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LOCALLY-REGIONALLY ADVANCED TONSILLAR SQUAMOUS CELL CARCINOMA TREATED WITH CONCURRENT CHEMORADIOTHERAPY

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Abstract – **Purpose: To perform a retrospective review of stage III-IV squamous cell carcinoma of the tonsil managed by definitive concurrent chemoradiotherapy (CCRT) in order to analyze the patients' outcome and to evaluate the acute and late toxic effects of this treatment modality.**

Material and methods: Between January 2005 and December 2010, 36 patients with locally and/or regionally advanced tonsillar cancer underwent three dimensional conformal radiotherapy (3DCRT) with concurrent platinum-based chemotherapy. The dose prescription of the planning target volume for gross tumor and low-risk subclinical disease was 70 Gy and 50 Gy, respectively. Conventional fractionation with a daily dose of 2.0 Gy, 5 times per week was used. Concurrent chemotherapy consisted of cisplatin 30 mg/m2 given on a weekly basis. Acute and late radiotherapy-related toxicities were recorded using European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group (EORTC/RTOG) grading system. The 3-year locoregional relapse-free survival (LRRFS), disease-free survival (DFS), and overall survival (OS) rates were calculated using the Kaplan-Meier method.

Results: The median follow-up of all patients was 20.5 months (range, 5 to 90 months). The median follow-up of living patients was 59 months (range, 30 to 90 months). Complete response rates of the primary tumor and of the nodal disease were 72.2% and 64.0%, respectively. A complete composite response was present in 25 patients (69.4%). Treatment failure occurred in 15 out of 25 patients who achieved complete composite response following CCRT. The 3-year LRRFS, DFS, and OS rate was 38.8%, 27.8%, and 27.3%, respectively. Grade 3 mucositis occurred in 58.3% of patients. Xerostomia grade 2 was revealed in 72.2% of patients.

Conclusion: Taking into account the low 3-year survival rates observed in our study and the high percentage of grade 2 xerostomia, it can be concluded that in the future, instead of 3DCRT with concurrent chemotherapy, intensity modulated radiation therapy (IMRT) in combination with concomitant chemotherapy should be considered a fully recommendable treatment option for advanced tonsillar carcinoma in order to improve locoregional control and survival with simultaneous reduction of late salivary toxicity and therefore prevention of late xerostomia.

Keywords – **tonsillar carcinoma, radiotherapy, chemotherapy, concurrent chemoradiotherapy, xerostomia**

1. INTRODUCTION

Squamous cell carcinoma of the tonsil represents the most common oropharyngeal cancer with the incidence described as steadily increasing due in part to human papilloma virus infection [1-4]. The tonsils are characterized by deep crypts in which squamous cell carcinomas may arise without causing obvious surface ulceration which enables small tumors to cause only little distress and remain unnoticed by the patient for a substantial period of time [5, 6]. The dominantly manifested advanced stage of patients' disease at admission is a consequence of the anatomic location of tonsillar carcinoma, as well as of its origin in the lymphatic field of the oropharynx [7, 8]. There is a high frequency of nodal involvement at presentation of the patients with tonsillar cancer. Hence, Perez et al. [9] in their study reported that 58% of patients were initially diagnosed with metastases in the lymph nodes of the neck.

The treatment for advanced but resectable tonsillar carcinoma has traditionally been radical surgery and postoperative radiotherapy. Radiotherapy alone has

been the treatment approach used for advanced unresectable lesions and has been accepted also as an alternative to surgery in patients with resectable lesions in order to provide organ preservation. In recent years, based upon the results of several randomized studies and meta-analyses, chemotherapy administered concurrently with radiotherapy has become the standard of care for advanced head and neck cancer [10-15]. The results of the French Head and Neck Oncology and Radiotherapy Group (GORTEC 94-01) phase III randomized trial favoring the use of chemoradiotherapy vs. radiotherapy alone for advanced stage oropharyngeal cancer [16, 17)] have also confirmed that definitive CCRT should be considered a recommended treatment option for advanced stage tonsillar sqaumous cell carcinoma.

