CARCINOMA EPIDERMÓIDE DE OROFARINGE: ANÁLISE DE RESULTADOS DO TRATAMENTO CIRÚRGICO EM 2 INSTITUIÇÕES

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RESUMO

Souza TRB. **Carcinoma epidermoide de orofaringe: análise de resultados do tratamento cirúrgico em 2 instituições.** São Paulo; 2012. [Tese de Doutorado-Fundação Antônio Prudente].

O objetivo deste estudo foi avaliar os resultados tardios do tratamento cirúrgico de pacientes com carcinoma epidermóide de orofaringe visando a identificação de fatores prognósticos nessa população. Os prontuários de 325 pacientes tratados nos Serviços de Cirurgia de Cabeça e Pescoço do Hospital A C Camargo e Hospital Heliópolis foram revisados. Todos os pacientes foram submetidos à cirurgia com ou sem radioterapia pós-operatória, de 1990 a 2005. Dois estudos foram realizados, o primeiro com 89 pacientes com lesões em estádios clínico I e II. Neste estudo incluímos 20 pacientes tratados no Hospital de Câncer de Barretos. Trinta e sete pacientes (41,6%) apresentavam tumores em estádio I e 52 (58,4%) em estádio II. Sessenta e dois pacientes (69,7%) foram tratados apenas com cirurgia e 27 pacientes foram tratados com cirurgia e radioterapia pós-operatória (30,3%). Durante o seguimento pós-operatório observamos que: 26,9% dos casos apresentaram recidiva local, 10,1% recidiva regional e 3,4% metástases à distancia. As taxas de sobrevida global e livre de doença aos 5 anos foram de 60,4% e 59,7% respectivamente. O modelo de Cox demonstrou que os fatores prognósticos independentes para sobrevida global foram grau histológico pouco diferenciado e pN2. No segundo estudo incluímos 256 pacientes com lesões ressecáveis em estádios III e IV. Noventa e cinco pacientes (37,1%) tinham tumores estádio III e 161 em estádio IV (62,9%). Cinquenta e cinco pacientes foram tratados apenas com cirurgia e 201 foram tratados com cirurgia e radioterapia pós-operatória (78,5%) Durante o seguimento pós-operatório observamos: 29% de recidiva local, 10,5% de recidiva regional e 7,4% de metástase à distancia. As taxas de sobrevida global e livre de doença aos 5 anos foram de 43% e 54,5%, respectivamente. O modelo de Cox demonstrou que os fatores prognósticos independentes para predição das taxas de sobrevida global foram: tamanho do tumor >3cm, pN+RC+ e presença de intenso infiltrado linfocitário peri-tumoral.

SUMMARY

Souza TRB. **[Oropharyngeal squamous cell carcinoma: outcomes of primary surgical treatment at two head and neck surgery departments]**. São Paulo; 2012. [Tese de Doutorado-Fundação Antônio Prudente].

The purpose of this study was to review the late outcomes of primary surgical treatment of patients with squamous cell carcinoma of the oropharynx, aiming to identify prognostic factors in this population. The records of 325 patients treated at Hospital A C Camargo and Hospital Heliópolis were reviewed. All included patients were treated with surgery with or without postoperative radiotherapy from 1990 to 2005. Two different studies were conducted, the first one with 89 patients who had clinical stage I or II cases. For this study 20 patients treated at Hospital de Cancer de Barretos were included. Thirty-seven patients (41.6%) had tumors at stage I and 52 (58.4%) at stage II. Sixty-two patients (69.7%) had surgery only and 27 patients had surgery and postoperative radiotherapy (30.3%). During follow-up, there were 26.9% local recurrences, 10.1% regional recurrences and 3.4% distant metastasis. The 5-year overall survival rate was 60.4% and the 5-year disease free survival was 59.7%. The Cox model demonstrated poorly differentiated (histological grade) and pN2 as independent prognostic markers for decreased overall survival. For the second study 256 patients who had resectable clinical stage III and IV tumors were included. Ninety-five (37.1%) had tumors at stage III, 161 at stage IV (62.9%). Fifth-five patients had surgery only and 201 had surgery and postoperative radiotherapy (78.5%). During follow-up, there were 29% of local recurrences, 10.5% of regional recurrences and 7.4% of distant metastasis. The 5-year overall survival rate was 43.0% and the 5-year disease free survival was 54.5%. The Cox multivariate model demonstrated tumor size >3cm and pN+ECS+ as independent prognostic markers for decreased OS. The presence of intense lymphocytic infiltrate was associated with higher OS rates.

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LISTA DE SIGLAS E ABREVIATURAS

ASA	American Society of Anesthesiologists - Physical Status Classification System
BT	Brachytherapy
BMI	Body Mass Index
CEC	Carcinoma Epidermóide
CI	Confidence Interval
CT	Chemotherapy
DFS	Disease-Free Survival
DOC	Dead of Other Causes
DOD	Dead of Disease
DSL	Dead of Second Localizations
DSS	Disease Specific Survival
ECS	Extracapsular Spread
ECOG	Eastern Cooperative Oncology Group
HPV	Papiloma Vírus Humano
HPV	Human papillomavirus
HR	Hazard ratio
IC	Intervalo de Confiança
INCA	Instituto Nacional do Câncer
LR	Local Recurrence
NCCN	National Comprehensive Cancer Network
ND	Neck dissection
NED	No evidence of Disease
Oroph	Oropharynx
OS	Overall Survival
OSCC	Oropharyngeal Squamous Cell Carcinoma
PORT	Postoperative Radiation Therapy
QOL	Quality of life
RC	Ruptura capsular de linfonodo
RR	Relative Risk

RT Radiation therapy

RT Radioterapia

SCC Squamous Cell Carcinoma

UICC Union of International Cancer Control

ÍNDICE

1 INTRODUÇÃO

A orofaringe compreende o palato mole, a base da língua, a valécula, as tonsilas palatinas e parede posterior. O câncer de orofaringe ocorre mais frequentemente em tonsilas e base da língua, e é originado das células escamosas, sendo que mais de 90% dos casos são do tipo carcinoma epidermóide (CEC) (FORASTIERE et al. 2001; JEMAL et al. 2006). É diagnosticado em cerca de 136.622 casos anualmente em todo o mundo (BOYLE e LEVIN 2008), é o sexto câncer mais comum em todo o mundo, correspondendo a 4% de todos os cânceres (PARKIN et al. 2005). Nos Estados Unidos foram estimados 13,580 novos casos em 2011 (SIEGEL et al. 2011). Em diversas partes do mundo, especialmente Índia e sudeste da China, o câncer de cabeça e pescoço é o mais comum de todos os tipos de neoplasias malignas. A incidência e mortalidade do câncer oral e da orofaringe têm aumentado em várias regiões do mundo, incluindo Europa, centro-sul da Ásia (particularmente Taiwan e Japão) e Austrália (PARKIN et al. 2005). No Brasil corresponde a 5-8% das neoplasias malignas em homens e 2% em mulheres (FRANCO et al. 1989, Ministério da Saúde 2011).

Os fatores de riscos mais aceitos são o tabagismo e a ingestão de bebida alcoólica, havendo também uma crescente evidência na literatura sobre o papiloma vírus humano (HPV) desempenhando um importante papel na carcinogênese, particularmente no câncer de tonsila (SYRJANEN 2005). Muitos autores têm relatado o aumento de incidência de CEC de orofaringe em adultos jovens assim como a incidência de infecção pelo HPV, enquanto a incidência de câncer da

cavidade oral tem permanecido constante (FRISCH et al. 2000; SYRJANEN 2004; NASMAN et al. 2009; KOFLER et al. 2012). Este fator de risco parece definir uma outra entidade com um comportamento diferente (KLUSSMANN et al. 2003). O carcinoma epidermóide de orofaringe é frequentemente diagnosticado em estádios avançados, tendo prognostico pobre com resultados funcionais e cosméticos regulares, portanto estratégias terapêuticas devem proporcionar não só um bom resultado oncológico, mas também qualidade de vida, uma vez que a orofaringe desempenha importante papel em funções básicas, como respiração, mastigação, deglutição e fala (GILLISON e FORASTIERE 1999).

A conduta terapêutica ideal para o carcinoma epidermóide de orofaringe permanece controversa. Considerando-se os tratamentos com intenção curativa, o controle do tumor e sobrevida são os mais importantes fatores empregados na avaliação de eficácia do tratamento. Em estádios precoces, a cirurgia e a radioterapia oferecem resultados oncológicos comparáveis, enquanto em estádios avançados os pacientes com lesões ressecáveis podem ser tratados com cirurgia radical seguida de radioterapia pós-operatória ou ainda quimioradioterapia com esvaziamento cervical, acreditando-se que duas modalidades radicais de tratamento são mais efetivas do que apenas uma (GALATI et al. 2000; GENDEN et al. 2003; SESSIONS et al. 2003; CARVALHO et al. 2005). As informações provenientes de estudos clínicos de tratamento do câncer de orofaringe são limitadas e nenhum estudo randomizado comparando controle locorregional e sobrevida em pacientes tratados com cirurgia versus quimioradioterapia foi publicado (CHEN et al. 2007). A modalidade de tratamento deve ser individualizada, valorizando-se sintomas de aspiração, obstrução de vias aéreas, comorbidades, nível de compreensão do paciente, suporte social e

habilidade de completar o tratamento (CHEN et al. 2007). Alguns estudos compararam ambos tratamentos e concluíram que a radioterapia é melhor devido às complicações relacionadas ao tratamento cirúrgico (MENDENHALL et al. 2000, PARSONS et al. 2002, CARVALHO et al. 2005). Entretanto, a radioterapia também causa significante morbidade, produzindo mucosite moderada e severa em 80 a 100% dos pacientes, xerostomia, dor e disfagia, que pode ser permanente (TROTTI et al. 2003).

A superioridade da quimioradioterapia em relação à radioterapia exclusiva já está estabelecida (BRIZEL et al. 1998; WENDT et al. 1998; CALAIS et al. 1999; ADELSTEIN et al. 2000). A preservação de órgão através da quimioradioterapia tem sido considerada a modalidade de tratamento de escolha no câncer em estádio avançado em várias instituições por oferecer melhor resultado funcional (CALAIS et al. 1999; MENDENHALL et al. 2000; SELEK et al. 2004; SPRING et al. 2005), e o esvaziamento cervical deve ser realizado em casos que não apresentem resposta completa no pescoço (SU et al. 2002; JONES et al. 2003; SAPUNDZHIEV et al. 2004; KLUG et al. 2005). Outra conduta tem sido proposta: o esvaziamento cervical seguido de radioterapia em pacientes com lesões pequenas na orofaringe e metástase linfonodal (REDDY et al. 2005). Na literatura encontramos taxas de sobrevida global em 5 anos entre 41 e 62%, influenciadas pelo regime da radioterapia, associação de quimioterapia, número de ciclos de quimioterapia, realização de resgate cirúrgico após a radioterapia, assim como condição clínica e presença de comorbidades (CARVALHO et al. 1986; HART et al. 1995; MAK-KREGAR et al. 1996; PEREZ et al. 1998; CALAIS et al. 1999; MENDENHALL et al. 2000; GOURIN e JOHNSON 2001; PARSONS et al. 2002; JONES et al. 2003; SESSIONS et al. 2003;

DENIS et al. 2004; NIJDAM et al. 2005; POULSEN et al. 2007; PEDRUZZI et al. 2008; AGARWAL et al. 2009).

