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Original article

Prognostic factors in stage IV oropharyngeal Squamous Cell Carcinoma: the "punto" experience

Alessia Piccinini[1], *Matteo Alicandri Ciufelli*[1], *Angelo Ghidini*[1], *Vincenzo Vincenti*[2], *Teore Ferri*[2], *Livio Presutti*[1]

[1] Otolaryngology-Head and Neck Surgery Department, University Hospital of Modena, Modena, Italy; [2] Otolaryngology and Otoneurosurgery Department, University Hospital of Parma, Parma, Italy

Summary. *Purpose:* Squamous Cell Carcinoma (SCC) of Oropharynx is often diagnosed in advanced stages. Treatment options have improved during recent years, however the choice of most appropriate treatment is still controversial. Prognostic factors can help to optimize the care. This study investigate the role of 9 potential prognostic factors, including HPV status, in Oropharyngeal SCC. *Materials and Methods:* Nine prognostic factors were investigated in a retrospective chart of 98 patients treated for stage IV SCC of Oropharynx from january 2006 to january 2012, including age (<60 or >60), gender, tumor subsite, histological grading, T stage, N stage, AJCC stage, BMI pre-treatment and HPV status. Moreover treatment modalities were compared and the data regarding the treatment factors, like radiotherapy technique and kind of chemotherapy were collected and compared. Primary endpoint was the impact of the prognostic factors on OS, DFS and DSS. Seconrdary endopoint were the impact of these factors on QOL and Toxicity. *Results:* On univariate analisys significant improved OS was associated with age < 60 (p=0,004), grading G3 (p=0.003), BMI > 25 (p=0.03), radiotherapy with IMRT/SIB IMRT technique (p=0,01) and AJCC stage IVa (p=0,01). No prognostic factor was associated to DFS improvement. Instead a significant improved DSS was associated with age <60 (p=0,01), Grading G3 (p=0,04), T stage (p=0,02), AJCC stage IVa (p=0,03) and tonsil subsite (p=0.04). in the analysis of hazards ratios for OS age (HR 2.22; 95% CI 1.00-4.93; p=0.019), grading (HR 0.17; 95% CI 0.047-0.64 ; p=0.008), AJCC stage (HR 4.81; 95% CI 1.34-17.2; p=0.016) and radiotherapy technique (HR 0.2; 95% CI 0.08-0.87; p=0.02) maintained significance, whereas BMI (HR 0.45; 95% CI 0.09- 2.2; p=0.3) did not. In the analysis for DSS only age (HR 2.22; 95% CI 1.22-7.81; p=0.017) and grading (HR 0.11; 95% CI 0.02- 0.59; p=0.009) maintained significance. *Conclusion:* improved outcomes were significantly associated with lower age and tumor stage, grading G3, tonsil subsite, radiotherapy performed with IMRT technique, and BMI > 25. (www.actabiomedica.it)

Key words: ??????

Introduction

Because oropharyngeal cancer may remain asymptomatic until large and have easy access to the draining lymphatics resulting in nodal metastases, these cancers are often diagnosed in advanced stages (1). Treatment options for locally advanced SCCHN have improved during recent years, in particular with the introduction of high precision rediotherapy techniques, new systemic agents and less invasive surgical approaches. (2,3). However the most appropriate treatment regimen is still controversial, so prognostic factors can help

the physician in selecting the appropriate treatment regimen for individual patient.

Moreover in recent years the prognostic value of the human papillomavirus (HPV) status has gained attention in clinical research: several studies in literature suggest that Oropharyngeal Squamous Cell Carcinoma caused by HPV are associated with favorable survival (4). Infact the HPV positive tumors show different risk factors profile and different survival outcome, but actually there aren't clinical trials stratified according to HPV status and treatment options are not based on HPV status(4).

The aim of present study would be to investigate the role of 9 potential prognostic factors, including HPV status, for Overall Survival (OS) Disease Free Survival (DFS) and Disease specific Survival (DSS) in Squamous Cell Carcinoma of the oropharynx.

