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1. Introduction to cancer

Cancer, this disease that is widely spread all over the world, is still introducing millions of new cases and considered as one of the major causes of deaths among the humankind with all its types every year.

Cancer can be simply defined as a genetic disease characterized by the uncontrolled division of abnormal cells anywhere in the body that may have the ability to invade other tissues. However, there are other several definitions to illustrate this disease (Drev 2014, WHO 02.08.2015).

Cancer arises in the body by unlimited causes and risk factors and varies from a person to another (i.e. a person can develop cancer by a certain cause, while another can resist it under the same conditions), it may also develop through some daily habits the individuals use to pass by in their normal life as smoking or ordinary life styles as working in certain industries or mines, plus, the similarity in symptoms of cancer with other diseases, all of these, are reasons which delay the diagnosis and thus complicating the treatment plans in most of the cases, thus, it is impossible to terminate cancer completely out of our planet, although it is not classified as a transmitted disease (cannot be transferred from an individual to another).

1.1. Epidemiological facts

In 2012, a study counted more than 8 million deaths of cancer in the mentioned year and estimated that the number of new cancer cases reaches about 14 million people all over the world annually (Torre et al. 2012).

It is the main cause of more than one tenth of the deaths in many countries and the ratio may reach one fourth of deaths in some others (Pelengaris and Khan 2013).

Breast and lung cancers are globally the most types causing deaths with different percentages among the world regions, the most frequently diagnosed types among males are the prostate, lung, liver and colorectal, while in females, breast, gynecological

malignancies (including ovarian, cervical, vaginal....etc.), stomach and colorectal cancers are the most diagnosed (Torre et al. 2012).

1.2. Definitions

Mutation: alterations in the coding sequence of the DNA.

Apoptosis: programmed cell deaths which occur as a result of series of molecular stages to clear off abnormal or useless cells.

Metastasis: the diffusion of cancer cells from a tissue to another all over the body.

Neoplasm: an abnormal tissue that is created when the rate of cells division is higher than normal and their deaths is lower than normal.

Angiogenesis: formation of new blood vessels (National-Cancer-Institute 1.8.2015).

Warburg effect: production of lactic acid through aerobic glycolysis regardless the amount of oxygen offered in an abnormal respiration processed by cancer cells (Heiden et al. 2009).

Tumor, malignancy, carcinoma, lymphoma, leukemia, sarcoma and many other terms are used to describe different cases and types of the disease depending mainly on either the tissue or the organ of origination, as it can initiate in any of the different body tissues through any of the billions of cells the body consists of (National-Cancer-Institute 1.8.2015).

1.3. Mechanism of incidence

To understand the mechanism of the cancer incidence, there are some facts that must be clearly explained about the cell.

Any cell in the body contains the nucleus (except some types of cells as the red blood cells) that carry the DNA, this DNA consists of huge number of genes which are responsible for the different cell's functions.

3 main types of genes control the function of cell replication:

Proto-oncogenes (more than 100 were identified e.g. K-ras): control the cell growth and division.

Tumor suppressor genes (more than 30 were identified e.g. p53 and APC): involved in limiting the cell division.

DNA repair genes (e.g. mlh1): have the main role in restoring the damaged DNA (Deininger 1999).

These genes always maintain the balance between new cells formation (proliferation) and the programmed cells death (apoptosis).

Some alterations (mutations) may occur by many factors in some of these genes to disrupt this balance, leading to an extreme acceleration in the rate of cell proliferation compared to the rate of apoptosis and thus the tissue expands uncontrollably.

If this expansion is tied within noticeable borders then it is called benign, if it diffuses (metastasis) to other tissues or organs by any means, it is called malignant.

In addition, new blood vessels (angiogenesis) are created as a reflex to the new tissues formed.

Mutations include the activation of proto-oncogenes to oncogenes, the inhibition of the function of the DNA repair genes and the function of tumor suppressor genes which is presumed as the turning point in cancer initiation (Rang et al. 2012).

It was proved that mutation in one single oncogene is incapable for carcinogenesis, there are always numerous mutations in many genes.

The main hallmarks which guide the mechanism of cancer incidence are:

Persistent proliferation through increasing the sensitivity of some of the cell's growth receptors as fibroblast growth factor receptor.

Replication immortality.

Limited apoptosis through the activation of anti-apoptotic factors.

Inhibited growth suppressors leading to lack of growth control.

Angiogenesis through arising from the surrounding tissue's blood vessels for nourishing the neoplasm formed.

Metastasis through blood vessels or lymphatics or suppression of what is called adhesion proteins (cadherins) which control the coalescence of neighboring cells together (Pelengaris and Khan 2013, Drev 2014).

Conclusion:

Cancer tissue characterized by genetic disorder leading to rapid cells proliferation, undifferentiated cells, inhibited apoptosis, angiogenesis and metastasis as a result of lack of cells adhesion either to a neighboring tissue or far ones through blood vessels or lymphatics.

1.4. Risk factors and causes

Many risk factors and causes are related directly or indirectly to the disease incidence, some are intrinsic (degree of sensitivity of the genes to mutations) which cannot be avoided and some others are extrinsic (carcinogens) which can be kept away or inhibited, including -for example- :

Age: A study in 2007 divided the cancer cases into three age groups and stated that children till the age of 10 group rarely develop the disease (1:612), this ratio increases from then till 30 years old to be (1:134) and above 65 years old, the ratio reaches almost the half of the men and one third of the women (Hayat et al. 2007).

Family history with cancer: As mentioned before, cancer is neither transferred nor inherited, but actually the genes may show similar degree of sensitivity to mutations in different generations.

Race: Statistics showed that the white women develop breast cancer in a rate much higher than the black ones, while colorectal and pancreatic cancer incidence are higher in black women (Siegel et al. 2014, Hayat et al. 2007).

Obesity: Risk of prostate cancer highly increases with obese men.

Smoking: A study in 1950 compared a group of cigarettes heavy smokers to another of non-smokers showed that the smokers are at 20 times more risk of developing lung cancer than the non-smokers group (Weinberg 2014). Passive smoking or regular exposure to different sorts of smoking also may be the cause of death of thousands of people annually (Pensiero et al. 2004).

Unhealthy diet: High consumption of red meat may enhance the risk of colorectal carcinoma (Oostindjer et al. 2014).

Hormones: Using oral contraceptives that consist mainly of hormones is the leading cause of cervical and breast cancer, although the oral contraceptives decrease the risk of ovarian and endometrial tumors (Backwell and Bellenir 2010).

Alcohol: Alcohol consumption specially with smoking, synergistically causes cancer in the oral cavity and pharynx.

Other diseases: Schistosomiasis is strongly related to bladder's squamous cell carcinoma cases in the middle east, also, chronic hepatitis B is responsible for the most cases of hepatocellular carcinoma in many regions in Asia and Africa (Coppola 2014).

Long exposure to some chemicals or metals: Methothelioma and lung cancer is common with the continuous exposure to asbestos which is used in many industries (Bakewell and Bellenir 2010).

Ultraviolet rays and radiation: A recent study showed a link between x-ray used in dental purposes and meningioma (Claus et al. 2012).

1.5. Diagnosis

In general, it is impossible to diagnose a case of cancer through single method but series of clinical investigations, lab tests, imaging and sometimes invasive techniques are required to detect clearly the stage and severity of the case.

The main target of diagnosis simply consists of three parts, the first one is to detect the organ or the tissue where the tumor has initiated, the second is to detect the other locations of metastasis because the patient may suffer some symptoms related to sites other than the original tissue of incidence in case of malignancy and finally the third part is to detect the size of the tumor/s diagnosed.

Like any disease, the diagnosis at early stages of any tumor will probably facilitate the plan of therapy, but, unfortunately, many cases cannot be discovered and treated at early onset due to many reasons:

There are no clinically characteristic symptoms can be a clear evidence for malignancy, if there are no further analysis held, most of the symptoms at the beginning may interfere with those of an inflammation, for example: ulcerative colitis patients when they are not cured properly, colorectal carcinoma may develop, showing similar symptoms of the colon inflammation, so, malignancy is not usually diagnosed until an advanced state is reached (Eaden et al. 2001, Kiesslich et al. 2003).

The diseased tissue may interfere with the normal ones at the early onset, as it is originated from an ordinary tissue and because it may start by only one cell, usually, it take months to show symptoms or to be noticed by the patient.

As mentioned before, in the case of metastasis, the diseased cells invade or diffuse to another tissue which may be far from where they were originated, so, false diagnosis may be concluded due to the existence of symptoms related to these far sites(paraneoplastic syndrome) while the tumor at the initiation site may be asymptomatic.

Even if the tumor is clearly detected and diagnosed, in many cases, it may be integrated within a viable organ, blood vessel or nerve, as a result, any attempt of removal or therapy by any means may put them at a high risk of partial or complete damage.

Some clinical manifestations:

According to the location of the tumor, tough and severe symptoms are always associated with the brain tumors, which begin with headache, vomiting and drowsiness passing by paralysis when the tumor arises at the motor cortex, epilepsy if it is at the temporal region, ataxia and visual disturbances are most probably the signs of cerebellum tumors and hormonal elevations as hypercortisolism (Cushing syndrome) which cause obesity and hypertension when the pituitary gland is involved. In case of the spinal cord tumors, defecation and urinary problems gradually appear and may reach paralysis if there is no medical action taken quickly.

Breast cancer may be easier to be diagnosed clinically, as it shows abnormal lumps, local pain and difference in the shape of the nipple, all these symptoms are clearly observed even by the patient personally. Recently, awareness programs are held globally on regular basis to teach the people how to be cautious and train them on some simple ways to discover breast tumors as soon as possible. However, metastasis may occur into bones, lungs and liver resulting in abdominal pain caused by hepatosplenomegaly.

Patients with lymphoid malignancies suffer from many symptoms based on the lymph nodes' swelling's location and extent, starting by simple symptoms like fever, weight loss, night sweat and abdominal discomfort ending up to severe ones like jaundice and renal failure.

Leukemic patients suffer from general weakness as a natural result of anemia, there may be pain in the joints and bones, bleeding and abdominal pain as a secondary symptom of hepatosplenomegaly.

In the case of lung tumors, it always affects many surrounding locations with severe symptoms including pressure on superior vena cava which may lead to its obstruction, chest pain which may be falsely diagnosed as a cardiac problem, hoarseness voice and

respiratory complications as cough, dyspnea, fatigue, weakness and cyanosis which may also give false conclusion as pneumonia, especially with the history of smoking or past pulmonary disease. Metastasis to the liver, lymph nodes, brain and bones are possible in many cases showing secondary symptoms as jaundice, swelling in the neck, headache and pain respectively (Pelengaris and Khan 2013).

Lab tests:

Blood tests may be a complementary evidence of malignancy, but ,separately, they are not enough.

For different cancer cases, blood tests may show a decline or an elevation in the level of many elements: hemoglobin, WBC count, urea, potassium, sodium, calcium, magnesium, albumin, creatinine, alkaline phosphatase and many others which alter due to many dysfunctions or disorders as hepatic impairment, renal or bone marrow failure, biliary obstruction, inflammations, anemia, diarrhea, neutropenia, dehydration, malnutrition, infections or gastrointestinal hemorrhage.

That is normal outcome due to the effect of different tumors on the various organs and body systems, at the end, further investigations are required to reach a complete accurate result (Coppola 2014).

