4.1.3. *Discovery 3*: ***Exogenous Impacts of Living Systems: Similarity between Anthill Provocation Stimulus Phenomenon and Autonomous Tumor Substance***

4.1.3.1 *Anthill Provocation Stimulus Phenomenon (APS-Phenomenon)*

There are natural phenomena that can be characterized by their analogy with physiological and pathological processes in the human organism.

An anthill that constitutes an autonomous balanced subsystem can be transformed immediately into a "dynamic chaos" by exogenous interventions.

Small impacts can already turn a snowfield into an avalanche through exponential dynamics.

I am using these images in order to demonstrate a dead end of surgical oncology resulting very frequently in fatal consequences and human tragedies.

a

Fig. 12.4.1.3.1.1a,b. Anthill - the process in living nature. Begin of the exegenous provocation (a) by a wooden "needle" (b). Myself in Wienerwald (Vienna Woods).

Lower Austria, Austria

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An external intervention ("operation") in an anthill will cause a defect which opens the previous "balanced state" of the entire closed ant autonomy locally (Fig. 12.4.1.3.1.1).

b

The "gate" being created constitutes an anomaly to the system. This results in the destabilization of the entire system. A state of chaos being created – in this case temporarily only – will give impulses for activities by ants. The confused ants will accelerate their motion dynamics not only within the present system space, but expand it outwards as well.

Fig. 12.4.1.3.1.2. Development of local "anomaly" after the first external mechanical impact on the anthill. A small number of ants remains on the "needle". Pulling the "needle" out, they are extracted into the surrounding

On the first intervention of an exogenous agent, e.g. stick, branch etc. which is considered to be a mechanical factor for anthills, a certain number of ants will adhere to the material (Fig. 12.4.1.3.1.2). This is how they come out into the field surrounding the previous structure. At this place, the biological system passes over to an expansive, exploding development.

a

b

Figures 12.4.1.3.1.3 a, b. Each repeated impact on the anthill increases the amount of ants coming into the environment

At each repetition of the intervention, the quantity of the ant substances present on the exogenous branch will increase resulting in an increase in its volume in the system environment at an exponential rate (Figures 12.4.1.3.1.3 a, b).

The expansive chaos and the outward extension of the biological system are accompanied by repair processes at the local place of anomaly that start later (Fig. 12.4.1.3.1.4).

Fig. 12.4.1.3.1.4. The repair process starts immediately after exogenous provocation. The arrows show the initial acitvity of the anthill

These processes in living nature as described above are very similar to the behavior of malignant tumor structures after exogenous provocations in some ways.

A demographic model of ant colony, undisturbed and disturbed

The own mathematical reasoning can illustrate the anthill provocation stimulus phenomenon. The main content of this mathematical reasoning lies in the following:

Colony dynamics under disturbance can be described by a simple demographic-type system

$$dx/dt = f(y) - x$$
$$dy/dt = f(y) + x - y - k(t,z)y$$
$$dz/dt = f(y) + x - y + k(t,z)y,$$

where
x is a sum number of brood forms (eggs and larvae)
y is a worker (ant) number
z is a number of "excited" ants after colony disturbance
f(y) describes eggs and larvae production rate that depends on worker ant number (their ability to get resources from the environment)
f(y) is monotoneously growing with ***y***, other properties are not essential for our task
Two members ***[-x,+x]*** describe brood to ant transition
Member ***[-y]*** describes ant death due to aging
k(t,z) is a function that describes extemal disturbance applied to a colony, and it works as follows