Material and Methods

Since 2011 Patient diagnosed with oropharyngeal cancer at our department have been evaluated by PUNTO (Percorso Unitario Trattamento Oncologico) multidisciplinary team meetings, which discussed and proposed to patients appropriate treatment options. All information about patients and pathology have been collected in an appropriate database. Patients were also periodically followed for post-treatment controls by the same team. Between february 2012 and september 2012 digital charts of patients treated for locally advanced oropharyngeal squamous cell carcinoma (Stage IV) at the University Hospital of Modena and followed for periodical post-treatment control by PUNTO between january 2006 and january 2012 were retrospectively analyzed. Exclusion criteria were patient underwent palliative treatments and patients treated elsewhere.

The main endpoints were Overall Survival (OS), Disease Free Survival (DSF) and Disease Specific Survival (DSS).

Potential prognostic factors were analyzed, including age (<60 or >60), gender, tumor subsite (tonsil, base tongue, soft palate), histological grade (G1-2-3), T stage, N stage, AJCC stage, BMI pre-treatment. The HPV status was investigated in 20/98 pts (20,4%): Formalin fixed paraffin-embedded tumor specimens were evaluated for the HPV 16 DNA with the use of the in situ hybridization-catalyzed signal amplification method; HPV 16 negative tumors were further avaluated for additional oncogenic HPV types.

Moreover treatment modalities were compared (Surgery +/- adiuvant treatments vs Radiotherapy +/- Chemotherapy vs Induction chemotherapy followed by chemoradiotherapy) and the data regarding the treatment factors, like radiotherapy technique (SIB IMRT vs 3DCRT) and kind of chemotherapy (Cisplatin 100mg/m2 vs Cisplatin 30 mg/m2 vs Cetuximab), were collected and compared.

Second endpoints were QOL and Toxicity. We analized the correlation between previous prognostic factors (in particular BMI pretreatment, Site of disease, radiotherapy technique) and the data of QOL and toxicity.

The data regarding early (<120 days) and late (>120 days) toxicity (5) was collected

The data inherent quaity of life (QOL) were collected using the Performance Status Scale for Head and Neck Cancer (PSS-HN) and Karnofsky Performance Status (KPS)(6)

Statistical consideration

OS, DFS, DSS were calculated with Keplan-Meier method and referenced from the first day of treatment. The potential prognostic factors were analized using the univariate log-rank method. A p value <0,05 was considered statistically significant. The factors with significant p value to univariate analysis were analized with Cox proportional-hazards models to estimate hazards ratios.

The correlation between prognostic factors and data of QOL and Toxicity has been calculated using Fisher Exact Test.

Results

98 patients were included in the study. Patient and tumor characteristic are detailed in table 1.

The median age was 61 (± DS 9,8; range 36-78).

Median follow up was 22,7 months (range 2-92 months).

Table 1. Patient characteristics

	EntireCohort (n=98) N. Patients (%)
Age	
< 60	45 (45.92)
> 60	53 (54.08)
Gender	
M	78 (79.59)
F	20 (20.41)
Tumor Site	
Tonsil	67 (68.37)
Base tongue	27 (27.55)
Soft palat	4 (4.08)
Grading	
G1	4 (4.08)
G2	16 (16.33)
G3	50 (51.02)
GX	28 (28.57)
T stage	
T1	13 (13.27)
T2	25 (25.51)
T3	6 (6.12)
T4a	41 (41.84)
T4b	13 (13.27)
N stage	
N0	13 (13.27)
N1	9 (9.18)
N2a	3 (3.06)
N2b	33 (33.67)
N2c	36 (36.73)
N3	4 (4.08)
AJCC stage	
IVa	77 (78,5)
IVb	16 (16,3)
IVc	5 (5,2)
BMI pretreatment	
Sottopeso (<20)	6 (6.12)
Regolare (20-25)	42 (42.86)
Sovrapeso (25-30)	41 (41.84)
Obesità (>30)	9 (9.18)

Of the patients studied for HPV status, 16 were HPV positive tumors (75%). The majority of cases were subtype 16 (12 pts) only one patient was subtype 18 and 3 patients were subtype 33.

Radiotherapy was performed in 87 pts (88,7%): only 7 pts performed exclusive radiotherapy, concomitant chemotherapy was associated in 80 pts; of these 80 pts, concomitant treatment was associated to induction chemotherapy in 31 pts.

