Development of the new infrared imaging for avoiding of cancer recurrence after radical prostatectomy and Partial nephrectomy

Part 1

Prostate cancer

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INTRODUCTION:

A comprehensive review of global cancer statistics confirms that prostate cancer is the **second most common cause of cancer death in men**, directly after lung cancer, emphasizing its significant impact on men's health worldwide [1].

A studies indicated that prostate-specific antigen (PSA) screening resulted in a 20% reduction in prostate cancer mortality. Despite the benefits of screening, prostate cancer remains a leading cause of cancer-related deaths, with significant mortality rates persisting Schröder 2003, McLaughlin 2024.

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Therefore, instrumental screening methods are of great importance. However, each of them has its weaknesses. For example: A digital rectal examination (DRE) is highly subjective and is based on the skills and expertise of the doctors Leen 2018. The next method is Trans-rectal ultrasound (TRUS). Prostate cancer may be identified on TRUS as a hypoechoic lesion. However, only 60% of prostate cancers appear hypoechoic on ultrasound. Consequently, TRUS should not be used as a first-line screening study as it lacks acceptable specificity Harvey 2012. Magnetic resonance imaging (MRI) is an expensive and complicated method, that requires a radiologist and a physician specifically trained to supervise and interpret radiology examinations. Besides, the strong magnetic field might be harmful. Sometimes it is difficult to obtain clear images due to the presence of an implant or other metallic object. The same result can be achieved via patient movement. A prostate biopsy can occasionally result in inflammation or the presence of blood products within the prostate, which MRI cannot always discriminate from cancer tissue Coakley 2003. Computer tomography CT is not regarded as primary method for prostate cancer diagnosis. CT usually is used as an additional tool in prostate cancer diagnosis. Restrictions: X-rays are not non-invasive Daryanani 2022.. Positron emission tomography (PET) is extremely complicated, expensive, and partially invasive. Thereby this method could not be used in common clinics widely Bailey 2005.

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An effective treatment for prostate cancer is a radical prostatectomy, however it is not the final step. Unfortunately, 30-40% of patient's after surgery develop a local recurrence (Scattoni et al. 2004). Probability of recurrence in prostate cancer is directly proportional to the degree of aggressiveness of tumor and is higher in the case of higher aggressiveness of tumor Grossfeld et al. 2003 Han et al, 2001, Bianco et al, 2003).

In prostate cancer, the degree of aggressiveness is determined by the sum of Gleason score [https://www.cancer.net/cancer- types/prostate-cancer/stages-and-grades]. The aggressiveness of cancer is not dependent on the developmental stage. It may happen so that the initial cancer may be very small, however very aggressive (Murata et al., 2018).

Postoperative management of needed treatment is determined by histo-morphological investigations, performed on isolated prostate specimens after surgery and largely depends on how aggressive the cancer was in the prostate. **If a high degree of aggressiveness (i.e. high sum of the Gleason score) is not accurately detected, then postoperative management would be incorrectly selected and the risk of cancer recurrence increases** (Vachani 2018).

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In order for the patho-morphological response to be 100% accurate, microscopic investigation of all parts of the entire prostate should be made, which is a highly laborious and time-consuming activity. Thereby, this type of examination is not practiced. Most clinics use partial selection practices. The reason for the high percentage of cancer recurrence is that the **partial sampling method often fails to fully detect areas with a high degree of aggressiveness, resulting in incorrect postoperative management selection and recurrence of cancer.**

The main weaknesses of this approach that lead to the mentioned errors are the following:

a) Usually, from each prostate gland, 30-40 slices are prepared for examination under the microscope. To do this, the isolated prostate is firstly processed into formalin, then cut into layers 5-6 mm thick. Then slices are randomly taken from layers in a non-automatized manner (True, 1994; Bova et al.1993). This is extremely insufficient to examine the entire prostatic tissue.

b) The prostate tumor is morphologically diverse and multifocal. Cancers of different aggressiveness can be found in the same prostate. It is virtually impossible to detect the location of the tumor with the naked eye. Often, cancer is spread in the whole prostate gland with small islets called acinus (Faraz et al., 2015). Different acini may have different degrees of aggressiveness.

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Thus, it is likely that small part of highly aggressive tumor could be missed during preparation of the slices and would not be detected. Consequently, targeted histological examination is not possible. Considering this, we would not have the information about highly aggressive cancer. **Thereby, the treatment management plan would be incorrect.**

Existing approaches to computer-assisted evaluation of histo-pathological preparations of the prostate employ gland histo- morphometry or context-based gland quantification to distinguish benign, and low- and high-grade cancer zones - Salman et al. (2014). In order to perform any quantifications the glands are usually first separated from stroma. This task is difficult and prone to detection errors due to a large spectrum of gland architectures in benign and cancer areas. Besides, computer-assisted gland segmentation techniques utilize the presence of the glandular lumen as a prominent feature that requires highly sophisticated image processing routines.

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Due to the limitations of current imaging techniques, we were motivated to seek alternative technique that would enable us to identify prostate cancer at an early stage of development, which would then serve as a basis for performing a targeted biopsy. In order to meet this challenge, we made an effort to create a new technique for visualization of a prostate cancer employing infrared light.

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In the experiments, prostates obtained after radical prostatectomy were utilized. It is well known that a certain technique is used to cut the prostate in order to detect the aggressiveness based on the Gleason score of cancer after surgery. For this purpose a formalin-fixed paraffin embedded tissues (FFPE) are obtained for processing the specimens. After this a microtome is used to cut slices from FFPE for microscopic analyses. The slices mounted on the slide glass (SMSG) are obtained after a well-known processing step. It is easy to understand that FFPE and SMSG are complementary. Their localized cancer distributions are one and the same. Additionally, their distribution of aggressive patterns is also one and the same.

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Using the infrared method, we get a two-dimensional (2D) IR image of a FFPE. We compare the various illumination intensities on the infrared image to the tumor's aggressiveness on SMSG as assessed by the Protocol for the Examination of Radical Prostatectomy Specimens with Prostate Cancer (PERPS) [**21**].