As radiotherapy technique employed in the treatment of tonsillar carcinoma has evolved from two-dimensional radiotherapy (2DRT) to three-dimensional conformal radiotherapy (3DCRT), a significant improvement of tumor coverage and the capacity for sparing sensitive organs has been shown [18].

Intensity-modulated radiotherapy (IMRT) achieving higher total doses in tumors by delivering larger doses per fraction to the tumor only, has also been shown as an effective treatment technique for locally advanced oropharyngeal carcinoma [19], offering excellent results of locoregional control while limiting the dose to the surrounding critical tissues [20-23].

In order to summarize the results of non-surgical treatment approach we retrospectively analyzed patients with locally-regionally advanced tonsillar cancer treated with 3DCRT and concurrent chemotherapy.

2. MATERIALS AND METHODS

Thirty six patients with stage III or IV tonsillar cancer were treated with radiotherapy concurrent with platinum-based chemotherapy from January 2005 to December 2010 at the University Clinic of Radiotherapy and Oncology in Skopje. All patients had histologically proven squamous cell carcinoma of the tonsil and no radiologic evidence of distant metastases. Pretreatment evaluation other than medical history and clinical examination consisted of fiberoptic endoscopy with biopsy to obtain the histological proof, fine-needle aspiration biopsy in cases with detectable neck adenopathy, complete blood count, basic blood chemistry, chest x-ray, abdominal ultrasound and bone scan. The disease evaluation also included computed tomography (CT) scanning and/or magnetic resonance imaging (MRI) of head and neck region. Patients were staged according to the 2002 classification of the American Joint Committee on Cancer Staging (AJCC) [24].

2.1. Treatment

2.1.1. Radiotherapy

For 3DCRT, we used the Eclipse Version 7.3.10, a commercial 3D treatment planning system manufactured by Varian Medical Systems. In patients with clinically negative neck the gross tumor volume (GTV) was represented by the gross tumor volume of the primary tumor (GTVt70) only and defined as any visible tumor revealed on imaging studies and/or physical examination. In patients with clinically positive neck the GTV70 was an union of GTVt70 and GTVn70. The GTVn70 was defined as the gross nodal disease revealed on imaging studies and/or physical examination. Neck lymph nodes were considered metastatic when their smallest axis diameter was greater than 1.0 cm. Definitions of clinical target volume (CTV) are shown in Table 1.

Table 1.Clinical target volume definition

Target	Target delineation
CTVt50	GTVt70 plus a margin of 1.0-2.0 cm for the potential microscopic extension of the disease
CTVn50 in patients with clinically negative neck	Nodal regions in the neck at levels II–IV
CTVn50 in patients with clinically positive neck	GTVn70 with a margin of 0.5-1.0 cm, nodal regions in the neck at levels I-V, retropharyngeal lymph nodes plus retrostyloid space if positive lymph node(s) in level Ib plus supraclavicular fossa if positive lymph node(s) in levels IV or V
CTV50	Created by integration of CTVt50 and CTVn50

The planning target volumes were PTV50 and PTV70. The PTV50 provided a margin of 0.5 cm around CTV50. If there were no positive lymph nodes in the neck, the PTV70 encompassed the GTVt70 plus a 0.5 cm margin. In patients with nodal disease, PTV70 was obtained by adding a margin of 0.5 cm around GTV70. Radiotherapy was delivered on linear accelerator using photons with beam qualities of 6 MV and 15 MV and electrons with energies 9-16 MeV. Conventional fractionation was used with a daily dose of 2.0 Gy, 5 times per week.

2.1.2. Chemotherapy

Chemotherapy consisted of weekly cisplatin (30 mg/m2) given concomitantly with radiation started at the first day of radiotherapy. Hydration and antiemetics were delivered according to standards of care. The full blood count and biochemical analysis of serum urea and creatinine were checked every week.

2.2. Response assessment

Evaluation of tumor response was performed three months after completion of chemoradiotherapy by physical examination, CT or MRI, and fiberoptic endoscopy. An examination under anesthetic and biopsies were performed in the event of clinical, endoscopic or radiological abnormalities. Response to treatment was documented by the World Health Organization (WHO) response grading system [25].

