Archives of Community and Family Medicine
ISSN: 2638-4787
Volume 2, Issue 1, 2019, PP: 19-33

Biomineralogical Studies of Oral Squamous Cell Carcinoma

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Abstract

Biomineralogical studies - microscopic histology examination and EDS - of the tissues of oral squamous cell carcinomas were conducted. Elevated levels of Ca, P, Ni, K, S, N and others were found in the tissues. Those elements may have played a part in defecting DNA structure responsible for cell proliferation and development of cancerous tissue. It is also possible that elevated levels of those elements are the result of cancerous activities instead. Finding the answer requires further studies.

Introduction

The etiology and pathogenesis of neoplastic diseases is still not fully understood, even though this problem is studied by researchers all around the world. The extensive literature concerning those issues often goes beyond the scope of oncology. Recent years have brought dynamic growth in research both particular (1, 2, 7, 8, 12, 13, 22, 24, 25, 29, 30, 31, 33, 34, 38, 40, 42, 45, 46, 49, 50, 53, 55, 56, 63, 67, 68), general (8, 14, 23, 37, 39, 41, 43, 44, 59, 64, 66), and statistical (9, 11, 15, 17, 32, 35, 47, 52, 60, 81, 65, 68, 69, 70, 71). There are fewer publications on cancer research techniques, especially in mouth, neck, head and tongue cancers (25, 25, 28,48, 51, 54, 57, 58), publications on treatment and different types of cancer therapies (4, 5, 10, 16, 18, 19, 35, 28), and genetic research (20, 21, 62). The least numerous are publications regarding experimental creation of cancer phenomena (6).

Recently publications related to the use of mineralogical methods in tissue studies, including cancer, appear more frequently (37-46). They bring new information on tissue mineralization and the relation between mineralization and other phenomena, including carcinogenesis.

In laryngology, superficial structure of peripheral blood lymphocytes was examined and their chemical composition was analyzed using mineralogical methods in patients with larynx cancer, showing disorders in their structure and chemical composition. Premalignant states and laryngeal squamous cell carcinoma were also examined, indicating statistically significant differences in the content of elements in healthy and diseased tissues.

In oncology, by observing several types of connective tissue sarcomas, it was noticed that phosphate crystallization may occur in them especially when there is a rapid change in the pH of the environment in the tumor tissue.

For example, in general surgery, the concentrations of some elements in colorectal cancer were examined - showing significant fluctuations in both their type and amounts in diseased tissues.

However, there are still only a few reports on the use of mineralogical methods in maxillofacial oncology.

Types of Oral Cancer and Their Frequency

In the mouth itself, more than half of the cancers affect the tongue, and the rest breaks down as follows:

tongue	52%
floor of the mouth	16%
crest of the alveolar ridge	12%
palate	11%
cheek	9%

Oral cancer affects men about 4 times as often as women. The differences are particularly visible in the case of lower lip cancer, where squamous cell carcinoma is about 30 times more frequent in men than in women. In the case of tongue cancer, it is only twice as frequent in men as in women. It is usually diagnosed at the age of 50 to 70. The majority - almost 80% - of squamous cell carcinomas develop on the face and in the mouth.

Prognosis

The prognosis depends on cancer's location. It's the best in lip and salivary glands cancers, as well as mouth and throat cancers. All the other cancers have bad prognosis.

Research Material

The research material consisted mainly of histological preparations from four patients representing different levels of cancer development, as well as comparative material from a healthy patient. Histopathological preparations originated entirely from the archives of the Department of Pathomorphology of the Silesian Medical Academy in Zabrze, and were medically consulted with dr. T. Męcik.

The results of histopathological examination included cancer type - carcinoma planoepitheliale - with determination of its degree of differentiation.

Based on microscopic histological assessment of the extent of the cancer, the material was divided into three groups:

G1 – squamous cell carcinoma, well differentiated

G2 - squamous cell carcinoma, moderately differentiated

G3 - squamous cell carcinoma, poorly differentiated

Blocks used for analysis were prepared with tissue sections fixed in 10% neutralized formalin solution. They were prepared in a typical manner and embedded in paraplast. They were cut using a Reichert microtome (manufactured in Austria) into 6 µm thick sections and placed on slides.

A portion of the sliced preparations were deparaffinized and left on the slides to be tested using a scanning microscope with an EDS chemical analysis attachment.

The control group consisted of fragments of oral mucosa obtained during surgical management of wounds in a patient treated at the Maxillofacial Surgery Clinic in Zabrze due to oroantral fistula after extractions of premolars and molars (Photo SO-1).

During the morphological analysis of oral squamous cell carcinomas (RP), the histoarchitecture of cancer was assessed.

Results

Highly developed squamous cell carcinoma grows and infiltrates the stroma with large, irregular and interconnected sockets (Photo S0-1). On the surface of neoplastic lesions, signs of necrosis were occasionally observed, with the formation of extensive ulcerations. Stroma under normal epithelium around ulcerations may be infiltrated by cancer foci. Spots with preserved cellular system revealed their maturation with the formation of characteristic keratin pearls in the middle (Photo S2-1).

