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The Axis "Human Papillomavirus - Anal Squamous Cell Carcinoma": A Review

Type of article: Review.

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Abstract

Background: Anal Squamous Cell Carcinoma (ASCC) is an infrequent neoplasia that represents 2% of the digestive tumors and it has a growing incidence.

Objective: This investigation (i) studies the pathogenesis of an increasingly prevalent disease, (ii) its treatment and prognosis along with (iii) a bibliographical review of the main characteristics of the Human Papillomavirus (HPV) as well as its effects on humans.

Methods: A literature review is performed, comprising articles up to 2019 and cross-research manuscripts with the initial research.

Results: Several studies demonstrate the HPV role as a significant risk factor to the development of ASCC, as well as its higher incidence in HIV-positive individuals and in those who engage in receptive anal intercourse. Future trends in theragnostic using information technology are examined.

Conclusions: ASCC is a neoplasm mostly associated with HPV. Many studies are needed to improve the treatment as well as in the evaluation of the tumor characteristics.

Keywords: Human Papillomavirus, HPV, Anal Squamous Cell Carcinoma, ASCC, STD, Anal Canal Lesions, Anatomy, Histopathology, HIV.

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1. Introduction

Anal Squamous Cell Carcinoma (ASCC) is cancer on the rise. According to the Global Cancer Observatory (GCO), there were well over 48,000 new cases in 2018 alone, with Asia, Europe and North America holding the top three positions for incidence in both sexes [1]. ASCC impacts the mucosa, submucosa and the muscularis of the anal canal. Prior detection frequently encountered patient complaints include pain and prolonged anal bleeding. The diagnostic investigation involves visual and histological anorectal examination, and, at a later stage - anoscopy or rectoscopy. Deciding on a final diagnosis is slow to come as initial complaints mirror those of external or internal hemorrhoids.

ASCC's onset is a person-specific process. A common denominator seems to be infection with the human papillomavirus (HPV), present in 70 – 90% of diagnosed ASCC cases [2]. HPV is a virus with tropism by differentiating tissues. Its pathogenesis is related to the disorder of genes that inhibit cell apoptosis and cell suppression. This fact favors its action and spread by an organism. Due to these characteristics, HPV is associated with cervical, anus, head and neck cancer.

The current article explores the HPV - ASCC connection in Section 2. While it reflects scientific research on the matter published between 2003 and 2019, the article also provides in-house specialist analysis. The macro- and micro-anatomy of the anal canal are discussed in Section 3. Section 4 examines cancer precursor lesions. The ASCC is investigated in Section 5. Current treatments, future trends, and conclusions appear, respectively, in Sections 6, 7, and 8.

2. Human Papillomavirus (HPV)

The study of human papillomavirus (HPV)-related infections is relatively new. Its origins date back to the 1970s when Prof. Harald zur Hausen, chairman of the Institute of Virology at the University of Freiburg, Germany, chose HPV as the center-theme of his research. Studying cervical cancer biopsies, in 1983, Prof. zur Hausen's team was successful in isolating the DNA of the high onco-risk HPV-16 variant, and in 1984 – that of HPV-18. For his significant contributions to science, Prof. zur Hausen went on winning the 2008 Nobel Prize in Medicine. Based on his findings, HPV-related research has since flourished [3, 4, 14].

HPV is a frequently encountered virus. Statistics show that 2/3 of all sexually active people (irrespective of involvement in vaginal or anal sex) have acquired it. During the first two years post defloration, 40% of women fall victim to it. Condoms do not prevent infection.

The virus has many strains. Not all of them are oncogenic, and the immune system can suppress them successfully. The non-oncogenic HPV infection often manifests visually as warts or condyloma acuminatum. The oncogenic strains of the virus can either stay dormant for years (embedded in anal tissues [5] or circulating in the blood and lymphatic systems, thus reaching other tissues and organs) or starts replicating immediately post-infection. In descriptive terms, HPV is a 72-capsomer, non-enveloped virus, belonging to the Papovaviridae family. Its mean diameter is 55 nm. HPV is a recombinant retrovirus. Retroviruses transform the single-stranded RNA genome they carry into a double-stranded DNA molecule that integrates into the genome of dividing target cells. HPV's genes encode 2 structural (L1 and L2) and 7 non-structural (E1, E2, E4, E5, E6, E7) proteins [15-21].

