Oncology of Different Populations and the Ethical Impact of the HeLa cell case and Physician Assisted Suicide on Patient Autonomy

Neha Bakshi

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Oncology of Different Populations and the Ethical Impact of the HeLa cell case and Physician Assisted Suicide on Patient Autonomy

Abstract
An in depth analysis of different types of cancers in various populations such as pediatrics, adults of all ages, and babies that are still in the womb. Discusses the importance of funding research and finding new methods of treatment. This explains the ethical impact of the Henrietta Lacks case and Physician Assisted Suicide (PAS) on patient autonomy and the importance of allowing patients to decide if they want to start or even continue cancer treatments.

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What is Leukemia?

What makes leukemia such an interesting yet different type of cancer is that it normally doesn’t manifest as a solid tumor like many other cancers. Leukemia is an aggressive neoplasm that originates from blood cells made in the bone marrow which circulate throughout the body as malignant cells instead of normal, functioning cells that fight off infections. These malignant leukocytes proliferate uncontrollably (Perry et al, 2014). A study was done on the incidences of major cancers worldwide in 2008 and leukemia accounted for 2.8% (350,434 cases), but the number of deaths that occur worldwide due to leukemia is about 3.4% (257,161 cases) (Hesketh, 2013). According to the National Cancer Institute (2016b), leukemia occurrence rates have been on the rise since the 1970s. Many cases of leukemia that are identified are seen frequently in children. however leukemia is not restricted to children but actually occurs quite frequently in older adults as well. With children in the age range of 0-14 years old, childhood leukemia accounts for 33% while the other 67% of those occur in adults. Leukemia occurs in adults ten times more frequently than in children because there is a high incidence rate in children that leukemia ends up being more frequent in adults (Berman, 2009). This paper will focus on four major types of leukemia that are specific to certain age groups. The four major types of leukemia, discussed are, acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML). The types of leukemia are classified based on duration (acute or chronic), type of proliferating white blood cell (myeloid or lymphocytic), and the fluctuation of abnormal cells in the blood (one form may be more aggressive than other forms) (Ashwell, 2010).
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**Acute Myeloid Leukemia (AML)**

Acute Myeloid Leukemia (AML) encompasses is a type of leukemia that shares a group of molecularity distinct accumulation of undifferentiated blast cells that have originated in the bone marrow. Patients will develop infections that are quite persistent and don’t respond to the usual course of antibiotic for that infection. The cause of these infections are bacterial and also results in a fever with, or without local symptoms. A few common sites of infection may be the skin, chest, throat, or gums (Ashwell, 2010). AML is also the most common type of leukemia seen in adults where there are an estimated 19,950 new cases and 10,430 deaths in the United States in 2016. This form of leukemia is mostly seen in adults at the average age of 80 years (NIH: National Cancer Institute, 2016c). The risk of developing acute myeloid leukemia goes up drastically when exposed to radiotherapy, chemotherapy, or having a rare genetic disorder such as Fanconi’s anemia (Berman, 2009). Other risk factors of developing acute myeloid leukemia will be discussed in further detail later in this paper.

**Acute Lymphocytic Leukemia (ALL)**

Another type of leukemia is Acute Lymphocytic Leukemia (ALL), which is a more prevalent form of childhood leukemia that mostly affects children from the ages of 3-7. It is a form of cancer where the bone marrow makes abnormally high amounts of immature lymphocytes. In a child with ALL, the stem cells that are produced by the bone marrows such as the B and T lymphocytes, are abnormal and don’t have the ability to fight off infections like normal. There is a massive accumulation of these malfunctioning cells and eventually there is not enough room for the healthy white blood cells, red blood
cells, and platelets. More frequent infections occur, since the white blood cells are malfunctioning, and anemia develops, since there isn’t enough room for healthy red blood cells, due to this occurring at the cellular level (NIH: National Cancer Institute, 2016a). According to Thibodeau & Patton (2010), about 80% of childhood leukemia’s are acute lymphocytic and are highly curable in children, but not so much in adults.

