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Photodynamic Therapy Using Endoscopy Capsule Robot

Sherif Hamdy ElGohary (Corresponding Author)
Department of Biomedical Engineering and Systems, Faculty of Engineering, Cairo University, 12613, Cairo, Egypt
Healthcare Engineering and Management Department, Cairo University Faculty of Engineering, Cairo, Egypt
Email: sh.elgohary@eng1.cu.edu.eg

Yomna Sabah Mohamed
Healthcare Engineering and Management Department, Cairo University Faculty of Engineering, Cairo, Egypt

Mennatallah Hany Elkhodary
Healthcare Engineering and Management Department, Cairo University Faculty of Engineering, Cairo, Egypt

Omnya Ahmed
Healthcare Engineering and Management Department, Cairo University Faculty of Engineering, Cairo, Egypt

Mennatallah Hesham
Healthcare Engineering and Management Department, Cairo University Faculty of Engineering, Cairo, Egypt

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Abstract

Among the photosensitizers used in Photodynamic therapy (PDT) technique for cancer treatment, it is found out that the Methylene blue and glycoconjugates chlorine are the best ones for this purpose. In this paper, it is suggested to use Active Capsule Wireless Endoscopy Robot instead of the traditional endoscope. The capsule has many valuable features. It uses LEDs as a source of light in the PDT to kill the colon cancer cells. So, the doctor can make use of the advantage of applying the LED light locally at the tumor which was previously injected by the photosensitizers, the light activates these photosensitizers and a photochemical reaction starts that makes the colon cancer cells die. The light with effective wavelength and power density, energy level and controlled LED light intensity will be applied. Active locomotion capsule endoscopy with an electromagnetic actuation system that can achieve a 3-D locomotion and guidance within the digestive system. The paper also discussed how to manage the required power in the capsule for all parts, LEDs, camera, transceiver, and locomotion.

Keywords: Photodynamic therapy; Photosensitizers; Wireless capsule; Endoscopy; Colon cancer; Photochemical reaction.

1. Introduction

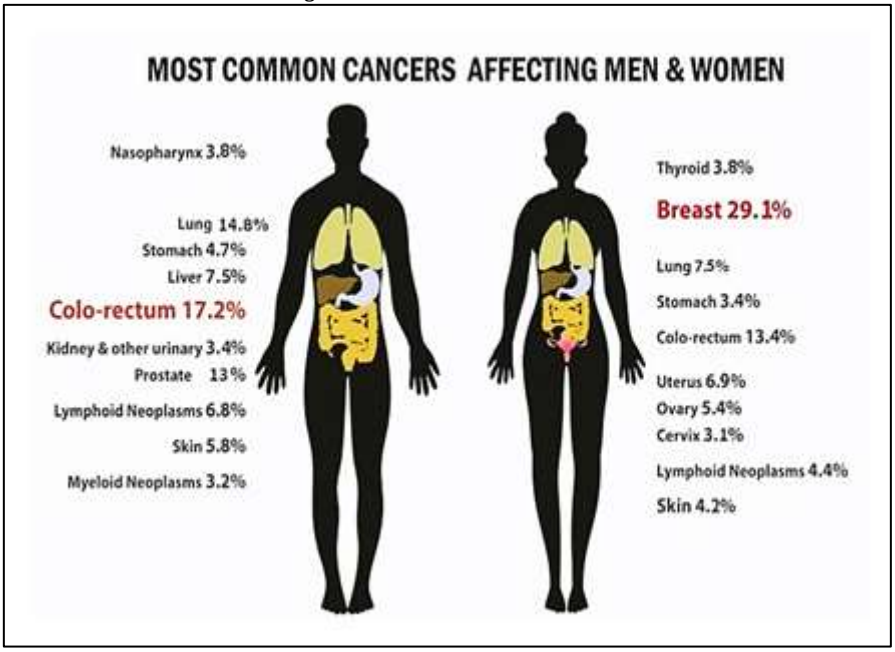
Colon cancer is a type of cancer in the large intestine (large bowel). It can be also named Colorectal cancer. Colon is the ultimate portion of the digestive tract. As shown in figure 1 Colon cancer is the second most widespread cancer in women of about 13% and the most commonly occurring cancer in men of about 17%. 2018 saw more than 1.8 million new cases in 2018 [1, 2].

