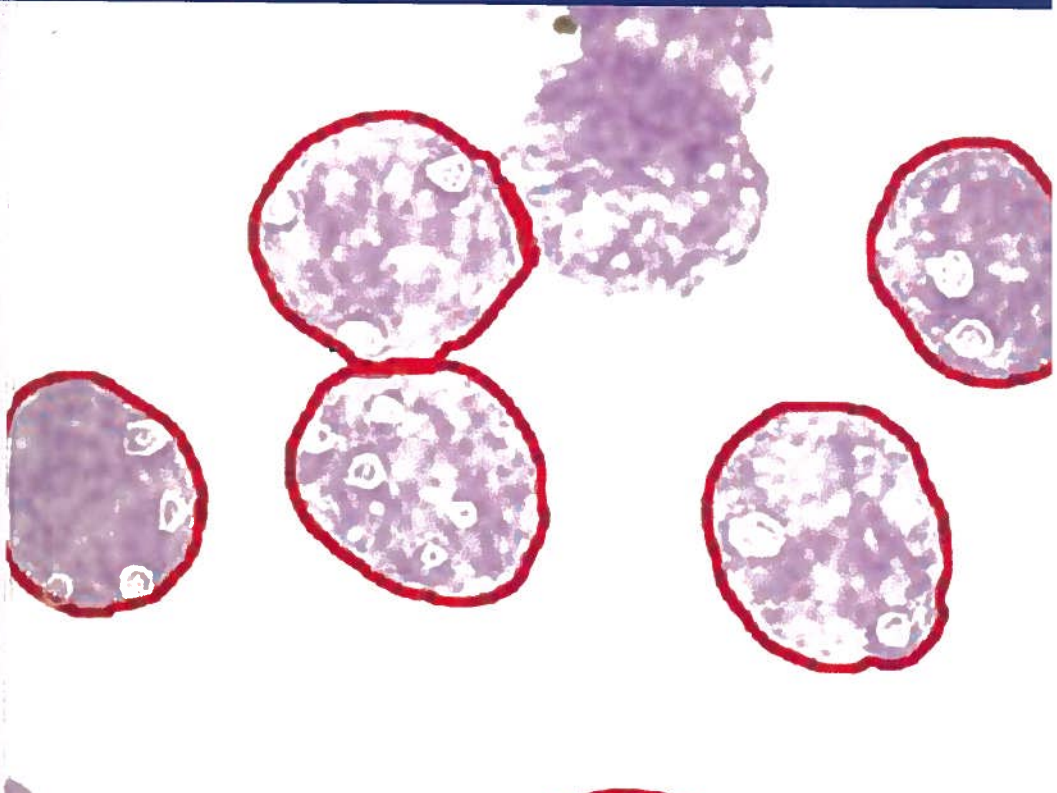
Identifying Cancer – Gentle, Safe and Fast

Cancer can be cured, if identified early and treated adequately. However, patients frequently avoid diagnostics, because these are associated with painful procedures. Yet, there exists a scientifically approved method which in many cases allows to accurately check for cancer without pain or complications: Cytopathology. Instead of removing a piece of the affected organ (biopsy), physicians obtain a few cells, for example with a tiny brush, which are then investigated under a microscope for evidence of cancer. Unpleasant invasive procedures and operations can often be avoided this way. Making use of highly sophisticated modern methods of analysis, cytopathology mostly can decide if cancer is present at all and how it should be treated.

"With Cells Instead of Scalpels" was written for both patients and physicians. It describes how cytopathology works, when it is indicated, and when not, and how cells can be obtained. It also explains how the low efforts and quick results of diagnoses make the method interesting for hospitals and the health care system. Presenting 17 real case reports the author, himself an experienced cytopathologist, illustrates the benefits of the method for different organs. Many tables documenting diagnostic accuracy of cytopathology allow readers to form their own judgment.

Preface from Prof. Dr. Dagmar Schipanski, president of the German Cancer Aid and Prof. Dr. Werner Schlake, chairman of the German Board of Pathologists.

Alfred Böcking • With Cells Instead of Scalpels



Alfred Böcking

With Cells Instead of Scalpels

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Preface I

This book intends to close a knowledge gap. The analysis of cell samples for evidence of cancer – cytopathology – is mostly unknown throughout the population and often even in specialist circles. Its application is manifold and especially in the field of early cancer diagnosis, benedictory. Each woman from the age of 20, who attends the annually preventive checkup for cervical cancer, is examined by means of cytological methods. The "Pap-test" has contributed that the tumor, which was once common amongst young women, has lost its horror. In most cases it can be identified at an early stage and be removed in a rather harmless operation.

Cytopathology presents a good diagnostic alternative to the removal of tissue samples for some diseases, such as the suspicion of cancer of the oral mucosa or the thyroid gland. In other suspicious cases – e.g. prostate or breast cancer – the use of cytopathology is less significant than a histological analysis. The demand for research and improvement still persists in these fields. Some diseases – such as intestinal-, renal-, or ovarian cancer – are not accessible for cytology. Therefore, it is important to consult your doctor about the individual diagnostic procedures.

Modern medicine of today offers numerous procedures which complement one another. Which procedure or which combination of methods is most suitable for the individual patient, lies within the judgment of the specialist. What is important from our point of view, however, is that the patient is well and comprehensively informed by a doctor. Pamphlets and books play an important factor in this regard; however, they cannot replace the consultation of a specialist.

The early diagnosis of cancer is an important aspect to the German Cancer Aid Organization. If detected early, most tumors are very likely to be cured. Yet, still only every second woman and only one out of six men make use of the opportunity of early cancer diagnosis. The fear of unpleasant examination methods is often the main obstacle. A lot would be gained, if this book contributes to reducing the fear and improving the willingness for an early diagnosis!

If you have any questions on the topic of cancer, you may always contact the German Cancer Aid Organization (see Chapter 9). Cancer concerns everybody – use the chance to inform yourself extensively! Cancer may then be able to lose some of its horror.

Prof. Dr. Dagmar Schipanski
President German Cancer Aid

Preface II

The more "gentle" a cancer suspicion can be analyzed, the more likely it is that patients will consult their physician for examination. Through this, more tumors can be detected early and eventually get cured. This book explains how pathologists are able to analyze a cancer suspicion on cells, which are extracted painlessly from many body regions with the help of modern microscopic methods.

This form of cancer diagnosis, cytopathology, looks back – since Johannes Müller and Rudolf Virchow – upon a long tradition in Germany. Methodical innovations now give the procedure a new enhancement. Only if patients and physicians are informed about the improved options of cell diagnostics, are they able to request them.

Pathology is a medical field, in which the microscopic analysis of cells presents an integral element. Only after having offered diagnoses for 10,000 cell samples and 15,000 tissue samples, a doctor is allowed to apply for specialist's status in pathology. However, a pathologist is not only a specialist for microscopic cancer diagnostics, but also a counselor for patients who are diagnosed with cancer.

A thus far inimitable success model in the application of cytopathology is the early detection of cervical cancer with a smear. Since its introduction in 1972, the mortality rate from this tumor has decreased by approximately 60 percent in Germany. If more women would take part in the regular preventive check-ups, even less would have to die from this type of cancer.

One particular advantage of cytopathology is that the extraction of cell samples, which are needed for the analysis, can be taken painlessly from most mucosal membranes and from many inner organs. Moreover, modern molecular biological methods for early diagnoses are well applicable on cell samples. Lastly, cytopathology is also suitable for confirming the diagnosis with a computer. Through this innovation, a new "multi-modal" type of cytological diagnostic is made possible (see p. 19).

Cytopathology also assists in cutting down public health care costs. It is fast, inexpensive, and occasionally substitutes unnecessary surgical interventions. With their high level of education, German pathologists are well prepared for the increasing demand for cytological cancer diagnoses.

Prof. Dr. med. Werner Schlake
President of the Board of Pathologists

Introduction

No doubt, there are many more pleasant topics for a book than "cancer". Not only a possible disease, even the check-up for cancer – that so far frequently has been associated with an operation – causes anxiety in most people.

This is why I would like to encourage you to continue reading this booklet, especially if a suspicion for cancer has been raised in your case. Today physicians are able to identify an increasing number of cancers completely "bloodless": instead of removing a piece of the affected organ, they just remove some cells from it. A pathologist will then analyze these under a microscope and most cases make a definite diagnosis. An operation to render an accurate diagnosis can hence be avoided – physicians works with "cells „instead of scalpels". This procedure is uncomplicated, nearly always painless and nevertheless safe. And it mostly results in a reassuring diagnosis: in about 72% of cases pathologists do not find cancer in specimens containing cells[1].

If the pathologist does find cancer, he often can contribute to its effective control. He may identify the degree of aggressiveness (malignancy) and the type of an individual tumor from different cellular markers. Physicians thus are enabled to choose an adequate therapy – and in case of benign or low malignant tumors again to avoid operations. This way Patients often are saved from unpleasant side effects – like impotence and incontinence in case of operative removal of the prostate. Following conservative treatment of cancers, pathologists mostly are able to monitor if therapy has been effective.

This booklet addresses laymen as well as medical personnel. It aims at spreading knowledge about a method that still is insufficiently known, yet internationally accepted by scientists[2]. Please use the booklet in accordance with your personal interest. If you are interested in a specific application of cytopathology you can simply skip chapters 1 – 4, concerning the methodological background. For better understanding, all medical terms are marked in italic letters and explained in a glossary at the end of this book.

All described examples are based on real case histories and all figures come from peer reviewed scientific publications. As a physician and scientist I am hoping for an intensified discussion about the chances of cytopathology in comparison with other methods of cancer diagnostics. Any criticism of this booklet therefore is explicitly welcome (please mail to Alfred.Boecking@web.de).

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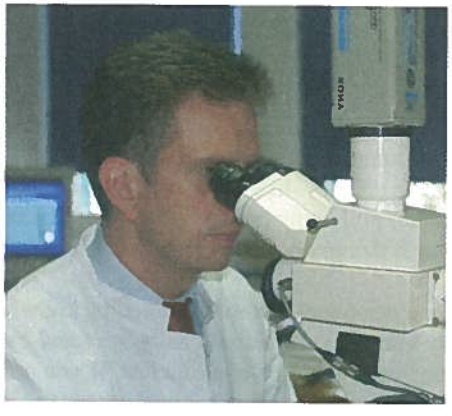
1. What is Cytopathology?

Histology and Cytology

Many people know about pathologists only from crime movies, in which they are the ones who examine corpses. In reality, forensic doctors are responsible for performing such autopsies on crime victims today. In contrast, pathologists are especially concerned with the early detection of cancer and infections of inner organs.



A pathologist at a microscope.

For that purpose they analyze probes taken from the human body under the microscope and test them for diseases[1].

Probes can be composed of a small piece of skin or inner organ, so called tissue-biopsies. The examination of tissue is called histopathology or histology. A pathologist can also examine single cells. This procedure is known as cytopathology or cytology.

Which method will be applied is determined by the doctors and depends on what they are looking for. If something suspicious, for example a node, is found in a patient, tissue samples or cells can be extracted and sent to a pathologist for further analysis.

The tissue used for a histological examination is obtained during surgery or in a surgical procedure, also known as a biopsy. In contrast, cytopathology requires only a few cells. These can be taken from body fluids, mucous membranes, or with the help of a thin needle, from inner organs. Initially the tissue and cell samples will be examined under a microscope; other methods may follow. If a part of the body is affected by cancer, it can be analyzed certain morphological properties by means of identifying certain properties in these samples.

For over 100 years histopathology has been applied, thus making it the standard method when it comes to diagnosing all types of cancer. In many situations this method is irreplaceable. Tissue, which has been extracted during surgery, always needs to be examined. Also during surgery a rapid frozen section can help to decide whether cancer is present or if it has to be removed completely.

However, cytopathology is increasingly becoming a supplement and to some extent a replacement for histopathology. The advantage lies in the avoidance of pain and unnecessary surgery. In addition, some superficial types of cancer can be detected earlier with cytopathology.

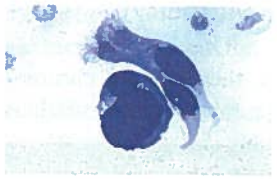
Rudolf Virchow

The different application options of cytopathology are not very well-known yet. Even many health professionals do not know enough about cytological methods, so often patients need to inform themselves. This book will explain when and where cytopathology can be used for diagnosing cancer; either by itself or in combination with other methods.

Cytopathology also has a long history. In 1855, the German medical doctor Rudolf Virchow discovered that cancer emerges from mutated cells[2]. Approximately 20 years earlier, the physiologist Johannes Müller first described the appearance of cancer cells . The Greek doctor George Papanicolaou, who emigrated to the United States about 80 years ago, established the early detection of cervical cancer in cells[3].

Cancer and Cells

The fact that cancer can be examined especially well in cells lies in its origin. Cancer is an unregulated and unhindered growth (proliferation) of cells. Such a proliferation is referred to as a tumor. If it is the origin of the cancer, it is known as a primary tumor.



Two cancerous cells (left) next to two healthy mucous membrane cells.

But not all tumors are cancerous. Benign tumors grow slowly and hardly do any damage. Malignant tumors, on the other hand, grow rapidly, destroy tissue, and can spread out in the body by means of metastases. Only malignant tumors are referred to as cancer.

Different types of cancer are distinguished from one another depending on the origin. Carcinomas (skin, mucous membranes, inner organs), sarcomas (connective tissue, bones), lymphomas (lymph glands), and leukemias (blood).

So cancer is not always cancer. A suspicion often turns out to be unsubstantiated. If the suspicion does prove to be true, then the type of cancer, its metastases, and its aggressiveness are crucial for the choice of the therapy. Cytopathology can not only help when looking for cancer, but also with the evaluation, treatment, and monitoring of the disease.

The Methods of Cytopathology

Microscopy

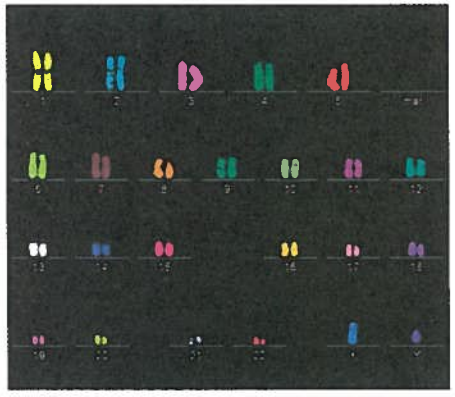
Pathologist's most important tool is the microscope. In order to examine cells with it, they will be dyed with plant pigments. Important elements, such as the nucleus containing the genetic information deoxyribonucleic acid (DNA), or the surrounding cell fluid (cytoplasm), will then be marked and become visible.

High resolution electron microscopes have also been in use for a long time. They especially make very fine cell structures visible. Often doctors can recognize cells that show an indication of cancer with their bare eyes. However, cytopathology has developed many procedures that make diagnoses more reliable and secure.

Rudolf Virchow's microscope (around 1850).

DNA-Image-Cytometry

In a healthy cell, there are 46 chromosomes which are found in the nucleus and mainly consist of DNA, the genetic information. In cancer cells, single chromosomes or parts of chromosomes are either structurally mutated, present in a larger number, or missing completely.



The chromosomal set of a male's healthy somatic cell displayed as a so-called karyogram.

These alterations are referred to as chromosomal aneuploidy. The most fully developed and widespread cytological method today – after microscopy and immunocytochemistry (see p. 17) – is DNA-image-cytometry, which is based on detection and quantification of aneuploidy. This method, which was developed around 20 years ago, measures the amount of DNA per nucleus with the help of a computerized microscope (see box on p. 15). If the DNA amount deviates significantly from the norm in a certain number of cells, then it is a proof that the patient has cancer[4].

DNA-image-cytometry has three functions:

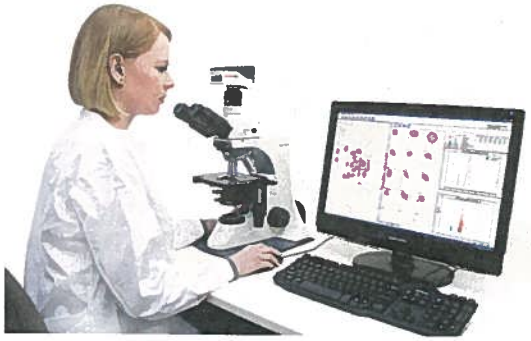
- Helping with early diagnoses of cancer by checking on suspicious presence of cancer (diagnosis, see p. 32). This method can provide evidence of cancer in certain mucous membranes two years before it is visible under a conventional microscope[5].
- Defining the degree of malignancy of a tumor (grading, see p. 34). By classifying the tumor into one of four "Grades of Malignancy", it can predict the behaviour of an individual cancer.
- Observing the success of a cancer treatment. The reaction of a tumor towards its treatment can be monitored (see Monitoring of Therapeutic Success p. 72).

The Technology of DNA-Image-Cytometry

Personal computer (PC) was crucial for the development of DNA-image-cytometry. By connecting it to a microscope in a so-called "work station", it enables the digital analysis of the cells. The measuring software has been constantly enhanced since 1987, when the first machine MIAMED was introduced.

DNA-image-cytometry has been internationally standardized in detail[6]. This applies to the definitions and use of terminology, the preparation and methodology, the internal calibration, error corrections, the interpretation of measurement results, and the quality checks.

The German Society for Pathology and the Board of Pathologists supervise the DNA-image-cytometry with an initiative for quality insurance (QuIP).

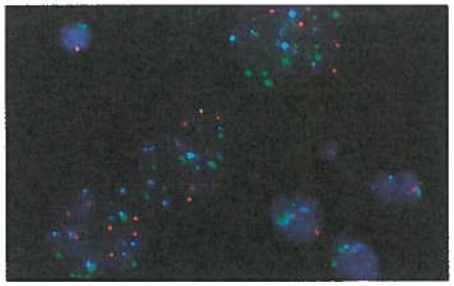


A work station for DNA-image-cytometry: the "MotiCyte-DNA-i"[7]

In Situ-Hybridization (FISH)

In contrast to DNA-image-cytometry, where the amount of DNA of all chromosomes in the nucleus is measured, In situ-hybridization tests single chromosomes for mutations. This method takes advantage of the fact that the two strands of the DNA connect to complementary sequences.

When looking for a specific segment of DNA, a pathologist will let a matching, dyed strand of DNA, which is called a DNA-probe, act upon the cell nucleus. If the segment is present, the dyed DNA-probe will link itself to it. Then a colored marker in the nucleus will show that the DNA segment has been found. Because the colored appearance is due to flourescent light, this method is also called

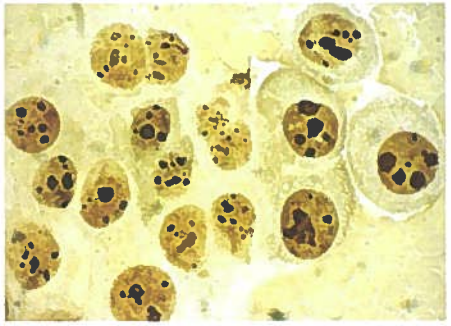


Nuclei of a renal cell carcinoma, which have been examined with FISH.

Flourescence-In-Situ-Hybridization (FISH). An examination requires knowing which chromosomes are affected by specific types of cancer. Often, this is not known. That is why this relatively expensive method is rarely used at this time.

AgNOR-Analysis

When suffering from cancer, the cells in the affected body region grow exceptionally rapid. The growth occurs due to the production of proteins. They are synthesized in the ribosomes, which consist of ribonucleic acid (RNA). The RNA is produced in the nucleolus organizer regions (NOR's) of the nucleus. As soon as a cell starts to produce a lot of proteins, the number and size of the NOR's increase. By measuring the NOR's, it is possible to find out if a patient may have cancer.



Increased number and size of AgNORs in the nuclei of a colon carcinoma.

The proteins in the NOR's are dyed with silver nitrate for the analysis. Thus, the name AgNOR derives from the Latin word "argentum" (Ag), which means silver. The dyed proteins are visible as small black dots in the nucleus. For a diagnosis, a pathologist will count the number of NOR's or their area in 100 cell nuclei.

