Polymorbidity and heterogeneity of intact bone tissue in patients with malignant and metastatic bone tumors

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The classical therapeutic minimally invasive concept of onco-orthopedics (the urgent task of which is to preserve the bone that is affected by the tumor process) is based on medical imaging data, endoprosthetics (the advantage of endoprosthetics is the simultaneous resection of the bone affected by the tumor and early restoration of supporting ability and function of the operated limb [9]), bone grafting and has available and cost-effective resources to increase the treatment effectiveness.

In particular, the treatment of concomitant diseases in patients with malignant and metastatic tumors (for example, stomach cancer, pancreatic cancer) is an important factor in increasing their survival and life quality. This aspect practically doesn't comprise onco-orthopedics [1, 6, 12, 15, 16].

Medicine is moving from the epoch of "one chronic disease" to the epoch of "polymorbid medicine" [13]. The term "comorbidity" (from Latin *co* – together, *morbus* – disease) was introduced in 1970 by Professor A. Feinstein (in the process of studying the prospects of cancer treatment in patients with concomitant chronic diseases: coronary heart disease, cerebral arteriosclerosis, pulmonary dysfunction), who understood this as additional clinical conditions that already exist or have arisen against the background of the current disease and are always different from it [14]. Synonyms of the term: multimorbidity, polymorbidity (discussion on the different semantics interpretation of these terms continues today), multifactorial diseases, polypathy, comorbidity, polypathology, double diagnosis, pluripathology [1, 8]. The coexistence of several diseases in one patient in the domestic literature is described as "combined", "concomitant", "associated" diseases or conditions.

Comorbidity is the coexistence of two and/or more diseases in one patient, pathogenetically and genetically interconnected.

Principal clarification of the term [17]: comorbidity is the combination in one patient of two or more

chronic diseases, pathogenetically interconnected or coinciding in time in one patient, regardless of the activity of each of them. There are 3 known forms of human comorbidity: direct comorbidity (syntropy), reverse comorbidity (dystropy) and comorbidity between multifactorial (complex) diseases and Mendelian (monogenic) diseases.

Multimorbidity is a combination of several chronic diseases of various genesis in one patient [5].

Polymorbidity is the presence of several simultaneous diseases (genetically or pathogenetically related or unrelated to one another) in one person in different stages and phases of their development. The division of polymorbidity into multimorbidity and comorbidity very often is only conditional.

Polymorbidity is a broad concept. The relationship of several diseases can be represented by such options: one disease may be the cause of another disease; two diseases may have common risk factors or common pathogenesis mechanisms; two diseases may not have a causal relationship or have only a weak association [19]; one disease can be caused by iatrogenic factors that may be caused by another disease [18].

Polymorbidity is accompanied by higher mortality rates, higher disability rates, side effects of treatment, increased use of the patient's body resources, lower quality of life [11].

Comorbidity, to some extent, affects the entire "trajectory" of the tumor process, starting from the moment of predisposition formation up to the diagnosis is established, treatment requires use of supplemental resources [15]. So, for example, chronic obstructive pulmonary disease (COPD) is described as a part of systemic inflammatory syndrome and is associated with lung cancer, osteoporosis, atherosclerosis progression, and chronic kidney disease (CKD) [8]. **The purpose of the article** is to demonstrate the association of polymorbidity and intact bone tissues' heterogeneity in patients with malignant and metastatic bone tumors.

Material and Investigation Methods

The main group consisted of 63 patients with benign, primary malignant and metastatic bone tumors (table 1): 33 (52.4%) men and 30 women (47.6%) aged 25 to 75 years (mean age 51.8 ± 1.5 months). Benign tumors were found in 8 (50.1 %) men and 8 (50.0 %) women, malignant tumors – in 13 (52.0 %) men and 12 (48.0 %) women, metastatic bone lesions – in 12 (54.5%) men and 10 (45.5 %) women. 37 patients of the control group were investigated for suspected bones tumor lesions on a multispiral tomograph, but the diagnosis was not confirmed: 20 (54 %) men and 17 (46%) women aged 26-75 years, average age 51.7 ± 1.5 months. All patients gave informed consent for participation in the study.