**Chronic Lymphocytic Leukemia (CLL)**

The third type of leukemia is Chronic Lymphocytic Leukemia (CLL), and this type of leukemia is different because B lymphocytes build up slowly over time. Some people are asymptomatic never exhibiting any symptoms for years on end. Over the years, the cells accumulate slowly and eventually may spread to other parts of the body such as the lymph nodes, the liver, or even the spleen. It causes the individual to not be able to produce normal antibodies which results in more frequent infections. This form of leukemia is relatively common, with the average age of onset being 65 years old and appearing more frequently in men than in women (Thibodeau & Patton, 2010). One of the many aspects that sets chronic and acute leukemia’s apart is that chronic leukemia’s are the most serious and are more difficult to treat since they take root in the patient’s blood longer without going noticed. Patients can live for years with CLL with little to no treatment. When lab tests are done, a protein called ZAP-70 and CD38 are indicative of whether the chronic lymphocytic leukemia will grow slowly or quicker (American Cancer Society, 2016).
Chronic Myeloid Leukemia (CML)

The last type of leukemia is Chronic Myeloid Leukemia (CML). This type is also a more slowly progressing blood and bone marrow disease that results from cancerous transformation of granulocytes which are precursor cells in the bone marrow (Thibodeau & Patton, 2010). In fact, chronic myeloid leukemia is a disease that exclusively adults in the age range of 25-60 years old. CML also evolves into an acute phase which is similar to AML. The prognosis for CML is not as good but with a bone marrow transplant, CML is 70% curative. However the patient may suffer graft-versus-host disease (GVHD) where the donor cells attack their own body (NIH: National Cancer Institute, 2016). According to the National Cancer Institute (2016b), in the United States there has been an estimated 8,220 new cases of CML with 1,070 cases that resulted in death. With CML, anyone who may develop this later in life will probably have Philadelphia chromosome where the bone marrow makes an enzyme called tyrosinase kinase which causes an accumulation of too many stem cells to mature into blast cells. One benefit is that this chromosomal condition cannot be passed down from parent to child. It is important to know about the different forms of leukemia so patients know what their chances of survival may be, but it’s also crucial to know about the variety of risk factors that can bring about any of these forms of leukemia (Berman, 2009).

Risk Factors for developing Leukemia

Like many cancers, changes or damage that come to the DNA puts an individual at risk if more mutations accumulate. One way that damage is done to our DNA is through clastogens. Clastogens are a mutagenic agent that can be either chemical or
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physical and known to break chromosomes. They have also been known to cause leukemia, which is a rarer cancer, but not normally caused by non-clastogenic carcinogens. Another trait of clastogens is that they are not strong compared to other mutagenic agents (Berman, 2009). A few types of clastogens are benzenes and ionizing radiation. Benzene is a ring-shaped aromatic hydrocarbon that originates from petroleum and found in a vast number of chemical products (glues, pesticides, inks and ink markers, and kerosene). When benzene is filtered by our liver, no damage to our liver is done however what makes it deadly is but how it affects our bone marrow. Benzene affects our bone marrow profoundly because the active metabolite is absorbed by the adipocytes in bone marrow infiltrating the hematopoietic stem cells, therefore making bone marrow weaker and causing it to weaken to the point where it can’t produce normal functioning blood elements and eventually cause disorders like aplastic anemia (Berman, 2009).

With aplastic anemia, the bone marrow essentially functions abnormally and too often, leukemia follows soon after. The occurrence rate is much higher compared to rates seen in the general public that does not develop aplastic anemia and then gets leukemia (Berman, 2009). Some other clastogenic conditions that are often associated with leukemia are Fanconi’s anemia, bloom’s syndrome, ataxia telangiectasia, and benzene toxicity. Fanconi’s anemia is a hereditary form of anemia and the incidence rate of AML in children with Fanconi’s anemia is 15,000 times higher compared to the general population of children that do not have Fanconi’s anemia. Bloom’s syndrome is a rare autosomal recessive syndrome where an individual possesses a short height and develops a skin rash after being exposed to sun light, and has an overall increased risk of developing cancer (Berman, 2009).
Ataxia telangiectasia is also another recessive disorder that mainly causes neurological complications like lack of balance, recurrent sinus and respiratory issues, dilated blood vessels in the eyes and the skin. This also causes immune system malfunctioning where an individual is hypersensitive to infections and the effects of radiation therapy, the individual is at an increased risk of developing both leukemia and lymphomas so when this does happen, the option of receiving radiation therapy would not even be considered (NIH: National Cancer Institute, 2006).