Initially, up to the moment $t = t_1$, $k = 0$ (see illustrative Fig. 12.4.1.3.1.5.), the system is in stable "balanced state" $[x_0, y_0]$, that is found from $dx/dt = dy/dt = 0$.
The number of "excited" ants $z(t) \equiv 0$.
At the moment t_1 the system is disturbed by an "exogeneous agent", that within our formalization corresponds to $k(t_1) > 0$.
This immediately leads to the origin of "excited" ants, $z(t) > 0$. If then excitement stops, or became $k = 0$, number of "excited" ants will stay constant, but will grow again when and if we disturb the colony, that is make $k(t_2) > 0$, and so on.
We can refine the model further in order to describe the effect of "auto excitement": the more "excited" ants we have, the greater is the rate of their accumulation. In formal terms, ***z*** increasement grows with growing ***z***; to reach this effect, one can introduce function ***k(z)*** having $dk/dz > 0$.
This mathematical model characterizes the analogy between both autonomous living substances in nature. Thus, the analogy between work ants and tumor malignant cells behavior can explain some features of tumor reaction to preoperative or intraoperative tumor provocation. Initially, the system of malignant cells is in stable "balanced state". Mechanical stimulus and opening of the tumor lets part of the cells transit to the "excited" state and emigrate outside the tumor autonomy, i.e. like ants. Possibility of "auto excitement" (that can also be modelled if one supposes $dk/dz > 0$), leads to an avalanche effect of spreading the released cells. In order to keep the system of malignant cells in an immobile state, which is the only one safe for the patient, we have to refuse "the gold standard" of surgical intervention provoking malignant cells expansion. The model offered above helps to mimic the system behavior in formal terms.

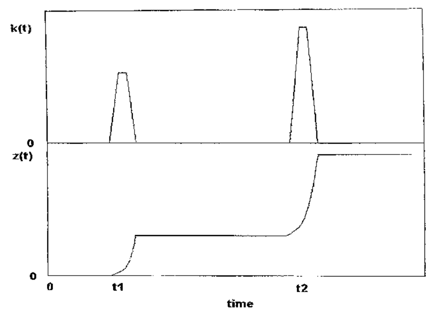


Fig. 12.4.1.3.1.5. Mathematical reasoning: Qualitative dynamic behavior of the number "excited" ants, ***z(t)***, under external colony perturbation, described by ***k(t)*** function. When ***k(t) = 0***, ***z(t) =*** const, but experiences rapid growth during ***k(t) > 0***

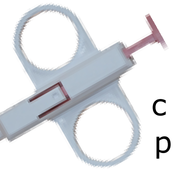
4.1.3.2 *Autonomous Tumor Substance Response to Exogenous Provocation – Dike Burst to the Tumor Cells Spreading Out and Forming New Tumor Colonies*

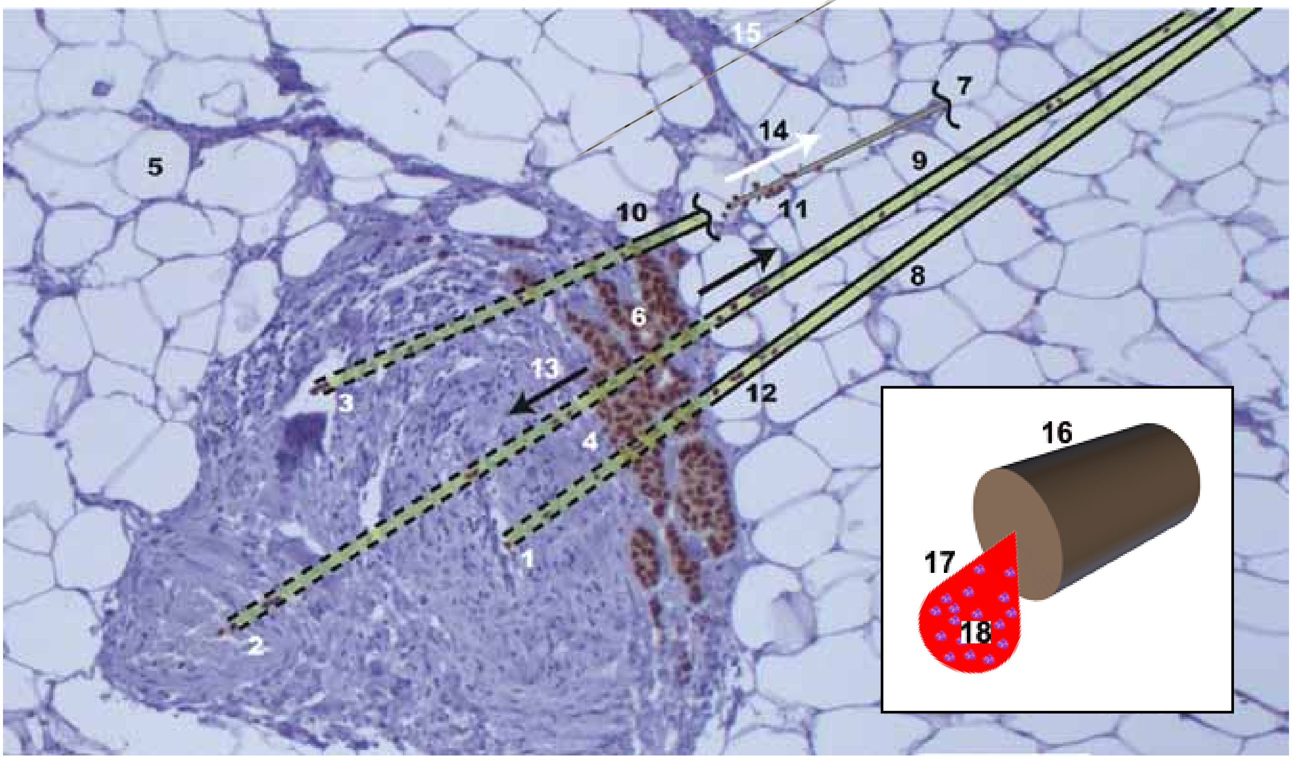
4.1.3.2.1 *Preoperative tumor provocation: invasive diagnostic, radiological images and non-invasive factors*