The described genes are organized in three regions: an early region (E), a late region (L), and a regulatory region (URR). The L1 and L2-encoding genes are responsible for the structure of the viral capsid, as well as for proteins involved in viral replication and cell transformation. When L1 is produced in a heterologous expression system, it can self-assemble. The E1 and E2-encoding genes contribute to viral replication. The E5, E6, and E7-encoding genes take care of proteins responsible for infected cells' transformation.

Based on the histological target of their action, HPV infections can be divided into two major types: cutaneous or mucosal [6].

Current scientific literature shows a further differentiation into over 200 strains. Approximately 45 of them target the anogenital tract. In terms of the potency of their oncogenic potential, HPV's strains can be classified as low-risk (types 6, 11, 42, 43 and 44) and high risk (types 16, 18, 31, 33, 35, 39, 45, 46, 51, 52, 56, 58, 59 and 68) [6] [7].

HPV infection can ensue in many ways. The virus can disseminate through direct contact with surface lesions on an infected human body (e.g., oral cavity, skin), or contact with desquamated cells or body fluid residue left on previously touched the inanimate surface [22-30].

Vertical transmission during pregnancy and delivery is observed on occasion.

The HPV infection is also the most frequently encountered, undesirable result of unprotected sex involving anorectal intercourse.

3. Macro- and Micro-Anatomy of the Anal Canal

The anal canal is not a part of the human reproductive system. As such, it has no gender. It does not lead to an organ supporting impregnation and the creation of life. The anal canal is the terminal portion of the gastro-intestinal (GI) tract. Following rises in intra-abdominal pressure, it serves for the expulsion of feces– by-products of human food consumption and the recycling of heme. The passage is mono-directional – from the anal canal, out of the human body [32-36].

Macro-anatomically speaking, the anal canal is approximately 3 cm long. It extends from the lower margin of the rectum up to the external margin of the anus.

In its upper half, the lumen of the anal canal exhibits 8 – 10 vertical columns. Also known as anal or rectal columns (columns of Morgnani), they are produced by the push-out of the mucosa by the longitudinal outer muscle layer of the rectum. In their upper portion, the anal columns are raised. Moving downwards, they gradually flatten out.

Adjacent anal columns are separated via furrows. Below, the so-called anal sinuses are limited by the anal valves (Ball's) - transverse mucosal folds with a half-moon shape. Collectively, the anal valves form a line known as the anal pecten.

The space between the anal pecten and 8 mm to the external margin of the anus is called the zona haemorrhoidalis. Here, the mucosa is smooth.

The submucosa contains the haemorrhoidal plexus. The soft, malleable nature of the haemorrhoidal plexus protects the mucosa from mechanical harm of passing hard feces. It is also instrumental in the tight closing of the anus.

The zona haemorrhoidalis terminates with the pectinate line (Hilton's white line).

Beyond the pectinate line, up to the external margin of the anus, lies zona cutanea - the skin-covered portion of the anal canal. The zona cutanea contains hair follicles, sebaceous and sweat glands.

Normal anal continence is maintained via muscles of the pelvic floor - the levator ani and the sphincter ani internus (involuntary) et externus (voluntary), as well as the aforementioned plexus haemorrhoidalis. The upper half of the anal canal (above the anal pecten) is sensitive to stretch, while the bottom half - to pain, touch, and temperature differences [8]. The viscerosensory experiences in the anal canal are explained through the action of submucosa's haemorrhoidal plexus, muscularis' myenteric plexus (Auerbach's) and the mechanoreceptors Vater-Pacini corpuscles.

The normal histology of the anal canal shows a smooth, top-down transition:

- starting below the lower margin of the rectum with
    - the simple columnar epithelium of the anal columns
- passing below the anal pecten with
    - the non-keratinized stratified squamous epithelium of the zona haemorrhoidalis (histologically marked as the anal transition zone), and
- ending below the pectinate line with
    - the keratinized stratified squamous epithelium of anus' epidermis.

4. Cancer Precursor Lesions

During anorectal intercourse, the pronounced mismatch between the circumference of the glans penis and the maximum stretching capability of the external and the internal anal sphincters determines the rougher thrusting nature of the sexual act. The outcome

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is the presence of mid-size and deep abrasions - traumatic desquamation, often combined with longitudinal lesions and rugae (Figure 1).