Colon cancer can cause several diseases like unexplained weight loss, iron deficiency anemia, blood in stool that may or may not be visible, changes in stool consistency, loose and narrow stools, irritable bowel syndrome, and abdominal pain and cramping [3].

The most cited dangers for advancement of colon cancer is age, genetic syndromes, family history, and inflammatory bowel disease [4]. Most cases of colon cancer start from noncancerous tumors called adenomatous polyps that cause no symptoms and it becomes a greater risk of cancer if its diameter becomes greater than 1 cm and if it is not removed, they will grow continuously and can become cancerous [5].

Treatment options depend on the type and stage of the colon cancer, overall health, possible side effects, and the patient's preferences. Treatment options are chemotherapy, surgery, and radiotherapy, which have long recovery periods and many side effects. So, there is an alternative treatment which is Photodynamic therapy (PDT) and it seems to be a safe and a feasible treatment option for colon cancer.

Figure-1. Most Common Cancers [6]



There are 3 essential components of PDT which are photosensitizers, light, and oxygen. Photosensitizers are the non-toxic dye that is injected into the bloodstream. Each photosensitizer is stimulated by light with a particular wavelength that differs from the other photosensitizers. After about 48-72 hours, the colon cancer cell is exposed to visible light. There is an interaction between the light and the photosensitizer in the presence of oxygen and this causes oxygen reactive species to be and thus, cell death. PDT also stimulates the immune system to attack cancer cells. For light delivery, traditional colonoscopes are modified with optical fibers. The light can be laser or light emitting diodes. Colonoscope have clear disadvantages, the exam examination may not identify all little polyps and cancers, food system and medications may need to be adjusted, before the test it is required a thorough cleansing of the colon, Sedation is nearly continuously utilized, and it can take a few hours to wear off, bleeding from a tear in the colon or rectum wall, and cramping or bloating might happen a short time later [7]. To overcome these issues, wireless capsule endoscopy has been proposed mainly as a diagnostic solution in recent years. Wireless capsule endoscopy is a non-invasive diagnostic that diminishes the level of discomfort and can be well endured by the patients, with exceptionally few contraindications. Despite this technique being developed for the screening of the small bowel originally, later it applied on the colon, esophagus, and stomach [8].

In this paper, instead of using the traditional colonoscope in the PDT we will use the active locomotion wireless endoscopy capsule controlled by the doctor. The capsule will be used to apply light into the colon cancer cells which is previously injected by the photosensitizers. LEDs are the source of light with wavelength, power density, and energy level suitable for the photosensitizers used.

2. Material and Method

2.1. Photosensitizers

Photodynamic therapy (PDT) is still an experimental modality which uses red light in conjunction with a systemic or topical photosensitizer. Compared with the normal surrounding tissue, the photosensitizers have a longer retention time in malignant tumors. It is found out that the Methylene blue and glycoconjugates chlorine are the best photosensitizers to use in the photodynamic therapy for cancer.

2.1.1. Methylene Blue (MB)

Methylene blue has been used in clinical medicine for many years and has been accepted as a drug for photodynamic therapy (PDT). Based on characteristics of Methylene blue [9]. Because of that, the antitumor effect of MB mediated PDT was evaluated by using 635nm LED light source to colon cancer cells. After 72 hours of injection, significant antitumor effects were noticed when MB mediated PDT was used with LED light sources,80% of cell death took place [10].

2.1.2. Glycoconjugates Chlorine (H2TFPC-SGlc)

H2TFPC-SGlc was developed as a chlorine-based photosensitizer and was made to have some advantage. It is examined on the off chance that H2TFPC-SGlc may act as a potential photosensitizer of PDT in gastric and colon cancer in vitro as well as in vivo or not. In vitro, H2TFPC-SGlc-mediated PDT can initiate apoptosis and is around 30 times more cytotoxic than other-mediated PDT. In xenograft tumor models, H2TFPC-SGlc-mediated PDT suppressed tumor growth and had no adverse effects on surrounding tissues, as compared to light alone. The results indicate that PDT with H2TFPC-SGlc offers a minimally invasive therapeutic modality for clinical treatment of gastric and colon cancer.

In conclusion, we demonstrated that H2TFPC-SGlc mediated PDT effectively suppressed the growth of xenograft tumors, inducing apoptosis.had superior selectivity of cancer cells and was able to decrease the side effects, such as chronic phototoxicity of skin. Based on the potential and characteristics of H2TFPC-SGlc [11], it was confirmed that H2TFPC-SGlc is a potential photosensitizer for PDT in gastric and colon cancer.

