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# Design Requirements for the Device for Differentiating Pathological States of Biological Tissues

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**Abstract**: The appearance of the device for mini-gamma-quantum differentiation of biological tissues, the arrangement of units (research unit and control unit), units (cassette holder, electronic units, etc.) and individual parts (cassette, etc.), as well as control panels (front and rear) have ergonomic indicators that ensure convenience use (preparation for operation – ease of installation of the device on the table, connection to the electrical network and grounding, loading/unloading of biological tissue samples into/from the cassette, etc.); ease of use (ease of working with the control panel and the cassette with the cassette holder); the convenience of preventive maintenance work (cassette disinfection, etc.). The control unit and the research unit are located in different housings of the device: a) control unit – in a high-strength plastic case; b) research unit – in a stainless steel metal case. A measuring device in the form of a scintillation detector is located in the metal case of the research unit, consisting of: a case, a scintillator (crystal, plastic, liquid), a photoelectric multiplier, a power cell, a source of ionizing low-energy gamma radiation in a special protective case that ensures compliance with sanitary requirements and radiation safety standards, and a cassette for biological tissue to be examined (a sample of biological tissue is placed in the biopsies section of the cassette), which is installed in the cassette holder. The design of the cassette holder includes a knife for cutting excess biopsies. The cassette holder is firmly fixed in the housing of the device's research unit. The control unit houses power elements, a microprocessor controller for processing information and maintaining a database, providing communication with peripheral electronic devices. The front panel of the device houses the information monitor and control points. On the back panel there is a device on/off switch, a fuse and places for connecting additional devices. The device has the possibility of applying protective grounding.

**Keywords:** Device, Mini-gamma-quantum, Differentiation, Tissues

## Introduction

Today, modern medicine is used in the treatment of many diseases, from diseases that can be treated on an outpatient basis to diseases that require long-term bed treatment (Sulyma, Bereznytskyy, Duka, &Malinovskyj, 2021; Sulyma & Sulima, 2022; Sulyma, 2022). The quality of the diagnosis of oncological diseases mostly depends on the accuracy of the results of studies that determine the type of neoplasm. The tactics of further examination and treatment of the patient are based on the results of these studies, with the



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selection of necessary programs of possible complex combined treatment (radiation therapy, chemotherapy, surgery).

An inexpensive instrumental method of differential diagnosis of biological tissues developed by us and currently being implemented in medical practice, which will not only speed up the time of obtaining research results, but also significantly increase their objectivity and reliability on the basis of evidence and fixation of results in physical quantities in a computer program. The developed device is a portable medical apparatus for non-invasive and non-contact differential express diagnostics of normal and pathologically changed tissues of the human body based on the study of biopsies directly during surgical intervention in patients with suspected cancer. The proposed device allows differentiation of biological tissues according to 3 groups:

1. normal biological tissue without pathological formations;
2. biological tissue with non-malignant neoplasms;
3. biological tissue with malignant neoplasms.

Our biological tissue analyzer enables the doctor to establish the nature of the tumor, assess the local or regional spread of the process, determine the boundaries of neoplasms of different localization, assess the extent of surgical intervention and surgical tactics, ensure a negative result at the edges of the resection and reduce the risk of tumor recurrence after its removal.

The industrial production of the developed device will ensure the availability of a tool in every medical organization, which makes it possible to detect cancer early, start quick and high-quality complex combined treatment, reduce the development of complications of the disease and save the lives of patients. Such a device should be in every hospital, every oncology care center, every scientific medical and clinical research center.

The novelty of the proposed solution in the developed small-sized device for express diagnosis of tissues of the human body in the verification of oncological diseases is that the device is a portable medical apparatus for non-invasive and non-contact differential express diagnosis of normal and pathologically changed tissues of the human body based on the examination of biopsies directly during execution surgical intervention.

