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Coagulation disorders in patients with locally advanced head and neck cancer – should they really be disregarded?

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The aim of the study was to analyse coagulation disorders in patients with locally advanced cancer of the head and neck (CHN)and with no other clinical cause for coagulation disorders treated with radiation therapy alone or concurrent chemo-radiotherapy. We also assessed the duration of disorders in the course of therapy.

The analysed group consisted of 33 patients with locally advanced CHN documented as stage T3 or T4 acc. to the TNM classification. Coagulology tests (activated partial thromboplastic time /APTT/, prothrombin time, fibrinogen concentration, euglobulin lysis time, C – reactive protein and anti–thrombin III concentration, d-dimer level, PAI–1, plasminogen level and plasmin-anti-plasmin assays) were performed before, during and after the completion of treatment.

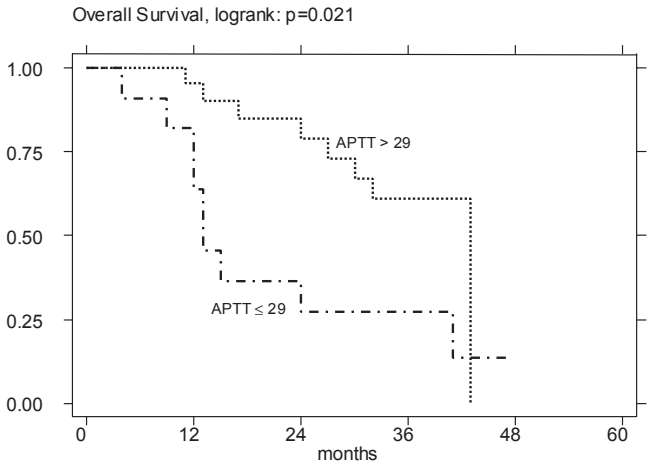
In all cases pre-tratment abnormal fibrinolysis was observed. We observed elevated PAI–1 levels in all blood tests regardless of the treatment stage, while elevated plasminogen concentration and euglobulin lysis time was observed in a majority of tests. Increased PAI-1 level persisted independently of tumor regression during treatment. Half of our patients also presented with a tendency towards shortened APTT. One patient had a significantly higher d-dimer level at the end of the treatment. Decreased APTT was the sole factor influencing overall survial (OS) confirmed in multivariate analysis (Cox's proportinal hazard model). Despite the occurence of abnormal fibrinolysis and decreased APTT, we did not observe an increased risk of coagulation disorders.

We conclude that among caogulation tests only a decrease in APTT is, at present, a stasistically confirmed predective factor of shorter OS in CHN patients. Autothrombotic prophylactic treatment may be an effective option in this clinical setting. There is need for further studies on large patient groups.

Key words: Head and neck cancer, radiotherapy, hypercoagulation, coagulopathies,

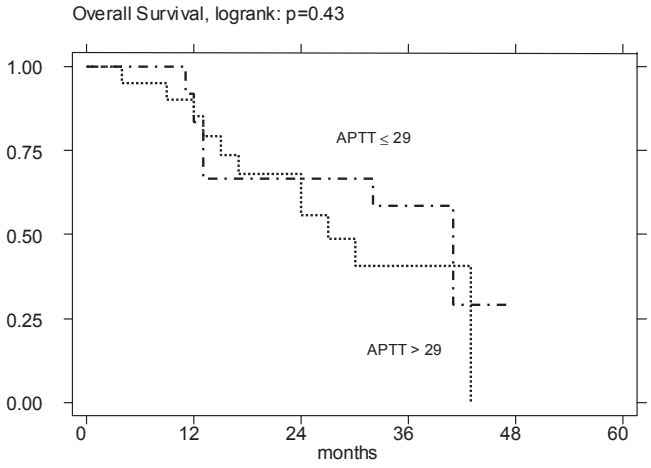
Over the last decades we have observed a constant increase in the number of patients with squamous cell carcinoma of the oral cavity, the pharynx and the larynx. In head and neck cancer stages diagnosis is often made in advanced stages, and therefore calls for aggressive treatment despite which treatment results remain poor. It apperas that molecular abnormalities, including coagulation disorders, may play an important part in the development and course of these malignancies and, in due course, affect treatment outcomes.