Another way an individual is at risk for developing any of the four types of leukemia- is having the chromosome abnormality called Philadelphia chromosome, where part of chromosomes 9 and 22 translocate and form a fusion gene that consists of a part of the breakpoint cluster region (BCR) gene and a part of the abelson leukemia 1 (ABL1) gene. These are fused genes that create protein products with several functions, one of them is causing a tyrosinase kinase signaling protein to always be "on" and cause the cell to divide uncontrollably. Due to this abnormality, it is exhibited mostly in individuals who have CML and sometimes about 25% of AML (Berman, 2009).

Acute lymphoblastic leukemia and acute myeloid leukemia usually occur quite often in children who have other genetic conditions like Down syndrome, Neurofibromatosis type 1, TP53 mutation, or Li-fraumeni syndrome as well as the other disorders that were previously mentioned (Elliot et al, 2006). Another major cause of leukemia that has been linked to its development is having childhood leukemia. For instance having acute lymphocytic and being treated with chemotherapeutic agents, increases the risk because chemotherapy drugs not only kill the malignant cells, but damage the DNA of healthy cells. When damaged cells go through mitosis, the
chromosomal damage is passed onto its clones and increases the risk of leukemia development later during adulthood (Elliot et al, 2006).

Another external factor that can significantly increase someone’s probability of getting leukemia is smoking; smokers are 2-6 times more likely to develop myeloid leukemia due to the carcinogenic effects of the cigarette smoke. It is extremely crucial to quit smoking or never touch cigarettes (Hesketh, 2013). Along with the chemotherapeutic agents, genetic disorders, and smoking; radiation therapy also has the ability to weaken the bone marrow as well as being exposed to high amounts of ionizing radiation (a clastogen). There has also been some speculation that certain drugs and chemicals may affect a woman’s pregnancy that may increase the risk of her child developing leukemia. Some of these substances may be alcohol, cannabis/marijuana, benzenes, and pesticides; when consumed these substances can harm the baby’s DNA and cause mutations that could lead to genetic disorders like Down’s syndrome. There still is no definitive data to support this correlation but there is speculation (Ashwell, 2010).

**Signs and symptoms of Leukemia**

With leukemia, it can be difficult to decipher which type of leukemia an individual has based on their signs and symptoms, because many of them are quite similar to one another. According to Ashwell (2010), the first signs and symptoms an individual can be aware of is:

- Anemia (specifically aplastic anemia)
- Infection and Fever
- Enlarged and painless lymph nodes
Inadequate clotting (either it is too quickly or abnormally slow)

Disturbances of normal functioning organs (malignant cells have the potential to spread to a variety of organs)

Leukemia is always considered malignant and never considered benign, although some leukemias are known to have a long and prolonged course characterized by increases in the number of cells that may closely resemble the other types of leukemia, like (CLL) (Berman, 2009). According to the NIH: National Cancer Institute (2016a), some signs and symptoms that may be indicative of (ALL) are:

- Swelling of the abdomen due to the buildup of malignant cells that can cause the liver and spleen to enlarge. Sometimes this is felt as swelling in the belly or the feeling of fullness after eating a small amount of food
- Enlarged lymph nodes that are close to the surface of the skin like sides of the neck, groin, or underarm.
- Bone or joint pain due to a build-up of leukemia cells near the surface of the bone or even inside the joint
- Fever and increased rates of infection
- In rarer cases, the malignant cells may spread to the brain and spinal cord manifesting in symptoms such as headaches, seizures, vomiting, trouble with balance, facial numbness, or blurred vision.

Other general signs of leukemia are:

- Weakness
- Pale look to the skin
• Loss of appetite

With AML, it is more likely to infiltrate soft tissues such as gums causing swelling, pain, and bleeding (Bunn & Aster, 2011). Leukemia is a blood cancer, which is extremely lethal since our blood goes to all corners of our body, resulting in it being difficult to get rid of. So early detection is crucial to get a diagnosis and begin treatment.