Circulating tumor cells is a very important guide to detect malignancy, the method was discovered in the nineteenth century and depends on detecting the existence and count of the tumor cells that was separated from the neoplastic tissue of origination, in the blood. The count is directly proportional with the extent of spreading and toughness of the disease, the test is a very useful marker for detecting metastasis, staging, relapse, therapeutic management and effectiveness. In addition, it is very simple, cheap and non-invasive test but unfortunately, it is still not effective in many cases and not specific for any type of tumors (Plaks et al. 2013).

Urine specimens may be more specific in some cases of urothelial carcinoma (kidney or bladder cancer), urine specimen is collected, stained and cytologically examined under the microscope, neoplasm can be clearly detected (Coppola 2014).

However, there are some tumor markers that may appear in blood tests, most of them are protein in nature, their presence and concentration may not always mean the occurrence of malignancy, they just confirm after further tests and investigation, but they are mainly used as a guide to observe the response of the case to the treatment (Pelengaris and Khan 2013).

For example, PSA (prostate specific antigen) is one of the most important tumor markers which is involved in the diagnosis of prostate cancer the most common cancer in men, elevation in the PSA is also observed in men suffering prostatitis and benign prostatic hypertrophy that is very common in men above 50 or 60 years old. When malignancy is detected and the patient begins an efficient treatment, the PSA level in the blood is supposed to decrease gradually, but if the PSA level remained high, so, another treatment option should be provided (Coppola 2014).

Non-invasive imaging:

Plain film radiography (x-ray), ultrasonography, computerized tomography (CT scanning), Magnetic resonance imaging (MRI) are the most famous and widely used techniques for the diagnosis of cancer and many diseases in general and used in many medical applications as well (American-Cancer-Society 22.08.2015).

In addition to the diagnostic aim, ionizing radiations are used as a non-invasive therapeutic tool in many cases as it has many advantages over using the chemotherapy and surgery with fewer side effects (Airley 2009), although it was mentioned as one of the causes and risk factors causing malignancy.

X-ray was the first imaging technique discovered and used since 1895 for many medical aims as the detection of bone fractures and dental imaging, the technique is upgraded continuously and many screening applications rely on it (Momose 2005). For cancer, x-ray has been used for different tumors imaging as the early diagnosis of breast tumors through mammography (Pelengaris and Khan 2013). In addition to the clinical manifestations, x-ray is the only imaging evidence for lung cancer in several undeveloped countries as mentioned in a report issued by the international agency for research on cancer (Stewart and Kleihues 2003).

Computed tomography (CT) scan is the advanced phase x-ray but here with the aid of computer and capturing numerous images to give more detailed and clear image of the required organ, some dyes or solutions are to be injected intravenously-if there is no allergy- to improve and give clearer image, it is the main imaging method in the case of lung cancer because it may help also in the diagnosis of a metastasized lymph nodes tumors if it is found and it can also show more bone details as an advantage over the MRI.

Ultrasonography is well known for the prenatal testing and screening during the pregnancy follow-up, its application for malignancy is limited due to many reasons, as ultrasounds lacks deep penetration, also, it diffracts upon displaying to gases containing organs as colon and lungs and the underlying organs as well resulting in false images, on the other side it has some advantages against the other imaging technologies as it is safer because it is a non-ionizing method, does not consume much time and not expensive. Ultrasonography can distinguish whether the mass is benign or malignant in some organs and adequate for few gynecological tumors cases specially if applied through a transvaginal probe (Pelengaris and Khan 2013).

Magnetic resonance imaging (MRI), spectroscopy (MRS), angiography (MRA) and others are methods performing the same technique which creates a clear cross-sectional image specially with soft tissues with all its contents by inducing a magnetic field, it is the most effective imaging technology of the central nervous system tumors and the american cancer society recommends using MRI with the mammograms for the early diagnosis and prevention of breast cancer specially for the women with family history of the disease (American-Cancer-Society 24.08.2014, Saslow et al. 2007).

Other diagnostic tools:

The endoscope is of many types and designs, is used for many medical purposes. In case of esophageal cancer, the tumor is classified into four main stages based on the degree of invasion through the esophagus wall layers, the ultrasonic endoscope is very efficient in the differentiation between these stages and this differentiation is very important to detect whether a surgery is a must or chemoradiation is an option (Hayat 2008).

Trans-bronchial fine needle aspiration (TBNA) is one of the widely used method in obtaining different specimens for the diagnosis of lung, bronchi and the chest lymph nodes diseases including cancer for more than 30 years, because of their low cost and availability worldwide, with the aid of endobronchial ultrasound (EBUS) in the modern TBNA devices, the diagnosis efficiency may improve (Jiang et al. 2014).

Recently, modern nanotechnology researches reached an advanced levels in the imaging applications of tumors in several ways, either in vivo or in vitro diagnostics, separately or in combination to give more efficient results (Cai et al. 2008).

For example, gold nanoparticles offer a spectroscopic tool through the conjugation with anti-epidermal growth factor receptors (anti-EGFR) and arranged on the surface of neoplastic cells to produce a firm surface enhanced Raman scattering (SERS). Another way of using gold nanoparticles in the field of imaging through the usage of the light-scattering imaging which is cheap, easier to apply than others methods as MRI and requires very simple equipments as a light microscope (Huang et al. 2007).

1.6. Stages of cancer

Upon diagnosing a tumor, it is very important for the oncologist to record the stage the cancer reached for many reasons, first of all to know if it is benign or malignant, extent of metastasis, size and to decide the most suitable treatment method (Bakewell and Bellenir 2010).

The TNM staging system was performed by the international union for cancer control (IUCC) and the american joint committee on cancer (AJCC) to be the most usable system worldwide and updated regularly with the advanced cancer researches.

As an overview, T stands for primary tumor and has three main marks: Tis (the tumor is superficial and does not invade deeper tissues), TX (the tumor is immeasurable) and T0 (the primary tumor cannot be detected) with a number T1 till T4 describes the size or extent of spread of the tumor to the surrounding tissues, T1 is the smaller and the least invasion.

N stands for the regional lymph nodes involved in the metastasis whether NX (the nearby lymph nodes cannot be diagnosed clearly) or N0 (malignancy does not affect the lymph nodes), numbers from N1 till N3 describes the size, the location and may be the number of nodes involved, N1 is the least degree of spread to the lymph nodes.

M stands for metastasis where M0 means there is no metastasis to a distant organ or tissue and M1 means the cancer has spread. However, there are more subcategories for each sign for more illustration of the stage (Edge et al. 2010).

After determining T,N and M, a combined assessment is stated in the form of roman sign whether stage 0,I, II, III or IV, where stage IV is the worst condition and stage 0 means that the tumor is very small, limited and no metastasis (Bakewell and Bellenir 2010).

There are many other systems found for the assessment of the cancer stages as the international classification of diseases for oncology (ICD-O) by the world health organization(WHO) and the cancer bioinformatics grid (caBIG) by the national cancer institute of the USA (Edge et al. 2010).

Not all the measurements are always used to assess the different types of cancer due to the difference in the types of diseased tissues and organs, for example, the size is the most important feature when evaluating breast cancer (American-Cancer-Society 26.8.2015), while the spread extent is the most important in case of leukemia in which no size can be measured or cannot be specifically located (Bakewell and Bellenir 2010).

The stage of the tumor is recorded only at the time of diagnosis and fixed, many patients have a false idea that after treatment the stage should improve as a better sign for the positive response to the treatment, but that does not happen, the tumor is classified and recorded by the initial degree of diagnosis and will always be defined with it even after complete recovery (American-Cancer-Society 26.8.2015).

1.7. Treatment

Cancer treatment methods are various and regularly upgraded with the daily researches and discoveries with the aid of the advanced technologies.

There is a theory in tumors treatment mainly based on classifying the tumors into three classes: the first class includes some tumors that are very small, asymptomatic, noninvasive, nonmetastatic, not-life-threatening and diagnosed incidentally also known as "incidentalomas", some of the diagnosed organs include thyroid gland and pancreas for example and leaving them in such state may be much better than exposing the patient to surgery and its unfavorable postsurgical morbidity or the side effects of any treatment method.

The second class includes all the vigorously metastasized tumors which went out of any control, so that it is not worth treating and unfortunately all the trials done are just relieving the pain and symptoms and improving the quality of life.

The third class are the intermediate tumors, those which are worth treating because they may be life-threatening and their diagnosis are clear and still possible to deal with, may be invasive but within a specific location, may be large in size but benign, may be small and limited but symptomatic or painful (Weinberg 2014).

Surgery, radiotherapy, chemotherapy, hormonal and monoclonal antibodies therapy are the most common methods of tumors treatment, with the following modern methods as the usage of gold nanotechnology either for the aim of therapy directly or for drug targeting and delivery systems to make the methods more specific for the cancerous tissues and do not interfere with the normal healthy ones.

All these methods may be used separately and sometimes the oncologist can depend on more than one sort of treatment combined for synergism or to avoid the strong side effects resulted from one method of them.

As mentioned before, the cancerous tissue in many cases is usually integrated with one or more healthy neighboring tissues and may invade either organ, major blood vessel or nerve

and any trial of excision or any sort of treatment used, usually affects the integrated part and that is the most important challenge facing the success of the treatment plan.

A huge difficulty in managing tumors is that the diagnosis is always relatively late and the rate of the cells proliferation differs from a type to another, for example, some leukemia cases need about 2 weeks to reach the level of diagnosis while some types of lymphomas do not need more than 1 day, tumors in other organs as the liver may grow to be more than 2 cm with about one billion cells and still asymptomatic or unnoticeable (Rang et al. 2012).

After diagnosing and staging, the oncologist responsible of the case decides the most efficient method with the least side effects and the best patient compliance possible, after consulting a full oncology team which consists usually of a surgeon, pathologist, radiation therapist, pharmacist and others.

Surgery

Surgery is the preferable option in case of a solid tumor, if the location and the size are clearly bounded, the tumor is removed or the full organ is completely resected as in case of prostate cancer, if benign, the prostate is completely removed by surgery (Pelengaris and Khan 2013).

In the past, surgery was the only method known for tumors treatment as well as a diagnostic way before the discovery of the other treatment and diagnostic methods.

Surgery in the branch of oncology, can be used for a therapeutic aim as a primary method for cure with or without the aid of another one or may be a secondary method adjuvant to the main one as chemotherapy for example, in many cases the combination is a must (Bolognese and Izzo 2009).

Rather than the therapeutic aim, many oncology cases are subjected to surgery for the aim of prevention as in the case of women with inherited gene faults of breast cancer genes (BRCA1 and BRCA2), studies stated that about 45-90% of those genes faults carriers develop breast cancer, so, mastectomy is a preventive solution that should be recommended by the physician, preferably with the excision of the ovaries which are also under the same risk.

In the case of mastectomy, another surgery may be offered for the aim of reconstruction through implantation if the patient has the desire, done immediately with mastectomy in the same operation or later as a separate one (Cancer-Research-UK 31.8.2015).

Cryotherapy is also a method used for treating small tumors (less than 4 cm) through a liquid nitrogen probe that is directed to sites of metastasis, in spite of some complications that appear during the operation, as freezing makes the part involved brittle and may result in bleeding (Primrose 2002).

Success of therapy by surgery is proportional to the degree of cooperation between the surgeon and the rest of the team members.

Radiotherapy

Treatment by the exposure to ionizing radiation is the main idea of radiotherapy, in which the formation of free radicals highly damage the DNA of the neoplastic cells.

