The categories of the conjunction of the 2 classifications were then consolidated to create an extended clinical severity staging system, also composed by 4 stages (Figure 1). Five-year overall survival for this extended clinical severity staging system was as follows: stage 1, 76.7%, stage 2, 64.4%, stage 3, 44.8%, stage 4, 25.5% (χ2=64.16, p<0.001). The survival curves are shown in Figure 2.

The comparison among the systems demonstrated that extended clinical severity staging system overcame TNM, exhibiting a higher survival gradient (51.2 vs. 37.4) and also a higher value of the χ^2 test (64.16 vs. 44.33). When both variables (TNM and ECSS) were on the multivariate models for recurrence or tumor-specific survival, statistical significance was lost. Therefore, it was decided to keep ECSS in final models, adjusted by the type of reconstruction, type of complications, and APACHE II. In this way, the extended clinical severity staging system also could be recognized as better than TNM alone in the prediction of tumor-specific survival and recurrences (Table 6).

The occurrence of perioperative complications was associated with the following variables: APACHE II (p<0.001), surgical time (p<0.001), TNM clinical stage (p<0.001), ECSS (p<0.001), neck dissection (p<0.001), type of reconstruction (p<0.001), intraoperative blood transfusion (p<0.001), staying in na ICU (p<0.001), ASA surgical risk (p=0.015), POSSUM index (p<0.001), and race (p=0.025) (Table 7). In the multivariate analysis, only APACHE II score (RR=2.6, p<0.001), neck dissection (unilateral, RR=4.5, p<0.001 and bilateral, RR=5.0, p<0.001), POSSUM

index (RR=1.7, p=0.023) and type of reconstruction (RR=2.1, p=0.001) were identified as independent risk factors for perioperative complications (Table 8).

The final predictive prognostic model included the development of local plus systemic complications (Figure 3) (HR=2.2), ECSS (stage 3, HR=2.1; stage 4, HR=3.4), type of reconstruction (myocutaneous or microvascular flap, HR=1.6) and APACHE II score > 10 (HR=1.3) (Table 9).

Discussion

Patients with head and neck cancer are especially likely to have comorbidities as a result of chronic alcohol and tobacco consumption. Comorbidities can impact the diagnosis, prognosis and treatment for patients with cancer (PICCIRILLO 2000).

The TNM classification has been universally accepted and widely used to describe tumor characteristics and predict survival. However the system fails for not taking into account the clinical biological features of the cancer, which is expressed by structural changes and its physiological detriments in the patient (RIBEIRO et al. 2000). The gross anatomical aspects (extent of the disease), the microscopic appearance (cell type and degree of differentiation), and the biomolecular characteristics (tumor markers and ploidy) are different modes to describe tumor morphologic structure (PICCIRILLO e FEINSTEIN 1996). Cancer symptoms (type, duration and severity) (FEINSTEIN 1985) and the performance status of the host (SATARIANO 1992) are clinical factors that represent the seriousness of illness in a patient. Even though comorbidity is not a variable related to the cancer itself, it is an important clinical aspect for being able to affect the choice of treatment and

prognosis (FEINSTEIN 1970; WELLS et al. 1984; CLEMENS et al. 1986; SATARIANO e RAGLAND 1994).

The purpose of utilizing symptoms as a prognostic factor in cancer is not new, since important prognostic information is already described for different types of cancer (WELLS et al. 1984; CLEMENS et al. 1986). Neel et al. demonstrated that when patients with nasopharyngeal cancer were grouped into two categories, based on the number and duration of symptoms (e.g., epistaxis, loss of sense of smell, tinnitus) at initial presentation, they had significantly different survival rates in each category (NEEL et al. 1985). In patients with osteosarcoma, weight loss had an notable prognostic impact that remained important in a multivariate analysis even after controlling for other possible prognostic factors such as symptom duration, tumor site, regional spread, grade, microscopic morphology of tumor, swelling at tumor site, and lytic appearance of tumor (TAYLOR et al. 1989). The presence of chills, fevers, or night sweats have been correlated to a worse survival in patients with lymphoma for many years, being used as a modifier in the staging system (PUGLIANO et al. 1999a).

Previous studies on laryngeal, oral and oropharyngeal cancer proved that symptom severity contributes with additional prognostic data not available from anatomical staging alone (PICCIRILLO et al. 1994, PUGLIANO et al. 1997, 1999b; RIBEIRO et al. 2000). Our findings that symptoms such as neck lump, dysphagia, weight loss and oral cavity bleeding are prognostic factors validate results from previous studies (PUGLIANO et al. 1997, PUGLIANO et al. 1999a; RIBEIRO et al. 2000; PUGLIANO et al. 1999b).

Odynophagia had not yet been proved as having an independent impact on overall survival of patients with oral or oropharyngeal cancer until this publication. Pugliano et al. demonstrated the influence of this symptom on survival only in a univariate analysis (PUGLIANO et al. 1999a). However, this symptom had been already reported as an independent prognostic factor in patients with squamous cell carcinoma of hypopharynx (RAPOPORT e FRANCO 1993). A previous study reported that the presence of odynophagia was associated to advanced stages due to lateness of diagnosis (KOWALSKI et al. 1994b), but in our series the same frequency of the symptom has been found among initial and advanced stages (data not shown).

Alcohol consumption remained related to survival, as in our previous study (RIBEIRO et al. 2000), which emphasizes that the high prevalence of alcohol abuse among these patients justifies the inclusion of alcohol use in a prognostic system (DELEYIANNIS et al. 1996).

Smoking determined a worse prognosis, which is in agreement with other reports (BUNDGAARD et al. 1994; EL-HUSSEINY et al. 2000). Other authors also emphasized the negative influence of smoking on survival of young patients with head and cancer (LACY et al. 2000). Tobacco consumption seems to induce the tumor cells of oral squamous cell carcinomas to undergo a more pronounced dedifferentiation that makes them more aggressive (BUNDGAARD et al. 1995). Therefore, our results suggest that smoking and alcohol cessation programs should be warranted not only with prophylactic but also with a therapeutic purpose (BUNDGAARD et al. 1994).

Gender was also identified as a prognostic factor in this study. A lower risk of death was found among female patients. The survival advantage experienced by females, independent from the effect of other clinical factors, had been already reported in other series (FRANCO et al. 1993; FAYE-LUND e ABDELNOOR 1996).

Malnutrition has been recognized for many years as a comorbid condition in cancer patients (WARREN 1932), and it is reported to affect 30-50% of all patients with head and neck cancer (VAN BOKHORST-DE VAN DER SCHUEREN et al. 1999). Although, in this study, the evaluation of the nutritional status had been limited only to BMI and weight loss before treatment, the results are in concordance with the literature that already described the negative effect of a poor nutritional status on survival (VAN BOKHORST-DE VAN DER SCHUEREN et al. 1999; BROOKES 1985). Immune depression, represented in this study by the total lymphocytes count, is recognized as a consistent metabolic effect in oral cancer and the monitoring of the immunoregulatory status has been shown to be correlated with prognosis (BALARAM e MEENATTOOR 1996). It is reported that preoperative level of malnutrition is associated significantly with postoperative complications and death. Therefore, it seems likely that an improve in the nutritional status before surgery, particularly in the elderly, might decrease postoperative morbidity rates (LINN et al. 1988).