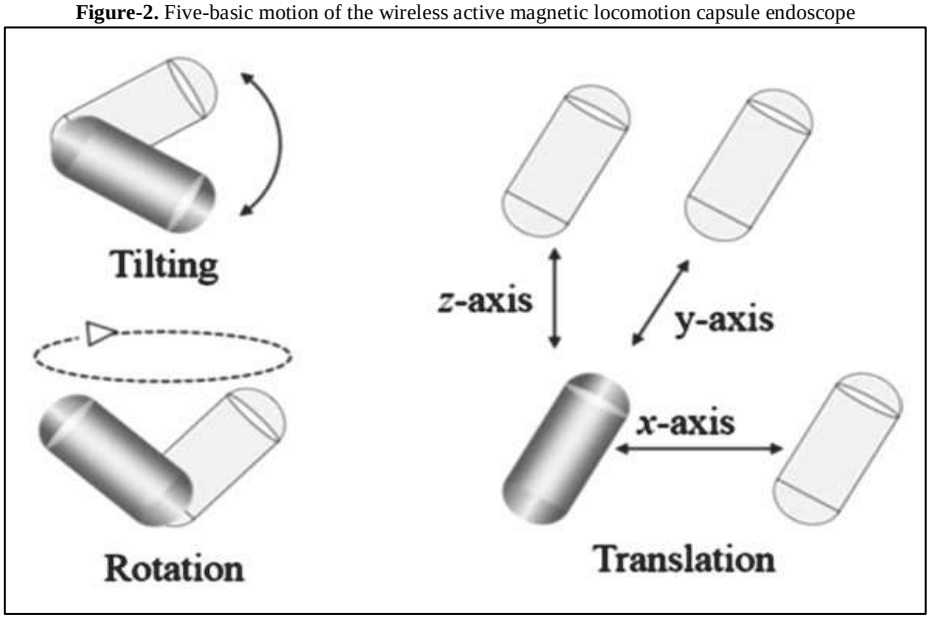
2.2. Endoscopy Capsule and Light Emission

We will use the Active Capsule Endoscopy Robot instead of the traditional endoscope. This capsule will use LEDs as a source of light in the photodynamic therapy to kill the colon cancer cells. So, the LED light will be applied locally to the tumor.

2.2.1. Type of the Active Locomotion

Apart In this operation, we will use the active locomotion capsule endoscopy with an electromagnetic actuation system that can achieve a 3-D locomotion and guidance within the digestive system. This type of capsule can achieve adequate degrees of freedom and sufficiently diverse capsule motions. It consists of five pairs of solenoid components and a capsule endoscope with a permanent magnet. It can perform various movements with the magnetic field generated by the solenoid components [12]. This type of capsule saves energy and power. Thus, the doctor can easily reach the cancer cell and apply the light and to control the direction and the space between the cells and the capsule that are sufficient to kill the cancer cells in the colon.

Figure-2. Five-basic motion of the wireless active magnetic locomotion capsule endoscope



2.2.2. Being Powering of the Capsule

Managing the power is the major challenge in the capsule, since the capsule will use LEDs as a source of light to kill the colon cancer cells. So, we need more power and energy for this operation than that used in a capsule for diagnosis. The batteries usually used in the capsule are the silver oxide button batteries. Some capsules use two or three of them that allow up to 15 h operation [13].

To overcome the power shortage, we have three solutions:

1- Wireless inductive power transfer:

- We can use rechargeable batteries and wireless inductive power transfer. wireless inductive power transfer can transfer up to 330mW to the capsule under all possible directions using a 3D inductive coil and within a 0.63cm³ volume [14].
- Inductive-based wireless recharging system that can provide 1W power and is able to recharge a VARTA CP 1254 battery in 20 minutes [13].

2- Micro-batteries that enhance power density and reduce battery dimensions.

- We can use lithium ion micro-batteries with power densities up to 7.4 mW cm^{-2} μm^{-1}, which is 2,000 times higher than that of other micro-batteries [15].

3- Magnetic field which is used for capsule locomotion can be harnessed for capsular power generation and battery charging from the position, orientation, and velocity of the capsule [16].

2.2.3. LEDs of the Capsule

In this operation, we have 2 groups of LEDs.