Table 1.
Distribution of patients by clinical diagnoses (n = 63).

Clinical diagnosis	abs	%
Benign tumors	16	25,4
Malignant tumors	25	39,7
Metastatic tumors	22	34,9

Histogram analysis of radiographic density (RGD) of the computed tomographic images' texture was carried out by a known method [2]. The heterogeneity coefficient K_1 was calculated by the described method [9]. The scale "homogeneity → heterogeneity" K_1 corresponds to 0.00 → 1.00.

The investigation design did not include the study of the diseases' pathogenetic relationships, and therefore we use the term **polymorbidity**. To assess the severity of polymorbidity in patients, the CIRS-G system (Cumulative Illness Rating Scale for Geriatrics) was applied. In the calculation, points corresponding to concomitant diseases are summerized, and also one point is added for every ten years of life when a patient exceeds forty years (that is, 50 years – 1 point, 60 years – 2 points, etc.) [20].

According to the CIRS-G system, a separate summary assessment of the state of each of the organ systems is carried out: "0" corresponds to the absence of diseases

of the selected system; "1" – a slight deviation from the norm or past diseases; "2" – diseases requiring the drug therapy; "3" – a disease that caused disability; "4" – severe organ failure requiring emergency treatment.

The CIRS-G system evaluates polymorbidity by the sum of points, which can vary from 0 to 56, taking into account the age of the patient. According to its developers, maximum results are not compatible with patients being alive. Statistical processing of quantitative indicators was carried out with the package "Microsoft® Excel 97".

Results and their discussion

Polymorbidity assessment in persons of the control group and patients with benign, primary malignant and metastatic bone tumors is presented in table 2.

Only 4 (25.0 %) of the 16 patients with benign tumors needed drug therapy for concomitant diseases (arterial hypertension, arthrosis, arthritis, diabetes mellitus 2, cholecystitis).

8 (32 %) of 25 patients with malignant tumors and continuous drug therapy for peptic ulcer, hypertension, chronic venous insufficiency, osteoporosis, consequences of myocardial infarction and ischemic stroke needed, and in 6 (24 %) patients the concomitant diseases (myocardial infarction and ischemic stroke) caused disability.

9 (40.9 %) of 22 patients with bone metastases of prostate, breast, lung and kidney cancer, required drug therapy for concomitant diseases (coronary atherosclerosis, coronary heart disease, CKD, COPD, arthrosis, arthritis, diabetes mellitus 2), 13 patients (59.1 %) the concomitant diseases (myocardial infarction and ischemic stroke) caused disability.

For comparison: more often concomitant diseases are characteristic for malignant tumors of the lungs (58 %), kidneys (54 %), stomach (53 %), bladder (53 %) and prostate gland (51 %) [1, 8].

The measurement results of the quantitative characteristics of intact bone tissue on the affected side 3-4 cm from the tumor site are summarized in table 3.

Table 2.
Polymorbidity assessment of patients according to the CIRS-G system.

Group	Quant.	Polimorbidity, points				
		0	1	2	3	4
Control group	37	15/40,5	22/59,5	–	–	–
Benign tumors	16	6/37,5	6/37,5	4/25,0	–	–
Malignant tumors	25	4/16,0	7/28,0	8/32,0	6/24,0	–
Metastatic tumors	22	–	–	9/40,9	13/59,1	–

Table 3.
Bone texture indicators.