Table 2. Radiotherapy technique

Radiotherapy technique	N. Patients (%)
3DCRT	32 (34%)
IMRT	19 (20%)
SIBIMRT	44 (46%)

Table 3. Chemotherapy technique

Chemotherapy technique	N. Patients(%)
Platin 100 mg/m2	46 (56%)
Platin 30 mg/m2	11 (13%)
Cetuximab	26 (31%)

Table 2 and 3 summarize respectively the modality of radiotherapy and the kind of chemotherapy.

Surgery was performed as resection of the primary tumor plus bilateral modified radical neck dissection in 11 patients (11,2%). A microscopically complete resection (R0 resection) was achieved in 8/11 pts . Adiuvant radiotherapy was permormed in 8 pts, and in 3 pts radiotherapy was associated to chemoterapy

The data regarding early and late toxicity was collected respectively in 93 pts and in 85 pts.

The data inherent QOL were collected in 94 pts (95,9%) Table 4 reports data inherent early and late toxicity in the patient underwent radiotherapy.

The analysis of quality of life reveals that the mean PSS-ND was 81,4, mean PSS-EP was 89, and mean PSS-US was 94,4. The mean KPS was 88.

The 3 years OS, DFS and DSS rates in the entire cohort was respectively 62,1%, 87% and 67,4%

Table 5, 6 and 7 summarized the results of univariate analysis regarding the impact of the different prognostic factors respectively on OS,DFS and DSS.

On univariate analisys significant improved OS was associated with age < 60 (p=0,004), grading G3 (p=0.003), BMI > 25 (p=0.03), radiotherapy with IMRT/SIB IMRT thecnique (p=0,01) and AJCC stage IVa (p=0,01).

No prognostic factor was associated to DFS improvement.

Instead a significant improved DSS was associated with age <60 (p=0,01), Grading G3 (p=0,04), T

Table 4. Early and late toxicity in patients underwent radiotherapy

	0 N. pazienti (%)	G1 N. pazienti (%)	G2 N. pazienti (%)	G3 N. pazienti (%)	G4 N. pazienti (%)
TCa	11 (11.6)	38 (40)	28 (29.5)	14 (14.7)	2 (2.1)
TMa	8 (8.4)	12 (12.6)	54 (56.8)	18 (18.9)	1 (1.1)
TFa	17 (17.9)	37 (38.9)	31 (32.6)	8 (8.4)	0 (0)
TSa	17 (17.9)	46 (48.4)	29 (30.5)	0 (0)	1 (1.1)
TLa	76 (80)	11 (11.6)	4 (4.2)	2 (2.1)	0 (0)
TCc	49 (51.6)	31 (32.6)	5 (5.3)	0 (0)	0 (0)
TMc	38 (40)	40 (42.1)	7 (7.4)	0 (0)	0 (0)
TFc	55 (57.9)	27 (28.4)	3 (3.2)	0 (0)	0 (0)
TSc	17 (17.9)	48 (50.5)	20 (21.1)	0 (0)	0 (0)
TLc	61 (64.2)	20 (21.1)	4 (4.2)	0 (0)	0 (0)

stage (p=0,02), AJCC stage IVa (p=0,03) and tonsil subsite (p=0.04).

The factors with significant p value to univariate analysis were analized with Cox proportional-hazards models to estimate hazards ratios. In the analysis for OS age (HR 2.22; 95% CI 1.00-4.93; p=0.019), grading (HR 0.17; 95% CI 0.047-0.64 ; p=0.008), AJCC stage (HR 4.81; 95% CI 1.34-17.2; p=0.016) and radiotherapy technique (HR 0.2; 95% CI 0.08-0.87; p=0.02) mantained significance, whereas BMI (HR 0.45; 95% CI 0.09- 2.2; p=0.3) did not.

In the analysis for DSS only age (HR 2.22; 95% CI 1.22-7.81; p=0.017) and grading (HR 0.11; 95% CI 0.02- 0.59; p=0.009) mantained significance.

Relatively to the analysis of QOL only the KPS and BMI pretretment showed a significative correlation (p=0.01): the 77.7% of the patients with BMI pretreatment ≥25 have shown a KPS=100 respect the 34,2% of patients with BMI pretreatment < 25.