Polymerase-Chain-Reaction (PCR)

A relatively new method of examining DNA is the Polymerase-Chain-Reaction. It uses the enzyme polymerase to copy a specific segment of DNA as often as it is necessary to be isolated for further examination.

With the help of PCR, the carcinogenic HPV viruses, (especially type 16 and 18, see p. 43), can be detected. This method can also show any changes in so-called tumor suppressor genes, which can indicate cancer itself or the risk of getting the disease[8].

By doing so, it is possible to detect some tumors early and determine the degrees of their malignancy (see chapter 3).

Preparation of cells for the Polymerase-Chain-Reaction in a lab.

Immunocytochemistry

Immunocytochemistry helps if the origin or the type of a cancer needs to be clarified, and also if it has spread throughout the body. This method looks for specific antigens – proteins, which are typical for a certain type of tumor.

So far, a panel of approximately 100 antibodies permits the cytochemical distinguishment of about the same number of primary tumors. Evidence of an antigen can be provided because the binding site will be dyed red or brown in the cell when it binds to a matching antibody. This is called a marker. This exact typing is usually possible with just a few cells and without extracting tissue from the body. Furthermore, the examined cells can derive from metastases.

Immunocytochemistry has three functions:

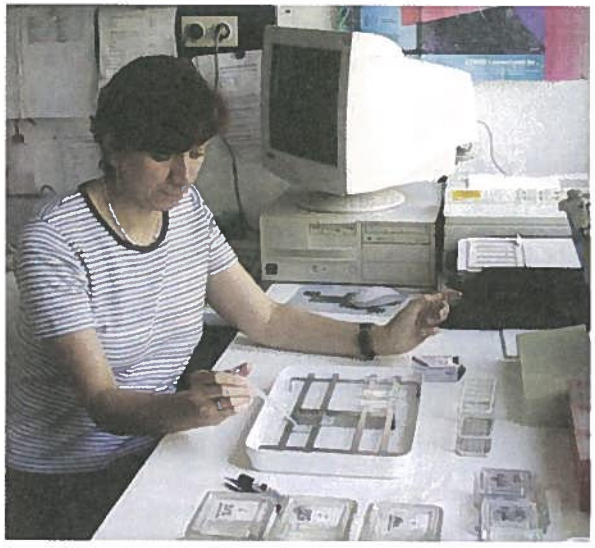
- With the help of markers, the cell and tissue types can be determined and consequently also the location of the primary tumor. If, for instance, tumor

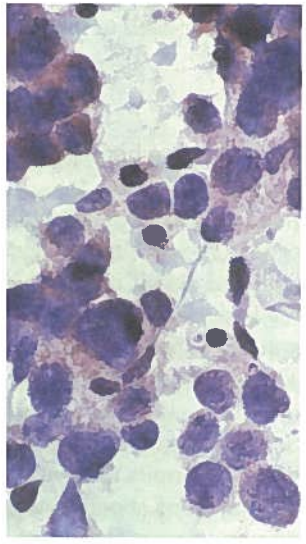
cells, which were extracted from the abdominal cavity, show the prostate specific antigen (PSA, see p. 68), then the primary tumor is located in the prostate, and not in the stomach.

- Immunocytochemistry also helps with the determination of the type of tumor and thus the appropriate treatment. While some types require surgery, others only need radiation or chemotherapy. If, for example, a pancreatic tumor is tested positively for the marker chromogranin (see picture), then there is a neuroendocrine neoplasia, which does not necessarily need to be surgically removed.

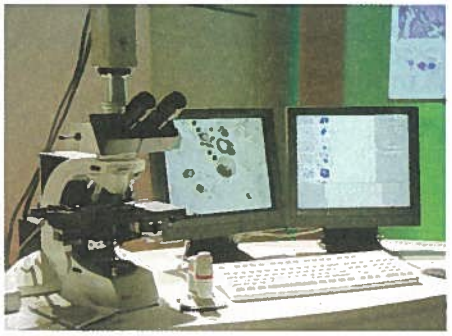
- Lastly, even tumor cells that are not present in a large number can be found by using cytochemical markers. Through this method a pathologist can detect metastases at an early stage in effusions of the pleural cavity, the pericardium, the abdominal cavity, or the lymph nodes. In a patient with lung cancer, for example, it can be determined whether enlarged lymph nodes at the hilus of the lungs are affected by cancer, or if the swelling has a different cause. Surgery of the lymph nodes could possibly be avoided that way.

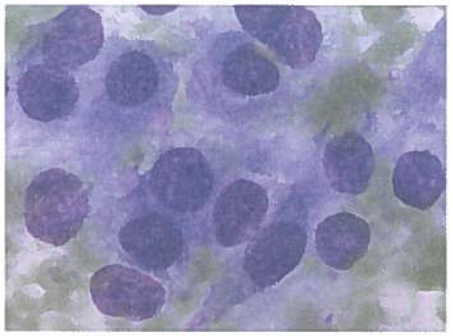
All immunological examinations can also be performed on tissue samples, in which case they are called Immunohistochemistry.

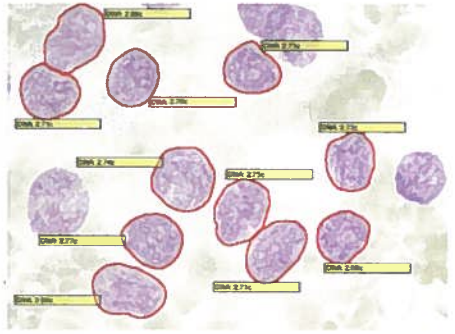


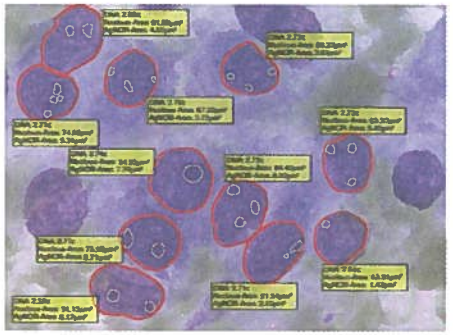


A work place for immunocytochemistry (left): this is where markers, such as chromogranin (right, seen as red specks), are made visible.









The fully automated examination at an MMCA work station (top left): The dyed cell-sample (top right) is examined with the help of various methods, among them DNA-image-cytometry (bottom left). In the end, all measured data can be read next to each nucleus (bottom right).[9]

Multimodal Cell Analysis (MMCA)

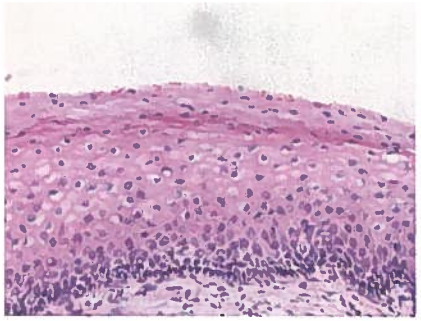
In the meantime, the technology of cytopathology has progressed greatly, so that it is now possible to apply more than one method on the same cell. In the multi modal cell analysis (MMCA), an electronically controlled microscope repeatedly looks for individual cells and examines it, among other methods, with:

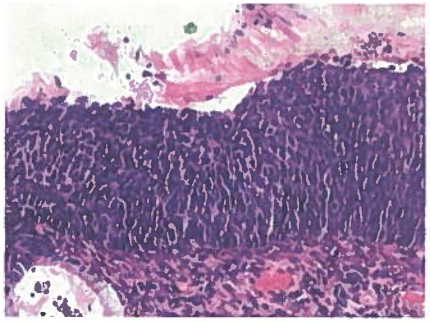
- Conventional dyeing
- Immunocytochemistry
- DNA-image-cytometry
- Distribution of the DNA (chromatin pattern)
- AgNOR-Analysis

The MMCA method, which is not yet applied routinely, is especially helpful if pathologists have only available a small cell sample, or if they are looking for cancer at a very early stage. This can e.g. help to detect pleural cancer on the basis of only a few cells.

Healthy or Cancerous - Diagnoses in Pictures

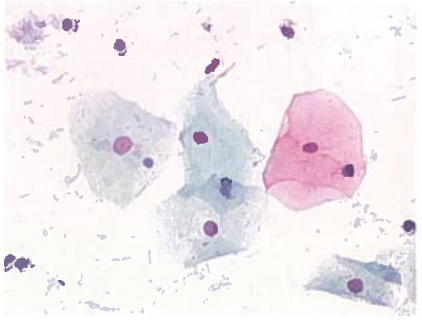
Histology

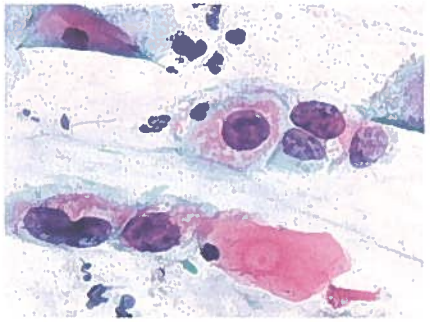




A pathologist looks for different morphological evidences of cancer with either method. The arrangement and form of the cells, which nuclei are stained purple, are very important in tissues like these samples from the uterine cervix. In the left picture, the cells are in layers, whereas in the right picture, there is no specific arrangement and the nuclei are larger in size and number. These are criteria of a carcinoma.

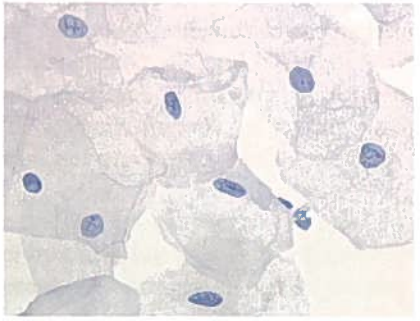
Cytology

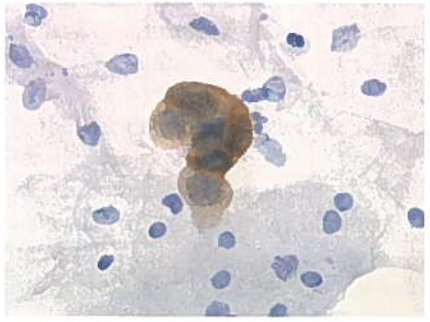




Two smears taken from the same body region (the uterine cervix): Here pathologist can examine each cell on its own. The right picture shows cells, which have nuclei, that not only have a larger diameter, but that are also darker in color and are of abnormal shape – these are characteristic features of an abnormal increase in DNA.

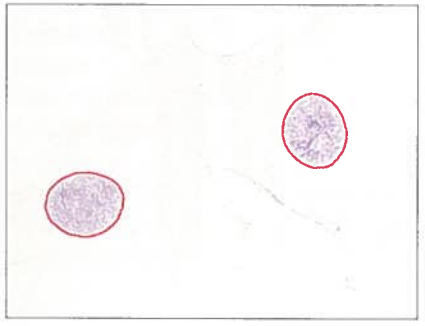
Immunocytometry

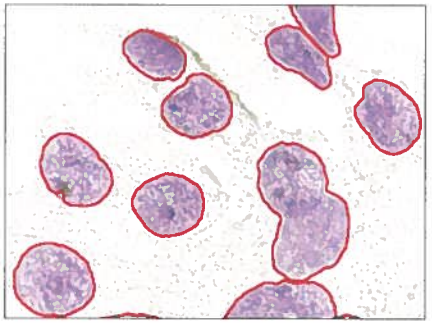




While histology and cytology examine the size and form of tissues and cells, other methods make chemical indications for cancer visible. As seen in the right picture, Immunocytometry can mark tumor cells specifically in a cervical smear, because it stains products of the tumor suppressor gene p16 brown.

DNA-Image-Cytometry

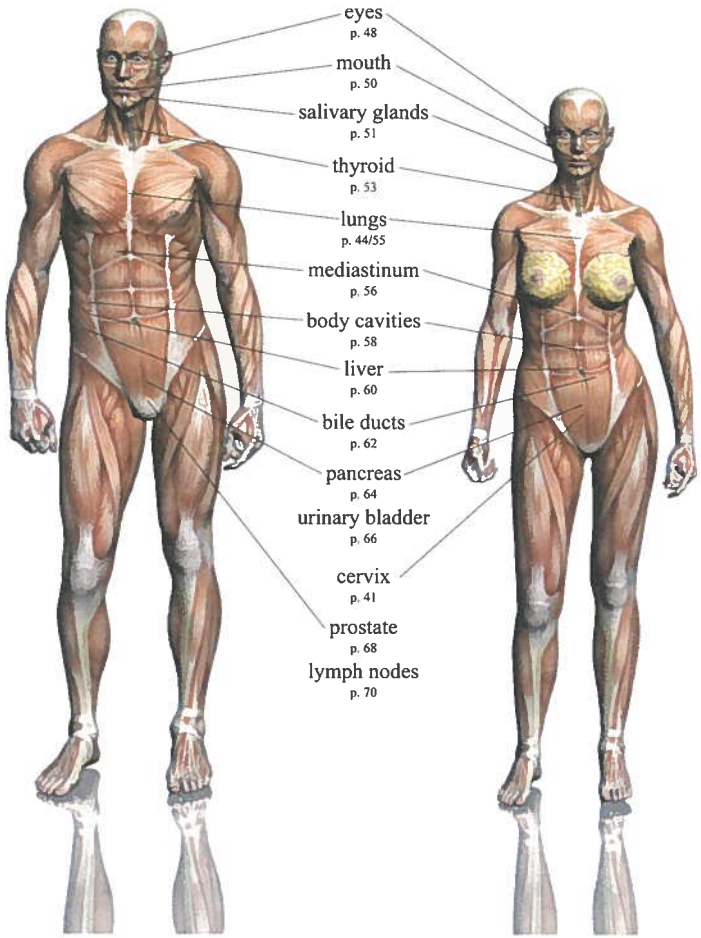




DNA, which is what DNA-image-cytometry measures, can also be specifically stained in a cervical smear. The nuclei, which are encircled by a red frame by a computer, contain more DNA in the right picture than in the left picture. This can be seen by the darker purple color. As with the rest of the methods, the measurements resulted in evidence of a carcinoma in an early stage.

Application of Cytopathology

Due to the fact that cytopathology is a comparatively young field with modern methods, it is quite likely that not all possible procedures are accessible yet. About a dozen different organs can already be cytologically examined for cancer. The figure gives an overview of the organs and the page numbers on which further information for each examination method can be found.



Advantages of Cytopathology

An examination done with cytopathology offers a wide range of advantages, both for patients as well as for hospitals.

- It is "unbloody", almost always painless and associated with only few complications. A tissue extraction performed with scalpels, forceps, or cutting needles is not necessary (see Chapter 2).

- It helps prevent unnecessary surgery, either by clarifying that there is no cancer present (for example in over 90 percent of thyroid gland proliferations or white spots of the oral mucosa[10]), or by detecting a tumor that does not need to be surgically removed (for example some forms of prostate carcinomas, benign lipomas, or small cell bronchial carcinomas).

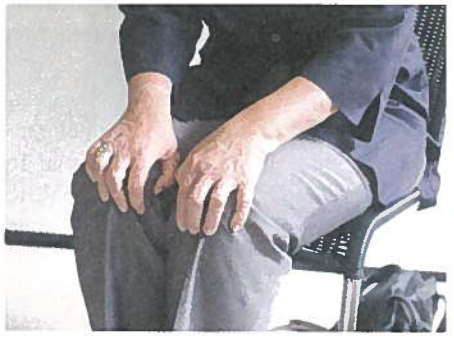
- It helps avoid expensive and time-consuming X-ray examinations or endoscopies by examining cells. In doing so, hospital stays will become shorter or even unnecessary.

- The costs are almost always lower than a tissue examination or other clarifying methods (see Chapter 8).

- Cells are usually extracted ambulatorily, so patients hardly lose time at work. The diagnosis can usually be made on an average of one and a half days earlier than with histology. This shortens anxious waiting periods for patients as well as expensive waiting periods for hospitals.[11]

- Surgical procedures can be planned better and performed more gently with the help of a cytological diagnosis.

- If the doctor finds a tumor, he can determine the exact, malignancy type, and the appropriate treatment faster with the help of cytopathology (see Chapter 3)[12].



Intimidating waiting periods are shortened by the means of fast cytological diagnoses.

Despite these advantages, the cytological cancer diagnostics are insufficiently offered and not made use of often enough. One of the essential reasons for this in Germany are the tariffs, through which the method was put in a worse position than diagnoses performed through surgery, biopsies or X-rays, for a long time (see p. 80).

In addition, the situation for the cytological staff in Germany is not good. There are not enough pathologists that special-

ize in cytopathology. Cytotechnicians have, so far, been predominantly trained for gynecological screening. Also, their education is hardly possible anymore in Germany due to political decisions, which triggered the closing of almost all cytotechnician schools in the 1990's. Pathologists will only start offering and increasingly developing cytological methods if the request from doctors and patients increases and the cell examinations are cost-effectively compensated.

What Cytopathology is Not Capable of

This book is not here to leave the impression that cytopathology is definitely the best examination method for cancer. In some areas this method is not applicable, in others it only helps in combination with further examinations.

- A cytological examination does not generally replace a histological analysis. To some extent, it is especially reasonable to combine both methods with one another.

- The cytological examination does not replace the histological analysis of removed tumors. If it is necessary and possible, a tumor should always be removed completely and then examined histologically.

- In most cases, cytopathology cannot give information about the spread of a primary tumor (staging, see p. 36).

- Cytopathology can only achieve the same accuracy as tissue biopsies in certain cases. For example in the thorax, stomach, liver, and oral mucosa.

- For the exact classification of some tumors (classification, see p. 34), cytopathology is inferior to histology (for example with malignant lymphomas or bone tumors). In this case, the pathologist will recommend the removal of tissue. Often, the cytological analysis is sufficient to decide if the cancer needs to undergo surgery. In this case, the tumor will ultimately be histologically classified anyway.

2. The Cytological Examination

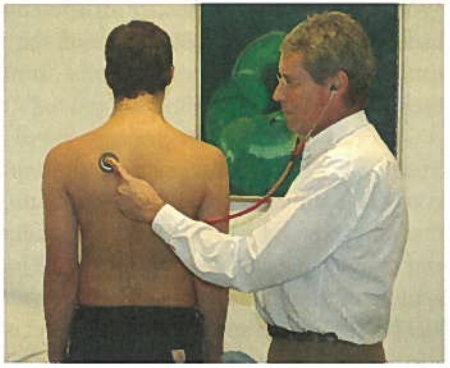
The cytopathological examination process comprises several steps. Initially, cells are taken from the patients and are subsequently analyzed by the pathologists under a microscope or in the lab. Lastly, the pathologist formulates a diagnosis, with the help of which the doctor and the patient are able to determine any further proceedings.

Which Doctor Does What?

Two groups of physicians are involved in cytological examinations: Some are involved in gathering the cellular samples from patients, others are in charge of examining the samples obtained. The extraction of the cells can be performed by many different physicians. However, it would be most obvious to select someone from a specialized field of study, primarily concerned with the specific organ or organ system from which the cells are to be taken. Therefore, one would primarily submit urinary samples to general practitioners, internists, urologists, and gynecologists, whereas a smear of the oral mucosa is best taken by a dentist, an otolaryngologist, or a general practitioner. A radiologist should be seen for a puncture of the adrenal gland.

Since the use of cytology in cancer diagnostics is not sufficiently widespread and universally accepted thus far, rivaled by other methods, it is possible that a physician is not familiar with a given method and will therefore dissuade from its use. Chapter 8 describes how patients can react in such a situation.

In most cases, only trained pathologists are permitted to carry out the examination and



First contact person for cytological examination is often the family doctor.

diagnosis of the cell samples. Gynecologists, who are allowed to microscopically examine cervical smears after having obtained special training, and internists, who inspect blood samples for leukaemia cells, provide an exception to this rule. Also with additional training, urologists may test urine samples for cancerous cells.

In Germany, a physician has to prove 15,000

histological and 10,000 cytological diagnoses under the supervision of an experienced pathologist, before he or she is allowed to apply for specialist status in pathology. It is only after having passed the examinations that he or she is allowed to single-handedly evaluate tissue or cell samples under the microscope. The physician who takes the cell samples usually knows pathologists, who specialize in cytopathology and work in a private practice, a local or university hospital, or another (research) institution.

