



## Comorbidity as a factor of prognosis in patients with locoregionally advanced, inoperable squamocellular head and neck cancers

Komorbidity kao prognostički faktor kod bolesnika sa lokoregionalno uznapredovalim, inoperabilnim planocelularnim karcinomima glave i vrata

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### Abstract

**Background/Aim.** Patients (pts) with tumors often have other diseases or conditions in addition to their index cancer which are generally referred to as comorbidities. Due to the fact that well known risk factors for development of squamocellular head and neck cancers (HNSCC) such as tobacco and alcohol abuse can also damage other important organs, pts with this type of cancer are suitable for analyzing the influence of comorbid conditions on prognosis of the disease. The aim of our work was to assess the prevalence of comorbidities, most frequent conditions and their prognostic impact on overall survival in this particular population. **Methods.** Between July 2002 and January 2007 in the Institute for Oncology and Radiology of Serbia, 100 pts with locoregionally advanced, inoperable HNSCC were initially treated with neoadjuvant chemotherapy regimen, cytarabine-5 fluorouracil-cisplatin. Median age of pts was 55 years, most of them (91%) were males with median number of applied chemo cycles being 4. Data on comorbidities were collected in prospective manner from various sources prior to the treatment. For grading of the severity of comorbid conditions, the Adult Comorbidity Evaluation 27 (ACE-27) comorbidity index was used with four degree scale (0–3). The average follow-up of pts was 15 months

with range from 3–59 months. **Results.** Comorbidities were present in 69 (69%) pts, and 31 (39%) pts had no comorbidities prior to the treatment. Among pts with comorbid conditions prevailed alcoholics, active and former (71%), pts with chronic lung diseases (25%) and cardiovascular diseases (18%). Overall comorbidity score was defined according to the highest ranked single ailment, except in the case where two or more grade 2 ailments occurred in different organ systems in which case the overall comorbidity score was designated as grade 3. Median overall survival for the whole group was 12 months. Median ACE-27 score was grade 1 (range 0–3) which was observed in 43 (43%) pts. Pts without comorbidities survived significantly longer than those with any kind of comorbidity ( $p = 0.0089$ ), and the same was observed comparing survival of pts without comorbidities and those with comorbidity index 2 and 3 taken together ( $p = 0.0047$ ). Results of other intergroup comparisons were of no statistical significance. **Conclusion.** Comorbidity is important prognostic variable in patients with locoregionally advanced HNSCC and should be properly assessed prior to therapy.

### Key words:

carcinoma, squamous cell; head and neck neoplasms; comorbidity; prognosis; survival.

### Apstrakt

**Uvod/Cilj.** Kod bolesnika sa malignim bolestima često se javljaju druga oboljenja ili stanja, nevezana za sam tumor koja se zajednički nazivaju komorbiditetom. Zahvaljujući činjenici da poznati faktori rizika od nastanka planocelularnih karcinoma glave i vrata, kao što su zloupotreba duvana i alkohola, mogu dovesti do oštećenja drugih važnih organa, bolesnici sa ovom vrstom tumora pogodni su za analizu uticaja komorbidnih stanja na prognozu maligne bolesti. Cilj rada bio je procena prevalence komorbiditeta, i najčešćih komorbidnih stanja kao i njihovog uticaja na prognozu preživljavanja u ovoj populaciji bo-

lesnika. **Metode.** U periodu od jula 2002. godine do januara 2007. Godine, 100 bolesnika sa lokoregionalno uznapredovalim, inoperabilnim, planocelularnim karcinomima glave i vrata lečeno je na Institutu za onkologiju i radiologiju Srbije neoadjuvantnom hemioterapijom u sastavu: citarabin-5 fluorouracil-cisplatin. Medijana starosne dobi obolelih bila je 55 godina. Ispitanici su bili najvećim delom muškarci (91%), sa prosečno 4 primenjena hemioterapijska ciklusa. Podaci o komorbidnim stanjima prikupljeni su prospektivno korišćenjem različitih izvora podataka i to pre početka samog lečenja. Za procenu ozbiljnosti komorbidnih stanja korišćen je ACE-27 komorbidni indeks (*Adult Comorbidity Evaluation 27*) sa četvorostepenom