The BMI pretreatment is also significatively correlated to the acute mucosa toxicity (p=0.03): grade 2 toxicity was observed in 61% of patients with BMI pretreatment ≥25 respect 74% of patients with BMI pretreatment < 25; Grade 3 toxicity was observed in 20% of patient with BMI pretreatment ≥25 respect 26% of patients with BMI pretreatment < 25.

The analysis of toxicity also showed a significant correlation between the radiotherapy technique and cronic mucosa toxiity (p=0.02): the distribution of toxicity in patients treated with SIBIMRT was 22,9% Grade 0, 69,9% Grade 1 and 7,2% grade 2 vs 28,5%, 44,3% and 27,2% respectively for patients treated with 3DCRT.

Also the site of disease resulted significatively correlated to acute and cronica pharyngeal toxicity (p=0.007 and p=0.02 respectively) with a lower toxicity in patient affected by tonsil carcinoma (1,56% of grade 3 acute toxicity respect 23,8% and 33,3% respectively for the base tongue and soft palate).

Discussion

Squamous cell Carcinomas of the Oropharynx are often diagnosed in advanced stages. Treatment options for locally advanced SCCHN have improved during recent years, in particular with the introduction of high precision rediotherapy techniques, new systemic agents and less invasive surgical approaches (7).

These novel approaches have greatly diminished the role of open surgery as initial therapy for oropharyngeal cancers. Open surgery which is often reserved for salvage on relapse, may still be an appropriate therapy for certain early stage primary lesions (3). The growing treatment armamentarium requires careful consideration for optimal individualized care.

Intensity modulated radiation therapy (IMRT) technology and altered fractionation schedules have contributed to state-of-the-art definitive therapy for oropharyngeal cancers (8). Moreover several randomized studies have demonstrated improved local-regional control rates and also improved overall survival with concurrent administration of chemotherapy with radiotherapy for patients with locally advanced squamous cell carcinoma of the head and neck. (9,10) The studies that have directly compared induction chemo-

Table 5. Univariate analysis of OS

	OS a 1 anno (%)	OS a 2 anni (%)	OS at 3 years (%)	P value
HPV neg	50	50	50	0.05
HPV pos	93	93	93	
Age < 60 aa	84.8	74.8	74.8	0.04
Age > 60 aa	78.8	54.6	50.7	
Male	79.9	60.1	60.1	0.28
Female	87.3	79.4	69.5	
Tonsil	83.9	69.6	66.1	0.36
Base tongue	74.3	52.1	66.6	
Soft palate	66.6	52.1	66.6	
G1	33	na	na	0.003
G2	81.8	34	34	
G3	79.9	67.2	63.3	
Gx	87	80.3	80.3	
T1	100	100	100	0.13
T2	92.3	84.6	84.6	
T3	75	75	75	
T4a	70.4	55.8	51.5	
T4b	84.6	51.2	51.2	
N0	100	100	100	0.27
N1	60	60	60	
N2a-b	86	61.5	61.5	
N2c	82.1	66.2	61.8	
N3	37.5	-	-	
AJCC stage IVa	83.6	73.6	70.5	0.01
AJCC stage IVb	74	44.8	44.8	
AJCC stage IVc	60	-	-	
Surgery(±adiuv)	100	60	60	0.68
RT ± CT	77.2	63.5	59.3	
CT Induction	82.7	68.2	68.2	
Cisplatin 100 mg/m2	83.9	71.6	71.6	0.33
Cisplatin 30 mg/m2	70	60	60	
Cetuximab	72.1	59	51.6	
3DCRT	70.8	58	53.2	0.01
IMRT / SIB IMRT	89.5	83.5	83.5	
BMI <20	60	60	60	0.03
BMI 20-25	70.8	49.6	45.4	
BMI 25-30	89.9	73	73	
BMI > 30	100	100	100	