Methods

Light with a wavelength of 750 to 1000 nm (near infrared range, so-called NIR - i.e. invisible range) is a non-invasive optical tool for detecting tissue abnormalities and obtaining images.

Methods

Studies imply the obtaining and analyses of 2D trans-illumination images. It is well known that light at wavelengths in the invisible near-infrared (NIR) range (from 750 to 1350 nm) is a noninvasive optical tool to detect and image tissue abnormalities. Optical mammography, for example, has been studied as an alternative NIR technique, which utilizes NIR light to image cancerous breast lesions Fantini and Angelo 2012.

Optical densities of the tissues of the cancerous and healthy tissues are different, and the intensities of the infrared rays after passing through them will be different from each other. I.e. The intensity of the infrared light coming out of the cancerous tissue will be much less than the intensity of the infrared rays passing through the healthy tissue Partsvania et al. 2014. Partsvania et al. 2016, Partsvania et al. 2017.

In our experiments infrared rays travel in about 5-6 mm thick in a prostate tissue. Infrared rays in biological tissue are characterized by multiple scattering. However, the NIR in the 750-1000 nm range is characterized by fairly deep penetration and minimal scattering (Caerwyn at al. 2017). The infrared method allows us to obtain 2D IR images and study the correlation of different light intensities with the agressivness of cancer in prostate specimens.

Experimental unit

Experimental unit consists of: infrared radiation source, holder for cancerous tissue, and CCD camera. Rays emanating from the infrared source pass through tissue. Rays after passing the tissue, carring the information about optical density inhomogeneity, fall into the infrared-sensitive matrix. The output of the CCD camera is connected to the computer, where our computer program converts electrical signals coming from the CCD camera into visual images –IR images.

Experimental setup.

Figure 1. FFPE is placed between CCD camera. The LEDs (indicated by the arrow) are placed below the prostate tissue. The CCD camera, indicated by the arrow, is placed above the FFPE.

Methods

The CCD camera matrix contains a certain number of pixels. The intensity of infrared radiation falling on each pixel is determined by the intensity after passing from the investigated biological tissue. Therefore, the distribution of the intensities on the CCD matrix corresponds to the pattern of the intensities of the IR passing from the biological tissue. As it is well known, a CCD camera converts the intensity of an infrared ray falling on each pixel into an electrical signal of the corresponding magnitude, the value of which is proportional to this intensity. Thus signals are transmitted from the CCD camera to the computer.

In the case of homogeneity of the study tissue, the intensity of the infrared rays passing from all points of the tissue will be the same. If the tissue is heterogeneous, for example, it contains both cancerous and healthy tissue because the optical densities of these tissues are different, the intensities of the infrared light passing from them will be different from each other (Partsvania 2014, Partsvania 2016, Partsvania 2017).

Results

To use an infrared approach for investigating the aggressiveness of prostate cancer, we utilized both **FFPE** and their corresponding SMSG.

The experiment was carried out in the following order: at first, SMSGs were examined under a microscope. The structure of the cancerous tissue was determined, the aggressiveness according the **PERPS** was evaluated in individual areas. Then we examined FFPE and studied those areas that contained the point from which the mentioned SMSG was taken. Mutual compliance was determined.

Software Development

We developed software for IR image analysis. The program assigns to each point of the IR image the number from 0 to 255 according to its brightness. 0 is given to a minimally dark point and 255 to a point with the maximum brightness. In this way, the program measures the light intensities at each point on the IR image which corresponds to both the tumor and the healthy tissue. Then the program calculates the mean values of these illuminations intensities separately to maliglnt and helthy areas . After this, the program calculates the ratio of these numbers (malignant to healthy ratio MHR). The obtained ratio is stored in the memory of the program. Hence, on the one hand, we know the aggressiveness degree of the tumor areas identified by histo-morphological studies according to Protocol of the College of American Pathologists for the examination of radical prostatectomy specimens (2023) https://documents.cap.org/protocols/Prostate_4.3.0.0.REL_CAPCP.pdf

and on the other hand, the ratio of the mean value of the illumination of corresponding tumor area to the mean value of illumination of healthy tissue. Thus, results obtained from histo-morphological studies were compared to the results obtained by the infrared method. In this manner determined degree of aggressinvness mentioned above corresponds to the certain ratio of intensities.

5 grade of prostate cancer aggressiveness according to Protocol for the Examination of Radical Prostatectomy Specimens with Prostate Cancer (PERPS) [21]