A ressecção cirúrgica seguida de radioterapia adjuvante tem sido frequentemente utilizada nas últimas duas décadas, resultando em controle locorregional e sobrevida razoáveis (ZELEFSKY et al. 1992; DENITTIS et al. 2001; RÖÖSLI et al. 2009). É considerado um tratamento desafiador porque requer suporte multidisciplinar, com apoio nutricional, serviço social, cuidados adequados de enfermagem, terapia de voz e deglutição. Portanto, idealmente deve ser realizado em centros especializados (CHEN et al. 2007). As melhorias nas técnicas cirúrgicas, especialmente na reconstrução com retalho livre microcirúrgico (NETSCHER et al. 2000; SEIKALY et al. 2003; BARATA et al. 2012), têm facilitado a reabilitação destes pacientes e avanços tecnológicos na cirurgia robótica têm tornado a orofaringe mais acessível com menor morbidade pós-operatória (HOCKSTEIN et al. 2005; WEINSTEIN et al. 2010; GENDEN et al. 2011). Publicações relatam taxas de sobrevida global em 5 anos entre 49 a 65% para o grupo de pacientes tratados com cirurgia seguida ou não de radioterapia pós-operatória, taxas estas influenciadas por fatores como sexo, condição clínica, estádio T e N, presença de margens comprometidas e ruptura capsular linfonodal (ZELEFSKY et al. 1992; FOOTE et al. 1993; GÓIS FILHO e RAPOPORT 1995; MAK-KREGAR et al. 1996; MACHTAY et al. 1997; PEREZ et al. 1998; DENITTIS et al. 2001; PARSONS et al. 2002; JONES et al. 2003; LACCOURREYE et al. 2005; POULSEN et al. 2007; PREUSS et al. 2007a e b; LIM et al. 2008; MOORE et al. 2009).

Em nosso meio CARVALHO et al. (1986) estudaram pacientes com lesões avançadas de orofaringe tratadas com quimioterapia intra-arterial e radioterapia

primária e observaram sobrevida de 16,5% em 2 anos. Ainda nos anos 80 à procura de melhores resultados oncológicos iniciou-se mudança na conduta terapêutica com a maior utilização do tratamento cirúrgico, apresentando avanços significativos nos resultados de sobrevida a longo prazo (GÓIS FILHO 1993; GÓIS FILHO e RAPOPORT 1995; FRANZI 2002). No estudo de GÓIS FILHO E RAPOPORT (1995) a sobrevida global aos 5 anos foi de 46% com o tratamento cirúrgico seguido ou não de radioterapia em pacientes portadores de câncer da região tonsilar. Mais recentemente PEDRUZZI et al. (2008) observaram que os resultados da radioterapia e da radioterapia associada à quimioterapia em carcinoma epidermóide de orofaringe são desfavoráveis com taxas de sobrevida global de 17,4% e 19,2%, respectivamente. A grande experiência no tratamento cirúrgico tem mostrado que, com a abordagem multidisciplinar, muitos pacientes são reabilitados, apresentando melhores resultados quanto à qualidade de vida e satisfação com os resultados (MAGRIN et al. 1996; VARTANIAN e KOWALSKI 2009; VARTANIAN et al. 2010). No entanto, não foram publicados até o presente resultados, que além de sobrevida avaliassem resultados funcionais em uma grande série de pacientes. Dois Serviços de Cirurgia de Cabeça e Pescoço de São Paulo empregam a cirurgia como tratamento principal até os anos recentes. A combinação de dados dessas duas instituições pode proporcionar uma análise detalhada dos resultados do tratamento cirúrgico, podendo contribuir para a discussão do porque desse tratamento no câncer de orofaringe.

2 OBJETIVO

Avaliar os resultados tardios do tratamento cirúrgico do carcinoma epidermóide de orofaringe, visando à identificação de fatores prognósticos nessa população.

3 PACIENTES E MÉTODOS

Selecionamos 325 pacientes com carcinoma epidermóide de orofaringe, admitidos e submetidos ao tratamento cirúrgico com intenção curativa, entre 1990 e 2005, nos serviços de Cirurgia de Cabeça e Pescoço do Complexo Hospitalar Heliópolis (150 casos) e do Hospital A C Camargo (175 casos). Foram considerados elegíveis para o estudo os pacientes que preencheram os seguintes critérios: carcinoma epidermóide de orofaringe e cujo tratamento inicial tenha sido a cirurgia com intenção curativa realizada nas instituições participantes. Os critérios de exclusão: presença de metástase à distancia, qualquer tipo de tratamento prévio e antecedente de qualquer outro tipo de câncer.

Após a seleção dos casos, foram coletadas informações dos prontuários, referentes a dados demográficos, clínicos, de tratamento e histológicos (Anexo 1: ficha de coleta de dados). Realizamos a revisão histológica dos casos, feita por 2 patologistas, Dr. Clóvis Antonio Lopes Pinto do Hospital A.C. Camargo e Dra. Ana Maria da Cunha Mercante do Hospital Heliópolis. Em aproximadamente 20% dos casos a revisão histológica não foi possível pela qualidade na coloração das laminas e os blocos de parafina não foram encontrados. Após a revisão dos prontuários e das lâminas os casos foram reestadiados de acordo com o TNM, (SOBIN e WITTEKIND 2004).

A realização do estudo não acarretou custos às instituições. O projeto foi aprovado pelos Comitês de Ética em Pesquisa dos Hospitais Heliópolis e A.C.

Camargo. Solicitamos a dispensa de termo de consentimento livre e informado, pois se tratou de estudo retrospectivo e garantiu-se o anonimato dos pacientes envolvidos.

Após o levantamento dos dados a casuística foi avaliada e decidimos por dividir o estudo em dois, o primeiro com os casos de estadiamento inicial e o segundo com os casos avançados (estádios III e IV).

Para o estudo de casos iniciais selecionamos 89 casos, sendo 38 pacientes do Hospital Heliópolis, 31 do Hospital A C Camargo e incluímos também 20 pacientes do Hospital de Câncer de Barretos.

Para o segundo estudo selecionamos 256 pacientes, sendo 144 do Hospital A.C. Camargo e 112 do Hospital Heliópolis.

Análise estatística: o tempo de seguimento foi considerado da data da cirurgia até a data de óbito ou a data da última informação. Para a análise de sobrevida livre de doença calculamos o tempo decorrido da cirurgia até a ocorrência de recidiva. A perda de seguimento ocorreu em 15% dos casos. A técnica de Kaplan-Meier foi utilizada para estimar as probabilidades de sobrevida global e livre de doença (KAPLAN e MEIER 1958) e o teste de Log-Rank foi adotado para a comparação das curvas de sobrevida. O nível de significância de 5% foi considerado para todos os testes estatísticos. O modelo de regressão de Cox foi utilizado para estimar os riscos relativos para óbito e seus respectivos intervalos de confiança de 95% (IC 95%), e através do modelo multivariado, visando identificar os possíveis e potenciais fatores prognósticos independentes. O software STATA 10.0 foi utilizado em todas as análises estatísticas.

4 ARTIGO 1

4.1 Outcomes of Primary Surgical Treatment of T1-T2 N0 Squamous Cell Carcinoma of the Oropharynx

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Abstract

Objective: To review the oncologic outcomes of patients with early-stage squamous cell carcinoma of the oropharynx, who underwent surgical treatment with or without postoperative radiotherapy. **Design**: Retrospective cohort study of patients treated from 1990 to 2005. **Setting**: Tertiary referral centers. **Patients**: The records of 89 patients, 79 (88.8%) men and 10 women with a median age of 57.9 years, who had clinical stage I or II squamous cell carcinoma of the oropharynx were reviewed. Statistical analyses included univariate and multivariate survival analysis. **Results**: Thirty-seven patients had tumors at stage I and 52 at stage II. Sixty-two patients had surgery only, 27 had surgery and postoperative radiotherapy. During follow-up, there were 24 (26.9%) local recurrences, 9 neck recurrences (10.1%), and 3 distant metastasis (3.4%). Twenty-eight patients (31.4%) presented second primary cancers. The 5-year overall survival rate was 60.4%. Statistically significant differences were demonstrated for: age (p=0.0441), histological grade (p=0.0076), muscular infiltration (0.0301) and desmoplastic reaction (p=0.0038). The 5-year disease free survival rate was 59.7%. Univariate analysis demonstrated impact of age (p=0.0006) and status of surgical margins (p=0.0117) on the incidence of recurrences. The Cox model demonstrated poorly differentiated (histological grade) and pN2 as independent prognostic markers for decreased overall survival. **Conclusions**: Long term results of surgery on T1-T2 N0 oropharyngeal squamous carcinoma are as good as reported for radiotherapy. Moreover, surgery alone makes it possible to spare patients the complications and aftereffects of radiotherapy. Selected patients with loco-regional and second primary cancers can be salvaged by surgery performed in a non-radiated area.

Key words: oropharynx, squamous cell carcinoma, surgical treatment, survival, surgery, prognosis, complications

Introduction

The management of patients with primary oropharyngeal squamous cell carcinoma (SCC) remains controversial. It is often stated that radiation therapy (RT) and surgery are equally effective for the treatment of patients with early-stage disease [1,2]. Studies with T1 to T4 patients comparing both treatments have concluded that RT is better owing to the complications linked with surgical treatments [3,4], but this treatment, however, cannot also be done without significant morbidity. RT produces moderate to severe mucositis in 80- 100% of patients [5], in addition to xerostomia, which may be permanent. Progressive fibrosis of normal surrounding tissues may impact on the functions of speech and swallowing [6]. Osteoradionecrosis can be a significant long-term problem [7]. Furthermore, radiation-induced malignancy and permanent xerostomia are very important considerations in young patients [8].

Several studies showed that surgery alone in the treatment of early-stage lesions has at least comparable oncological results, while at the same time avoiding the aftereffects of radiotherapy and keeping this therapeutic weapon for subsequent oncological occurrences (recurrence or second primary cancer), which often occur in these patients [1,9,2,10,11]. Difficulties with access to the oropharynx and the morbidity of mandibular splitting surgery have argued against primary surgery [12,13], but a transoral approach without mandibulotomy and technological advances in robotic surgery and endoscopic CO2 laser resection may make this region more accessible with improved functional outcomes [12,13,14,15].

The purpose of this study was to review the oncologic outcomes of patients with early-stage SCC of the oropharynx who underwent surgical treatment with or without postoperative RT at three Head and Neck Surgery Departments.

Patients and methods

The records of 89 patients, 79 (89.8%) men and 10 women with a median age of 57.9 years (range: 42-80), who had clinical stage I or II squamous cell carcinoma of the oropharynx were reviewed. The patients were treated from 1990 to 2005, in 3 tertiary care departments: 38 patients at Heliopolis Hospital, 31 at A C Camargo Hospital and 20 at Barretos Cancer Hospital. The cases were usually presented and discussed at a multidisciplinary head and neck board including surgeons, radiation and medical oncologists, speech therapists, social workers and nurses. In one institution (Heliópolis Hospital) radiation oncologists were not always participating of the discussions. In the same period of study patients with tumors that could be difficult to expose, poor surgical risk patients and those who preferred not be operated were submitted to radiotherapy. The results of radiotherapy or radiochemotherapy from one institution (Hospital A C Camargo) were previously published by Pedruzzi et al. [16], and from Heliópolis Hospital by Carvalho et al [17]. The patients were informed about the options. A written informed consent became practice during the 1990's.

The eligibility criteria for inclusion in the study were: patients with histologically confirmed diagnosis of clinical stages I and II SCC of the oropharynx; patients not previously treated; and patients that did not have other previous primary tumors. In this study demographic factors (age, gender, race), clinical factors (tumor

site, stage), therapeutic factors (surgical approach, neck dissection, mandibulectomy, reconstruction, complications, hospital stay, nasogastric tube use and time of removal, tracheotomy use and time of decannulation, food intake status, postoperative radiotherapy) and reviewed pathological factors (pT, tumor size, histological grade, tumor thickness, surgical margins, muscular infiltration, vascular embolization, perineural infiltration, desmoplastic reaction, lymphocytic infiltrate, pN) were analyzed.