Radiotherapy is used either in the form of photons radiation (as x-rays and gamma rays) or particle radiation (as protons) as a primary method for treatment or a complementary method for the main one, as in the case of brain tumors surgery, where the tumor is exposed to radiation as a palliative treatment to reduce its size for easier excision, or after the surgery to confirm getting rid of any remaining cancerous cells that may proliferate again (Baskar et al. 2012).

There are some cytological factors control the response of the neoplasm to the free radicals as:

DNA repair ability: it is well known that cancerous cells has low ability to repair their DNA compared to the normal ones (Baskar et al. 2012).

The type of tissue: tissues as lymphoma are more sensitive to radiotherapy than others (Carachi et al. 2008).

The different phases of the proliferative cycle: the cell may be more sensitive to radiation in some cell division phases than others.

The oxygen content: the oxygenated cells are much more sensitive than the hypoxic ones that show high resistance, so, choosing the right time where the tumors cells are re-oxygenating may give better results.

Repopulation: the rate of proliferation of cancer cells is much more higher than the normal tissue, so, the period of exposure to radiation is critical in the treatment procedure to confirm complete eradication of all the generations (Pelengaris and Khan 2013).

So, patients treated by radiotherapy are given small doses for many days rather than single large dose to cover all the phases and conditions the cells pass by to overcome any resisting stage and also to reduce the possible damage of the surrounding normal tissue (Carachi et al. 2008).

There are two types of radiotherapy:

External-beam radiation therapy: treatment through applying beams as x-rays and sometimes protons on the body from an external source called linear accelerator, it is the most common radiotherapy method used.

Internal radiation therapy (brachytherapy): treatment through ingestion as iodine 131, injection as mIBG or implantation of a radioactive material inside the body. In case of endometrial carcinoma, vaginal brachytherapy shows better efficiency with lower risk of recurrence and fewer side effects when compared to the treatment with external-beam radiation therapy (Carachi et al. 2008, Nout et al. 2010).

Treatment by radiation usually results in unfavorable side effects during the period of therapy or even after that by months regarding the case and the type of cancer, patients may suffer from nausea and vomiting when the exposure includes different organs of the GIT or the brain, lethargy and tiredness as a result of anemia, hair loss at the area of exposure (in some cases it is permanent), sore skin and dry mouth (Carachi et al. 2008, Cancer-Research-UK 01.09.2015).

Chemotherapy

Treatment using chemotherapeutic agents is the most widely used in cancer therapy among all the other methods, researches began in the first half of the last century, when the mustard gas was used in world war I and its effect on the bone marrow tissues and lymphatic tissues was observed and opened a huge gate for the concept of using other related alkylating agents as cyclophosphamide or antimetabolites as aminopterin-which was discovered in the same period and showed a success in treating childhood leukemia- for the aim of treating tumors (Weinberg 2014, DeVita and Chu 2008).

Several types of chemotherapeutic agents are used alone or combined with other methods in different ways and many strategies during the treatment process as:

Induction: for reducing the size of tumor or complete eradication.

Maintenance: relatively small doses given on a long term plan to reach full cure by prolonging the time of administration (Whalen 2015).

Neoadjuvant: as a pretreatment for surgery (as mentioned before referring to radiotherapy) to limit the tumor and reduce its size (Whalen 2015).

Adjuvant: as a post-treatment for surgery or radiotherapy to kill any remaining neoplastic cells and avoid any possible relapse, used since the seventies with some breast cancer cases (DeVita and Chu 2008).

Consolidation or intensification: the usage of the same drug or a different one respectively, after induction to help and confirm full eradication.

Combination: the usage of more than one agent of different mechanisms of action in small doses in the treatment plan to prevent resistance from the tumor cells and to avoid toxicity of an agent that must be used in large doses when administrated singly.

Salvage: administration of an agent as a replacement solution after the failure of the primary strategy used or to be just an attempt to control the disease or to relief symptoms for a better life quality at advanced stages of a hopeless case malignancy (Airley 2009, Whalen 2015).

Treatment via chemotherapeutic agents shows many common side effects between mild and severe ones because they act mainly on the process of cell division inhibition, so, the tissues that are usually affected include bone marrow, hair follicles, gastric epithelium, gametes and affects the growth of infants and embryos causing teratogenicity (Rang et al. 2012).

The side effects include weakness and fatigue, which are the most reported, vomiting, hair loss, sterility, dry mouth and mouth sores, abdominal cramps and diarrhea are also common (Aslam et al. 2014, Airley 2009).

Not only physical side effects were mentioned, but some side effects that affect the patient's work, family and social relations were also reported including anxiety, tension, some memory loss, depression, loss of sexual desire and impotence (Carelle et al. 2002).

Classes of chemotherapeutic agents:

1. Alkylating agents: drugs that create one or more covalent bonds between the DNA nitrogen bases (mainly guanine) after its synthesis, forming cross-links within the DNA strand inhibiting its function (Airley 2009), some examples of these agents:

Cyclophosphamide (nitrogen mustard): widely used agent in many cases of lymphomas, leukemia, breast, ovary, lung cancers and retinoblastoma. It is nonspecific for any of the cell division phases as it prevents the DNA replication by forming an interstrand cross-link or between the DNA strand and another protein (De Jonge 2004). For reducing the graft rejection, cyclophosphamide is also used as an immunosuppressant agent (Rang et al. 2012), so, it can be used for treatment of some autoimmune diseases as rheumatoid arthritis (De Jonge 2004).

Carmustine (nitrosoureas): targets the guanine bases in the DNA specially when there is many successive guanine bases (Siddik 2002). They are lipid soluble compounds that can penetrate the blood brain barrier and used in treating brain tumors (Pelengaris and Khan 2013).

Carboplatin (platinum compounds): activates to an unstable intermediate with water to create covalent bonds with the DNA bases leading to cross-linking (Airley 2009), used in

testicular cancer. Carboplatin is a modern generation of this group that is less nephrotoxic and neurotoxic than the firstly discovered cisplatin (Chabner and Roberts Jr 2005).

Other alkylating agents: ifosfamide, melaphalan, lomustine, oxaliplatin, busulphan, thiotepa.

2. Antimetabolites: drugs that interfere with some metabolites used by the cell necessary for the formation of new DNA and RNA as:

Methotrexate (folate antagonists): its polyglutamated form inhibits dihydrofolate reductase enzyme, the enzyme that is responsible for the conversion of folic acid into the active form tetrahydrofolic acid necessary for DNA formation and its long chain polyglutamated form decreases the synthesis of RNA as well (Chabner and Roberts Jr 2005), preventing cell division at S-phase and some other metabolic reactions. Methotrexate is one of the widely used agents for treatment of some types of lymphomas, acute lymphocytic leukemia, breast and bladder cancers (Whalen 2015).

5-fluorouracil (pyrimidine analogue): the similarity of its structure with deoxyuridine monophosphate decreases the rate of synthesis of thymidine necessary for the DNA formation (Rang et al. 2012).

6-mercaptopurine (purine analogue): the inhibition of DNA and RNA activities through the interference with the nucleotide monophosphate essential for nucleic acids synthesis after conversion to 6-mercaptopurine-ribose phosphate due to their structure similarity, It is used mainly for treating leukemia cases (Whalen 2015).

Cytarabine (pyrimidine antagonist): inhibits DNA polymerase by conversion into cytosine arabinoside triphosphate instead of 2'-deoxycytidine during the S-phase and used in treatment of acute myelogenous leukemia (Rang et al. 2012).

Other antimetabolites: fludarabine, vinblastine, cladribine, capecitabine, azacitidine and gemcitabine.

3. Cytotoxic antibiotics: cell cycle nonspecific agents with some exceptions, their destructive action on DNA and the formation of free radicals are the main mechanisms of cytotoxicity (Whalen 2015), examples:

Doxorubicin (Anthracyclins): one of the most used anticancer agents, affects the complex formed between topoisomerase II and DNA inhibiting its replication thus inhibiting the synthesis of DNA and RNA during replication (Airley 2009). It is a quinone derivative that has the ability to form free radicals that also have a damaging effect on the DNA but at the same time has a cardiotoxic effect as a fatal side effect (Rang et al. 2012).

Bleomycin (glycopeptide): G2 stage specific, requires formation of metal complex in the presence of oxygen to form free radicals that break down the DNA strand, administering with caution because pulmonary fibrosis is usually diagnosed upon using bleomycin (Rang et al. 2012). Bleomycin is used in treating testicular cancer and always exist in most of the chemotherapeutic combinations used in treatment of hodgkin lymphoma as ABVD and BEACOPP which also contain doxorubicin (American-Cancer-Society 09.09.2015).

Other antibiotics: idarubicin, epirubicin, daunorubicin, dactinomycin and mitomycin.

4. Anti-mitotics: agents which prevent mitotic division through inhibiting spindle function. Spindles consists of microtubules which are the main target of these agents, vinca alkaloids and taxanes are the most famous microtubules inhibitors, bind to the microtubules beta-subunit causing their dynamics disruption (Pasquier and Kavallaris 2008):

Vincristine (vinca of plant origin): causes cell arrest during metaphase, is usually used in combination therapy to treat lymphoma, some types of sarcoma and leukemia but it causes high irreversible neurotoxicity (Gascoigne and Taylor 2009).

Paclitaxel (extracted from pacific yew tree): used in the treatment of many types of cancer as lung, breast and ovarian cancers, it is very common to use corticosteroids with them due to the common hypersensitivity which occurs with many of the patients (Whalen 2015).

Other anti-mitotics: vinblastine, vindesine, docetaxel and carbazitaxel.

Hormones

These endogenous or exogenous messengers were mentioned as one of the risk factors for many tumors as breast and prostate cancers. At the same time, their antagonists or agonists were exploited and widely used for the aim of treating different types of tumors (Schally et al. 2001), as:

Tamoxifen (selective estrogen receptor modulator): commonly used for the treatment of breast cancer, competes with estrogen and binds to estrogen receptors to form a complex which decrease the rate of genes transcription in breast tissues, it is used also as a prevention tool in women with risk of breast cancer development, but it should be used with caution because it increases the risk of endometrial cancer (ESHRE 2004).

Prednisone (corticosteroids): anti-inflammatory hormone used in treating leukemia and lymphomas, it has to be hepatically activated to the active form prednisolone. Glucocorticoids in general are usually used as a palliative tool with many cancer patients to decrease and relief the unfavorable side effects induced with the different chemotherapeutic agents used (Rang et al. 2012).

Other hormonal therapies include: flutamide, degarelix, megestrol, goserelin, triptolerin, medroxyprogesterone, anastrozole and letrozole.

Some modern aspects for treatment

Monoclonal antibodies

The first monoclonal antibody was officially approved by FDA for the first time to be used for cancer therapy at the end of the last century, they do not cause severe side effects as the chemotherapeutic agents used (Scott et al. 2012) -except hypersensitivity in some cases-, plus, they are targeted and highly specific to the neoplastic cells (Vacchelli et al. 2014). They act by several mechanisms: either through induction of apoptosis, increasing the sensitivity to some cytotoxic agents or signaling for cellular arrest. Monoclonal antibodies can be used alone or in combination with other methods (Weiner 2010). At the beginning they were only used against few types of tumors as melanoma but recently they are widely applied in much more types (Pelengaris and Khan 2013). Monoclonal antibodies can be

used also as a targeting tool for other cytotoxic agents as drugs, enzymes or radionuclides by conjugation (Weiner et al. 2012).

