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Blood volume flow rate of the femoral bone malignant tumors – the predictor of the 1st remission duration after combined treatment

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4 types of tumor cells microenvironment are traditionally considered [2, 5]: **pathophysiological tumor microenvironment:** angiogenesis and microcirculation perfusion, vascular permeability; lymphatic system (blood vessels); interstitial space, interstitial fluid pressure (osmotic and oncotic); tumor **metabolic microenvironment**: oxygenation (hypoxia); glycolysis (lactate); restriction of supply; extracellular acidosis of intracellular alkalinity; bioenergetic status; redox status; **tumor stromal microenvironment; immunological microenvironment**.

Intratumoral vasculature may vary considerably in tumors of the same localization, histological structure, and even the degree of differentiation. Vascular tumor bed is the system that supplies the tumor with everything necessary for vital function, and also the transit route for tumor cells that leave the primary tumor site and give rise the to regional and distant metastases formation [3, 4]. Functional characteristics of vasculature and perfusion attracted attention as prognostic markers of tumor progression, and surrogate markers of hypoxia as well. There exists the known informed opinion [5, 7] that the high level of vascularization and perfusion can identify the aggressive and metastatic potential of the tumor. The experience of study of intratumoral perfusion is described in the works [2, 5].

Purpose - to show in the framework of the retrospective analysis the possible association of intratumoral blood volume flow rate (BF) of the femoral bone malignant tumors and the 1st remission duration after combined treatment.

Material and Methods

Malignant tumors perfusiongraphy was performed in 15 patients with 4 nosological forms of femur malignant tumors: osteosarcoma (5 patients), chondrosarcoma (4 patients), Ewing's sarcoma (3 patients), fibrosarcoma (3 patients) before treatment as the part of multidetector computed tomography (MDCT) with X-ray contrast enhancement on the unit "Somatom Volume Zoom" to increase topographic and anatomical sensitivity of tumors diagnosis, accurate identification of the prevalence and borders of tumor foci [10]. All the patients were treated according to the algorithm **mebifon** + **operation** + **arthroplasty** + **mebifon**. Perioperative application mebifon is aimed at devitalization of real and potentially aggressive tumor cells (already, possibly/guaranteed, of the cells scattered throughout the body, the cells that inevitably remain in the postoperative tumor bed) and of simultaneous osseointegration of hip/knee replacement [9]. After treatment, the patients 1 time in 3 months were clinical and radiological (at suspected recurrence) investigated. Retrospective analysis of MDCT digital images and correlation of perfusion indices with the duration of the 1st recurrence-free remission was held after the registration of recurrent or metastatic foci. Time of the 1st remission was calculated from the date of hospital discharge to the date of radiological recurrent tumor diagnostics.

Statistical processing of quantitative indicators (using the arithmetic average of M indices from M_1 to M_n inclusively, errors of arithmetic mean m, number of observations n, mean-square deviation b, nonparametric Mann-Whitney, Wilcoxon criteria, arithmetic means M_1 and M_2 compared series of indicators, errors M_1 and M_2 – m_1 and m_2, respectively), and regression analysis were carried out within variation statistics [6] on the PC 1BM "Pentium" with software package "Statgraphics" version 3.0 and "Microsoft Excel" version 5.0.

Results

During postprocessing of perfusiongramms quantitative intratumoral BVFR indicators for 4 nosological forms of malignant tumors were obtained (Table). Retrospective regression analysis of the 1st remission duration dependence from BVFR of malignancies was carried out.

Taking into account the phenomenon of tumor growth stability [1], we note the certain conventionality of the 1st disease-free remission duration definition.

Osteosarcoma. The correlation coefficient (r) = -0.988. The bond between the investigated signs – feedback, bond tightness (power) according to Cheddok scale – very high. The number of freedom (f) degrees is 3t – Student's criteria is 11,208. The critical value of the Student's t-criteria for a given number of freedom degrees is 3.182. Dependence of symptoms is statistically significant ($p < 0,05$). The determination coefficient r^2 is equal to 0.977 (factor sign x determines 97.7 % of the dependent feature depression y). The average approximation error (characterizes the regression model adequacy) is 1.1 %. The evaluation of rank correlation according to Kendal coefficient based on 2 tests is statistically significant.

Chondrosarcoma. r = -0.991. The bond – reverse, bond tightness (power) – functional. **f** is 2t-criteria = -10,304. The critical value of the t-criteria = 4.303. $p < 0,05$. $\mathbf{r}^2 = 0.982$. The average approximation error is 0.6 %. The evaluation of rank correlation according to Kendal coefficient based on 2 tests is statistically significant.