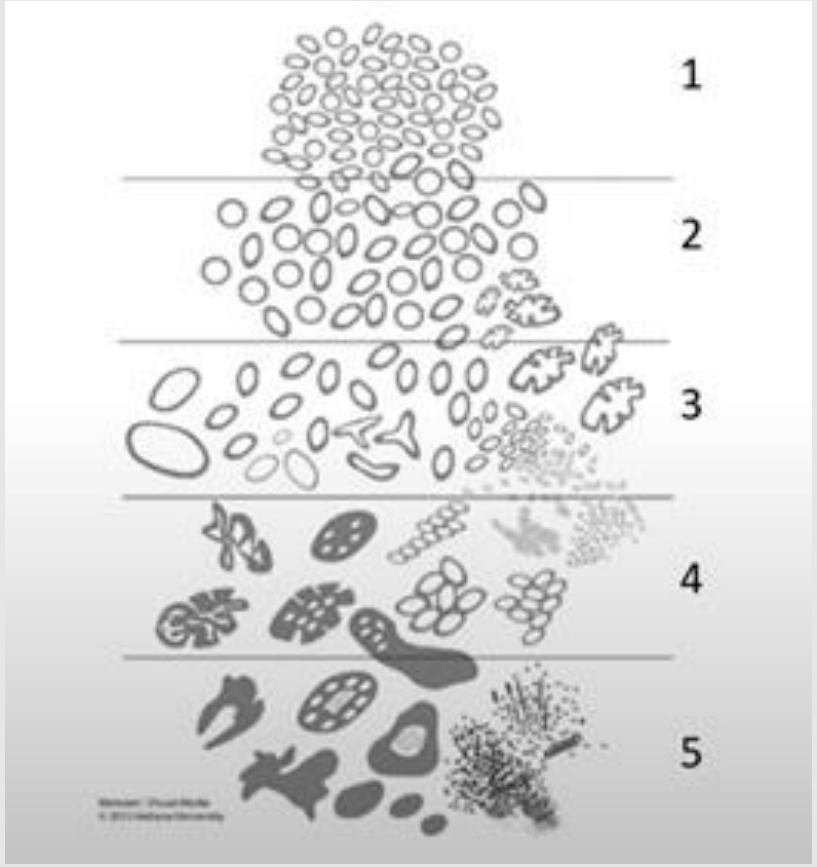
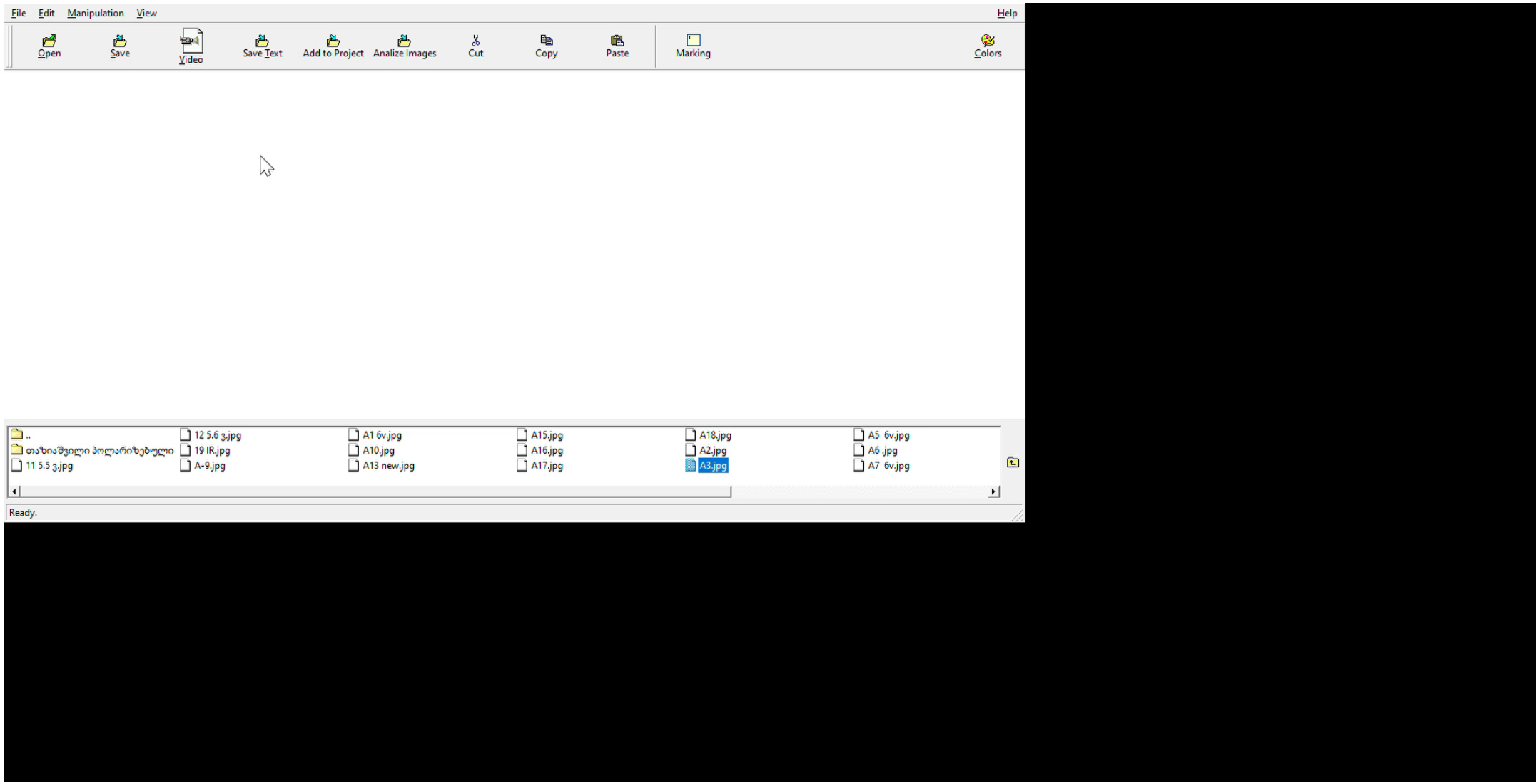


Figure 2. 5 grade of prostate cancer aggressiveness according to College of American Pathologists. (2023). Protocol for the examination of radical prostatectomy specimens from patients with carcinoma of the prostate gland (Version 4.3.0.0). https://documents.cap.org/protocols/Prostate_4.3.0.0.REL_CAPCP.pdf