For over a hundred years it has been obvious that there exists a direct relationship between neoplasms and coagulation disorders with thrombosis listed as the second most common cause of death in cancer patients. Oncolytic treatment may both induce and exacerbate thrombo-embolic disorders associated with the course of the disease [1]. But despite the fact that the correlation between the presence of malignant disease and hemostatic disorders is unquestionable the ethiopathogenesis of this phenomenon has not been elucidated. It is assumed that the most common causes include such factors as (i) tumor-cell induced platelet activation leading to excessive aggregation and adhesion, (ii) the production of procoagulants by the tumor cells themselves and (iii) the production of inflammatory mediators by monocytes and macrophages. It is postulated that aggregates containing thrombocytes, fibrin and tumour cells may be responsible for the development of distant metastases [1, 2]. Tissue factor (TF) appears to be one of the key elements of this process as initiates the cascade which activates coagulation. It has been shown that the prothrombotic activity of tumor cells depends, up to a great extent, on the presence of TF, which is bound to the cell membrane and released within the plasmatic membrane vesicles. TF expression is also observed in monocytes both infiltrating the tumour and circulating in the blood. Numerous studies have confirmed the significant



APTT ≤ 29, median survival = 13, 95% C.I. = [10, 16.2]
APTT > 29, median survival = 43, 95% C.I. = [-]

Figure 1. APTT – baseline value



APTT ≤ 29, median survival = 41, 95% C.I. = [27.8, 54.2]
APTT > 29, median survival = 27, 95% C.I. = [17.4, 36.6]

Figure 2. APTT – end value

increase in TF expression in many malignancies. It correlates with disease progression in breast cancer, lung cancer and melanoma. In case of breast cancer TF is considered to be an independent prognostic factor of overall survival [3].

Data from literature shows that the fibrinolytic system is also an important element in the pathogenesis of malignant tumors. Its central element is plasminogen – the precursor of plasmin serine protease activated by the tissue plasminogen activator or by the urokinase-type plasminogen activator. Under normal conditions t-PA and u-PA inhibitor is type-1plasminogen activator inhibitor (PAI-1). Research performed on many types of tumors has revealed excessive concentration of plasminogen activators. For this reason they are hypothetised to be an important element in cancer progression. It has also been shown that in case of a wide range of tumors the expression of proteolytic factors correlates with prognosis [4].

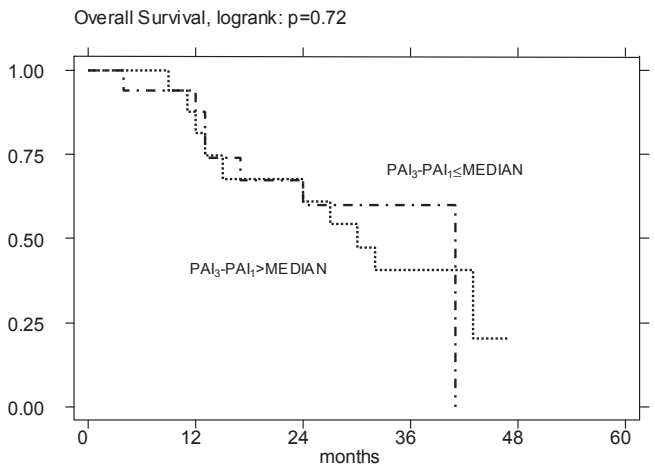
In a retrospective analysis of 502 patients treated surgically for head and neck cancer over a period of 37 years pulmonary embolism had been observed only in 30 cases (6%) and only in 5 of these the condition was clinically relevant. It has been postulated that in this particular patient group pulmonary embolism has no clinical impact and was recognised only during autopsy [5], i.e. that in head and neck cancer patients hypercoagulation is a lesser isssue than in the case of other malignancies. We decided to perfrom an initial evaluation of the degree of coagulative disorders in head and neck cancer patients basing on the assumption that in this particular patient group the impact of caogulation disorders on survival does exist, but is overlooked due to the typical complications – i.e. infections and haemorrhage. We performed a detailed analysis of the caogulation disorders in patients with locally advanced cancer of the head and neck. The analysis was performed before, in the course of and after the completion of radical irradiation or combined treatment. We also attempted to correlate the results with overall survival and the time to disease progression.