1- For lightning the colon.

- The number of LEDs used for lightning differs from one capsule to another (2 to 6 LEDs).

- We can use 4 white light LEDs in our capsule and it's sufficient. The power consumption of one LED is about 1.75 mW. The four LEDs could provide illumination of about 210 lx in 10mm or 363 lx in 5 mm and this at the working voltage of 3V [17].

2- Source of light in the photodynamic therapy to kill the colon cancer cells.

- The wavelength of the light depends on the photosensitizers used in the process. The doctor can control the intensity of the LEDs by controlling the current passing through it.

Table-1. Properties of LED light with respect to Photosensitizers [10, 11]

Photosensitizers Properties	Methylene blue (MB)	$H_2TFPC-SGIc$
LED light wavelength	635 nm	633 nm
Power density	16 mW/cm²	37 mW/cm²
Energy level	3J/cm²	16 J/cm²
Exposure time	188 sec	432 sec

In photobiology and photo-physics, the integral of irradiance over the treatment time is often referred to as "energy dose" or simply "dose" (D, J/cm^2), and it depends on the radiant flux ϕ_{watt} (W) of the considered source, on the irradiated surface "S" and irradiation time "T" by this formula [8]:

$$D = \frac{1}{S}\int_0^T \phi_{watt}\, t\ .dt$$

2.2.4. Camera and Transceiver

The CMOS camera is used in the capsule. It is a monolithic 320×240 active-pixel RGB/gray level camera-on-a-chip sensor. It has been fabricated using 0.18μm CMOS technology from UMC. The obtained images need a compression system to compress them and send them to the RF transceiver to enable high frame rate. So, we can add the compression system in the RF transceiver or in the CMOS camera [18].

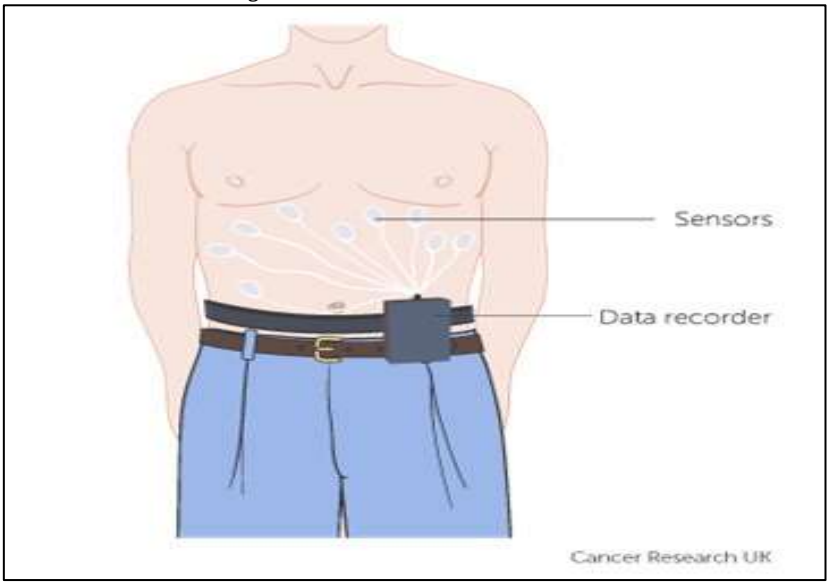
3. Results

3.1. Scenario Solution and Mechanism

Researchers have focused on photodynamic therapy (PDT), an adjunctive cancer therapy in which light-sensitive tumor- treating drugs which we call photosensitizers are injected by the intravenous. In the first step of PDT for cancer treatment, a photosensitizer is injected into the blood. The agent is retained by cells all over the body but remains in cancer cells (tumors) longer than it does in normal cells. Nearly about 24 to 72 hours after the injection with this agent, it is found that most of the agent has left normal cells but remains in cancer cells, LED light is applied to the tumor. The photosensitizer within the tumor absorbs the light and produces an active form of oxygen that kills most of the cancer cells. Also, PDT appears to shrink or destroy cancer tumors in two ways. The photosensitizer can damage blood vessels within the tumor, then prohibit the cancer from receiving necessary nutrients. PDT also may activate the immune system to attack the cancer cells [19]. LED light activation offers essential improvement over lasers, a LED probe produces longer-wavelength, broad-spectrum, near-infrared light, enabling both deeper and wider penetrations [20].