Extraction of Cells

Body Fluids

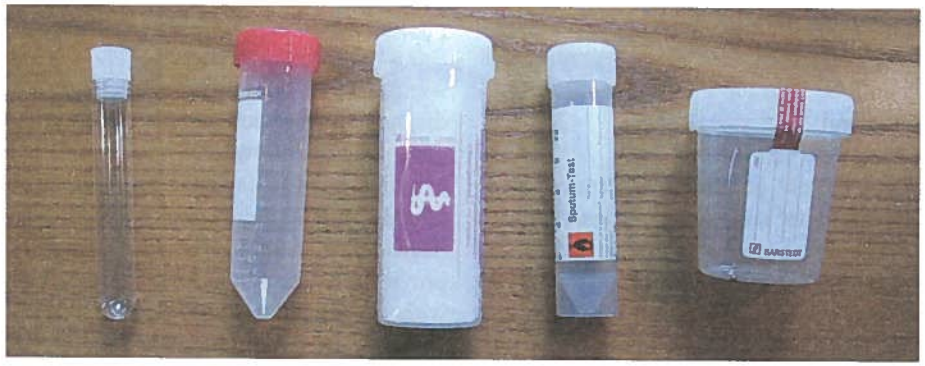
Body fluids mostly contain cells, which stem from the mucosa of certain organs. When mucous membranes are afflicted by cancer or a preliminary state thereof, they usually also shed tumorous cells from their surface.

Such cells can be found, for example, in coughed up mucus, the so-called sputum, that smokers and patients with bronchitis can cough up easily in the morning. The sputum of the patient is mixed (fixed) with alcohol, filled into special test tubes, and is then sent out to a cytological institute for analysis (see p. 46).

Urine samples are also obtained very facilely, they must, however, be processed immediately. Fluids from the body cavities, the spinal canal, or joint effusions are also well-suited for a cytological examination. They are obtained by means of puncture and aspiration (see p. 28).

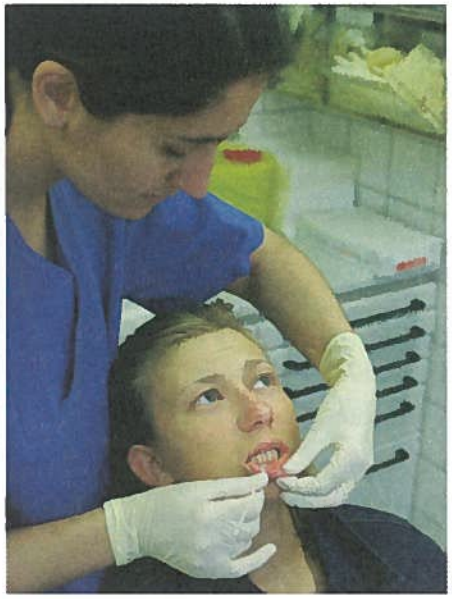
Useful for the Analysis are:

Cerebrospinal fluids (liquor cerebrospinalis), fluids of the anterior chamber of the eye, sputum, effusions of the visceral cavities, urine, joint effusion, and bile.



Containers for various body fluids (from left to right): Liquor cerebrospinalis, effusions from the visceral cavities, outer packaging for mail order, sputum, urine.

Mucous Membrane Sampling



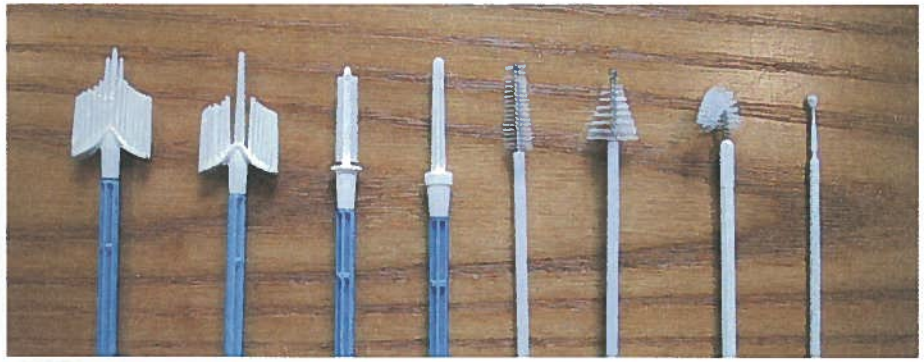
Completely painless: Obtaining a sample from the oral mucosa.

To directly examine cells from the mucosa, they must be obtained through what is called a swab or a smear using brushes of various forms and sizes.

The smallest brushes used have a diameter of only one millimeter. With the exception of the cornea of the eye, a smear or swab does not require any anesthetization, because the patient feels no more than a light tickling. There is also no bleeding involved in taking swab samples of mucous membranes.

Smears/Swabs Can Be Taken from:

The cornea and conjunctiva of the eyes; the oral mucosa, the esophagus, the trachea and bronchi, the bile ducts, the uterine cervix, the vagina, the labia, and the penis.



Various brushes used in the gathering of smears/swabs (from left to right): Six brushes for cervical smears, one for the oral mucosa, one for swabs of cells from the eye.

Organ Biopsies

When a doctor detects a node or a neoplasm in an organ — by means of palpation, ultrasound, or X-ray — he or she is able to puncture the organ with a very fine hollow needle and can easily extract hundreds or even thousands of cells. This procedure is referred to as puncture or fine needle aspiration[1].

Very fine needles (0.7 mm diameter; see photo on p. 60) are attached to an empty syringe and inserted into the suspected node. The skin around the respective area can be anesthetized. However, this is not necessary in most cases, for only a very small incision is made. Pulling on the end of the syringe creates a negative pressure by which the cell samples can be aspirated into the cannula of the syringe.

Ultrasound-guided punctures during gastrointestinal endoscopy are particularly precise. Here, the doctor uses a thin, flexible endoscope with an ultrasound head. With its help, the doctor is able to look into the space between the lungs (mediastinum) from a patient's esophagus and puncture suspicious lymph nodes.

Accurate diagnoses can often be obtained from the cell samples gathered during the puncture, thus frequently averting the need of open surgery. Today, with the use of ultrasound and X-ray, puncture accuracy is exact down to as little as 3 millimeters.

Punctures Can Be Performed at:

The eyes, salivary glands, the thyroid gland, lymph nodes, the lungs and the space in between the lungs (mediastinum), the thoracic wall, the liver, the pancreas, the adrenal glands, the prostate, the space behind the abdominal cavity (retroperitoneum), soft tissues.

Preparation and Staining

After extracting cells from a bodily fluid by means of puncture or smears, the treating physician will then refer them to a pathologist. There the cell extractions will be transferred onto the microscope slides as so-called streak cultures. Initially, fluids are catapulted within a centrifuge, in order to collect as many cells as possible.

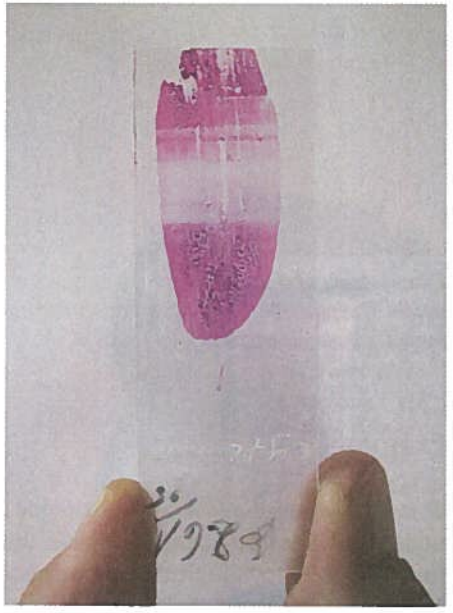
Rotor of a centrifuge, which catapults the cells directly onto a microscope slide.

A technician operating an automated staining machine. The percentages on the containers indicate the alcohol content of the various staining solutions.

Before the probe can be examined further, it is stained with various plant pigments in order to make the cells visible under the microscope. Depending on the desired stain, the cell samples are preserved by letting them air dry or by fixing them in alcohol. Especially the nucleus should be distinguishable in color from the surrounding cytoplasm.

A special procedure for preparing a slide is liquid based cytology. In order to create a slide which is particularly easily examined by microscopy, the cell samples are firstly transferred from the brush into a fixation solution. Next, they are transferred, either through a filter (stamp technique) or after a purification step using a special centrifuge (density gradient centrifugation), onto the microscope slide. In this procedure, the cell samples are cleaned from mucus, dirt, and bacteria.

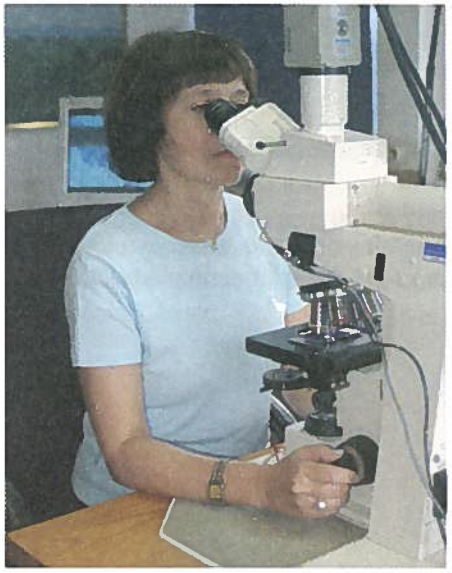
The aim of liquid based cytology is to create slides with particularly clean and

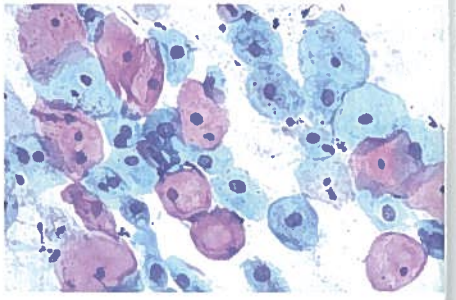


A fully stained blood sample.

evenly spread cells. Scientific research has shown that more tumor cells in preliminary stages can be detected with these slides[2].

Up to now, liquid based cytology has been used primarily by gynecologists, because slides of cervical smears are often of insufficient quality. It is the most widespread method in Great Britain and Scotland, yet German health insurances do not cover the costs of this procedure up to date, because its reliability has not yet been proven sufficiently.





Examination of a smear under the microscope: Light shines through the slide from underneath. The pathologist looks at the stained cell samples through different lenses, which magnify the cells up to 1,000 times.

Examination

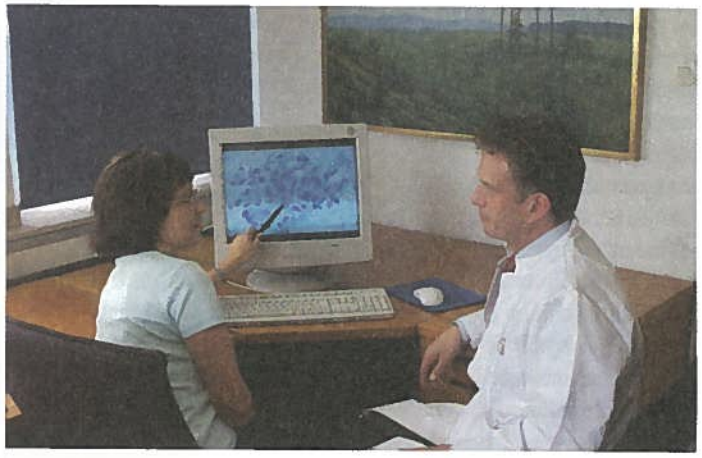
The analysis of the stained cell samples under the microscope always marks the first step of a cytological examination. In many cases, the pathologist is able to see with the naked eye, if the cells show structural evidence of cancer. The nuclei of healthy cells of the oral mucosa, for example, all have the same size, are round, and their DNA appears finely-granular. Contrary to this, nuclei of cancerous cells are enlarged, irregularly shaped, and their DNA is much more coarsely-grained than that of healthy cells.

If the pathologist is not able to make a diagnosis based solely on the given cell morphology, he is able to revert to other methods such as DNA-image-cytometry, immunocytochemistry, In situ hybridization or the AgNOR analysis (see pp. 14-17 and pp. 20-21).

Diagnosis

At the end of the examinations, the pathologist informs the treating physician of his results, his diagnosis. In case he has detected cancer cells, he might suggest that a surgery be performed. The localization of the origin (identification of the primary tumor), the accurate typing of the tumor, and the identification of its grade of malignancy then help to identify the most adequate therapy. Only in rare cases is a tissue extraction (biopsy) necessary in addition to a cytological exam.

On many occasions – in up to 96 percent of cytologically examined cases of suspected thyroid or oral cancer[3] – the doctor can refrain from taking tissue samples. The aspects, of which the pathologist's diagnosis is comprised, are depicted in the following chapter.



Pathologists often discuss their results amongst themselves. They can even confer with colleagues from other cities or countries via "teleconsultation".

3. Diagnostic Criteria

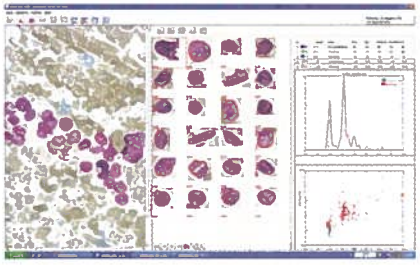
Benign or Malignant?

The first thing a pathologist does at the microscope is to decide if the extracted cells are tumor cells. If this is the case, the tumor cells can be benign as well as malignant (see page 13). A pathologist calls this distinction diagnosis. A tumor that only shows some properties of malignant cells is called semi-malignant. If a pathologist sees possible presence of a tumor, then this is referred to as a dysplasia. If the pathologist is in doubt as to whether the cells are malignant or benign, the tumor is referred to as a borderline tumor.

For the most part, the dignity can be determined solely by using a microscope. If that is not possible, primarily DNA-image-cytometry (see box below) and immunocytometry are used to give clarification. In-Situ Hybridization (bladder, lungs, body cavity effusions), or Ag-NOR-Analysis (pleura, peritoneum, thyroid gland) are applied less frequently.

Definitive Diagnosis with DNA-Image-Cytometry

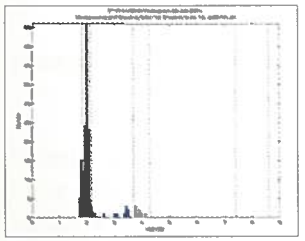
In many cases there are not enough cells for an examination with a microscope, or the appearance of the cells does not permit a definite diagnosis yet. In these cases a pathologist may be able to identify changes in the amount of nuclear DNA with the help of a computer (see page 14 and the box on page 33). In doing so, some tumors could be detected years earlier than by using a microscope with the naked eye.

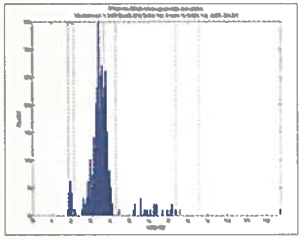


Measuring monitor for the analysis of DNA (MotiCyte-DNA-i)

Occasionally, the diagnostic accuracy of histology can even be exceeded by DNA-image-cytometry. Due to an increased amount of nuclear DNA, a pathologist can detect cancer in the mouth as well as in mucous membranes of the bronchi, the cervix, and the larynx, about two years earlier than in tissue[1].

The evidence of one cell with a heavily increased amount of DNA or about 100 cells with lightly increased amount is possibly sufficient to make a reliable cancer diagnosis. Given that, DNA-Image-Cytometry does not only permit a very early cancer diagnosis, it also only needs few cells to do so[2].





A pathologist is comparing histograms. While healthy cells have a large peak at 2c and a small one at 4c (top left picture), all peaks outside of these ranges are an indication of cancer (bottom left).

DNA Histogram

Results of an examination with DNA-image-cytometry are presented in a so-called histogram. It is worth knowing how to interpret a histogram, even as a patient, because it often decides about the further treatment.

On the x-axis, the DNA histogram displays the DNA concentration of the examined cells in the unit "c". Healthy cells are diploid, meaning they have 2 copies of each chromosome. The peak will be at 2c on the histogram. Minor amplitudes between 2c and 4c are not uncommon, as up to 5% of a cell population can be dividing (undergoing mitosis) while the genome is being duplicated. Under certain conditions, healthy cells can duplicate their genome multiple times, so that results of up to 8c are possible.

However, if the DNA concentration is at least 10% above or below the common results, the situation is known as DNA-aneuploidy, which is an indication of a malignant tumor. If the distribution of DNA in an already known tumor is around 2c, then the cancer is usually low malignant (peridiploid). A second peak at 4c indicates more malignant (peritetraploid), and potential peaks outside of 2c and 4c indicate highly malignant (multiploid) cancers.

Therefore a histogram does not only answer the question whether the examined cells are cancerous, it also contributes to knowing how malignant the cancer actually is (Grading, see p. 34). This is especially relevant for patients with prostate cancer (see p. 68).

Type of Tumor

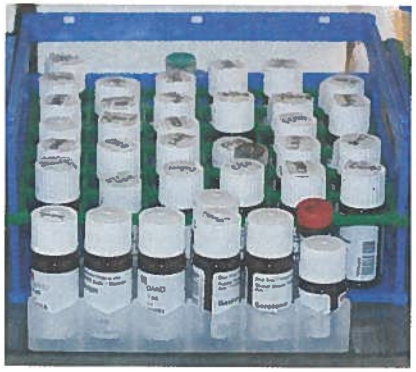
If a pathologist discovers cells or tissues of a tumor, it is his job to clarify where it originates from and what type of tumor it is. In humans, there are approximately 2,300 different tumors and almost each one requires a specific treatment.

The lungs, for instance, can contain carcinomas which need to be surgically removed, as well as carcinomas which need to be treated with chemotherapy and radiation. The classification of a tumor is also known as typing.

In two-thirds of the cases, the microscopic picture is enough to classify a tumor. If there are any obscurities, immunohistochemistry and immunocytochemistry, respectively, are the most common and accepted supplementary methods. In rare cases (pleura, abdomen), In-Situ Hybridization is also applied.

Classification Done with Immunocytochemistry

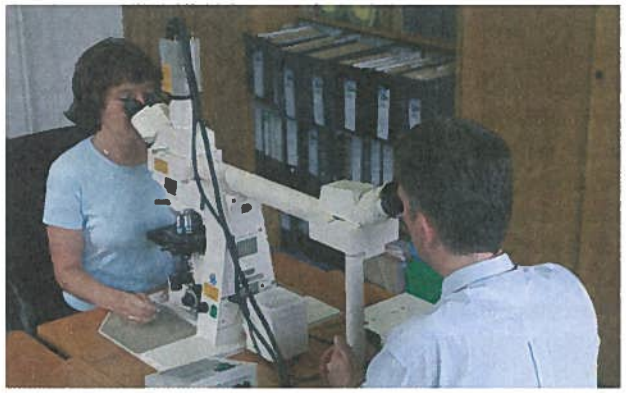
Pathologists have access to over 100 antibodies as "markers" for the classification of tumor cells (see p. 17). The marker TTF1, for example, is an indication of a primary tumor in the lungs. If, on the other hand, the marker CDX2 is tested positively, then there is probably a metastasis of a colon tumor. The question whether a lung tumor should be surgically removed can be determined by using the marker CD56.



Markers for Immunocytochemistry in small bottles

Degree of Malignancy

In the next step of the examination, the degree of malignancy of the tumor is determined. Pathologists speak of grading. In the process, the similarity between the cancer tissue and the original tissue is assessed using a microscope. Subsequently, the tissue will be assigned to a grade of malignance from 1 to 4, with 4 being the most malignant. Different criteria are effective for the assessment of each type of tumor. The grading helps pathologists distinguish between dangerous and less dangerous tumors. This distinction is sometimes also described using the image of domestic cancer and wild cancer.



If pathologists are not completely sure about a specific aspect of the diagnosis, they can regard and discuss a slide by using a so-called discussion microscope.

An early prostate carcinoma, grade 1, hardly puts the life of a 70-year old at risk and possibly does not need to be treated – it is like a tamed pet that you just need to keep an eye on. A carcinoma with the grade 4, on the other hand, could, by all means, endanger the life of the 70-year old. This "predator" would need treatment in the form of surgery or radiation.