Rituximab: it was the first antibody to be approved by the FDA, shows efficient results when it is used in treating lymphomas as it forms complex with CD20 antigen found on all the immature, mature and active B-lymphocytes surface, which makes it specific for B-lymphocytes but not specific for malignant B-lymphocytes. Resistance to rituximab was observed (Rezvani and Maloney 2011) but still it is used in many cases of non-hodgkin lymphomas and also in combination with other chemotherapeutic agents because it increases the cells sensitivity to such agents (Rang et al. 2012), it has to be infused slowly with caution as it may cause severe hypotension and bronchospasm specially with the first dose but pre-administration of corticosteroids may prevent this problem (Whalen 2015).

Trastuzumab: binds to the human epidermal growth factor receptor 2 (HER2) which is overexpressed by the breast and some gastric cancer cells (Whalen 2015), so, it is usually used in a combination with other methods for the treatment of breast cancer and adenocarcinoma (type of stomach tumors) (Cancer-Research-UK 10.09.2015). Congestive heart failure is a common adverse effect upon administration of trastuzumab specially when it is used with anthracyclins (Hudis 2007).

Other monoclonal antibodies: tositumomab, alemtuzumab, labetuzumab, huA33 oregovomab, bevacizumab, volociximab, MM-121, cetuximab, denosumab, F19, and sibrotuzumab.

Gold nanotechnology

Gold nanoparticles (GNPs) was mentioned before as a modern aspect used for diagnosis through the conjugation to anti-EGFR antibodies, they can be used also as a therapeutic targeted tool with the aid of an immunotargeting strategy as the photothermal specifications of such particles show a very high damaging effect on the cancer cells (Huang et al. 2007).

Since two centuries, GNPs was used for non-medical aims till the end of the following century, further studies and trials were held to explain their properties that allow them to be used in the medical field for diagnosis and treatment of tumors, as they have the ability

to conjugate with different molecules to be used as a targeting method for these agents because their nano size range (less than 100 nm) gives them the ability for penetration and accumulation at the leaky, randomly distributed, heterogenic blood vessels of the tumor (Jain et al. 2012).

SR9243

Werborg effect is a main regulator in the respiration, viability and survival of the cancer cells specifically, compounds as SR9243 are liver-X-receptor (which regulates main enzymatic reactions for glycolysis) inverse agonists, can be used to inhibit this pathway inhibiting cancer progression, recurrence and treatment resistance. The advantage of such method is lacking of toxicity for normal cells, as they do not undergo the Werburg pathway, enhancing the sensitivity of the cancer cells towards the chemotherapeutic agents and showing a better efficiency upon combination with cisplatin and 5-flurouracil (Flaveny et al. 2015).

Malarial protein

A study released in 2015 explains that there is a specific protein (VAR2CSA) found in the malarial cells has the affinity to bind to specific type of sugar (chondroitin sulfate) expressed in the placenta, this sugar was also discovered in a huge percentage of many malignant cells, the protein can be used in targeting anticancer agents by forming a complex with it. The discovery still needs more studies to be certified for therapeutic aims (Salanti et al. 2015).

1.8. Treatment resistance

Cancer cells have the ability to defend themselves against any kind of damaging agent or hazard that may put their survival under a risk.

Changes in the membrane lipids, losing specific receptor or transporter, reducing the uptake, stimulating the repair of DNA, drug efflux and shifting of the drug target to another

are examples of several ways the cancer cell genetic and epigenetic changes that happen for treatment resistance.

Some other physiological changes may happen far from the tumor site or the neoplasm as reducing the drug absorption or increasing the rate of excretion and metabolism to decrease its serum level.

Therefore, the usage of multidrug plans is an efficient way to reduce the resistance of the body and the neoplasm towards the anti-cancer agents (Gottesman 2002).

Also, understanding the environment surrounding the neoplasm greatly helps in selecting the most efficient method and treatment plan, as the neoplasm usually have special conditions that should be in consideration when applying any treatment method. For example, the irregular angiogenesis surrounding any tumor does not provide enough blood supply to all the tissue, so, hypoxia stimulates anaerobic respiration that increases the lactic acid offering an extracellular acidic medium, this is a very suitable condition for increasing the efficiency of weakly acidic drugs as cyclophosphamide as their uptake by the cells is facilitated, on the other hand, suppressing the action of the other weakly basic drugs as the vinblastine, studies showed also that acidic medium is not suitable for some radiotherapy applications but enhance the effect of hyperthermia induced apoptosis (Teicher 2006).

1.9. Prevention and control

As mentioned before, some risk factors that lead to cancer development can be avoided some others cannot, so, unfortunately, cancer cannot be prevented 100% but it is a matter of avoiding the famous and common known risk factors. Screening, regular medical check-ups and the early detection of the tumors always facilitate the treatment.

Avoiding the several risk factors that may cause cancer as much as possible or making some changes to the personal life style may reduce the risk, however, the existence of some of these factors in the daily life and the regular exposure to them as the ultraviolet rays of the sun and smoking -even if passively- is a challenge in cancer prevention.

Preventing cancer can be through quitting smoking, using sunscreens and preventing or minimizing exposure to sunlight, avoiding obesity by doing regular physical activities or sports and eating healthy balanced diet with high intake of fruit and vegetables which contain antioxidants and other anticarcinogens, Careful administering of hormones with cautions after discussing with an expert, proper gowning and following safety precautions against the laboratory and industrial hazards when dealing with any sorts of chemicals, metals or radiations, proper quick treatment of different diseases that may lead to cancer as hepatitis B and ulcerative colitis and others (Pensiero et al. 2004, Bakewell and Bellenir 2010).

As mentioned before, mastectomy is a preventative option for women whom under a high risk of contralateral breast cancer due to having either a history of mantle radiation when they were younger or BRCA inherited genes mutations (Yakoub et al. 2015).

Since 2000, The american cancer society issues some major guidelines and recommendations every year that helps in the early detection of some tumors and malignancies as the breast, prostate, lung, cervical, colorectal and others, with some statistical data for the ratio of prevalence among the screening examination (Smith et al. 2006).

1.10. Some incidences

As mentioned before, cancer is not classified as a transmitted disease, but some studies suggested that some cases of leukemic mothers infected with HTLV-I virus -which is usually associated with specific type of leukemia- may transmit it to their infants through breastfeeding (Li et al. 2004).

In 2013, a Columbian AIDS patient was presented with some gastrointestinal symptoms and tapeworms (intestinal parasites: *Hymenolepis nana*) were diagnosed, tests also concluded metastasis in several organs and tissues. Upon testing neoplasm, non-mammalian proliferating cells were observed and further investigations concluded that the neoplasm consists of the *H.nana* stem cells. This means that the tapeworm developed

malignancy and metastasized all over the host body showing up cancer common symptoms and diagnosis in a very rare condition, although the host own tissues did not launch any tumor (Muehlenbachs et al. 2015).

2. Colorectal carcinoma

More than million cases of colorectal carcinoma are diagnosed annually (Fabio et al. 2014) to be one of the most widely spread types with lung, breast, prostate and liver cancers among males and females around the whole world, its incidence in well developed countries is much more than in the undeveloped ones as it spreads highly in North America, Western Europe and Australia, more than one quarter of the population by the age of 70 in these regions develops colorectal tumors (Oostindjer et al. 2014, Torre et al. 2012, Rodriguez-Bigas et al. 2010), it was predicted to be the second most common cancer type causing deaths among men and the third most common type among women in Europe during 2014 (Malvezzi et al. 2014).

2.1. Anatomy and histology

The colon is a part of the gastrointestinal tract (GIT) which has similar histological features as the rest of the tract (mucosa, submucosa, circular and longitudinal muscles layers and serosa or adventitia), measures about 150 cm length, its diameter varies regarding the site or the extent of fullness approximately between 7.5 cm and 2.5 cm and consists mainly of 3 segments:

1. Cecum and ascending colon: the first segment that is connected and begins at the last part of the small intestine (ileum) by the ileocecal junction and ileocecal valve with the fusion of the vermiform appendix from the inferior end of the cecum and ends superiorly by the hepatic flexure.
2. Transverse colon: the longest part of the 3 segments, links the ascending with the descending colons and it extends between what are called the hepatic and splenic flexures.
3. Descending and sigmoid colon: the last division of the colon which begins at the splenic flexure and ends at the rectum, its lumen is narrower than the ascending colon.

The rectum extends from the sigmoid colon at the rectosigmoid junction, measures about 12-15 cm length and ends by what is called anorectal ring as a junction with the last part of the GIT, the anal canal.

The colon absorbs a huge volume of the water content remained in the feces and some ions as sodium and chloride with the loss of some others as potassium and bicarbonates, while the rectum acts as a reservoir for the feces until excreting it out of the body through the anal canal. When the rectum is full, stretch receptors are stimulated to induce the defecation desire (Wexner and Stollman 2007).

Under the microscope, the colon mucosa is formed of many small concave units called crypts (intestinal glands) which consists of about 2000 cells each, stem cells at the base of the crypt divide continuously and migrate to be committed progenitor and transient amplifying cells which then differentiate into cells at the epithelium to be in contact with the passing food substances by the colonic lumen.

The continuous friction with food causes damage of these epithelial cells to be renewed approximately every week and that may offer a very suitable target for developing polyps and then tumors with consideration of many risk factors that will be discussed later (Koneczny 2009).

2.2. Carcinogenesis

There were 2 theories to illustrate carcinogenesis, one suggests that the gene defects occur by the cells in the intra-cryptal site, while the other shows that carcinogenesis is from the stem cells of the crypt base, both theories are thought to be right which may be an evidence that it may occur in both ways (Koneczny 2009).

As any tumor, colorectal carcinoma initiates through a genetic mutation by several mechanisms, usually through 5 main reactions: either hydrolysis, oxidation or alkylation of bases, formation of bulky adduct or an error in the formation of the DNA that leads to bases mismatch (Centelles 2012).

Colorectal carcinoma is caused by a series of mutations through 3 main pathways: chromosomal instability (CIN) or the gatekeeper pathway, microsatellite instability (MSI) or the caretaker pathway and CpG island methylator phenotype (CIMP) (Armaghany et al. 2012).

In case of CIN, the epithelium develops into early adenoma, late adenoma then invasive cancer through the inactivation of tumor suppressor genes as APC and TP53 and the activation of oncogenes as K-ras.

The inactivation of the mismatch repair genes (MMR) is associated with MSI with the inactivation of APC as well (Mundade et al. 2014)

CIMP is an epigenetic pathway by which the tumor suppressor genes are inhibited by methylation of CpG islands of the promoter region (Armaghany et al. 2012).

Various stages are diagnosed for different colorectal carcinogenesis cases between early and late adenoma, carcinoma and metastasis. Loss of alleles of certain genes found in chromosomes 7, 18 and 21 are commonly associated with different colorectal cancers cases (Pelengaris and Khan 2013).

More than 90% of colorectal carcinoma are sporadic not related to familial history or inheritance, it occurs by exposure to many risk factors that will be discussed later (Josep 2012). Overexpression of cyclo-oxygenase-2 (COX-2) and mutations in genes K-ras and p53 and are common features in both types (Allgayer 2003).

There are 2 common inherited syndromes that almost lead to the development of the disease, the hereditary nonpolyposis colorectal cancer (HNPCC) which helps in the progression of the colorectal tumor and the familial adenomatous polyposis (FAP) which induce the tumor initiation (Pelengaris and Khan 2013). Inheritance of the mutated genes is responsible for about 5% of all colorectal cancer cases (Cantelles 2012).