The main novelty of the development is that the construction of the proposed device is based on the gamma absorption method - a method of elemental analysis based on measuring the degree of attenuation of the gamma radiation flux passing through the biological tissue under investigation, or, in other words, the dependence of the degree of absorption on the biological tissue of a monochromatic beam of gamma quanta with a low energy value ranging from 5 to 17 keB, at which a sample of biological tissue with a thickness of 3 to 5 mm will intensively absorb gamma quanta. At the same time, the weakened flux of gamma quanta, which was not absorbed by the biological tissue and recorded by the device after its irradiation, will have a specific value for a biological tissue, characteristic separately for normal tissues, non-malignant tumors, and tissues affected by a malignant neoplasm.

Irradiation of a tissue sample with a mini-gamma-quantum causes cells to lose their negative charge, thus creating a photoelectric effect (Stoletov effect), which will be strictly individual for tumor, inflammatory and normal tissues. To differentiate various pathological formations, the authors measure the intensity of absorption of gamma quanta by cells, as well as the characteristic emission of microelements present in the tissue. A thallium-NaI (TL) activated sodium-iodine scintillation gamma spectrometric detector converts the energy of gamma quanta entering its sensitive area into flashes of visible light with a brightness proportional to the energy of the gamma quanta.

The current state of differentiation of pathological changes in tissues, and even more so in tumors, requires the use of not only the knowledge, skills and abilities of a pathologist, but also the use of much more informative molecular genetic methods (Kopnyn, 2002). However, the terms of performance of both traditional and modern methods of studying pathologically changed tissues are very significant (from 1 to 7 days), which is especially undesirable in patients with malignant tumors when performing organ-preserving surgical interventions on the biological tissues, which must end with the formation of an any anastomosis .

Usually, the assessment of the state of the ends of the connecting intestine for the presence of parts of the tumor is carried out by the surgeon only visually and by palpation, and only after 5-7 days it is possible to obtain a histological conclusion about the state of the ends of the removed drug. Sometimes, unfortunately, the presence of cancer cells is possible, which leads to a high probability of tumor recurrence in the formed anastomosis

(Sulyma et al., 2007; Сулима et al., 2008). It is important to develop and implement a new instrumental method of differentiation, which will not only speed up the time of obtaining results, but also increase their objectivity and reliability on the basis of evidence and fixation of physical units. There must be a morphological basis for such a method. Normal tissue growth is characterized by two main features: constancy of the cell population (achieved by the balance between proliferation and cell death), and full maturation and differentiation of cells after proliferation (Kopnyn, 2002). With sublethal damage to the genetic material of cells, both fundamental laws of normal tissue growth will be violated. The most frequent types of mutations are translocation, amplification, deletion and point mutations, as a result of which the expression of genes and their products can be excessive (hyperexpression) or suppressed (suppression). This unregulated growth ends with population expansion (cell expansion) and insufficient cell differentiation (Kaz'min & Smirnova, 1989).

## Method

One of the main tasks of a surgeon is to determine the extent of surgical intervention in the treatment of colorectal cancer. The choice of the scope of the operation - intestinal resection without restoration of intestinal patency with the formation of a permanent colostomy or sphincter-preserving surgery with restoration of colonic anastomosis patency - depends on the degree of invasion and tumor dissemination (Sulyma, & Malinovskyj, 2021). Since the determination of the borders of the tumor field and the degree of cancer dissemination with carcinoma of the lymphatic and blood vessels is beyond the intraoperative capabilities of the doctor, he relies exclusively on his own experience, intuition, operative findings and the results of preoperative studies.

For radical surgical treatment and to prevent postoperative complications and early recurrences, the surgeon must be sure that the line of bowel resection is not damaged by the neoplastic process. The most common and highly informative diagnostic method is intraoperative express biopsy of intestinal tissue taken from the resection line. When tumor complexes are detected in the line of resection, the surgeon can expand or change the scope of the surgical intervention. Unfortunately, in most hospitals, the method of intraoperative express biopsy is impossible, and even when it is used, the edges of the removed intestine are not completely studied by express examination, but only a few pieces of it, the analysis of which will not give answers about the condition of the ends of the drug. As a rule, the operative material is examined only after the operation, and the doctor receives a conclusion at least a day later, or even 5-7 days after the operation. A modern express method is proposed, which allows determining the extent of tumor spread to neighboring tissues and differentiating tumor and non-tumor processes by means of gamma radiation and residual measurement of samples removed during surgery (Sulyma et al., 2007). The positive achievements of the method consist in the expansion of the surgeon's intraoperative capabilities to determine the type and scope of the operation, which, in the end, is directly related to the improvement of the quality of life of the operated patient.