Often, a microscope is not sufficient for grading. The most common helping method here is DNA-image-cytometry (see box below). Every so often immunocytochemistry is applied as well.

Grading with DNA-Image-Cytometry

In addition to the customary way of grading using a microscope, it is also possible to classify some types of tumors according to their genetic information. The more malignant the tumor cells are, the greater is the number of the chromosomes in the cells that differs from the normal number (see page 14). While a relatively harmless prostate carcinoma with grade 1 still contains the normal number of 46 chromosomes, cells of a malignant carcinoma with grade 3 have a different number of chromosomes in almost every cell. They can have up to ten times as many chromosomes. If these changes in the number of chromosomes increase, it is known as tumor progression.

The DNA grade of malignancy can be derived by measuring the amount of DNA in at least 300 nuclei.[3] As in the conventional way of grading, the DNA-grade of malignance can help decide if treatment is necessary and sometimes also which kind of therapy should be chosen.[4]

Tumor Stage

In addition to the type and degree of malignancy of a tumor, how far it has spread throughout the body is also very important. The determination of the spread is known as staging and is crucial for the choice of treatment.

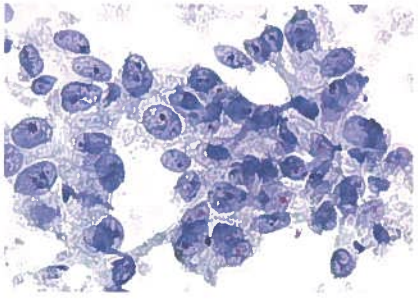
The staging is measured in a so-called TNM-System, which measures the size and spread of a tumor (T), the affection of lymph nodes (N) and the presence of metastases (M), all in inner organs. While the size of a tumor is determined mainly by X-ray and ultrasound imaging before treatment, pathologists determine cytologically and histologically if the lymph nodes, bone marrow or inner organs are affected by metastases. If a patient complains about shortage of breath and a pleural effusion is found (see page 58), pathologists can use a microscope to clarify if the cause is metastases or just a harmless infection.

The first step in staging is to take a look through a microscope. If the result is not a definite picture, then immunocytochemistry is primarily applied (see the box below).

Staging with Immunocytochemistry

Checking a suspicion of metastases is the same as looking for a needle in a haystack: A few tumor cells need to be found among hundreds of thousands of normal cells. For that purpose, markers (see p. 17) are used to help look for a specific protein which is foreign in that region of the body.

For example, the marker BerEp4 marks so-called epithelial cells, which are never present in healthy pleura. If a pleural effusion is tested positively for BerEp4, it is an indication of metastases in the body.



Five cells of metastases of a lung carcinoma are marked with BerEp4.

4. Accuracy of Cytopathology

Criteria of Diagnostic Accuracy

Like most approved medical methods, cytopathology is continually scientifically examined for its reliability. The accuracy, which is divided into different categories, is crucial for the reliability. These are the categories:

Sensitivity – the percentage of the correctly identified sick people amongst all sick people.

Specificity – the percentage of the correctly identified healthy people amongst all healthy people.

False-positive rate – the percentage of disease diagnoses which turn out to be wrong afterwards. This rate and the particular specificity add up to 100 percent.

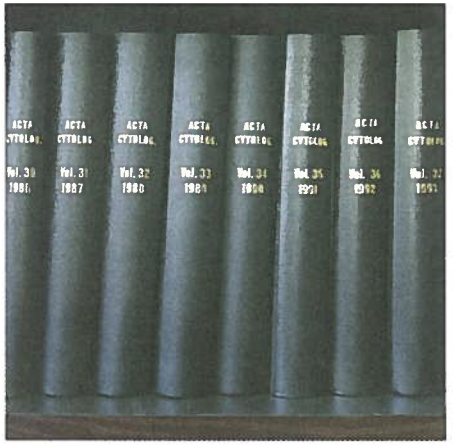
False-negative rate – the percentage of sick people which were overlooked in a diagnosis. This rate and the particular sensitivity add up to 100 percent.

Positive predictive value – the percentage of disease diagnoses which turn out to be correct afterwards.

Negative predictive value – the percentage of correctly diagnosed benign findings.

Typing accuracy – the percentage of cancer diagnoses whose histological classification turns out to be correct afterwards.

Total accuracy – the percentage of all correct positive and negative diagnoses.



The accuracy of cytopathology is examined in around a dozen different professional journals.

The ideal case is that the sensitivity, the specificity, the positive and negative predictive value as well as the typing accuracy and the total accuracy should all equal 100 percent.

Furthermore, the measured values for the cytological as well as the histological cancer diagnostics and for every organ should be known. However, even histology often has insufficient numbers available (see next page).

Comparison to Histology

The accuracy of cytopathology always has to be measured using corresponding histological diagnoses.

However, histology often does not levy any numbers, because so far it has been considered the "golden standard". Thus, the impression that histology is 100 percent correct arises. But actually, the performance of both methods depends on the respective body region.

The accuracy of cytopathology and supplementary methods are currently

- Better than histology when locating lymph node metastases in the mediastinum and epigastrium.

- Equally as good as histology around the eyes, the mouth, the lungs and the liver.

- Slightly worse than histology at the prostate and lymph nodes, which lie under the skin.

Particularly when the accuracy of both methods is almost the same, it is important to consider the pain associated with the examination when deciding between cytopathology and histology. Cytopathology, with its soft cell extraction, comes off better than histology, which requires scalpel and punch-needle biopsies.

A further criterion is the possible complications which can arise from the extraction of tissue. Among these are hemorrhages, infections, scar formations, and pain, which make a further treatment necessary. The probability that these consequences do occur is given in the complication rate, which is usually better in cytopathology. The complication rate, provided that it was available in the professional journals, is given in the following chapters along with the values of accuracy.

There are also body regions in which the accuracy of cytopathology is clearly worse than histology, so far. That is why this book does not name the method as an alternative. This is applicable, for example, for gastric cancer.

On the other hand, there are many procedures in which cytopathology is unrivalled so far: the analysis of bodily fluids, the clarification of lumps in the thyroid gland and pancreas, the screening for cervical cancer or the early detection of cancer with DNA-image-cytometry.

In specific areas, for example the bronchi or the bile ducts, cytopathology is a reasonable supplement to histology.

Microscope slides with cell swabs are kept in an archive for at least 10 years. In doing so, cytological diagnoses can be checked for their reliability for a long time.

About Numbers in this Book

To enable each reader to make an independent judgment, the following three chapters about the application options of cytopathology contain information about the accuracy of each method. The complication rate of those methods, in comparison to the histological examination of tissues from biopsies, is also partly included.

All numbers come from scientific papers which can be found and verified with the help of the references. Because cytopathology, as well as other medical fields, has a large number of studies, the author chose a representative number for the accuracy and the complication rate.

The choices were selected on the basis of four criteria:

1. Average from the literature In many scientific papers, the mean will be calculated for a certain measured value using all research analyses available up to then, for example when searching for the average specificity of effusion cytology. If a so-called average from the literature (review) exists, it will be named.

2. Comparability Studies that contained the numbers of accuracy of both the cytological and the histological examinations were preferred.

3. Case numbers If an average from the literature does not exist, then the study with the most examined cases is cited. If it is not stated elsewhere, then each number of studied cases that is mentioned in this book is at least 100.

4. Topicality If the number of cases were the same in two different studies for the accuracy, then the more up-to-date one was chosen. The reason is that the accuracy of the methods improves over the years because mistakes made in earlier studies are recognized and prevented in later studies. Studies older than 15 years were not regarded.

In addition to the mean values which are summarized in a table at the end of each chapter, the text sometimes contains the optimal values for studies performed with cytology. This has two reasons. First of all, the mean numbers can contain older studies, whose premises are outdated, in them. Secondly, the accuracy is also influenced by the training and experience of the staff involved. Well established cytological institutes and laboratories often achieve better results than less experienced ones.[1] To get a good impression of what cytopathology can achieve under beneficial circumstances, the highest accuracy that the editor found in the evaluated references was also mentioned occasionally.

Moreover, the text and the tables also contain the measured values of supplementary methods, such as immunocytochemistry or DNA-image-cytometry provided that they are applied to an organ frequently or can noticeably improve the accuracy.

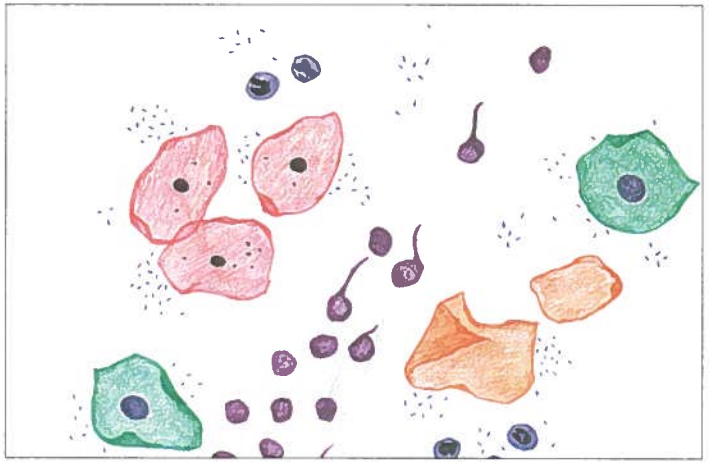
5. Screening

Cytopathology is especially qualified for cancer preventive medical checkups because routine cell extractions are possible without any difficulty. Thus far, cytological methods are only common in the early detection of cervical and lung cancer. However, cytopathology can basically also be applied in other areas. Industrial workers, for example, that have made contact with the carcinogenic aniline dye, are regularly examined for bladder cancer.[1]

Currently, the application of cytopathology is being tested in the early detection of oral cancer.[2]

Cervix

Case Study Renate Weilmann[3] had regularly gone to her gynecologist for years for early cancer detection, the findings were always inconspicuous. In February 2000, the 51-year-old teacher received a result for the first time after a cervical smear, which was IIID, the identification code for a mild to moderate dysplasia. This could mean cancer, but in an average of 87 percent of all cases, doctors do not find a tumor.[4] To make the diagnosis reliable, the swab was also examined with DNA-image-cytometry. It resulted in a probability of 63 percent that cancer would occur in the next 3 months.[5]



A hand-made drawing of normal stained cervical cells, created during the training of medical technicians.

Renate Weilmann's gynecologist advised her to undergo a so-called conization, in which the suspicious piece of tissue would be removed from the outer part of the cervix. Three weeks later, Weilmann underwent surgery in a nearby hospital. Three days later she received the result: The doctors had found a so-called carcinoma in situ, mucosal cancer in an early stage. It was removed completely and Renate Weilmann was considered cured. She still goes to the preventive medical checkups and an indication of cancer was not discovered in the last 5 years.

The result of the annual preventive medical checkup for cervical cancer is usually comforting. If a carcinoma is found, it can almost always be removed surgically.

Applications No other method can diagnose cervical cancer as early as cytopathology. If applied early enough, a complete cure is likely, as in the case of Renate Weilmann.

The experiences made with the cytological early detection of cervical cancer are substantial. In the 1940's, the medical doctor George Papanicolaou examined cervical swabs for indications of a cervical carcinoma. Since 1971, every insured woman in Germany over the age of 20 has the right to get the "Pap-Test", which was developed by Papanicolaou, for free. However, only 60 percent of all women make use of this opportunity so far. Nevertheless, the death rate due to cervical cancer – the most common type of cancer among women, worldwide – had been reduced by 65 percent in Germany since the introduction of the Pap-Test.[6]

With routine checkups, a definite cure is almost always possible because pathologists can identify preliminary and early stages of a cervical carcinoma by using a microscope. These lesions can be removed with a comparatively harmless surgery known as a conization. In a conization, gynecologists remove a cone-shaped piece of tissue, approximately a centimeter in size, from the cervix. The surgery does not have any affect on the sexual sensibility or the ability to give birth.

As an alternative to the Pap-Test, many businesses are offering Human Papilloma Virus (HPV) tests. Certain types of this sexually transmitted virus (particularly type 16 and 18) cause cervical carcinomas. As many as 30 percent of young women are infected with these viruses. For women who do not show evidence of HPV, there is a high probability that they will not be affected by cervical cancer in the next 5 years.[7]

However, only 13 percent of all women who are HPV-positive fall ill with cervical cancer. Because of the fact that the HPV tests can lead to many unnecessary operations, the German Cancer Society currently declines them as preventive medical checkups.[8] For the surveillance of the success of treatment following surgery of cervical carcinomas, it is reasonable to determine the HPV viruses with the polymerase chain reaction (see p. 17).

The Pap-Test is not without controversy. The German product testing company, Stiftung Warentest, thought the test was only "applicable with restrictions".[9] One reason is that the test provided a high rate (5 percent) of false positive results

The Pap-Test

The Pap-Test is a method for the early detection of cervical cancer and has been around and approved for over decades. It was developed by George Papanicolaou, a doctor from Greece, who worked in New York at that time.

At a convention in 1928, Papanicolaou presented the basic principles of the method, which have hardly been altered to this day, to his skeptical colleagues. The gynecologist takes a smear of the cervix and subsequently, the cells will be examined for any changes using a microscope.

George Papanicolaou was honored in 1978 in USA (his adopted country) with a US postage, as a pioneer of cancer screening

These changes are classified in a so-called Pap-scala, which ranges from PAP I (normal cell image) to PAP V (advanced malignancy). The reliability of the test has been additionally improved by combining it with DNA-image-cytometry.

in the US.[10] This supposedly has to do with the fact that pathologists in the USA are more likely to express a suspicion than the colleagues in Germany, for fear of being sued for underdiagnoses of cancer. Moreover, they have a different system for cervical cell diagnoses so that the numbers are hardly comparable. In the long run, the number of unnecessary tissue biopsies can be reduced enormously by applying DNA-image-cytometry (see p. 14). This examination, which has been covered by health insurances in Germany for over 10 years, is hardly applied in the USA.

However, even on average of all literature initially argues against the Pap-Test. The rate of false positive diagnostic findings is, after all, 5 percent; the sensitivity, on the other hand, only 47 percent (see table below). This is also due to the bad quality of many smears. For this reason, since 2006 in Germany, cells need to be extracted using an appropriate spatula and a little brush instead of the traditional cotton swab.

When applied professionally by specialists and cytological institutes, 70 percent of all cervical cancers can be detected from the first swab with the Pap-Test; only 1.4 percent of the positive results turn out to be false afterwards.[11] The new method of liquid-based cytology (see p. 29) could enable an additional improvement of the sensitivity.[12]

Despite the need for further improvements, the possibilities of cytopathology for the early detection of cervical cancer are good. A routine Pap-Test, supplemented by DNA-image-cytometry in dubious cases, is definitely advisable.

ACCURACY OF THE PAP-TEST	
Sensitivity	47 %
Specificity	95 %

Nannda et al., 2000 (Review)

Lungs

Case study Klaus Marnow worked in a power plant as an engineer for 27 years. Three times a year, he monitored the inspection of turbines. Because they were insulated with asbestos mats, the 62-year-old was constantly exposed to the carcinogenic material for decades. Due to these circumstances, there was a high risk of him falling ill with cancer. This risk was additionally increased because Marnow had smoked about a pack of cigarettes a day for 37 years.

Particularly smokers and people that work with cancer-causing materials such as asbestos (left) should regularly go to cytological checkups for lung cancer.

During a preventive medical checkup in May 2003, doctors found scars in Marnow's lungs and pleura which are referred to as "asbestos lung". Cancer was not detected at that point. One year later Marnow went to the checkup again, and this time the computer tomography showed a suspicious spot. Because it could not be identified as cancer right away, Marnow submitted four samples of mucus (sputum) that he coughed up in the morning. During the cytological examination, the pathologist discovered grade 2 lung cancer cells. Shortly after, Marnow's upper right lobe of the lung, including the tumor, was removed during surgery.

During the operation, a histological examination (rapid section) confirmed that it was lung cancer in the earliest stage (pT1). Subsequently, 25 removed lymph nodes were examined and all were tumor-free. The cancer in Marnow was removed before it could develop metastases.

Application Lung cancer belongs to the most widely spread cancer types worldwide, and especially smokers are at risk, 30 times higher risk than non-smokers, of getting a bronchial carcinoma.[13] This quite common type of lung tumor is fatal in later stages. If it is detected soon enough, approximately 67% of all patients can be cured.[14] An early discovery of lung cancer can be enabled by applying sputum-cytology in specific risk groups. Patients can collect mucus, known as sputum, from their lungs themselves by applying an uncomplicated method (see box on p. 46), and can then send it to a cytological lab. The cells contained in the sputum are examined under a microscope for any indications of cancer. This examination can also be done by fully automated means a procedure known as sputumcytometry.

The Sputum-Test

The sputum that pathologists need for the early detection of lung cancer can easily be obtained by patients themselves. They only need specific transportation vial which they can receive at their doctor's office or in a cytological lab.

It is best to carry out the test in the morning because a lot of mucus will have accumulated in the bronchi during sleep. After brushing their teeth and thoroughly rinsing out the mouth, patients will take a deep breath, forcefully cough up the mucus and then spit it into a cup. The patients will then pour alcohol, which has been provided with antibiotics, out of the transportation vial over the sputum to conserve the cells and inhibit the growth of bacteria. After the sputum and the alcohol have admixed, both are poured back into the transportation vial.

As soon as the patient has prepared four different samples, they are sent to a cytological lab in a special envelope for further examination. The results of the sputum-test are usually available after three days.

A complete set for sputumcytology, patient can get, without problems, necessary cells for a study on lung cancer.

Although the average sensitivity of sputumcytology is comparatively low, the specificity is very high (see table on p. 47). That means that this method cannot detect every kind of lung cancer, but if cancer is detected, the chance of there being a false diagnosis is extremely small. In addition, a further clarification always follows a positive diagnosis before treatment potentially begins. There is no histological alternative to the sputumcytology, due to the fact that it is not possible to easily remove the tissue from the lungs. X-ray pictures can achieve a remarkable sensitivity of 87 percent[15], but they are not suitable for regular checkups because of the radiation exposure. Even if the radiation is reduced (low-dose or spiral-CT), the exposure is still so high that, according to a study, new tumors could develop.[16] The false-positive rate of 21 percent also results in a risk of unnecessary operations.[17]

For this reason, sputumcytology is the only "gentle" preventive medical checkup for lung cancer. The insufficient accuracies have methodical reasons. The microscopic examination of sputum requires trained staff which is not sufficiently available in Germany due to the closure of schools for cytotechnicians. The sensitivity of sputumcytology could be increased to 85 percent if it was applied professionally.[18] Another chance lies in sputumcytometry, which has a smaller error rate due to the automation and already achieves a sensitivity of approximately 80 percent.[19] In the future, a special form of the Polymerase-Chain-Reaction (see p. 17) called QMSP could help with the early detection of lung cancer.[20]

As long as there is no other "gentle" method for the early detection of lung cancer, sputumcytology is especially recommendable to risk groups such as heavy smokers or former asbestos workers and chrome-nickel welders.

ACCURACY OF SPUTUMCYTOLOGY	
Sensitivity	66 %
Specificity	99 %

Schreiber and McCrory, 2005 (Review)

6. Diagnosis

The cytological clarification of a cancer suspicion is commonly used on at least a dozen organs today - they are described in this chapter. In addition to this, there are also other body regions that can be cytologically examined for the presence of cancerous cells; these include the esophagus[1], larynx[2], nose, lining of the stomach[3], adrenal glands[4], anus and penis. However, since only little experience exists with regard to these regions, they will not be discussed further.

For other kinds of cancers – such as breast cancer, uterine cancer (carcinoma of the endometrium), cancer of the oral and intestinal mucosa, cancer of the labia, or of testicles – the reliability of cytological results is inferior to that of the results obtained by tissue – biopsy, so that these forms of cancer purposely are left out.

Lastly, there are organs, such as the kidneys or the ovaries that are strictly not suitable for an extraction of cell samples, because in doing so the cancer could spread by way of metastases.