The closed structure of a local malignant tumor system still existing autonomously is opened by introducing an exogenous mechanical agent (biopsy needle) or mechanical manipulation (palpation, mammography, etc.) from the outside of the organ affected by a malignant tumor. This creates new outflow pathways.

On the one hand, the malignant tumor cells may "emigrate" through the created tunnel into the healthy surrounding structure of the human organism, or may be "carried over" to the human tissue as well with an exogenous material, for example, biopsy needle (Fig. 12.4.1.3.2.1a,b). The most common pathway of spreading for tumor cell dissemination is the destruction or erosion of the local blood vascularisation and lymph circulation, especially metastases (Fig.12.4.1.3.2.1a). Similarly, the tumor cells can easily leave from the volcanic cluster in the malignancy system into the healthy tissue (Fig.12.4.1.3.2.1b).

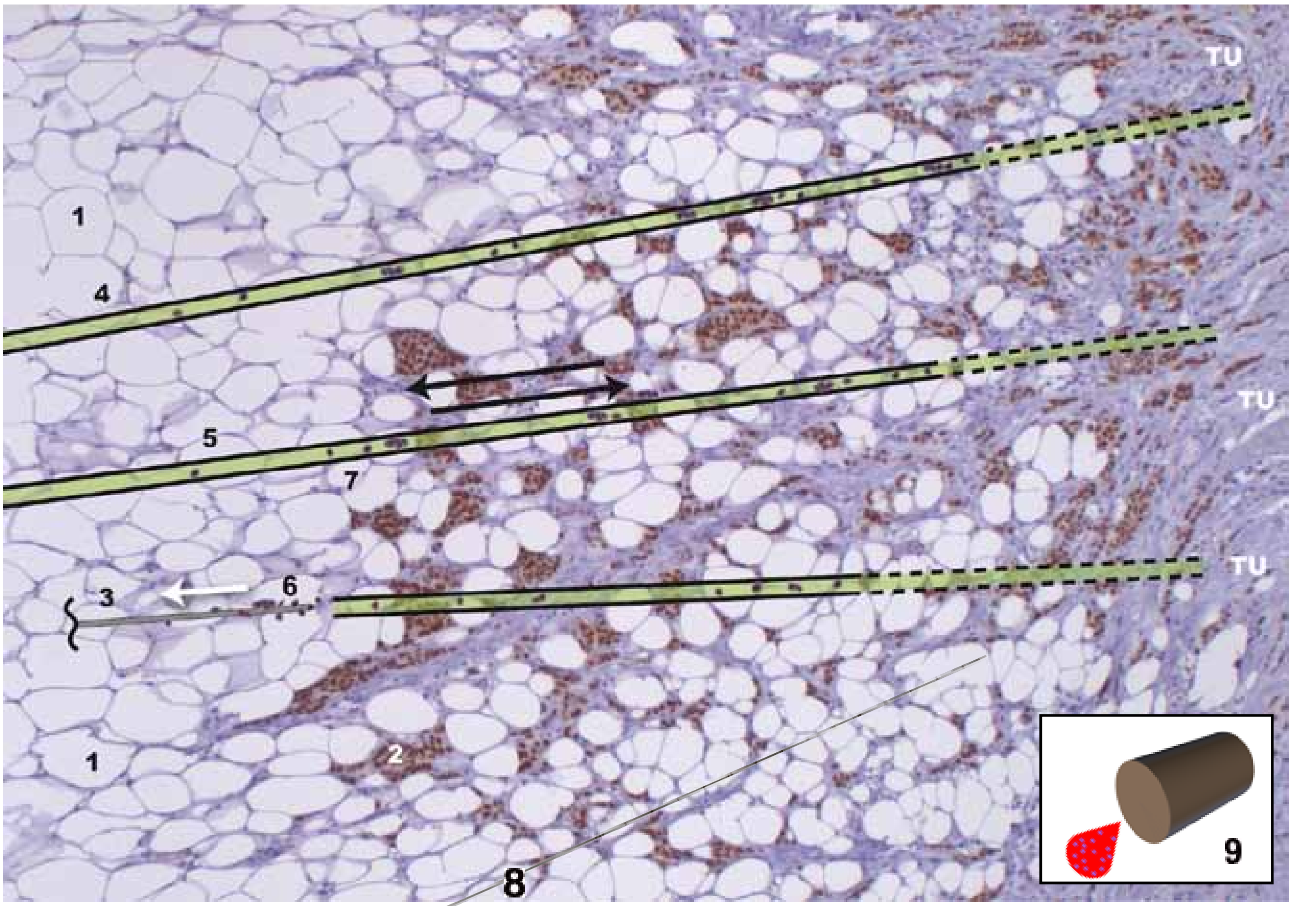
On the other hand, they can also open a new connection with capillaries, blood or lymphatic vessels.

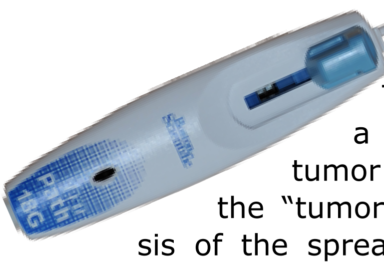




a