**Diagnostic tests**

One of the first ways to help diagnose leukemia is through a basic physical exam and health history which helps doctors to look for general signs of health such as abnormal lumps or enlarged painless lymph nodes that could be indicative of leukemia. It also helps to get an idea of the patient’s health habits and past illnesses that may connect to why a patient may have issues with their health in general. Another step further is getting a complete blood count (CBC) done to check the number of red blood cells (RBCs), platelets, white blood cells (WBCs), amount of hemoglobin attached to the red blood cells (RBCs), and hematocrit levels (ratio of red blood cells to the total blood volume). According to the Mayo Clinic, a normal complete blood count would consist of:

- **Red Blood Cells (RBCs):**
  - Women: 4.32-5.72 trillion cells/L
  - Men: 3.90-5.03 trillion cells/L

- **Hemoglobin**
  - Women: 120-155 grams/L
  - Men: 135-175 grams/L

- **Hematocrit**
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- Women: 34.9%-44.5%
- Men: 38.8%-50%
  - White Blood Cells (WBCs): 3.5-10.5 billion cells/L
  - Platelets: 150-450 billion/L

If any of these CBC values are abnormally high or low, further testing would be ordered by the physician. Another screening test done is a blood chemistry study, where the blood is checked for levels of certain substances released into the blood by organs & tissues when thrown out of their homeostasis. Usually a higher or lower than normal level of that substance can be a good indicator of a malfunctioning organ indicator which could then indicate there is something larger going on in the body. For example, if the kidneys are not able to remove urea from the blood, blood urea nitrogen (BUN) levels would go up (NIH: National Cancer Institute, 2016b).

Another diagnostic test done is a bone marrow aspiration and biopsy where a hollow needle is inserted into either the pelvic bone or sternum obtaining a sample of the bone marrow which is sent to the pathologist where they examine under the microscope. The pathologist then can make a diagnosis of what type of leukemia the patient may have based on the abnormalities that they see in the bone marrow. Next, a cytogenic analysis is done on the bone marrow sample looking for certain changes in the chromosomes of the lymphocytes such as Philadelphia chromosome. This helps the pathologist look for parts of the chromosome that may have translocated to another chromosome (NIH: National Cancer Institute, 2016a).

Immuno-phenotyping is another lab test done to determine surface antigens in the blood are checked to see if they are lymphocytes or myeloid cells and if they are
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malignant or not. With immune-phenotyping a good distinction of what kinds of cells are actually malignant and their origin can be determined. In the case that physicians suspect that the leukemia has spread to the brain or spinal cord (patient is exhibiting neurological symptoms that were previously mentioned), a lumbar puncture can be done. If the sample of cerebrospinal fluid (CSF) comes back positive for leukemia, then intrathecal chemotherapy is infused directly into the cerebrospinal fluid (CSF) given through the lumbar puncture (NIH: National Cancer Institute, 2016c).

Most leukemia's do not normally manifest as solid masses compared to other types of cancer. A chest X-ray is done as a precaution to make sure there are no masses; if there are masses then they can be shrunk by chemotherapy then excised or completely removed surgically (NIH: National Cancer Institute. 2016). Screening for leukemia in children is difficult because sometimes the cancer is dormant until it metastasizes when symptoms can be detected. A high proportion of CLL patients are diagnosed while completely asymptomatic where the leukemia is discovered due to the presence of lymphocytosis. Sometimes a biopsy of a lymph node can also be taken and typically those lymph nodes are expanded by leukemia cells that are mitotically active and characteristic of chronic lymphocytic leukemia. The microenvironment that the lymph nodes provide help sustain the growth and survival of the malignant cells (Bunn & Aster, 2011).