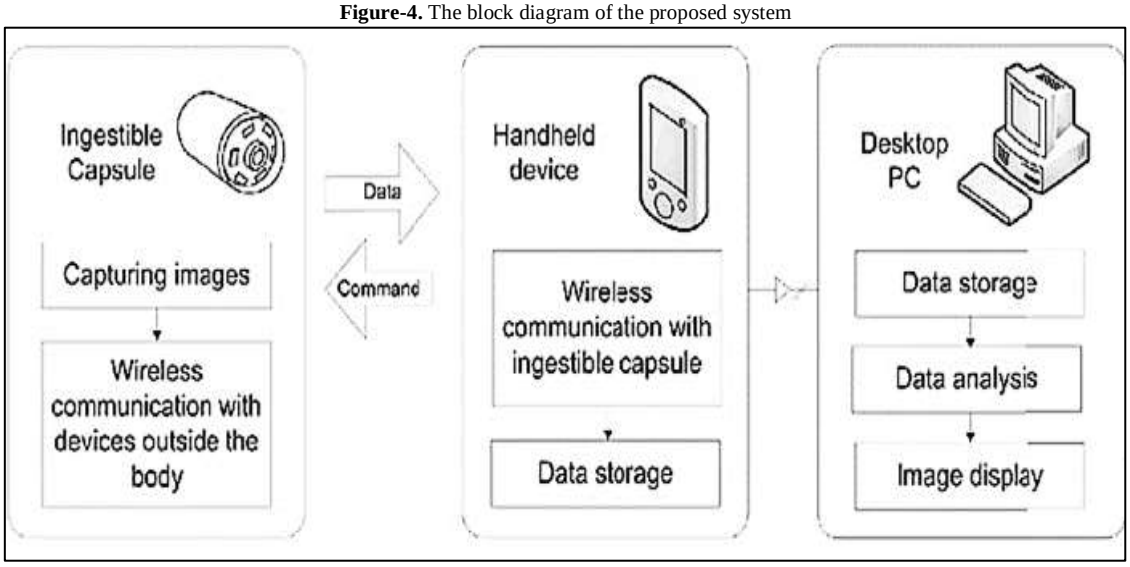
In the proposed technique, a capsule endoscopy will be used to generate LED light on the tumor instead of the normal endoscopy because Capsule endoscopy helps doctors see inside the small areas that aren't easily reached with more-traditional endoscopy properties. After a patient swallows a capsule endoscope, the patient's digestive tract images are wirelessly sent to the storage device worn on a belt around the patient's waist that has sensors on patient's body that connected to the storage device as shown in (Fig.3).

Figure-3. Data recorder device and sensors



For example, in every capsule endoscope system, the patient wears specified clothes for the capsule that has important equipment inside. The equipment is basically a battery-powered micro-computer with wireless communication ability. The meant capsule endoscope communication system is shown in (Fig.4). The capsule endoscope sends the data to the storage tool in a mobile unit for the patient [21].

Figure-4. The block diagram of the proposed system



The first way is when we put the magnetic sources in the capsule and the sensing modules outside the patient's body, And the second way is by putting the sensing module in the capsule and the magnetic sources outside of the patient's body [22].

