Zinc serum level in correlation with GPX1, SOD2 and CAT genotypes as prognostic marker of survival in laryngeal cancer.

Jakub Lubiński[1], Ewa Jaworowska[1], Róża Derkacz[2], Wojciech Marciniak[2], Katarzyna Białkowska[3], Piotr Baszuk[3], Jan Lubiński[2,3]

[1]*Clinic of Otolaryngology, Pomeranian Medical University, Szczecin, Poland*
[2]*ReadGene, Grzepnica, Poland*
[3]*Department of Genetics and Pathology, International Hereditary Cancer Centre, Pomeranian*
Medical University, Szczecin, Poland

Key words: laryngeal cancer, zinc, antioxidant enzymes

Introduction:

Oxidative stress contributes to various aspects of malignant tumours and could be one of possible mechanisms that influence the survival in laryngeal cancer. Antioxidant mechanisms are divided into non-enzymatic and enzymatic. Among non-enzymatic zinc plays a major role. Among enzymatic mechanisms one of the most important factors are: superoxide dismutase 2 (SOD2), catalase (CAT) and glutathione peroxidase 1 (GPX1). Their polymorphisms can have an impact on tumours occurrence and progression. The aim of the study is a prospective evaluation of the results of treatment of patients with laryngeal cancer depending on the level of zinc in the serum in correlation with genotypes of antioxidant enzymes – GPX1, CAT and SOD2.

Material and methods:

Study group: 300 patients treated surgically in the period from July 2009 to February 2017 due to squamous cell carcinoma of the larynx, from whom blood was collected before the beginning of treatment in order to assess the levels of zinc in the serum.

Clinical information on the age of onset, sex, clinical stage, radiation therapy, chemotherapy and pack-years was collected from all patients.

To determine the levels of zinc in the serum, the technique of inductively coupled mass spectroscopy (ICP-MS) was used.

Genotypes of antioxidant enzymes were established using real-time PCRs. Following polymorphism were studied: 1) GPX1 599C/T, rs1050450, Pro198Leu; 2) CAT 262C/T, rs1001179; 3) SOD2 47T/C, rs4880, Val16Ala.

The results of the treatment were evaluated on the basis of the number of deaths that occurred during the prospective observation period.

Study group was divided into subgroups depending on antioxidant enzymes genotypes. Entire group and each subgroup were divided into three parallel subgroups depending on Zinc serum concentrations. The relationship between serum zinc levels and survival was analysed

statistically uni and multivariate, taking into account the influence of age, sex, clinical stage, chemotherapy, radiotherapy and pack-years.

Results:

1. Zinc level in the serum in entire group (n-300): statistically significant increased risk of death in patients with the lowest zinc levels (<579 μg /l) in comparison with patients with the highest levels (> 688 μg /l): HR= 2.57; Cl= 1.442 - 4.643; p-value=0.012

2. Polymorphisms of antioxidant genes were not correlated with survival of laryngeal cancer patients

3. Serum zinc level impact on survival in laryngeal cancer patients was influenced by genotypes of antioxidant enzymes. Zinc was statistically significant factor of survival in subgroups with following genotypes: GPX1nonCC (HR= 2.66; Cl= 1.244 - 5.681; p-value=0.012), CATCC (HR= 2.34 ; Cl= 1.245 - 4.615; p-value= <0.01) and SOD2nonCC (HR= 2.443 ; Cl= 1.375 - 4.339; p-value= <0.01). In subgroups with GPX1CC, CATnonCC and SOD2CC there was no statistically significant correlation between zinc serum level and survival.

4. Impact on death risk in laryngeal cancer patients was multiplicated in subgroups combining too low serum zinc level with antioxidant enzymes polymorphisms of positive influence on survival: 1) GPXnonCC and SOD2nonCC subgroup HR = 5,77; Cl=1.58 - 23.70; p-value=0.0; 2) GPX1nonCC and CATCC and SOD2nonCC subgroup HR=10.42; Cl=1.05 - 103.15; p-value=0.04.

Conclusions:

The level of zinc in the serum is important, regardless of the clinical stage, prognostic factor in laryngeal cancer. The influence of zinc serum level on survival in laryngeal cancer patients can be higher if correlated with adequate antioxidant enzymes polymorphisms: GPX1nonCC, CATCC and SOD2nonCC - 90% of all laryngeal cancer patients have at least one of those genotypes what makes survival dependent on serum Zinc level with HR – 2.4. 15% of all laryngeal cancer patients have all three of those genotypes, which results in extremely strong dependence between survival and Zinc serum level with HR > 10.