Thirty-seven 37 cases (41.6%) were at stage I and 52 (58.4%) stage II. The tumor was located in the tonsillar fossa in 50 cases (56.2%), soft palate in 35 cases (39.3%), base of the tongue in 3 cases (3.8%) and posterior pharyngeal wall in 1 case. The principles of surgical techniques employed in our patients were previously established by Barbosa [18] and consisted in a wide resection of the soft palate or tonsil with wide clear margins. In selected cases of tonsil carcinoma, the tonsil, tonsillar pillars and pharyngeal constrictor muscle are removed en bloc. In base of the tongue cancers, a suprahyoid access was performed. A mandibulectomy was usually not necessary and in the most recent cases it was avoided in most cases. Most of the mandibulectomies that were done at the initial part of the study, and 8 out of 12 were marginal mandibulectomy. Mandibulotomies were done at surgeon's discretion aiming to get wide exposure allowing resection with free margins.

Sixty-two patients had surgery only (69.7%). Surgical treatment consisted in a resection by transoral approach in 57 patients (64%); pull-through (resection of primary tumor en bloc with neck dissection, preserving the mandible) in 2 patients; via a lip-split with median, paramedian or lateral mandibulotomy in 25 patients (28.1%); via a lip-split without mandibulotomy in 3 patients; lateral pharyngotomy in

2 cases. An elective ipsilateral neck dissection was performed in 48 patients (53.9%) and a contralateral neck dissection was performed in 4 cases. Reconstruction of the primary defect was achieved by primary closure in 81 patients (91%), local flap in 1 patient, myocutaneous flap in 2 patients (2.2%) and free-flap in 5 patients (5.6%).

Temporary feeding tubes were placed in 68 patients and all but one patient had the tubes removed, after a mean time of 25 days (range from 2 to 413 days). Temporary tracheostomy was done in 32 patients, and it was needed for a mean duration of 24 days (range: 2-351 days, 31 were decannulated). The median hospital stay was 5.5 days (range 1-36).

Adjuvant RT was given to 27 patients (30.3%). Postoperative RT was indicated in cases with close or involved margins, perineural infiltration and metastatic lymph nodes diagnosed in the surgical specimen (pN+). The primary site was treated with a median dose of 62.7Gy (range 50-70Gy).

The microscopic slides were reviewed by one pathologist at each institution using to the following criteria: (1) histological grade determined on the basis of classification proposed by the World Health Organization [19]; (2) tumor thickness; (3) muscular infiltration; (4) desmoplastic reaction; (5) inflammatory infiltrate; (6) vascular embolization (classified according to the presence or absence of tumor cells, located both in the wall and in the light of the blood or lymphatic vessels); (7) perineural infiltration (considered present when the tissue adjacent to the peri and/or intra-tumoral nerves were involved by tumor cells); (8) surgical margins (considered involved when the presence of invasive carcinoma and/or carcinoma “in situ” on the margins of the mucosa). After the review, the tumors were re-staged according to the criteria of the *International Union Against Cancer* (UICC 2002) [20]: pT1: 41 cases

(46.1%), pT2: 46 cases (51.7), pT3: 2 cases and pN0: 34 cases (43.8%), pN1: 6 cases (6.7%), pN2: 8 cases (9%) and 41 (46.1%) patients did not undergo elective neck dissection. The size of tumor in pT3 cases was of 5 cm. Of the cases that could be reviewed, muscular infiltration was found in 28 of 54 cases (31.5%), vascular embolization was found in 2 of 82 cases (2.4%), lymphatic embolization in 19 of 82 cases (23.2%), perineural infiltration in 9 of 82 cases (11%), involved margins in 9 of 79 cases (11.4%), intense desmoplastic reaction in 8 of 68 cases (11.8%) and discrete inflammatory infiltrate in 22 of 67 cases (32.8%). In 26 cases (30.9%) the histological grade was well differentiated (Grade I), in 44 cases (52.4%) moderately and 14 poorly (16.7%) differentiated (Grades II and III) (Table 5). Extracapsular spread was found in 11 of the 14 cases with metastatic lymph nodes (78.6%).

Statistical analysis: the follow up time was considered from the date of surgery to the date of death or the last information for censored cases. The overall and disease free survival probabilities were estimated using the Kaplan-Meier method and the log-rank test was performed to verify the differences among survival curves. The 5% level of significance was considered for statistical tests. Prognostic factors, risk of death and respective 95% confidence intervals were estimated by Cox regression model. The statistical computer software STATA release 10.0 was used to perform all statistical analysis [21].

Results

A total of 25 patients (28.1%) were treated in the first period of data collection (from 1990 to 1997) and 64 (71.9%) during the second period (1998-2005). There were no cases treated in Barretos Hospital during the first period, and

there were less patients treated in A.C. Camargo Hospital during the first period than in the second. At Heliopolis and A.C. Camargo Hospitals most cases were sited at tonsil, T2 and submitted to elective neck dissection. On the contrary, at Barretos Hospital most cases were sited at the soft palate, T1 and not submitted to an elective neck dissection. Most mandibulectomies were done in the first period. Although the rates of involved surgical margins did not varied according to the institution and period of treatment, most patients who underwent postoperative radiation were treated during the first part of the study in Heliópolis and A.C. Camargo Hospitals (Table 1).

After the feeding tube removal, 42 patients have not showed swallowing complaints, 9 patients have been eating only soft foods and 2 patients only liquids. From the 11 patients with swallowing complaints, a mandibular intervention had been performed in 6 cases (54.5%), 8 had T2 lesions (81.8%) and adjuvant RT was indicated in 5 cases (45.4%). The overall rate of surgical complications was 35.9%. These included delayed wound healing (12.4%), wound collections (10.1%), wound infections (6.7%), shoulder pain (7.9%), mandibular pain (4.5%), pulmonary infection (2.2%) and alcoholic abstinence (2.2%). There was 1 patient with skin necrosis followed by bleeding and death.

The median follow-up time was 49.3 months (range: 1-184 months), in this period there were 46 deaths: 18 patients have died of cancer, 15 died of second primary cancer (4 lung, 3 oropharynx, 2 gastric, 2 esophagus, 1 mouth, 1 larynx, 1 prostate, 1 skin) and 13 died of other non cancer causes: 2 pulmonary diseases, 3 cardiovascular, 1 malnutrition, 7 undetermined or unknown. Recurrences occurred in 33 patients (37.1%), within a period of 1 to 87 months with a median of 11 months.

The incidence of distant metastasis was of 3.4% (all 3 in patients with local or locoregional recurrences). There were 24 local recurrences (26.9%), including 2 patients with locoregional (local and neck) lesions, 1 patient with local recurrence and distant metastasis, and 1 patient with locoregional lesions and distant metastasis. The primary tumor was cT1 in 9 patients, cT2 in 15 patients, tonsil in 19 patients and soft palate in 5 cases; 6 patients had involved surgical margins when initially treated. The salvage treatment of these events was salvage surgery in 14 cases, radio-surgical associations in 2 cases, RT in 3 cases and 5 were not candidates for further treatment. Nine of these 24 patients are alive without further evidence of the disease, 11 patients died of cancer, 1 was without evidence of disease but has died of non cancer related cause and 1 died after treatment of a second primary cancer (Table 2).

There were 9 regional (neck) recurrences (10.1%), including 1 patient with associated distant metastasis, within a period of 23 days to 24 months (mean time of 9 months). They occurred mainly in the group not initially submitted to elective neck dissection (only one patient had neck dissection); the primary tumor was cT1 in 5 patients, cT2 in 4 patients, tonsil in 1 patient and soft palate in 8 cases. The treatment of these events was surgery in 5 cases and radio-surgical associations in 4 cases. Three patients are alive without evidence of disease, five patients have died of cancer and 1 patient died after the treatment of a second primary cancer (Table 2).

Twenty-eight patients presented second primary cancers (31.5%), the median time was 34.8 months (range 1-101 months). The localizations were: 6 oropharynx, 4 oral cavity, 4 larynx/hypopharynx, 4 esophagus/stomach, 4 lung, skin 3 cases and prostate in 3 cases. The main treatment of these second primary cancers was surgery in 18 cases, RT in 4 cases and 6 patients were not treated. Fifteen have died of

second cancer (53.6%), 4 died of the primary oropharygeal cancer, 3 died of non cancer related causes and 6 patients are alive and free of disease.

The 5-year overall survival (OS) rate was 60.4% (Figure 1). Regarding the univariate analysis, statistically significant differences were demonstrated for: age (p=0.0441), histological grade (p=0.0076), muscular infiltration (p=0.0301) and desmoplastic reaction (p=0.0038) (Tables 3, 4 and 5, Figure 2). The 5-year disease-free survival (DFS) rate was of 59.7% (Figure 1). Univariate analysis demonstrated impact of age (p=0.0006) and status of surgical margins (p=0.0117) on DFS (Tables 3, 4 and 5). The 5-year DFS was of 27.4% for cases with positive margins and 63.2% for negative margins. There was a survival difference between the group of cases with tumor thickness ≤4mm (86.1%) and thickness >4mm (50.9%), but it was not statistically significant (p=0.0733). There was no significant survival difference when comparing other factors: T1 or T2 (p=0.4424), localization of tumor (p=0.7289) and perineural infiltration (p=0.1486).

The multivariate Cox model demonstrated poorly differentiated (histological grade) (hazard ratio 3.89 [95% CI 1.4-10.6]) and pN2 (hazard ratio 3.03 [95% CI 1.4-7.3]) as independent prognostic markers for decreased OS (Table 6).

Discussion

This is a retrospective study analyzing the therapeutic results in 89 consecutive patients with oropharyngeal SCC who underwent conventional primary surgery with or without adjuvant RT at 3 tertiary cancer center institutions. The treatment of patients with primary T1 and T2 lesions of the oropharynx is still controversial, and it is noted that the decision between surgery or RT as primary

therapy depends on the primary tumor characteristics (location, size), the institutional and patient´s preferences [3,4,22]. The advantages of each treatment modality should be considered, with the goal of achieving the best oncologic and functional results [4,23,24].

In the literature, the assessment of survival in accordance with tumor staging and treatment is difficult to make. Parsons et al., in a systematic review, compared the results of surgery with or without RT versus RT with or without neck dissection and observed similar rates for both local and locoregional control and 5-year OS for all stages of the disease, the 5-year survival for T1 ranged from 76%-94% and for T2 from 63 to 81% for both treatment modalities [4]. Other series of patients with T1 to T2 lesions treated with RT showed a range of 5-year survival from 36% to 83% [7,16,25,26,27]. Few studies on early-stage lesions treated with surgery have been published. Cosmidis et al. in a European multicenter study, showed a disease-specific survival rate of 100% in T1 or T2 without lymph node metastasis [2]. Moncrieff et al. in a retrospective study on T1 to T2 tumors with any type of lymph node involvement treated with primary surgery, showed 5-year survival of 83% [10]. In our study, the 5-year OS rate was of 60.4%.

Few authors have studied prognostic factors specifically in early-stage lesions of the oropharynx: Walvekar et al. found difference in DFS between cT1 and cT2 tumors, but it was not statistically significant (p=0.06) [8]. Moncrieff et al. observed worse prognosis in cN3 lesions [10] and Cosmidis et al. found no significant factors [2]. In our study, we observed some factors associated with better DFS: age < 45 years, tumor thickness ≤ 4 mm and free resection margins. The factors associated with better OS were age < 45 years, tumors with well-differentiated histological

grade, without muscular layer infiltration (superficial lesions) and discrete or moderate desmoplastic reaction. Histological grade and pN stage were independent prognostic factors found in the OS analysis. We observed occult lymph node metastasis in 15.7%, while 46.1% of patients did not undergo neck dissection (pNx) due to the lack of uniformity to perform a neck dissection among the 3 institutions (in one of the institutions, neck dissection was performed in only 10% of the cases). We noted that regional recurrences occurred mainly in patients not submitted to elective neck dissection. Taking into account the occurrence of lymph node metastasis is frequent even in early-stage lesions, elective neck dissection is essential both in staging and treating these lesions, allowing the selection of patients requiring adjuvant therapy [1,28,8].