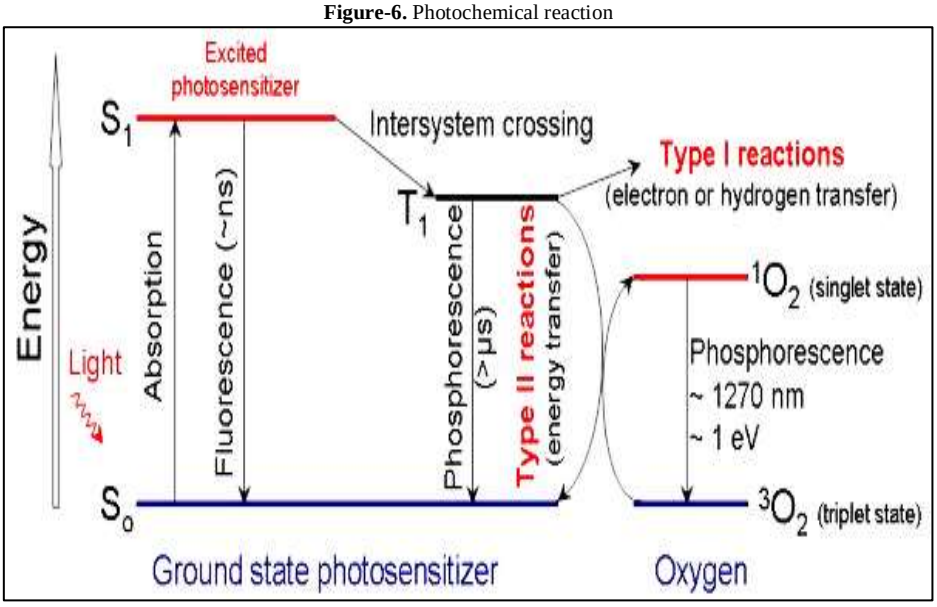
In both cases the doctor detects the tumor's place and uses the magnetic control system and the sensing modules to lead the capsule inside the patient's body to generate the LED light with a specific wavelength that activates the photosensitizers to kill the tumors. The capsule magnetic control system as shown in (Fig. 5). The magnetic field produced by the MCE (magnetic capsule endoscopy) can be edited and can reach a maximum of 200 mT. The capsule location was captured through a simulation, based on the magnetic field produced by the guide system. We can find gravity and magnetic sensors within the capsule. The gravity sensor can be used to calculate the angle between the orientation of the capsule and the gravity direction, the magnetic sensor can calculate the outside magnetic field. The outside magnet with its magnetization direction over the direction of gravity moves around by the capsule, and the MCE sensor results are captured and transmitted to the computer. By a programmed search process, the outside magnet can be put just over the capsule. At this synchronization position, while the outside magnet rotates, the capsule also rotates, and the capsule's orientation and location can be measured. The outside magnet moves according to the calculation results so that it always stays just above the small magnet of the capsule. In case the outside magnet and the capsule are out of location synchronization, the search procedure can be used to find the capsule again. Although the capsule can be controlled manually, this automatic procedure greatly minimizes the complicated process to navigate the capsule inside the patient's body [23].

Figure-5. The Capsule magnetic control system

3.2. Dynamic Process of PDT

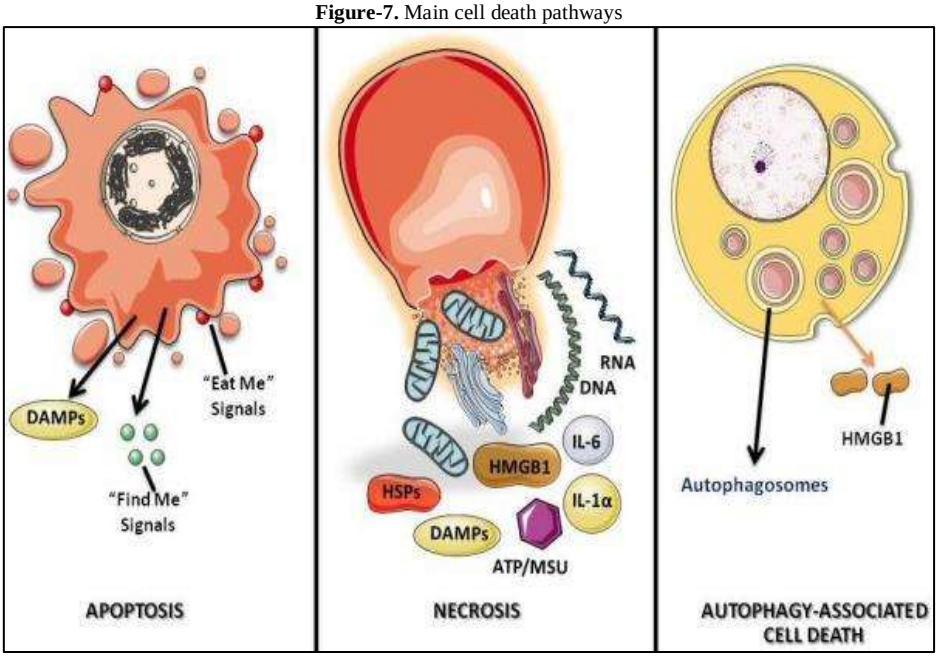
Most of the Photosensitizers which are the molecules that PDT process relies on, have two electrons in their ground state and these electrons spin in opposite directions, located in an adequate orbit for them. the photochemical process starts as soon as photosensitizer absorbs light photon in its ground state (S0), Then it raises this photon to an excited state (S1) with an energy of approximately 170–190 kJ.mol−1 which corresponds to a wavelength of 620–690 nm to become very unstable and emits this excess energy as fluorescence and/or heat. And photosensitizer has high intersystem crossing (ISC) which requires a spin flip of one of the unpaired electrons and it gives PS the ability to transfer from S1 to an excited a more stable triplet state (T1) with an energy of about 110–130 kJ.mol−1. In triplet state the photosensitizer can decay without any radiation or to transfer its energy to a unique molecular oxygen (3O2), which can be a triplet in its ground state. Then (3O2) is excited to its highly reactive singlet state (1O2) with an energy of approximately 94.5 kJ.mol−1. The lifetime of singlet oxygen (1O2) is very short (~10-320 ns), its diffusion is limited to approximately 10-55 nm in cells [24-26].