skalom (0–3). Prosečno vreme praćenja bolesnika iznosilo je 15 meseci, sa rasponom od 3 do 59 meseci. **Rezultati.** Komorbiditet je bio prisutan kod 69 (69%) bolesnika, dok 31 (31%) bolesnik nije imao komorbidnih stanja pre početka lečenja. Najčešća komorbidna stanja odnosila su se na alkoholizam, aktivni ili raniji (71%), zatim hronične plućne bolesti (25%), kao i kardiovaskularne bolesti (18%). Ukupni komorbidni zbir bio je određen na osnovu najviše rangiranog opserviranog komorbidnog stanja, osim u slučaju gde su opservirana dva ili više oboljenja gradusa 2, u različitim organima, u kom slučaju je ukupni komorbidni zbir iznosio 3. Prosečno preživljavanje za celu grupu bolesnika iznosilo je 12 meseci. Srednji ACE-27 skor iznosio je 1 sa rasponom od 0 do 3 i bio je prisutan kod 43 (43%) bolesnika. Bolesnici bez komorbiditeta imali su značajno duže pre-

življavanje u odnosu na one sa bilo kojom vrstom komorbiditeta ( $p = 0.0089$ ), a isto je bilo zapaženo poređenjem preživljavanja kod bolesnika bez komorbiditeta u odnosu na bolesnike sa komorbiditetima gradusa 2 i 3, uzeto zbirno ( $p = 0.0047$ ). Rezultati ostalih poređenja između grupa nisu bili statistički značajni. **Zaključak.** Komorbiditet je važan prognostički parametar kod bolesnika sa lokoregionalno uznapredovalim planocelularnim karcinomima glave i vrata, pa se savetuje odgovarajuća procena pre početka lečenja.

#### Ključne reči:

**karcinom, planocelularni; glava i vrat, neoplazme; komorbiditet; prognoza; preživljavanje.**

## Introduction

Head and neck squamous cell carcinomas (HNSCC) include a wide range of malignant tumors that originate in the different structures of this region of the body. This tumor type is the sixth most common malignancy worldwide, accounting for about 6% of all cancer cases and responsible for an estimated 1–2% of all cancer deaths. Oral cavity and laryngeal cancers are the most frequent globally, with age-adjusted standardized incidence rate of 3, 9 and 2.3 per 100,000, respectively<sup>1,2</sup>. Similar situation is in Serbia with HNSCC incidence rate of 7% and larynx cancer as the most common entity<sup>3</sup>.

Although not leaders in the field of oncology, HNSCC are important because their presentation can cause aesthetic alterations of the face and neck with disturbance of vital functions such as a breathing, swallowing, phonation and hearing. Common risk factors for the development of HNSCC include male gender, advanced age, smoking habits, alcohol consumption and human papillomavirus (HPV) infection. Most of the cases are still attributed to heavy smoking and alcohol abuse, and majority of them (60%) initially present with locoregional disease where therapy consists of surgery, radiotherapy or their combinations while inoperable patients are offered chemoradiation as a standard treatment. When therapeutic goal is organ preservation, reliable option might be neoadjuvant chemotherapy which is followed by definitive irradiation<sup>4</sup>.

Besides, HNSCC, tobacco and alcohol use is also associated with the development of other medical conditions ranging from cardiovascular to psychiatric disorders. So, many middle-aged patients with head and neck cancers present with a variety of coincident diseases which are known as comorbidities<sup>5</sup>. From practical point of view, comorbidity in oncology could be defined as any co-existing medical disorder unrelated to the index cancer. The concept of comorbidity and its prognostic importance was first developed from early works of Alvin Feinstein<sup>6</sup> who first had studied the influence of comorbid conditions in patients with diabetes mellitus. Although not a feature of cancer itself, comorbidity is a relevant attribute of the patient and may adversely affect his/her quality of life and survival<sup>7-9</sup>. It is common among

patients with HNSCC and incidence of moderate and serious conditions in this particular population is about 25% portending higher mortality risk<sup>10,11</sup>. So, careful pre-therapy assessment of comorbidity should help in treatment decision making and proper utilization of health care resources.