HNPCC is also known as the Lynch syndrome, it was the first discovered syndrome related to hereditary cancer, as it is associated with the development of many types of tumors including the colorectal carcinoma, characterized by mutations in certain type of genes

called mismatch repair genes (MMR) as: MLH1 and MSH2 which leads to MSI which is observed in most cases of cancers caused by Lynch syndrome.

FAP is an autosomal dominant inherited disease, commonly happens when the patient has a missed APC gene's (one of the tumor suppressor genes) allele, as a result of inheritance from one or more first degree family members. The affected individuals develop benign colonic tumors that may not be life threatening in some cases, but in other cases they are diagnosed to be invasive, also, extracolonic tumors were diagnosed, associated with FAP including, for example: osteomas, tumors of the nasopharyngeal region, liver and brain tumors (Kinzler and Vogelstein 1996, Half et al. 2009, Pelengaris and Khan 2013).

Other inherited syndromes include juvenile polyposis syndrome (JPS), MYH-associated polyposis (MAP) and Peutz-Jeghers syndrome (PJS) (Cantelles 2012).

2.3. Risk factors

Carcinogenesis in most cases initiates at the distal sites of the colon, that may be due to the loss of water content from the passing substances including the carcinogenic matters which hardens them and hence slowing down their movement to increase their contact time with the colon tissues and enhancing their effect on these tissues more than any of the other sites, many risk factors are related to the development of the colorectal carcinoma, although, the mechanism of many factors is not clearly known (Pelengaris and Khan 2013).

As explained before, people with a first degree familial history of colorectal cancers are usually at a much higher risk of developing the disease compared to those having no familial history with it (Johnson et al. 2013), it is not a must to develop cancer under such condition only but with the aid of other factors (Kinzler and Vogelstein 1996).

Rates of developing colorectal carcinoma in males are much higher than females (Nelson et al. 1997).

About 80% of colorectal cancer cases are above 60 years old (Cancer-Research-UK 08.10.2015).

Statistics showed that colorectal carcinoma mortality is much higher in black people than any other race (Chien et al. 2005).

High consumption of red meat, specially with an unbalanced diet through the reaction between heme iron found in the meat and the gut environment is associated with enhancing the risk of developing colorectal cancers and that may explain the wide spreading of this disease in the developed countries, however, there are other factors that should be in concern when assessing the correlation (Oostindjer et al. 2014).

In October 2015 the international agency for research on cancer (IARC) under the supervision of the world health organization (WHO), has ranked the processed meats as group 1 colorectal carcinogenic substance for humans due to their possession of some carcinogenic compounds as polycyclic aromatic hydrocarbons and N-nitroso-compounds, unfortunately, frying and grilling enhance the effect by providing new carcinogenic compounds as the heterocyclic aromatic amines upon heating (Stewart et al. 2015).

Statistical relation is shown between obesity and colorectal cancers, with the increase in the body mass index (BMI), the risk of developing colorectal cancers significantly increases, specially, in males and associated with some other factors as high fats intake, the insulin resistance or the menopausal status for females (Johnson et al. 2013, Bakewell and Bellenir 2010, Pensiero et al. 2004).

Smoking is always an important risk factor that increases the chance of developing many types of cancers including the colorectal cancer. A study was made over current and past smokers with considering some other factors as the daily consumption and the age of starting smoking, showed that the risk of developing colorectal cancer with cigarettes smoking is much higher than with non-smokers and there was a strong evidence that cancer develops at the rectal site more with cigarettes smoking than at the colon (Liang et al. 2008).

Alcohol in high consumption is one of the factors which has a strong association with increasing the risk of colorectal cancer, the ratio in males is higher than females but there is no clear evidence whether the gender has a role or just because alcohol intake by men is usually higher (Moskal et al. 2006).

Inflammatory bowel diseases (IBD) patients, specially, ulcerative colitis and Crohn's disease are always at a high risk of developing colon cancer when an IBD is left for a long period of time without proper or complete cure. Crohn's disease may also help in developing small bowel adenocarcinoma when it occurs in the small intestine (Lakatos and Lakatos 2008, Dabaja et al. 2004).

2.4. Staging

Detecting the tumor size, extent of invasion and metastasis of the colorectal carcinoma is very important for the oncologist for proper treatment planning specially in the case of surgery, in following up the treatment efficiency and the avoidance of relapse.

Several staging systems are used in the case of colorectal cancers including Dukes system, Astler-Coller system and TNM system which is the most advanced one and used for most of the cancer cases (Akkoca et al. 2014, Gordon and Nivatvongs 2007).

After detecting the T, N and M as illustrated before, colorectal cancers are classified into either stage 0, I, IIA, IIB, IIIA, IIIB, IIIC or IV.

Stage 0 : (Carcinoma in situ) it is a very early stage, where the tumor is limited within the mucosa.

Stage I : The tumor reaches the submucosa but still located inside the wall with no spread.

Stage IIA : The tumor penetrate the outer layer of the wall but without spreading to other organs.

Stage IIB : The tumor grows to include near surrounding organ/s but still there is no spread to lymph nodes.

Stage IIIA : The tumor grows through all the wall layers and reaches the near lymph nodes.

Stage IIIB : The tumor reaches near surrounding organ/s and less than 4 surrounding lymph nodes.

Stage IIIC : The tumor appears at more than 3 near lymph nodes.

Stage IV : The tumor spreads to any number of near or distant lymph nodes and/or organs (CA A Cancer Journal for Clinicians 2004).

The Dukes staging system was organized in the thirties of the last century as the first system to be used for colorectal cancer staging and was upgraded many time. it divides the case into grades by A, B1, B2, C1, C2 or D, where A describes a limited tumor only within the mucosa without any metastasis while the most invasive tumors are graded C2 which describes a very deep tumor that reached all the bowel wall's layers accompanied by surrounding monitored metastasis and the involvement of lymph nodes and D in the case of a distant metastatic spread.

In 1954, Astler and Collier have upgraded the Dukes system and named it with their names, however, the Dukes system have been modified several times for more description accuracy. Recently, the TNM and the Dukes systems are the most used in the case of colorectal tumors (Akkoca et al. 2014, Gordon and Nivatvongs 2007).

2.5. Pathology

Tumors that are enclosed at the submucosa are identified as early carcinoma by which the lesions are flat and the height is not more than double the mucosa. Before invading the submucosa, the colorectal neoplasm cannot be described as metastatic.

In case of late carcinoma, Borrmann has divided the lesions into 4 categories: I. polypoid, II. ulcerated with elevated distinct borders, III. ulcerated with indistinct borders and IV. diffuse with indistinct borders (Cassidy et al. 2007).

Type I projects into the lumen but rarely shows malignancy, type II is the most common and appears as a circular rough irregularly edged mass, type III occurs more often in the transverse and the descending colon and penetrates deeply into the colonic wall and type IV the most infiltrating type, appears with higher frequency at the rectosigmoid region and the most associated type with ulcerative colitis (Gordon and Nivatvongs 2007).

Histologically, the tumor is identified by UICC into 4 grades depending on their differentiation from G1, G2, G3 and G4 to well, moderately, poorly differentiated or undifferentiated, respectively. While WHO categorize them into only 2 grades: low or high grade (Cassidy et al. 2007).

2.6. Diagnosis

Clinical manifestations

Abdominal pain, bleeding and a change in the bowel habits are the most common symptoms the patients suffer because of a colorectal tumor and such symptoms most probably lead to anemia.

Abdominal pain with no specific location to describe is the most symptom associated with the colorectal carcinoma, with or without nausea and vomiting. Appendiceal pain may give a false diagnosis of appendicitis when the neoplasm is proliferating at the cecum.

Bleeding (normal red or abnormal blood) is a very critical symptom and many cases that suffer from bleeding through the anus are falsely diagnosed as hemorrhoids specially if the patient had a history of hemorrhoids, delaying the diagnosis of cancer to complicate the treatment. Mucus discharge may also occurs.

Either constipation or diarrhea is a change in the bowel habits that may happen specially with carcinoma of the distal sites of the colon and the rectum.

Anemia occurs as a common complication as well, weight loss, malaise, bowel obstruction, pelvic pain, back pain and jaundice are the symptoms associated with colorectal carcinoma cases with different ratios and regarding the site, extent of invasion and the stage of the tumor (Gordon and Nivatvongs 2007).

Imaging

Colonoscopy as an optical method is very important device to be used in the diagnosis of the colon diseases generally, in the case of the colon tumors, it is essentially used for the

aim of preoperative investigations that is very useful for deciding many of the surgery procedures and is very useful in screening colorectal cancers in people that are under a high risk. Evacuation of the colon is the main problem facing its efficiency as it works by passing a fiber scope through the lumen. The ability of imaging, biopsying and the removal of some polyps in one operation enhances the role of colonoscopy in colorectal carcinoma cases (Pelengaris and Khan 2013, Gordon and Nivatvongs 2007).

Barium enema is the radiologic method by which a lot of colorectal carcinoma cases are diagnosed with, many types are offered as air-contrast barium enema, full column barium enema or double-contrast enema (Gordon and Nivatvongs 2007). Barium and air are administrated anally as an unfavorable procedure for the patient and the lack of high sensitivity in some cases are the main disadvantages of such method (Hayat 2009).

CT colonography (virtual colonoscopy) is a radiologic non-invasive method that is widely used for the aim of diagnosing colon tumors in symptomatic patients and screening the other asymptomatic cases whom suspected to be under a risk by forming 2 and 3 dimensional images of the colon and the rectum (Shapiro et al. 2012, Robinson et al. 2011). Regarding patient discomfort, CT colonography was the preferred choice of most of the patients when compared with the colonoscopy or the barium enema (Gluecker et al. 2003).

Other imaging techniques involved in diagnosing colorectal tumors and different sites of metastasis include: endorectal ultrasound, MRI, positron emission tomography (PET) angiography and sigmoidoscopy (Gordon and Nivatvongs 2007).

Fecal occult blood testing (FOBT)

Any disorder take place in the colon or the rectum may cause bleeding due to the weakness of the blood vessels surrounding these tissues. Sometimes, the bleeding is mild, masked by the feces and cannot be noticed by the patient.

FOBT (also known as Guaiac test) is a simple cheap test that can confirm if there is blood within the feces or not but separately, FOBT is not enough to confirm cancer as well as it is not specific for any of the GIT sites, further investigations are required if the test shows positivity.

So, the fecal occult blood testing is necessary for the aim of screening and the early diagnosis of any colon or rectal disease as a regular medical check-up test, specially for the people under specific risk and people over 50 years old and also, to confirm that there is a specific problem in the GIT when the patient is suffering nonspecific symptoms (American-Cancer-Society 07.10.2015).

Carcinoembryonic antigen (CEA)

CEA was first discovered in 1965 and described as an antigen found in colon cancer tissues only, but later, it was discovered in the serum of any healthy individual as well but with lower levels.

It is a very important tumor marker which is widely used for diagnosis and staging of colorectal tumors and some other types as it is a stable molecule with high difference in its serum level between normal and cancer patients, the test is done by a sensitive radioimmunoassay (Hammarström 1999).

Biopsy

As mentioned before, colonoscopy is widely used as an imaging technique for diagnosis of bowel disorders with an additional option of biopsying which is unavailable by the other techniques, 2 operations (imaging and tissue sampling) are held once is a great advantage (Gordon and Nivatvongs 2007).