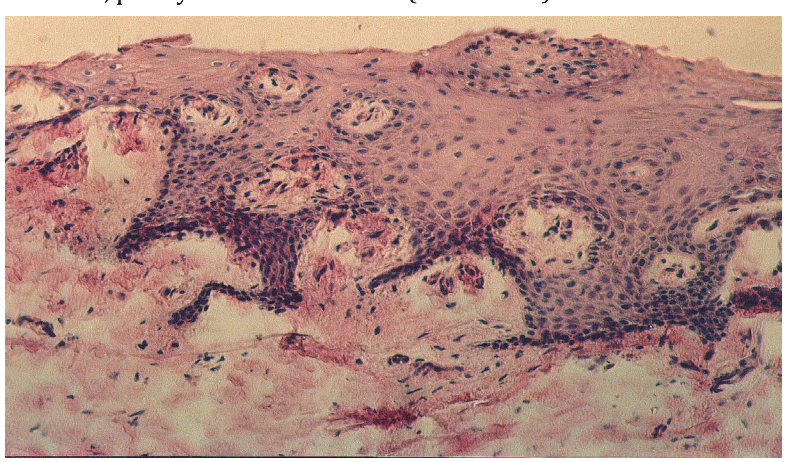

Fig S0-1. *Comparative sample. The healthy image of oral mucosa with stratified squamous epithelium. Biological microscope, stain H-E, magnification 120 x.*

Sample S1, Squamous cell carcinoma

Woman, age 52

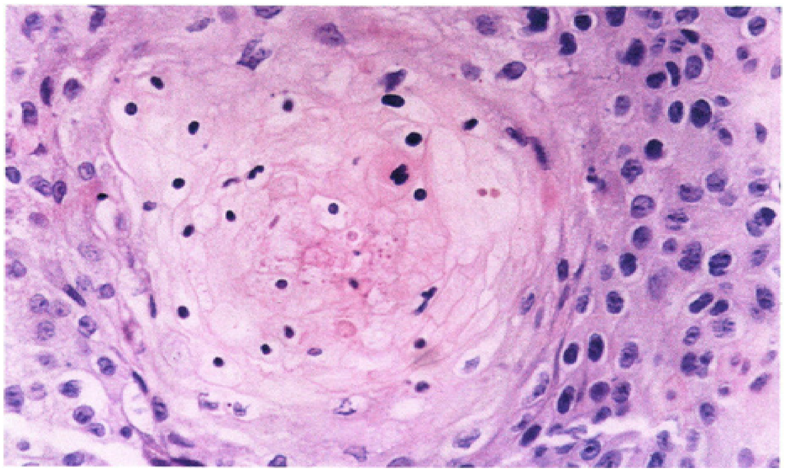

Photo S1-1. *Squamous cell carcinoma, G1. Keratin pearl with signs of homogenization. Biological microscope, stain H-E, magnification 420 x.*

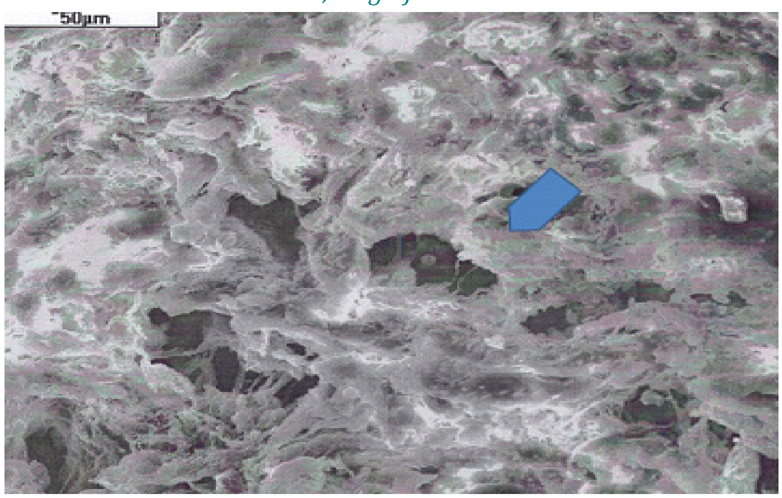

Photo S1-2. *Fragment of tissue from the area of the keratin pearl subjected to chemical analysis by the EDS method. Analyzed spot marked with an arrow. SEM.*

Chemical analyses conducted at several spots in described tissue revealed (Tab.1) increased levels of not only calcium and phosphorus, but also iron, potassium and silica (Fig. 1). That indicates that the main mineralizing substances in the region of the keratin pearl are calcium phosphates. The remaining elements probably do not form separate mineral phases and appear in biological structures inserted into the atomic structures of biological components.