2.3. Treatment toxicity assessment

During treatment, the patients were examined on a weekly basis. After completion of therapy, each patient was followed up clinically after 4-6 weeks to assess acute toxicity. Acute radiotherapy-related toxicities were assessed according to the Acute Radiation Morbidity Scoring Criteria of the RTOG [26]. Chemotherapy-related toxicities were assessed according to the World Health Organization (WHO) criteria [25]. Late radiotherapy-related toxicities were evaluated according to the scales of the EORTC/RTOG [26] and were recorded starting at 4 months after treatment completion.

2.4. Follow-Up

All patients were followed up every month over the first year, every other month in the second year, every 3 to 6 months in the third through the fifth years after treatment, and every 12 months thereafter. A physical examination and fiberoptic endoscopy, or indirect mirror exam were performed during each follow-up examination. Baseline CT and/or MRI of the neck were done every 6 months over the first 2 years. Biopsy was performed in order to obtain histological proof of any lesion clinically suspicious for recurrent disease. Chest radiography and ultrasonography of the liver were performed each year.

2.5. Statistical analysis

Statistical end points of this study were LRRFS, DFS, and OS. LRRFS for patients who achieved complete composite response to CCRT was measured from the first day of treatment to the date of reappearance of disease either at the primary site and/or regional lymph nodes, or until the day of the last follow-up. For patients initially staged as N0 who manifested complete primary response to treatment, LRRFS was calculated from the date of treatment beginning until the date when appearance of metastatic lymph node(s) in the neck and/or reappearance of disease at the primary site were first reported, or to the last follow-up date. For patients with persistent primary and/or nodal disease LRRFS was measured from the first day of treatment to the date of the first follow-up visit. DFS was calculated from the date of commencement of treatment to the date when local, regional, locoregional or distant failure was first recorded or, in the case of local and/or regional persistent disease, to the date of first follow-up visit. OS was measured from the start date of treatment to the date of the last follow-up or to the date of death from any cause. LRRFS, DFS and OS were calculated using the method of Kaplan-Meier [27].

3. RESULTS

3.1. Patient and Tumor Characteristics

Summaries of baseline patient and tumor characteristics are provided in Table 2. The median age for the entire group was 58.5 years (range, 36-69 years), 88.9% were male, and 69.4% had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0. The predominant T and N stage was T3 (69.4%) and N2 (36.1%), and well and moderate histological differentiation of the tumor were equally represented (38.9%). Stage IVA disease was recognized in 58.3% of the patients.

Table 2. Baseline patient and tumor characteristics (n = 36)

Characteristics	Number of patients (%)
Patient characteristics	
Gender:	
male	32 (88.9%)
female	4 (11.1%)
ECOG performance status:	
0	25 (69.4%)
1	11 (30.6%)
Tumor characteristics	
T stage:	
T3	25 (69.4%)
T4	11 (30.6%)
N stage:	
N0	11 (30.6%)
N1	8 (22.2%)
N2	13 (36.1%)
N3	4 (11.1%)
Stage:	
III	11 (30.6%)
IVA	21 (58.3%)
IVB	4 (11.1%)
Histological differentiation:	
well	14 (38.9%)
moderate	14 (38.9%)
poor	8 (22.2%)

ECOG, Eastern Cooperative Oncology Group

3.2. Compliance with treatment

The prescribed total radiotherapy dose of 70 Gy was given in all the patients (100%). Twenty nine patients (80.6%) completed the radiotherapy course in a period of time ≤ 7 weeks. Twenty two patients (61.1%) received all seven cycles of concurrent cisplatin. The mean total dose of cisplatin given was 192 mg/m2 ± 14.8 SD.

3.3. Response to treatment

At 3 months post treatment assessment 26 patients (72.2%) achieved complete response at the primary

site (Table 3). Complete response of the nodal disease was seen in 16 out of 25 patients presented with metastatic lymph node(s) in the neck (64.0%) (Table 3). There was no salvage neck dissection performed for residual neck disease in the remaining 9 patients (36.0%) who achieved a partial response of the nodal disease. Complete composite response was achieved in 25 patients (69.4%) (Table 3).