Ewing's sarcoma. r = -0.954. The bond – reverse, bond tightness (power) – is very high. **f** is 1t-criteria = -3,175. The critical value of t-criteria = 12.706 $p < 0,05$. $\mathbf{r}^2 = 0.910$. The average approximation error is 1.2 %. The evaluation of rank correlation according to Kendal coefficient based on 2 tests is statistically significant.

Fibrosarcoma. r = -0.956. The bond – reverse, bond tightness (power) – is very high. **f** is 1t-criteria = -3,272. The critical value of t-criteria = 12.706 $p < 0,05$. $\mathbf{r}^2 = 0.915$. The average approximation error is 1.4 %. The evaluation of rank correlation according to Kendal coefficient based on 2 tests is statistically significant.

Regression is the value expressing the dependence of the mean value of the random variable **y** (in our analysis – the duration of the 1st remission) from the values of the random variable **x** (BF). The regression equation expresses the duration of the 1st remission (in conventional months) as BF function. Formal assumption: intratumoral BF (and only it) reflects the level of malignant tumor aggressive growth potential.

It is known two types of relationships between **x** and **y** [6]: may be unknown which of the two variables is independent and which – dependent, variables are equal, it is the relationship of correlation type (this type does not correspond to the research definitely); if **x** and **y** are unequal, and one of them is regarded as an explanatory (independent) variable (BF), and the other – as the dependent one (1st remission duration), then it is the relationship of regression type.

Pair regression equation between two variables x and y is represented by a model of the following type: $\mathbf{y = E + f(x)}$, where **y** – dependent variable (effective sign), **x** – independent, explanatory variable (BF), **E** – variable (for different nosological forms of malignancies) including unaccounted factors impact (e.g., factors of tumor cells' macro- and microenvironment) in the model.

Note that the terminology of *dependent* and *independent* variables reflects primarily only mathematical dependence of variables, but not the real-life and highly variable causal relationships. Independent variables are called predictors [6].

At all regression equations BF has a significant correlation coefficient **R** with the 1st remis-

Table

Dependence of the 1st remission duration (months) from the intratumoral blood volume flow rate

Nosological form	BVFR, мл/мин/100 г	1st remission duration (months)	Regression equation
Osteosarcoma	51,1±4,9	17, 18, 19, 20, 21	y=45.40146- 0.51951*x
Chondrosarcoma	22,7±3,4	22, 23, 24, 25	y=45.34340- 0.96226*x
Ewing's sarcoma	18,3±3,0	28, 29, 31	y=41.10526- 0.64327*x
Fibrosarcoma	14,6±1,7	29, 31, 33	y=62.41772- 2.15190*x

sion duration. Theoretically, when BF is → 0 variable **E** corresponds to the maximum possible theoretically duration of the 1st remission (at assumptions made a priori within selected model). Note that the maximum patients' survival rate at ceteris paribus is higher just at hypovascular cancers with low level of BF [7, 8]. Regression equations obtained for 4 nosological forms of malignant tumors accurately reflect this conformity.

Conclusion

The inversely proportional relationship between the BF of femur malignant tumors and the 1st remission duration after treatment of patients within the algorithm **mebifon + surgery + arthroplasty + mebifon** was identified within the framework of regression analysis. BF is a surrogate predictor of the 1st remission duration. BF application provides qualitative assessment of the 1st remission duration at one or another type of tumor.

Connection of the work with scientific programs, plans, themes. The study was performed within the framework of the planned research work of the R. E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology NASc of Ukraine: "Optimization of diagnostic and palliative treatment of patients with malignant bone lesions" (2014-2016, state registration № 0110U006646).

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BLOOD VOLUME FLOW RATE OF THE FEMORAL BONE MALIGNANT TUMORS - THE PREDICTOR OF THE 1ST REMISSION DURATION AFTER COMBINED TREATMENT

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The functional characteristics of the vasculature and perfusion have been attracting attention as a predictor of tumor progression, as well as surrogate markers of hypoxia. It is known that a high level of vascularization and perfusion can determine aggressive and metastatic potential of the tumor. **Objective –** to show a possible link intratumoral blood flow rate of malignant tumors of the paranasal sinuses and the duration of the 1st remission after combined treatment.