Table 1. *Results of chemical analysis, sample S 1-1*

Element	Content (wt%)
Na	0
Mg	0
Al	0
Si	0,21
Ca	6,93
Fe	0,12
P	3,92
S	0
K	0,10
N	0

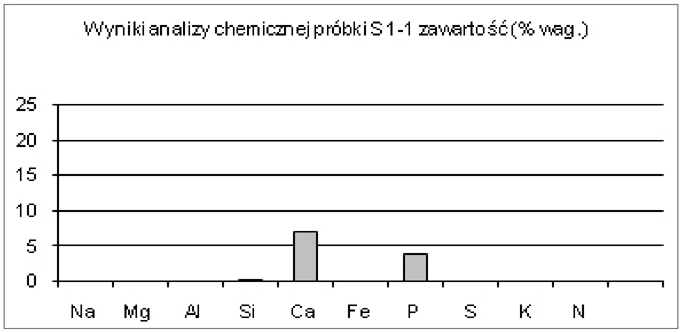

Fig 1. *Graph of the content of elements in the examined cancer tissue area*

Chemical analyses in other spots (Photo S1-3), slightly more distant from the keratin pearl, also showed elevated levels of certain elements. Calcium phosphates are dominant here as well, but in addition to iron and silica, slightly elevated contents of nitrogen and sulfur are present (Tab. 2, Fig. 2).

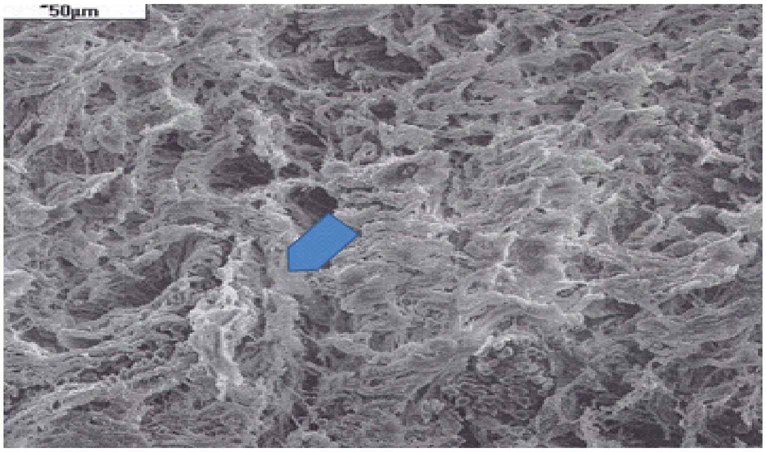

Photo S1-3. *Tissue structure in a spot more distant from the keratin pearl. Analyzed spot marked with an arrow. SEM.*

Table 2. *Results of chemical analysis, sample S 1-2*

Element	Content (wt%)
Na	0
Mg	0
Al	0
Si	0,10
Ca	5,31
Fe	0,08
P	3,30
S	6,12
K	0
N	0,19

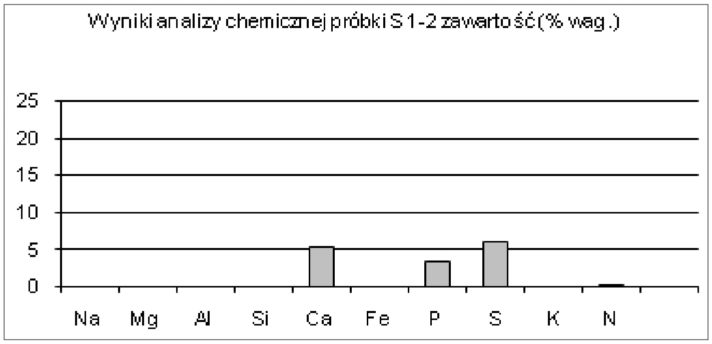

Fig 2. *Graph of the content of elements in the examined tumor tissue area, slightly farther from the keratin pearl*

Sample S2, Squamous cell carcinoma
Man, age 65

The progressing changes in this case caused a gradual obliteration of cellular systems in keratin pearls with their gradual homogenization, as observed in histological preparations (Photo S2-1).

In the moderately matured forms, a larger diversity of cancer cells infiltrating the stroma with smaller and more dispersed foci was also observed. They formed wedge shapes. The keratosis lesions were also smaller. The stratified arrangement of cancer cells has been eradicated. On the other hand, a greater variety of cell nuclei and more numerous mitotic divisions were observed. Furthermore, areas of cancer cells infiltrating the stroma under normal epithelium were found.

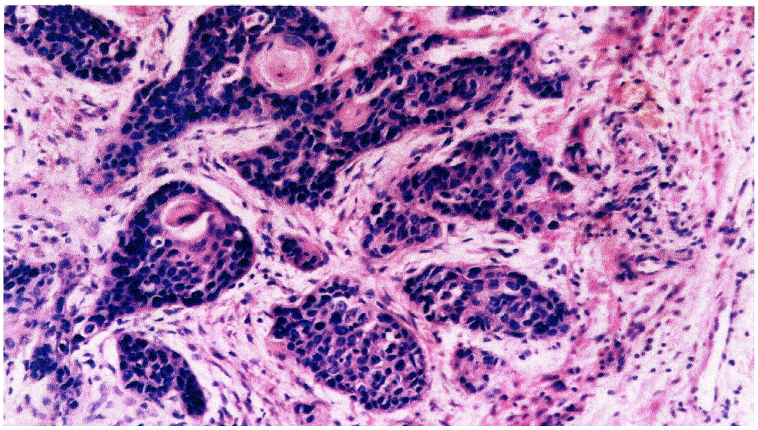

Photo S2-1. *Squamous cell carcinoma, G2. Numerous small foci of cancer infiltrating the stroma. Biological microscope, stain H-E, magnification 220 x.*