Our study focused on the impact of patient conditions classified using the Adult Comorbidity Evaluation 27 (ACE-27) index in population with locoregionally advanced, inoperable head and neck cancers treated initially with neoadjuvant chemotherapy. Our aim was to evaluate the prevalence of comorbidities, most frequent conditions among them and their prognostic influence on overall survival in this group of patients.

## Methods

This study represents the single institution experience. The research was conducted in the Institute for Oncology and Radiology of Serbia, Belgrade, on the sample of 100 patients with locoregionally advanced, inoperable HNSCC, during the period from July 1, 2002 – January 1, 2007. All of patients were initially treated with neoadjuvant chemotherapy. The study was approved by the institutional Ethics Committee.

Before treatment, the patients were presented to multidisciplinary oncology team for proper decision making.

In this prospective, randomized, clinical study, patients received neoadjuvant chemotherapy with 3 drugs. Randomisation was performed electronically, and the first group received cytosine-arabioside in a dose of 500 mg/m<sup>2</sup> (D1), 5 fluorouracil in a dose of 750 mg/m<sup>2</sup> (D1-5) given as a 4-hour infusion, and cisplatin in a dose of 120 mg/m<sup>2</sup> (D1). The second group received the same regimen with 5 fluorouracil given continuously (120 hours). All drugs were applied intravenously.

The aims of the study were to assess the overall survival and efficacy of therapeutic regimens. Surveillance period was from July 1, 2002 – January 1, 2007.

Inclusion criteria were: histologically confirmed squamocellular carcinoma, locoregionally advanced, inoperable disease, patients' age 18–75 years, performance status 0–2 [Eastern Cooperative Oncology Group (ECOG) scale], ex-

pected survival more than 3 months, the presence of at least one measurable lesion, the absence of previous chemotherapy and preserved hematological, renal and hepatic functions.

Maximal number of cycles was 6 and assessment was done before every odd cycle and four weeks after completion of the 6-th cycle.

Depending of response, patients proceeded with definitive radiotherapy with TD 60–70 Gy or surgery and radiotherapy. In case of progression, patients were given palliative chemotherapy or symptomatic treatment.

Data on comorbidity were collected prospectively from previous medical reports and opinions, discharge lists from various hospitals, reports from retirement commissions, and reports from penitentiary and detention institutions.

The instrument to measure the severity of comorbidity was ACE-27 index, a 27-item index developed through modification of the Kaplan-Feinstein Comorbidity index (KFI) which classified specific diseases and conditions into four groups: none, mild, moderate and severe according to severity of the organ decompensation. Overall comorbidity score was defined according to the highest ranked single ailment, except in the case where two or more grade 2 (moderate) ailments occurred in different organ systems. In this situation, the overall comorbidity score was designated as grade 3 (severe).

The analyzed comorbid conditions had to be present before starting chemotherapy in order to avoid false conclusions concerning possible toxicity of therapy itself. Survival was calculated from the first day of chemoapplication until death or loss from surveillance, and data about death were obtained from hospital or communal death registries.

The Kaplan – Meier method and Log-rank test were used for survival analysis. The Cox proportional hazards regression was used to investigate the independent effects of ACE-27 scoring on survival.

## Results

Within a period of 54 months we analyzed 100 patients with a poor prognosis HNSCC of whom 91 were men and 9 women. The median age for the whole group was 55 years (range 37–75 years).

Tumors were dominantly located in the hypopharynx (46%), then oropharynx (30%) and larynx (20%) while epipharyngeal and sinonasal tumors much less occurred (4%). Most tumors were locally advanced either T3 (21%) or T4 (68%) and regarding the nodal neck metastases most patients had high nodal volume disease – N3 (62%), while bilateral neck metastases – N2C were found in 38 (38%) patients. Tumor tissue in over two thirds (72%) of the patients was of moderately differentiated histological grade (grade 2).

Chemoregimen with continuous 5 fluorouracil infusion was given to 59 (59%) patients while 41 (41%) of them received short infusion (4 hours). The median number of given cycles was 4 (range 1–6).

The response rate [complete response (CR) + CR + partial response (PR)] with therapy was achieved in 45 (45%)

patients and 44 (44%) patients (44%) progressed during the chemotherapy. Disease control rate [CR + PR + stable disease (SD)] was observed in 56 (56%) patients (Table 1).