Table 6. Univariate analysis of DFS n.a. not available

	DFS a 1 anno (%)	DFS a 2 anni (%)	DFS a 3 anni (%)	P value
HPV neg	n.a	n.a	n.a	-
HPV pos	n.a	n.a	n.a	
Age < 60 aa	96.8	92.8	87.3	0.86
Age > 60 aa	94.3	94.3	87.5	
Male	94.2	91.5	83.3	0.45
Female	100	100	100	
Tonsil	93.5	90	85.8	0.44
Base tongue	100	100	87.5	
Soft palate	100	100	100	
G1	100	100	100	0.84
G2	90.9	77.9	77.9	
G3	94.2	94.2	94.2	
Gx	100	100	82.5	
T1	100	100	100	0.15
T2	95.2	95.2	84.6	
T3	100	100	100	
T4a	100	94.4	94.4	
T4b	81,8	81.8	61.3	
N0	100	100	100	0.44
N1	100	100	100	
N2a-b	n.a	n.a	n.a.	
N2c	95.8	95.8	87.8	
N3	100	n.a.	n.a.	
AJCC stage IVa	98	95	90.8	0.22
AJCC stage IVb	81.8	81.8	61.3	
AJCC stage IVc	100	n.a.	n.a.	
Surgery(±adiuv)	97.2	97.2	90.7	0.99
RT ± CT	80	80	80	
CT Induction	95.8	89.4	78.2	
Cisplatin 100 mg/m2	93.5	88.3	80.3	0.22
Cisplatin 30 mg/m2	100	100	100	
Cetuximab	100	100	85.7	
3DCRT	100	93.3	93.3	0.4
IMRT / SIB IMRT	96.6	96.6	74.5	
BMI <20	100	100	100	0.19
BMI 20-25	91.9	86.8	79.6	
BMI 25-30	100	100	100	
BMI > 30	88.8	88.8	71.1	

Table 7. Univariate analisys of DSS

	DFS a 1 anno (%)	DFS a 2 anni (%)	DFS a 3 anni (%)	P value
HPV neg	50	50	50	0.054
HPV pos	93.7	93.7	93.7	
Age < 60 aa	87.32	83.35	83.35	0.01
Age > 60 aa	78.83	57.86	53.56	
Male	81.5	66.8	66.8	0.48
Female	87.3	79.4	69.5	
Tonsil	86.3	73.4	70	0.04
Base tongue	75.4	58.6	58.6	
Soft palate	75	75	75	
G1	50	25	25	0.04
G2	86.6	52	52	
G3	79.2	70.1	66	
Gx	92	85.4	85.4	
T1	100	100	100	0.02
T2	88.1	88.1	88.1	
T3	83.3	83.3	83.3	
T4a	70.4	55.8	51.5	
T4b	92.3	55.9	55.9	
N0	100	100	100	0.07
N1	60	60	60	
N2a-b	90	64	64	
N2c	82.1	69.5	64.9	
N3	37.5	na	na	
AJCC stage IVa	98	95	90.8	0.03
AJCC stage IVb	81.8	81.8	61.3	
AJCC stage IVc	100	na	na	
Surgery(±adiuv)	77.25	66.2	61.8	0.64
RT ± CT	100	60	60	
CT Induction	86	71	71	
Cisplatin 100 mg/m2	83.9	74.8	74.8	0.24
Cisplatin 30 mg/m2	80	68.5	68.5	
Cetuximab	72.1	59	51.6	
3DCRT	81.2	61.3	54.5	0.17
IMRT / SIB IMRT	87.9	76.9	76.9	
BMI <20	66.6	66.6	66.6	0.11
BMI 20-25	76.2	58.3	54.1	
BMI 25-30	88.5	75.3	75.3	
BMI > 30	100	100	100	

therapy to concomitant chemotherapy didn't showed a greater effect on survival, but the data did not reach statistical significance (11).

The most thoroughly studied biologic therapy combined with radiation for patients with head and neck cancer to date is cetuximab, a monoclonal antibody which has high affnity for the EGFR, preventing ligand binding to the EGFR and inducing receptor downregulation. Although these initial results clearly demonstrate the potential of cetuximab as a radiosensitizing agent, the optimal role of cetuximab in curative settings is undefined given the extensive body of evidence supporting more traditional chemoradiotherapy approaches (12).

In our study, the survival rates at three years was 61.8%, similar to the data reported in literature.