Fig. 12.4.1.3.2.1a,b. Suspicion of breast cancer: Diagnostic preoperative percutaneous needle biopsy in a combined schematic illustration. a) vessel bundle consists of arteria (1), vein (2), lymph vessel without tumor cells (3), lymph vessel filled with tumor cells (4), 5 - adipose connective tissue, 6 - tumor cells, 7 - biopsy needle, 8 - first biopsy tunnel, 9 - second biopsy tunnel, 10 - third biopsy tunnel, 11 - displaced tumor cells on the needle surface, 12 - tumor cells spread into the biopsy tunnel, 13 - tumor cells spread in both tunnel directions (black arrows), 14 - tumor cells spread into the healthy tissue (white arrow), 15 - inseration of a biopsy needle for the next retrieval of tissue sampling, 16 - taken biopsy sample, 17 - blood drop with tumor cells (18). H&E, original magnification x400; b) 1 - surrounding healthy tissue, 2 - tumor cells, 3 - withdrawn biopsy needle (white arrow), 4 - first biopsy tunnel with existing tumor cells, 5 - second biopsy tunnel with displaced tumor cells, 6 - tumor cells on the surface of the biopsy needle, 7 - movement of tumor cells in the biopsy tunnel in both directions (black arrows), 8 - the next needle impact of the active tumor mass, 9 - view of tissue cylinder taken by means of a biopsy needle. H&E, original magnification x400





b

This creates a "highway" for tumor cells out of the "tumor hill". The basis of the spreading of tumor cells and/or formation of distant tumor metastases has been established (Fig. 12.4.1.3.2.2).