Tissue samples from the area shown in Photo S2-1 were examined using SEM with EDS analysis to determine their chemical composition (Photo 2-2, Tab. 3, Fig. 3). It shows that in addition to phosphates, the tissue contains elevated levels of sodium and magnesium.

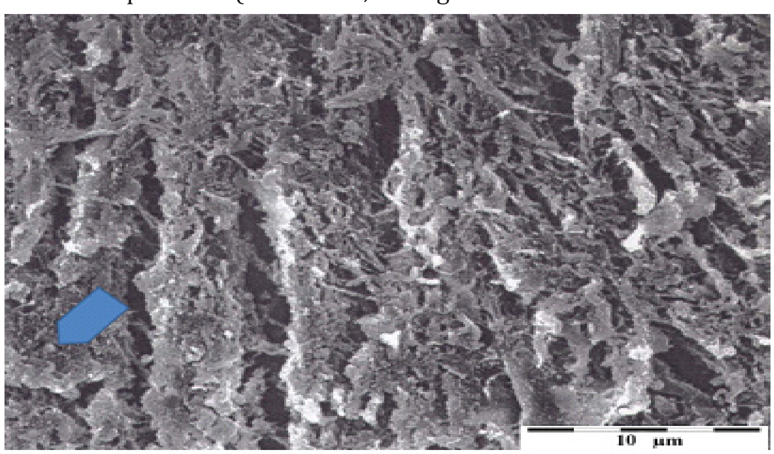

Photo S2-2. *Cancer tissue structure in the area analyzed by EDS. Arrow marks the analyzed spot. SEM.*

Table 3. *Results of chemical analysis, sample S 2-1*

Element	Content (wt%)
Na	0,38
Mg	0,09
Al	0
Si	0
Ca	1,13
Fe	0
P	0,67
S	0
K	0
N	0

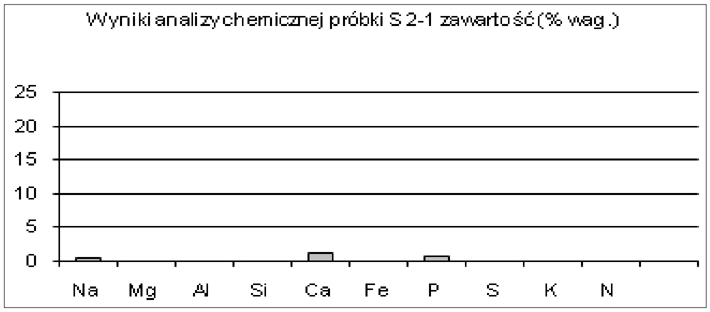

Fig 3. *Graph of the content of elements in the examined tumor tissue area*

Studies conducted in many other spots of cancer tissue show its structural diversity (Photo S2-3).

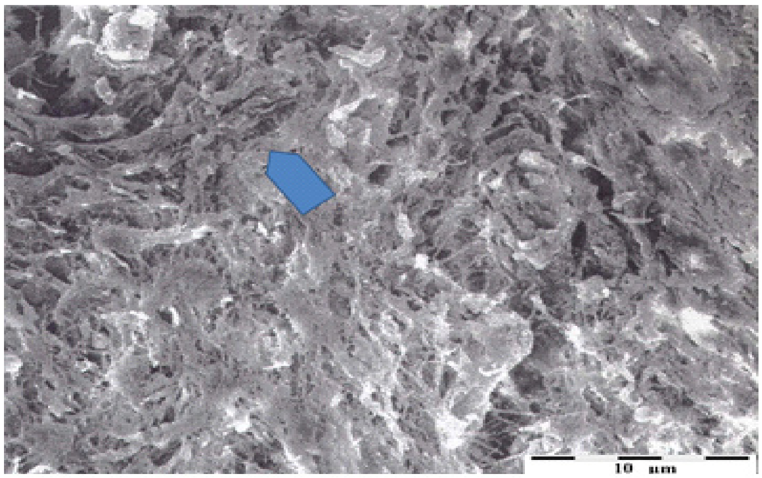

Photo S2-3. *Photograph of diverse cancer tissue in the vicinity of infiltrating structures. SEM.*

Chemical analyses (EDS) conducted in that area show presence of many elements in the tissues (Tab.4, Fig. 4).

Table 4. *Results of chemical analysis, sample S 2-2*

element	content (wt%)
Na	0,43
Mg	0,12
Al	0
Si	0,11
Ca	1,43
Fe	0,07
P	0,56
S	0,15
K	0
N	0

In this area there are elevated contents of more elements than in the area described above.