T1-T2 lesions can be resected by transoral access, with the same oncologic results of surgery with mandibulotomy, but with a reduction in hospitalization, tracheotomy and nasoenteral tube time [12,13]. Recently, Holsinger et al. and Weinstein et al. have showed that transoral robotic surgery allows better visualization and access to tumors via a minimally invasive and less morbid approach [12,15]. In our study, transoral resection was achieved in 64% of the cases, with only 8% having needed reconstruction of primary defect; mandibulectomy was performed in 13.5% of the cases. The median hospital stay was of 5.5 days and most of the surgical complications were solved in this period. Eleven patients were able to eat only liquid or soft diet, of these cases a mandibulotomy or mandibulectomy was performed in 54.5% and adjuvant RT in 45.4%. Our data has limitation because it is a retrospective study and an objective assessment of swallowing and speech as proposed by Mlynarek et al. was not a routine [24]. A specific study on functional

results after palate resection and reconstruction from Hospital A C Camargo was recently published [23].

Even with the latest strategies (modern techniques), RT is a treatment modality with late toxicity: xerostomia and fibrosis, causing dysphagia, pain, speaking difficulties, radiation caries and osteoradionecrosis [6]. In our study, 69.7% of the patients were treated with surgery alone, avoiding additional morbidity of adjuvant RT.

The highest rate of second primary tumor in head and neck occurs in primary lesions of the oral cavity and oropharynx, ranging from 20 to 29% [29,30,2,11]. In our study, 31.5% of the patients developed second primary tumors; therefore, if RT had been used as primary treatment, it could not be used in other primary tumors or recurrences.

In our previous study we reported a overall survival rate of 62.5% for cT1 and 36.2% for cT2 oropharyngeal cancer after radiation or chemoradiaton therapy [16]. Although survival results of surgery were similar to the already described for non-surgical treatment, surgery alone improves staging and spares patients the complications and sequelae of RT. It also allows salvage surgery due to loco-regional recurrences or the very frequent second primary cancers in a non-radiated area with lower morbidity and mortality, with the possibility of keeping RT to treat these frequent events.

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Table 1: Distribution of cases according to the period of treatment, institution, and selected clinical, pathological and therapeutic variables.

	1990-1997			1998-2005			
Institution	**Heliópolis**	**ACCamargo**	Total	**Heliópolis**	**ACCamargo**	**Barretos**	Total
Number of cases	16	9	25	15	29	20	64
Site							
tonsil	10	7	17	7	19	8	34
base	1	1	2	0	1	0	1
soft palate	5	1	6	8	9	12	29
cT							
cT1	3	3	6 (24%)	6	13	12	31 (48.4%)
cT2	13	6	19	9	16	8	33
Neck dissection							
Yes	11(68.7%)	7(77.8)	18 (72%)	10(66.7%)	18(62%)	2(10%)	30 (46.9%)
No	5	2	7	5	11	18	34
RT							
Yes	8(50%)	2(22.2%)	10 (40%)	4 (6.9%)	6 (20.7%)	7 (35%)	17 (26.5%)
No	8	7	15	11	23	13	47
Surgical margins							
Free	14	8	22 (88%)	14	26	18	58 (90.6%)
Involved	2	1	3	1	3	2	6
Mandibulectomy							
Marginal	2	2	4	0	4	0	4
Segmentar	0	3	3	0	1	0	1

Table 2. Outcome according to Local and Regional Recurrences and Site of Primary Tumor

	N. patients	NED	DOD	DSL	DOC
Local Recurrences					
Site					
Tonsil	19/50	6	10	1	2
Base of tongue	0/3	0	0	0	0
Soft palate	5/35	2	2	0	1
Posterior wall	0/1	0	0	0	0
Total	24/89	8	12	1	3
Regional Recurrences					
Site					
Tonsil	1/50	0	1	0	
Base of tongue	0/3	0	0	0	
Soft palate	8/35	3	4	1	
Posterior wall	0/1	0	0	0	
Total	9/89	3	5	1	

Abreviations: NED, no evidence of disease; DOD, dead of disease;
DSL, dead of second localization; DOC, dead of other causes.

Table 3. Survival rates according to demographic and clinical factors

Variables	Categories	5-y DFS	P	5-y OS	P
	N (%)				
Gender	Male 79 (89.8)	61.5	0.9394	58.5	0.1622
	Female 10 (11.2)	46.0		77.1	
Age (years)	≤ 45: 9(10.1)	55.6	0.0006	76.2	0.0441
	46 – 65: 60 (67.4)	72.4		63.3	
	> 65: 20 (22.5)	18.9		44.2	
Race	White 69 (80.2)	58.9	0.4672	62.8	0.7468
	Non white 17 (19.8)	69.7		57.6	
T stage	T1: 37 (41.6)	62.5	0.6391	59.3	0.8567
	T2: 52 (58.4)	56.6		60.9	
Site	Tonsil 50 (56.2)	60.4	0.7289	64.2	0.1248
	Base of tongue 3 (3.4)	100.0		33.3	
	Soft palate 35 (39.3)	55.4		58.4	
	Posterior wall 1 (1.1)	100.0		100.0	

DFS: Disease-Free Survival, OS: Overall Survival

Table 4. Survival rates according to treatment characteristics

Variables	Categories N (%)	5-y DFS	P	5-y OS	P
Surgical Approach	transoral 57 (64)	52.5	0.2267	58.0	0.6430
	others 32 (36)	66.2		68.4	
Neck Dissection	ND 48 (53.9)	63.1	0.7438	67.8	0.8839
	Without ND 41 (46.1)	54.7		49.5	
Mandibulectomy	Yes 12 (13.5)	83.3	0.1982	68.6	0.3338
	No 77 (86.5)	60.0		59.4	
Reconstruction	Yes 8 (9)	85.7	0.2099	73.3	0.7425
	No 81 (91)	62.0		60.0	
Complications	Yes 32 (36.0)	74.0	0.1479	62.2	0.1631
	No 57 (64.0)	52.5		58.6	
Postoperative Radiotherapy	Yes 27 (30.3)	69.0	0.1399	63.0	0.5051
	No 62 (69.7)	54.6		58.4	

DFS: Disease-Free Survival, OS: Overall Survival, ND: Neck Dissection

Table 5. Survival results according to pathologic variables

Variables (N)*	Categories N (%)	5-y FDS	P	5-y OS	P
pT stage (89)	pT1: 41 (46.1)	60.1	0.4424	62.2	0.8805
	pT2: 46 (51.7)	56.5		56.9	
	pT3: 2 (2.2)	100		100	
pN stage (89)	pN0: 34 (38.2)	62.3	0.7961	72.3	0.0874
	pN1: 6 (6.7)	81.8		83.3	
	pN2: 8 (9)	51.4		37.5	
	Without ND: 41(46.1)	54.7		49.5	
Histological Grade (84)	Grade I: 26 (30.9)	54.4	0.6144	79.7	0.0076
	Grade II: 44 (52.4)	56.4		54.2	
	Grade III: 14 (16.7)	65.7		37.5	
Size (82)	≤ 1cm: 13 (15.8)	72.3	0.2961	67.9	0.8257
	1.1 - 2cm: 25 (30.5)	56.2		66.2	
	>2cm: 44 (53.7)	61.9		60.2	
Thickness (76)	≤ 4 mm: 16 (21)	86.1	0.0733	54.2	0.7179
	> 4mm: 60 (78.9)	50.9		55.5	
Muscle Infiltration (54)	No 26 (48.1)	50.5	0.5105	66.0	0.0301
	Yes 28 (51.8)	63.6		56.5	
Surgical Margins (79)	Uninvolved 70 (88.6)	63.2	0.0117	62.0	0.2363
	Involved 9 (11.4)	27.5		44.4	
Vascular Embolization (82)	No 80 (97.6)	59.6	0.3199	58.3	0.9763
	Yes 2 (2.4)	50		50.0	
Lymphatic Embolization (82)	No 63 (76.8)	61.3	0.2972	58.1	0.6379
	Yes 19 (23.2)	51.0		56.9	
Perineural Infiltration (82)	No 73 (89.0)	56.2	0.1486	58.2	0.1532
	Yes 9 (11)	87.5		44.4	
Desmoplastic Reaction (68)	discrete 32 (47.1)	51.8	0.9439	60.6	0.0038
	moderate 28 (41.2)	58.0		63.1	
	intense 8 (11.8)	33.7		25	
Inflammatory Infiltrate (67)	discrete 22 (32.8)	46.6	0.4497	58.2	0.7665
	moderate 31 (46.3)	56.3		57.2	
	intense 14 (20.9)	57.1		52.5	

*(N): number of cases revised, DFS: Disease-Free Survival, OS: Overall survival, ND: Neck Dissection

Table 6. Cox regression model for the risk of death

Variables	Categories	HR (95% CI)	RR (95% CI)
Histological Grade	I	1.0 (ref.)	1.0 (ref.)
	II	3.18 (1.4 - 7.3)	3.36 (1.4 -7.9)
	III	3.89 (1.2 – 10.6)	4.22 (1.5 – 11.9)
pN	pN0	1.0 (ref.)	1.0 (ref.)
	pN1	1.41 (0.5 -4.2)	1.41 (0.5 -4.3)
	pN2	3.03 (1.4 – 7.3)	3.25 (1.3 – 8.1)
	pNx	1.23 (0.6 – 2.4)	1.40 (0.7 – 2.9)

HR: Hazard ratio, RR: relative risk, ref.: reference category, 95% CI: 95% confidence interval

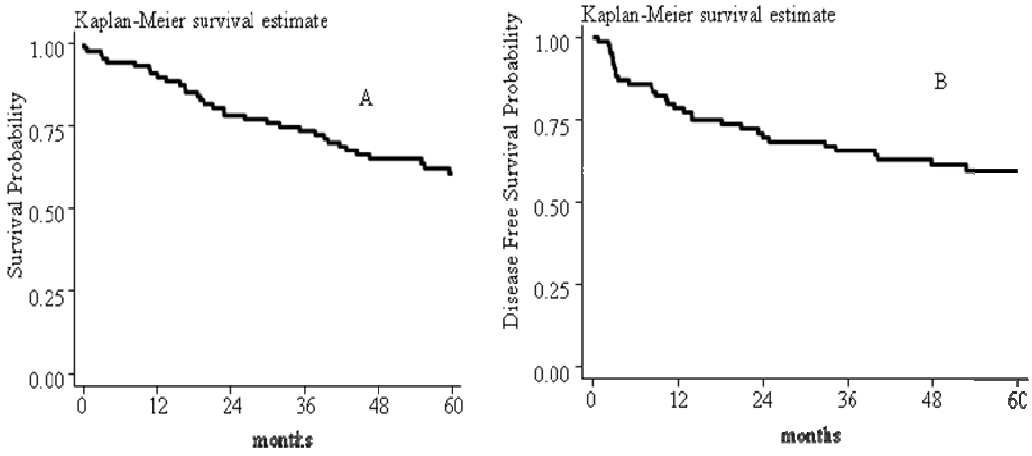

Fig. 1: Kaplan-Meier curves: (A)Overall Survival, (B) Disease-Free Survival.