Bleeding from the site of provocation constitutes another pathway for tumor cell dissemination. In this case, tumor cells are transported from the tumor subsystem damaged by exogenous impact together with the created flow of blood, quasi passively, to the surrounding healthy structures as well and form metastases.

Through the "floodgate" to the malignant "tumor hill" resulting from the exogenous intervention, tumor cells can flow off or can be distributed into the capillaries, blood and lymphatic vessels adjacent to the tumor that already have become connected with the active tumor mass through exogenous provocation.

In the area affected by the local autonomous malignancy subsystem the tumor cells will be stimulated to intensively proliferate. Thus, the volcanic cluster will be formated. A "repair process" occurs at the local provocated place of the already open malignant tumor autonomy (white arrows).

The mechanisms described above may both result in local recurrences and distant metastases of malignant tumors just due to outward provocation. If the tumor cannot be provoked from the outside during the developmental stage of local encapsulation from healthy surrounding structures, we will be able to remove the tumor radically. The probability of a local recurrence or distant metastasis reaches a minimum value in this constellation.

As soon as the "floodgate" is opened through a "tunnel" (biopsy channel,

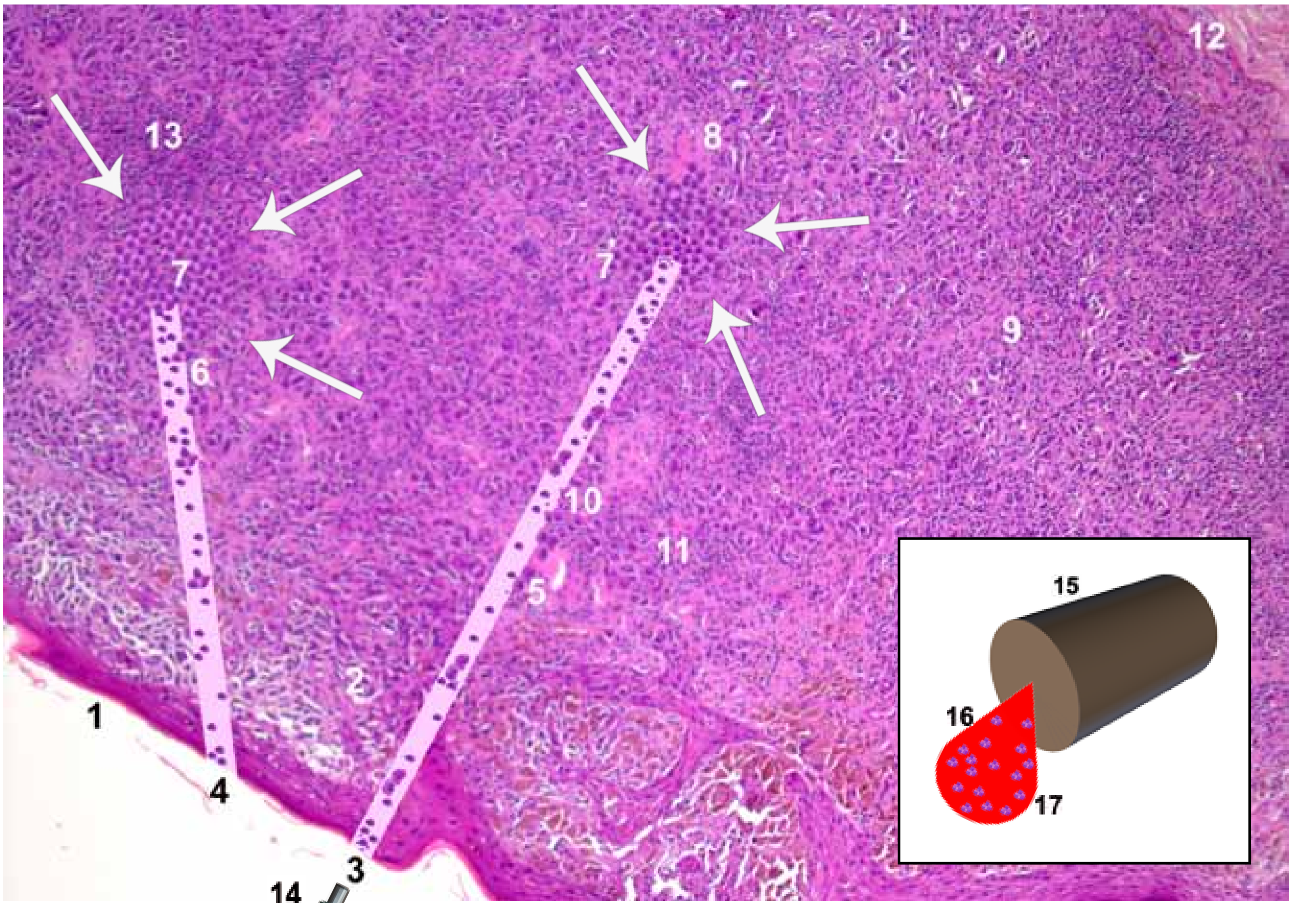