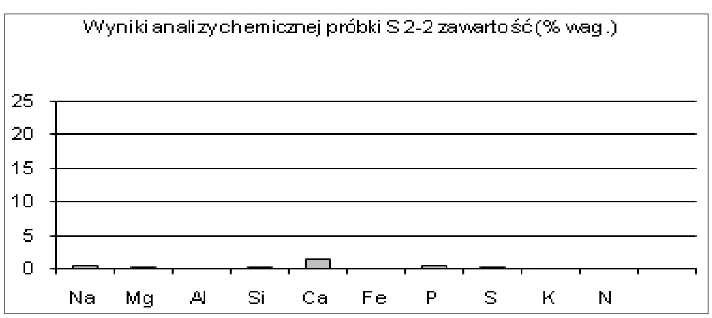

Fig. 4. *Graph of the content of elements in the examined tumor tissue area*

Sample S3, Squamous cell carcinoma
Woman, age 69

Histological examinations revealed the presence of slightly different structures in this sample, which allowed for the qualification of this case as squamous cell cancer, G3 (Photo S3-1).

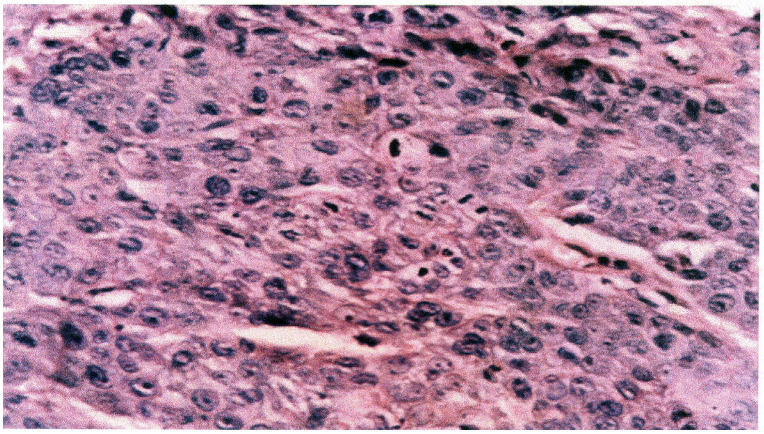

Photo S3-1. *Squamous cell carcinoma, G3. Consistency of low-maturity squamous cell carcinoma with a characteristic cellular structure and numerous mitotic features. Biological microscope. Stain H-E, magnificaton 420 x.*

Observations of histological preparations showed that in low-maturity types of this cancer only single cells or groups of cells underwent keratinization. Sometimes it was difficult to notice them. However, a complete blurring of the structure of cancer focus with a chaotic cell structure was observed.

The cell nuclei showed significant heterogeneity with numerous nucleoli. There were also many shrunken (pyknotic) nuclei and a great many figures of the mitotic division. Sometimes cells with elongated, spindle-shaped nuclei resembling the consistency of sarcoma were also seen.

Analyzing the evaluated histopathological preparations under the biological microscope, no calcifications were found that would indicate visible mineralization of deposits, neither in the group of patients nor in the control group.

However, observations conducted under a scanning microscope at magnifications of about 500x revealed that the preparations contained numerous irregular “voids” left after cells (Photo S3-2). Spot EDX analyses indicate that tissue in areas close to tumor cells is chemically heterogeneous and locally enriched in calcium, nitrogen and sulfur (Tab. 5, Fig. 5).

EDS analyses from the entire surface of the preparation reveal that, on average, the amount of calcium and nitrogen in the slice slightly outweighs the amount of potassium. Numerous EDS spot analyses performed at 5000x magnification also reveal elevated calcium, sulfur and phosphorus contents. Analyses from the entire observed surface gave almost identical results. The chemical map of the surface of the slice at the magnification of 5000x reveals clear calcium precipitation in the vicinity of the cancer cells, which in most of the analyzed preparations formed granular, i.e. visible forms of concentrations.

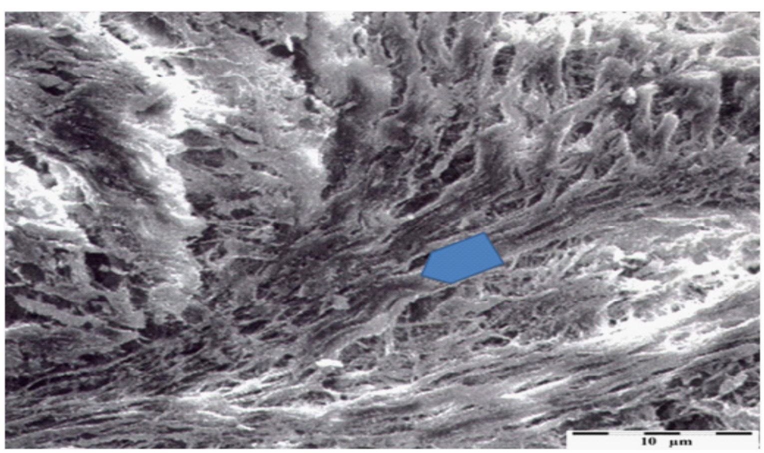

Photo S3-2. *Image of diverse tissues in the area affected by squamous cell carcinoma, G3. SEM, magnification 300x.*