How works software



Results

On this slide is shown one of the FFPEs, MSSG taken from it

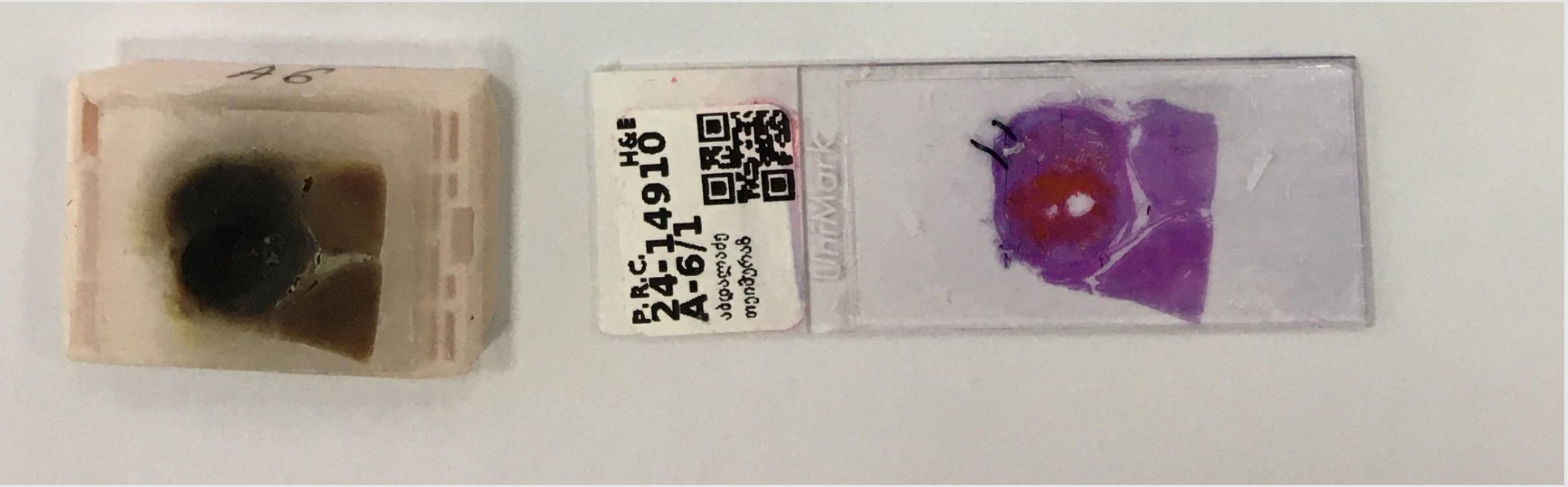


Figure 3. One FFPE is shown on the left, MSSG taken from it.

Results

Prostate cancer is typically multifocal. It is common to detect different levels of aggression in the same prostate, but if prostate cancer is still in its early stages, we typically encounter one type of aggressiveness. One of such PERPS is shown on this slide, together with its infrared image and histomorphological images of several sections extracted from the relevant SMSG.

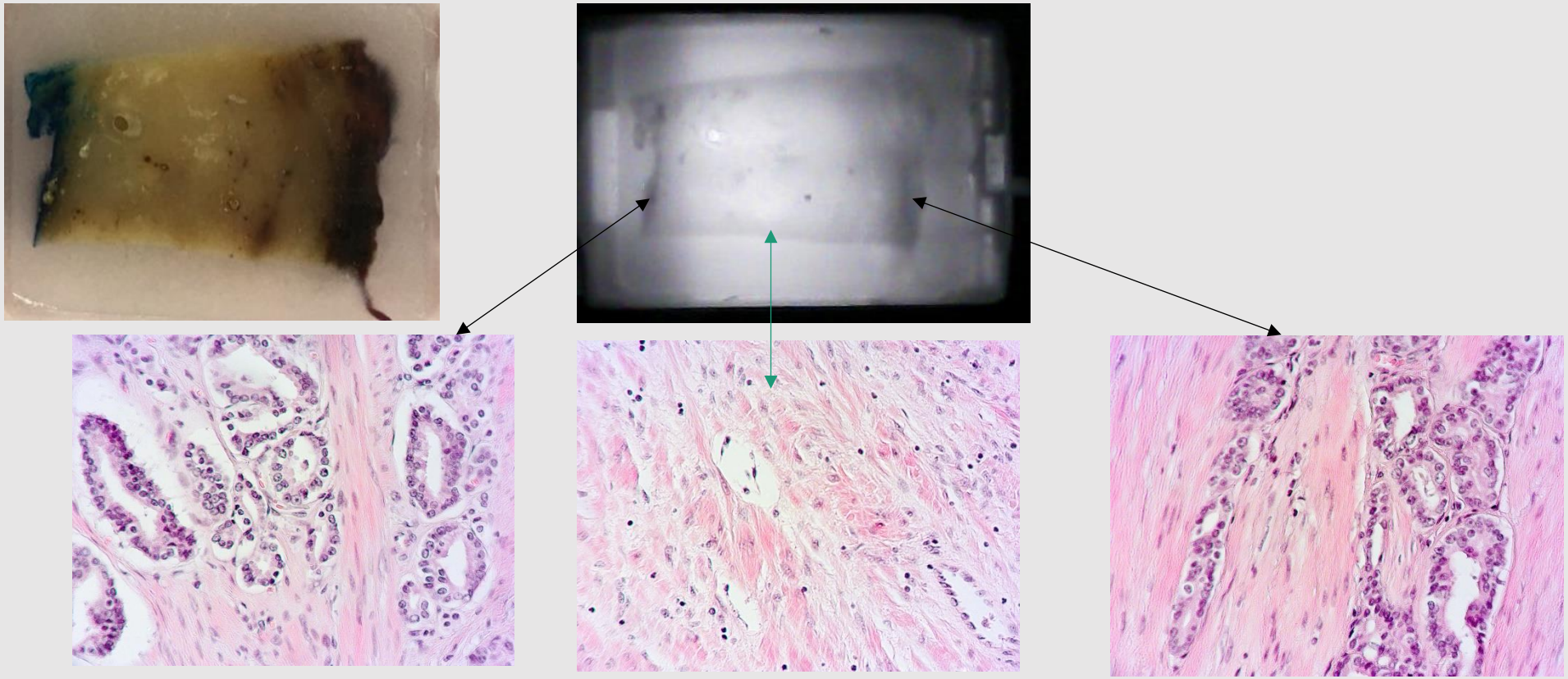
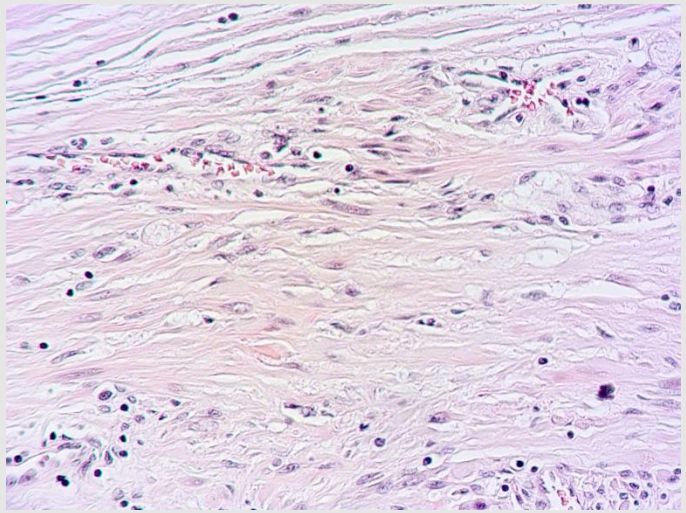
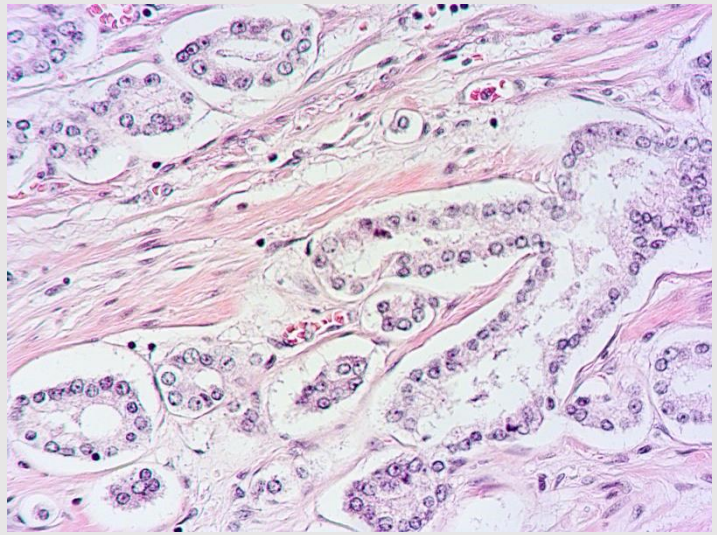
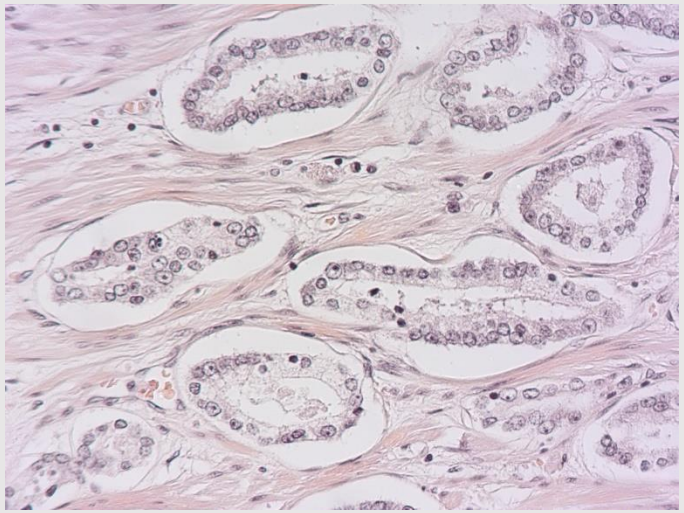