The ASA classification represents a simple estimation of physiological status without the need for clinical resources and can be applied to every patient before operation (WOLTERS et al. 1996). The correlation between ASA classification and postoperative morbidity and mortality had been shown in previous studies (MENKE

et al. 1993; WOLTERS et al. 1996). The association between ASA and prognosis noted in our study is other indication of the influence of poor physical status on outcome. A recent study with patients with head and neck cancer concluded that ASA class is comparable to the Charlson index, displaying equal if not greater prognostic value for mortality. This ability was still observed beyond the perioperative period (REID et al. 2001).

We could not confirm the prognostic value of age found in our previous study (RIBEIRO et al. 2000), probably because of the low number of elderly patients with oropharyngeal carcinomas in this sample. Since surgery carries the risk of aspiration and postoperative complications, there is a tendency to refer these patients to exclusive radiotherapy.

In addition to symptoms, the presence of comorbidities has been shown to decrease survival in several chronic diseases (KAPLAN e FEINSTEIN 1974), demonstrating in many cancers higher prognostic impact than tumor size or stage (PICCIRILLO 1995). Moreover, there are preventive implications since alcohol abuse and smoking are major risk factors in head and neck cancer and also related to other chronic diseases. Primary prevention that begins in an early age and continues throughout life is critical to the reduction of the burden of these illnesses (PICCIRILLO 1995).

Perioperative complications are defined as unexpected but avoidable events, that arise during surgery or in the postoperative period (SHAHEN 1984; ARVIDSSON et al. 1994). Complications after major surgery for oral cancer patients increase treatment costs, delay adjuvant treatment, augment late sequels, affect quality of life, and can also cause patient's death, if not promptly diagnosed and

treated (EVANS 1989). During the last years, several advances in the medical knowledge and techniques improved the safety of major head and neck oncological surgery decreasing the risk and severity of complications (KOWALSKI et al. 1994a). However, the rates of complications are still high and the identification of associated risk factors can reduce morbidity and mortality in oral and oropharyngeal cancer patients (YODER et al. 1979; PELCZAR et al. 1993; GIROD et al. 1995).

In our study, the incidence of perioperative complications was similar to other reports in the literature (DONALD 1978; YODER et al. 1979; PELCZAR et al 1993; KOWALSKI et al. 1994a; GIROD et al. 1995).

Wound infection was the most frequent among local and systemic complications, as already described in the literature (ROBBINS et al. 1990; GRANDIS et al. 1992; GIROD et al. 1995; DE MELO et al. 2001). Many recent studies have addressed the issue of identifying patients at high risk for developing a wound infection following head and neck oncological surgery (BECKER 1986; BROWN et al. 1987; COLE et al. 1987). Advanced stage of tumor (ROBBINS et al. 1990), type of reconstruction (ROBBINS et al. 1990; LOTFI 2001) preoperative radiotherapy (YODER et al. 1979), nutritional status (ROBBINS et al 1990), comorbidities (ROBBINS et al. 1990; LOTFI 2001), duration of surgery (ROBBINS et al. 1990), classification of procedure (ROBBINS et al. 1990), antibiotic prophylaxis (ROBBINS et al. 1990; LOTFI 2001), tobacco (LOTFI 2001) and alcohol consumption (ROBBINS et al. 1990) have been significantly related to postoperative wound infection. However, the prognostic significance of postoperative wound infection on head and neck cancer remains controversial (RODRIGO e SUÁREZ 1998).

Chylous fistula is an uncommon complication after neck dissection, occurring in 1 to 2.5% of radical neck dissections (DE GIER et al. 1996) and the incidence in this study is similar to other series (SMITS et al. 1972; MYERS e DINERMAN 1975; CRUMLEY e SMITH 1976; YODER et al. 1979). Our incidence of hematoma is higher than the rates reported by other authors (GALL et al. 1977; YODER et al. 1979), but it is lower than the 4.2% rate described by JOHNSON AND CUMMINGS (1978).

In the present series, a low rate of pneumonia was detected, whereas in other studies it ranged from 7% to 15% (PELCZAR et al. 1993; WEBER et al. 1993; MCCULLOCH et al. 1997). Although the head and neck surgery rarely approaches the pleural space, tracheostomy, pharyngolaryngeal tumor resection and the use of regional reconstructive flaps from the chest and abdomen may indirectly impact and impair respiratory function (MCCULLOCH et al. 1997). The etiology of pulmonary infections following head and neck surgery is most likely multifactorial. Factors may include prolonged anesthesia, resulting in alveolar hypoventilation and atelectasis, as well as aspiration of oropharyngeal secretions during surgery and in the immediate postoperative period (WEBER et al. 1993). Probably, the intensive pulmonary care and a few number of patients submitted to hemiglossectomy or total glossectomy with risk for aspiration are responsible for this low rate of pneumonia in our patients (DE MELO et al. 2001).

The mortality rate (2.6%) in our study is comparable to other studies (PELCZAR et al. 1993; KOWALSKI et al. 1994a). The causes of postoperative death in our study were: arterial rupture and hypovolemic shock, respiratory distress,

bronchopneumonia, acute pulmonary edema, pulmonary embolism, cardiac arrhythmia, and sudden death.

The choice of a neck dissection is based on the primary site as well as the number, size, and location of positive lymph nodes. In addition, the results and morbidity associated with each type of neck dissection must be considered. Bilateral radical neck dissection has been used for many years for the treatment of proved or suspected bilateral metastatic disease, carrying significant morbidity and mortality rates (BALLANTYNE e JACKSON 1982).

The use of microvascular free tissue transfer has warranted the reconstruction of increasingly complex defects in high risk patients after head and neck cancer surgical treatment (SINGH et al. 1999). However the association of these factors also originates a higher risk for complications (SINGH et al. 1999; DE MELO et al. 2001), as occurred in our study.

Prognostic value of APACHE II has been shown in patients having major general surgery with indications that included colorectal cancer, breast cancer, gastric cancer, ovarian cancer, lymphoma, and pancreatic cancer (GOFFI et al. 1999). In this study we could confirm our previous finding (DE MELO et al. 2001) that APACHE II score predicts perioperative complications. To our knowledge, this is first study that established the prognostic value of the APACHE II score for patients with head and neck cancer.

Clinical staging systems including patients´ clinical characteristics have been developed and have shown prognostic gradients for several types of cancer. Although the customary staging systems describe the morphological appearance and structural damage produced by the tumor, no attention is given to the tumor's

duration and rate of growth, which can be revealed as the functional effects of the cancer in structures or systems that may or not be anatomically involved (FEINSTEIN 1966, 1968).

The extended clinical severity staging system developed in this study provided a better estimate of the 5-year overall survival as well as tumor-specific survival and recurrence when compared to the TNM. The superiority of this kind of staging system was already reported in various other studies focusing on oral (PUGLIANO et al. 1999b; RIBEIRO et al. 2000), oropharyngeal (PUGLIANO et al. 1997) or laryngeal cancer (PICCIRILLO et al. 1994), confirming the hypothesis that clinical variables have important prognostic value.