Table 3. Tumor responses assessed clinically and radiologically 3 months after completion of concurrent chemoradiotherapy

Response to treatment	Number of patients (%)
Complete response of the primary tumour	26/36 (72.2%)
Partial response of the primary tumour	10/36 (27.8%)
Complete response of the nodal disease	16/25 (64.0%)
Partial response of the nodal disease	9/25 (36.0%)
Complete composite response	25/36 (69.4%)
Partial composite response	11/36 (30.6%)

3.4. Survival outcomes

The median follow-up of all patients was 20.5 months (range, 5 to 90 months). Nine patients (25%) remain alive, with a median follow-up of 59 months (range, 30 to 90 months). In those 25 patients who achieved complete composite response, treatment failure occurred in 15 patients (60.0%). The site of the primary tumor was the most common location of isolated recurrence noted in six patients. An isolated regional recurrence was present in only one patient, while four patients developed locoregional recurrence. Distant tumor failure was observed in six patients. Two of these six patients experienced locoregional failure. The sites of distant metastases included the lung, bones and liver. Lung was the distant metastases site in all the patients. One patient had non-small cell lung cancer as a second primary malignancy.

Eleven patients died because of the progression of local, regional, or locoregional persistent disease, six patients died due to a local recurrence, one patient died because of isolated regional recurrence, two patients died due to a recurrence at both primary and nodal site, four patients died after developing distant metastases, and two patients died because of development of locoregional recurrence and distant metastases. One patient died due to a second primary tumor.

At 3 years, the LRRFS rate was 38.8% (Figure 1). Three years DFS rate was 27.8% (Figure 2). The 3-year OS rate was 27.3% (Figure 3). The median duration of LRRFS and DFS was 12 months (range, 3-90 months), and the median duration of OS was 20.5 months (range, 7-90 months).

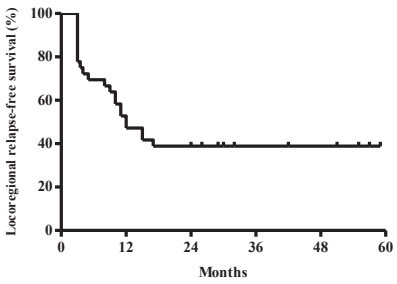

Fig. 1 – Locoregional relapse-free survival for all patients

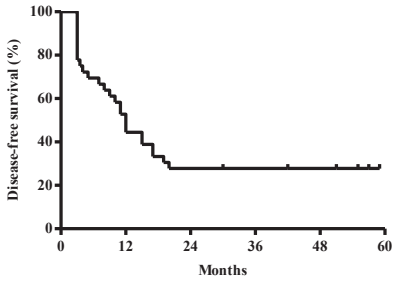

Fig. 2 – Disease-free survival for all patients

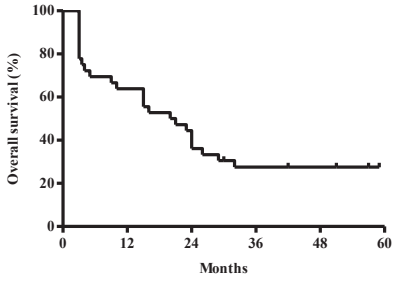

Fig. 3 – Overall survival for all patients

3.5. Treatment induced toxicity

Acute toxicities are shown in Table 4. The most frequently manifested radiation induced acute mucosal reaction was grade 3 mucositis experienced in 58.3% of patients. The most commonly present skin toxicity was grade 2 acute skin reaction. Grade 2 nausea was the most frequently recognized nonhematological chemotherapy-related toxicity while grade 1 leucopenia was the most commonly seen hematological chemotherapy-related toxicity.