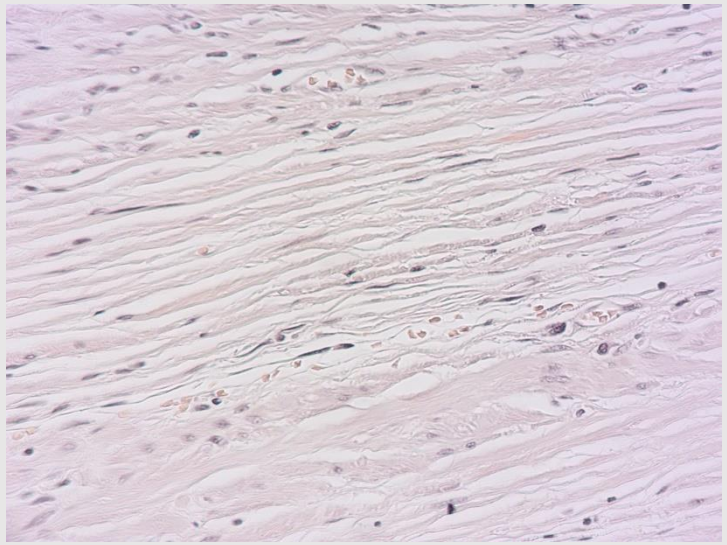
Figure 3. Arrows are used to connect histo-morphological images to their respective locations on the infrared image. In this case Grade according to College of American Pathologists was 2. Middle histo-morphological picture corresponds to healthy tissue of prostate.

Another example of the IR imageof the **FFPE** with cancer aggressiveness 2 .









The FFPE IR image and histomorphological images from several locations are displayed on this slide. Here, aggression mostly was rated at 3 (yellow arrow), however small portions of higher aggressiveness was met (red and orange arrows).