№	Polomorbidity, level	RGD, HU		C1	
		spongy	compact	spongy	compact
		1	2	3	4
Control group					
1	0 – 1	319±16	1381±45	0,415±0,012	0,309±0,010
Benign tumors					
2	0 – 1	312±11 P ₁₁₂ >0,05	1175±26 P ₂₁₂ >0,05	0,436±0,010 P ₃₁₂ >0,05	0,367±0,011 P ₄₁₂ <0,02
3	2	297±15 P ₁₁₃ >0,05	923±31 P ₂₁₃ < 0,01	0,484±0,012 P ₃₁₃ <0,05	0,401±0,012 P ₄₁₃ <0,02
Malignant tumors					
4	0 – 1	278±10 P ₁₁₄ >0,05	993±21 P ₂₁₄ <0,01	0,542±0,011 P ₃₁₄ <0,01	0,443±0,011 P ₄₁₄ <0,01
5	2 – 3	223±14 P ₁₁₅ <0,01	790±33 P ₂₁₅ <0,01	0,597±0,016 P ₃₁₅ <0,01	0,481±0,013 P ₄₁₅ <0,01
Metastatic tumors					
6	2 – 3	204±16 P ₁₁₆ <0,01	784±34 P ₂₁₆ <0,01	0,626±0,015 P ₃₁₆ <0,01	0,533±0,016 P ₄₁₆ <0,01

In early stage tumors, polymorbidity of level 0-1 does not affect the RGD of bone tissues, level 2 is associated with reliably reduced RGD of only compact tissue (compared with the control group). At the same time, K_1 was reliably increased with polymorbidity level 0-1 in compact tissue, level 2 – in spongy and compact tissues (compared with the control group).

In malignant tumors, polymorbidity of the level 0-1 is associated with reliably reduced RGD of only compact tissue (compared with the control group) and an increase in the texture heterogeneity of compact and spongy tissue according to the values of C_1 (compared with the control group), level 2-3 – with reliably reduced RGD of compact and spongy tissue and an increase in the heterogeneity of their texture according to C_1 values (compared with the control group).

In metastatic bone tumors, polymorbidity of level 2-3 is associated with reliably reduced RGD of compact and spongy tissue and an increase in the heterogeneity of their texture according to K_1 values (compared with the control group).

In the symmetrical skeleton zones, the indicators (RGD and heterogeneity) of the bone tissue texture in order of magnitude corresponded to the ones we described earlier [9].

The texture heterogeneity of computed tomographic images of malignant and metastatic tumors is characteristic practically for tumors of all body tissues of any localization [3].

It is possible to interpret the detected phenomenon within the framework of the tumor field concept [4].

The effect of polymorbidity on physical characteristics, in particular, on RGD and heterogeneity of intact/conditionally intact tissues' texture in patients with malignant and metastatic bone tumors, has hardly been studied in oncorthopedics and radiology.

Conclusion

Concomitant diseases requiring drug therapy had 25 % of patients with benign bone tumors, 32 % of patients with malignant bone tumors, and 40.9 % of patients with metastatic bone tumors. 24.0 % of patients with malignant bone tumors and 59.1 % of patients with metastatic bone tumors had concomitant diseases that caused disability.

An increase in polymorbidity level is associated with a decrease in RGD and an increase in the texture heterogeneity of computed tomographic images of the spongy and compact bones (the pattern is reliable, $P < 0.01$) in the series: practically healthy individuals, patients with benign tumors, patients with malignant tumors, patients with metastatic tumors.

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The authors declare no conflict of interest.

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POLYMORBIDITY AND HETEROGENEITY OF INTACT BONE TISSUE IN PATIENTS WITH MALIGNANT AND METASTATIC BONE TUMORS

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Polymorbidity is the presence of several synchronically occurring diseases (genetically or pathogeneti-

cally related or unrelated) in one person at different stages and phases of their development, is accompanied by higher mortality rates, higher disability rates, treatment side effects, increased consumption of the patient's body resources, lower quality of life.

The purpose of the article is to demonstrate the association of polymorbidity and intact bone tissues' heterogeneity in patients with malignant and metastatic bone tumors.

Material and methods. 16 patients with benign bone tumors, 25 – with primary malignant bone tumors and 22 – with metastatic bone tumors were investigated with multispiral tomography scanner: 33 (52.4 %) men and 30 (47.6 %) women aged 25 to 75 years. The control group consisted of 37 patients with suspected tumor lesions of the bones, but the diagnosis was not confirmed. To assess polymorbidity in patients, the CIRS-G system was applied.