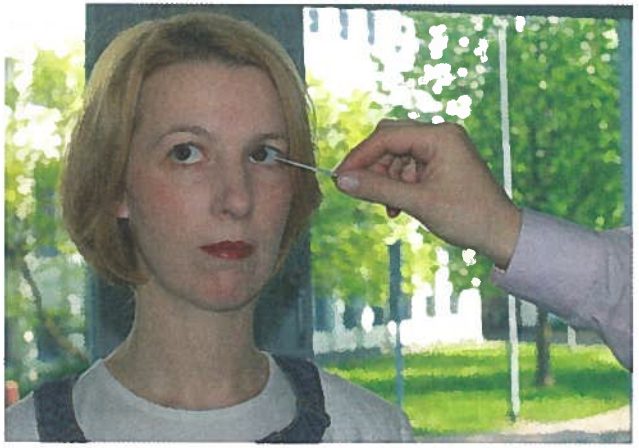
In case the reader is unsure whether cytopathology should be considered for determining a form of cancer that is not listed in this book, he or she should not hesitate to contact one of the contact persons listed in Chapter 9.

Eyes

Case study Upon looking into the mirror in June 1997, Rita Geschke noticed a brown spot, about the size of a match's tip, on the conjunctiva of her right eye. Her ophthalmologist suspected a tumor and sent the 67-year-old for further examinations to the University hospital in August of 1997. The ophthalmologist there agreed with the cancer diagnosis. They took a swab of the suspicious spot – a harmless procedure, which Geschke could not feel, because of the application of local anesthesia.

Spots or swellings on the eye could indicate cancer.

After the microscopic examination and with the help of the DNA-image-cytometry, the diagnosis was unambiguous: Malignant melanoma in T1 state – a black skin cancer in the earliest stage. The melanoma was removed two days later by a minor surgery. A pathologist later confirmed that the surgeon had completely removed the tumor. However, because the tumor was positioned close to the edge of the removed tissue, it was necessary to treat Rita Geschke also with radiotherapy in order to avoid a relapse. There were no further tumors detected in the follow-up examinations.



The extraction of conjunctiva cells with a small brush (swab) is completely painless and in contrary to a scalpel biopsy also risk free.

Application White or brown spots on the cornea and conjunctiva of the eye, such as in the case of Rita Geschke, are signs of a squamous cell carcinoma or so-called black skin cancer. Also chronic inflammations of the conjunctiva, often occurring in allergic people and, can in rare cases develop into cancer. If these infections are detected early enough, they are easily treatable and the eye can be preserved.

So far, a so-called hockey-knife has been used to take tissue samples of the eye when there is a suspicion of cancer. This biopsy method can leave behind scars which have a negative impact on the vision. A cytological exam is a good alternative to this method, because when taking a swab only a few cells are collected with the help of a brush from the surface of the eye. The procedure is completely painless, because the eye is anesthetized using drops of a local anesthetic prior to the collection of the samples.

Extensive studies regarding the use of cytological diagnostics on the eye do not exist to date, however many smaller studies report an accuracy that is well comparable to that of an incision biopsy.[5]

With the help of DNA-image-cytometry, cancerous cells could even be detected several months earlier than with the help of a tissue sample.[6]

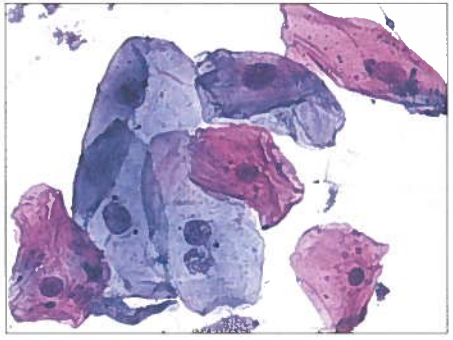
The success of an eye cancer treatment through surgery or chemotherapy can be determined with the help of cytology. In case a tumor reappears, it can be detected very early and re-treated immediately.[7] The pathologist is also able to identify benign tumors of the eye, such as moles. Malignant tumors must be obviously removed and examined. Nevertheless, when it becomes apparent that, with a high likelihood, there is no cancer, the patient must not undergo the risks of an incision biopsy.

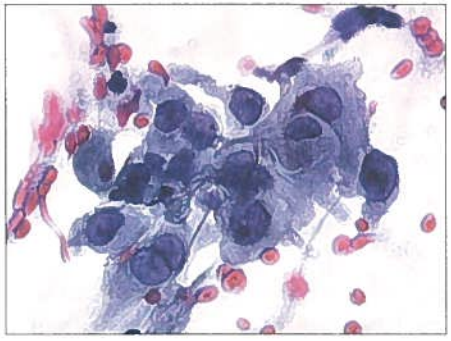
ACCURACY EYE	cytological
Sensitivity	100 %
Specificity	100 %

Vemuganti et al., 2004, 45 cases

Mouth

Case study When the dentist noticed a white spot on Hubert Siering's oral mucosa, she referred him to a specialized clinic for further examinations. There, tissue and cell samples were taken of the 63-year-old's oral mucosa. The analysis of the tissue sample returned a harmless alteration of the skin (leukoplakia). On the contrary, the analysis of the cell samples gave reason for suspicion of a so-called squamous cell carcinoma. Further examination using DNA-image-cytometry confirmed the diagnosis. Later, the histopathologist also found a carcinoma when he examined the tissue sample for a second time. The cancer was still in an early stage and could therefore be removed completely. In the following years, Hubert Siering was examined several times, however the doctors could not find another indication for a return of the carcinoma.





The oral mucosa cells in the left picture show a harmless reactive epithelium alteration of the skin, as was suspected in the case of Hubert Siering. Cancer cells (blue) are visible on the right.

Application Each year, more than 5,000 Germans are diagnosed with oral cancer.[8] Within the last 50 years, there have hardly been any advances in the fight against this disease. One reason for this could be that the conventional taking of tissue samples with a scalpel keeps many patients from letting suspicious red or white spots on the oral mucosa be examined in time.

In fact, most of these spots have harmless causes such as yeast infections or inflammations. Even spots where these causes can be excluded (leukoplakia, erythroplakia, or lichen planus) do not develop into cancer in 90 percent of all cases.[9] Nonetheless, such alterations should be examined, especially in smokers and people with augmented alcohol consumption.

Cytopathology offers a harmless and inexpensive method to examine suspect lesions, which has been covered by health insurances since 2005. Cells are swabbed off the affected mucosa with a small brush and then examined under the microscope. An extensive study of over 1,000 patients at the University of Leipzig proved that with an accuracy of 99.1 percent, this method is just as efficient as incision biopsy (see the table below for further numbers).[10]

As with Hubert Siering, in some cases cancer could be cytologically diagnosed, although histology did not yet show any indication of a cancerous lesion. When examined with the help of DNA-image-cytometry (see p. 14), an "advantage" of up to two and a half years could be attained.[11]

ACCURACY MOUTH	cytological	histological
Sensitivity	98.3 %	98.1 %
Specificity	99.3 %	100 %
Complication Rate	0 %	5 %

Remmerbach et al., 2006

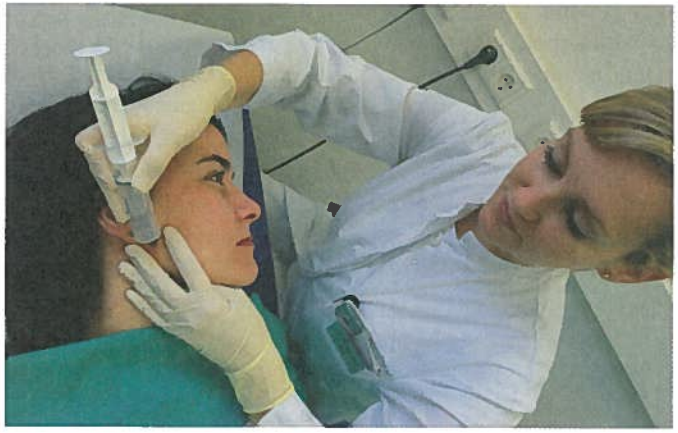
Salivary Glands

Case study When Friedbert Lichtenberger detected a small node below his left ear, he waited at first. However, because the node seemed to continue growing, the 42-year-old went to see his general practitioner, who, in turn, referred him to a surgeon. The surgeon took tissue samples in what is called an excision biopsy. The

histological exam showed no indication of cancer. Lichtenberger was then additionally examined by magnetic resonance imaging (MRI). The surgeon then found an additional node and he furthermore noticed that the lymph nodes surrounding it were of increased size. Since a suspicion of cancer now existed, Lichtenberger was transferred to a hospital's outpatient clinic. There, an ultrasound examination confirmed the MRI results. What exactly the nodes were, however, remained unclear.

It was not until the radiologist had taken cell samples by fine needle puncture, that tumor cells were found. They were benign and the node did not pose a serious threat to the patient's health.

Because the surgeon now knew that the tumor was benign and therefore locally restricted, he was able to avoid the very sensitive facial nerve (nervus facialis) during surgery. The tumor was removed without further difficulties and the histological examination confirmed that it was indeed benign.



Cells for a cytological examination of the salivary gland are taken during a fine needle puncture.

Application People who are diagnosed with a tumor of the salivary glands are usually between 50 and 80 years of age. The large salivary glands of the ear are most often affected by a tumor, however, any one of the hundreds of other smaller salivary glands can also be affected. Nodes or hardenings of the salivary glands should always be examined under the microscope, because malignant forms of salivary gland cancer must be removed at a very early stage. 60 percent of all tumors that pathologists discover are benign, the so-called adenomas.[12] Yet, in most cases, an adenoma must also be removed surgically, because it can turn malignant over time or it can be harmful to the surrounding nerves and tissues because of its increasing size.

The so-called punch biopsy offers an alternative to a cytological exam of suspicious nodes. In this method, tissue is taken with the help of a one to two millimeter thick hollow needle. However, this procedure only detects 83 percent of all tumors[13] and is not recommended by most renown ENT specialists because complications occur in more than 2 percent of all cases.[14] A prophylactic surgery of the nodes is in most cases unnecessary, because the cause is most often just a harmless inflammation or a cyst.

Today, fine needle biopsy (see p. 28) is the method of choice to investigate a suspicious cancerous node of the salivary glands, due to the above reasons.[15] With the help of an ultrasound head, a dropsized amount of gland cells is taken with a 0.6 thin millimeter needle. This method almost always proceeds without complications (see table below) and the pathologist is able to uncover 92 percent of all tumors. In addition, the cytological exam is almost always able to determine if the tumor is benign or malignant.

Differentiation of benign and malignant tumors is also very important because the surgeon is able to operate much more gently, knowing that a tumor is benign. With better planning, additional surgeries can usually be avoided. With the aid of the cytological diagnosis, the physician and patient can then, in turn, make a well-informed decision regarding the necessity and extent of a possible operation.

ACCURACY SALIVARY GLAND	cytological
Sensitivity	92 %
Specificity	100 %
Complication Rate	0.5 %

Stewart et al., 2000; Atula et al., 1996

Thyroid

Case study One day, 47 year old Antonia Beer detected two small nodes on her throat. After having undergone an ultrasound examination and a so-called radioiodine scintigraphy, she had to find out that one of the hardenings was a so-called "cold" node with a reduced iodine intake – possibly a thyroid carcinoma.

Different doctors told Beer that both the radioiodine therapy as well as a removal of both nodes could be expedient. Because Beer was very afraid of surgeries, she followed one doctor's advice to undergo a fine needle puncture exam. This uncovered that the nodes were a result of a harmless lack of iodine. Her treating physician now changed his mind and advised her to wait and observe the nodes while undergoing an iodine therapy.

In many cases, thyroid troubles are initiated by harmless causes, such as iodine insufficiency or hypofunction.

Six years later, both nodes have considerably decreased in size and Antonia Beer does not have any troubles. She describes the puncture, which prevented her from undergoing an operation or a long therapy, as "not very bad at all".

Application Almost one fourth of the German population is affected by nodular changes of the thyroid tissue, as it was diagnosed in the case of Antonia Beer.[16] If the first examination with an ultrasound or radioactive substances (scintigraphy) offers a reason for a cancer suspicion, it is essential that this suspicion is investigated further. Doctors often suggest an operation of the thyroid gland, which is one of the most common operations in Germany.[17]

However, the surgeon is able to detect malignant tumors only in less than one fifth of all surgeries.[18] Consequently, there are about 70,000 unnecessary thyroid glands operations each year in Germany. If all suspicious cases would first be examined by means of cytology, the number of surgeries could – according to a study – be reduced by 87 percent.[19]

For an examination of this kind, cell samples are taken in a fine needle puncture during an ultrasound examination (EUS-FNAB, see p. 28). This procedure is uncomplicated and inexpensive, its accuracy is unmatched by any other non-operational examination.[20]

Therefore, 96 percent of hospital physicians in the USA found – 20 years ago already – the fine needle puncture of the thyroid gland to be indispensable for the clarification of a cancer suspicion.[21] In 85 percent of all cases, the pathologist is able to rule out thyroid gland cancer.[22]

ACCURACY THYROID GLAND	cytological
Sensitivity	98 %
Specificity	98.5 %
Complication Rate	0 %

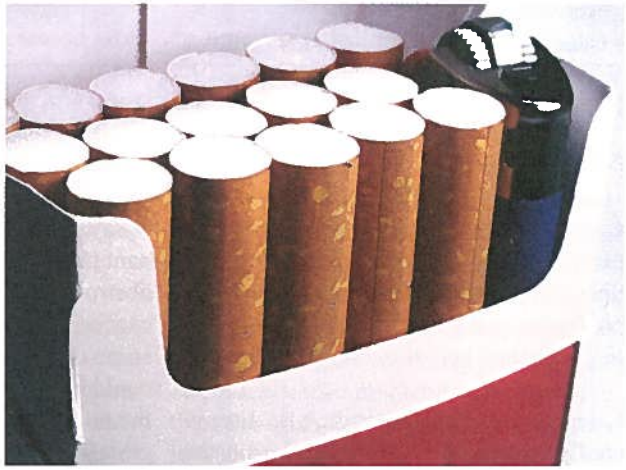
Giuffrida and Gharib, 1995 (Review); Schmidt and Tötsch, 2006

Lungs

Case study Hans Engesser had gotten used to his continuous coughs, after all, he did smoke about 3 packs of cigarettes each day. However, when the 60 year old suddenly started coughing up blood, his general physicist referred him to a specialist for pulmonary medicine. He, in turn, was not able to detect a cancer through X-ray, and a bronchoscopy did not offer any results either. Even two tissue samples of Engesser's bronchial mucosa indicated an ordinary bronchitis. It was not until mucus, which was taken from the lungs during a so-called bronchoscopy, was examined, that cells of a squamous epithelial carcinoma were discovered.

Hans Engesser's right superior lobe of the lung was then removed in an operation. Within it, a pathologist then discovered the approximately 1 centimeter sized carcinoma. Some lymph nodes, which were also removed, did not yet show any tumorous indications. Through this, the lung cancer had been removed in its earliest stage (Ia), it had not yet had a chance to spread. Engesser was able to leave the clinic after two weeks and no cancer was detected in the following years.

Application Lung cancer is the most lethal form of cancer amongst the German population.[23] Since the chances of a full recovery increase with an early treatment, it is very important that suspicious symptoms always get examined immediately. Such symptoms are – aside from the long lasting and bloody coughs, such



Smokers are 30 times more likely to be diagnosed with lung cancer (see p. 45). Smokers with suspicious symptoms, such as long lasting coughs, should get their lung cells examined indications of cancer.

as in the case of Hans Engesser – suspicious nodes, which can be discovered when taking an X-ray of the lung.

Usually, the first step to an examination of lung cancer is a so-called bronchoscopy. To do so, the doctor inserts a glass fiber endoscope through the nose into the bronchi, which lead from the trachea into the lungs. When the doctor finds suspicious tissue within the bronchi, he takes a small sample with his tongs for a histological examination (forceps biopsy). Through this, the pathologist is able to detect 74 percent of all lung carcinomas of the inner most (central) part of the lungs (see table below).

The histological accuracy for the outer (peripheral) part of the lungs is much lower (46 percent). In this procedure, cell samples can be taken with a brush during a bronchoscopy or through the suction of bronchial mucus. If the suspicious node is located on the very far side of the lungs under the ribs, the physician could take a probe by a fine needle aspiration biopsy. The advantage of this method is that the complication rate is much lower than in often applied punch biopsies.[24]

While the tumors located in the center of the lungs can best be determined through a tissue examination (histologically), a cell examination (cytologically) is best suited for those tumors located in the periphery (see the table below). If all methods are combined, they reach a sensitivity of 95.8 percent.[25] A combined cell and tissue probe should therefore always be taken from the bronchi.

ACCURACY LUNGS	central tumor		peripheral tumor		
	cytological	histological	cytological (smear)	cytological (FNAB)	histological
Sensitivity	59%	74%	52%	90%	46%

Schreiber and McCrory, 2003 (Review); Specificities not available

Mediastinum

Case study For Alfons Lejeune the complaints were surprising: When walking up a stairway, the 42 year old University professor could not breathe well, he had to cough, and his joints were aching.

Lejeune visited a radiologist, who discovered many swollen lymph nodes on the X-ray. The radiologist suspected a malignant tumor of the lymph nodes, a chronic obstructive lung disease, or even lung cancer. He recommended the removal of some nodes in an operation, so that they could subsequently be examined under the microscope. A befriended doctor suggested an examination of the nodes in an ultrasound-guided fine needle puncture (EUS-FNAB).

Lejeune was examined the next day: after applying local anesthesia, a thin, flexible glass fibber endoscope was inserted through his nose into the esophagus. From this point, the physician was able to spot the enlarged lymph nodes with an ultrasound head, puncture them with a fine needle, and aspirate thousands of cells. The entire procedure was painless.

Breathing difficulties are possible signs for a disease of the mediastinum

Alfons Lejeune then brought the cell samples to a cytopathological institute for further examinations. After only one hour, a diagnosis could be made: Lejeune suffered from a sarcoidosis of the lymphatic nodes. This inflammation, which was possibly caused by a virus, had to be treated simply with cortisone for several weeks. Lejeune completely recovered after that – without any sort of operation.

Application Mediastinum refers to the region between the lungs. Apart from the heart, the trachea, and the esophagus, many lymph nodes are located here (see p. 70). If they are of increased size, it could possibly be the result of an inflammation, such as in the case of Alfons Lejeune. However, other causes could be tumors, which were formed within the lymph nodes (malignant lymphoma), or metastases that have spread from the lungs into the mediastinum.

If the lymph nodes of the mediastinum are swollen, it is essential to investigate the cause. An X-ray examination in a computer tomography (CT) has a restricted accuracy and should therefore only be the first step.[26] An examination of the lymph nodes by a pathologist, who can inspect not only tissue samples but also cell samples from the mediastinum, is much more precise. In order to examine the tissue samples, an operation (mediastinoscopy) is necessary, during which several lymphatic nodes are removed.

Alternatively, the physician could take cell samples from the trachea or esophagus with an ultrasound-guided fine needle puncture. This method is not only more accurate than the taking of tissue samples in regard to staging of lung cancer, but it is also much more inexpensive than the mediastinoscopy (approximately 600 Euro compared to 1,500 to 3,000

Euro)[27], and in comparison, it is much less prone to complications (see table on p. 58).

The examination is also a decisive factor in selecting the next method of therapy. In 71 percent of all cases, the physicians change their therapy concept according to the results of the cytological analysis.[28]

In 60 percent, they refrain from operation.[29]

Particularly when making a decision about the appropriate treatment of lung cancer, a cytological analysis of the mediastinum can be of great help. It can determine whether the tumor has spread to the surrounding lymph nodes.

ACCURACY MEDIASTINUM	EUS-FNAB (cytological)	Mediastinoscopy (histological)
Sensitivity	95.6 %	91.8 %
Specificity	100 %	100 %
Complication Rate	0.6 %	2.3 %

Böcking, 2005 (Review); Jolly et al., 1991; Luke et al., 1986, Kramer et al,. 2004

Body Cavities

Case study Because Arno Rieger suffered from increasing breathing difficulties, he consulted a doctor. On an X-ray picture, the doctor discovered that fluids had accumulated in Rieger's thoracic cavity – a so-called effusion, which could be a cancer indication. A year ago, a tumor was removed from the 60 year old's esophagus, and now the specialists assumed that metastases had expanded into Rieger's thoracic cavity.
The suspicious effusion was punctured: Twice the physician aspirated the excessive fluids from his thoracic cavity with a fine needle and sent them to a pathologist. A satisfactory diagnosis could be made after the pathologist examined the cells contained in the fluids: Arno Rieger's cancer did not return, instead, he had an innocent inflammation of the parietal pleura, the membrane which lines the thoracic cavity. The inflammation soon cured itself. In the following years, the specialists did not find any cancerous forms.