Fine needle aspiration is a very efficient technique used for the aim of tissue sampling in various abdominal diseases including colorectal tumors, in most cases, it gives accurate results and gives rare complications. Some studies have mentioned that this method may cause seeding of metastasis when biopsying malignancy tissues along the sites exposed to the needle during the operation or even by increasing the permeability of the vessels surrounding the tumor to help in spreading (Lundstedt 1991).

Other biopsy instruments include: cup-shaped biopsy forceps, alligator-type biopsy forceps and Turrell biopsy forceps (Gordon and Nivatvongs 2007).

3. Ulcerative colitis

Ulcerative colitis is a chronic inflammatory bowel disease characterized by the continuous inflammation of the colon mucosa that may affect the rectum causing motility and secretion abnormalities with the possibility of relapse (Guo et al. 2011).

Thousands of years ago, many physicians from different eras and regions have described some similar symptoms as chronic diarrhea with rectal bleeding and abdominal pain (Lichtenstein 2014).

It is one of the most important risk factors that leads to colorectal cancer, specially, when it is not completely cured or in case of the prolonged existence as it occurs in the mucosa of the colon (Stange et al. 2008).

3.1. Epidemiology

Recently, ulcerative colitis is widely distributed in most of the world countries, although, previously, it was stated that the Western regions have the major percentages of incidence, in Britain, Northern half of Europe, North America and Australia (De Dombal 1971).

3.2. Etiology

Ulcerative colitis cases are divided according to the site of inflammation of 3 main sites: inflammation of the rectum only (proctitis), inflammation of most of the descending colon and the rectum (left-sided colitis) and inflammation extending along the whole bowel (pancolitis) (Guo et al. 2011).

The causes of ulcerative colitis are not clearly understood but it was proved that there are some factors usually associated with ulcerative colitis, several theories and mechanisms were discussed and suggested for reaching the real cause.

A study in 2006 suggested a mechanism consisting of 4 elements: genetically susceptible host, environmental factors, bacterial action and an immune response are linked together illustrating a cause and a way of developing such inflammatory disease.

Immune mediated inflammation of an aggressive response is the main reaction against normal bowel flora that show up an abnormal metabolic pathway and interrupt the mucosa due to certain factors, in case of a genetically susceptible individual to the disease.

Altered MDR1 (multidrug resistant gene found in chromosome 7) is always associated with ulcerative colitis and Crohn's disease as well. When it was deleted from mice, colitis occurred.

Immune response by macrophages, neutrophils and T-lymphocytes was observed at the intestinal inflamed mucosal tissue through activation and release of cytokines (Sartor 2006).

Nuclear factor kappa-B (NF- κ B), tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6) and interferon-gamma (IFN- γ) are found to be the main regulators of such immune response (Ahmed et al. 2014).

Factors as stress, usage of non-steroidal anti-inflammatory drugs (NSAIDs) or antibiotics may disrupt the mucosal barrier and alter the normal gut environment stimulating the mentioned immune response (Sartor 2006).

Sometimes, the normal flora of the gut initiates or/and maintains an inflammation, also, many studies showed a link between GIT bacterial infections including *Escherichia coli*, *Salmonella*, *Shigella*, *Yersinia* and other species and ulcerative colitis (Cummings et al. 2003).

3.3. Risk factors

Caucasian people are the most noticeable in many studies to have a higher incidence among Europeans to the disease, males and females are under equal risk (Head and Jurenka 2003).

The inheritance cannot be ignored as a risk factor in case of first degree family member who suffered such disease before (Stange et al. 2008).

Ages varying between twenties and thirties are the most affected by ulcerative colitis, however, people over 60 years old are also involved (De Dombal 1971).

Anxiety, depression and stress showed a noticeable role in such disease, many studies observed a link between these psychological conditions and ulcerative colitis incidence, the delay in its healing process and increasing the chance of its relapse (Tabatabaeian et al. 2015).

Quitting smoking is followed by an increase in ulcerative colitis risk, while the smoker's colon is relatively protected against such disease and using nicotine as a replacement therapy for the aim of stopping smoking is very useful for avoiding such risk. Smoking does not provide this protective action in all the IBD cases as Crohn's disease but actually it has an opposite effect (Lakatos et al. 2007).

3.4. Diagnosis

Clinical manifestations

About half of the patients diagnosed with ulcerative colitis are suffering from the left colon i.e. proctosigmoiditis (inflammation of the sigmoid colon and the rectum), the majority of cases are firstly diagnosed with moderate symptoms and about 10% of them suffer from severe ones (Wexner and Stollman 2007).

Symptoms include abdominal pain and cramps, urgency, tenesmus, diarrhea, fecal blood, fatigue, anemia, weight loss, loss of appetite, fever, mucus in stool and may reach dehydration and shock due to the huge loss of electrolytes (Head and Jurenka 2003, Stange et al. 2008, Wexner and Stollman 2007).

Some extra-intestinal symptoms appear with different percentages in patients with ulcerative colitis as sclerosing cholangitis which affects the biliary tract and the liver and

may lead to cirrhosis and hepatic failure as the most severe symptom, acute arthropathy affecting the joints as a bowel independent symptom which is not relieved after the complete cure of the colon and some other inflammations affecting the eye and the skin.

Imaging

Almost, the same devices mentioned for imaging colorectal tumors are used in diagnosing ulcerative colitis including sigmoidoscopy, colonoscopy and CT.

Lab tests

Anemia, thrombocytosis, leukocytosis, eosinophilia, hypoalbuminemia and liver enzymes elevation are common features in the diagnosis of ulcerative colitis (Wexner and Stollman 2007).

4. Colorectal carcinoma and ulcerative colitis

The development of colorectal carcinoma as result of ulcerative colitis represents about 1% of all the colorectal carcinoma cases and 15% of all the bowel diseases deaths with a noticeable involved percentage in males which is almost double the number of females, 43 years old is the average age of diagnosis (Lakatos and Lakatos 2008).

4.1. Carcinogenesis and some genetic features

From a biopsy of an inflamed mucosa from a patient with ulcerative colitis, a possible explanation for the mechanism of developing carcinoma through bowel inflammation was concluded, as the continuous proliferation of the epithelial cells to overcome the high rate of death of the colonic mucosal tissues as a result of the inflammation offers a very suitable medium and conditions for neoplasm formation with the aid of some genetic mutations and the damage of the DNA (Triantafillidis et al. 2009).

Toll-like receptor4 (TLR4) signaling is always associated with cancer derived from colon chronic inflammations by increasing the expression of COX-2 and the signaling of epithelial growth factor receptor (EGFR), at the same time, it was observed that mice lacking this receptor resist colitis associated cancer (Fukata et al. 2007).

Regarding genetic changes, the epithelium in case of ulcerative colitis develops first into low then high grade dysplasia before turning to be cancer through MSI pathway which was mentioned as one of the mechanisms that leads into sporadic colorectal carcinoma as well, the other mechanisms were concluded to occur also but with less frequency (Lakatos and Lakatos 2008). Mutation of gene p53 is common in the early periods of ulcerative colitis associated colorectal carcinoma compared to sporadic type that shows p53 mutation in later onset (Triantafillidis et al. 2009).

MSI is thought to occur in most of the cases, as the early stages of ulcerative colitis malignancy shows MSI with some defected mismatch repair genes as MLH1, PMS2 and others. Some oncogenes as BRAF, which is activated in many types of malignancies, are

also observed to be mutated during this pathway (Coppola 2014). In some ulcerative colitis cases, MSI can be screened before the diagnosis of colorectal carcinoma by 2-12 years.

Mutations of K-ras gene is also involved, but with lower percentages in these cases compared to sporadic cases and it is always associated with polyps to give an explanation for the flat figure the neoplasm following a bowel inflammation appears (Lakatos and Lakatos 2008).

Dysplasia associated lesion or mass (DALM) is discovered by endoscope and acts as an evidence for the increased risk of this dysplasia to develop into carcinoma (Triantafillidis et al. 2009).

Dysplasia appears either flat or elevated, but there is a more specific classification that is used mainly in Europe and Japan, it was established under the name of Vienna classification in 1988 by a group of gastrointestinal experts to divide the dysplasia depending on its pathological phase into 5 divisions: negative, indefinite, non-invasive low and high grade and invasive which is also subdivided into invasive submucosal and intramucosal. In the United States, pathologists use another older system called IBD dysplasia morphology study group but Vienna system is more advanced and specific (Odze 2006).

4.2. Risk factors

The inflammation severity in ulcerative colitis cases is linked with the risk of developing colorectal neoplasm, moreover, the occurrence of other inflammatory diseases as sclerotic cholangitis enhance this risk more.

Duration of the bowel inflammation was shown in a meta-analysis to have a strong link with cancer, patients suffering ulcerative colitis more than 10 years are under 2% cumulative risk and those whom suffering it more than 20 years are under 8% while those whom suffering it more than 30 years are under 18% cumulative risk (Loftus 2006).

Extent of the inflammation also cannot be ignored, the greater the colonic inflamed area, the greater will be the chance of developing carcinoma.

Expression of cytokines as IL-6 and IL-23 which are stimulated by NF- κ B has a great role in bowel inflammation and colon associated carcinogenesis as well.

Cultured cells tests showed that TNF- α causes chromosomal instability, gene mutation, amplification and may damage the DNA promoting cancer development.

Oxidative stress with the damage of nitrogen bases are very characteristic for the inflammation of the colon due to the phagocytic action by the leukocytes and facilitates carcinogenesis.

Familial history of colorectal cancer is a very important factor that put the individual with ulcerative colitis under double the risk of malignancy, compared to people without a first degree familial history of the disease.

The presence of pseudopolyps, backwash ileitis, the incidence of bowel inflammation at younger ages and quitting smoking are all factors that increase the risk of colon carcinogenesis through ulcerative colitis.

Males are under a much higher risk than females (Lakatos and Lakatos 2008).

4.3. Treatment of colorectal carcinoma and ulcerative colitis

The most common treatment used in colorectal cancers is the surgery with the aid of radiotherapy and chemotherapy (Ahmed et al. 2014).

Surgery

Although complete proctocolectomy is the choice as a prophylactic method against the risk of developing cancer with the complete abdominal colectomy, it is not the preferable option due to the unclear link mechanism between ulcerative colitis and risk of colorectal carcinoma (Wexner and Stollman 2007).

Proctocolectomy is a first-line treatment method in acute severe ulcerative colitis cases and when treatment via corticosteroids is prolonged for more than 40 days without a noticeable amelioration (Travis et al. 2008).

With ulcerative colitis associated colorectal carcinoma, surgery is recommended mostly for treatment in case of diagnosing low or high grade dysplasia and in case of documented adenocarcinoma with the aid of adjuvant or neoadjuvant therapy.

Surgery is recommended also to avoid cancer in patients under high risk with obstructive strictures, unresectable DALM or suffering ulcerative colitis for long years (Stucchi et al. 2006).

Children of FAP families should be screened before being 10 years old, if FAP is diagnosed, total colectomy, ileal pouch anal anastomosis or rectal mucosectomy are recommended for avoiding turning out into malignancy, although colorectal carcinoma is not common in children (Carachi et al. 2008).

Restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) is the removal of the diseased colon and rectum with conserving the normal function of the rest of the GIT and anal defecation. Recently, it became the preferred surgical option in ulcerative colitis treatment as it shows minimal postsurgical complications (Michelassi et al. 2003).

Colonoscopy plays an important role in screening, diagnosis, treatment and even posttreatment follow up of colorectal carcinoma, individuals under risk of developing the disease should be screened to avoid the incidence or to start therapy as early as possible if cancer is diagnosed.