Fig.12.4.1.3.2.2. Suspicion of melanoma: Diagnostic transcutaneous needle biopsy in a combined schematic illustration: 1 - epidermis, 2 - dermis, 3 - first biopsy tunnel, 4 - second biopsy tunnel, 5 - destruction of local vascularisation through vessel perforation, 6 - dissemination of tumor cells into the biopsy tunnel, 7 - accelerated tumor cell proliferation and formation of the volcanic cluster in the area affected by the melanoma, 8 - beakthrough (perforation) of the volcanic cluster into the vessel, 9 - melanin, 10 - migration of tumor cells into both biopsy tunnel and vessel damaged by the biopsy intervention, 11 - formation of the next volcanic cluster, 12 - subcutis, 13 - melanoma cells, 14 - needle for skin lesion biopsy, 15 - biopsy tissue cylinder for histological investigation, 16 - blood with melanoma cells (17). H&E, original magnification x100

etc.) to the local, closed tumor system by exogenous mechanical interventions performed in a conventional manner, the risk of local recurrences and distant metastases will increase enormously although the primary tumor has been removed after the exogenous provocation.

Furthermore, after exogenous provocation, in particular after repeated exogenous impacts, a "tumor hill" can provoke an exponential release of tumor cells into healthy tissue, similar to an avalanche effect.

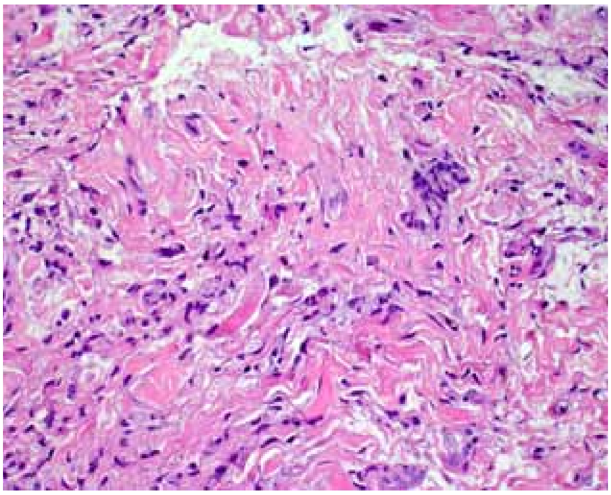
The clinical experience with different kinds of malignancy tumor in oncological surgery indicates the above illustrated ethiological pathways for local recurrence and metastases (Fig. 12.4.1.3.2.3a-c).

The rapidly developed volcanic clusters which are immediately formated after carrying out of conventional biopsy lead to both tumor subsystem oscillation and vacillation in the patient's organism.