**Table 1**  
**Characteristics of patients, disease and treatment regimens**

Characteristics of patients	Values
Number (%) of patients	100 (100)
Age (years), median range	55 (37–75)
Gender, n (%)	
male	91 (91)
female	9 (9)
Localisation of tumours, n (%)	
epipharynx	3 (3)
oropharynx	30 (30)
hypopharynx	46 (46)
larynx	20 (20)
cavum nasi	1 (1)
TNM category (T), n (%)	
T1	1 (1)
T2	10 (10)
T3	21 (21)
T4	68 (68)
TNM category (N), n (%)	
N2c	38 (38)
N3	62 (62)
Histological grade, n (%)	
1	8 (8)
2	72 (72)
3	20 (20)
Therapeutic regimens, n (%)	
Car 500-5FU-CDDP (short infusion - 4h)	41 (41)
Car 500-5FU-CDDP (continuous infusion)	59 (59)
Number of cycles, median (range)	4 (1–6)

**TNM – tumor (T), node (N), metastasis (M); Car – cytosine arabinoside; 5FU – 5 fluorouracil; CDDP – cisdiaminodiplatin; n (%) – number (percentage) of patients.**

The median time of surveillance was 12 months. Efficacy of the treatment is presented in Table 2.

**Table 2**  
**Efficacy of treatment**

Maximal therapeutic response	Patients, n (%)
CR	4 (4)
PR	41 (41)
SD	11 (11)
PD	44 (44)
DCR (CR+PR+SD)	56 (56)

**CR – complete remission; PR – partial remission; SD – stable disease; PD – progressive disease; DCR – disease control rate.**

About one third (31%) of the patients was without comorbid conditions while 69 (69%) patients had some kind of concomitant disorders. The most frequent among them was alcoholism (active and previous) which was present in 49 (71%) patients. The next category of comorbid conditions belongs to the chronic pulmonary diseases and was noted in 25 (36%) patients, and the third were cardiovascular diseases present in 18 (26%) patients with arterial hypertension as a leading condition. Among gastrointestinal disorders, chronic hepatic disease was present in 9 (13%) patients, and diabetes mellitus was present in 10 (14%) patients. The other comorbid conditions were encountered much less frequent (Table 3).

**Table 3**  
**The most prevalent comorbid conditions in the study**

Comorbidities	Patients, n (%)
Alcoholism	49 (71)
active	10 (14)
former	39 (57)
Chronic pulmonary diseases (obstructive/restrictive)	25 (36)
mild	20 (29)
moderate	5 (7)
Cardiovascular diseases	18 (26)
arterial hypertension	9 (13)
DVT	4 (6)
rhythm disturbances	4 (6)
myocardial infarction	1 (1)
Gastrointestinal diseases	16 (23)
chronic liver disease	9 (13)
stomach ulcer	5 (7)
chronic pancreatitis	2 (3)
Diabetes	10 (14)
Cerebrovascular diseases	3 (4)
Neuromuscular diseases	2 (3)
Mental problems	1 (1)

**DVT – deep venous thrombosis.**

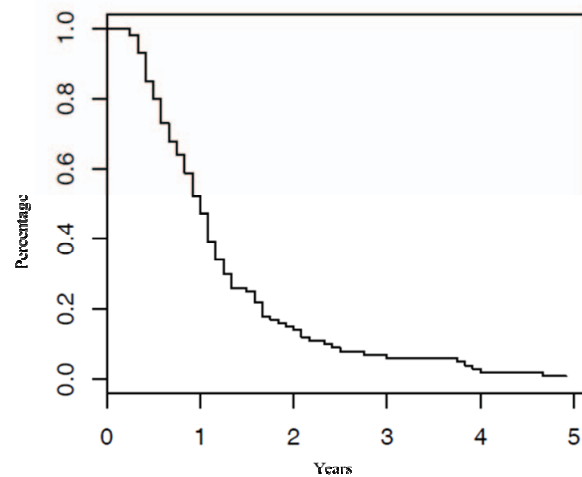
The comorbidity was measured using ACE-27 index with most frequently observed score being grade I (mild) in 43 % of patients, while grades II (moderate) and III (severe) were present in 20% and 6% of them, respectively (Table 4).