Survival estimates in head and neck cancer can be improved by the addition of clinical elements to the TNM classification, creating a more powerful and precise staging system. Prediction of outcome is important in disease stratification and subsequent decision-making process (GOFFI et al. 1999). The identification of risk factors for perioperative complications may help the surgeon in classifying patients into groups with distinct probabilities of postoperative morbidity and mortality. Thus, the reduction of risk factors for perioperative complications and chronic diseases can turn to a better prognosis in patients with oral or oropharyngeal cancer.

Table 1 The APACHE II severity of disease classification system

Physiologic Variable	Score				
	0	1	2	3	4
Temperature (°C)	36-38.4	34-35.9 38.5-38.9	32-33.9	30-31.9 39-40.9	≤ 29.9 ≥ 41
Mean Arterial Pressure (mmHg)	70-109	-	50-69 110-129	130-159	≤ 49 ≥ 160
Heart rate (ventricular response)	70-109	-	55-69 110-139	40-54 140-179	≤ 39 ≥ 180
Respiratory rate (non-ventilated or ventilated)	12-24	10-11	6-9	35-49	≤ 5 ≥ 50
Oxygenation: A-aDO_2 or PaO_2 (mmHg) a. FiO_2 < 0.5 – record only **A-aDO_2**	< 200	-	200-349	350-499	≥ 500
b. FiO_2 ≥ 0.5 – record only **PaO_2**	> 70	61-70	-	55-60	< 55
Arterial pH	7.33-7.49	7.5-7.59	7.25-7.32	7.15-7.24 7.6-7.69	< 7.15 ≥ 7.7
Serum Sodium (mmol/l)	130-149	150-154	120-129 155-159	111-119 160-179	≤ 110 ≥ 180
Serum Potassium (mmol/l)	3.5-5.4	3-3.4 5.5-5.9	2.5-2.9	6-6.9	< 2.5 ≥ 7
Serum Creatinine (mg/100 ml) (double point score for acute renal failure)	0.6-1.4	-	< 0.6 1.5-1.9	2-3.4	≥ 3.5
Hematocrit (%)	30-45.9	46-49.9	20-29.9 50-59.9	-	< 20 ≥ 60
White cell blood count (total/mm^3) (x 1000)	3-14.9	15-19.9	1-2.9 20-39.9	-	< 1 ≥ 40
Glasgow Coma Score (GCS) (Score = 15 minus actual GCS)					
A. Total Acute Physiology Score (APS) (sum of the 12 individual variable points)					

B. Age points

Age (years)	Points
≤ 44	0
45-54	2
55-64	3
65-74	5
≥ 75	6

C. Chronic Health Points

If the patient has a history of severe organ system insufficiency or is immunocompromised assign points as follows:
a. for nonoperative or emergency postoperative patients – 5 points
b. for elective postoperative patients – 2 points

Definitions

Organ insufficiency or immunocompromised state must have been evident **prior** to this hospital admission and conform to the following criteria:
LIVER: Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma.
CARDIOVASCULAR: New York Heart Association Class IV.
RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, i.e., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mmHg) or respirator dependency.
RENAL: Receiving chronic dialysis.
IMMUNOCOMPROMISED: The patient has received therapy that suppresses resistance to infection, e.g., immuno-suppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukemia, lymphoma, AIDS.

APACHE II score = A + B + C

Table 2 POSSUM score

	Score			
	1	2	4	8
Age (years)	≤ 60	61-70	≥ 71	-
Cardiac signs	No failure	Diuretic, digoxin, antianginal or hypertensive therapy	Peripheral edema; warfarin therapy	Raised jugular venous pressure
Chest radiograph			Borderline cardiomegaly	Cardiomegaly
Respiratory history	No dyspnea	Dyspnea on exertion	Limiting dyspnea (one flight)	Dyspnea at rest (rate ≥ 30/min)
Chest radiograph		Mild COPD	Moderate COPD	Fibrosis or consolidation
Blood pressure (systolic) (mmHg)	110-130	131-170	≥ 171	≤ 89
		100-109	90-99	
Pulse (beats/min)	50-80	81-100	101-120	≥ 121
		40-49		≤ 39
Glasgow coma score	15	12-14	9-11	≤ 8
Hemoglobin (g/100 ml)	13-16	11.5-12.9	10.0-11.4	≤ 9.9
		16.1-17.0	17.1-18.0	≥ 18.1
White cell count (x 10^{12}/l)	4-10	10.1-20.0	≥ 20.1	-
		3.1-4.0	≤ 3.0	
Urea (mmol/l)	≤ 7.5	7.6-10.0	10.1-15.0	≥ 15.1
Sodium (mmol/l)	≥ 136	131-135	126-130	≤ 125
Potassium (mmol/l)	3.5-5.0	3.2-3.4	2.9-3.1	≤ 2.8
		5.1-5.3	5.4-5.9	≥ 6.0
Electrocardiogram	Normal	-	Atrial fibrillation (rate 60-90)	Any other abnormal rhythm or ≥ 5 ectopics/min Q waves or ST/T wave changes
Operative severity	Minor	Moderate	Major	Major+
Multiple procedures	1	-	2	> 2
Total blood loss (ml)	≤ 100	101-500	501-999	≥ 1000
Peritoneal soiling	None	Minor (serous fluid)	Local pus	Free bowel content, pus or blood
Presence of malignancy	None	Primary only	Nodal metastases	Distant metastases
Mode of surgery	Elective	-	Emergency resuscitation of > 2 h possible Operation < 24 h after admission	Emergency (immediate surgery < 2 h needed)

Table 3 Patients distribution according symptoms

Variable	**Category**	**N(%)**
Burning sensation	No	506 (95.5)
	Yes	24 (4.5)
Neck lump	No	437 (82.5)
	Yes	93 (17.5)
Dysphagia	No	481 (90.8)
	Yes	49 (9.2)
Pain	No	210 (39.6)
	Yes	320 (60.4)
Weight loss	No	310 (58.5)
	Yes	220 (41.5)
Odynophagia	No	408 (77.0)
	Yes	122 (23.0)
Earache	No	439 (82.8)
	Yes	91 (17.2)
Oral bleeding	No	462 (87.2)
	Yes	68 (12.8)

Table 4 Patients' distribution according type of surgery and neck dissection.