Material and methods. Perfusiongraphy malignant tumors of the paranasal sinuses were examined for multidetector computed tomography "Somatom Volume Zoom". The study included 15 patients with 4 nosological forms of malignant tumors. All patients were treated according to the algorithm **mebifon + surgery + arthroplasty + mebifon**. After treatment, the patients 1 time every 2-3 months were clinical and radiological (for suspected recurrence) investigated.

Results. The regression analysis of the dependence of the duration of the 1st remission from the blood flow rate of malignant tumors in the preoperative period was fulfilled.

Conclusion. Inverse proportional relationship between the rate of volumetric blood flow of bone malignant tumors with the 1st remission duration after treatment was stated. Maximum survival of patients at paribus is higher at hypovascular cancers with blood volume flow rate.

ШВИДКІСТЬ ОБ'ЄМНОГО КРОВОТОКУ ЗЛОЯКІСНИХ ПУХЛИН СТЕГНОВОЇ КІСТКИ - ПРЕДИКТОР ТРИВАЛОСТІ 1-Й РЕМІСІЇ ПІСЛЯ КОМБІНОВАНОГО ЛІКУВАННЯ

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Функціональні характеристики судинної мережі і перфузії давно привертають до себе увагу як маркери прогнозу пухлинної прогресії, а також сурогатні маркери гіпоксії. Відомо, що високий рівень васкуляризації і перфузії може визначати агресивний і метастатичний потенціал пухлини.

Мета дослідження – показати можливий зв'язок внутрішньопухлинне швидкості об'ємного кровотоку злоякісних пухлин навколоносових пазух і тривалості 1-й ремісії після комбінованого лікування.

Матеріал і методи. Перфузіографію злоякісних пухлин стегнової кістки досліджували на мультідетекторний рентгенівському комп'ютерному томографі «Somatom Volume Zoom». Обстежені 15 хворих з 4 нозологічними формами злоякісних новоутворень стегнової кістки. Усі хворі пройшли лікування у відповідність з алгоритмом **мебіфон + операція + ендопротезування + мебіфон**. Після лікування хворі 1 раз в 2-3 місяці проходили клінічне та радіологічне (при підозрі на рецидив) обстеження.

Результати. Проведено регресійний аналіз залежності тривалості 1-й ремісії від швидкості об'ємного кровотоку злоякісних пухлин в доопераційний період.

Висновки. Встановлено обратно пропорційний зв'язок швидкості об'ємного кровотоку злоякісних новоутворень стегнової кістки з тривалістю 1-й ремісії після лікування хворих. Максимальна виживаність хворих за інших рівних умов вище при гіповаскулярних ракових пухлинах з низьким рівнем швидкості об'ємного кровотоку.

СКОРОСТЬ ОБЪЕМНОГО КРОВОТОКА ЗЛОКАЧЕСТВЕННЫХ ОПУХОЛЕЙ БЕДРЕННОЙ КОСТИ – ПРЕДИКТОР ДЛИТЕЛЬНОСТИ 1-Й РЕМИССИИ ПОСЛЕ КОМБИНИРОВАННОГО ЛЕЧЕНИЯ

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Функциональные характеристики сосудистой сети и перфузии привлекают внимание как маркеры прогноза опухолевой прогрессии, а также суррогатные маркеры гипоксии. Известно, что высокий уровень васкуляризации и перфузии может определять агрессивный и метастатический потенциал опухоли. **Цель исследования –** показать возможную связь внутриопухолевой скорости объемного кровотока злокачественных опухолей и длительности 1-й ремиссии после комбинированного лечения.

Материал и методы. Перфузиографию злокачественных опухолей исследовали на мультидетекторном рентгеновском компьютерном томографе "Somatom Volume Zoom". Обследованы 15 больных с 4 нозологическими формами злокачественных новообразований Все больные прошли лечение в соответствие с алгоритмом **мебифон + операция + эндопротезирование + мебифон**. После лечения больные 1 раз в 2–3 месяца проходили клиническое и радиологическое (при подозрении на рецидив или жалобах) обследования.

Результаты. Проведен регрессионный анализ зависимости длительности 1-й ремиссии от скорости объемного кровотока злокачественных опухолей в дооперационный период.

Выводы. Установлена обратно пропорциональная связь скорости объемного кровотока злокачественных новообразований кости с продолжительностью 1-й ремиссии после лечения больных. Максимальная выживаемость больных при прочих равных условиях выше при гиповаскулярных раковых опухолях с низким уровнем скорости объемного кровотока.