Table 5. *Results of chemical analysis, sample S 3-1*

Element	Content (wt%)
Na	0
Mg	0
Al	0
Si	0
Ca	0,37
Fe	0
P	0
S	0
K	0,12
N	0,32

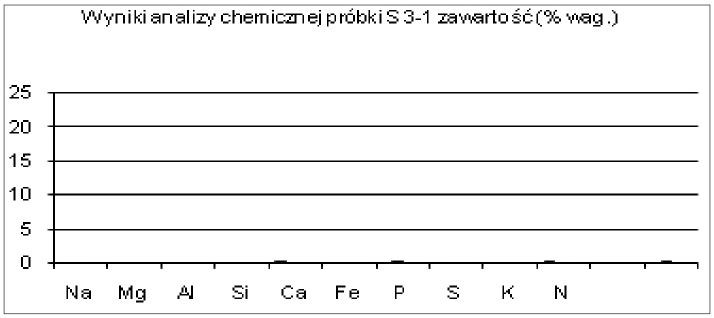

Fig 5. *Graph of the content of elements in the examined tumor tissue area*

Studies of other sites in the area of neoplastic changes show further differentiation of the chemical composition of tissues (Photo S3-3). This variability is observed even at points located only slightly apart from each other.

Calcium and phosphorus are found in the largest, although variable, amount (Tab. 6, Fig. 6). Nitrogen, potassium and silicon appear frequently. Magnesium and sulfur appear sometimes and in variable amounts.

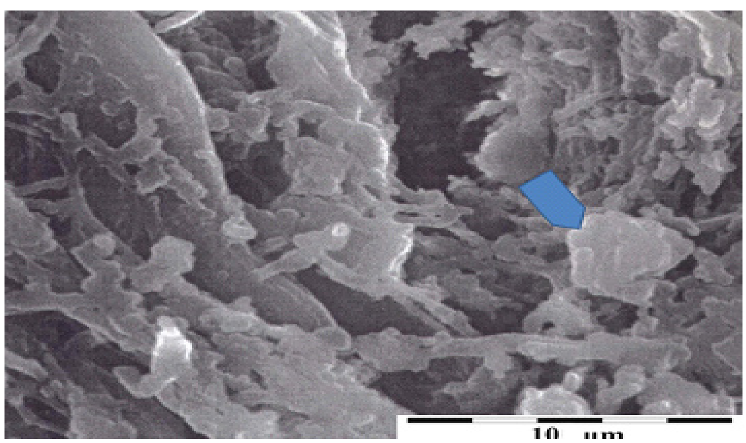

Photo S3-3. *Cancer tissue structure seen under scanning microscope. Area analyzed with EDS. Arrows show points of spot analyses.*

Table 6. *Results of chemical analysis, sample S 3-2*

Element	Content (wt%)
Na	0
Mg	0,39
Al	0
Si	0,12
Ca	0,73
Fe	0,10
P	0,39
S	0
K	0,11
N	0,49

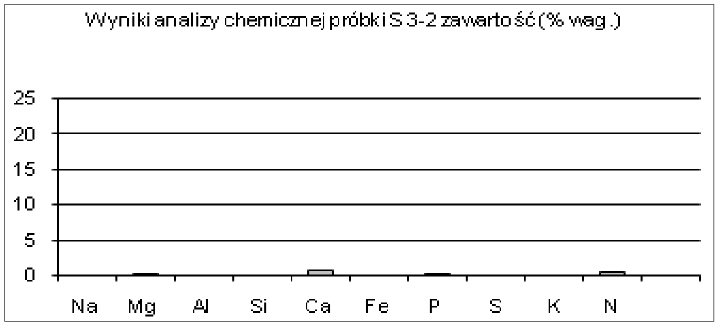

Fig 6. *Graph of the content of elements in the examined tumor tissue area*

Sample S4, Squamous cell carcinoma

Woman, age 58

This sample was mostly analyzed with biomineralogical tests within the tumor area. The focus was on finding mineralization in pathological tissues where signs of mineralization were found under the scanning microscope (Photo S4-1).