Treatment options

Thanks to medical innovation, there are a few more options to treat leukemia. Even though leukemia doe not normally manifest as a tumor, surgical resections of
leukemia are not normally the best course of treatment. Treatment is withheld until patients become symptomatic, but there are some exceptions where an asymptomatic patient can start treatment such as CLL (Bunn & Aster, 2011). The usual treatment options for leukemia patients are chemotherapy and radiation therapy but deciding how much of a certain chemotherapy drug regiment to be given and for how long varies with each individual case. With ALL, the typical course of treatment spans over 2 ½ to 3 years with a survival rate at 80% (Bunn & Aster, 2011). With AML, the treatment is more aggressive and treatment lasts over a full year. When children are diagnosed with AML, a bone marrow transplant is an option if the child has a sibling that is a match, or they can receive aggressive chemotherapy but this can lead to more serious side effects that would lead to the child to be hospitalized for an extended period of time. In children between the ages of 1 to 9, the rate of survival for AML is 50% and 30% of adults achieve long term survival (Bunn & Aster, 2011). With CML, it can be treated with oral chemotherapeutic agents, however the only true cure, a bone marrow transplant (which can be quite difficult to obtain if the patient is hard to match) and the survival rate for children who have the transplant is on the lower end (Elliot et al, 2006). CLL is not currently curable but can be controlled over a span of years with gentler forms of chemotherapy drugs or with the anti-B monoclonal antibody, rituximab, which is a monoclonal antibody against the CD20 protein found on B cells and it destroys these dysfunctional B cells (Bunn & Aster, 2011).

According to Gullatte (2007), chemotherapy drugs, can be used in combination regimens or as single agents. The use of combination regiments has been proven to be the most effective. Some drugs used as both single agents and combination regiments are:
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- Prednisone
- Methotrexate
- L-asparaginase
- Cytanabine

These agents are used in varying phases of each type of leukemia and the dosages for each drug as tailored to each patient based on how severe their case is (Gullatte, 2007). In the recent years, targeted therapy has been developed and this form of therapy uses drugs and other substances to identify and attack specific cancer cells without harming normal healthy cells. One type of targeted therapy is tyrosinase kinase inhibitors (TKIs) which are targeted therapy drugs that block the enzyme, tyrosine kinase helps to prevent stem cells from producing more white blood cells. Another form of targeted therapy is imatinib mesylate, which is another type of TKI used in the treatment of children who have Philadelphia chromosome (Gullatte, 2007). A slightly newer form of leukemia therapy is chimeric antigen receptor (CAR) – T cell therapy, a type of immunotherapy that has the ability to change the patient’s T cells so they attack certain proteins on the surface of cancer cells. The T cells are harvested from the patient and are modified so that special receptors are added to the surface. The CAR-T cells are grown in the lab- and given to the patient through an infusion. The CAR- T cells then multiply in the patient’s blood and attack the malignant cells (NIH: National Cancer Institute, 2016c).

Delivery methods of treatment and the effects of treatment on children
Leukemia is known as a childhood cancer, but managing the care of a child while they are receiving treatment can make a big difference in how quickly they go into remission. When delivering chemotherapy and radiation therapy, dosages need to be carefully monitored and double checked in children since they are smaller and there is greater margin of error. Depending on the age of the child, their kidney and liver function may be immature, so metabolism and excretion of these drugs may be different from adult patients (Elliot et al, 2006).

When administering chemotherapy medications to children, the margin of error for doses that a small mistake in the dosage delivered could be potentially devastating (Elliot et al, 2006). The method of delivery varies and one method that can be used are internal devices such as subcutaneously implanted vascular access devices or a tunneled external multi lumen intravenous catheter that are commonly used for children that are receiving their chemotherapy drugs frequently. Using central access devices has become the standard of care with Pediatric Oncology so a child does not have to deal with frequent needle sticks and has a less traumatic experience with treatment and a decreased risk of any chemotherapy drugs leaking into the surrounding tissue causing extravasation (Elliot et al, 2006). In response to the chemotherapy drugs, children and preadolescents do not typically experience frequent nausea and vomiting compared to older individuals that are undergoing chemotherapy. This shows how unaware a child can be of what is going on and lucky for them, ignorance is bliss. However, when children do experience nausea and vomiting it is important to keep them hydrated and next time give them an antiemetic drug so their chances of experiencing nausea and vomiting are lower. Younger children who have more adipose reserves may have a better experience in longer sessions of
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Chemotherapy and may not experience as many severe symptoms (Elliot et al, 2006). Normally, chemotherapy patients may become malnourished but not all treatments cause protein-energy malnutrition because approximately 50% of survivors of acute lymphocytic leukemia become obese young adults. A patient’s state of nourishment may vary from case-to-case depending on how well the patient responds to the chemotherapy, but due to the fact that chemotherapy is essentially toxic ensuring the patient is eating nutrient dense foods is vital (Elliot et al, 2006).