Application An unusual accumulation of fluids, as it was discovered in the case of Arno Rieger, can occur in each one of the body cavities. This is the name for the hollow areas in the body, in which organs such as lungs, heart, or intestines are located and which are lined with a thin membrane such as the parietal pleura. Usually, these cavities contain only a small amount of fluids in order for the organs to move about more freely.

A drastic increase of the fluidal amount is referred to as an effusion. An effusion typically causes complaints: effusions in the thoracic cavity cause breathing difficulties, heart problems can be caused by effusions in the pericardium, a swollen abdomen may find its origin in an abdominal cavity effusion.

Tumor cells are frequent causes for effusions, which inhibit the drainage of the tissue fluids from the body cavities.[30] If the physician does not instantly detect a different cause for the effusion, for example an infection, it should be examined by a pathologist for tumorous cells. In one fifth of all cases, an, up to that point, unidentified cancer is discovered.[31]

When examining by a microscope, a pathologist finds only 53.4 percent of all tumors in effusions. Nonetheless, if he uses not only DNA-image-cytometry but also immunocytochemistry (see pp. 14 & 17), he is able to increase this rate to 61 percent on average (see table on p. 60). When a cell sample has been rated "suspicious", both methods can each reach an accuracy of over 75 percent[32], the AgNOR-Analysis even reaches 97.5 percent.[33]

If no tumor cells are found in an effusion, the probability that a patient does not have cancer in the affected body cavity is 87 percent.[34] Further negative examination results increase the reliability of the diagnosis.

The cytological analysis of body cavity effusions with the help of immunocyto-

The search for tumor cells in body cavities tumors under the microscope is complemented by methods such as immunocytochemistry.

chemistry has a special purpose. It is a very useful method, even when cancer has already been diagnosed, however, the location of its primary tumor has not yet been found.

During the search for this so-called Carcinoma of Unknown Primary (CUP), the patients must often undergo numerous X-ray and ultrasound examinations as well as endoscopies. These procedures are often expensive and physically demanding. An immunocytochemical test, on the other hand, is able to detect primary carcinomas in 85.1 percent of all cases in an inexpensive and little invasive manner.[35]

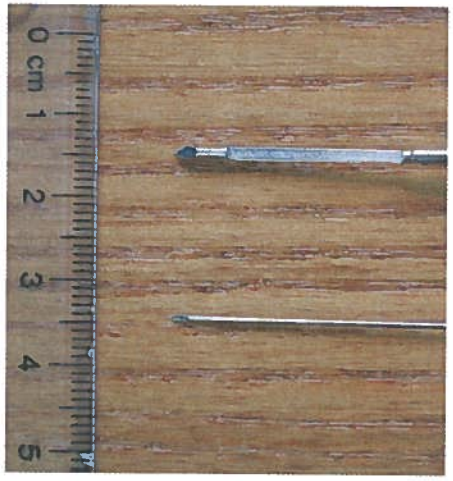
The cytological examination of effusions also plays an important role in the search for malignant tumors of the pleura, the so-called malignant mesothelioma. The AgNOR-Analysis, in particular, is able to diagnose this form of cancer early on, which is difficult to cure in an advanced stage.[36] With the help of immunocytochemistry, the malignant mesothelioma can be distinguished from other primary carcinomas with an accuracy of 97 percent.[37]

ACCURACY BODY CAVITIES	cytological (microscope)	cytological (DNA-image-cytometry and immunocytochemistry)
Sensitivity	53.4 %	61 %
Specificity	93.3 %	99 %

Motherby et al., 1999 a/b

Liver

Case study For quite some time Claudia Böhm suffered from dizziness. Apart from that, the 35 year old noticed a small node in the area of her thyroid gland. Böhm's physician examined her with ultrasound and detected a node, four by five centimeters in size, in the right lobe of the liver.



People, who frequently consume alcohol face an increased risk of liver cancer. The examination of a node with a fine needle (below right) is much less painful than a punch needle biopsy (above right).

A radiologist further examined the node in an MRI, the result indicated a so-called focal nodular hyperplasia (FNH), a harmless scaring of the liver tissue, which is occasionally caused by the taking of contraceptives. Claudia Böhm, too, had taken the pill for four years, so that the explanation seemed plausible.

However, Böhm's physician wanted to make sure that it was not a liver carcinoma and suggested a puncture under ultrasound guidance (EUS-FNAB). Some of Böhm's liver cells were extracted with an ultrasonically operated fine needle. The analysis revealed a cell pattern, which was well compatible with the FNH diagnosis – a simultaneously performed punch biopsy could not provide any evidence. Claudia Böhm was discharged from the hospital without further treatment. Half a year later, the node had demagnified and the FNH diagnosis could therefore be confirmed. The cause for Böhm's dizziness turned out to be a harmless hypofunction of the thyroid gland.

Application Ever since most general and internal medicine practices in Germany have good ultrasound equipment, physicians often detect nodes in the livers of their patients. As in the case of Claudia Böhm, these nodes could have innocent causes. Most so-called cavernous haemangioma or cysts must – just like the FNH – not necessarily undergo treatment. However, innocuous changes are often not distinguishable from serious illnesses by means of ultrasound or X-ray; cell and tissue samples from nodes of the liver should therefore be additionally examined under the microscope.

Up to now, the most common method for the extraction of liver tissue is the punch biopsy, where a 1.4 millimeter sized "Menghini-needle" is inserted. For one third of all patients, this procedure produces pain that demands treatment[38] and leads to significant bleeding in one percent of all cases.[39] A cell sample extraction with a needle half the size (fine needle aspiration) is less painful and less often associated with complications (see table on p. 62). The tumor can furthermore be hit much more precisely with a fine needle than it would be possible with a punch biopsy, even under ultrasound guidance.

The fine needle puncture of the liver surpasses even a tissue extraction in sensitivity, in regard to specificity the outcomes are slightly worse (see table). When applied by experienced physicians, both methods reached a specificity of 100 percent, in terms of sensitivity the fine needle puncture was even ahead of the punch biopsy by ten percent.[40] Cytological examinations of liver carcinomas were further improved through immunocytochemistry.

Immunocytochemistry also finds primary tumors, which have caused metastases in the liver, in 89.1 percent of all cases.[41] This makes any further diagnostic investigations of the patients unnecessary and reduces the costs for the hospitals

immensely. The fine needle aspiration-biopsy of the liver is not suited for so-called diffuse parenchymal liver diseases like hepatitis or liver cirrhosis.

ACCURACY LIVER	cytological (fine needle aspiration)	histological (punch biopsy)
Sensitivity	88.2 %	81 %
Specificity	95.8 %	100 %
Complication rate	2.6 %	5.6 %

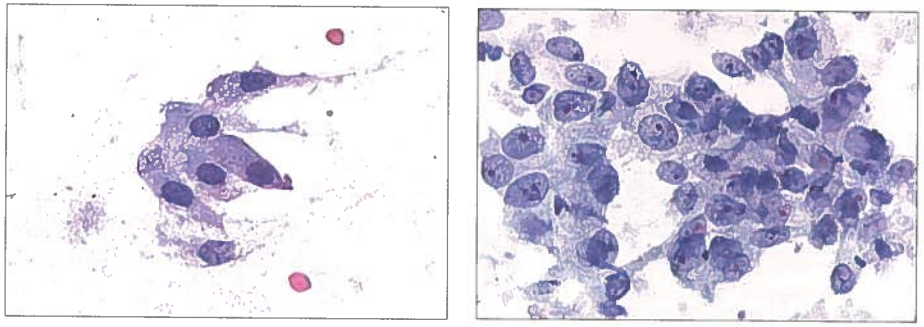
Michalik, 2006 (Review / recent numbers); Schönnenbeck, 2003

Bile Ducts

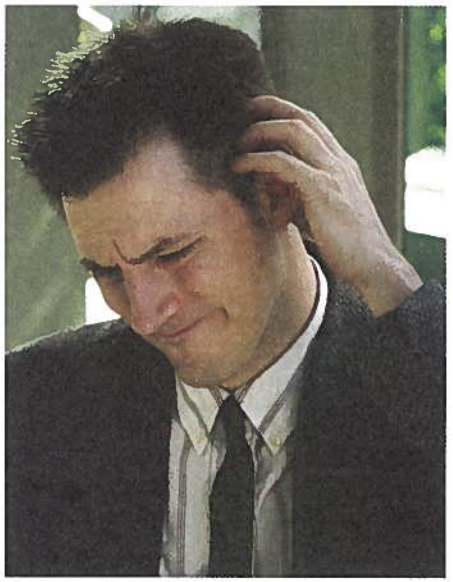
Case Study In November 2003, Johann Rust noticed that his eyes had changed their color from white to yellow. He also felt an itching throughout his entire body, his urine was a discolored brown, and his bowel movement was unusually light-colored.

The PE-teacher went to his general practitioner, who referred him to a hospital. There, the specialists discovered when doing an X-ray examination, that Rust's bile ducts were clearly enlarged. They predicted a tumor to be interfering with the drainage of the bile – the bile had apparently entered the bloodstream and caused the yellow skin color of the 52 year old. However, the suspected tumor could not be found either by ultrasound or in a computer tomography (CT). Also the tissue, which was taken in biopsies from the bile ducts, appeared to be salutary.

It was not until cell samples were taken through an endoscope, that the pathologist was able to detect cancerous evi-



Healthy and cancerous mucosa cells of the bile duct in a brush smear.



If symptoms of an icterus – such as itching – are caused by a tumor, can only be determined under the microscope: healthy mucosa cells of the bile ducts are shaped oval and lie orderly next to each other (see p. 62, left). If the nuclei are unshaped and arranged disorderly, if the numbers are increased and if many nucleoli can be found (see p. 62, right) – a tumor is the cause..

dence under the microscope. When he further examined the cell samples with DNA-image-cytometry, an abnormal alteration of Rust's DNA (aneuploidy) was discovered – the cancer suspicion was confirmed. To make sure, the pathologist analyzed a second smear, once again, it contained cancerous cells.

Six weeks later, a part of Johann Rust's bile ducts was removed. A tumor had in fact formed in the lower part. It was so small, that even the surgeon was not able to spot it with the naked eye. The pathologist confirmed under the microscope, that the tumor had been removed completely and in its earliest stage (T1). In March 2004, Johann Rust was completely cured and discharged.

Application The discoloration of the skin and the eyes into yellow, can indicate an increased bile coloring in the blood, a so-called icterus. This can be, as in the case of Johann Rust, caused by a tumor in the bile ducts. However, the cause could also be gallstones or an inflammation of the bile ducts.

The diverse diseases can, nevertheless, not simply be distinguished by the analysis of an X-ray picture. Yet, a prophylactic operation is in turn unnecessary if the bile ducts are just infected.

A narrowing of the bile ducts should therefore first be examined under the microscope

on tissue and cell samples. An extraction of the cells with a smear is not connected with any complications[42], apart from that, the sensitivity rate of its examination is about 10 percent higher than with the histological analysis of tissue samples (see table on p. 64). In cell samples the pathologist is able to detect cancer especially well with the help of DNA-image-cytometry – the cancer might have formed from a chronic inflammation of the bile ducts (sclerosing cholangitis)[43]. A cytological examination of the bile ducts might therefore be more precise than a histological analysis. Most precise is a combination of both procedures, its accuracy rate is 64 percent.[44]

ACCURACY BILE DUCTS	cytological	histological
Sensitivity	53 %	43 %
Specificity	100 %	100 %

Elek et al., 2005

Pancreas

Case study In April 2005, Henning Reuter suffered from an acute pancreas infection. Because he had suffered from chronic abdominal pains for a year, his general practitioner referred him to a hospital.

The specialists there did not uncover any indications for a tumor. Neither were they able to do so by computer tomography nor by MRI with contrast agents. Through an ultrasound examination, a node was eventually detected in the outer part of the pancreas. Reuter was advised to get the node examined, when he would get the opportunity.

When the 75 year old suffered strong abdominal pains again in September, he went back into treatment. This time, the physicians found a tumor in the outer part of the pancreas. Cell samples were immediately taken with a fine needle puncture. The result of the cytological analysis with help of immunocytochemistry: it appeared to be a benign, so-called neuroendocrine tumor. One month later, Reuter underwent surgery. The surgeons removed the outer part of the pancreas including a two centimeter large tumor, the rest of the vital organ could be saved. The histological examination of the tumor later proved that it had been benign. No metastases were found in either the lymph nodes or any other organs. Henning Reuter recovered completely and two weeks later, he was discharged from the hospital. His pancreas did not need to be removed.

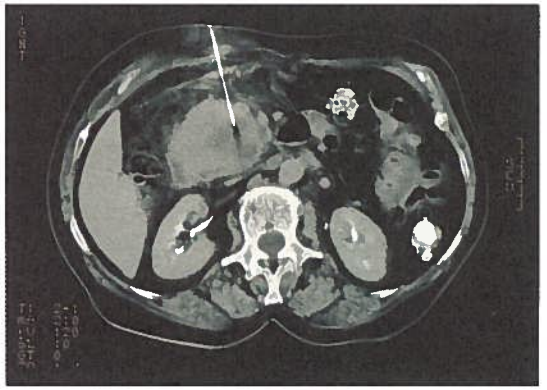
Application Regarding suspicious changes of the pancreas, doctors are often facing a dilemma: The organ, which is located in the upper part of the abdomen and is difficult to reach, is able to produce malignant tumors that need to be operated in time. However, if the pancreas gets partially removed for prophylactic reason in a so-called Whipple operation, it can lead to major complications in 28 percent of all cases.[45] The pancreas is very sensitive and easily reacts to medical interventions with a dangerous infection and possibly self-digesting (pancreatitis).

Complaints of the pancreas can also be provoked by harmless cysts, infections (e.g. sarcoidosis), or scar forming – an operation in these cases is not necessary. However, it can also be caused by a benign or less malignant tumor, as in Henning Reuter's case. In such cases, the removal of the affected part of the pancreas is sufficient.

Since a specialist is not able to distinguish diseases such as pancreatitis from cancer by means of ultrasound or X-ray, a search for a possible tumor with a cytological exam should always precede an operation. To do so, the pancreas gets punctured either from the outside through the skin, or better under ultrasound-guidance (EUS-FNAB) from inside the duodenum. The EUS-FNAB method is especially precise[46], in contrast to the puncture from the outside, the risk of tumor cells reaching the abdominal area is not given.

The disadvantage of the EUS-FNAB method is its low sensitivity of only 61.6 percent on average (see table on p. 66). Even special clinics can thus far only reach a sensitivity of 82.1 percent – therefore, about one fifth of all tumors remain undetected.[47]

Nevertheless, the fine-needle puncture of the pancreas is advisable. If it confirms the cancer suspicion, an operation can be started fast and without further examinations. With certain types of cancer and with elderly people, it can also lead to the decision of treating the tumor with chemotherapy instead of an operation.



This X-ray of a fine-needle puncture of the pancreas was taken by computer tomography.

ACCURACY	cytological
PANCREAS	(EUS-FNAB)
Sensitivity	61.6 %
Specificity	79.2 %
Complication rate	0 %

Vemuganti et al., 2004, 45 cases

Urinary Bladder

Case study Paul Willke had reason to be especially careful: Ever since he had suffered from renal infections in this youth, small amounts of blood could often be found in his urine. This increased, however, when he had surgery for a benign enlargement of his prostate. Willke knew that blood in the urine could be an indication of urinary cancer. He therefore had his urine cytologically examined regularly – for many years, no tumor cells were found.

In February 2006, Willke again discovered blood in his urine over several days. He personally brought his urine sample to a cytological institute. After four hours, he received a phone call and was told the assuasive result: The pathologist again found no tumorous cells.

To clarify the actual cause of the blood in this urine, a urologist examined Willke a couple days later by cystoscopy. It confirmed the cytological diagnosis that there was no cancer in the urinary bladder. The urologist instead discovered that the blood came from the old wound of Willkes prostate operation.

Complaints or pain when urinating and blood in the urine can be possible indications of a tumor in the urinary bladder.

The cytological exam once again ruled out a cancer suspicion as it had done many times within the last 20 years and it had once again taken away Paul Willke's fear of a cancer diagnosis.

Application If blood is discovered in the urine over a longer period of time, as in Paul Willke's case, or if urinating itself causes pain, an examination is very advisable – the cause could be urinary cancer, or urethral cancer, or cancer of the renal pelvis. In Germany 26,000 people are diagnosed with urinary cancer every year affecting mostly men and senior citizens.[48] The chances of recovery have significantly increased since the 1970's which is attributed to, the detection and removal of earlier forms of the tumor which also holds true for most other types of cancer.

Smoking is one of the main causes for urinary cancer. Patients, who have taken high dosages of the pain medication Phenacetin, also belong to the risk group. Amongst workers in aniline dye or aromatic nitro and amine- compounds production, urinary carcinoma is regarded as an occupational disease. The responsible professional association (employers' liability insurance association) requires frequent cytological examinations of the urine. These are the only possibilities to inspect cancer suspicions of the urinary bladder without undergoing surgery.

Fresh urine[49] is centrifuged for the examination. Through this method, cells are sedimented and are then investigated by the pathologist under the microscope after they are stained. With this method, the pathologist is able to uncover about three fourths of all urinary bladder carcinomas. The accuracy of the urine-cytology is increased by ten percent, if three urine samples are examined instead of just one.[50]

The accuracy improves in a similar fashion, if suspicious cells of the urinary bladder mucosa are further tested with DNA-image-cytometry in regard to the content of substance. The in situ-hybridization (FISH) also provides satisfying results[51], especially when only a few cell samples are available (see table below). 94 percent of urinary bladder carcinomas can be discovered in an immunocytochemical test, yet one fifth of all positive findings later turn out to be wrong.[52]

Despite its overall high accuracy and its numerous application possibilities, urinary cytology does have one known flaw: the pathologist is only able to detect low malignant tumors of the urinary bladder (grade 1) under the microscope in 37.5 percent of all cases.[53] However, because these tumors reach into the urinary bladder like a tree, they can be easily discovered by cystoscopy. A suspicion of urinary bladder cancer should therefore always be investigated with a combination of both urine-cytology and cystoscopy.

ACCURACY URINARY BLADDER	cytologically	cytologically (DNA cytometry)	cytologically (FISH)
Sensitivity	76.4 %	87 %	81 %
Specificity	93.5 %	100 %	96 %

Jochims, 2002; Planz et al., 2000

Case study About 14 years ago, a urologist discovered – by means of punch biopsy – a carcinoma in Gerhard Ludwig's prostate. He advised the 68 year old to a so-called prostatectomy – the complete surgical removal of the prostate. Because Ludwig used to work in a clinic himself, he knew that the consequences of this operation might be impotence and incontinence.

Ludwig, therefore, decided to get his cell samples examined by means of DNA-image-cytometry in two different institutes. Both institutes diagnosed a less malignant tumor with a low rate of proliferation. Ludwig had a "clinically insignificant carcinoma" – a "dormant cancer", which required supervision but no surgery. Due to this diagnosis, Ludwig decided not to undergo surgery despite the vehement advice of his urologist. He instead gets his prostate examined once every year with a fine needle aspiration-biopsy and DNA-image-cytometry. Thus far, either no tumor cells at all were found or only some that had an almost normal DNA-distribution. Ludwig says that he feels "completely free of complaints". He has told neither his wife nor his children about his "dormant cancer" up to this day.