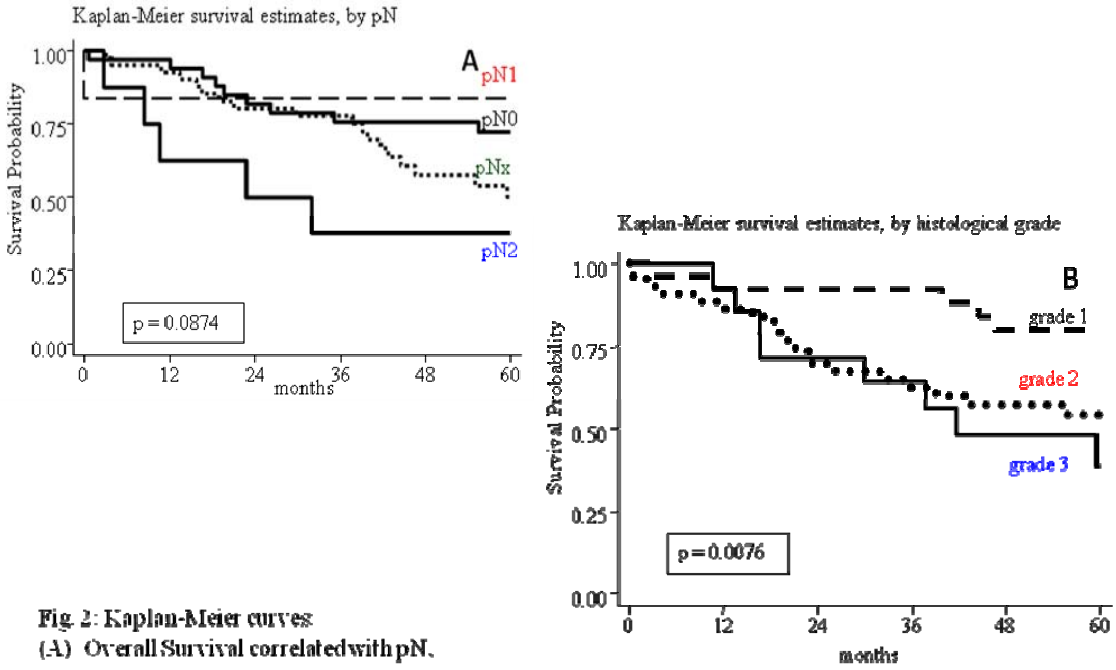

Fig. 2: Kaplan-Meier curves
(A) Overall Survival correlated with pN.
(B) Overall Survival correlated with histological grade.

5 ARTIGO 2

5.2 Long term results of the surgical treatment of advanced oropharyngeal squamous cell carcinoma

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Abstract

Backgroung The purpose of this study was to review the oncologic and functional outcomes of patients with clinical stage III or IV squamous cell carcinoma of the oropharynx submitted to tumor resection and neck dissection with or without postoperative radiotherapy. **Methods** This study was conducted with a retrospective review of medical charts of 256 consecutive patients. **Results** Fatal postoperative complications were registered in 5 patients (1.9%). During follow-up, there were 74 (29%) local recurrences, 27 neck recurrences (10.5%), and 19 distant metastases (7.4%). The 5-year overall survival was 43.0%. The Cox multivariate model identified tumor size >3cm and pN+ECS+ as independent prognostic markers for decreased OS. The presence of an intense lymphocytic infiltrate was associated with higher OS rates. The 5-year disease-free survival rate was 54.5%. **Conclusion** Surgical treatment of oropharynx carcinoma can be performed with a low risk of postoperative mortality but with a risk of long-term use of tracheostomy and feeding tubes.

Introduction

Oropharyngeal cancer includes cancers of the soft palate, tonsil, base of the tongue, vallecula and posterior wall. Approximately 136,622 cases of oropharynx cancer are registered annually worldwide.[1] In the United States, 13,580 new cases were estimated in 2011.[2] Most tumors originate in the tonsils and base of tongue, and more than 90% of oropharyngeal cancers are squamous cell carcinomas.[3,4] The accepted risk factors include smoking and excessive alcohol consumption. There is increasing evidence in the literature that human papillomavirus (HPV) plays an important role in the carcinogenesis of oropharyngeal cancers, particularly in tonsillar carcinomas.[5] Oropharyngeal squamous cell carcinoma (OSCC) is often diagnosed in the advanced stages and therefore has a poor prognosis. In addition, the functional outcomes of OSCC are poor because several fundamental activities may be affected by treatment, specifically speech and swallowing, thereby requiring significant lifestyle changes.[6]

The ideal treatment for this cancer remains controversial. Radiotherapy (RT) and surgery are equally effective in the treatment of patients with early-stage disease, and chemoradiotherapy or a combination of surgery with postoperative chemoradiotherapy is recommended for advanced cancers.[7,8] Surgical resection followed by adjuvant radiotherapy has been frequently used in several institutions worldwide, resulting in reasonably good locoregional control and survival. [6,9,10] Improvements in surgical techniques, especially in reconstruction with microvascular free flaps to facilitate the rehabilitation of these patients and technological advances in robotic surgery, have made this oropharyngeal region more accessible with less morbidity. [11,12,13,14] Some studies of patients with early or advanced oropharyngeal

cancer comparing both treatments have concluded that RT is better owing to the complications linked with surgical treatments.[7,15] However, RT also presents significant morbidity, producing moderate to severe mucositis in most patients in addition to xerostomia, pain and dysphagia, which may last a long time or be permanent.[16]

The purpose of this study was to review the long-term oncologic outcomes of 256 consecutive patients with advanced-stage squamous cell carcinomas of the oropharynx who underwent surgical treatment with or without postoperative radiotherapy (PORT) at one of two Head and Neck Surgery Departments.

Patients and methods

We reviewed the records of 256 patients, 232 (90.6%) men and 24 women, with a median age of 55 years (range: 30-83) who had clinical stage III or IV OSCC. The patients were treated between 1990 and 2004 at Heliopolis Hospital and AC Camargo Hospital, São Paulo, Brazil. All of the included patients were treated with surgery, and most patients were also treated by PORT.

The eligibility criteria for inclusion in the study were as follows: patients with histologically confirmed diagnosis of clinical stage III or IV squamous cell carcinoma of the oropharynx; patients not previously treated; and patients that did not have other previous primary tumors. In this study, demographic factors and environmental exposures (gender, age, race, smoking habit, alcohol intake), clinical factors (T stage, N stage, tumor site, stage, subsites, comorbidities, American Society of Anesthesiology's Physical Status Classification [ASA], weight loss, BMI, hemoglobin, Goldman [Multifactorial index of cardiac risk]), treatment-related

factors (neck dissection, mandibulectomy, reconstruction, complications, hospital stay, nasogastric tube use and time of removal, tracheotomy use and time of decannulation, food intake status PORT, chemotherapy) and pathological factors (pT, histological grade, surgical margins, tumor size, thickness, deep infiltration, lymphovascular embolization, perineural infiltration, lymphocytic infiltrate, pattern of invasion, pN, extracapsular spread [ECS]) were reviewed and analyzed.

Ninety-five cases (37.1%) were diagnosed as stage III, and 161 cases (62.9%) were diagnosed at stage IV. The tumor was located in the tonsillar fossa in 171 cases (66.8%), the soft palate in 20 cases (7.8%), the base of the tongue 62 cases (24.2%) and the posterior pharyngeal wall in 3 cases.

Fifth-five patients underwent surgery only (21.5%). The types of resections included buccopharyngectomy (tonsil resection with both tonsillar pillars, pterygoid muscles, ascending ramus of the mandible and ipsilateral neck dissection) in 38 cases (14.8%), lateral paramedian or median mandibulotomy and pharyngectomy in 70 cases (27.3%), total glossectomy in 11 cases (4.3%), supraglottic laryngectomy with the resection of the base of tongue in 25 cases (9.8%), total laryngectomy with the resection of the base of tongue in 16 cases (6.2%), resection of the base of the tongue tumor in 18 cases (7.0%), resection of a tonsil tumor in 66 cases (25.8%), resection of a soft palate tumor in 15 cases (5.9) and resection of the posterior wall in 1 case. An ipsilateral neck dissection was performed on 253 patients (98.8%), and contralateral dissections were also performed in 70 cases (27.3%). Reconstruction of the primary defect was achieved by primary closure in 136 patients (53.1%), a local flap in 21 patients (8.2%), a myocutaneous flap in 73 patients (28.5%) and a free-flap in 26 patients (10.1%).

The median hospital stay was 12.3 days (range: 2-216). The overall rate of surgical complications was of 75%. These included wound infection or collections (54.7%), shoulder pain (17.2%), pulmonary infection (15.2%), cardiovascular causes (2.3%), nicotinic or alcoholic abstinence (1.5%), dyspeptic symptoms (1.9%) and severe depression (0.8%). There were 5 deaths (1.9%), including 2 patient with wound complications and 3 patients due to systemic causes.

Adjuvant radiotherapy was given to 201 patients (78.5%). Radiotherapy was indicated in cases of pT4, close or involved margins, vascular embolization, perineural infiltration or lymph nodes metastasis. The primary site was treated to a median of 61Gy (range 14-75Gy). Concomitant chemotherapy was performed in only 9 cases.

The microscopic slides were reviewed by a pathologist at each institution using to the following criteria: (1) histological grade determined on the basis of the classification system proposed by the World Health Organization,[17] [well differentiated (Grade I), moderately differentiated (Grade II), poorly differentiated (grade III)]; (2) tumor thickness; (3) depth of infiltration; (4) vascular embolization (classified according to the presence or absence of neoplasic cells, located both in the wall and in the light of the blood or lymphatic vessels); (5) perineural infiltration (considered present when the tissue adjacent to the peri- and/or intra-tumoral nerves were involved by neoplasic cells); (6) surgical margins (considered involved when the presence of invasive carcinoma and/or carcinoma “in situ” on the margins of the mucosa); (7) lymphocytic infiltrate in close relation to invasive tumor cells; and (8) pattern of invasion.[18,19] After the review, the tumors were re-staged according to the criteria of the International Union Against Cancer (UICC 2002)[20]: pT1 14 cases

(5.5%), pT2 88 cases (34.6%), pT3 89 cases (35%), pT4 65 cases (25.4%) and pN0 58 cases (22.8%), pN1 38 cases (15%), pN2 144 cases (56.2%), pN3 16 cases (6.3%), pN+ECS- 51 cases (20.4%), and pN+ECS+ in 141 cases (56.4%). Of the cases that could be reviewed, infiltration of muscular layer was observed in 85.7% (179⁄209), vascular embolization in 11% (26⁄236), lymphatic embolization in 50.2% (120⁄239), perineural infiltration in 32.9% (78⁄237) and involved margins in 19.4% (49⁄253). In 58 cases (23%), the histological grade was well differentiated (Grade I). One hundred forty-eight cases (58.7%) had a moderate grade, and 46 cases (18.2%) were poorly differentiated (Table 3).

Statistical analysis: The follow up time was from the date of treatment to the date of death or the last information for censored cases. The overall and disease free survival probabilities were estimated using the Kaplan-Meier method, and the log-rank test was performed to verify the differences among survival curves. The 5% level of significance was considered for statistical tests. The multivariate risk of death and respective 95% confidence intervals were estimated by Cox regression model. The statistical computer software STATA release 10.0 was used to perform all statistical analysis.[21]

Results

Temporary feeding tubes were placed in 253 patients (98.8%) for a median time of 29.5 days (range: 4-1233 days). A total of 199 patients had the tubes removed. We could not retrieve information about feeding tubes removal in 34 cases. The feeding tubes were not removed in 21 patients (8.2%). A gastrostomy was performed in 6 of these cases. Of the152 cases for which information regarding

swallowing after feeding tube removal was available, 79 patients had no swallowing complaints (30.9%), 69 were eating only soft solids (27%) and 4 were eating only liquids.

Tracheostomies were performed in 248 patients (96.9%) and were required for a median duration of 22 days (range: 3-3659days). Of these, 224 were decannulated, 6 patients were temporarily maintained on a tracheostomy and definitive tracheostomy was necessary in 18 patients (after larynx procedures). After the tracheostomy was removed, 63 patients considered their voice quality good (24.6%), whereas 49 (19.1%) patients exhibited voice problems: hoarseness (19), hypernasal (22), whispered (4), nasal (2) or wet (2). In the remaining cases, we could not access the registered information about the quality of the voice.

Recurrences occurred in 110 patients (42.9%) within a period of 1.3 to 85 months, with a median of 6.6 months. The incidence of distant metastases was 7.4% (19 patients). In 10 patients, distant metastases were associated with local or regional (neck lymph nodes) recurrence. There were 74 local recurrences (29%), including 14 patients with locoregional lesions, 3 patients with local recurrence and distant metastases and 2 patients with locoregional lesions and distant metastases. The primary tumor was cT1 in 1 patient, cT2 in 11 patients, cT3 in 38 patients, cT4 in 24 patients. The primary tumor was tonsillar in 51 patients, at the base of tongue in 18 patients and at the soft palate in 5 cases. Eighteen patients had involved surgical margins when initially treated. The salvage treatment of local recurrences was salvage surgery in 15 cases, radio-surgical associations in 2 cases, RT in 9 cases, and chemotherapy in 8 cases. Forty patients were not considered candidates for further treatment and underwent supportive care. Only 3 of these 74 patients are still alive

without further evidence of the disease. Sixty-eight patients died of cancer; 2 exhibited no evidence of disease but died of non-cancer- related causes, and 1 died after treatment of a second primary cancer.