Variable	Category	N(%)
Type of surgery	Partial glossectomy/pelvectomy	41 (7.7)
	Total glossectomy/Hemiglossectomy	24 (4.5)
	Pelviglossectomy	118 (22.3)
	Sectional pelviglossomandibulectomy	66 (12.5)
	Marginal pelviglossomandibulectomy	79 (14.9)
	Intraoral resection/wide excision	77 (14.5)
	Classic or modified retromolar operation	53 (10.0)
	Inframesostructure resection	9 (1.7)
	Bucopharyngectomy/other types	54 (10.2)
Neck dissection	No	52 (9.8)
	Unilateral classic radical neck dissection	121 (22.8)
	Bilateral classic radical neck dissection	27 (5.1)
	Unilateral modified radical neck dissection	82 (15.5)
	Bilateral modified radical neck dissection	12 (2.3)
	Unilateral supraomohyoid neck dissection	113 (21.3)
	Bilateral supraomohyoid neck dissection	28 (5.3)
	Classic radical + supraomohyoid neck dissection	57 (10.8)
	Modified radical + supraomohyoid neck dissection	31 (5.8)
	Classic radical + modified radical neck dissection	7 (1.3)
Type of reconstruction	None (primary closure)	216 (40.8)
	Local flap	15 (2.8)
	Skin graft	8 (1.5)
	Tongue flap	85 (16.0)
	Pectoralis major myocutaneous flap	133 (25.1)
	Other myocutaneous/osteomyocutaneous flaps	38 (7.2)
	Microvascular	25 (4.7)
	Combined flaps	10 (1.9)

Table 5 Frequency of postoperative complications according to the type

Complications	n (%)
None	218 (41.1)
Infection	172 (32.5)
Dehiscence	139 (26.2)
Flap necrosis	117 (22.1)
Fistula	86 (16.2)
Pneumonia	40 (7.5)
Seroma	29 (5.5)
Hematoma (conservative management)	16 (3.0)
Death	14 (2.6)
Respiratory failure	14 (2.6)
Bleeding (requiring re-operation)	13 (2.5)
Cerebral vascular accident	4 (0.8)
Chyle fistula	3 (0.6)
Sepsis	2 (0.4)
Acute myocardial infarction	1 (0.2)

Table 6 Prediction of recurrence and tumor specific survival rates using extended clinical severity staging system

Staging system	Recurrence OR_{adj} [95% CI OR_{adj}]§	Tumor Specific Survival HR_{adj} [95% CI HR_{adj}]*
ECSS		
1	1.0 [Ref.]	1.0 [Ref.]
2	1.4 [0.6-3.5]	1.4 [0.6-3.3]
3	3.1 [1.4-7.0]	2.7 [1.3-5.6]
4	4.0 [1.8-8.9]	3.8 [1.9-7.7]

§ Adjusted by type of reconstruction and APACHE II score

* Adjusted by type of reconstruction, type of complications and APACHE II score

Table 7 Univariate analysis of predictive variables for the occurrence of perioperative complications.

Variable	**Category**	**OR_{crude}**	**CI 95% OR_{crude}**	**p**
APACHE II	≤10	1.0	-	
	>10	3.4	[2.1-5.3]	<0.001
Operative time	≤360 minutes	1.0	-	
	> 360 minutes	2.9	[2.0-4.3]	<0.001
Clinical Stage TNM	I	1.0	-	
	II	2.8	[1.2-6.5]	0.013
	III	4.7	[2.1-10.3]	<0.001
	IV	6.5	[3.0-13.9]	<0.001
ECSS	1	1.0	-	
	2	2.6	[1.2-5.5]	0.014
	3	2.9	[1.5-5.8]	0.002
	4	4.9	[2.5-9.4]	<0.001
Neck dissection	No	1.0	-	
	Unilateral	6.2	[3.0-12.9]	<0.001
	Bilateral	9.7	[4.5-20.8]	<0.001
Type of reconstruction	No/Local flap	1.0	-	
	Myocutaneous/microvascular	3.4	[2.3-5.1]	<0.001
Blood transfusion	No	1.0	-	
	Yes	2.7	[1.9-3.8]	<0.001
ICU	No	1.0	-	
	Yes	2.3	[1.6-3.3]	<0.001
ASA	I-II	1.0	-	
	III-IV	1.7	[1.1-2.5]	0.017
POSSUM	≤ 24	1.0	-	
	> 24	3.4	[2.3-5.0]	<0.001
Race	Non-black	1.0	-	
	Black	9.9	[1.3-74.6]	0.025

Table 8 Multivariate analysis of predictive variables for the occurrence of perioperative complications.

Variable	**Category**	**OR_{crude}**	**$OR_{adjusted}$**	**95% CI $OR_{adjusted}$**	**p**
APACHE II	≤10	1.0	1.0	-	
	>10	3.4	2.5	[1.5-4.2]	<0.001
Neck dissection	No	1.0	1.0	-	
	Unilateral	6.4	4.3	[2.0-9.5]	<0.001
	Bilateral	9.9	4.8	[2.0-11.6]	<0.001
Type of reconstruction	No/Local flap	1.0	1.0	-	
	Myocutaneous/microvascular flap	3.5	2.1	[1.3-3.2]	0.001
POSSUM	≤ 24	1.0	1.0	-	
	> 24	3.3	1.7	[1.1-2.7]	0.021

Figure 1 Algorithm for determination of the extended clinical severity staging.

A. Patients Characteristics:

1. Daily alcohol consumption
   ☐ No = 1.0
   ☐ Yes = 1.5

2. Dysphagia
   ☐ No = 1.0
   ☐ Yes = 2.3

3. Weight loss
   ☐ No = 1.0
   ☐ Yes = 1.4

4. Odynophagia
   ☐ No = 1.0
   ☐ Yes = 1.4

5. Oral bleeding
   ☐ No = 1.0
   ☐ Yes = 2.0

6. Earache
   ☐ No = 1.0
   ☐ Yes = 1.5

7. Pain
   ☐ No = 1.0
   ☐ Yes = 1.5

8. Neck lump
   ☐ No = 1.0
   ☐ Yes = 1.5

9. ASA
   ☐ I/II = 1.0
   ☐ III/IV = 1.5

10. Hematocrit
    ☐ ≥ 34.5 = 1.0
    ☐ < 34.5 = 1.5

11. BMI
    ☐ ≥ 22.3 = 1.0
    ☐ < 22.3 = 1.3

12. Total lymphocytes count
    ☐ ≥ 1,200 = 1.0
    ☐ < 1,200 = 1.6

13. Smoking
    ☐ No= 1.0
    ☐ Yes = 1.5

14. Gender
    ☐ Female = 1.0
    ☐ Male = 1.4

15. Comorbidity (NCI)
    ☐ Level I = 1.0
    ☐ Level II = 1.4

☐ x ☐ x ☐ x ☐ x ☐ x ☐ x ☐ x ☐ x ☐ x ☐ x ☐ x ☐ x ☐ x ☐ x ☐ = ☐ FSI

B. Functional Severity Index (FSI)

≤ 6.14 = Low Grade
> 6.14 and ≤ 12.90 = Intermediary Grade
> 12.90 = High Grade

C. Clinical Severity Staging System

	Clinical Stage/TNM	FSI
Stage 1	I/II	low
Stage 2	I/II	intermediate
	III	low
Stage 3	I/II	high
	III	intermediate
	IV	low
Stage 4	III	high
	IV	intermediate/high

Figure 2 Five-year overall survival curves, according to the extended clinical severity staging system