Table 4. Acute toxicity recorded during treatment

Toxicity	Grade of reaction (% of 36 patients)			
	0	1	2	3
Acute normal tissue reactions according to RTOG criteria				
Organ/Tissue				
Skin	0	0	94.4	5.6
Mucous membrane	0	0	41.7	58.3
Acute toxicity according to WHO criteria				
Nonhematological				
Nausea	44.4	55.6	0	0
Vomiting	77.8	22.2	0	0

Hematological				
Leucopenia	36.1	55.6	5.5	2.8
Anemia	55.6	38.9	5.5	0
Thrombocytopenia	52.8	44.4	2.8	0

The average weight loss during treatment as a percentage of weight on treatment start was 9% with a range between 3.0% and 15.0%.

Late toxicities are shown in Table 5. Xerostomia was the most important late complication with grade 2 late salivary gland toxicity revealed in 72.2% of patients. Grade 2 late mucosal reactions was experienced in 58.3% of patients.

Table 5. Late toxicity recorded following treatment

Organ/Tissue	Grade of reaction (% of 36 patients)	
	1	2
Skin	61.1	38.9
Subcutaneous tissue	61.1	38.9
Mucous membrane	41.7	58.3
Salivary gland	27.8	72.2

4. DISCUSSION

CCRT using cisplatin as the chemotherapy agent of choice has been widely adopted as the standard of care for locally-regionally advanced HNSCC [12-14]. The benefit of synchronous administration of radiotherapy and chemotherapy compared with radiotherapy alone in the treatment of advanced oropharyngeal cancer has also been well established in the GORTEC 94-01 study [16, 17].

In our study of CRCT using 3DCRT and concurrent weekly cisplatin, the observed 3-year rates of LRRFS, DFS, and OS were 38.8%, 27.8%, and 27.3%, respectively. Unfortunately, the impressive feature when comparing our results with those achieved in studies using definitive radiotherapy alone in the treatment of advanced tonsillar cancer, is the fact that, despite the combination of chemotherapy and radiotherapy used in our study, the obtained results are lower than those reported by authors who used radiotherapy alone. For example, Poulsen et al. [28], comparing outcomes of primary surgery and definitive radiotherapy in patients with stage III and IV squamous cell carcinoma of the tonsil, reported 5-year locoregional control and OS rate of 73% and 41% in the group treated with radiotherapy alone, respectively. In the study of Lee et al. [29] of 243 patients with squamous cell carcinoma of the tonsillar region treated with radical radiotherapy, the reported 5-year absolute and cause-specific survival rates for stage III were 55% and 85%, respectively, for stage IVA were 35% and 60%, respectively, and for stage IVB were 23% and 38%, respectively. Mendenhall et al. [30], in their retrospective study of definitive radiotherapy for carcinoma of the tonsillar area, reported that 5-year cause-specific survival rates for stage III, IVA, and IVB were 84%, 73%, and 46% respectively.

Regarding the analysis of the role of CCRT, specifically in the treatment of locoregionally advanced tonsillar carcinoma, the reported results in the literature are scarce. In the retrospective study of Koo et al. [31], treatment outcome following definitive chemoradiotherapy versus postoperative radiotherapy in patients with stage III-IV tonsillar cancer was analyzed. The reported rates of 5-year locoregional progression-free survival and OS for patients treated with CCRT were 83% and 76%, respectively. One of the studies exploring the efficacy of chemotherapy, as a part of a multimodality approach in locally advanced stage IV tonsillar cancer is the retrospective study of Prestwich et al. [32] reporting the results of induction chemotherapy followed by cisplatin CCRT. The achieved 3-year locoregional control rate in complete responders following induction chemotherapy was 91%. The authors reported 3-year progression-free survival and OS rate of 75% and 66%, respectively. In the retrospective analysis of therapy in 61 patients with pathologically confirmed tonsillar carcinoma without distant metastasis reported by Wang et al. [33], CCRT was used in 21 out of 45 patients with stage III-IV disease. The 5 years survival for this patient's category was 36.4%. In the study of Shirazi et al. [34], aimed to review their experience in the management of advanced tonsillar squamous cell carcinoma and to compare treatment outcomes between patients treated with and without surgery to the primary site, 74 patients were retrospectively analyzed. Thirty six of these patients were treated with an organ preservation approach using radiotherapy alone or chemoradiotherapy, and 38 patients were treated with definitive surgery. The rates of 4-year local control and 4-year OS for organ preservation group were 86% and 48%, respectively. All these results of the studies using combined treatment approach with radiotherapy and chemotherapy for advanced tonsillar cancer regarding both LRC and survival are remarkably superior to the results obtained in our study.