The method is based on the difference in concentrations of intracellular microelements in tumors and intact intestinal tissues using the phenomenon of the photoelectric effect. Irradiation of the specimens with mini-γ-quanta causes the cells to lose their negative charge, causing a photoelectric effect that is strictly individual for normal, reactively and non-plastically transformed tissues. To differentiate pathological processes of different quality, the intensity of mini-gamma quanta absorption by cells is measured and compared, as well as the characteristic emission of microelements contained in tissues, where the measurement results are represented by the formula.

Biochemical studies of tumors revealed that malignant cells have a different concentration of intracellular ions Na+, K+, and Cl- compared to normal cells. Thus, the concentration of intracellular sodium is increased, while the level of potassium ions is decreased. The ratio of Na+/K+ ions in tumor cells is five times higher than in normal cells. One of the possible explanations for disturbed ion homeostasis of tumor cells is the abnormal activity of Na+/K+-ATP-ase and the altered functioning of the co-transport systems for Na+, K+, Cl- ions, when a shift in the Na+/K+/Ca ion ratio is not only observed in a malignant cell ++, but also their possible influence on the abnormality of the cell shape, its mobility and cellular interactions (Latzkovits et al., 1983; Mtskhvetadze, et al., 1987).

## Results and Discussion

Research results indicate that the enzyme Na+/K+-ATPase (sodium pump), in addition to ion transport, is part of the protein complex that transmits growth signals from the extracellular environment to the intracellular

pathway of the replicative signal. The sodium pump acts as a transmembrane receptor for growth factors and is involved in the mechanism of tissue growth, where Na+/K+-ATPase regulates intracellular calcium content (Kaplan,2005).

Changes in metabolism and interactions with Na+/K+-ATPase may be associated with the development of malignant tumors. This is explained by the abnormal activity of Na+/K+-ATPase and its sensitivity in malignant cells, high concentration in the plasma of cancer patients. Na+/K+-ATPase α1-isoform expression is decreased and α3-isoform expression is increased in all colon cancer tissue samples compared with intact colonic mucosa, and poorly differentiated colon carcinomas have reduced Na+/K+-ATPase β1 subunit easy (Espineda et al., 2004;Espineda et al., 2003). These disturbances can explain changes in the level of Na+ and K+ in the cytoplasm of precancerous and tumorous epithelial cells of the colon mucosa (Kometiani et al., 2005).

Determination and fixation of the difference in the concentration of microelements in the tissues of the colon allows to differentiate its states: from normal to damaged by the tumor process. The difference in the composition of pulses for various pathological processes was 30%, which confirms the possibility of differentiating benign, malignant tumors and inflammatory processes of the rectum with the involvement of this energy at a measurement time of 60 seconds (Сулима et al., 2008).

The photomultiplier converts the visible light flashes of the scintillation detector installed opposite the photocathode into electrical pulses with an amplitude proportional to the brightness of the visible light flashes. The pulse amplifier brings the value of the amplitude of electric pulses at the output of the gamma quanta detection unit to several volts, depending on the energy of the output gamma quanta. Thus, the possibility of diagnosing the quality of biological tissue by absorption follows from the fact that the absorption of the same type of radiation will be significantly different in biological tissues of different states. The attenuation of a narrow monoenergetic beam of gamma radiation when passing through biological tissue is described by an exponential law:

$$I = I_0 e^{-\mu_\pi d},$$

where:

$I_0$ – is the intensity of the gamma radiation beam falling on the biological tissue;
$I$ – is the intensity of the gamma radiation beam that passed through a layer of biological tissue, with a thickness of d cm;
$\mu_\pi$ – is the linear absorption coefficient.