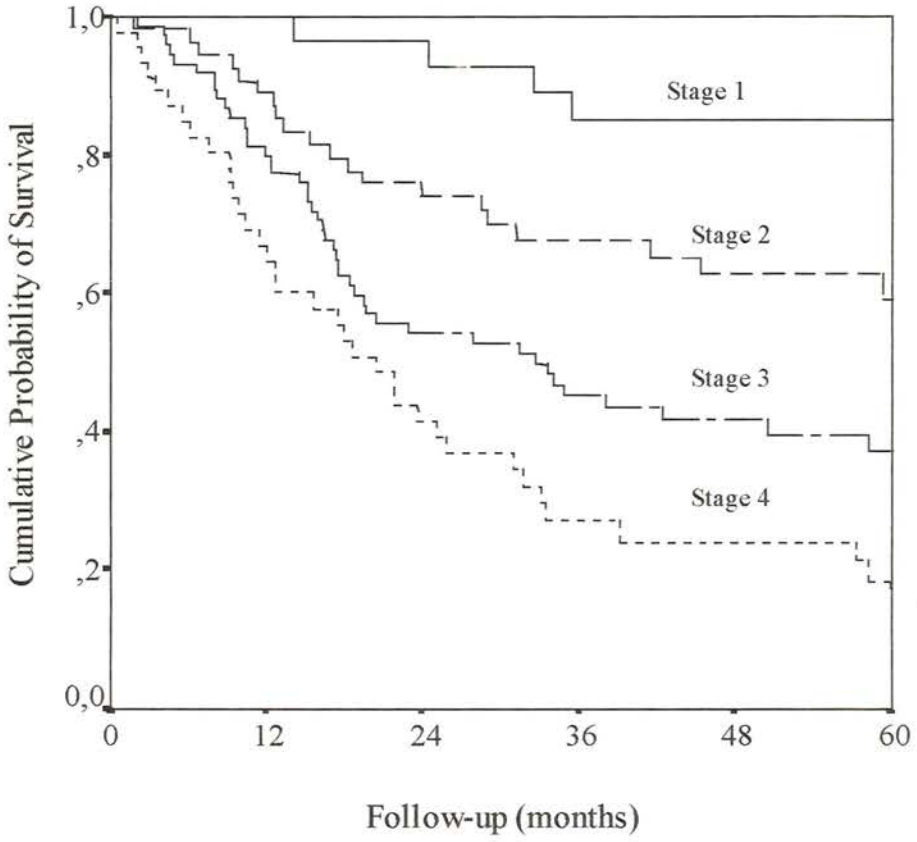

Figure 3 Five-year overall survival according to the type of complications.

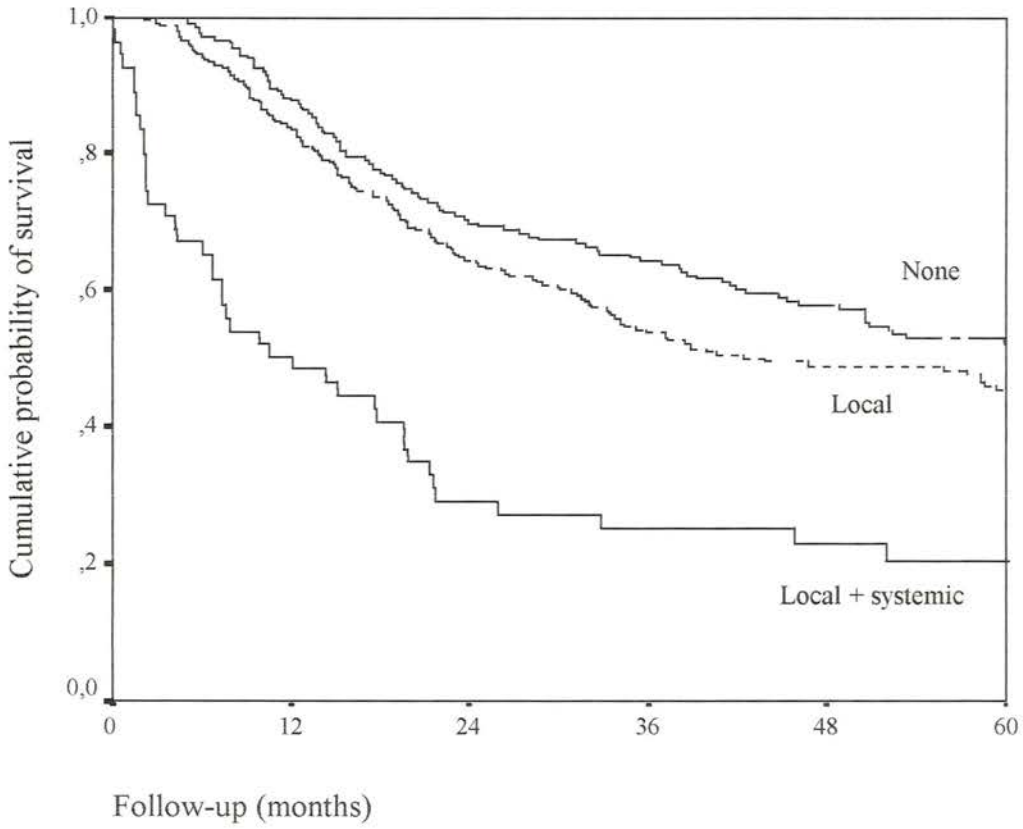

Table 9 Multivariate analysis of predictive variables for 5-year overall survival.

Variable	**Category**	**HR_{crude}**	**$HR_{adjusted}$**	**95%CI $HR_{adjusted}$**	**p**
APACHE II	≤10	1.0	1.0	-	
	>10	1.6	1.3	[1.0-1.7]	0.059
ECSS	1	1.0	1.0	-	
	2	1.6	1.5	[0.8-2.8]	0.238
	3	2.7	2.1	[1.2-3.8]	0.009
	4	4.9	3.4	[2.0-6.0]	<0.001
Type of reconstruction	No/Local flap	1.0	1.0	-	
	Myocutaneous/microvascular flap	2.1	1.6	[1.2-2.1]	0.001
Type of complications	None/Local	1.0	1.0	-	
	Local plus systemic	2.6	2.2	[1.5-3.2]	<0.001

4 DISCUSSÃO

As complicações perioperatórias podem ser definidas como eventos inesperados, que não são conseqüências inevitáveis do procedimento cirúrgico e que ocorrem no momento da cirurgia ou no período pós-operatório (SHAHEEN 1984; ARVIDSSON et al. 1994). As complicações decorrentes das cirurgias para tratamento de câncer de boca e orofaringe acrescem os custos do tratamento, atrasam o início do tratamento adjuvante, aumentam as seqüelas tardias, afetam a qualidade de vida, e podem até causar o óbito dos pacientes se não diagnosticadas e tratadas adequadamente (EVANS 1989).

Nos últimos anos, o risco e a gravidade das complicações perioperatórias têm diminuído devido a avanços nas técnicas cirúrgicas e anestésicas, à introdução de novos antibióticos, a um melhor entendimento do balanço hidroeletrolítico, ao aperfeiçoamento nos métodos de administração de hemoderivados e ao estabelecimento de unidades de terapia intensiva (KOWALSKI et al. 1994a). No entanto, apesar da padronização das indicações de cirurgias na maioria das instituições, as taxas de complicações perioperatórias permanecem elevadas. A identificação dos fatores de risco associados a estas complicações pode reduzir a morbidade e a mortalidade em pacientes com câncer de boca e orofaringe (YODER et al. 1979; PELCZAR et al. 1993; GIROD et al. 1995).