Excision of polyps (polypectomy), if found, using endoscope is widely spread method during screening or diagnosis of colon tumors in the same operation, but if the endoscope shows any neoplastic lesions, specimen is collected and examined to determine the stage and whether malignancy occurs or not (Hassan et al. 2013).

Resection is done according to the site of the tumor diagnosed, either right hemicolectomy, transverse colon resection, descending colon resection or sigmoid resection with the aid of adjuvant radiotherapy, chemotherapy or immunotherapy (Gordon and Nivatvongs 2007).

For the rectum, transanal endoscopic microsurgery (TEM) is a method to remove adenomas from any site of the rectum using an endoscope with minimal invasion, safety, efficiency and few complications on the long term. Either mucosectomy or the resection of full thickness rectal wall are the operations done through TEM according to the case (Schäfer et al. 2005).

Total mesorectal excision (TME), anterior resection, abdominoperineal resection (APR) are different surgeries for treating tumors of the rectum with different probabilities of the cancer recurrence risk (Marr et al. 2005).

Radiotherapy

Usually, radiotherapy cannot be used separately for treatment of colorectal tumors, but used as an adjuvant therapy supporting surgeries or chemotherapy.

In cases of colorectal carcinoma, radiotherapy is mainly applied as a preoperative method for better local control of the tumor before submitting the patient to surgery as the total mesorectal excision.

Risk of recurrence after surgery is very common in treating colorectal tumors cases but after applying pre- and postoperative radiotherapy, statistics showed that the ratio of recurrence has extremely decreased compared to cases of which surgery was the only treatment method applied (Kapiteijn et al. 2001).

Radiotherapy can be used in 3 adjuvant techniques: short course preoperative radiation, preoperative and postoperative chemoradiation for rectal cancer treatment (Cassidy et al. 2007).

Combination of preoperative and postoperative chemotherapy with preoperative radiotherapy in rectal cancer surgeries, facilitates the treatment by limiting the tumor size and also decreases the risk of recurrence, however, it does not prevent any postoperative complications or improve the rate of survival significantly (Bosset et al. 2006)

Stereotactic body radiotherapy (SBRT) is a modern radiological technology, applied in many cases of metastasis. Hepatic, pulmonary and lymph nodes metastasis are common

features of colorectal carcinoma cases and surgery is not efficient for treatment due to poor prognosis and high morbidity, so, a study was made to observe the efficiency of such technology to treat paraaortic lymph nodes metastasis and concluded better prognosis and decreased risk of recurrence compared to chemotherapy that failed to reach similar results (Kim et al. 2009).

Colorectal cancer chemotherapy

Combination of fluorouracil (5-FU), leucovorin, irinotecan or oxaliplatin with or without bevacizumab is the standard first-line therapy used in colorectal cancer, specially, the metastatic type (Cutsem et al. 2009). Capecitabine is the oral prodrug of 5-FU, both have similar efficacy and safety when combined with oxaliplatin for treating colorectal cancer. They are used, although they cause bone marrow depression as a serious side effect (Homer 2013).

FOLFOX (FOL: folinic acid (leucovorin), F: fluorouracil and OX: oxiplatin) combination is widely used for the treatment of metastatic colorectal cancer and very effective. After adding the new member irinotecan to be named FOLFOXIRI, results were improved but side effects increased (Ruzzo et al. 2007).

5-FU is classified as anti-metabolite, administered as intravenous (IV) infusion due to its gastric toxicity, metabolized by liver and kidney and excreted in the urine, thus, hepatic and renal functions should be monitored regularly during treatment (Whalen 2015). It was the main chemotherapeutic agent used for treating colorectal cancers for many years (Cassidy et al. 2004).

Recently, 5-FU is administrated with leucovorin to complete the mechanism of action of inhibiting thymidylate synthase enzyme necessary for the process of cell division as leucovorin maintains the complex formed between 5-FU and the enzyme, the results showed much better response to treatment compared to cases treated using 5-FU singly (Saltz 2007). IV prolonged infusion is more efficient and safe than the bolus (Cassidy et al. 2004).

Oxaliplatin is an alkylating agent, member of platinum coordination complex class that targets guanine bases of the DNA to form covalent bonds preventing its replication and inhibiting RNA synthesis, administrated also as IV infusion and excreted in urine. Hepatotoxicity, neurotoxicity and myelosuppression are the adverse effects with frequent vomiting which is a common feature when using this class (Whalen 2015).

Irinotecan is a member of class camptothecins, extracted from plant origin (*Camptotheca acuminata* tree), inhibits topoisomerase I action of resolving the 2 DNA strands. Side effects including diarrhea and bone marrow depression are the least, compared to those of other chemotherapeutic agents (Rang et al. 2012).

Capecitabine is an oral fluoropyrimidine prodrug, it is activated through enzymatic action to give free 5-FU at the cancer site. Oral administration twice daily gives better compliance by many patients more than the IV route of 5-FU and better activity than bolus 5-FU/leucovorin resulting also in less side effects as diarrhea, stomatitis neutropenic fever and alopecia. It was used in combination with oxaliplatin (XELOX) that was more efficient than using it alone and such combination is well tolerated even on the long term plan treatment (Cassidy et al. 2004).

Antibodies

Bevacizumab is an IV monoclonal antibody approved to be a first-line therapy for metastatic colorectal cancer (Whalen 2015), known to have antiangiogenic action through targeting the vascular endothelial growth factor (VEGF), a glycoprotein regulator in the process of angiogenesis, added to a combination of 5-FU, leucovorin and irinotecan to show improvement in the treatment results and is tolerated by the body (Hurwitz et al. 2004). Treatment efficacy was also improved upon adding bevacizumab on combination of oxaliplatin with either oral capecitabine or 5-FU/leucovorin bolus or IV infusion (Hochster et al. 2008).

Adverse effects as hypertension and leukopenia appears upon administering bevacizumab, also, delayed wound healing, bleeding and proteinuria are expected and should be considered (Hochster et al. 2008, Whalen 2015).

Cetuximab is an immunoglobulin G1 monoclonal antibody that has different mechanism of action from that of bevacizumab by binding to EGFR which is overexpressed on the tumor cells surface to inhibit signaling and alters the tumor cell growth, used in treatment of head, neck and colorectal cancers in combination with irinotican and the results improved compared to using irinotican alone with decreased resistance. Side effects are skin rash and losing electrolytes (Jonker et al. 2007, Whalen 2015). Panitumumab is another antibody of similar mechanism of action (Rang et al. 2012).

Gold nanotechnology

Gold nanoparticles is considered as one of the most important and advanced technologies which is under investigations and researches of imaging and treatment of gastrointestinal tumors including the colorectal ones and for targeting the cytotoxic agents to the tumor sites by conjugation. Lab tests and animal models were used for researches and showed promising results, however, more clinical trials should be held to understand and standardize such modern aspect that might be a superior method for colorectal tumors treatment (Singh et al. 2015).

Cancer stem cells

A modern strategy of treating cancer in general including colorectal tumors, based on studying the cytological and genetic specifications of the cancer stem cells that are suggested to be responsible for the development of tumors from initiation until metastasis, driven by their metastasis-related proteins and specific biomarkers overexpression. Such strategy may improve the neoplasm local and metastatic targeting and therefore, decreasing the systemic side effects.

Stem cells are undifferentiated, rapidly proliferating cells. In case of colon and rectum, they grow at the base of the mucosal crypts as mentioned before, biomarkers expressed in colorectal tumors include: CD44, CD133, EpCAM, SOX2, SOX9, BMI1, ALDH1 and others.

The idea of targeting stem cells is a golden gate for further researches and studies which are required for more evaluation of the efficacy and safety of using this method in the future for treating cancer and many other diseases (Rassouli et al. 2015, Brungs et al. 2015).

Ulcerative colitis medications

So far, there are no drugs that may cure ulcerative colitis completely, but they are used to decrease the rate of recurrence, improve quality of life and minimize the postsurgical complications.

Since ulcerative colitis is an inflammatory disease, so, the majority of cases are treated by either anti-inflammatory agents as corticosteroids or immunosuppressor agents that either decrease the immunity cells or decrease the proteins that motivate the immunity but unfortunately, both classes have many systemic side effects that cannot be ignored (Guo et al. 2011).

Prednisolone (corticosteroids) was the first drug approved by food and drug administration (FDA) (Lichtenstein 2014), they are usually prescribed moderate or severe cases that the other medications fail to treat, their systemic side effects are numerous including hypertension, osteoporosis, diabetes and mood swings (Guo et al. 2011), however, some patients do not respond to such treatment and relapse occurs in many of them after months of remission (Hanauer 2004). Budesonide is another steroid used for the same aim with lower side effects compared to other steroids (Lichtenstein 2014) and hydrocortisone is also used (Bebb and Scott 2004).

Many trials along the last century were held to study the remission effect of different steroids routes of administration for treating ulcerative colitis. Oral, intravenous, rectal enema and suppositories showed different efficiencies, different systemic side effects and different probabilities of relapse, all of them are used according to the case conditions (Lichtenstein 2014).

Aminosalicylates or 5-aminosalicylic acid (5-ASA) are anti-inflammatory agents that are the first-line drugs used in remission and maintenance treatment of ulcerative colitis include sulfasalazine, mesalamine, olsalazine and balsalazide (Nikfar et al. 2009).

5-ASA shows higher efficiency during maintenance therapy of ulcerative colitis than corticosteroids, although corticosteroids are more efficient in inducing remission (Bebb and Scott 2004).

Inhibiting the immune mediators IL-1, IL-2 and NF- κ B, suppressing the activity of lymphocytes and monocytes and offering an antioxidant effect are the main anti-inflammatory mechanisms of aminosalicylates, however, there are other mechanisms of action (Head and Jurenka 2003).

Sulfasalazine was approved officially by FDA in 1977 (Lichtenstein 2014), it is the most common used, although it has many unfavorable side effects due to the presence of antimicrobial moiety (sulfapyridine molecule) combined with the 5-ASA moiety by an azo bond (Karagozian and Burakoff 2007).

Sulfasalazine is used for the treatment of mild and moderate ulcerative colitis and during the acute attacks to prolong the remission time between them and as an adjuvant in severe cases, it has the advantage of targeting, because it stays inactive until being in contact with the bacteria of the large intestine that separate the 2 moieties. 5-ASA molecule cannot penetrate the colon mucosa, so, its effect is local and has no systemic side effects. It is also cheaper than mesalamine.

On the other hand, sulfapyridine moiety is responsible for many side effects according to the dose, sometimes mild as nausea and headache or severe as hepatotoxicity as it is systematically absorbed (Lichtenstein 2014), also, sulfa hypersensitivity is common and must be considered (Guo et al. 2011).

Mesalamine or mesalazine lacks the antimicrobial moiety found in the sulfasalazine having an advantage of lower side effects, it is found in many routes, tablets and capsules, normal or modified release forms, suppositories and rectal enema for treating inflammations of the last part of the colon (Guo et al. 2011).

Modified release oral mesalazine is found in 2 forms, either in pH-dependant coat of resin, which disrupt and release the active ingredient in basic medium above pH 6 or in the form

of multiple microgranules enclosed in ethylcellulose membrane and slowly release the active ingredient along the gut wall (Ragunath and Williams 2001).