The choice of treatment and the kind of chemotherapy used were not impacting on OS, DFS and DSS, probably because of their small numbers and the non-uniformity of the sample. Although the analysis wasn't significant, the comparison between surgery and chemoradiotherapy did not show a clear difference in OS at three years (60% in patients undergoing surgery and 59.3% in patients receiving concomitant treatment). Instead OS was improved in patients undergoing induction treatment. Induction treatment is a more aggressive treatment and is usually reserved for patient with a better performance status and a lower age in order to obtain a better tolerability. This could have created a bias in the examination.

In literature there are no prospective studies comparing cisplatin and cetuximab, so actually the choice is based on factors related to the patient like comorbidities, renal or cardiac function, performance status,ecc.. Basing on the data of literature Cisplatin currently remains the treatment of choice (11).This implies that patients who receive cetuximab are patients with reduced performance status, advanced age, associated comorbidities or impaired cardiac function or kidney failure, in which is contraindicate the use of cisplatin, this fact can explain the difference in the higher values of OS detected in patients who executed cycles of chemotherapy containing cisplatin (71.6% at three years compared to 51.6% in patients which performed Cetuximab).

On the other hand it is considered that regimens containing cisplatin are characterized by high toxicity (11). Our study has shown that, in patients underwent platinum, the DSS appears lowered by 3.2% compared to OS, while in patients who received Erbitux there is no difference between DSS and OS. This might be interpreted as a less morbidity of the treatment.

Relatively to radiotherapy treatment, preliminary single institution reports have suggested that IMRT can reduce salivary toxicity without sacrificing tumor control in patients with oropharyngeal carcinoma (13). Given these considerations, at the our Center we now routinely treat our patients with oropharyngeal carcinomas with IMRT, typically in the context of concurrent chemotherapy.

Until recently, clinical outcomes data regarding the use of IMRT for oropharyngeal cancer have been limited. Collectively, these studies highlight the ability of IMRT to provide excellent target coverage while sparing adjacent normal structures in patients with oropharyngeal cancer. In the published literature to date, 2-year locoregional control values for oropharyngeal cancer treated with definitive chemoradiation using IMRT have been around 85-90% (14).

Chao et al. (15) recently reported on the experience using IMRT for mostly Stage III and IV oropharyngeal tumors. A total of 74 patients were included; 42% were treated definitively and 58% were treated postoperatively. Of the 31 patients treated definitively, 17 of them received concurrent platinum-based chemotherapy. With a median follow-up of 33 months, the 4-year estimate of locoregional control was 87% and disease-free survival was 81%. The treatment was well tolerated, with Grade 2 xerostomia and skin toxicity being the worst side effects experienced in the acute setting .

In our serie we compared patient treated with SIBIMRT vs those who underwent 3DCRT. The OS in patient treated with SIB IMRT was significatively better (83.5% vs 53,2%; HR=0.2) and similar to the data in literature (15). The SIB IMRT technique also impacted significatively on cronic mucosa toxicity (p=0.02) resulting in a lower toxiciy.

Relatively to the prognostic factors investigated, higher values of OS were detected in HPV-positive group (93% vs 53%), but without statistical significance.

HPV infection is now recognized to play a role in the pathogenesis of a subgroup of head and neck

squamous cell carcinomas. The prognotic role of HPV status in the treatment of head and neck cancer has gained importance in recent years: in literature the superior prognosis for HPV-positive oropharyngeal SCC appears to have multifactorial underpinnings. Several studies infact provide strong evidence that HPV positive and HPV negative oropharygeal SCC are distinct and have different causes, risk factor profiles, and survival outcomes (16, 17, 4) Malignant neoplasms belonging to this specific category are poorly differentiated, develop at a young age in patients with high socioeconomical level and are correlated to sexual habits (16).

The higer survival rate among patients with HPV positive tumor is due in part to greater locoregional control, reflecting higher intrinsic sensitivity to radiation or better rediosensitization with the use of cispaltin (18). Although several studies have shown that HPV positive oropharyngeal cancer is genetically distinct from HPV negative cancer with respect to patterns of loss of heterozygosity, chromosomal abnormalities, and gene expression profiles (19,20) and is inversely correlated with biomarkers for a poor prognosis (es.p53 mutationsor expression of epidermal growth factor receptor (21), no specific mechanism has been shown to explain the higher rates of response to radiation therapy and chemotherapy among patients with HPV positive tumor.