A incidência de complicações perioperatórias em nosso estudo foi semelhante a outras taxas já descritas na literatura (DONALD 1978; YODER et al. 1979; PELCZAR et al. 1993; KOWALSKI et al. 1994a, GIROD et al. 1995). A infecção de ferida operatória (32.4%) e a deiscência (26%) foram as complicações mais

freqüentes. A incidência de infecção de ferida operatória em cirurgia oncológica de cabeça e pescoço, segundo dados da literatura, varia de 0 a 87% (PENEL et al. 1999). Esta variação nas taxas de infecção de ferida cirúrgica pode ser uma conseqüência da falta de um consenso nos critérios para diagnóstico (PENEL et al. 1999). Vários fatores têm sido relacionados a uma maior ocorrência de infecção de ferida cirúrgica em pacientes com câncer de cabeça e pescoço. Tais fatores incluem o estádio avançado da doença, o tipo de reconstrução (ROBBINS et al. 1990), radioterapia pré-operatória (YODER et al. 1979), estado nutricional, comorbidades, duração da cirurgia, classificação do procedimento cirúrgico, consumo de álcool e profilaxia antibiótica (ROBBINS et al. 1990). Em nosso estudo, estádio clínico, comorbidades, alcoolismo, duração da cirurgia e tipo de reconstrução também estavam associados à infecção de ferida operatória, assim como tabagismo e transfusão de sangue. ROBBINS et al. (1990) têm descrito que o uso de drenos, sondas nasogástricas e o emprego de transfusões de sangue são preditores significativos de infecção de ferida cirúrgica, mesmo que este achado possa somente estar relacionado à extensão e à duração da cirurgia (ROBBINS et al. 1990).

As variações no tipo e na duração dos antibióticos utilizados, oriundas da falta de uniformização de um esquema em todo o período analisado, não permitiram que fosse demonstrada a vantagem da adequação da antibioticoterapia profilática em nosso estudo. Contudo, tal benefício já está claramente comprovado, ainda que a literatura ainda seja controversa em relação à escolha das melhores drogas e tempo de utilização (ROBBINS et al. 1979, BRAND et al. 1982, FEE et al. 1984, BECKER 1986; COLE et al. 1987).

O ducto torácico é uma estrutura linfática cervical que conduz o quilo para a veia subclávia. A anatomia deste ducto é variável, e o ducto na maioria das vezes (75%) situa-se do lado esquerdo. A falha na ligadura deste ducto pode causar o aparecimento de uma fístula quilosa. As fístulas com pouca drenagem podem ser tratadas conservativamente (curativo compressivo, drenagem e dieta com ácidos graxos de cadeia média) e as fístulas maiores necessitam de re-exploração cirúrgica (SMULLEN e LEJEUNE 1999). A incidência de fístula quilosa deste estudo é similar à descrita por outros autores (SMITS et al. 1972; MYERS e DINERMAN 1975; CRUMLEY e SMITH 1976; YODER et al. 1979), enquanto para a incidência de hematoma, taxas menores (GALL et al. 1977; YODER et al. 1979) e maiores (JOHNSON e CUMMINGS 1978) do que a apresentada em nosso estudo podem ser encontradas na literatura.

Nesta série, a taxa de incidência de pneumonia é baixa quando comparada a outros estudos, onde variou de 7 a 15% (JOYCE e McQUARRIE 1976; PELCZAR et al. 1993; WEBER et al. 1993; McCULLOCH et al. 1997). Esta incidência pode ser ainda maior, quando os pacientes também apresentam doença pulmonar (BENTZ e SNYDERMAN 2000). As complicações perioperatórias sistêmicas mais comuns nos pacientes com câncer de cabeça e pescoço são as complicações pulmonares. A presença de comorbidade grave é um fator de risco independente para a ocorrência das mesmas (SINGH et al. 1999).

Em nosso estudo somente um episódio de infarto agudo do miocárdio foi registrado. Os principais fatores de risco cardiológicos para as complicações cardiovasculares perioperatórias são: doença coronariana, doença valvular cardíaca, cardiomiopatia e insuficiência cardíaca congestiva (BELZBERG e RIVKIND 1999).

Entre os fatores de risco não-cardiológicos podem ser destacados: doenças pulmonares, hipertensão arterial sistêmica, diabetes mellitus, idade e obesidade (BELZBERG e RIVKIND 1999). Os eventos isquêmicos perioperatórios parecem estar relacionados a um aumento do tônus simpático associado a um aumento da freqüência cardíaca observado durante o período de internação. Além disto, as alterações metabólicas, hemodinâmicas e eletrolíticas, que ocorrem nestes pacientes em um curto intervalo, podem desencadear fenômenos isquêmicos agudos. Entre estas alterações estão incluídas a anemia secundária a sangramentos perioperatórios, variações na pressão arterial e as condições propícias para eventos trombóticos associadas ao procedimento cirúrgico (DURAZZO et al. 1999).

Existem várias condições, comumente encontradas em pacientes com câncer, que podem ter um efeito significante no período perioperatório. Estas condições podem ser amplamente categorizadas em anatômicas e funcionais e podem ser resultantes da ação do próprio tumor ou da terapia utilizada. Nos tumores avançados de cabeça e pescoço, uma das alterações anatômicas é a obstrução das vias aéreas. A radioterapia aplicada para o tratamento dos tumores malignos de cabeça e pescoço pode ser responsável pela distorção da anatomia das vias aéreas, além de causar edema e fibrose dos tecidos (LEFOR 1999).

A determinação do risco cirúrgico inclui a realização de exames e testes para estratificar os pacientes nas categorias de baixo, intermediário e alto risco (SCHROEDER 1999). Uma avaliação precisa do risco operatório do paciente proporciona uma determinação mais acurada do prognóstico e a escolha do tratamento mais adequado. O risco de complicações em um grupo de pacientes, calculado por diversos escores, pode ser comparado à real taxa de complicações, com

propósitos de auditoria ou pesquisa (JONES e DE COSSART 1999). Os resultados deste estudo suportam o valor dos índices *Acute Physiology and Chronic Health Evaluation II* (APACHE II) e *Physiological and Operative Severity Score for Enumeration of Mortality and Morbidity* (POSSUM) na predição de complicações perioperatórias. O escore APACHE II é provavelmente o mais conhecido e utilizado na avaliação dos cuidados de terapia intensiva. O sistema APACHE original utiliza 34 variáveis fisiológicas, registrando o pior valor obtido nas últimas 24 horas desde a admissão na Unidade de Terapia Intensiva, combinadas a uma avaliação simples do estado geral de saúde. O APACHE II é uma modificação do sistema original, onde as variáveis fisiológicas foram reduzidas a 12, e escores para idade e avaliação da saúde crônica foram adicionados, resultando em um escore total que pode variar de 0 a 71. O APACHE II foi validado para pacientes de unidade terapia intensiva geral (KNAUS et al. 1985; ROWAN et al. 1994; WONG et al. 1995) e cirúrgica (GIANGIULIANI et al. 1989; BERGER et al. 1992). Além disto, tem sido utilizado para a predição da evolução de pacientes com infecção intra-abdominal (BOHNEN et al. 1988), pancreatite aguda (LARVIN e McMAHON 1989) e hemorragia gastrointestinal devida à úlcera péptica (SCHEIN e GECELTER 1989). Em pacientes submetidos à hepatectomia, por tumor primário ou metastático, o escore APACHE II pré-operatório pode ser usado com sucesso para a predição das taxas de morbidade e mortalidade (GAGNER et al. 1991).