The device developed by us examines mini-samples of biological tissue (biopsies) selected and placed in a special cassette of the measuring part of the analyzer and visually reproduces physical values that are characteristic only for certain tissue states (normal, inflammatory, with non-malignant or malignant growth) with a measurement period from 1 to 6 minutes based on residual characteristic radiation results.

The initial gamma quanta passing through the tissue sample under investigation can receive one of three types of interaction with the electrons of the carbon, nitrogen and oxygen atoms that make up, mainly, the deoxyribonucleic acid molecule, that is, the cell (at the same time, the probability of such a process will be the higher, the more important the density of the study sample will be):

- fluorescent absorption by the electrons of the K- or L-shell of the indicated atoms, while one of the electrons from a more distant orbit, having released excess energy at this time, will move to the vacancy created;
- characteristic radiation, which is cut off by the information processing unit;
- coherent scattering without energy change;
- incoherent scattering with energy change (Compton effect).

The development of a small-sized device for express diagnostics of human body tissues for verification in oncological diseases allowed us to substantiate, manufacture and test a sample of the analyzer, which implements the gamma absorption measurement method using low-energy gamma quanta for differential express diagnostics of the state of normal and pathologically changed tissues of the human body, which are studied during a surgical operation on an oncological patient.

The device allows the doctor to determine the correct and complete volume of surgical intervention when determining the borders of a cancerous tumor, reduces the need to perform a repeat operation (without using the proposed device and method at the edges of the resection, the growth of a cancerous tumor is possible, which will require a new operation), and also provides information on the state of the pathologically changed tissues to confirm the diagnosis.

*The main technical parameters that determine the functional, quantitative (numerical) and qualitative characteristics of the developed device.*

Functions provided by the proposed device:

1. The device is used in non-invasive, non-contact medical research.
2. The device has such a level of complexity that personnel who have learned only the device's operating instructions are allowed to work with it.
3. The device differentiates the tissues examined according to the following criteria:
- normal biological tissue without pathological formations;
- biological tissue with non-malignant neoplasms;
- biological tissue with malignant neoplasms, and records the obtained results in the form of physical (digital) values.

4. The device has the functional ability to ensure the following actions for express diagnostics:

- calibration with the help of specialized equivalents included in the device package, for working with defined tissue biopsies of a specific part of the human body, as well as re-calibration when switching to another type of biological tissue during operation and in the place of operation of the device using the same equivalents included to the configuration of the device;
- insertion of the biopsy specimen into the cassette of the device's research unit and formation of the defined dimensions of the sample of biological tissue to be examined with the help of the cassette, the cutting mechanism and the cassette holder;
- positioning of the cassette holder with the inserted cassette with the sample to be examined in a molded form in the device's examination unit;
- formation of a low-energy monochromatic collimated stream of gamma radiation with energy from 5 to 17 keV to pass through the research sample;
- measurement of the intensity of the gamma quanta flow after passing through the sample of biological tissue under investigation using a scintillation detector and a photoelectron multiplier;
- perform mathematical processing of the received information;
- display on the monitor the information of the final result in the form of a physical (digital) value and the corresponding category of the state of the biological tissue;
- maintaining a database with the necessary amount of information: numbering of the sequence of research, date, first and last name of the patient, male/female, date of birth, address, digital research result, conclusions based on the research results;
- preservation of the required amount of information;
- communication (wired and wireless) with various electronic devices for data entry;
- transfer of information to a higher-level device for system input of the database and use for official purposes;
- processing of information from the database using artificial intelligence.