Conclusion. An increase in polymorbidity level is associated with a decrease in RGD and an increase in the texture heterogeneity of computed tomographic images of the spongy and compact bones (the pattern is reliable, $P < 0.01$) in the series: practically healthy individuals, patients with benign tumors, patients with malignant tumors, patients with metastatic tumors.

ПОЛІМОРБІДНІСТЬ І ГЕТЕРОГЕННІСТЬ КІСТКИ У ХВОРИХ ІЗ ЗЛОЯКІСНИМИ ТА МЕТАСТАТИЧНИМИ ПУХЛИНАМИ КІСТОК

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Поліморбідність – наявність декількох захворювань (пов'язаних або не пов'язаних між собою генетично або патогенетично), що синхронно протікають в одній людині в різних стадіях і фазах свого розвитку; супроводжується більш високими показниками смертності, більш високими показниками інвалідності, побічними ефектами лікування, підвищенням використання ресурсів організму хворого, більш низькою якістю життя.

Мета статті – показати асоціацію поліморбідності і гетерогенності кісткових тканин у хворих із злоякісними та метастатичними пухлинами кісток. **Матеріал і методи.** Обстежено на мультиспіральному томографі 16 хворих з доброякісними пухлинами кісток, 25 – з первинними злоякісними пухлинами кісток і 22 – з метастатичними пухлинами кісток: 33 (52,4 %) чоловіки і 30 жінок (47,6 %) у віці від 25 до 75 років. Контрольна група – 37 пацієнтів з підозрою на пухлинні ураження кісток, але діагноз не був підтверджений. Для оцінки

поліморбідності у хворих використовували систему CIRS-G.

Висновки. Збільшення рівня поліморбідності асоціюється зі зменшенням рентгенівської щільності і збільшенням гетерогенності текстури комп'ютерно-томографічних зображень губчастої і компактною кістки (закономірність достовірна, $P < 0,01$) в ряду: практично здорові особи, хворі з доброякісними пухлинами, хворі із злоякісними пухлинами, хворі з метастатичними пухлинами.

ПОЛИМОРБИДНОСТЬ И ГЕТЕРОГЕННОСТЬ ИНТАКТНЫХ КОСТНЫХ ТКАНЕЙ У БОЛЬНЫХ СО ЗЛОКАЧЕСТВЕННЫМИ И МЕТАСТАТИЧЕСКИМИ ОПУХОЛЯМИ КОСТЕЙ

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Полиморбидность – наличие нескольких синхронно протекающих заболеваний (связанных или не связанных между собой генетически или патогенетически) у одного человека в различных стадиях и фазах своего развития, сопровождается более высокими показателями смертности, более высокими показателями инвалидности, побочными эффектами лечения, повышенным использованием ресурсов организма больного, более низким качеством жизни.

Цель статьи – показать ассоциацию полиморбидности и гетерогенности костных тканей у больных со злокачественными и метастатическими опухолями костей.

Материал и методы. Обследовано на мультиспиральном томографе 16 больных с доброкачественными опухолями костей, 25 – с первичными злокачественными опухолями костей и 22 – с метастатическими опухолями костей: 33 (52,4 %) мужчины и 30 женщин (47,6 %) в возрасте от 25 до 75 лет. Контрольная группа – 37 пациентов с подозрением на опухолевые поражения костей, но диагноз не был подтвержден. Для оценки полиморбидности у больных использовали систему CIRS-G.

Выводы. Увеличение уровня полиморбидности ассоциируется с уменьшением рентгеновской плотности и увеличением гетерогенности текстуры компьютерно-томографических изображений губчатой и компактной кости (закономерность достоверна, $P < 0,01$) в ряду: практически здоровые лица, больные с доброкачественными опухолями, больные со злокачественными опухолями, больные с метастатическими опухолями.