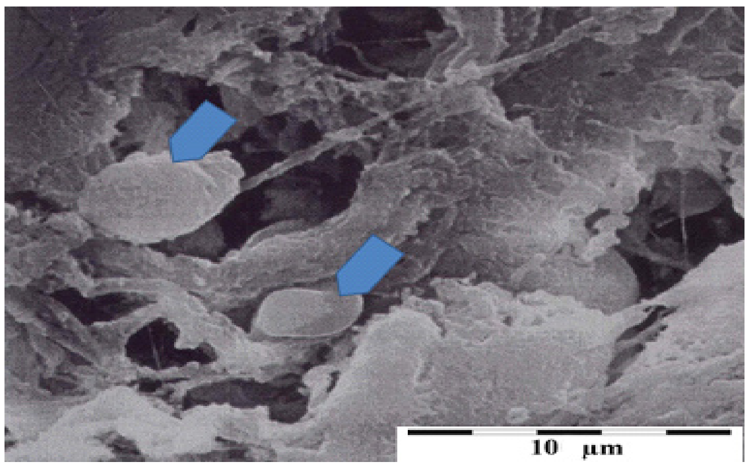

Photo S4-1. *Image of the pathological squamous cell carcinoma tissue with two phospate grains (arrows). SEM.*

Table 7. *Results of chemical analysis, sample S 4-1*

Element	Content (wt%)
Na	0,37
Mg	0
Al	0,21
Si	0,19
Ca	2,10
Fe	0
P	1,11
S	0,13
K	0
N	0

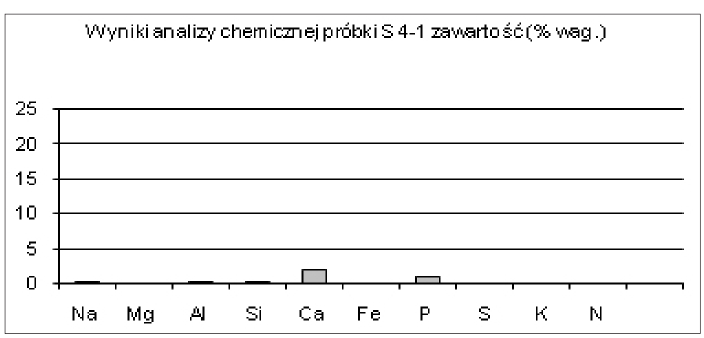

Fig 7. *Graph of the content of elements in the examined tumor tissue area*

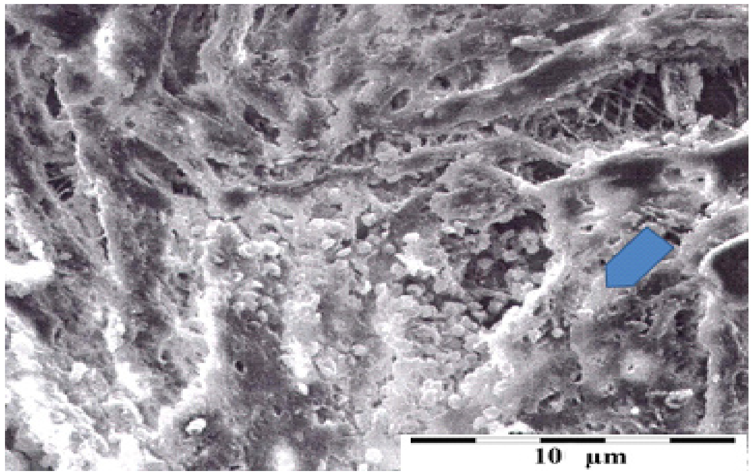

Photo S4-2. *Cancer tissue affected by secret mineralization consisting of the substitution of elements into a biological structure (without visible mineral grains). The arrow shows the place of conducted chemical analysis (EDS). SEM.*

Table 8. *Results of chemical analysis, sample S4-2*

Element	Content (wt%)
Na	0,27
Mg	0
Al	0,03
Si	0,31
Ca	3,39
Fe	0,11
P	0,97
S	0,12
K	0,08
N	0,27

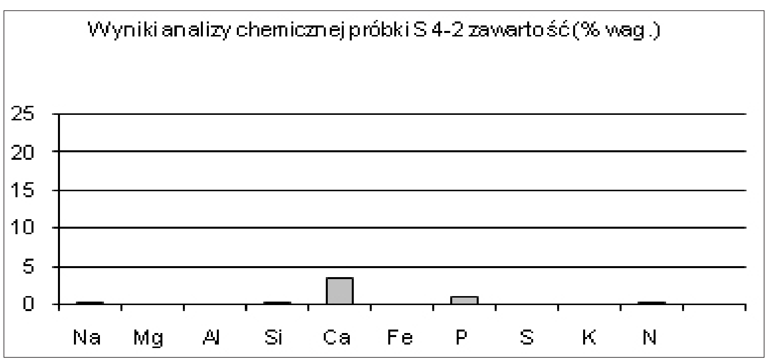

Fig 8. *Graph of the content of elements in the examined tumor tissue area*

Sample S5, Squamous cell carcinoma

Man, age 66

Microscopic observations (SEM) of tumor tissue showed its structural differentiation (Photo 5-1). Chemical analyses performed in many spots show variable, but mostly small amounts of elements such as Na, Si, Al, Ca, Fe, P, S, N and others. Interestingly, the elements differ from spot to spot. There are also places where the chemical composition of tissues is similar (Tab. 9, Fig. 9).

This suggests complexity of pre-cancerous processes as well as chemical processes at the time of cancerous tissue development. Distinction between elements concentrating in the tissues before the development of cancer, and those that are the result of the cancer phenomena is impossible at this stage of the development of cancer processes.