Figure 1. Example of external anal margin lesions, consistent with histological changes due to previous anorectal intercourse (photo courtesy of Société Nationale Française de Colo-Proctologie, [5])

The abrasions expose both sex partners to fecal bacteria present in the anal canal.
The contact between the by-products of fecal bacteria's living cycle and the HPV may cause mutation of the virus.
Abrasions may also increase the risk for infection with parasites, other viruses (e.g. Herpes simplex virus, HSV) [9], as well as sexually-transmitted bacteria. Some notable examples of the latter are:

- Campylobacter jejuni
- Chlamydia trachomatis
- Neisseria gonorrhoeae
- Shigella sonnei
- Haemophilus ducreyi
- Calymmatobacterium granulomatis
- Treponema pallidum [10]

For a healthy receiving sex partner, the abrasions ensure HPV's access not only to anus' epidermis, but also to the deeper layers of the anal mucosa (lamina propria and associated blood and lymph vessels), the submucosa, and muscularis. Abrasions in the anus and the anal canal of an HPV-positive receiving partner lead to leakage of the virus onto the glans penis' mucosa, the prepuce, and the penis body's skin of a healthy thrusting sex partner.
The integrity of the penis of the latter is already compromised, as a result of the rough friction between the penile mucosa and skin on one side, and the anus' skin and the mucosa of the anal canal on the other. Micro-hemorrhaging occurs. As a result, the leaked HPV virus enters the healthy thrusting sex partner's blood and lymph circulation. A worse effect happens when an HPV-positive thrusting sex partner causes abrasions onto the anal tissues of a healthy receiving sex partner.
Due to the rough nature of the anorectal intercourse, the penis of the infected thrusting partner causes abrasions, while pushing the virus deep inside them. Observed is a simultaneous "plow and seed" action of sorts. Desquamated epidermal cells from the skin of the body of the HPV-positive penis remain in the anal canal. With deeper

penetration, they reach the rectum. The contact of the HPV virus and foreign skin cells with the abrasions triggers an immune system defense response. Other known symptoms of anorectal intercourse with HPV infection may cause are *pruritis ani*, pain, rectal bleeding, and mucus or fecal discharge [9].

5. Anal Squamous Cell Carcinoma (ASCC)

Once HPV infects the nuclei of host cells, the virus follows two routes – it either activates and replicates, or, most often than not, stays dormant for years prior to the onset of detectable symptoms [6]. This period of latency is known as a "window period" and its duration is affected by a list of factors:

- engagement in sexual intercourse since an early age
- multiple sexual partners
- high number of non-surgically assisted births
- young chronological age
- smoking
- low socioeconomic status
- prolonged use of oral contraceptives
- fistulas
- nutritional factors [58, 59]
- Human Immunodeficiency Virus (HIV) infection
- other infections caused by agents throughout sex-related activities (e.g., Chlamydia trachomatis, Herpes simplex virus) [11].

As it was already mentioned, in 70 - 90% of anal HPV-positive cases, the end of the "window period" marks the rise of ASCC-related patho-histological changes.

ASCC is a collective term used to describe three sub-types of squamous cell carcinoma - large cell keratinzing, large cell non-keratinizing and basaloid. The three sub-types do not differ significantly in their prognostic features. Data from the US National Cancer Database, processed by the American Joint Committee on Cancer (AJCC), shows that more advanced ASCC is inversely proportionate to patients' survivability rates.

ASCCs have localized expression with or without associated regional lymph node activation. In the case of the latter, it has been noted that tumors found above the pectinate line spread primarily to the anorectal, perirectal, and internal iliac lymph nodes. Tumors below the pectinate line impact mostly the superficial inguinal lymph nodes. ASCC can metastasize to any distal organ. Yet, the liver and the lungs seem to be the most frequently impacted. Secondary spread to the abdominal cavity is not unheard of [12]. Some examples of ASCCs are as follows:

Figure 2. ASCC with out-growths restricted to the anal canal (photo courtesy of Société Nationale Française de Colo-Proctologie, [5])