In an effort to explain such unexpectedly poor results of 3DCRT given with concomitant weekly cisplatin in patients with advanced tonsillar carcinoma in our study, and taking into account that the presence of large primary tumors (T3–T4) or advanced stage (N2–N3) metastatic neck lymph nodes had a detrimental effect on prognosis, we underline that these results could only be partially attributable to the high percentage of stage IVA (58.3%) and stage IVB (11.1%) disease at admission. Another possible explanation for such disappointing results would be insufficient target coverage of the gross tumor, leading to insufficient response of the primary tumor and metastatic nodes in the neck, and also insufficient target coverage of the subclinical disease, leading to local and/or regional failure in patients with complete composite response.

Regarding the acute toxicity, 58.3% of patients in our study experienced grade 3 mucositis. However, the fact that should be emphasized is that besides the

poor outcome of CCRT in our study, when evaluating late radiotherapy-related toxicities starting at 4 months after treatment completion, we revealed that xerostomia was the most prominent late effect with grade 2 present in 72.2% of patients.

Considering the unfruitful rates of locoregional control and survival obtained in our study, and the high incidence of high grade xerostomia as the primary quality-of-life complaint among long-term survivors following radiotherapy in head and neck region, we consider necessary to accentuate the role of IMRT representing an advance in technology that allows the radiation oncologist to "shape" radiation dose profiles around normal structures while fully dosing the tumor and risk nodal regions [35]. IMRT allows exquisite dose conformality with sparing of adjacent organs, and therefore orofaryngeal cancers, including those arising from tonsillar region, represent ideal sites for its application since the tumors often present in close proximity to sensitive normal tissues such as the parotid glands. Early experience with IMRT for oropharyngeal cancers shows encouraging results, providing local or locoregional control ranging between 89% and 98% [22, 36, 37]. In the study of Chao et al. [36], comparing tumor control, acute and late toxicity between IMRT and conventional radiotherapy, 460 patients with oropharyngeal cancer were analyzed. Tonsil primary tumors were present in 260 patients. Most of the patients (74%) had stage III-IV disease. The dosimetric advantage of IMRT resulted in a significant reduction of late salivary toxicity without negative impact on tumor control and disease-free survival. In the study of de Arruda et al. [22] the use of IMRT in 40 patients with histologically confirmed cancer of the oropharynx resulted with 2-year locoregional control and OS rate of 98%. The authors of this study conducted in the Memorial Sloan-Kettering Cancer Center reported 33% grade 2 xerostomia at follow-up of nine months or greater. The University of California-San Francisco experience with IMRT and concurrent chemotherapy for stage III and IV oropharyngeal carcinoma showed excellent locoregional control rates and grade 2 xerostomia at follow-up of two years or more reported in 22% of patients [23]. In the retrospective study of Clavel et al. [38] comparing the toxicity and efficacy of IMRT vs. conventional radiotherapy in 249 patients with locally advanced oropharyngeal cancer, the authors reported that IMRT was associated with favorable locoregional control and survival rates with less xerostomia and acute dermatitis than conventional radiotherapy, when both were given concurrently with chemotherapy.

5. CONCLUSION

Taking into account the low 3-year survival rates observed in our study and the high percentage of grade 2 xerostomia, it can be concluded that in the future, instead of 3DCRT with concurrent chemotherapy, intensity modulated radiation therapy (IMRT) in combination with concomitant chemotherapy should be considered a fully recommendable treatment option for advanced tonsillar carcinoma in order to improve locoregional control and survival with simultaneous reduction of late salivary toxicity and therefore prevention of late xerostomia.

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