Materials and methods

We performed an analysis of 32 patients (19 men, 13 women; age range: 25-75 years) with advanced (T3-T4) cancer of the head and neck. All patients were smokers. According to the inclusion criteria we analysed only those patients, who did not have any medical conditions associated with coagulation disorders, such as oral contraceptives or a history of thromboembolic problems. Diagnosis included 19 cases of cancer of the oropharynx and 13 cases of cancer of the nasopharynx. Study criteria were set so as to discard all patients with any concomittant conditions possibly affecting the coagulation system. In all patients treatment was administered according to plan, i.e. they received the total planned dose of irradiation. Detailed coagulation analyses included:

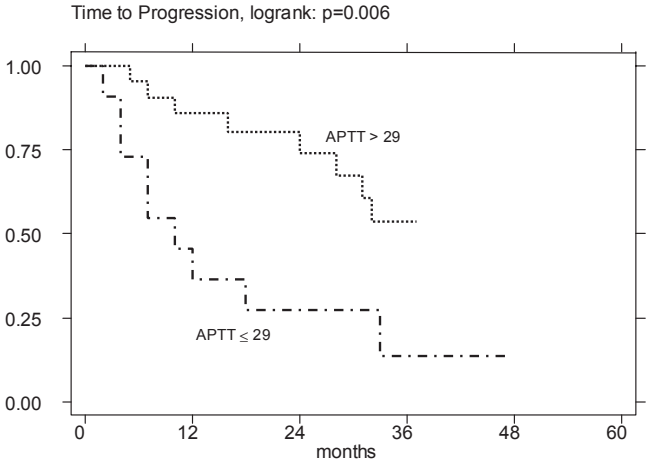
- Activated Partial Thromboplastin Time (aPTT)
- Prothrombin Time (PT) given as the prothrombin index (%)
- Fibrinogen level
- D-dimer level
- Plasminogen Activator Inhibitor-1 (PAI-1) level
- Plasminogen level
- TAT (Thrrombin-Antithrombin III complexes) level

The analyses were performed before the onset of radiotherapy, at the time when half of the planned dose had been administered and directly upon treatment completion, i.e. at the time of tumour regression. All the parameters were analysed acc. to standard statistical methods. In order to assess the impact of the analysed factors on the probability of overall survival, median survival time and the time to progression we used Cox's proportional hazard model (poly- and multifactorial) with the level of significance set at P=0.05. We used the



PAI_3-PAI_1 ≤ MEDIAN, median survival = 41, 95% C.I. = [-]
PAI_3-PAI_1 > MEDIAN, median survival = 30, 95% C.I. = [20, 40]

Figure 3. Calculation of median – PAI_3 PAI_1



APTT ≤ 29, median survival = 10, 95% C.I. = [3.5, 16.5]
APTT > 29, median surviavl = -

Figure 4. APTT – baseline value

log-rank test to analyse the influence of a number of parameters on survival time and time to progression.

Results

Before the onset of radiotherapy the results were as follows:
Significant increase in PAI-1 in 30/32 pts
Decreased aPTT 9/32 pts and lowest values of normal range aPTT 5/32 pts
Increased euglobulin lysis time 14/32 pts
Increased plasminogen level 18/32 pts
Increased fibrinogen level 18/32 pts
Increased d-dimer level 2/32 pts; did not exceed double nortmal value

In the course of radiotherapy (after the administration of half of the planned dose) the same results were as follows:
Significant increase in PAI-1 in 30/32 pts
Decreased aPTT 6/32 pts and lowest values of normal range aPTT 8/32 pts
Increased euglobulin lysis time 18/32 pts
Increased plasminogen level 20/32 pts
Increased fibrinogen level 23/32 pts
Increased d-dimer level 4/32 pts; did not exceed double normal value