**Table 4**  
**ACE-27 comorbidity score**

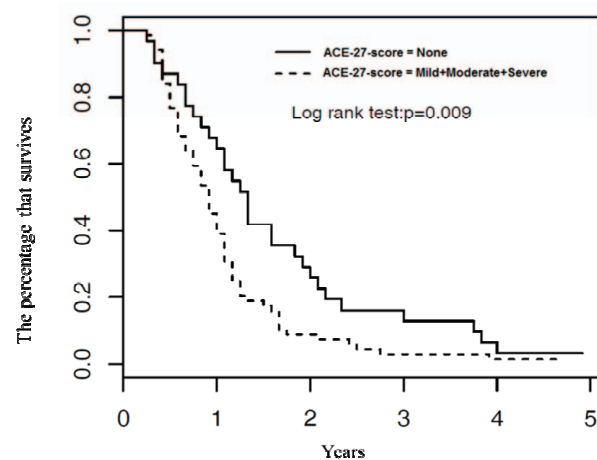
ACE-27 score	Values
Median (range)	1 (0-3)
None, n (%)	31 (31)
Mild, n (%)	43 (43)
Moderate, n (%)	20 (20)
Severe, n (%)	6 (6)

**ACE – Adult Comorbidity Evaluation; n (%) – number (percentage) of patients.**

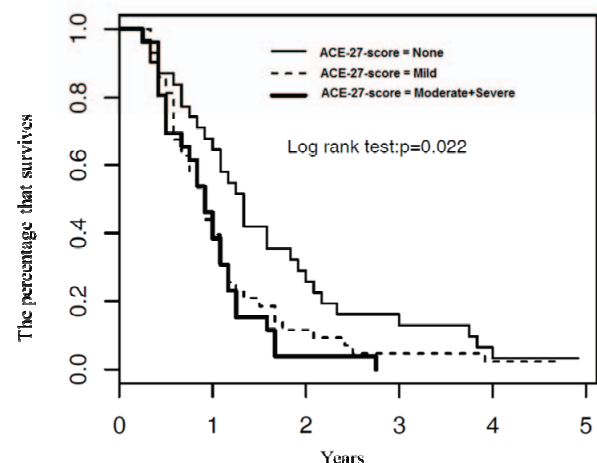
Median overall survival for the whole group was 12 months (Figures 1–3).



**Fig. 1 – Overall survival.**



**Fig. 2 – Overall survival (OS) and presence/absence of comorbidity according to ACE-27 index.**



**Fig. 3 – Overall survival and categories of ACE-27 score.**

Patients without comorbidities survived significantly longer (16 months vs. 11 months) in comparison with their counterparts who had any kind of a comorbid condition ( $p = 0.0089$ ).

Comparing the different pairs of comorbidity categories, there was no significant difference in overall survival

between patients without comorbidities and those with mild ones. The same situation was between those with mild comorbidities and patients with moderate and severe conditions taken together. However, patients without comorbidities survived longer in comparison to those with moderate and severe conditions taken together ( $p = 0.00474$ ) (Tables 5 and 6).

**Table 5**  
**Overall survival (OS) and relation to ACE-27 score**

ACE-27 score	OS (months), median (95% CI)
None	16 (12-24)
Mild	11 (8-13)
Moderate + severe	111 (8-14)

**ACE – Adult Comorbidity Evaluation; CI – confidence interval.**

**\*Log-Rank test:  $\chi^2_2 = 7.65$ ;  $p = 0.02181$ .**

**Table 6**  
**Overall survival between pairs of ACE-27 score categories**

Pairs	Log-rank test	
	$\chi^2_1$	$p$
None vs. Mild	$\chi^2_1 = 4.199$	$p = 0.04044$
None vs. Moderate + severe	$\chi^2_1 = 7.975$	$p = 0.00474$
Mild vs. Moderate + severe	$\chi^2_1 = 0.416$	$p = 0.51872$

**ACE – Adult Comorbidity Evaluation,**

**\*Bonferroni correction:  $0.05/3 = 0.0167$ .**

## Discussion

Being the most respected clinical skill in the past centuries, medical prognosis regained its importance in the present era of personalized medicine.