There were 27 regional (neck lymph nodes) recurrences (10.5%), including 5 patients with associated distant metastases. These recurrences were registered within a period of 1.3 to 66 months, median time of 9.1 months. The treatment of these events was surgery in 7 cases, radio-surgical associations in 2 cases, radiotherapy in 4 cases, and chemotherapy in 5 cases. Nine patients were not candidates for further oncologic treatment and received the best supportive care available. Two of these 27 patients are alive without further evidence of the disease. Twenty-four patients died of cancer, and 1 died of a non-cancer-related cause with no evidence of disease.

Fifty-two patients developed a second primary cancer (20.3%) between 0 to 162 months (median time of 29.4 months). The site of the second cancers were as follows: 12 lung, 11 oral cavity, 11 hypopharynx/esophagus, 6 skin, 4 oropharynx, 2 larynx, 2 bladder, 1 retroperitoneum, 1 colon and 2 lymphoproliferative diseases. The treatment of these events was surgery in 23 cases, radio-surgical associations in 3 cases, radiotherapy in 7 cases, chemoradiation in 3 cases, chemotherapy in 4 cases and 12 patients were not considered candidates for further treatment.

The mean follow-up time was 52.8 months (range: 1-213 months). In this period there were 165 deaths (64.4%). One hundred ten patients died of cancer (42.9%), 21 died of a second primary cancer (8.2%) and 34 died of non-cancer-related causes (13.3%). The 5-year disease-free survival (DFS) rate was 54.5% (Figure 1). Univariate analysis demonstrated the impact of pT ($p=0.0044$), vascular embolization ($p=0.0026$), lymphatic embolization ($p=0.0023$), lymphocytic infiltrate

(p=0.0013), pN ECS (p=0.0090), extracapsular spread (p=0.0023), status of surgical margins (p=0.0109), mandibulectomy (p=0.0273) and postoperative radiotherapy (p=0.0010) on the incidence of recurrences (Tables 1, 2 and 3).

The 5-year overall survival (OS) rate was 43.0% (Figure 1). Regarding the univariate analysis, a statistically significant difference was demonstrated according to the following factors: age (p=0.0177), weight loss (p=0.0097), pT (p=0.0004), tumor size (p=0.0184), lymphatic embolization (p=0.0009), lymphocytic infiltrate (p=0.0036), pattern of invasion (p=0.0358), pN (p=0.0177), extracapsular spread (p=0.0017), pN ECS (0.0062) and postoperative radiotherapy (p=0.0010) (Tables 1,2 and 3) (Figures 2 and 3).

The Cox multivariate model identified tumor size >3 cm (hazard ratio 1.87 [95% CI 1.23-2.86]) and pN+ECS+ (hazard ratio 2.04 [95% CI 1.22-3.39]) as independent prognostic markers for decreased OS. The presence of an intense lymphocytic infiltrate (hazard ratio 0.57 [95% CI 0.33-0.97]) was also associated with a higher OS rates (Table 4).

Discussion

There have been a large number of publications in the medical literature concerning oropharyngeal cancer biology, treatment and outcomes.[7] However, few trials have included only OSCC, and the studied groups included radiation or chemoradiation without any surgical arm.[22,23] Consequently, there is no agreement on the most appropriate treatment. NCCN guidelines recommend 4 different options for T3 and T4 tumors, including surgery, radiation, chemoradiation or combinations thereof.[8] A large meta-analysis evaluated several different treatment protocols and estimated a 5-year OS rate of 49.1%.[24] Parsons et al. in a systematic review

compared the results of surgery with or without radiotherapy versus radiotherapy with or without neck dissection and found similar rates of local control as well as similar rates of locoregional, specific and overall survival at 5 years for all stages of disease. The OS for tongue base lesions was 49% in the surgical group and 52% in the irradiated group. For tonsillar lesions, the OS of the surgical and irradiated groups was 47% and 43%, respectively.[7]

Several publications have compared the results of surgery versus RT for tonsil SCC. Perez et al. observed that surgery with postoperative radiotherapy offers higher rates of local control than preoperative procedures in patients with T3-T4 lesions and good general conditions but greater morbidity.[25] Poulsen et al. concluded surgery with postoperative radiotherapy provides superior outcomes in locally advanced tonsil SCC in patients with surgically resectable disease, good ECOG performance status, and medically operable tumors.[26] Other studies support this treatment modality, with OS rates ranging from 40-69% (Table 5).[6,8,26-35] Nijdam et al. observed similar rates of locoregional control between the surgical group and a brachytherapy group of patients with OSCC.[36] Other authors reported the results of primary concomitant chemoradiotherapy with or without neck dissection in advanced lesions, demonstrating comparable oncological outcomes. Some authors report less morbidity compared to surgery (Table 6).[15,23,24,26,27,31,32,36-42,] Two series of patients with oropharyngeal cancer from two of the institutions that collaborated in this study were previously published.[38,40] They reported that the long-term results of radiotherapy and chemoradiotherapy in patients not included in clinical trials and with clinicopathological characteristics similar to those included in the present study were disappointing (less than 20% in 2 to 5-years of follow up).[38,40] These results

were the basis for the shift in treatment in both institutions, favoring surgery as the primary treatment for resectable tumors of operable patients. In the current study, we report the long-term experiences of both hospitals and the observed 5-y OS of 43.0% and a DFS of 54.5%. It is important to consider that most patients included in this series had adverse factors[43] for the indication of radiation or chemoradiation: 62.9% of our patients were stage IV, 94.9% were smokers, 83.3% drinkers, 55.3% had comorbidities and 47.1% exhibited weight loss. Thus, the achieved long-term results are unique and from a population with these specific adverse characteristics. Most patients included in the present analysis (78.5%) underwent postoperative radiotherapy. A significant protective effect of this adjuvant treatment was observed in both overall survival and disease-free survival, emphasizing the need for multimodal treatment in these clinical stage advanced cases.

Several clinical factors influencing survival have been frequently reported, including gender,[28] tumor site,[29] and invasion of subsites.[44] In this study, we demonstrated that patients older than 65 years and those with weight loss had lower OS rates. These factors affect survival by causing the deterioration of clinical conditions that can be associated with greater treatment-related morbidity. Higher survival rates in non-smokers and non-drinkers were also observed. As previously reported by Ang et al., this is a favorable group of patients for non-surgical treatment,[43] most likely because most of these tumors are associated with HPV infection. Some studies have reported treatment factors influencing survival. As described by Zelefsky et al., treatment interruption had a negative effect on the local control rates in advanced oropharyngeal cancer treated with surgery and postoperative radiotherapy.[8] Mendenhall et al. observed that overall treatment time

significantly influenced local control in patients with a base of the tongue carcinoma treated with radiotherapy.[15]

A large number of pathological factors have been reported to influence the survival of OSCC patients. The status of surgical margins is one of the most significant factors.[28,29,34,41,44] Other factors include the number of metastatic lymph nodes[6] and the presence of extracapsular spread.[28] Woolgar described several other important histopathological factors, including histological grade, degree of invasion and lymphovascular and perineural invasion and emphasized the need of a partnership between the surgeon and the pathologist because the histopathology findings remain important prognostic factors that influence postoperative management and prognosis predictions in oral and oropharyngeal SCC patients.[45]

The significance of other pathological factors, like the biological activity of the tumor and its relationship with the adjacent host tissue (pattern of invasion), has been less studied. The pattern of invasion has been studied since 1973 when it was described by Jakobsson[46] in glottic carcinoma. Anneroth and Hansen in 1984 constructed a modified multifactorial grading system for studying oral carcinoma, which includes the mode of invasion and the lymphocytic response.[18] The authors noted a remarkable correlation between the degree of histological malignancy, the clinical staging and the patient's outcome. Brandwein-Gensler et al. also observed that the worst pattern of invasion and limited lymphocytic response were significantly associated with the risk of local recurrence and with decreased OS in patients with oral squamous cell carcinoma.[47] In the present study, histological slides were reviewed, and the following characteristics were determined to be associated with better OS and DFS: pT1 tumors, size of tumor $\leq$ 3 cm, absence of

lymphovascular embolization, no extracapsular spread of lymph node metastasis and tumors with intense lymphocytic infiltrate. In this study, the cases with pattern of invasion type 1 exhibited better OS, and the cases with free resection margins and without vascular embolization had higher DFS.

The significant independent prognostic factors included tumor size, lymphocytic infiltrate and pN ECS. Therefore, the pathological factors were more relevant than the clinical factors. It is possible that our study design might explain these results. First, only two pathologists reviewed the cases, resulting in a uniform evaluation of all histological variables. Second, a multidisciplinary approach was responsible for the adequate adjuvant treatments of the patients, including those with worse clinical conditions. The primary surgery was intended to excise all of the malignant tissue. However, remaining microscopic tumor cells can be present, and adjuvant therapy is considered necessary in high risk cases.

Tschudi et al. reported patients' quality of life (QOL) after different treatment modalities for oropharynx carcinoma.[48] Patients who underwent primary surgical resection achieved the highest quality of life scores, and patients seem to experience significantly more difficulties in coping with the long-term detrimental effects of radiotherapy than the effects of surgery. The authors concluded that surgical resection caused no major impairments in any of the different domains assessed by the questionnaires compared to primary radiotherapy. Mowry et al. also observed that patients with advanced oropharyngeal cancer had remarkably similar perceptions of long-term QOL whether the treatment was primary chemoradiation or surgery with postoperative radiotherapy.[49] The group of patients treated with chemoradiation had more difficulty with taste (trend to significance). On the other side, Parsons et al.

presented a systematic review and suggested superiority of primary radiation therapy with respect to functional outcomes and quality of life compared to primary surgery.[7] Our previous reported experience with radiation and chemoradiation was disappointing, considering the low rates of survival.[38] The significant experience with surgical treatment, on the contrary, demonstrated that with multidisciplinary approach, most patients are rehabilitated, had high quality of life scores and are satisfied with the outcomes.[50-52] In the current study, we had functional information about swallowing from patients records in 209 cases and about tracheostomy and quality of voice in 207 cases. Of these cases, 72% were able to swallow soft solids or maintain a regular diet, 30.4% were considered to have a good quality of voice and only 9.4% had a definitive tracheostomy. It is also important to emphasize that different approaches currently in use can improve the outcomes of patients with oropharyngeal carcinomas submitted to surgical treatment: robotic surgery,[10] transoral laser resection,[53] several advances in free flap reconstruction[54,55,56] and oral rehabilitation (dental implants and prosthesis). These approaches have resulted in the improved functional capacity of patients who undergo surgery.[11,49,56]

Finally, surgical treatment of oropharynx carcinoma can be performed with a low risk of postoperative mortality but with a risk of long term use of tracheostomy and feeding tubes. This morbidity can potentially be reduced with proper patient selection, the use of robotic surgery or with oral laser resection and a multidisciplinary rehabilitation program. Long-term survival rates achieved in this series can be considered similar to those reported by the most recent published series using chemoradiation, and both are valid alternatives that should be considered in multidisciplinary therapeutic planning.