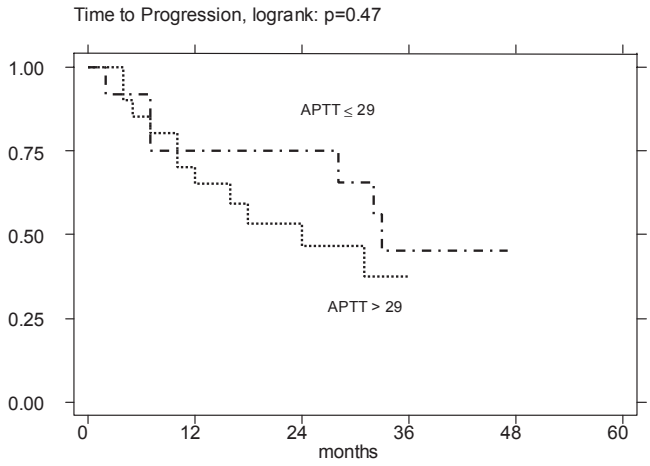
After the completion of irradiation the results were as follows:
Significant increase in PAI-1 in 30/32 pts
Decreased aPTT 5/32 pts and lowest values of normal range aPTT 6/32 pts
Increased euglobulin lysis time 18/32 pts
Increased plasminogen level 22/32 pts
Increased fibrinogen level 25/32 pts
Increased d-dimer level 3/32 pts; exceeding double normal value only in one case
A summary of results has been presented in Table 1.

Discussion

Despite the fact that coagulation disorders are an important issue in case of head and neck cancer patients there is very rare literature data regarding coagulation disorders in laryngeal cancer patients and even more scarce data regarding other localisations. In our material we observed coagulation disorders in as many as 30 patients with locally advanced cancer

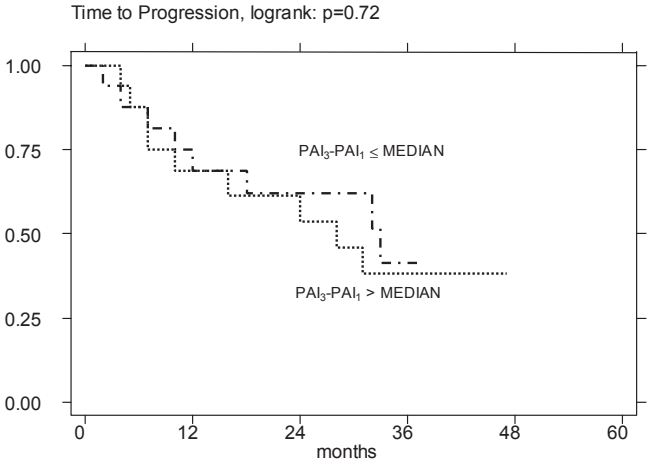
Table 1. A summary of coagulation disorders discerned in 33 pts. treated with radiotherapy or concomitant radiochemotherapy for head and neck cancer

APTT	*9 /32 pts. , 5/32 – pts. lowest value of normal range*	*6/32 – pts. 8/32 – pts. lowest value of normal range*	*5 /32 – pts. 6/32 – pts. lowest value of normal range*
Plasminogen	*18 /32 – pts.*	*20/32 – pts.*	*22/32 – pts.*
Fibrinogen	*18 /32 – pts.*	*23/32 – pts.*	*25/32 – pts.*
Euglobulin lysis time	*14 /32 – pts.*	*18/32 – pts.*	*18/32 – pts.*
D – dimers	*2/32 pts. (less than 2x normal value)*	*4/32 pts. (less than 2x normal value)*	*3/32 pts. (in 1 pt. over 2x normal value)*
PAI	*30 /32 pts.*	*30/32 pts.*	*30/32 pts.*



APTT ≤ 29, median survival = 33, 95% C.I. = [30.3, 35.7]
APTT > 29, median survival = 24, 95% C.I. = [8, 40]

Figure 5 APTT – end value



PAI_3-PAI_1 ≤ MEDIAN, median survival = 33, 95% C.I. = [12.4, 53.6]
PAI_3-PAI_1 > MEDIAN, median survival = 28, 95% C.I. = [11, 45]

Figure 6. Calculation of median – PAI_3 PAI_1

of the nasopharynx and the oropharynx. Cox's univariate proportional hazards model has shown, that decreased baseline aPTT was the only factor which corelated with the time to progression and with overall survival (p = 0,011; p=0,02, respectively). Literature data regarding the impact of aPTT on the natural course of the malignancy varies. This state of affairs may arise from the fact that patient groups are not uniform. In many cases other coagulation disorders coexist with altered aPTT, such as Disseminatec Intravascular Coagulation (DIC) or abnormalities associated with hepatic failure. Rutkowski et al. have shown, that mean aPTT values are higher in patients with advanced malignancies and that such abnormalities are rare [6]. On the other hand Wiwantikit et al. have shown that increased aPTT may be associated with advanced cholangiocarcinoma – however this study was performed on a small patient group[7].