Application Prostate cancer is not an exception amongst older men, but rather a regularity: more than 50 percent of all 70 year olds and more than 90 percent of 80 year olds have a prostate carcinoma. In the year 2000 in Germany alone, there were approximately 40,000 new diagnoses of this type of cancer.[54]

According to a statistic, only about ten percent of the affected actually die from the tumor.[55] Most prostate carcinomas, as in the case of Gerhard Ludwig, are less malignant and grow very slowly. Older men, in particular, must not necessarily undergo radiotherapy or hormone treatment. An operation, such as the prostatectomy, is also not necessary. Prostatectomies often lead to impotence and incontinence. A precise classification of the prostate carcinoma can hence preserve the quality of life for the affected men.

Today, a common method of testing for prostate cancer is the PSA-Test, in which the specialists search the patient's blood for the so-called prostate specific antigene (PSA). This test is reasonable, yet it gives many false-positive results. The PSA-value can be influenced through biking, sexual intercourse, or an inflammation of the prostate in such a way that it falsely indicates cancer.[56]

A combination of the PSA-Test and a prostate tissue or cell sample examination, are therefore most recommendable. The aspiration of cell samples with usually two fine-needle punctures is much more gentle, and it causes complications in less than one percent of the time. In the extraction of tissue samples, for which six to twelve punch biopsies are of necessity, complications occur

The quality of life of older men can be preserved by avoiding an operation of the prostate.

in one fifth of the cases (see table below). Pain, which requires treatment, occurs in even more than 60 percent of the time.[57]

The slightly higher accuracy rate of histological examinations, gives the edge to the extraction of a tissue sample from the prostate (see table). Since fine-needle punctures are increasingly guided by ultrasound, this difference will likely decrease. The clearly less painful and less complicated extraction of cell samples is an argument for cytology. It should encourage affected men to get suspicious PSA-values examined without hesitation.[58]

Although pathologists are able to detect prostate carcinomas under the microscope, they are not able to characterize their malignancy well enough to specify the needed therapy. The cells should therefore also be analyzed by DNA-image-cytometry, such as in the case of Gerhard Ludwig. With the analysis of possible changes of the amount of DNA, the pathologist is able to give a recommendation about whether a prostate carcinoma should be surgically removed, radiated, undergo a hormone treatment[59], or even just be monitored regularly.[60]

ACCURACY PROSTATE	cytological (fine-needle aspiration)	histological (punch biopsy)
Sensitivity	86 %	89.3 %
Specificity	96.6 %	98.7 %
Complication rate	0.9 %	19.8 %

Böcking, 1998b (Review); Miller et al., 2005; Epstein et al., 1996

Lymph Nodes

Case study In May 2003, the nodes on Torben Aigner's throat already had the size of pigeon eggs. The 34 year old computer specialist had watched the swellings grow for a year, now he consulted an otolaryngologistic clinic. Aigner was afraid, that the cause of his nodes was cancer.

The ultrasound examination revealed a hollow cavity behind the nodes, which was filled with a fluid. The physician extracted some of the fluid with a fine needle and a pathologist examined the contained cells. On the same day, the pathologist was able to give the all-clear: Aigner merely suffered from a "lateral cervical cyst" – a harmless, liquid-filled bubble, which sometimes develops from the remainders of bronchial clefts of embryos.

A surgeon removed the cyst on the following day. This was only a minor operation, because the surgeon already knew that it was not a tumor – Torben Aigner just needed local anesthesia. On the day after operation, the histological analysis of the removed cyst confirmed the diagnosis. Torben Aigner was completely cured and discharged after five days.

Application Torben Aigner's fear was reasonable despite the harmless outcome: Swellings in the throat or above the clavicula, in the axillary, in the chest or abnominal region, as well as in the groin can be indicators for lymph node cancer. These organs have roughly the same size as peas or beans, they contain different types of immune cells (lymphocytes) and play an important role in fighting infections.

If a few of the overall more than thousand lymph nodes starts swelling, it might only be provoked by a harmless infection (lymphadenitis). The swelling can also be caused by a tumor (malignant lymphoma), which originated in the lymph node, or by cancer in different organs, which has spread to the lymph nodes.

Tool for the fine-needle puncture of lymph nodes in the bronchial area.

Especially slim people are able to feel certain lymph nodes through their skin. Changes of lymph nodes that lay deeper in the chest and abdominal region, are only visible on X-ray or ultrasound. If the lymph nodes remain swollen over several weeks, and a doctor is not able to diagnose an inflammation, then the cause should be determined by a microscopic analysis.

If the suspicious lymph nodes are located directly underneath the skin, they will sometimes be removed in a minor operation. The subsequent histological analysis is said to be particularly precise.[61]

However, a cytological test, for which a physician extracts cell samples with a fine-needle, is gentle and completely uncomplicated. 97 percent of cancerous lymph nodes are detected through this procedure (see the table below), the sensitivity rate is just three percent below that of a histological examination. Patients should take part in deciding whether they are willing to take the risk of a lower accuracy rate in order to avoid the circumstances and possible complications involved with a tissue extraction.

Even for lymphatic nodes that are located deeper in the chest or abdominal area, the accuracy rate of cytopathology is very high (see table). In this case, cell samples are extracted with an ultrasound controlled fine-needle puncture (EUS-FNAB). More complex operations are needed for histological tissue analyses of deeper located lymph nodes – e.g. a mediastinoscopy for the extraction of lymph nodes of the mediastinum. This intervention through a cut in the throat leads much more often to complications than a fine needle puncture (see chapter on mediastinum).

Swollen lymph nodes should always be analyzed through cell examinations before an operation, because the accuracy rate of the cytological analysis in the chest and abdominal region is almost optimal (see table).

Even if physicians detect a metastasis within the lymph nodes, cytopathology can still be helpful. In these cases, specialists thus far tried to find the primary tumor with the help of numerous X-ray examinations and endoscopies. These tedious and expensive procedures are replaced today by cytological analysis with the assistance of immunocytochemistry (see p. 17): According to a study, this method finds a so far unknown primary tumor in 80 percent of all cases.[62]

ACCURACY LYMPH NODES	cytological (fine-needle puncture)	cytological (EUS-FNAB)
Sensitivity	97 %	98.3 %
Specificity	99.4 %	100 %
Complication rate	0 %	0 %

Prasad et al., 1996 (Fine-needle puncture of lymph nodes located underneath the skin); Chen et al., 2004 (EUS-FNAB of lymph nodes in thorax and abdomen)

7. Monitoring Therapeutic Effects

Cytopathology not only helps in detecting cancer at an early stage, it also enables one to monitor the treatment administered: With the help of the cell samples, physicians can ensure the effectiveness of particular therapies. After a cancer has been cured successfully, cytological follow-up analyses also allow new outbreaks to be detected in time.

Monitoring of Therapeutic Success

Case study Martin Luckow had suffered from recurrent urinary tract infections when in autumn 2003 blood was detected in his urine. An urologist at a University Clinic took eight tissue biopsies from his urinary bladder, the pathologist revealed a highly malignant carcinoma at an early stage.

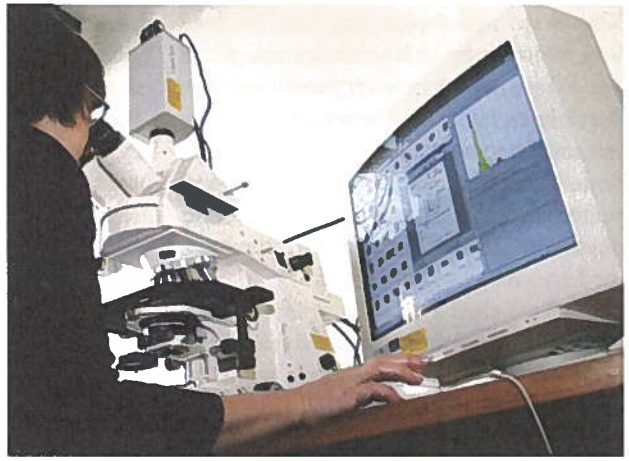
His physicians decided to cure the carcinoma with a so-called BCG treatment – an artificially-induced tuberculosis, which strengthens the immune system of the urinary bladder. In the meantime, Luckow had heard about the possibility of cytopathological analyses from a friend. The 72-year-old then decided to have his urine examined by DNA-image-cytometry in parallel to his treatment with BCG.

The analysis of cells contained in the urine proved that the tumor in Luckow's bladder was declining and eventually disappeared completely. As a back-up, additional tissue samples were taken. Their analysis confirmed the "unbloody" results of cytopathology each time. About two years after initiation of the treatment, Luckow is completely free from complaints. When looking back, the only thing he regrets is that he did not profit from the cytopathological methods earlier.

Application Not every malignant tumor must be surgically removed. In certain cases, it is more reasonable to fight cancer cells with chemo- or radiotherapy or, as in the case of Martin Luckow, with immunological therapies, which strengthen defenses of the body against cancer.

However, not all tumorous cells react in the same manner to these treatments. For example, radiotherapy initially destroys fast-dividing particularly malignant cells of a prostate carcinoma while the less malignant, less quickly dividing cells stay alive longer – the tumor decreases in malignancy (see p. 34).

A physician is able to clarify how well a tumor is responding to a treatment with the help of cytopathology: To do so, he or she extracts cell samples from the affected body region with a smear, a puncture, or directly from body fluids.



A workplace for DNA-image-cytometry. During the course of cancer therapy, it can be evaluated how well the tumor is responding to the treatment.

If the pathologist finds many damaged or even dead tumor cells under the microscope, it is an indication that the treatment is successful. If the number of tumorous cells in the sample is reduced, it is assumed that the treatment brought an improvement of the disease state. The monitoring of the therapy by analyzing extracted cell samples is referred to as regression grading.

Regression grading is especially useful for prostate carcinoma (see p. 68).[1] Well approved is its application in the management of urinary bladder carcinoma, such as in the case of Martin Luckow. In general, regression grading is possible for all types of cancer, however, there are often not enough studies to prove its reliability with regard to a given form of cancer.

Cervical lesions provide another instance of a possible use of cytopathologic methods in the monitoring of therapeutic effects. A pathologist is able to periodically search for nucleic acids of HPV-viruses using the polymerase-chain-reaction (see p. 17), which could be an indication for a renewal of the disease (see p. 43)[2].

Follow Up

Case study When Hannes Verhoeven took a look into the mirror in November 1997, the 76-year-old man detected a small white node on the surface of his right eye. A cell sample was taken by swabbing of the suspicious spot. When analyzing the cell sample, the pathologist found indications of cancerous cells. Shortly after,

Verhoeven underwent surgery. The doctors removed an in situ carcinoma of the eye lid – a tumor in a very early and not yet dangerous stage. However, under the microscope, the pathologist was not able to determine whether the tumor had been removed completely. To make sure, the doctors took monthly swabs of the operated area using a small brush.

After the cell sampling had provided negative results — no indication of any cancerous activity, that is – seven times in a row, the pathologist discovered suspicious cells again in a swab taken in October of 1998. Image cytometry was used to measure the DNA content of the sample which confirmed, that the cells were indeed malignant. The tumor had returned, one year after the initial operation.

Verhoeven had to undergo surgery again, the carcinoma was again in its earliest stage. After the operation, the physicians further monitored the eye with regular brush swabs, however, the cancer did not return in the following years.

Application Sometimes a tumor disappears during treatment but reappears after months or even years in the same spot. The earlier a so-called recidive is discovered, the more likely is its successful cure. The same thing holds true for metastases, which have spread from an already treated tumor to other organs or lymph nodes. This is why the doctors should best know about the reappearing cancer before it is visible with the naked eye or becomes painful.

Such an early search for reappearing tumors – the follow-up or surveillance – is made possible by cytology.[3]

In certain body regions, there is no alternative to having an intensive follow-up. In the case of Hannes Vorhoeven, it would not have been possible to extract another tissue sample from the very sensitive eye lid. Without cytopathology, the reoccurrence of the tumour would probably not have been discovered until it had reached an incurable stage.

The cytological surveillance is especially useful and effective for the eye, oral mucosa, and the uterus' cervical mucosa. An examination of enlarged lymph nodes or suspicious changes in other organs is also possible. If first indications for a reoccurence of the tumor become evident, the doctor can immediately begin the new therapy. Tissue extraction through "bloody" incision biopsies can be avoided. In follow-up examinations, a suspicion of recurrent cancer does not hold true in most cases. After a prostate operation, it sometimes occurs that small nodes and recidives grow, however, they are nothing more than re-growing remainders of the removed organs. Ultrasound-guided fine-needle puncture is usually sufficient to decide whether an operation or radiotherapy is necessary.

Cytological follow-ups are also very useful, if the patient suffers from headaches after a cancer operation. An analysis of liquor cells can then determine whether the cancer was able to spread to the brain as in the case of cerebral metastases. Using this method, the pathologist is also able to uncover a possible inflammation of the membranes surrounding the brain, also known as meningitis.

A physician is able to monitor cancer, even after it has been successfully cured, with regular cytological follow-up exams.

8. Benefiting from Cytopathology

Contact Persons

There are various reasons to become better informed about examinations performed with cytopathology. Some of the people who have previously been interested have already been diagnosed with cancer, others have made a suspicious discovery themselves, belong to a risk group or just want to go to a preventive medical checkup.

In any case, it is initially important to clarify if cytopathology can be applied in the affected body region and if it is reasonable. The chapters 5 to 7 of this book provide more information about that. Subsequently, the patients should discuss the desired examination with their general practitioner or the doctor that is currently treating them. If a specific body region, such as the eye, the lungs or the genitalia, is affected, then the medical specialists – ophthalmologists, specialists for lungs, otorhinolaryngologists, urologists or gynecologists – should be consulted.

If the doctor thinks a cytological diagnostic investigation is reasonable, he will discuss the appropriate removal of cells with the patient. In some cases, for instance with mucous membrane swabs or the puncture of surface area nodes, the removal of cells is possible right away. A separate appointment needs to be arranged for more complex procedures, such as an endoscopy, and the patient will possibly be referred to a specialist.

If a doctor advises not to work with cytopathological examinations, he will, for the most part, have plausible reasons. Many of these reasons are also described in this book (for example on p. 24). However, there is a range of reservation which can be invalidated – they are discussed in the box below.

Patients should discuss if a cytological examination is possible with their general practitioner or the doctor that is currently treating them.

If doctors want to gain a better understanding about the uncommon cytological examination methods, they can find sources of information in chapters 9 and 10, or they can get directly in touch with a cytopathologist.

If a doctor refuses a cytological examination for reasons that are not comprehensible, patients should not be afraid to get a second opinion from a different specialist.

Frequent Arguments against Cytopathology

The examination of cells is, in principle, inferior to the examination of tissues.

This argument is wrong and is not the case, particularly when other methods such as DNA-image-cytometry, In situ-hybridization, or immunochemistry are applied in addition to the microscopic assessment. The first two methods are actually cytologically superiorly applicable because the examined cells are not truncated, as in histological sections. If the cytological results are worse than the histological ones, it could be due to unprofessional withdrawal and treatment.

A diagnosis made with cells can never be as accurate as one made with tissue.

This is true, but it does not disagree with the concept of cytopathology. In fact, most tumors cannot be conclusively typed until after they have been surgically removed. The cytological diagnosis often contributes to the decision of performing surgery beforehand. The tumor does not have to be classified in detail. It is more important to determine whether surgery or radiation is necessary. The doctor and the pathologist must decide together if this decision can be made using the cytological results.

Few cells are not sufficient for a reliable diagnosis.

This is not true. The removal of cells per swab is usually more extensive and thus more representative than the removal of tissue in biopsies. Cells can be extracted from multiple areas at the same time without any difficulty. For biopsies, it is quite complex and a strain for patients. The number of extracted cells is only rarely a problem. In such cases, cytological supplementary methods such

In a procedure called "micro manipulation", single cells are released using a needle (left) and then sucked into a cannula (right) for an analysis with the Polymerase-Chain-Reaction. The analysis of the obtained DNA contributes to a reliable diagnosis.

as immunocytochemistry, nevertheless, frequently enable a diagnosis.

There is no reason to believe a negative cytological diagnosis.

This is only applicable when the cell sample was insufficient. In this case, either the cell extraction must be repeated or, instead, tissue must be removed. If the technically inadequate samples are not included, the negative predictive value of cytological diagnostics is very high. Negative cytological diagnoses should be confirmed by other examination methods, too.

The extraction of cells in mucous membranes disregards deeper layers.

This case only applies to the mucous membranes of the stomach and the intestines, which are not used in cytopathological examinations anyway. In the mucous membranes of the eyes, mouth, bronchi, esophagus, and genitalia, the cells of the deepest layer (parabasal cells) migrate to the surface within one week. Thus, surface cells are representative of the deeper layers as well.

When puncturing, cancer, cancerous cells can spread through the body.

Provided that this risk even exists, it is very small. There are no reliable studies about the emergence of metastases due to punctures; only sporadic cases have been reported. The rate, for example in lung cancer, is 0.08 percent.[1] Due to the fact that a diagnosis normally results in treatment of the cancer, a metastasis will either be removed or treated as well. Some organs in the visceral cavity are exceptions. When puncturing pleural tumors, the stitching channel is irradiated. Tumors in the kidneys and ovaries are not punctured, because there is in fact a risk of passing them on into the visceral cavity. By the way, theoretically the risk exists in biopsies, too, but it is not known to be increased either.

If cytopathology really is that good, it should be more common.

The lacking spread of cytopathology is particularly associated with the fact that, until quite recently in Germany, it was less compensated and simultaneously much more time-consuming than examinations of tissue (see p. 81). In addition, the situation for the training of cytological staff is bad (see p. 23) and the lack of its publicity among many doctors is not an advantage either. However, internationally, cytopathology has been an established scientific method, for a long time.

Expenses

Expenses for Patients

Normally, no additional costs will arise for patients through cytological examinations. In principle, both panel patients and private patients are entitled to all

The paying office at the University Hospital in Düsseldorf: Patients normally do not have to pay extra fees for obtaining cytopathological diagnoses.

cytological methods which are listed in the tariffs for doctors. Currently, every microscopic examination of cells, as well as, if necessary, analyses performed with the help of DNA-image-cytometry, immunocytochemistry, in situ-hybridization, or Polymerase-Chain-Reaction are included.

The most important condition for the costs to be covered by the insurance is that a doctor decides the examination is necessary and passes on the appropriate assignment to a pathologist. If patients desire cytological examinations that no doctor has recommended, they will have to pay for them themselves.

An up to date table of costs for cytological examinations and the comparison to histological examinations can be found at www.sanfte-krebsdiagnostik.de.

Expenses for the Health Care System

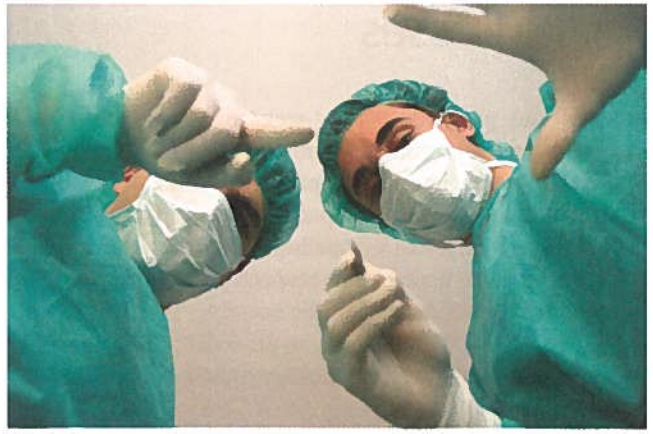
Concerning the costs of cytopathology for the general public, there are good news and bad news. The good news: In a health care system with increasingly scarce funds, cytopathology can help save costs. The extraction of cells usually does not require much more than a little plastic brush, while the extraction of tissue creates costs for anesthetics, sewing material and follow-up examinations.

As it is explained in this book, in many cases, doctors can do without complex procedures or operations after a cytological examination. Due to the fact that medical efforts are increasingly compensated for the diagnoses, the avoidance of unnecessary treatment measures is an advantage for clinics, too.

The bad news is that so far there is not much appeal to health professionals for applying cytopathology. Examinations with biopsies or prophylactic operations have been in conventional use for a long time, thus also more familiar to doctors and also more lucrative than cell extractions, for which they just receive 3.66 Euros.[2] Although the comparatively "unspectacular" analysis of cells achieves, to some extent, better results than a surgical procedure, it is neither well known among the public, nor among health professionals.