*Quantitative parameters that determine the device's performance of its functions.*

The device must provide the following quantitative parameters:

- distribution of biological tissues, which are studied according to three categories:

a) normal biological tissue without pathological formations;
b) biological tissue with non-malignant neoplasms;
c) biological tissue with malignant neoplasms,

in the form of a physical quantity corresponding to a specific category;
- time of one measurement (exposure time) from 1 to 5 minutes;
- measurement error in comparison with morphological laboratory results studies from 2 to 3%;
- the weight and geometry of the biopsy being studied, which is formed with the help cassette and cutting mechanism: a) weight — from 1.0 g; b) diameter — from 1 to 5 mm;
c) thickness — from 1 to 5 mm;
- the range of measuring the density of the investigated tissues from 1.00 to 1.20 g/cm3;
- use of a low-energy emitting isotope as a source of gamma quanta monochrome flux of gamma radiation with energy from 5 to 17 keV;
- the average working time of the device before failure is not less than 12,000 hours;
- the term of use of the device is at least 10 years.

*Design Requirements for the Device.*

The device is made in a desktop form with the possibility of moving from one workplace to another depending on the operating conditions (environmental comfort – the microclimate of a medical institution), the workplace – a desk.

The appearance of the device, the arrangement of units (research unit and control unit), units (cassette holder, electronic units, etc.) and individual parts (cassette, etc.), as well as control panels (front and rear) have ergonomic indicators that ensure convenience use (preparation for operation – ease of installation of the device on the table, connection to the electrical network and grounding, loading/unloading of biological tissue samples into/from the cassette, etc.); ease of use (ease of working with the control panel and the cassette with the cassette holder); the convenience of preventive maintenance work (cassette disinfection, etc.).

The control unit and the research unit are located in different housings of the device:
- control unit – in a high-strength plastic case;
- research unit – in a stainless steel metal case.

A measuring device in the form of a scintillation detector is located in the metal case of the research unit, consisting of: a case, a scintillator (crystal, plastic, liquid), a photoelectric multiplier, a power cell, a source of ionizing low-energy gamma radiation in a special protective case that ensures compliance with sanitary requirements and radiation safety standards, and a cassette for biological tissue to be examined (a sample of biological tissue is placed in the biopsies section of the cassette), which is installed in the cassette holder.

The design of the cassette holder includes a knife for cutting excess biopsies. The cassette holder is firmly fixed in the housing of the device's research unit. During the initial period of operation, the device undergoes calibration using equivalents from a set of specialized equivalents included in the device's configuration, for working with certain tissues of various specific areas of the human body.The design of the cassette provides the possibility of heat treatment.The control unit houses power elements, a microprocessor controller for processing information and maintaining a database, providing communication with peripheral electronic devices. The front panel of the device houses the information monitor and control points. On the back panel there is a device on/off switch, a fuse and places for connecting additional devices. The device has the possibility of applying protective grounding.

The core of the presented method is the determination and fixation of different concentrations of trace elements in neoplastically transformed and non-neoplastic tissues using mini-γ radiation. The transformation of a cell from normal to malignant is accompanied by altered expression of the Na+/K+-ATPase enzyme, which is a consequence of both genetic dysregulation of the sodium pump and altered concentration of endogenous agents to which this enzyme is sensitive. Its pumping function decreases, which is manifested by an imbalance of the ionic content of the cell - the concentration of sodium and calcium ions increases, while the level of potassium decreases.

## Conclusion

One of the essential characteristic of the malignant tumour is unregulated growth. Two major lows of normal tissue growth - (1) balance between cell proliferation and cell death and (2) complete cell maturation – are

altered as a result of the mutated DNA at the locus of protooncogenes. Various kinds of cancerogenes induce mutations (translocation, point mutation, amplification) in the protooncogenes converting them into oncogenes. The final result of these alterations in the genetic material is abnormal activation of genes responsible for cell proliferation (*sis, ras, abl, myc, N-myc, L-myc, erb,* others) and/or suppression of genes regulated cell death (*Rb, p53, APC, others)* with marked expansion of cellular population.

Well known cell enters cell cycle under the influence of special chemical signals such as hormones, cytokines, and growth factors that bind to correspondent transmembrane receptors on the cell membrane. This extracellular signal transmits via membrane and triggers the intracytoplasmic cascade of reactions of tyrosine kinase phosphorilation - intracellular signaling. In the end of this complex pathway the nucleus receives the signal that creates the expression of growth regulatory genes including *myc, fos, jun,* and pushes the cell to S stage of the mitotic cycle.