However, both invasive and other mechanical methods used for tumor diag-

a

b



c

Fig. 12.4.1.3.2.3a-c. Metastasis of the abdominal cavity wall as a settlement of a signet-ring cell carcinoma located in the stomach. H&E, original magnification x 400

nostics that are considered to be standard methods in medicine today increase the cancer patient's risk of not becoming disease free. This is how mechanical-invasive diagnostic methods considered to be state of the art today light a "fuse" that results in human tragedies.

4.1.3.2.2. *Intraoperative tumor provocation*: mechanical grabbing

In conventional surgical interventions performed on tumor patients without metastases, access to the malignant tumor is opened in various ways. After inspection, the tumor usually is palpated by the surgeon during the operation in order to determine dimension, locality and consistency, etc. This causes a first intraoperative mobilization of the entire local tumor system.

Fig. 12.4.1.3.2.2a. Intraoperative view of breast cancer left

In further steps, the tumor is separated from the adjacent structure and is exposed. During the intraoperative preparation, the tumor is continued to be provoked in various ways by mechanical grabbing.

Since the capillary network, venous and arterial vessels as well as lymphatic vessels, on the one hand, intensively vascularize the entire tumor mass, but, on the other hand, also connect the tumor autonomy closed up to now to the surrounding healthy structures, tumor cells can be released into the bloodstream and the lymph. This already creates the first intraoperative condition of tumor cell dissemination which will be responsible for new tumor growth later.

At the same time, the capillaries, blood and lymphatic vessels are cut between the tumor and the adjacent healthy tissue during tumor resection and tumor extirpation performed in stages. The already cut blood and lymphatic vessels of the tumor constitute another condition of tumor cell dissemination to healthy structures.

Therefore, the intraoperative graduate preparation and removal of the malignant tumor have already created two basic prerequisites.

The still existing vascular connection between the tumor and the surrounding tissue and organs constitutes a line through which tumor cells can be conveyed into healthy areas throughout the entire period of tumor removal.

The already cut tumor vascularization constitutes the second way in which tumor cells can flow into the environment and form metastases.

The first surgical manipulation in the area of the tumor already creates the basis of the two processes described above which are associated with fatal consequences for the patient's prognosis.

However, the formation of a local relapse and of a remote metastasis of malignancies upon preoperative invasive diagnostic investigation and intra-operative excision depends proportionally on the degree and the type of vascular development and perfusion in the area of the tumor.

The more intensive the vascular network and the vascularisation of the tumor sub-system (that is the more developed its connection to the adjacent sound tissue), the higher the risk of the formation of a local relapse respectively of the extension of the remote metastasis.

Similarly, the type of biopsy injury of capillaries, arteries, or veins in the area of the tumor has different influences on the development of a local relapse and a remote metastasis. A "scissors effect" can be observed.