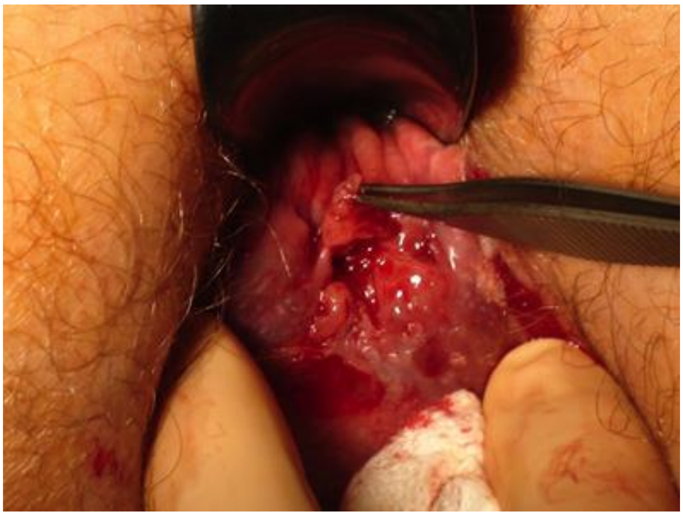

Figure 3. Rugae or fissure-incorporating ASCC (photo courtesy of Société Nationale Française de Colo-Proctologie, [5])

ASCC diagnosis starts with a visual examination of the affected area. In the absence of epithelial out-growths, an anal Pap smear test is administered. An anal swab or endocervical brush is introduced in a full circular motion into the anal canal. The collected cells and mucus are then histo-pathologically processed [13].

The anal Pap smear test is usually accompanied by more invasive diagnostic methods - an anoscopy, and on occasion, rectoscopy. Anoscopy allows better visual evaluation of the number, depth, distribution, and position of HPV-infected lesions, and rugae. Based on the experience of the proctologist performing the anoscopy, the latter is instrumental in recognition of areas of morphological urgency, i.e., in need of performing an immediate biopsy. Such need is also deemed proper in the presence of suspicious mucosal out-growths like the ones visualized in Figures 2 and 3. Then, the discovered ASCCs are classified according to the anatomically-driven TNM Classification system, devised by the Swiss-based Union for International Cancer Control (UICC). Each patient's condition is coded with the aid of three letters:

- T - indicates the primary tumor site
- N - notes any regional lymph node involvement
- M - draws attention to the presence of close or distant metastases.

To denote the specific stage of ASCC's development, TNM's classification system employs Roman numerals (i.e., stage I, II, III, and IV cancer).

Table 1. TNM classification of histopathological findings in the anal canal [36].

T primary tumor	
T0	No evidence of primary tumor
Tx	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Primary tumor with a maximum length ≤ 2 cm
T2	Primary tumor with a maximum length >2 cm, but ≤5 cm
T3	Primary tumor with a maximum length > 5 cm
T4	Invasive tumor in one, or several adjacent organs
N regional lymph nodes	
N0	No regional lymph node metastases
Nx	Regional lymph nodes cannot be assessed
N1	Regional, perirectal lymph nodes affected
N2	Unilateral internal iliac and/ or inguinal lymph nodes affected
N3	Bilateral internal iliac and/ or inguinal lymph nodes affected
M – metastases	
M0	No distant metastases
Mx	Distant metastases cannot be assessed
M1	Distant metastases present: Pulmonary (PUL) Osseus (OSS) Hepatic (HEP) Brain (BRA) Lymph nodes (LYM) Bone marrow (MAR) Pleura (PLE) Peritoneum (PER) Adrenal (ADR) Skin (SKI) Other (OTH)

ASCCs' pre-medicatory treatment potential is determined clinically (cTNM), following information collected from the visual examination, lab results from the anal Pap smear test, and histopathological evaluation of collected biopsy material. Due to the high immunogenicity of HPV-positive ASCC with lymph node activation. However, the majority of tumors are surgically excised.

Data obtained from the procedure and the subsequent histopathological examination of the excised mass allows a post-surgical pathologic classification (pTNM). The pTNM is then used to establish strategies for post-surgical adjuvant therapy and follow up [35]. In an attempt to predict patient survivability, the American Joint Committee on Cancer improved on the TNM classification:

Table 2. The hybrid AJCC- TNM classification of histopathological findings in the anal canal [12].

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ANATOMIC STAGE/PROGNOSTIC GROUPS			
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
	T3	N0	M0
IIIA	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
	T4	N0	M0
IIIB	T4	N1	M0
	Any T	N2	M0
	Any T	N3	M0
IV	Any T	Any N	M1

For tumors that cannot be removed, the international standard of medical care recommends chemoradiotherapy (CRT) using 5-fluorouracil and mitomycin C. It has been noted that about 30% of patients do not respond positively to the treatment [2].

6. Future Research

Future scientific work on the HPV - ASCC axis must target a timely, correct diagnosis of anal squamous cell carcinoma.

They should start with deep sequencing of fecal bacteria, matched with the observation on bacteria's interaction with anal canal lesions and the HPV, alike.