The influence of comorbidity on survival in patients with cancer may be direct in relation with heavier disease burden, or indirect through the choice and timing of proper anticancer treatment thus many recent studies show the clinical significance of comorbid conditions in oncology<sup>12-14</sup>.

Because of toxic effects of tobacco and alcohol, patients with head and neck cancers are especially likely to have various comorbid health conditions thus serving as a good model for investigating the relationship between comorbidity and survival. Indeed, in the past 15 years many authors have confirmed strong prognostic impact of associate illnesses in head and neck oncology<sup>10, 15</sup>.

Our study is unique in a way that it dealt exclusively with patients who had advanced, inoperable cancers initially treated with neoadjuvant chemotherapy. Most of them were predictably males. As one may expect, majority of patients had their primaries in hypopharynx, oropharynx and larynx with N3 nodal stage, which is in accordance with most recent epidemiological data<sup>1</sup>.

The median time of surveillance in our series was 15 months with range of 3–59 months which is much longer than in the pivotal work of Piccirillo<sup>5</sup>. Such a follow-up can provide a fair amount of information.

In our study alcoholism (former and active) prevailed, being present in 71% of patients with comorbid conditions which could be explained by the fact that alcohol abuse may lead to addiction but also it is the causative factor in most of HNSCC cases. The other reason might be the specific separation and inclusion of this condition in the ACE-27 scoring index. The second most prevalent group of conditions were pulmonary diseases observed in 36% of our population, while cardiovascular diseases with preponderance of the arterial hypertension were on the third place (26%). Of note was the absence of angina pectoris among our patients for which we do not have a plausible explanation. So, alcoholism aside our data are in concordance with results of Piccirillo and Vlahiotis<sup>11</sup>. The most common score of comorbidity in our patients was grade 1 (mild) present in 43% of cases, while grades 2 (moderate) and 3 (severe) were present in about quarter of patients. In Datema et al.<sup>16</sup> large study, results were partly different with smaller percentage of mild comorbidity (17%), while moderate (13,5%) and severe grades (6%) were much more in accordance with our results. However, among patients in that study the vast majority (74%) had the localized or locoregional disease (TNM stages I and II) where prognosis was better and presence of comorbid ailments was not so prominent.

In our series, 31% of patients were without any kind of comorbid diseases, and quite predictably they survived significantly longer compared with their counterparts with some kind of comorbidity ( $p = 0.0089$ ). Similar results although on far larger scale were obtained by Land et al.<sup>17</sup> and Patnaik et al.<sup>18</sup> analyzing more than 60,000 women with breast cancer where those without comorbidities had much better overall survival. Another statistically significant finding in our study referred to the fact that patients without comorbidities fare better in comparison to those with moderate and severe conditions taken together ( $p = 0.00474$ ). In statistical sense there was no difference in survival between patients with severe comorbidities and those with mild or moderate comorbidities. Although somehow paradoxical, this fact could be explained by the very small number of our patients with severe conditions (6%) which is not sufficient for any firm conclusion regarding the survival of this sole category. So, the only way to overcome this problem is to conduct large clinical studies properly designed to measure and explore the impact of various categories of comorbidity on survival of the patients with HNSCC.

The main limitations of our study are that it reflects the experience of patients at only one large academic institution, analyzing the only one end point – overall survival. This is important because the patients treated in academic centers are in general younger, healthier and with smaller tumors. On the other hand, dealing exclusively with survival, other pertinent end points as quality of life may be missed.

Although it is well known fact that the relative impact of comorbidity tends to be greater for cancers with better prognosis, we demonstrated that even in poor prognostic population this prognostic variable still holds its importance.

## Conclusion

The presence of comorbid illnesses is a frequent finding in patients with HNSCC. The most prevalent conditions in our study are alcoholism, chronic pulmonary disorders and cardiovascular disorders. Patients without comorbidities sur-

vive significantly longer in comparison to patients with some kind of associated ailment, particularly of moderate and severe intensity. So, proper measurement of comorbid conditions in patients with HNSCC before treatment is strongly recommended.

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