Phases of chemotherapy treatment

Strategies for treating leukemia are divided into phases. With acute leukemia’s, there are two to three phases; the first phase called induction therapy consists of dose-intensified chemotherapy. The second phase called post-remission therapy can include a bone marrow transplant with or without total body irradiation and additional high dose chemotherapy and this may cause a relapse. The third phase is the maintenance phase where the goal is to kill any remaining leukemia cells that may potentially regrow; the treatments are usually given in lower doses. Not taking medications as ordered by the Oncologist during the maintenance therapy can increase the chance of the leukemia coming back as more aggressive (Elliot et al, 2006).

Conclusion

In conclusion, Leukemia is a difficult and deadly disease which is difficult to detect it early since the symptoms can be vague. Treatment is extremely important and difficult. There is a lot of hope that more treatments will be further developed and approved and the survival rates will go up in the next few decades. The best thing many
health care professionals can do to help their patient get through Leukemia is educate them, support them, and most importantly listen to them.
Many of us have seen commercials on television about individuals who have had oral cancer, and either need assistance from a machine to speak or cannot speak at all anymore due to having surgery where parts of their mouth or jaw were resected. In these commercials, they plead with the watchers to not smoke, or quit smoking; and if they had someone to tell them what could happen if they continued to smoke that they never would have picked up that cigarette in the first place. This just goes to show how detrimental oral cancer can get, if it is treated too late, or even worse, a quick and painful death. In this research paper, I will identify what oral cancer is, overall pathophysiology/pathology of oral cancer, risk factors, signs and symptoms that manifest how HPV can affect someone’s likelihood of developing oral cancer, how it is staged, how it is diagnosed, treatment methods, and some prevention methods.

What is oral cancer?

Medicine has managed to decipher how to prevent some cancers like smoking-associated lung cancer and keeping teenagers from chewing tobacco that causes oral cancer (Berman, 2009). Oral cancer is known to be a malignant neoplasia which is an abnormal growth of the tissue which arises from the lip, or in the oral cavity (Rivera, 2015) and about half of all oral tumors involve the tongue, especially the posterior portion and lateral borders (McCann, 2010). Oral cancer is the most frequent type of cancer of the head and neck area with oral squamous cell carcinoma actually being the most common form of oral cancer. Oral cancer arises in certain areas where it is found more frequently such as the tongue and floor of the mouth (Noguti et al, 2012). Oral
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cancer is a highly relevant problem of global public health. Oral cancer is within the top
10 ranking incidence of cancers and despite the progress in research and therapy
developed; it has clearly shown oral cancer to still a major challenge for the medical
community. Oral cancer is two to three times more prevalent in men, than in women in
most ethnic groups. The incidence of oral squamous cell carcinoma (form of oral cancer)
is actually increasing among young white individuals from the ages of 18 to 44 years old,
and particularly in white women of these age ranges. According to Rivera (2015), the
average age an individual diagnosed with oral cancer is people over the age of 50 years
old. In some regions, the prevalence of oral cancer is higher where about 10% of oral
cancer worldwide is in Pakistan and 45% of cases are diagnosed in India (Markopoulos,
2012). According to the Global Burden of Cancer Study in 2012, less developed nations
had a much higher incidence number (199,550) and a higher mortality number (112,040)
compared to those regions that are more developed. The same year, the World Health
Organization (WHO) did a study, and found that the Western Pacific region, South- East
Asia region, and Europe had the highest incidence rates of oral cancer. Collectively
across the world, oral cancer is the sixth most common cancer (Rivera, 2015).