A common disorder observed in our patient group, practically present in a majority of our patients, was a significant increase in PAI-1 – one of the proteolytic inhibitors of fibrinolysis. Under normal conditions PAI-1 is synthetised by endothelial cells, megakaryocytes and vascular cells within smooth muscles. A number of authors have stated that an increase in PAI-1 expression within the tissue of head and neck tumors may correlate with poor prognosis. Hundsdorfer et al. have reported that an increase in PAI-1 expression within the tissue of oral cavity tumors is an independent prognostic factor of decreased disease-free time [8]. Itaya et al. have suggested that the increase in PAI-1 expression within the oropharyngeal and oral tumour tissue is in fact associated with increased tumour expansion within normal tissues, but does not influence the development of nodal metastases [9]. In our study PAI-1 levels were evaluated in the serum and we cannot rule out the fact that they, in fact, correlated with inflammation and with the release of endotoxins. Extensive cancerous infiltrations within the head and neck area significantly promote inflammation factors, and inflammation itself increases significantly in the course of radiotherapy. It is certain that this finding calls for further research. The levels of PAI-1 have not been found to correlate with the time to progression and with overall survival, although there exists literature data suggesting that increased levels of PAI-1 and PAI-2 may be associated with poor prognosis in patients with oesophageal, gastric, colorectal and pancreatic cancer [10].

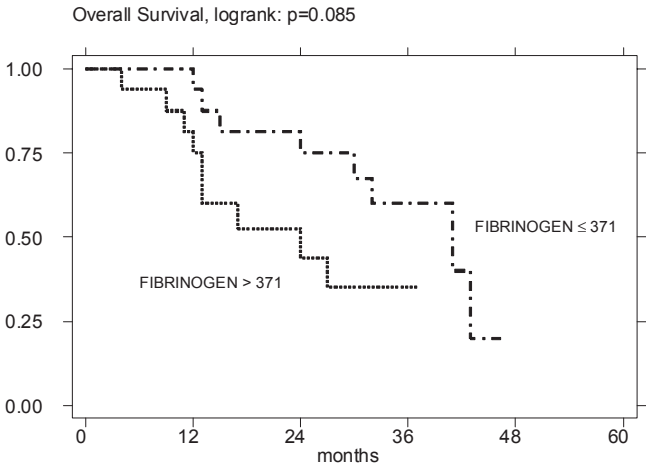
Table 2. Overall survival acc. to Cox's proportional hazard model

OS	HR [95% C.I.]	P
APTT		
> 29 vs ≤ 29	**0.30 [0.11, 0.82]**	**0.020**
FIBRiNOGEN		
> 371 vs ≤ 371	**2.72 [0.94, 7.92]**	**0.066**
Gender		0.37
Age		0.75
PAI > 10.95 vs ≤ 10.95		0.23
DDIM > 301 vs ≤ 301		0.96

Table 3. Time to progression acc. to Cox's proportional hazard model

TTP	HR [95% C.I.]	P
APTT		
> 29 vs ≤ 29	0.29 [0.11, 0.75]	0.011
FIBRYNOGEN		
> 371 vs ≤ 371		0.36
Płeć		0.92
Wiek		0.87
PAI > 10.95 vs ≤ 10.95		0.29
DDIM > 301 vs ≤ 301		0.50