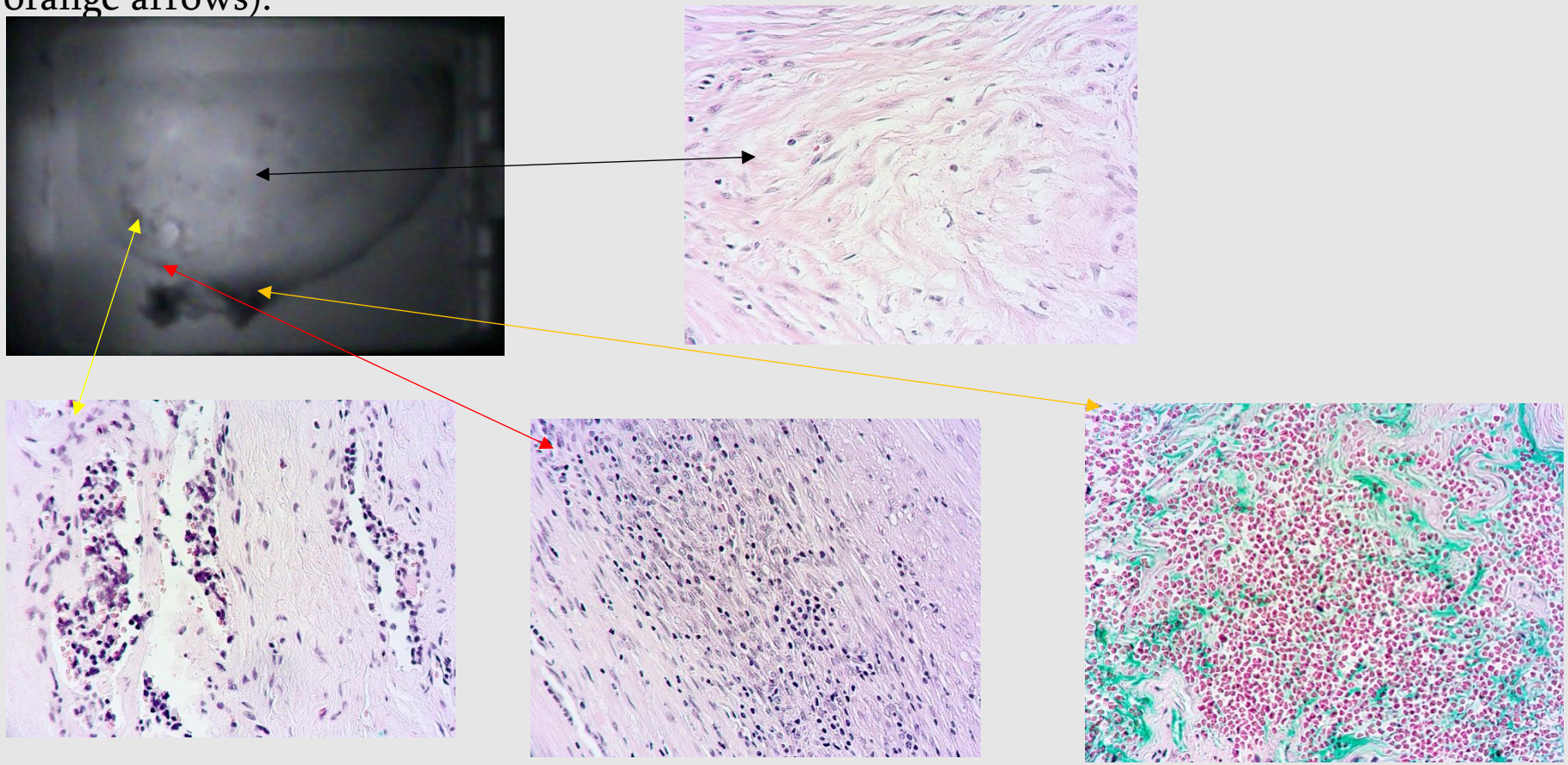


Figure 5. Arrows are used to connect histomorphological images to their respective locations on the infrared image.On the Right from the IR image is picture of healthy tissue (black arrow).

Resuts

IR image of prostate tissue (in **FFPE**) with aggressivness 4 according to protocol for the examination of radical prostatectomy specimens from patients with carcinoma of the prostate gland of the , College of American Pathologists.

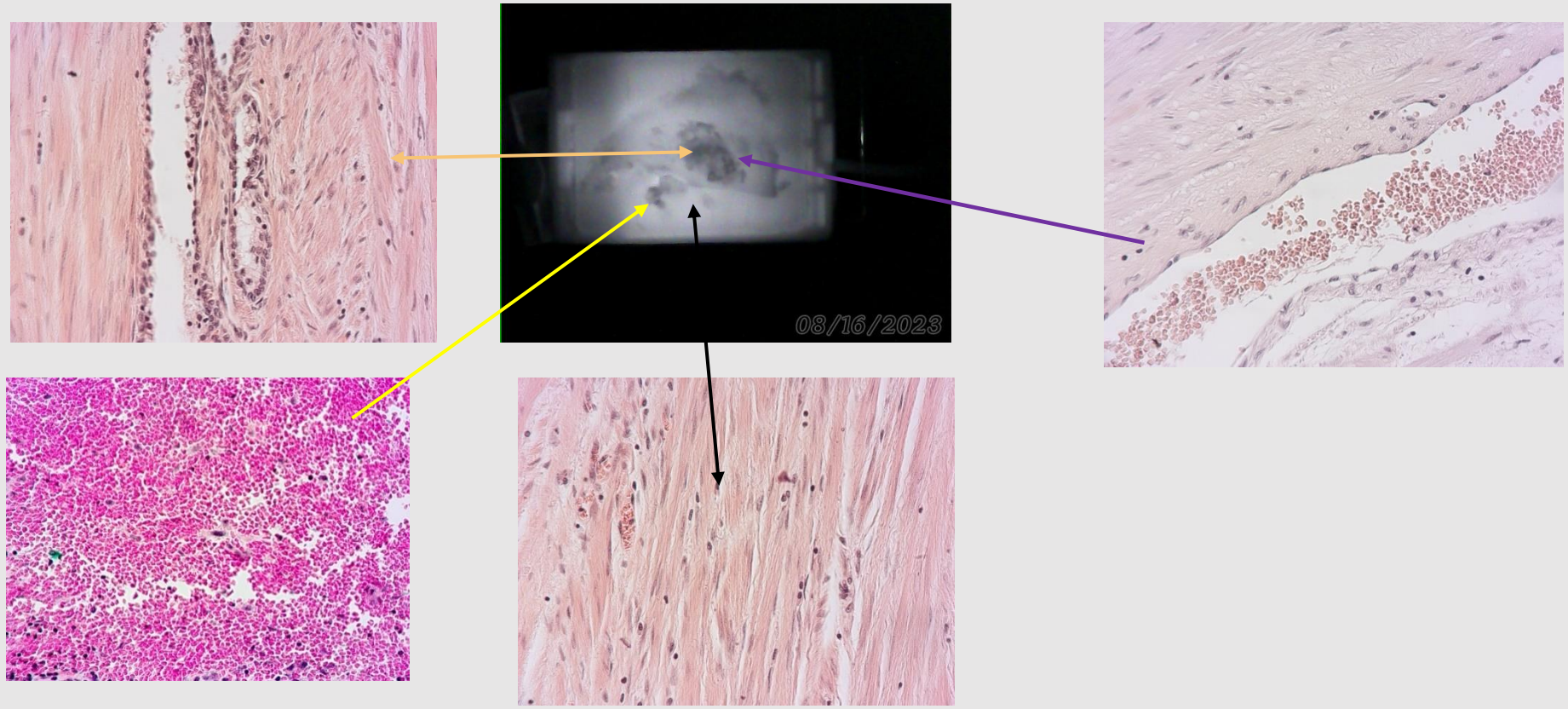


Figure 6. Here we see site with aggressiveness 5 (yellow arrow), aggressiveness 3 (green arrow), aggressiveness 4 (blue arrow), and healthy tissue (black arrow).