Pathophysiology/molecularity of how it occurs and metastasizes

Like many other cancers, oral squamous cell carcinoma develops over many years
(depending on what you are exposed to) and during this period there are several
neoplastic sites transforming and taking place in the oral cavity. Oral carcinogenesis is a
highly complex multifactorial process that occurs when epithelial cells are affected by
various genetic disorders which is why it can increase an individual's risk of developing
oral cancer if they also smoke or chronically drink alcohol. Oral carcinogenesis can be
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expressed through cytogenic changes and epigenetic processes that modify the expression of the normal cell cycle, DNA repair mechanisms, cell differentiation, and apoptosis, which can be caused by random mutation by exposure to a variety of biological factors, carcinogens or errors in the DNA repair process. This results in an unstable keratinocyte leading to malignant neoplastic changes where these alterations to the keratinocytes are passed onto its clones (Rivera, 2015). When oral squamous cell carcinoma grows it eventually invades surrounding tissues and in order to survive, they need nutrients from blood vessels and the carcinoma exhibits angiogenesis where new blood vessel formation occurs and this helps “feed” the carcinoma so it can metastasize further (Markopoulos, 2012).

Risk factors

Oral cancer has been shown that it is mainly a type of cancer that can be prevented by not being exposed to certain environmental factors such as alcohol, tobacco (chewing it or smoking it), chewing areca nuts or betel quid, a poor diet, or having the human papillomavirus (HPV). It has been estimated, that about 75% of all oral cancers are actually preventable and the remaining 25% of oral cancer cases who are not exposed to these substances are actually unknown. In India, the higher incidence rates of carcinomas of the head- neck region is in relation to the use of tobacco in different forms, consumption of alcohol, low socioeconomic status conditions related to poor hygiene, poor diet, and even rampant viral infections such as HPV (Mehrotra & Yadav, 2006).
In general, tobacco has been linked to other various forms of cancer whether it be direct like lung cancer or indirect like stomach cancer. With oral cancer, tobacco has been considered one of the major causes of oral cancer next to alcohol when used chronically. Individuals, who smoke, are two-to-six times more likely to develop mouth, pharynx, larynx cancer as well as others. The carcinogenic effects of tobacco arise because of specific chemicals in nicotine that can cause mutations that disable critical genes.

Tobacco smoke can also act as a tumor promoter by causing chronic inflammation (Hesketh, 2013). There has been quite a bit of research that establishes that smoke is carcinogenic and that it can greatly contribute to cancer of the oral cavity as well as the pancreas. Oral cancer is one of the many reasons why health care professionals ask their patients to quit smoking or chewing tobacco, as well as many other detrimental health complications. By deciding to stop smoking and succeeding, it can lower an individual’s risk of developing oral cancer by 35% compared to others who have smoked for 20 years. However, environments with cigarette smoke are still dangerous to those people who have never smoked because it increases their risk for oral cancer by over 87%. The reason why oral hygiene is stressed in patients who smoke or chew tobacco is because smoking or chewing tobacco can promote gingivitis, periodontitis, and oral cancer. In general smokers and chewers need to more aware of the damage that is being caused. The cigarette smoke contains elements that promote cancer such as Nitrosamines, benzopyrenes, and aromatic amines. these chemicals are considered pre-carcinogens because they are the catalase in causing alterations by oxidative enzymes so that the electrons will covalently bond to the DNA, causing a mutated region of the DNA.
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Tobacco can also produce carcinogens like free radicals (many of us have heard of) which are unpaired electrons that are very reactive and capable of promoting mutations by also binding with DNA and bringing about mutations (Rivera. 2015). Tobacco chewing and smoking does a fair amount of damage that we see, but also a great deal of damage at the molecular level.