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Table 1a: Survival rates according to selected demographic characteristics

Variables	Categories (%)	5-y DFS	P	5-y OS	P
Gender	Male 232 (90.6)	64.0	0.3327	41.5	0.4163
	Female 24 (9.4)	53.5		56.7	
Age	≤ 45: 34 (13.3)	52.0	0.8707	40.7	0.0177
	46-55: 99 (38.7)	51.5		47.8	
	56-65: 77 (30.1)	54.5		43.0	
	>65: 46 (18.0)	65.3		35.2	
Race	white 200 (78.1)	55.2	0.6938	43.0	0.8746
	non-white 56 (21.9)	51.7		42.8	
Smoking habits	Yes 240 (94.9)	53.4	0.1206	42.1	0.0512
	No 13 (5.1)	83.6		68.5	
Alcohol intake	Yes 210 (83.3)	53.8	0.4285	40.2	0.0551
	No 42 (16.7)	62.0		60.3	

DFS: Disease-Free Survival, OS: Overall Survival

Table 1b: Survival rates according to selected clinical characteristics

Variables	Categories (%)	5-y DFS	P	5-y OS	P
Comorbidities	No 115 (45.4)	52.4	0.4262	41.8	0.8327
	Yes 138 (54.5)	57.7		43.6	
ASA	I: 113 (44.7)	52.6	0.7081	43.4	0.6054
	II: 111 (43.9)	58.4		43.7	
	III: 29 (11.5)	49.1		38.9	
Weight Loss	Yes 108 (47.2)	47.6	0.1311	33.9	0.0097
	No 121 (52.8)	59.8		50.5	
BMI	≤18.5: 15 (8.2)	51.4	0.0856	29.1	0.2596
	>18.5-25: 133 (72.7)	51.9		41.6	
	>26-30: 25 (13.7)	75.5		59.7	
	> 30: 10 (5.5)	90.0		70.0	
Hemoglobin	≤13: 32 (23.3)	57.3	0.9034	29.0	0.3100
	> 13: 105 (76.6)	62.2		51.1	
Goldman	I: 227 (89.0)	53.9	0.4888	42.3	0.6522
	II: 25 (9.8)	58.0		49.4	
	III: 3 (1.2)	100.0		66.7	
T stage	T1: 9 (3.5)	77.8	0.4924	88.9	0.3081
	T2: 50 (19.5)	62.8		46.7	
	T3: 122(47.7)	53.5		42.4	
	T4: 75 (29.3)	47.6		35.7	
N Stage	N0: 55 (21.5)	56.3	0.8868	47.1	0.6646
	N1: 79 (30.9)	52.0		41.3	
	N2: 96 (37.5)	56.4		44.0	
	N3: 26 (10.2)	51.5		35.5	
Site	tonsil 171 (66.8)	55.1	0.4817	42.2	0.3865
	base of tongue 62 (24.2)	52.3		42.7	
	soft palate 20 (7.8)	49.2		41.2	
	posterior wall 3 (1.2)	100.0		66.7	
Subsites	≤ 2: 105 (41)	64.2	0.0624	49.6	0.0870
	> 2: 151 (59)	48.4		36.6	

DFS: Disease-Free Survival, OS: Overall Survival

Table 2: Survival rates according to treatment characteristics

Variables	Categories (%)	5-y DFS	P	5-y OS	P
Ipsilateral Neck Dissection					
	Yes 253 (98.8)	54.3	0.7641	42.4	0.2876
	No 3 (1.2)	66.7		35.4	
Mandibulectomy					
	Yes 103 (40.2)	45.4	0.0273	37.0	0.1098
	No 153 (59.8)	60.9		46.8	
Reconstruction					
	Yes 120 (46.9)	52.2	0.7367	40.0	0.3998
	No 136 (53.1)	56.6		46.0	
Complications					
	Yes 192 (75)	56.2	0.3427	41.3	0.6253
	No 64 (25)	52.3		46.2	
Postoperative Radiotherapy					
	Yes 201 (78.5)	57.4	0.0010	45.8	0.0010
	No 55 (21.5)	43.3		32.8	
Chemotherapy					
	Yes 9 (3.5)	28.5	0.0018	21.9	0.0737
	No 247 (96.5)	59.5		45.5	

DFS: Disease-Free Survival, OS: Overall Survival

Table 3. Survival rates according to selected pathological characteristics

Variables	Categories (%)	5-yr DFS	P	5-y OS	P
pT stage	pT1: 14 (5.5)	77.8	0.0044	77.9	0.0004
	pT2 88 (34.6)	69.7		56.1	
	pT3 89 (35.0)	44.5		31.1	
	pT4 63 (24.8)	42.7		31.8	
pN stage	pN0 58 (22.8)	63.9	0.1952	59.6	0.0454
	pN1 38 (15.0)	57.9		47.4	
	pN2 142 (55.9)	47.7		34.8	
	pN3 16 (6.3)	72.4		38.7	
Histological grade	Grade I: 58 (23.0)	47.7	0.4484	38.9	0.6255
	Grade II 148 (58.7)	57.4		47.0	
	Grade III 46 (18.2)	55.0		37.0	
Surgical Margins	Negative 204 (80.6)	59.0	0.0109	45.3	0.3153
	Involved 49 (19.4)	35.7		32.0	
Size	≤ 3cm 76 (34.1)	66.7	0.0586	57.2	0.0184
	>3cm 147 (65.9)	51.9		36.2	
Thickness	≤ 4 mm 7 (3.5)	57.1	0.8624	85.7	0.0511
	> 4mm 192 (96.5)	56.1		40.9	
ECS	Yes 141 (56.4)	45.7	0.0023	33.8	0.0017
	No 109 (43.6)	65.0		54.5	
pN ECS	pN0 58 (23.2)	63.9	0.0090	59.6	0.0062
	pN+ ECS- 51 (20.4)	66.4		49.1	
	pN+ ECS+ 141 (56.4)	45.7		33.8	
Vascular embolization	No 210 (89.0)	58.7	0.0026	45.1	0.0892
	Yes 26 (11.0)	25.6		22.9	
Lymphatic embolization	No 119 (49.8)	64.7	0.0023	52.6	0.0009
	Yes 120 (50.2)	44.8		32.7	
Perineural infiltration	No 159 (67.1)	59.5	0.1652	46.7	0.2519
	Yes 78 (32.9)	45.7		35.3	
Lymphocytic infiltrate	discrete 78 (40.2)	43.0	0.0013	32.7	0.0036
	moderate 69 (35.6)	47.8		34.3	
	intense 47 (24.2)	78.0		63.5	
Deep infiltration	superficial 30 (14.3)	71.9	0.2159	63.8	0.0590
	Muscle 159 (76.1)	50.1		38.2	
	deep 20 (9.6)	45.1		25.8	
Pattern of invasion	1: 39 (23.8)	51.0	0.1022	53.7	0.0358
	2: 45 (27.4)	64.2		43.2	
	3: 71 (43.3)	45.4		26.0	
	4: 9 (5.5)	85.7		66.7	

DFS: Disease-Free Survival, OS: Overall Survival

Table 4. The Cox multivariate model for the risk of death

Variables	Categories	HR (95% CI)	P
Size of tumor			
	tu < 3 cm	1.0 (ref.)	
	tu > 3 cm	1.87 (1.23-2.86)	0.003
pN ECS			
	pN0	1.0 (ref.)	
	pN+ECS-	1.52 (0.79-2.90)	0.209
	pN+ECS+	2.04 (1.22-3.39)	0.006
Inflammatory Infiltrate			
	Discrete	1.0 (ref.)	
	Moderate	1.16 (0.75-1.80)	0.499
	Intense	0.57 (0.33-0.97)	0.039

HR: Hazard ratio, ref.: reference category, 95% CI: 95% confidence interval

Table 5: Survival in selected series after radical Surgery ± PORT for OSSC

Author (Date)	Patients (N)	Site	Stage	5-y OS (%)	5-y DSS (%)
Preuss 2006	211	Oroph	all	63.9	DFS 68.8
Lim 2008	110	Oroph	all	58	65
De Nittis 2001	51	Oroph	advanced	40	_
Zelefsky 1992	51	Oroph	all	7y: 52	7y DFS: 64
Poulsen 2007	102	Tonsil	advanced	69	75
Moore 2009	102	Tonsil	advanced	85	93.9
Jones 2003	44	Tonsil	all	63	_
Perez 1998	86	Tonsil	I/II	_	DFS: 71
			III/IV	_	10y DFS: 43.4
Mak-Kregar 1996	101	Tonsil	all	_	53
Góis Filho, Rapport1995	31	Tonsil	all	46	_
Machtay 1997	17	Base	all	3y: 46	_
Foote 1993	55	Base	all	_	65
Present series	256	Oroph	III/IV	42.2	DFS: 55.1

OS: Overall Survival; DSS: Disease-Specific Survival; Oroph: Oropharynx; DFS: Disease-Free Survival.

Table 6: Survival in selected series after Primary Radiotherapy for OSSC

Author (Date)	Patients	Site	Stage	Treatment	5-y OS (%)	5-y DSS (%)
Agarwal 2009	446	Oroph	all	RT	_	3y: 38.3
	145			RT/QT	_	3y: 41.8
Pedruzzi 2008	264	Oroph	all	RT	17.4	_
	97			RT/QT	19.2	_
Nijdam 2005	157	Oroph	all	BT	65	DFS: 61
	77			RT + ND	40	DFS: 43
Denis 2004	226	Oroph	III/IV	RT	16	15
				RT/QT	22	27
Calais 1999	226	Oroph	III/IV	RT/QT	3y: 51	3y: 42
				RT	3y: 31	3y: 20
Hart 1995	408	Oroph	all	RT	_	36
Carvalho 1986	126	Oroph	III/IV	QT/RT	2y: 16.5	_
Perez 1998	144	Tonsil	T1-3	RT + ND	_	LR: 20-25
			T4		_	LR: 86
	154	Tonsil	T1-3	RT	_	LR: 31
			T4		_	LR: 47
Mak-Kregar 1996	231	Tonsil	all	RT ± ND	_	39
Poulsen 2007	46	Tonsil	III/IV	RT/QT	41	56
Jones 2003	52	Tonsil	all	RT + ND	74	_
Sessions 2003	58	Base	all	RT	_	40.4
Gourin, Johnson 2001	87	Base	all	RT	49	56
Mendenhall 2000	217	Base	all	RT ± ND	50	64

OS: Overall Survival; DSS: Disease-Specific Survival; Oroph: Oropharynx; RT: Radiotherapy; CT: Chemotherapy; BT: Brachytherapy; DFS: Disease-Free Survival; ND: Neck Dissection; LR: Local Recurrence

Figures: 1 and 2

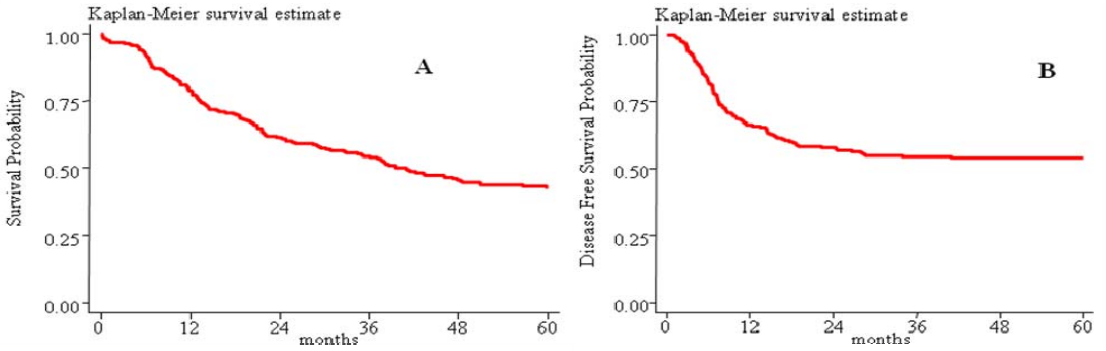

Fig.1. Kaplan-Meier curves: (A) Overall Survival. (B) Disease-Free Survival

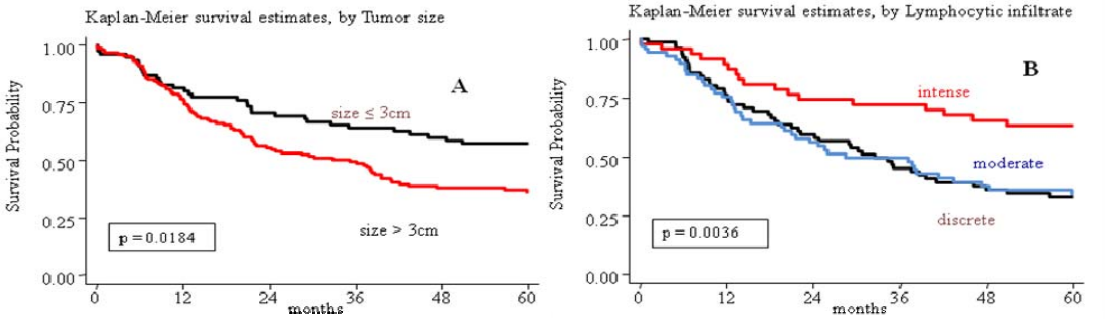

Fig.2. Kaplan-Meier curves: (A) Overall Survival correlated with Tumor size. (B) Overall Survival correlated with Lymphocytic infiltrate