Additional efforts should also be paid to the global distribution of anal HPV strains, once they have reached the blood and the lymphatic systems. This avenue should reflect research on the mutation capabilities of the virus in radically different tissue environments to the original one.

As most contemporary external imaging methods have not been particularly instrumental to the proper diagnosis of ASCC (and anoscopy/ rectoscopy are traumatic for the anal canal and the patient), a new human operator or Artificial Intelligence (AI) driven, light-, camera- and biopsy pince-fitted micro-robotic entities for anal entry are needed. Some discussions follow.

A) Image Analysis:

Computer image analysis can help to evaluate the alterations in the cells to discern between benign and malignant lesions where the samples can be obtained through biopsies and diagnosed as ASCC [38, 39].

The ever-growing availability of digital histopathological images augmented the demand for their automatic analysis, e.g., computer-aided diagnosis via machine learning. However, digital pathology and related tasks must consider some issues. Novel digital pathological techniques within image analysis can arise from the more intensive use of computational intelligence to address some particular and unsolved problems and recommend possible solutions [40-46, 61].

B) Multimodal Imaging

There are several types of image processing equipment. Each kind comprises an imaging modality.

Positron Emission Tomography (PET) and Computed Tomography (CT) scans are varieties of medical examination equipment that can be currently used in the theragnostics (that is, by selecting the best biopsy site, assessing the treatment response, seeking other related tumors, searching suspect tumor recurrence with markers, and radiation treatment planning) of cancers of several sites [46]. Since many tumors seek fluoro-D-glucose (FDG), a high FDG uptake is customarily linked with a high manifestation of glucose transporters. However, an increased FDG uptake does not necessarily indicate neoplasms because inflammatory processes may also show increased uptake (such as abscesses, fungal infections, tuberculosis, diverse types of inflammations, and inflammations related to radiation usage among others that cause false-positive results) [46, 47].

The Tissue Microarray (TMA) is a high-throughput technology employed in oncology to investigate molecular markers. It allows the rapid evaluation of biomarkers in thousands of tumor samples, using commonly available laboratory assays such as immunohistochemistry and in-situ hybridization. TMA has proven to be valuable to study tumor biology, help to develop diagnostic tests and explore oncological biomarkers. Up to now, TMA has a significant impact on clinical oncology, and it promises more potential applications [48, 49].

Multispectral Imaging (MSI) and Hyperspectral Imaging (HSI) comprise new modalities for biomedical applications initially developed for remote sensing [50]. They can extend vision to infrared in addition to near-infrared wavelength regions of the electromagnetic spectrum. One can use a Multispectral Image (MSI) or Hyperspectral Image (HSI) that, in combination with another immunohistochemical approach, can pinpoint and quantify immune cells in diagnostic tissue samples. The resulting images can be related to traditional visual evaluation of immune cells from an extensively annotated TMA to correlate immune cell counts from adjacent tissue sections with knowledge about the immune cells' distance mapping and the immune signatures associated with clinical parameters [51].

Whole Slide Imaging (WSI) or scanning for TMA core annotation and region selection for MSI/HSI can be done. A pathologist can visually examine the scanned image once the initial image analysis is ready. Additionally, regions/samples with staining artifacts and with large necrotic areas can be left out. Image processing comprises the training session and image analysis session. The training session can include manual annotation of three region types: tumor, stroma, and blank areas. Then, a machine-learning-based algorithm can execute the tissue segmentation based on the nuclear 4′,6-diamidino-2-phenylindole (DAPI) staining, for instance [39-45, 52].

Despite the overall reliability of the data produced by MSI and HSI, some limitations should be mentioned. There is some degree of crosstalk between a couple of the fluorophores with overlapping emission spectra. MSI unmixing of fluorescent signals is sensitive to deviations in the signal profile that may be slightly changed when staining becomes very intense. Future studies can solve this problem by ensuring that no cells are stained above a certain threshold. Studies must be validated using benchmark imaging datasets before utilization with more specific diagnostic tissue samples. Image analysis enables immune cell classification, along with the creation of in situ maps containing the spatial distributions of cells. The specific prognostic effects of different immune cell constellations can emphasize the use of this diagnosing strategy and, in the future, it may be part of the immune status routine characterization of cancer patients.