Another hemostatic disorder observed in our patient group was hypefibrinogenemia, which was present in more than 50% of patients both before, in the course of and after the completion of irradiation. We observed a trend towards statistical significance regarding its negative influence on survival, although there is no evidence as to its influence on the time to progression. Due to the fact that fibrinogen is one of the proteins characteristic of inflammation the objective analysis of the impact of its concentration on survival is difficult, as there is significant interference from the inflammatory process itself. Literature data does suggest a possible correlation between the increased concentrations of fibrinogen and the stage of malignancy. Such relations have been observed in patients with lung cancer and oesophageal cancer, as well as in case of adenoma of the kidney [6]. It has also been found that increased levels of fibrinopeptide A correlate with shorter survival times in patients with colorectal and lung cancer [11]. In case of patients with lung cancer fibrinogen levels may influence the response to cytotoxic tretament. The mechanisms behind the increase of the fibrinogen level in patients with cancer remain unclear. Hyperfibrinogenemia has an indirect influence on the activation of angiogenesis. In patients with malignancies the serum half-life of fibrinogen decreases. Analyses of mice with malignancies and co-existant fibrinogen deficiency have shown, that fibrinogen is not necessary for the activation of angiogenesis nor does its deficiency have a negative effect on tumour growth. At the same time there is evidence that fibrinogen deficiency decreases the metastatic potential of tumor cells in case of Lewis' cancer of the lung or B16-BL5 cell line melanoma [12]. It has been shown that in patients with laryngeal cancer increased fibrinogen levels which mainatained after the completion of radiation therapy may have correlated with shortened survival [13]. In case of head and neck cancer patients the analysis of the role of fibrinogen may be difficult, as fibrinogen is recognised as one of the positive acute-phase proteins and clinical observation suggest that its concentration relates directly to the degree of inflammation within the tumour itself. In the case of 4 of our patients we observed increased levels of d-dimers (the product of the degradation of stabilised fibrin by plasmin – i.e. a typical sign of the the presence of thrombin and plasmin circulating in the blood), but only in one case the value was doubled. An increase in the level of d-dimers is associated with secondary activation of fibrinolysis in the course of disseminated intravascular coagulation – the lysis of tumor-associated fibrin. In head and neck cancer patients the inflammatory process is an important factor and may in itself influence the increase in d-dimers, regardless of the presence of the tumour. It is, therefore, difficlut to state whether the level of d-dimers is a good marker of either the stage of malignancy or of the efficacy of treatment, as may be the case in patients with either colorectal or gastric cancer. In one of the very few papers regarding hemostatic disturbances in patients with cancer of the head and neck – i.e. in an analysis of patients with advanced maxillary cancer it has been reported that an increase in the d-dimer level may



FIBRINOGEN ≤ 371, median survival = 41, 95% C.I. = [25, 57]
FIBRINOGEN > 371, median survival = 24, 95% C.I. = [6, 42]

Figure 7. FIBRINOGEN – baseline value

Table 4. Changes in coagulation parameters as noted at the onset, midway through and at the completion of radiotherapy

	Baseline value	Midway value	End value
	1	2	3
APTT			
(min, max)	(24.5, 42.2)	(25.7, 42.2)	(21.2, 42.5)
mean (SD)	31.0 (3.9)	30.3 (3.5)	30.5 (4.2)
ANOVA: p=0.43			
EUGLOBIN LYSIS			
(min, max)	(4.2, 465)	(105, 410)	(135, 450)
mean (SD)	236.8 (96.8)	252.9 (79.1)	268.3 (70.1)
ANOVA*: p=0.17			
FIBRINOGEN			
(min, max)	(22, 674.6)	(221.9, 720)	(216, 720)
mean (SD)	375.1 (139.8)	493.4 (146.8)	480.7 (147.4)
ANOVA*: p=0.005			
pairs compared:	1 vs 2 p=0.0002	2 vs 3 p=0.62	3 vs 1 p=0.01
D-DIMER			
(min, max)	(248, 359.8)	(250, 448)	(251, 1016)
mean (SD)	290 (29.9)	309.5 (44.5)	341.7 (148.4)
ANOVA*: p=0.07			
PLASMINOGEN			
(min, max)	(98.9, 156)	(103.8, 158)	(97.6, 154.1)
mean (SD)	117.5 (14.7)	127.0 (14.1)	126.2 (13.4)
ANOVA: p=0.016			
pairs compared:	1 vs 2 p=0.0035	2 vs 3 p=0.74	3 vs 1 p=0.013
PAI			
(min, max)	(4.7, 20.9)	(5.0, 22.3)	(4.9, 23.8)
mean (SD)	11.6 (5.1)	12.3 (5.2)	12.1 (5.8)
ANOVA: p=0.55			

* using logaruthmic transformation

be associated with an increased risk of heamorrhage from the tumor itself (cytowanie), while in a paper devoted to the role of d-dimers in the tumour volume, the progression rate and survival in patients with breast cancer the authors have presented evidence of a correlation between the d-dimer level and increased fibrinogen, the number of metastatic sites, the dynamics of progresssion and survival [14].

Our initial results suggest that contrary to common belief coagulation disorders may be an issue in patients with cancer of the head and neck. We postulate the need for further research into the coagulative disorders in this clinically challenging patient group.

Laboratory results of coagulation parameters assessed before the onset, in the course of and after the completion of radiation therapy

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