O escore POSSUM foi desenvolvido especificamente para a avaliação de pacientes submetidos à cirurgia. Este índice utiliza 12 variáveis fisiológicas (idade, situação cardiológica, pulso, pressão arterial sistólica, estado respiratório, escala de coma de Glasgow, concentração sérica de uréia, potássio e sódio, concentração de

hemoglobina, contagem de leucócitos e achados do eletrocardiograma) e 6 variáveis operatórias [tipo de procedimento cirúrgico, número de procedimentos, perda sangüínea, contaminação peritoneal, presença de malignidade e a indicação da cirurgia (eletiva ou de urgência)] para o cálculo do risco de morbidade e óbito (COPELAND et al. 1991). Este índice tem servido como instrumento de auditoria para pacientes cirúrgicos em geral, assim como para grupos específicos de pacientes com doenças vasculares, colorretais e câncer de pulmão (COPELAND et al. 1993; SAGAR et al. 1994; BRUNELLI et al. 1999; JONES e DE COSSART 1999) . Em uma publicação recente, o POSSUM foi considerado o mais apropriado entre os escores atualmente disponíveis para avaliação do risco cirúrgico (JONES e DE COSSART 1999).

As complicações perioperatórias locais e sistêmicas podem piorar significativamente o prognóstico (DE MELO et al. 2001). A identificação dos fatores preditivos pode auxiliar o cirurgião a classificar os pacientes com riscos distintos de morbidade e mortalidade perioperatória A prevenção das complicações, por sua vez, pode ser convertida em melhora do prognóstico.

Os sistemas de estadiamento para o câncer têm quatro funções básicas: estimar o prognóstico, auxiliar no planejamento terapêutico, avaliar a efetividade do tratamento e padronizar a nomenclatura utilizada de forma a permitir a comparação de resultados entre diferentes instituições (BEAHRS e MYERS 1983). Entre todas as funções, a correta estimação do prognóstico é a mais importante (PICCIRILLO 1995).

O sistema TNM é universalmente aceito e amplamente utilizado para o estadiamento do câncer. Contudo, o sistema falha por ser baseado somente na

descrição morfológica do tumor e não incluir informações sobre a condição clínica do paciente (PUGLIANO et al. 1999b). Os sintomas relacionados ao câncer (tipo, duração e severidade) (FEINSTEIN 1985) e o estado geral de saúde do hospedeiro (SATARIANO e RAGLAND 1994) são elementos clínicos que representam a gravidade da doença em um paciente. Apesar de não estar diretamente relacionada ao câncer, a comorbidade é um outro aspecto importante, por ser capaz de afetar a escolha do tratamento e, conseqüentemente, o prognóstico (FEINSTEIN 1970; WELLS et al. 1984; CLEMENS et al. 1986; SATARIANO e RAGLAND 1994).

Os sintomas são o resultado da interação entre o paciente e o tumor. Sua influência no prognóstico de vários tipos de câncer já foi descrita (WELLS et al. 1984; CLEMENS et al. 1986). Estudos prévios em câncer de laringe e orofaringe comprovam que os sintomas contribuem com dados prognósticos adicionais, que não são obtidos quando se utiliza somente o estadiamento anatômico (PICCIRILLO et al. 1994; PUGLIANO et al. 1997). Os achados deste estudo, onde sintomas tais como "caroço" no pescoço, otalgia, sangramento bucal, disfagia, emagrecimento e dor são determinantes do prognóstico, corroboram os resultados similares para pacientes com câncer de cabeça e pescoço já publicados na literatura (PUGLIANO et al. 1997, 1999ab; RIBEIRO et al. 2000).

Este estudo comprova o efeito prognóstico da odinofagia em pacientes com câncer de boca e orofaringe (PUGLIANO et al. 1999a). Outros autores descreveram que a presença de odinofagia estava associada à doença avançada, causada por atraso no diagnóstico (KOWALSKI et al. 1994b). No entanto, esta casuística mostra a mesma freqüência do sintoma entre casos iniciais e avançados.

O consumo de álcool permaneceu associado à sobrevida, como já demonstrado em nosso estudo anterior (RIBEIRO et al. 2000), o que reforça a idéia de que a alta prevalência de alcoolismo nos pacientes com câncer de cabeça e pescoço justifica a inclusão desta variável em um sistema de estadiamento (DELEYIANNIS et al. 1996).

O efeito prognóstico dos valores de hematócrito encontrados neste estudo confirma que a anemia moderada é um fator prognóstico independente nos carcinomas de cabeça e pescoço tratados com cirurgia (RIBEIRO et al. 2000) ou exclusivamente com radioterapia (DUBRAY et al. 1996).

O tabagismo foi um fator determinante de mau prognóstico, como já descrito em outros estudos (BUNDGAARD et al. 1994; YU et al. 1997; EL-HUSSEINY et al. 2000). O tabaco parece induzir as células tumorais a tornarem-se mais indiferenciadas e, portanto, mais agressivas (BUNDGAARD et al. 1995). Um estudo americano que analisou 25.436 casos de câncer, originários um registro hospitalar de tumores, comprovou que o tabagismo tem uma importante influência na sobrevida dos pacientes com câncer de boca, pâncreas, mama ou próstata. Nos pacientes com tumores de boca ou pâncreas, este efeito é independente do alcoolismo (YU et al. 1997). Estes resultados reforçam a necessidade de programas de apoio à cessação do tabagismo e alcoolismo, não somente com finalidade preventiva, mas também terapêutica.

Neste estudo, o sexo foi identificado como fator prognóstico, uma vez que as mulheres apresentaram melhores taxas de sobrevida. Esta redução do risco de óbito é independente de outros fatores clínicos, como já relatado por outros autores

(FRANCO et al. 1993; BOFFETTA et al. 1994; FAYE-LUND e ABDELNOOR 1996).

A prevalência de comorbidades aumenta com a idade, o que pode ser a explicação para algumas diferenças que esta última produz no diagnóstico, tratamento e prognóstico do câncer (GREENFIELD et al. 1987; SILLIMAN et al. 1989; BENNETT et al. 1991; LAZOVICH et al. 1991; NEWCOMB e CARBONE 1993). A presença de comorbidades em pacientes com câncer está associada a atraso no diagnóstico, estádios avançados e maior mortalidade (GONZALEZ et al. 2001). As comorbidades podem afetar o estádio ao diagnóstico pelo mascaramento dos sintomas precoces do câncer, o que leva a um diagnóstico tardio. Por outro lado, a presença de comorbidades pode aumentar o número de pacientes que procuram o sistema de saúde e, consequentemente, as oportunidades para rastreamento do câncer ou diminuir a importância da prevenção do câncer, já que as outras doenças servem como demanda competitiva. Vários estudos clínicos têm encontrado baixas taxas de rastreamento de câncer em pacientes com comorbidades.