Many studies reported an apoptotic effect induced by mesalazine and the ability to block mitotic phases G1/M leading to suppression of the cell proliferation rate, the discoveries that opened a huge gate for studying the possibility of using 5-ASA drugs in the treatment and prevention of tumors, specially, colorectal carcinoma due to its suitable site of action of such drugs (Reinacher-Schick et al. 2003). Recently, ulcerative colitis patients known to be under high risk of developing colon cancers are better treated with 5-ASA compounds (Bebb and Scott 2004).

To overcome the disadvantages of sulfasalazine and keep the option of targeting, 5-ASA prodrugs as olsalazine and balsalazide containing azo bonds were formed and this bond is disrupted by the colon bacteria exactly as what happens with sulfasalazine to be activated only in the colon with neither absorption nor systemic side effects (Karagozian and Burakoff 2007). Azoreductase enzyme produced by the bacteria break the azo bond to set the 5-ASA active molecule free (Tursi 2008).

In comparison with other 5-ASA, balsalazide is faster in soothing the symptoms, providing full remission and more efficient than sulfasalazine with lower side effects in treating active ulcerative colitis (Tursi 2008).

It is a prodrug, approved by food and drug administration (FDA) for the treatment of mild and moderate ulcerative colitis (Kim et al. 2015), consists of 5-ASA linked by azo bond to 4-aminobenzoyl- β -alanine (4-ABA) which is an inert moiety avoiding crucial side effects to be pharmacologically safe and well tolerated. Studies concluded that balsalazide high doses decreases the ratio of relapse better than other 5-ASA agents (Kruis et al. 2001).

Balsalazide anti-inflammatory effect can be induced by inhibiting NF- κ B as one of several mechanisms, NF- κ B which was mentioned before as an important regulator of the inflammatory reactions that occur in both, ulcerative colitis and colorectal cancers.

As a result, Balsalazide was found to have a mutual role as therapy for ulcerative colitis and as a preventive method against ulcerative colitis associated colorectal carcinoma by supporting apoptosis through inhibiting NF- κ B (Kim et al. 2015).

Treating ulcerative colitis using probiotics is another successful method for remission. Probiotics are bacteria (for example: *E.coli* Nissle) that are useful to the host GIT by balancing the microbial environment and boosting the mucosal barrier through decreasing the adhesion on colon epithelium, it is very effective in cases of pediatric gastroenteritis. The results showed no significant differences between probiotics and 5-ASA in ulcerative colitis remission (Mallon et al. 2008).

4.4. Prevention

For colorectal cancer, regular screening is an efficient way for prevention and for decreasing the rate of mortality of the disease, specially, with individuals known to be under risk. The early diagnosis of ulcerative colitis and full proper medication help in decreasing the risk and the avoidance of reaching the level of developing tumors (Chan and Lichtenstein 2006).

FOBT, sigmoidoscopy, colonoscopy and barium enema are the commonly used methods for early detection with the acknowledgment if there is a family history with the disease. Some advanced methods include: CT colonography and virtual colonoscopy and testing the stool DNA mutations (APC, K-ras and p53), the different health guidelines usually advise to make some of these tests every year and others every 5 years, specially, people under specific risk (Gordon and Nivatvongs 2007, Smith et al. 2006).

Although using NSAIDs was mentioned as one of the factors that may lead to disrupting the mucosal barrier causing ulcerative colitis, these drugs and aspirin show a protective effect against colorectal carcinoma and a lower risk for individuals who intake NSAIDS regularly compared to others who do not. Colorectal tumors risk is also decreased in patients who depend on low doses (75 mg/day) of aspirin for cardiovascular aims to receive

a mutual protective effect (Din et al. 2010). Colorectal adenomas were found to be decreased by the NSAIDs specially, in FAP patients (Eaden et al. 2000).

5-ASA compounds including sulfasalazine used in treating ulcerative colitis offer protection against colorectal cancer (Eaden et al. 2000), mesalamine is chemopreventive against sporadic and ulcerative colitis associated colorectal cancers (Allgayer 2003), balsalazide reduce the number and size of colorectal polyps that may develop into tumors as a chemopreventive agent and can be used to decrease the rate of growth of neoplasm (Terdiman et al. 2009).

Quitting smoking may decrease the risk of colorectal carcinoma and many other tumors and diseases, but smoking itself has a preventive effect against ulcerative colitis at the same time as mentioned before. Using nicotine-replacement therapy and antidepressants is a suitable solution for quitting smoking and keeping such advantage (Lakatos et al. 2007).

Balanced diet with minimal amount of processed meat and lipids of animal source are very important in decreasing the risk of colorectal tumors, even if such sorts of meats are cooked, fried or grilled, carcinogenicity increases as mentioned before (Stewart et al. 2015).

Fruits and vegetables rich in fibers and phytochemicals as vitamin E refresh the gut environment, dairy products rich in calcium decrease the carcinogenic effect induced by the processed meats, polyunsaturated fatty acids as omega-3 found in fish induce anti-inflammatory effect (Oostindjer et al. 2014), garlic and onions rich in allium lower the risk of developing stomach and colon tumors (Pensiero et al. 2004).

Obesity is directly related to many diseases including colorectal cancer and regular physical activity is linked to lowering the risk as the individuals who train regularly avoid obesity, keeping healthy GI peristaltic movement thus avoiding constipation and balancing the diet with low lipids intake (Pensiero et al. 2004).

As mentioned before, high alcohol consumption is strongly linked with high risk of colon and rectal cancers, so, decreasing the daily alcohol intake may help in the avoidance of

such tumors (Moskal et al. 2006), although, red wine contains a phytochemical substance called resveratrol which inhibits metastasis (Oostindjer et al. 2014).

5. Summary

This is a general overview of cancer with focusing on colorectal cancer and its correlation with ulcerative colitis. Definitions, statistics, mechanisms of incidence and different methods of diagnosis, treatment, prevention and other topics are discussed.

How is cancer defined? What are its types and classifications? How does it initiate? Who are the individuals under the risk of developing this disease? What are the ratios of its incidence and mortality globally? What are the factors that lead to carcinogenesis and what are the main regulators of this mechanism inside the human body?

How is cancer diagnosed early? What are the different sorts of diagnosis? Highlights on the clinical manifestations, symptoms, lab tests, imaging techniques including some modern aspects as the usage of nanotechnology in diagnosis. Discussing the stages of cancer, indicating the different staging systems with the illustration of the TNM system, the most commonly used one.

Regarding the case, stage, type and many factors, how is the method of treatment detected? The commonly used methods include surgery, radiotherapy and chemotherapy which are used singly or in combination. How are the surgeries used in many cases of tumors removal, full organ excision and sometimes prevention? The indications with the aid of pre- or postoperative radiotherapy and/or chemotherapy. Radiotherapy mechanism of action, types, indication, route of administration, the factors that affect its efficiency and the adverse effects induced. Cancer chemotherapy different classes according to the mode of action and indications for treatment, combination and prevention, focusing on the properties of some agents of each class and their side effects. Hormones and hormonal agonists and antagonists that are used in different types of cancer either for treatment, relieving symptoms or decreasing the side effects induced by other agents. Some of the modern treatment options which are already used as the monoclonal antibodies or which are still in the research phase, including gold nanotechnology. These agents that may be used for treatment or by forming a complex with other agents for better targeting to be more specific than the ordinary delivery methods used.

How do the tumors resist the treatment methods? What are the physiological and cytological factors that control such mechanisms and what are the physical and chemical properties of the agents that should be concerned to avoid resistance?

Prevention of cancer indicating modifications of the life style, screening and regular medical check-up. However, there is no evidence that this disease can be avoided completely, it is always a matter of decreasing the risk as much as possible.

Overview of the colorectal carcinoma mentioning the colon and rectum anatomy and physiology passing by global statistics, mechanism of carcinogenesis and metastasis, some common genetic mutations, pathological features, causes and risk factors till the differences between its types whether sporadic or inherited.

Illustration of the different types of inherited syndromes that may lead to colorectal carcinoma including FAP and HNPCC and some genetic pathways that initiate carcinogenesis or help in propagation.

The widely used diagnostic methods is enumerated including clinical manifestations, imaging, lab tests and staging of the disease using the TNM and Dukes systems.

Ulcerative colitis statistics, mechanism of incidence, causes and risk factors. Pathology, clinical picture, lab tests and imaging techniques.

Finally, ulcerative colitis associated colorectal carcinoma as the inflammatory bowel disease is one of the most important risk factors that may lead to the development of GI tumors. Illustration of the causes and mechanism of carcinogenesis through ulcerative colitis with the risk factors.

The common used treatment methods of each disease are mentioned and explained including surgery, radiotherapy, chemotherapy, medications and probiotics with focusing on the drugs that may induce double action of treating ulcerative colitis and avoiding or decreasing the risk of developing cancer as balsalazide. Some new aspects and advanced techniques and strategies which are still under development as gold nanoparticles or targeting the cancer stem cells are also stated.

How to prevent both diseases? Different ways of lowering the risk of developing colorectal cancers through screening, some medications and altering dietary and daily life habits are discussed.

6. Abstract (English)

Colorectal carcinoma is one of the widely spread types of cancer and causes one of the high percentages of cancer deaths all over the world. In many cases, it is related to other gastrointestinal diseases as ulcerative colitis. Patients of ulcerative colitis are always at risk of developing colorectal tumors, both diseases have many common symptoms, ways of diagnosis, therapies and prevention.

This diploma thesis highlights some of these common features, how these diseases are related, the reasons, risk factors, statistics, the genetic role, pathological and clinical features, imaging techniques, lab tests and several types of therapies including surgeries, medications, chemotherapy, antibodies and other modern aspects that may be mutually efficient for both cases.

7. Abstract (German)

Kolorektales Karzinom ist eine weitverbreitete Krebsart. Weltweit ist es für einen hohen Todesrate verantwortlich. In vielen Fällen besteht ein Zusammenhang mit gastrointestinalen Erkrankungen, wie ulzerative Kolitis. Patienten mit ulzerativer Kolitis weisen ein erhöhtes Risiko für kolorektale Tumore auf. Beide Erkrankungen (Kolonkarzinom und ulzerative Kolitis) zeigen gemeinsame Symptome, haben ähnliche Diagnostik, Therapie und Prevention.

Diese Diplomarbeit beschäftigt sich mit den Gemeinsamkeiten, vor allem wie diese Erkrankungen zusammenhängen, deren Ursachen, Risikofaktoren, Statistik, genetische Rolle, pathologische und klinische Merkmale, Imaging-Techniken und Labortests. Außerdem werden verschiedene Therapien, wie Operationen, Chemotherapien, Verwendung von monoklonalen Antikörpern für beide Erkrankungen diskutiert.

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9. Curriculum Vitae

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Member of Cairo Pharmacists Syndicate since 2011 (membership no: 141304).

Education

2000-2003: IGCSE (Cambridge University) in St. Fatima school, Nasr city, Cairo.

2011: Bachelor Degree of Pharmacy, Ain Shams University, Cairo.

January 2015 - present: Nostrification student, faculty of pharmacy, Vienna University.

Professional experience

April 2012 to August 2014: Production Specialist at Eva Pharma (Haram Plant)

December 2011- March 2012: Community Pharmacist in Waseem Pharmacy, Nasr city.

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September 2012: Attended a course entitled 'General awareness for food safety management system' ISO 22000 /2005 at EVA Pharma premises.

Computer skills

Microsoft office (Picture, Power Point, Word).

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Languages

Arabic (mother tongue) and English: fluent in speaking and writing.

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