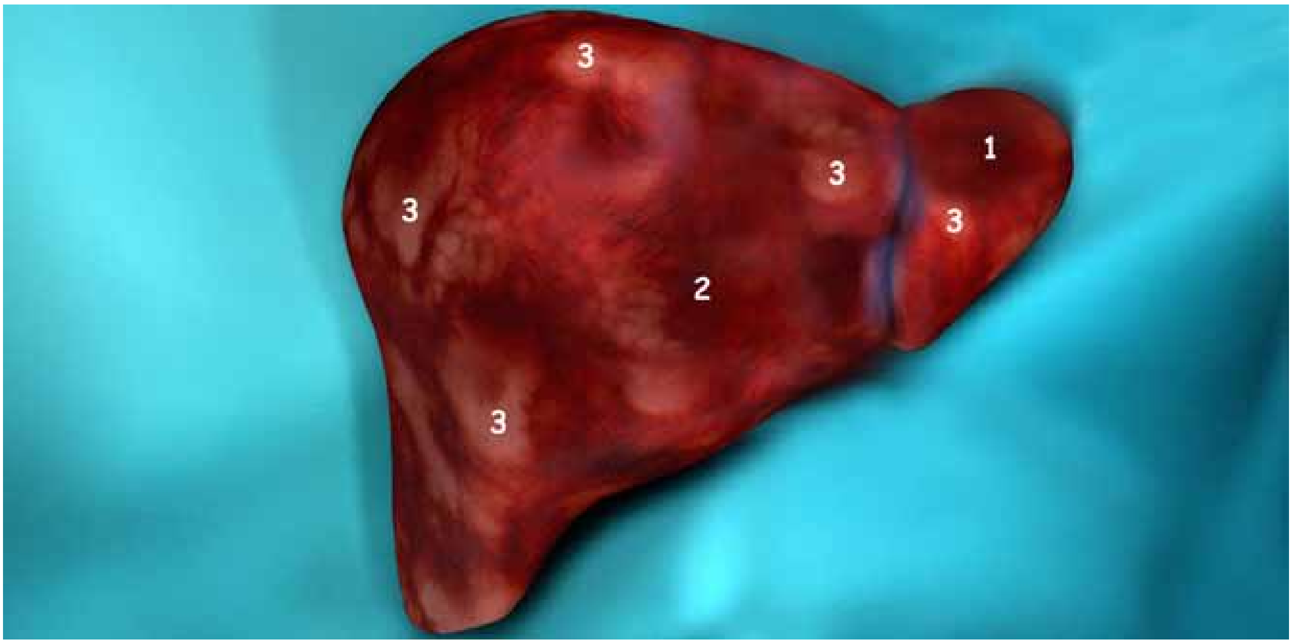
If the tissue structures are not injured during the conventional biopsy, there will be a higher risk of a local relapse and only a low risk of remote metastasis. If the tissue structure of the tumorous infiltrate and of the tissue located in the vicinity of the tumor is injured respectively penetrated or cut during the biopsy, the probability of both of a remote metastasis and of a local relapse will be increased, at which the risk of remote metastasis will be a lot higher then the one of a local relapse.

Fig. 12.4.1.3.2.2b. Intraoperative view of stomach adenocarcinoma

4.1.3.2.3. *Local and distant targets*

As is known in clinical practice and scientific literature, the main local and distant targets after the preoperative and intraoperative tumor provocation are liver, lung, brain (Fig. 4.1.3.2.3.1). Further targets are skin, bone, kidney and other organs and systems *in vivo*.

Fig. 4.1.3.2.3.1. a) Liver: 1-left lobe, 2-right lobe, 3-multiple metastases; b) lung (1) and metastases (2), kidney left (3) and right (4), kidney metastases (5); c) 1-brain, 2-metastases



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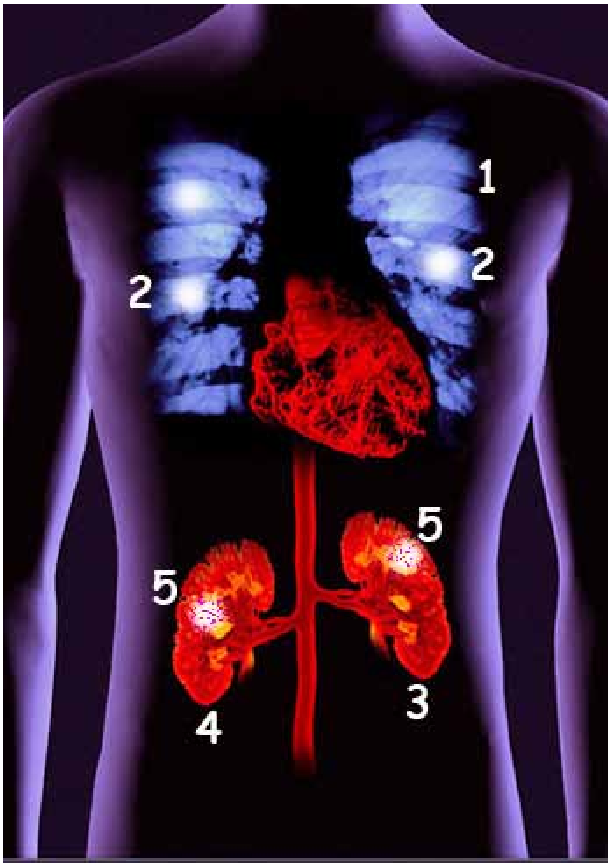

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