The situation when the majority of the aggressiveness was fifth order is depicted on this slide.

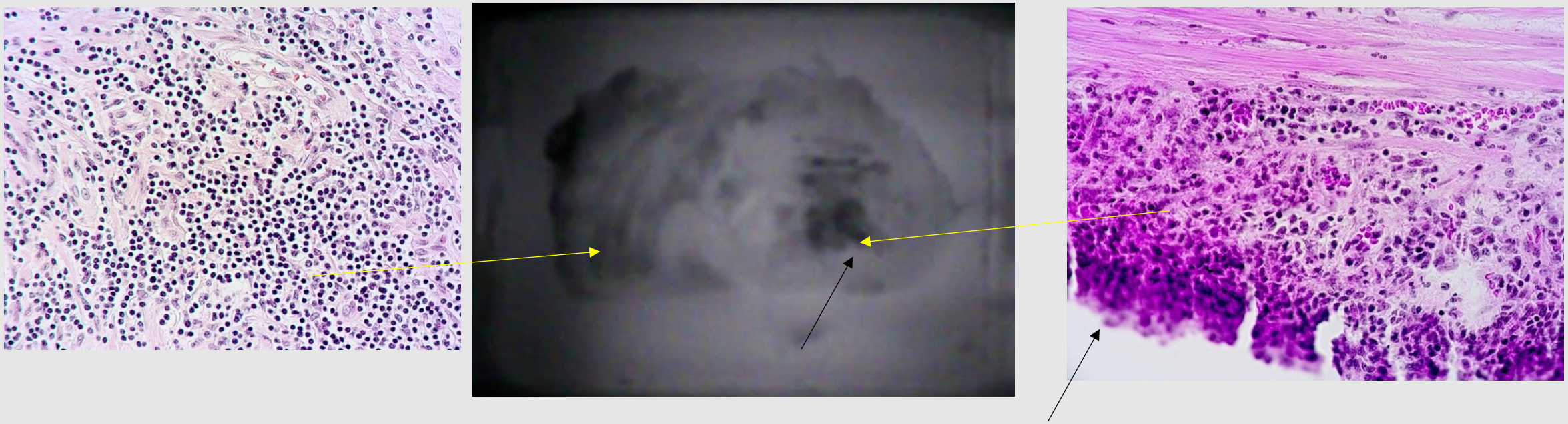


Figure 7. IR image of FFPE of prostate tissue with aggressiveness 5 according to PERPS. Arrows indicate sites on the IR image at which the histo-morphological images are taken. On the right histo-morphological image we see the margin of cancsrous formation which is well seemed on the IR image also see black arrows.

In this slide we see example when different aggressiveness are present, however, hinges one (aggressiveness 5) is of very low percentage (yellow arrows).

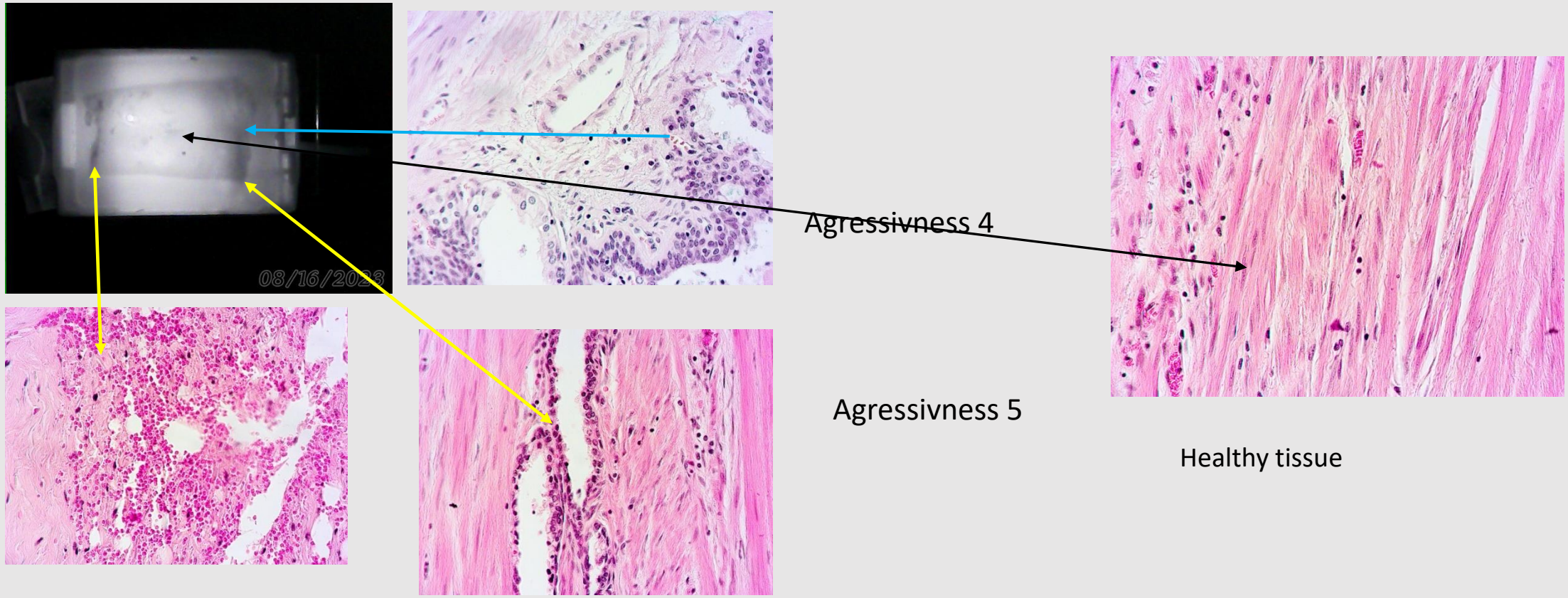
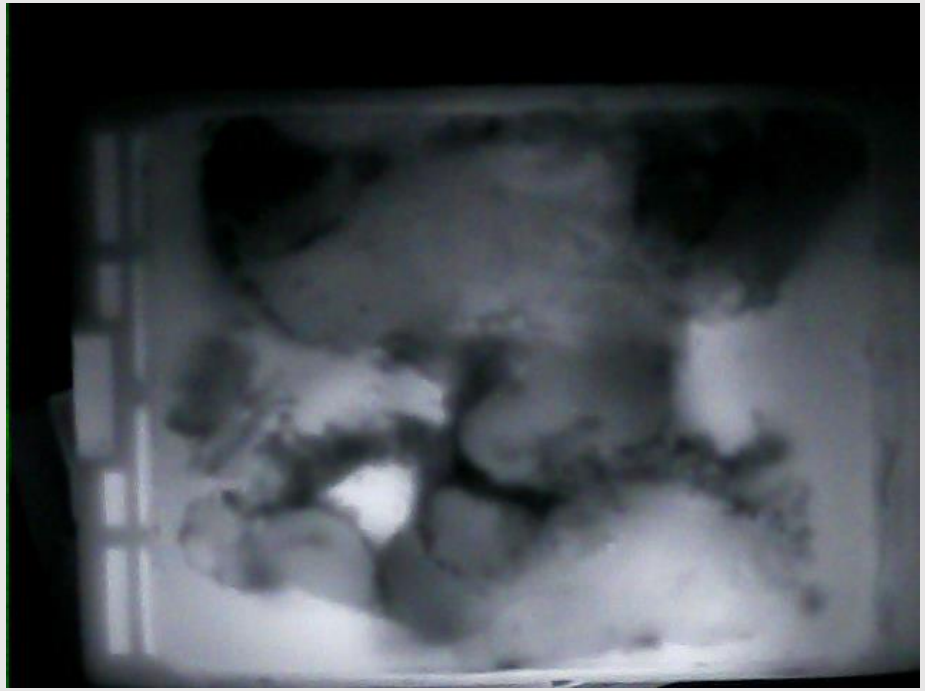