But up to now, even pathologists did not have many reasons to stand up for a greater application of cytological methods. Until 2005, the examination of cells was compensated far worse than the examination of tissue, according to the tariffs of panel doctors. That is why it is not a surprise that so far only few pathologists are specialised in cytopathology in Germany.

Since 2005, health insurances are paying the same amount for cytological procedures as for histological ones. However, the compenzation for the analyses of cells as well



Cytological diagnoses, without unnecessary surgery, is good not only for a patient, but also saves considerable costs for the health system.

as tissues is just 5.05 Euros. This amount is not only very small in consideration of the partly complex examination methods, it is also not very profitable for cytopathology either. The examination of a cell sample using a microscope is normally much more time-consuming than the examination of tissue. This is due to the fact that several smears need to be analyzed when examining cells. Furthermore, additional expertise is required for the evaluation.

Therefore, pathologists spend more time working on a cytological diagnosis without receiving more money for doing so. Because the health insurances have fixed budgets for such examinations, a higher number of examined cell samples will not be accordingly compensated. A good example for better compensations leading to an increased application of cytopathology is shown in the case of oral mucosa. Since dentists are receiving 15 Euros for swabs according to the tariffs, the number of examined cell samples from the mouth has increased in Germany.[3] Thus, a method which can discover cancer more gently and with less effort than tissue extraction is circulating. This is beneficial for the health care system as well as for patients.

As shown in the table below, other countries already reward cytological examinations in a much better way.

COMPENSATION OF CYTOLOGICAL DIAGNOSTICS	Germany	Austria	Switzerland
Cervical swab	6.60 €	10.90 €	13.25 €
Fine needle puncture	5.05 €	37.57 €	93.10 €
Urine	3.55 €	37.57 €	73.75 €

9. Addresses

Patients and physicians who seek further information or intent to make use of cytopathology have two options: either they directly ask a local pathologist, who regularly performs cytopathological analyses or they contact the respective international or national scientific society for cytology. Departments of cytopathology are often integral parts of academic institutes of pathology. Mostly the family doctor or the treating physician knows qualified cytopathologists or clinicians in the respective country.

American Society of Cytopathology (ASC)
www.cytopathology.org

Bundesverband Deutscher Pathologen (BDP)
www.bv-pathologie.de

Deutsche Gesellschaft für Pathologie (DGP)
www.dgp-berlin.de

Canadian Society of Cytopathology (CSC)
http://cap-acp.org/cytology.cfm

Deutsche Gesellschaft für Zytologie (DGZ)
www.zytologie.org

Diagnostic DNA-Image-Cytometry: Website
www.cytopathologie-DNA-ICM.uni-duesseldorf.de

European Federation of Cytology Societies (EFCS)
www.efcs.eu

Institute of Cytopathology, Heinrich-Heine-University Düsseldorf, Germany
www.sanfte-krebsdiagnostik.de

International Academy of Cytology (IAC)
www.cytology-iac.org

International Academy of Pathology (IAP)
http://iaphomepage.org

Papanicolaou Society of Cytopathology (PSC)
www.papsociety.org

10. Footnotes

Footnotes

Chapter 1

1. You can find more information about the job of a pathologist at www.bv-pathologie.de
2. Müller, 1838.
3. Papanicolaou, 1928.
4. Böcking et al., 1984; Böcking, 1995; Böcking and Nguyen, 2004.
5. Böcking et al., 1985, 1986 ; Auffermann and Böcking, 1985; Remmerbach et al., 2003, 2004; Maraki et al., 2005a/b.
6. See several consensus reports of the European Society for Analytical Cellular Pathology (ESACP); Böcking et al., 1995.
7. The workstation displayed here, was developed by Motic, Xiamen, P. R. China in cooperation with the Institute of Imaging and Computer Vision, RWTH Aachen University and the Institute of Cytopathology, Heinrich-Heine-University, Düsseldorf, Germany
8. Schiemann et al., 2005.
9. The workstation displayed here was developed together by the Institute of Imaging and Computer Vision, RWTH Aachen University and the Institute for Cytopathology of the University of Düsseldorf.
10. Carpi et al., 1994 ; Regezi and Sciubba, 1993.
11. Schönnenbeck, 2003.
12. Schönnenbeck, 2003.

Chapter 2

1. The abbreviation stands for fine needle aspiration biopsy. However, because of the very fine needle, the aspiration can not be compared to a tissue-biopsy.
2. Davey et al., 2006.
3. Capri et al., 1996; Regezi and Sciubba, 1993; Schmidt and Tötsch, 2006.

Chapter 3

1. Böcking et al., 1985, 1986, 1998 ; Böcking and Nguyen 2004 ; Auffermann and

Böcking, 1985; Remmerbach et al., 2003; Maraki et al., 2005b.
2. Remmerbach et al., 2001, 2003 ; Maraki et al., 2005a.
3. Böcking et al., 1984 ; Haroske et al., 2001.
4. Tribukait, 1993; Böcking, 1996; Holmberg et al., 2002.

Chapter 4

1. See Chapter 9 for contact persons that can help when searching for a qualified pathologist.

Chapter 5

1. Rathert and Roth, 1995.
2. Remmerbach et al., 2004.
3. The names of the patients were changed in all case studies.
4. Soost and Baur, 1990.
5. Because the cells showed an abnormally high concentration of DNA; compare Grote et al., 2004.
6. Siebert et al., 2006.
7. The negative predictive value is 99.7%; see Petry et al., 2003.
8. Beckmann, 2004.
9. Koch, 2004.
10. Nanda et al., 2000.
11. Cuzik et al., 2003.
12. Davey et al., 2006 ; Hussein et al., 2005.
13. Dreyer et al., 1997.
14. Mountain, 1997.
15. Henschke et al., 2001.
16. Brenner, 2004.
17. Henschke et al., 2001.
18. Schmiemann et al., 2005.
19. Xing et al., 2005.
20. Schmiemann et al., 2005.

Chapter 6

1. Due to the very spicy cuisine in the Chinese province of Henan, cancer or the esophagus is a regular diagnosis in this region. The cytological diagnosis in surveys reaches a sensitivity of 44% and specificity of 99%. Wang et al., 1997; Roth et al., 1997.
2. Suspicious areas on the mucosa of the larynx can be inspected with brush swabs that have a sensitivity of 93.3% and a specificity of 100%. Malamou-Mitsi et al., 1997.
3. For the identification of the so-called gastrointestinal stroma tumors a sensitivity and specificity of 100% can be reached through a combination with immunocytochemistry. Ando et al., 2002.
4. Despite the little experience in adrenal gland punctures does the sensitivity reach 100%, the specificity 98.1%. Fassina et al., 2000.
5. Vemuganti et al., 2004; Nadjari et al., 1999; Kallen et al., 2003.
6. Kallen et al., 2003 ; Donner, 2006 ; Vemuganti et al., 2004.
7. Donner, 2006.
8. There are 5,100 new cases each year according to Schön et al., 1995.
9. Shafer et al., 2005.
10. Remmerbach, 2006.
11. Remmerbach et al., 2003 ; Maraki et al., 2005b.
12. Eveson et al., 2005.
13. Wan et al., 2004
14. Stennert and Jungehülsing, 2001.
15. Stennert and Jungehülsing, 2001; Atula et al., 1996; Postema et al., 2004.
16. Reiners et al., 2004.
17. Pfannenstiel, 1993.
18. Schmid and Tötsch, 2006.
19. Carpi et al., 1996.
20. Carpi et al., 1996.
21. Solomon et al., 1982 ; Röher et al., 1987.
22. Dietlein et al., 1999.
23. Association of epidemiological cancer registers in Germany, 2006.
24. Schönnenbeck, 2003.
25. Kato et al., 1983.
26. The sensitivity of computer tomography of the mediastinum lies at 70.6%, the specificity at 86.3%. Jolli et al,1991; Chen et al., 2004.
27. Information provided by Prof. Romuald Joachim Adamek, chief physician for internal medicine at St. Vinzenz in Düsseldorf and DRG-Catalogue, 2005.
28. Annema et al., 2004.

29. Kramer et al., 2004.
30. Followed by infections (22%) and cardiac insufficiencies (12%). Bedrossian, 1994.
31. Motherby et al., 1999a; Spriggs and Boddington, 1989.
32. DNA image-cytometry reaches 77.8%, immunocytochemistry 76.1%. Motherby et al., 1999a.
33. Pomjanski et al., 2001.
34. Motherby et al., 1999b.
35. Pomjanski et al., 2005.
36. Pomjanski et al., 2001.
37. Pomjanski et al., 2006.
38. 31.4 percent ; Tan et al., 2005.
39. McGill, 1990.
40. Fine needle puncture : 90.4%, punch-biopsy 79.5% ; Schönnenbeck, 2003.
41. Onofre, 2006 ; 55 cases.
42. The complication rate of cell aspirations is 0%, no percentages were available for the complication rate of tissue aspirations. Rösch et al., 2004.
43. Osterheld et al., 2005.
44. Elek et al., 2005.
45. Hoshal et al., 2004.
46. The overall accuracy rate improves by 27% as opposed to a fine-needle puncture without ultrasound guidance. Ardengh et al., 2004.
47. Ryozawa et al., 2005.
48. Association of epidemiological cancer registers in Germany, 2006; Numbers for 2002.
49. Morning urine is inapt, because most cells have already dissolved.
50. Jochims, 2002.
51. Dalquen et al., 2002.
52. Planz et al., 2001.
53. Jochims, 2002.
54. Association of epidemiological cancer registers in Germany, 2006.
55. National Cancer Institute, 2006.
56. Bundesverband Prostatakrebs Selbsthilfe, 2004.
57. Up to 63.6% according to Rodriguez and Terris, 1998.
58. See GEK-Brochure : « Prostate cancer, Diagnosis and Prognosis », by A. Böcking and W. Samsel, 2005.
59. A certain prostate carcinoma may even, under special circumstances, become more malignant "hormone deaf" (Tribukait, 1993). DNA-image cytometry is able to detect this risk in time.

60. Böcking, 2006 ; Tribukait, 2006.
61. Concrete numbers for the accuracy of the histology were not available.
62. Onofre, 2006.

Chapter 7

1. Böcking et al., 1986.
2. Bollmann et al., 2006
3. Cartsburg et al., 2001 ; Schwarz et al., 2004.

Chapter 8

1. Kato et al., 1983.
2. EBM, 2005: reference is effective for both numbers in text.
3. Remmerbach et al., 2004 ; Maraki et al., 2005a.

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Technical Terms

Accuracy Generic term for the reliability of diagnoses. Is composed of different criteria e.g. sensitivity, specificity, or typing accuracy. (p. 37)

Adenoma A benign tumor of gland tissue, i.e. of the thyroid gland (p. 52)

AgNOR Structures within a nucleus of a cell that can be stained with silver nitrate (Latin = argentum) in which ribosomal RNA is synthesized. Their size and number correlates with the amount of protein synthesis of a cell. (p. 16)

Aneuploidy False chromosome set. In case of a numerical aneuploidy, too many or not enough chromosomes are found. If chromosomes have undergone a mutation, it is referred to as a structural aneuploidy. A healthy cell can turn into a cancerous cell through aneuploidy. (p. 14)

Antigen Protein molecule, against which immune cells (lymphocytes) can produce specific antibodies for it to become harmless. (p. 17)

Biopsy Usually, the extraction of tissue samples from the body. One distinguishes three types, punch-needle biopsies with forceps, scalpel biopsies with a scalpel, and cutting-needle biopsies with a hollow needle. The extraction of cell samples is sometimes also referred to as a biopsy. (p. 12)

Borderline Tumor Neoplasia with a biological behavior (benign or malignant) that can not be clearly determined through the analysis of cell or tissue samples (p. 32)

Cancer Uncontrolled and unstoppable cell growth, which destroys other tissue and might produce metastases. (p. 13)

Carcinoma Malignant tumor, which originates in a mucosa or a gland cells. (p. 13)

Cells The smallest structural units, which can live on its own and be visible under the microscope. They are composed of a nucleus, cytoplasm, and carry out different functions. (p. 12)

Classification Typing of a tumor according to the tissue type from which it originates. (p. 34)

Complication Rate Frequency of unwanted adverse effects, such as bleeding, infections, or pain which needs to be treated. (p. 39)

Cytology Study of cells (from Greek cyto = cell). Short for Cytopathology. (p. 12)

Cytopathology Microscopical study of cells for disease detection. (p. 12)

Cytoplasm Cell fluid, which surrounds the nucleus. (p. 14)

Chromosomes String formed object in the nucleus, in which the DNA is coiled spirally. Each human body cell contains 2x23 chromosomes. (see p. 14)

Dignity Differentiation between benign and malignant tumors. (p. 32)

DNA Abbreviation for Deoxyribonucleic Acid. The genetic substance which is contained in the chromosomes. (p. 14)

DNA – Aneuploidy Change of DNA content of nuclei, which is caused by aneuploidy of the chromosomes. (p. 33)

DNA-Image-Cytometry Method to measure DNA amount in nuclei in microscopic images with the help of a computer. (p. 14)

DNA-Probe Stained DNA string, which binds with a suitable part of the genetic substance and marks it. (p. 16)

Domestic Cancer Colloquial term for a less malignant tumor, which is not life threatening even without the treatment of it. (p. 35)

Dysplasia Change in the appearance of cells or tissue, which microscopically lead to a cancer suspicion but cannot prove it. (p. 32)

Effusion Unusual accumulation of fluid in a body cavity, which can indicate cancer. (p. 58)

Endoscope Optic tool for the examination of body cavities. In endoscopy, the physician inserts a pencil-thick, flexible glass-fiber cable with a lens at the end, into the body. He is able to look, for example, into the bronchia (bronchoscopy) or the stomach (gastroscopy). (p. 28)

Endoscopy Examination of hollow organs such, as the lungs, with the help of an endoscope. (p. 23)

EUS-FNAB Abbreviation for endoscopic ultrasound-guided fine - needle aspiration biopsy. The puncture of inner organs with an endoscope guided by ultrasound. (p. 28)

False-Negative Rate Percentage of sick people which were overlooked in a diagnostic. (p. 37)

False-Positive Rate Percentage of disease diagnoses, which later turned out to be false. (p. 37)

Fine Needle Puncture Extraction of cells with the help of a 0.7 mm thick hollow needle. The needle puncture is also referred to as fine needle aspiration biopsy (FNAB). It is, however, connected with less pain and complications than biopsies of tissue with a hollow needle. (p. 28)

FISH → In situ-Hybridization

Grade of Malignancy Degree of malignancy of a cancer, determined by microscopic analysis. (p. 34)

Grading Classification of the malignancy of a tumor with the help of a malignity scale. (p. 35)

Histogram Illustration of the frequency of measurement values in a graph. In a DNA Histogram, the amount of DNA in a few hundred nuclei is presented. (p. 33)

Histology Microscopical study of tissue (from Greek histo = tissue). (p. 12)

Histopathology Microscopical study of the tissue for disease detection. (p. 17)

Immunocytochemistry The search for tumorous cells or the determination of a tumor type through the staining of certain antigens in cells. (p. 17)
Immunohistochemistry Determination of tumor types through the staining of certain antigens in tissue samples. (p. 18)

In situ-Hybridization Staining of certain DNA parts in the microscope. If the display

is carried out with fluorescence light, it is referred to as Fluorescence – in – situ – Hybridization (FISH). (p. 16)

Leukemia Malignant cell growth in the blood. (p. 13)

Liquid Based Cytology New method to produce microscopic slides of cleansed, single lying cells. Supposedly reaches a higher accuracy rate than conventional smears. (p. 29)

Liquor Fluid of the brain and spinal marrow. (p. 26)

Lymphoma Swelling of lymphatic nodes. Can be a cancer indication. (p. 13)

Malignant Characteristic of a tumor to grow fast, and invasive to develop metastases and to therefore become life threatening. (p. 13)

Marker Molecule, which shows certain diseases – e.g. a stained antibody, which binds to a specific antigen and therefore uncovers a specific type of cancer. (p. 17)

Mediastinum Region between the lungs, in which the heart, larger blood vessels, and the esophagus are located. (p. 56)

Metastasis Cells of a primary tumor, which have spread to other body regions and have formed a secondary malignant tumor. (p. 13)

Multi Modal Cell Analysis (MMCA) Automatic procedure of examining the same cell samples subsequently with different methods – e.g. DNA-image-cytometry or immunocytochemistry. (p. 33)

Multiploid Term used in DNA-image-analysis describing multiple cell clones with different DNA content. (p. 33)

Negative Predictive Value Percentage of correctly diagnosed benign findings. (p. 37)

Node Accumulation of tissue, which might form a hardening that can be felt underneath the skin. (p. 12)

Nucleus Globular structure within each cell, in which the DNA is aligned in strings. (p. 14)

Panel Choice of antibodies or DNA probes through which a specific disease can be detected. (p.17)

Pathologist Medical specialist for microscopic analysis of cell and tissue samples. He also performs autopsies for the quality control of clinical diagnoses. (p. 12)

Peridiploid Term used in DNA-image-cytometry, referring to a normal DNA distribution; usually an indicator for a positive prognosis. (p. 33)

Peritetraploid Term used in DNA-image-cytometry, referring to a modification in DNA distribution, which corresponds to a double chromosomal set. (p. 33)

Polymerase-Chain-Reaction Molecular biological procedure in which DNA is reproduced for further examinations with the help of the polymerase enzyme. (p. 17)

Positive Predictive Value Percentage of disease diagnoses which turn out to be correct. (p. 37)

Primary Tumor Contradictory to metastases of a tumor; the origin of cancer. (p. 13)

Probe In pathology, a small amount of cells or tissue, which a pathologist examines for a disease diagnosis. (p. 12)

Prostate Specific Anti-gene (PSA) Protein, which usually accounts for the liquefaction of sperm that can also reach the blood. If the blood contains an increased amount, it could be an indication of a prostate carcinoma. (p. 68)

Rapid Section A tissue preparation produced within a few minutes, which is examined during an operation to decide on further procedures. (p. 12)

Regression Grading Monitoring of therapeutic success with the help of extracted cell or tissue samples. The more damaged or dead tumor cells can be found, the more successful the treatment has been. (p. 73)

Review Scientific overview article, which forms the average of the results of many studies. (p. 39)

Recidive Return of a tumor after its treatment. (p. 74)

Ribosome Granules composed of ribonucleic acid within the cytoplasm, in which proteins are produced. (p. 16)

Sarcoma Malignant tumor originating in the connective tissue. (p. 13)

Sensitivity Percentage of correctly diagnosed sick people amongst all sick people. (p.37)

Semi-Malignant Characteristic of a tumor that is neither clearly malignant nor clearly benign. Semi-malignant tumors destroy tissue, yet they do not produce metastases. (p. 32)

Smear Extraction of isolated cells of the surface of a mucosa with the help of a little brush, a spatula, or a cotton swab. (p. 27)

Specificity Percentage of correctly diagnosed healthy people amongst all healthy people. (p. 37)

Sputum Coughed up mucus from the bronchia. (p. 26)

Sputum Cytology Microscopic examination of sputum for an early detection of lung cancer. (p. 45)

Sputum Cytometry Completely automatic examination of sputum for an early detection of lung cancer. (p. 46)

Squamous Cell Carcinoma Carcinoma which stems from squamous epithelium. (p. 20)

Staging Classifying the spreading of a tumor in the body. (p. 36)

Tissue Formation of connected, similar cells, i.e. the protective squamous epithelium of the skin, the saliva producing gland tissue of the salivary glands or the connective tissue of ligaments. (p. 12)

Total Accuracy Percentage of all true positive and negative diagnoses. (p. 37)

Tumor In a broad sense, every swelling of an organ. In a more narrow sense, growth of tissue, which could be malignant and therefore cancerous. (p. 13)

Tumor Progression The growth of a tumor. Referring not only the spatial expansion, but also to the changes within. (p. 35)

Typing → Classification. (p. 34)

Typing Accuracy Percentage of cancer diagnoses which are classified or typed correctly. (p. 37)

Wild Cancer Colloquial description of a malignant tumor, which will threaten the life of the patient, if it is not treated. (p. 35)