Figure 3

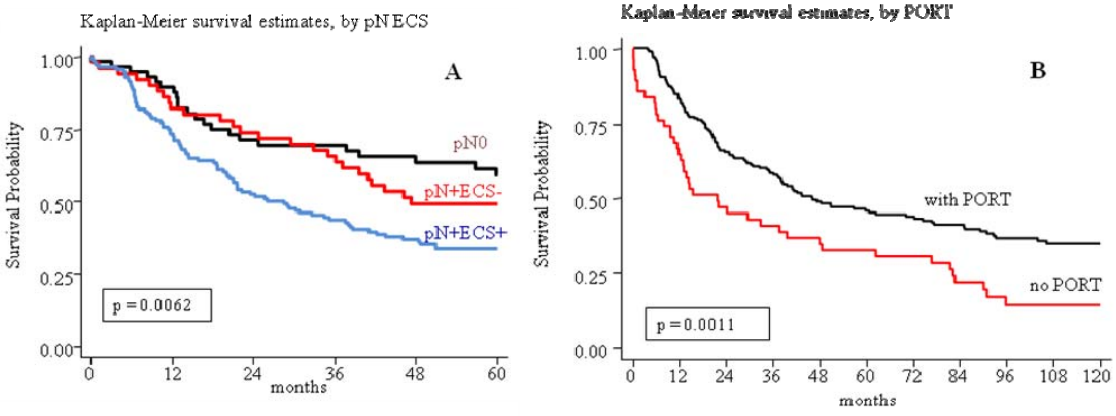

Fig.3. Kaplan-Meier curves: (A) Overall Survival correlated with pN ECS. (B) Overall Survival correlated with PORT

6 COMENTÁRIOS

O tratamento do paciente com carcinoma epidermóide de orofaringe tem sido baseado no estadiamento e localização do tumor, condições clínicas do paciente, estrutura do centro de tratamento e experiência da equipe médica (ZELEFSKY et al. 1992; MENDENHALL et al. 2000; PARSONS et al. 2002); diante destas razões o tratamento principal será a ressecção cirúrgica ou a radioterapia, sendo que na maioria dos casos haverá a necessidade de associação de terapias (GALATI et al. 2000; GENDEN et al. 2003; SESSIONS et al. 2003; CARVALHO et al. 2005).

Considerando-se que as lesões iniciais de orofaringe devem ser tratadas com monoterapia, os resultados oncológicos do tratamento cirúrgico e da radioterapia são extremamente semelhantes, mas em longo prazo estes pacientes evoluirão de forma diferente. Os pacientes submetidos à radioterapia apresentam sequelas permanentes como disfagia, xerostomia e cáries de irradiação (TROTTI et al. 2003), enquanto que aqueles submetidos à cirurgia apresentam sequelas estritamente relacionadas ao tamanho da ressecção. Apenas uma pequena proporção dos casos necessitará de mandibulectomia. Em nosso estudo esta ressecção ocorreu em 13,5% dos casos. Ressaltamos também a alta incidência de segundo tumor primário em tumores de cabeça e pescoço (SPIRO e SPIRO 1989; FRANCO et al. 1991; COSMIDIS et al. 2004; SELEK et al. 2004), que em nosso estudo ocorreu em 31,5% dos casos, comprovando a relevância do seguimento e vigilância para diagnóstico precoce destes eventos e adequado tratamento. O tratamento do segundo tumor primário NA região de cabeça e pescoço poderá ser a ressecção cirúrgica ou a radioterapia. A

ressecção.pode ser indicada e realizada em múltiplos eventos oncológicos, enquanto a radioterapia limita-se apenas ao tratamento de um evento em um mesmo campo de irradiação (GALATI et al. 2000; PIGNAT et al. 2002; COSMIDIS et al. 2004; MONCRIEFF et al. 2009).

Considerando-se as lesões avançadas observamos que na literatura os dados de avaliação de sobrevida relacionada ao estadiamento do câncer e ao tratamento empregado são muito heterogêneos dificultando a comparação de resultados oncológicos e/ou funcionais (PARSONS et al. 2002). As publicações relacionadas à radioterapia como tratamento principal mostram em sua maioria taxas de sobrevida abaixo de 40% incluindo todos os estadiamentos e nem sempre informam sobre a realização de esvaziamento cervical e quimioterapia concomitante (CARVALHO et al. 1986; HART et al. 1995; MAK-KREGAR et al. 1996; PEREZ et al. 1998; CALAIS et al. 1999; MENDENHALL et al. 2000; GOURIN e JOHNSON 2001; JONES et al. 2003; SESSIONS et al. 2003; DENIS et al. 2004; NIJDAM et al. 2005; POULSEN et al. 2007; PEDRUZZI et al. 2008; AGARWAL et al. 2009); enquanto as séries cirúrgicas mostram taxas de sobrevida melhores se comparadas às séries de radioterapia, mas também avaliam em sua maioria todos os estadiamentos (ZELEFSKY et al. 1992; FOOTE et al. 1993; GÓIS FILHO 1993; GÓIS FILHO e RAPPOPORT 1995; MAK-KREGAR et al. 1996; PEREZ et al. 1998; DENITTIS et al. 2001; JONES et al. 2003; PREUSS et al. 2007a, LIM et al. 2008; POULSEN et al. 2007; MOORE et al. 2009).

Em nosso estudo observamos taxas de sobrevida global aos 5 anos de 60,4% para o grupo de pacientes com lesões iniciais (T1 e T2) e de 43,0% para o grupo com

estádios III e IV, enquanto que as taxas de sobrevida livre de doença foram de 59,7% em lesões iniciais e de 54,5% para o grupo com lesões avançadas.

A revisão histológica de nossos casos, realizada por apenas 2 patologistas, uniformizou o estudo histológico e foi relevante na avaliação de fatores que causam impacto na sobrevida de nossos pacientes. A identificação de tais fatores permite a indicação mais precisa de terapia adjuvante: radioterapia ou quimioradioterapia.

A análise univariada do grupo de pacientes com lesões iniciais mostrou que os seguintes fatores tiveram impacto na sobrevida livre de doença: idade e estado das margens cirúrgicas e no estudo de sobrevida global: idade, grau histológico, infiltração da camada muscular e reação desmoplásica mostraram significância estatística.

A análise univariada do grupo de pacientes com lesões avançadas mostrou que alguns fatores tiveram impacto na sobrevida livre de doença: realização de mandibulectomia, de radioterapia pós-operatória, pT, embolização sanguínea, linfática, infiltrado linfocitário peri-tumoral, estado das margens cirúrgicas, presença de ruptura capsular do linfonodo e pNRC. No estudo de sobrevida global: idade, perda de peso, pT, tamanho do tumor, embolização linfática, infiltrado linfocitário peri-tumoral, padrão de invasão, ruptura capsular do linfonodo, pNRC e realização de radioterapia pós-operatória mostraram significância estatística.

A análise multivariada através do modelo de Cox do grupo de lesões iniciais demonstrou que tumores pobremente diferenciados e pN2 foram fatores prognósticos independentes para o risco de morte. No grupo de estádios III e IV identificamos o tamanho do tumor >3cm e pN+RC+ como fatores prognósticos independentes para

redução das taxas de sobrevida global enquanto que o intenso infiltrado linfocitário peri-tumoral para taxas mais altas de sobrevida global.

Embora não tenha sido nosso principal objetivo pudemos observar que nossos resultados funcionais sobre deglutição e voz são razoáveis, 12,3% dos pacientes com lesões iniciais apresentaram disfunção na deglutição aceitando apenas dieta com líquidos ou pastosa, e 72% dos pacientes com lesões avançadas conseguiram manter uma dieta com sólidos pastosos ou ainda uma dieta normal. Estudos mais recentes sobre qualidade de vida têm relatado que pacientes com câncer de orofaringe tratados com radioterapia também apresentam disfunção de deglutição e fala, e que os efeitos tardios da radioterapia causam maior dificuldade de adaptação do que aqueles causados pela ressecção (TSCHUDI et al.2003; SEIKALY et al. 2003; MOWRY et al. 2006; VARTANIAN e KOWALSKI 2009; VARTANIAN 2010; BARATA et al. 2012). Portanto, a superioridade da radioterapia primária com respeito aos resultados funcionais e de qualidade de vida deve ser questionada quando comparada ao tratamento cirúrgico primário.

7 CONCLUSÕES

1. Os fatores prognósticos independentes para diminuição de sobrevida global observados no estudo de pacientes com CEC inicial de orofaringe foram: grau histológico pouco diferenciado e pN2.

2. Os fatores prognósticos independentes observados no estudo de pacientes com CEC avançado de orofaringe para predição das taxas de sobrevida global foram: tamanho do tumor >3cm, pN+RC+ e presença de intenso infiltrado linfocitário peri-tumoral

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Anexo 1 - Ficha de coleta de dados dos prontuários e da revisão histológica

Instituição	pT
Registro	Espessura
Idade	Diferenciação
Gênero	profundidade de invasão
Cor	padrão de invasão
Comorbidades	invasão sanguine
Perda de Peso	invasão linfática
TNM	invasão perineural
Sítio	Desmoplasia
Subsítios	infiltrado inflamatório
Data de diagnóstico	margens de ressecção
Data da cirurgia	pN
Tipo de cirurgia	número de linfonodos comprometidos
Via de acesso	níveis comprometidos
Mandibulectomia	ruptura capsular
Reconstrução	níveis com ruptura capsular
Esvaziamento cervical unilateral	
Esvaziamento cervical contralateral	
Complicações pós-operatórias	
Período de hospitalização	
Uso de SNE	
Uso de traqueostomia	
Radioterapia	
Quimioterapia	
Recidiva tumor primário	
Recidiva linfonodal	
Segundo tumor primário	
Metástase à distância	
Status	
Data da última consulta	
Perda de seguimento	
Número do exame anatomo-patológico	

Anexo 2 - Cartas de submissão do artigo 1

Dear Dr. Souza,

Your submission entitled "Outcomes of Primary Surgical Treatment of T1-T2N0 Squamous Cell Carcinoma of the Oropharynx" has been been assigned the following manuscript number: EAORL-D-12-00399.

You will be able to check on the progress of your paper by logging on to Editorial Manager as an author.
The URL is http://eaorl.edmgr.com/.

Thank you for submitting your work to this journal.

Kind regards,

Jan Olofsson
Managing Editor
European Archives of Oto-Rhino-Laryngology and Head & Neck

Ref.: Ms. No. EAORL-D-12-00399

Outcomes of Primary Surgical Treatment of T1-T2N0 Squamous Cell Carcinoma of the Oropharynx

European Archives of Oto-Rhino-Laryngology and Head & Neck

Dear Dr. Souza,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please provide a revised manuscript with all changes clearly marked (e.g. in red) and with your point-by-point responses to each of the reviewers' concerns (with appropriate page, paragraph and line details) included at the start of the manuscript.

Your revision is due by 17-08-2012.

To submit a revision, go to http://eaorl.edmgr.com/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Jan Olofsson

Managing Editor

European Archives of Oto-Rhino-Laryngology and Head & Neck