Figure 8 .

Results

On this slide is shown example when only one higest agrssivness (5 according to protocol for the examination of radical prostatectomy specimens of the prostate gland of the , College of American) is present.



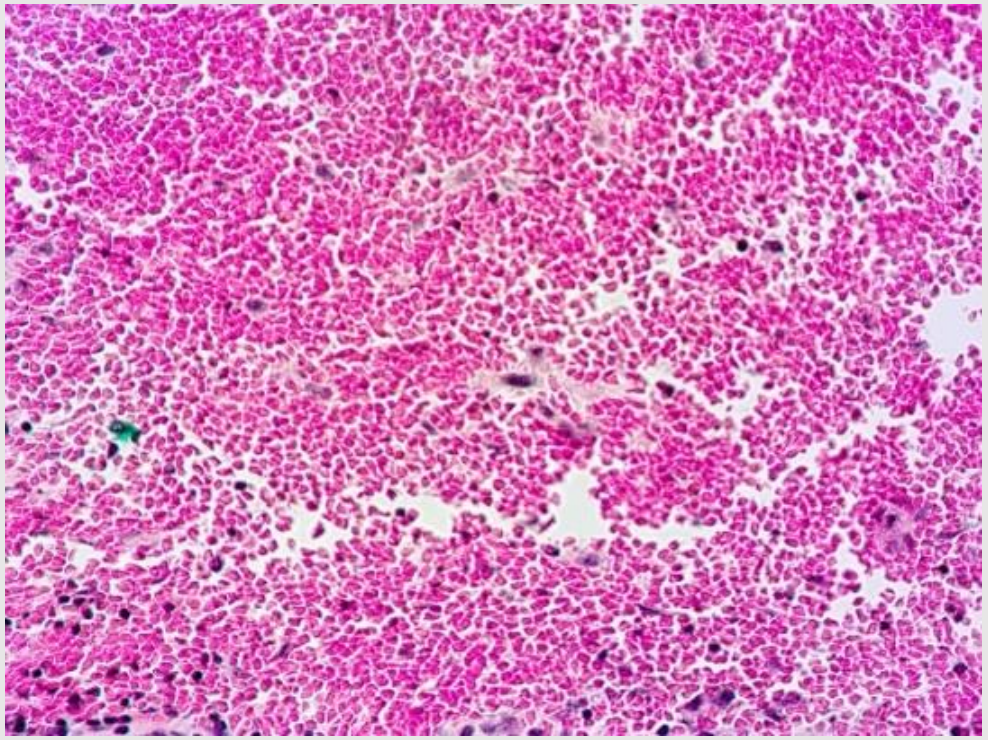


Figure 9.

Results

Each level of aggressiveness was the subject of at least 32 tests, for a total of 190. As it occurred our program can differentiate between three levels of aggressiveness. Specifically, the relative interval of lighting intensities for healthy tissue and tissue with a degree of aggression 2 is 6.8-7.2 with a 95% confidence interval. These two types of tissue experience the same item. Aggressiveness 3 and aggressiveness 4 are perceived as the same and the relative interval of their respective illuminance intensities is 5.2-6.1, and for aggressiveness of the 5th order the relative interval of illuminance intensities is 4.4-5.0. As we can see, these intervals do not overlap. At the same time, the infrared method perfectly perceives and distinguishes aggressiveness with higher aggressiveness's , which was the goal of the this project.

Conclusion

Infrared imaging method is characterized by hogher reliability for visualization of cancerous formations with higher degrees (4 and 5) of aggressiveness, which allows to perform targeted biopsy, reduce the number of biopsy points and Increase the accuracy of matting.

The IR method can be used as an alternative method to determine the aggressiveness of prostate cancer both before surgery and after radical prostatectomy, as the purpose of postoperative aggressiveness research is to identify areas of higher aggressiveness.

Therefore, on the one hand, we have the aggressiveness of the tumor areas determined as a result of histo-morphological studies, and on the other hand, the MHR of these tumor areas. After establishing 95% confidence intervals, we are able to find out the degree of aggressiveness of any new unknown prostate cancer. At the next stage of experiment, a new unknown prostate FFPE may be examined with our software, i.e., to determine the degree of aggressiveness.

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