Though no direct evidence from formal clinical trials exists to guide treatment decisions for individual patient on the basis of HPV status. Whether patients with HPV-positive tumors who are considered to be in the low-risk category can be spared the long term complications of intensive, multimodal therapy without compromising their survival is now highly relevant clinical question.

Our study reflects the data in literature about HPV positive oropharyngeal cancers, both as incidence and prevalence in males, prevalence for genotype 16, and better prognosis, although this benefit was not statistically significant.

In our study, on univariate analysis, improved OS and DSS was also significantly associated with age inferior than 60 years and grading G3. Also the site of disease showed a significatively correlation with improved values of DSS (p==0.04). infact the DSS in the lateral wall at the primary site was superior those in the other sites. One of those reason might be due to a patient population associated with HPV infection, infact also from the data in literature HPV infection resulted more frequently associated to tonsillar site (22)

The impact of grading on survival instead, might be associated with a greater radiosensitivity of poorly differentiated tumors compared to well differentiated.

Regarding the role of age, in current study the prognostic significance of age was defined as 60 years old or less. In literature a recent study (23) investigated the role of age on survival for tonsillar carcinoma with an age cut-off of 50 years old: the long-term increased survival for young patients in this study most likely reflects their HPV positive status, however the authors cannot exclude that the improved survival may be related to better general health status and treatment tolerance or to a more frequent use of concomitant chemotherapy in this age group. In our study the age cut-off was 60 years old in order to make the prognostic factor age as independent as possible by HPV positivity. In our study, with regard to overall survival, younger patients older showed survival rates of 74.8% compared to 50.7% of patients older than 60 yaers.

Another prognostic factor significantly associated with an improved OS in our study was the BMI pretreatment.

Significant malnutrition before treatment is common among patients with head-and-neck cancer because of diminished oral intake owing to the presence of tumors. Moreover the treatments have an impact on oral intake and may lead to difficulty in swallowing.

Several studies in literature (24,25)showed that poor nutrition diminishes the ability of the immune system to function effectively and increases the risk of infections, hospitalization, and treatment interruption, potentially resulting in poor treatment outcomes. However few studies have focused on the effect of BMI on treatment outcomes (26).

The present study revealed that lower pretreatment BMI is significantly associated with a poor prognosis. In our study the group of mildly overweight patients with BMI>25 is associated to improved OS and a lower hazard ratio(HR) for death (HR 0.45) than underweight patients . Probably this group of patients who are able to mantein their weight during treatment

may not experience compromised immunity and have a better survival rates. In our study BMI impacted significantly only the OS, not DFS an DSS. This data may indicate how BMI may rapresent a predictor of higher or lower tolerance to treatment, and then correlate with a better or worse outcome .

In addition to the above, that appears similar to the data in literature, the possible correlation between the preT BMI and the quality of life of patients and the acute and late toxicity has been conducted in our study. From the analisys of our data the preT BMI resulted significatively correlated to KPS (p=0.01). Infact values of BMI > 25 are significatively associated with higher values of KPS. Moreover higher preT BMI results significatively correlated to a lower acute mucosa toxicity(p=0.03) This result shows the correlation of BMI non only with survival rates, but also with the quality of life. Moreover the analisys of toxicity confirm that higher BMI values may be predictive of an higher tolerability to the treatment.

Our results confirm the importance, during clinical practice, of the role of the nutritionist within the multidisciplinary team,in order to obtein the best outcome

Conclusion

Improved treatment outcomes in patients with locally advanced oropharyngeal cancers are associated with lower age and tumor stage, grading G3, tonsil subsite, radiotherapy performed with IMRT thecnique, and BMI > 25. These factors, and also HPV status, should be consider in future trials in order to optimaze the care on individual patients.

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Correspondance:
Dr Alessia Piccinini, MD
Otolaryngology and Otoneurosurgery Department,
University Hospital of Parma
Via Gramsci 14, 43126 Parma, Italy
Tel. +39(0)521702195
E-mail address: alessiapiccinini@hotmail.com