Além disso, as comorbidades estão associadas a um tratamento menos agressivo e, consequentemente, a um pior prognóstico, mas tem sido demonstrado que as altas taxas de mortalidade não são somente efeitos do tratamento ou da falta deste (PICCIRILLO 2000). Em um estudo realizado nesta instituição, incluindo 808 pacientes com câncer de cabeça e pescoço que não foram submetidos a tratamento oncológico, o "performance status" foi o fator prognóstico mais importante (KOWALSKI e CARVALHO 2000), o que reforça a importância de uma avaliação do estado geral de saúde dos pacientes.

A desnutrição é reconhecida como uma comorbidade em pacientes com câncer (WARREN 1932), e pode afetar 30 a 50% de todos os pacientes com câncer de cabeça e pescoço (VAN BOKHORST-DE VAN DER SCHUEREN et al. 1999). Neste estudo, ainda que a avaliação do estado nutricional tenha sido baseada somente no índice de massa corpórea e na perda de peso anterior ao tratamento, o impacto negativo da má nutrição sobre o prognóstico foi comprovado (BROOKES 1985; VAN BOKHORST-DE VAN DER SCHUEREN et al. 1999).

A classificação ASA do estado físico foi desenvolvida para avaliação pré-operatória do risco de eventos perioperatórios adversos, incluindo a mortalidade (REID et al. 2001) e ,como não necessita de recursos clínicos para sua aplicação, pode ser empregada para todos os pacientes (WOLTERS et al. 1996). A correlação entre a classificação ASA e a morbidade e mortalidade pós-operatória já foi demonstrada em outros estudos (MENKE et al. 1993; WOLTERS et al. 1996). No entanto, esta classificação não é tipicamente usada como um preditor de sobrevida. A associação entre o risco cirúrgico e o prognóstico que foi encontrada neste estudo é mais uma medida que indica a influência do estado funcional na sobrevida, também descrita em um estudo recente incluindo pacientes com câncer de pescoço, no qual a classificação ASA apresentou valor prognóstico comparável, senão maior, ao do índice de comorbidade de Charlson (REID et al. 2001). A falta de consistência na atribuição do risco cirúrgico ASA, descrita em alguns estudos, poderia ser uma restrição ao seu uso como fator prognóstico (OWENS et al. 1978; HAYNES e LAWLER 1995; RANTA et al. 1997; REID et al. 2001). No entanto, como alguns autores já descreveram a classificação ASA como fator preditivo de morbidade e

mortalidade perioperatória, o grau de confiabilidade da classificação não exclui a possibilidade de também usá-la como um índice de comorbidade (REID et al. 2001).

O valor prognóstico da idade, descrito em uma publicação anterior (RIBEIRO et al. 2000) não foi confirmado neste estudo. Tal fato provavelmente deveu-se ao menor número de pacientes idosos com carcinoma de orofaringe presentes nesta amostra. Uma vez que a cirurgia traz consigo um maior risco de complicações perioperatórias, incluindo o risco de aspiração, estes pacientes são freqüentemente tratados exclusivamente com radioterapia.

Este estudo revelou uma melhor habilidade deste novo sistema na predição das taxas de recorrência e sobrevida livre de doença, quando comparado às outras classificações. A sobrevida específica para o câncer e a sobrevida livre de doença foi pior para os pacientes com estádios avançados deste novo estadiamento por severidade clínica, similarmente a um estudo já publicado na literatura, que descreve resultados inferiores para pacientes jovens com câncer de cabeça e pescoço e comorbidade avançada (SINGH et al. 1998). As razões para este fato podem ser: um nível mais baixo de atividade anti-tumoral nos pacientes com comorbidade avançada, ou, simplesmente, um viés do médico no planejamento terapêutico. Estes achados sugerem que um seguimento intensivo é especialmente importante em pacientes com comorbidade avançada, para garantir uma detecção mais precoce das recidivas (SINGH et al. 1998). No entanto, outros estudos para câncer de boca e orofaringe não conseguiram comprovar que o estadiamento por severidade clínica tem bom desempenho na predição de taxas de recorrência (PUGLIANO et al. 1997, 1999b).

O câncer ocupa uma posição especial entre as doenças que afetam os seres humanos e são tratadas pelos médicos. A Oncologia é a única especialidade que trata

somente de uma doença, e o tratamento do câncer tem sido planejado para a doença e não para o paciente doente. Este modelo, contudo, não está estático. As mudanças nos paradigmas científicos da Medicina, assim como novos conhecimentos nas áreas da Psicologia e da Sociologia, têm modificado o conceito de tratamento. O modelo biopsicosocial, que incorpora as múltiplas dimensões da doença em um único indivíduo, vem se integrando à prática clínica oncológica, principalmente através da introdução das equipes multidisciplinares. No entanto, ainda se dá pouca atenção ao fato de que os pacientes com câncer muitas vezes têm várias outras doenças.

As doenças crônicas são a "epidemia do futuro" e têm substituído as doenças infecciosas como principais causas de morbidade e mortalidade. A demografia do envelhecimento aponta duas importantes tendências: o contínuo aumento do número de indivíduos com doenças crônicas e de pessoas com mais que uma doença crônica. A história natural do câncer pode afetar tanto a gravidade quanto a evolução destas outras doenças crônicas (OGLE et al. 2000).

Desta forma, medidas de prevenção primária, que deveriam ser iniciadas precocemente, são atitudes essenciais para a redução da incidência destas doenças. (OGLE et al. 2000) e o início da melhoria do cuidado prestado aos pacientes com câncer seria o reconhecimento da necessidade de tratar o paciente com câncer e não o câncer no paciente.

5 CONCLUSÕES

- O esvaziamento cervical, o tipo de reconstrução cirúrgica e os índices APACHE II e POSSUM foram identificados como fatores de risco independentes para o desenvolvimento de complicações perioperatórias;
- A ocorrência de complicações perioperatórias locais e sistêmicas prejudica o prognóstico dos pacientes e, juntamente com o estádio por severidade clínica, tipo de reconstrução cirúrgica e escore APACHE II constitui o melhor modelo preditivo de sobrevida global em 5 anos;
- Comorbidades, sintomas ("caroço" no pescoço, emagrecimento, disfagia, otalgia, dor, odinofagia e sangramento bucal), sexo, alcoolismo, tabagismo, valor do hematócrito, contagem total de linfócitos, índice de massa corpórea e classificação do risco cirúrgico segundo a ASA tiveram impacto na sobrevida global a 5 anos dos pacientes com carcinoma espinocelular de boca e orofaringe;
- Estas variáveis, adicionadas à classificação TNM, permitiram a criação de um novo sistema de estadiamento por severidade clínica da doença, mais preciso na determinação de sobrevida global a 5 anos, sobrevida específica por tumor a 5 anos, sobrevida livre de doença e taxas de recorrência.

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