Figure-6. Photochemical reaction



There are two methodologies that reached studies about PDT dynamics. First one, can determine the concentration of singlet oxygen in cells microscopically as it considers the diffusion of oxygen and photosensitizer. Foster et al was the first one to present this model and show its results in multicell tumor spheroid models. And these models represent that most of the resulting effects in PDT is because the photochemical process itself consumes oxygen and if the rate of oxygen consumption in the photochemical process is greater than the rate at which oxygen can be resupplied by the vasculature or its surrounding medium. This part cannot receive enough oxygen for a period, and this is called transient hypoxia.

Figure-7. Main cell death pathways



Second one, it approximates oxygen and photosensitizer with simpler functions instead of their actual diffusion process. As it differs in its fluence rate based on the diffusion approximation. This model provides a quantity (reacted singlet oxygen) that can be used directly for clinical PDT dosimetry, and that relates directly to the three-dimensional distribution of photosensitizers, light fluence rate, and a mean tissue oxygenation distribution [26].

So briefly when photosensitizer accumulates in the tumor and the light activates it, photochemical reaction starts. As soon as ($^1O_2$) is produced. Then, a massive damage to cellular macromolecules leads to tumor cell death via an apoptotic, necrotic or autophagic mechanism. Accompanied by induction of an acute local inflammatory reaction that participates in the removal of dead cells, restoration of normal tissue homeostasis and sometimes in the development of systemic immunity

4. Discussion

It is found that one of the most challenging problems usually faced is the possible involvement between the localization system and used ferromagnetic modules, such as surgical tools. But also, the locomotion module itself, in case the capsule's active propulsion is detected by high-intensity permanent or electromagnetic devices. Therefore, this section has been organized to detail magnetic localization methods in the condition with and without the use of high-intensity, magnetically actuated modules. The most remarkable components of a magnetic tracking system are one or more magnetic devices (transmitters), and one or more sensor systems (receivers). Because of that, based on the close position between transmitters and receivers, two main ways are known for robotic capsule localization.

Finally, photodynamic damage will occur very close to the intracellular location of the photosensitizer. At this stage, the PDT process treats malignant cancer either in malignant cells or cells of the tumor vasculature by damaging these cells causing their death [27]. PDT can evoke the three main cell death pathways: apoptotic, necrotic, which are commonly applied by PDT, and autophagy-associated cell death Apoptosis is characterized by chromatin condensation, separation of chromosomal DNA, cell shrinkage, membrane blebbing and formation of apoptotic bodies without the breaking of plasma membrane then these cells release find me and eat me signals required for cleaning of remained corpses. Necrosis is characterized by vacuolization of the cytoplasm and breakdown of the plasma membrane and due to the release of cellular contents it is presented in an inflammatory reaction [24].

5. Conclusion

To sum up all the points that had been discussed in this paper, we introduced a more professional method for treatment of cancer in colon by PDT, which can be used also for cancer in any other difficult place to be reached like colon. This method is Photodynamic Therapy Using Endoscopy Capsule Robot. We knew the role of physics in this method and understood the parameters of this process as photosensitizer and the best type to be used. And how this effect on the decision of choosing the suitable led to be used in the capsule to manage the power needed to kill cancer cells, and finally the mechanism of this method and how the cancer cell is really damaged by the photochemical process the happen when the photosensitizer is exposed to the light and the cancer cell is damaged by the singlet oxygen produced by this process, in the same time we can activate the immune system to attack cancer.

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