C) *Robotics*

The prevention, early discovery, rapid diagnosis and timely management of cancer are crucial. Information Technology (IT) can expand the patient survival rate and increase the satisfaction of patients, caregivers, and healthcare providers as far as cancer goes [64]. Robots are utilized in different healthcare areas and their applications in surgery have arisen to the cancer treatment realm. IT devices can boost dexterity, efficient motion scaling skills while providing high-quality 3D computer vision for surgeons with reduced loss of blood, a noteworthy decline in narcotic usage, and low hospital stay period for patients. Nevertheless, many challenges persist, such as the absence of surgical community support, high costs, availability of different sizes, and lack of tactile/haptic feedback. Surgeons also need more evidence and proper support from physicians [57, 60, 62, 63].

Microbeads, microgels, and other nanodevices can be assembled within magnetic fields [53-56] to provide a cost-effective theragnostic without potentially toxic interactions. External magnetic fields can control these micro-robots and nanorobots. Their motion can be actuated accurately to bring together 2-D and 3-D hydrogels that encapsulate several types of cells. These methodologies deliver new ways to handle 3D engineering structures and offer extensive potential usages in regenerative medicine, experimental biology, and drug screening, among other scenarios.

Research with robotic surgery for cancer patients will continue because some patients are unable to undergo manually guided surgery or other invasive, high-risk procedures [56, 57].

Robotics will also help advances in 3D and 4D imaging with different types of cameras, augmented reality options, image processing techniques, and 3D printing [65-68].

Advances in databases will also impact ASCC theragnostic [69].

7. Conclusion

ASCC is a neoplasia mostly associated with HPV. Future studies will improve its theragnostic. This research is organized in a three-fold fashion: (i) studies about the pathogenesis of the disease, (ii) its theragnostic along with (iii) a bibliographical review of the central HPV characteristics, and the way it affects people.

Studies such as this can be seen as crucial elements for understanding and preventing this Sexually Transmitted Disease (STD), which has its highest incidence rates in underdeveloped and developing countries, where health and education policies are often scarce or nonexistent.

Chemoradiotherapy is the treatment of choice, with abdominoperineal resection kept for the cases of failed treatment or recurrence. Evidence progresses to adjust the treatment to patients individually, considering each person prognostic elements and biological tumor features. Hence, among the prevention measures, one can cite are the screening and vaccination programs of male individuals.

IT will bring in several improvements to ASCC theragnostic.

8. Conflict of interest statement

We certify that there is no conflict of interest with any financial organization in the subject matter or materials discussed in this manuscript.

9. Authors' Biography

Ana Carolina Borges Monteiro: B.Sc. in Biomedicine from Centro Universitario Amparense - UNIFIA, Brazil (2015). Currently, she pursues a D.Sc. degreee from the Department of Communications (DECOM), Faculty of Electrical and Computer Engineering (FEEC) at the State University of Campinas (UNICAMP), Brazil, and she is a researcher at the Laboratory of Visual Communications (LCV). She is also the Registration Chair and a reviewer for the Brazilian Symposium on Technology (BTSym) and has expertise in the areas of clinical analysis, histology, biomedical engineering, image processing and the medical internet of things. She operates several types of electronic medical equipment, has some knowledge on microscopy and some programming experience in MATLAB. She has performed work, research experiments/projects, and internship in municipal hospitals.

Dr Abdeldjalil Khelassi: is an Associate Professor at Tlemcen University, Algeria. He obtained his Doctor in Science (2013), Magister (2008) and Engineer (2004) in Computer Sciences from the Department of Computer Science at Tlemcen University. His research interest includes cognitive systems, knowledge-based systems, case-based reasoning, distributed reasoning, fuzzy sets theory and health science. He is the editor manager of Medical Technologies Journal and associate editor at Electronic Physician Journal.

Yuzo Iano: B.Sc., M.Sc., and Ph.D. degrees (1986) in Electrical Eng. at UNICAMP, Brazil. He has been working in the technological production field, with 1 patent granted, 8 filed patent applications and 36 projects completed with research and development agencies. He has supervised 29 doctoral theses, 49 master's dissertations, 74 undergraduate and 48 scientific initiation works. He has participated in more than 100 master's examination boards, 50 doctoral degrees, author of 2 books and more than 250 published articles. He is currently a professor at UNICAMP, Editor-in-Chief the SET International Journal of Broadcast Engineering and General Chair of the Brazilian Symposium on Technology (BTSym). He has experience in Electrical Engineering, with knowledge in Telecommunications, Electronics and Information Technology, mainly in the field of audio-visual communications and multimedia.

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