Mutation in the genome of somatic cell ultimately leads to activation of growth-promoting oncogenes, alterations of apoptosis-regulated genes, and cancer-suppressor genes with expression of altered genes products and loss of regulatory gene products.The molecular mechanisms by which oncogenes initiate and stimulate tumor growth are: (1) overproduction of the growth factors, (2) increased density of the growth factor receptors on the cell membrane, (3) mutation of the transducer mechanisms, and 4) mutation of the transcription factor.

Precise examination of tumour cell revealed altered concentration of intracellular ions of $Na^+$, $K^+$, and $Cl^-$ respect to normal cell. Intracellular sodium is elevated while potassium is depressed. Investigation of this question in urothelial carcinomas discovered the average intranuclear sodium content increased more than three-fold, the potassium content decreased from 32 to 13%, and the chloride level increased too. The $Na^+/K^+$ ratio were more than five-fold higher in the cancer cells. The possible explanation of such altered ions homeostasis is an abnormal activity of the Na/K-ATPase, as well as an abnormally active $Na^+$, $K^+$, $Cl^-$ co-transport systems.

One of the main tasks of the surgeon while carrying out of the resection of colon due to cancer is as more as exact to determine the borders of the intestine resection. Because of the area of tumour spreading and invasion is invisible, the surgeon commonly trusts on self experience and intuition. The histological examination of the frozen tissue samples obtained from the margins of the resection usually sufficient for establishing the presence or absence of complexes of tumour cells.

Although this method is the most reliable and commonly used throughout the world here there is an alternative or additional way that allows determining the precise margins of the resection of the affected colon and differentiation of malignant and non malignant lesions right during surgery. This method is based on the difference in the concentration of the intracellular microelements in tumour and non affected colonic tissue.

The authors use the phenomenon of photoelectrical effect. Radiation of the tissue sample by the mini-γ-quantum induces lost of negative charge by cells thereby creating the photoelectrical effect that will strictly individual for neoplastic and non-neoplastic tissues. For differentiation various pathologic lesions authors measure the intensity of γ-quantum uptake by cells as well characteristic radiation of microelements presence in the tissue.
Thus, the key position of presented method is distinction of the concentration of microelements in malignant and nonmalignant lesions. Taking in account the literature data adduced above this circumstance could be explained by complex and coupled function of sodium pump in cancerogenesis.

The enzyme $Na^+$,$K^+$ATP-ase possess unique properties because of combination of so different but interrelated functions – pumping and signalling activity essential for tissue growth. Malignant transformation of a cell accompanies by alterations in functions of this enzyme. So the intracellular concentration of some ions is change together with appearing of disorders of signalling pathway involved in tissue growth.

Presented literature facts regarding participation of $Na^+$, $K^+$ATP-ase in tissue growth allow to consider that sodium pump involves in signalling pathway and its acting associated with the expression of protooncogenes. Therefore, the mutated oncogenes caused the abnormal expression and functioning of $Na^+$,$K^+$ATP-ase. Some literature sources announced about interdependence between abnormal concentration of intracellular ions and disregulation of the some oncogenes and initiation of malignant transformation of the cell.

This biological tissue analyzer enables the doctor to establish the nature of the tumor, assess the local or regional spread of the process, determine the boundaries of neoplasms of different localization, assess the extent of

surgical intervention and surgical tactics, ensure a negative result at the edges of the resection and reduce the risk of tumor recurrence after its removal.

## Recommendations

In the future, the application of the proposed method can objectify and speed up the differential diagnosis of intestinal tumors, and a deep study on other neoplasms of organs and tissues can be the basis of a new direction of instrumental diagnostics in surgery and oncology.

## Scientific Ethics Declaration

The authors declare that the scientific ethical and legal responsibility of this article published in EPSTEM journal belongs to the authors.

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