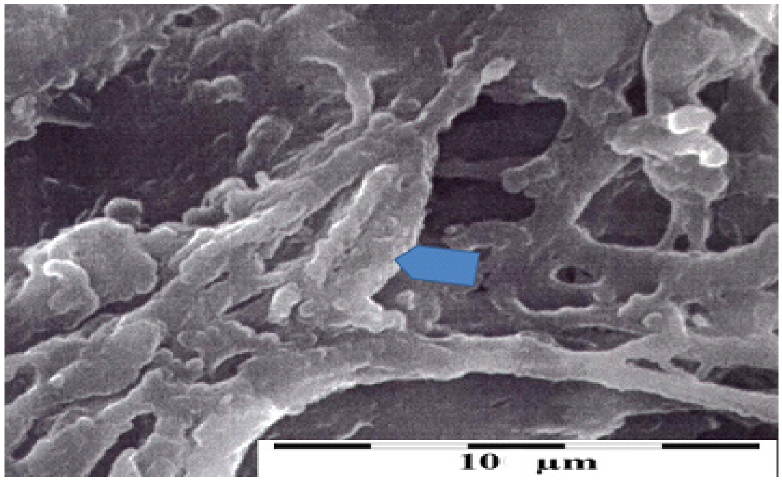

Photo S5-1. *Fragment of tumor tissue affected by secret mineralization (arrow). SEM.*

Table 9. *Results of chemical analysis, sample S5-1*

element	content (wt%)
Na	0,13
Mg	0
Al	0,11
Si	0,09
Ca	0,37
Fe	0,21
P	0
S	0,13
K	0
N	1,93

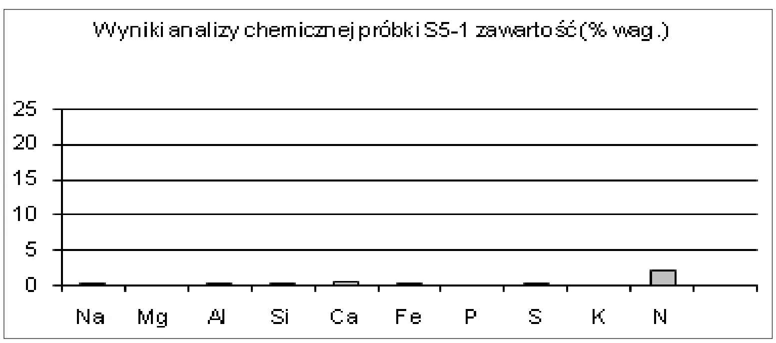

Fig 9. *Graph of the content of elements in the examined tumor tissue area*

Results Discussion

There are many methods to confirm the presence of cancer. Most often, it is diagnosed in clinical tests by conducting microscopic evaluation. The basic method is still collecting tissue sections from the boundary of healthy tissue - the place where the healthy tissue changes into the affected one – as well as from the place that is fully pathologically changed.

In the available literature there are not too many works dealing with the problem of the degree of mineralization of cancerous tumors, in particular in oral cancers. There are, however, reports about pathological hypermineralization. Postolski et al. (54) discovered the presence of microcalcifications in the vicinity of cystic-type pathological lesions while examining women's breasts with sonomammography. There are also some rare reports describing the mineralogy of lung, skin, and other tumors (43, 48). Calcium and phosphorus, and even phosphate grains with apatite features have been found in many cancer tissues using mineralogical studies (45, 47, 48, 49).

Chemical analyses carried out with the EDS method have shown significant differences in the proportions between calcium and phosphorus as well as magnesium and sodium in some areas affected by the cancer process. There were also noticeable differences in the distribution of these elements within the grains between individual patients.

It is known that tumor areas concentrate large amounts of cells undergoing constant divisions – a process that is promoted by rapid development of blood vessels. Research indicates that the chemical environment in which the cell division takes place may be important for the development of further errors in the neoplastic cellular DNA.

Difficulties in the discharge of metabolic products resulting from the rapid growth of cancer tissue cause acidification of the environment due to the increase in CO_2 level. However, when the pH of the "cancerous" environment in the tumor tissue returns to alkaline, phosphate crystallization may take place. This phenomenon was observed in several tumors, such as connective tissue sarcoma, bone tumors, thyroid cancer and others.

In presented research, it was discovered that mineralization of the area affected by cancer is initially secret and does not manifest as grains, but is only visible in chemical analyses as elevated contents of elements in tissue. It means that elements such as calcium, sulfur and phosphorus are built into tissue structures, which is why they cannot be discovered in studies using light microscopy. Secret mineralization can, but does not have to turn into visible mineralization. It may be visible as concentrations of micrograins – usually calcium phosphates.

An issue requiring further research is: which elements and in what quantities are accumulated in tissues in the precancerous phase, and which accumulate as a result of the activity of cancer tissues.

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Citation: Maciej Pawlikowski. *Biomineralogical Studies of Oral Squamous Cell Carcinoma. Archives of Community and Family Medicine. 2019; 2(1): 19-33.*