**Alcohol**

Alcohol is another huge environmental factor that has a big effect on an individual’s likelihood of developing oral cancer as well as many other forms of cancer and other major health issues. Alcohol consumption around the world has been estimated to cause 4% of all cancers and there has been evidence that it is linked to many major cancers such as breast, oral, esophagus, pharynx, larynx, stomach, bowel, lung, liver, ovary, and prostate cancer. However, the mechanism as to how alcohol causes cancer isn’t completely clear since cancer is a multifactorial disease, however it is known that alcohol does contain acetaldehyde which is known to be a mutagenic as well as a local anesthetic (Hesketh, 2013). Alcohol can act as both a locally and systemic risk factor by increasing permeability of the oral mucosa, where the lipid components of the epithelium get dissolved, causing atrophy of the epithelium and interference of DNA synthesis and repair. Alcohol is also genotoxic and has mutagenic effects, causes decreased salivary production and it impairs the liver’s ability to handle toxic, or potentially carcinogenic compounds. When an individual is chronically using alcohol, it is associated with an impairment of innate and acquired immunity which increases susceptibility to infections and neoplasms (Rivera. 2015). There has been a link demonstrated between bacterial overgrowth (and consequently higher levels of acetaldehyde produced) and poor oral
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hygiene among alcoholic heavy consumers, explaining why there appears to be an increased incidence of oral cancer among alcoholic patients with poor oral hygiene. There has also been an association between poor oral hygiene and increase number of missing teeth with oral cancer (Reidy, McHugh, and Stassen 2011). Alcohol can act both independently as well as synergistically with smoking and is implicated in oral carcinogenesis (Mehrotra and Yadav 2006).

Chewing of Areca Nuts and Betel Quid

In the United States, chewing tobacco has been a practice that many of us have heard of, but in other countries like India, Pakistan, and other South-East Asian countries, they chew on areca nuts and betel quid (bq). According to the CDC (2016), betel quid is used for its stimulant and relaxation effects and based on the region, it has spices or sweeteners that are added to it like catechu, cardamom, saffron, cloves, turmeric, and mustard and customarily a pinch of it is places in the mouth between the gum and check and gently sucked on and chewed. The use of betel quid, containing both areca nut and tobacco is associated with a much higher relative risk of oral cancer, between 8-15 times associated with using the quid, without tobacco. BQ chewing produces reactive oxygen species (ROS) that is detrimental to oral mucosa and can be directly involved in tumor initiation process by inducing mutations or by making the mucosa more susceptible to the betel quid ingredient and other environmental toxins. When production and the release of reactive oxygen species occur it happens under alkaline conditions while the individual is chewing on the BQ. The reactive oxidation species can be directly involved in the tumor initiation process by inducing genotoxicity and gene mutation or by attacking the salivary proteins and oral mucosa, leading to structural changes in the oral mucosa that may
facilitate the penetration by other BQ ingredients and environmental toxicants (Mehrotra & Yadav 2006).

Poor Nutrition

With cancer in general, there has always been a relationship between diet and cancer and has been a main focus for many nutritional epidemiologists in the past 40-50 years and has proven to be quite enlightening. Cancer is known to be a disease where on a cellular and molecular level, the cells are growing and dividing abnormally to the point where it can cause tumors. The most obvious way in which diet can increase the risk of cancer is directly delivering carcinogenic chemicals to the body, in the case of smokers and alcohol abusers, an individual will experience impaired nutrition intake and poor dietary habits. There have been some estimates suggesting up to 70% of all cancer deaths may be attributable to diet related factors (Elliot et al, 2006). When individuals who are alcohol and tobacco abusers it already weakens their overall health so if they do become diagnosed with oral cancer, it will become more difficult for them to receive proper nutrition since the oral cancer may impair their ability to chew and swallow so they may have to be placed on enteral nutrition. Being malnourished also decreases the likelihood that an oral cancer patient will have a good prognosis since their body will not be strong enough to handle radiotherapy, chemotherapy, or even surgery. The importance of diet and nutrition with oral cancer has been indicated that fruits and vegetables that are high in vitamins A and C are described as protective against the development of oral cancer, whereas meats and red chili powder are thought to be risk factors since they are considered irritants. Fruits and vegetables that protect against oral cancer and precancerous states are rich in beta-carotene; vitamin C and vitamin E have anti-oxidant
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properties. Having an iron deficiency can result in oral epithelial atrophy, which is associated with cancer of upper air and food passages and dietary iron may also play a protective role in maintaining the thickness of the oral epithelium (Mehrotra & Yadav 2006).

**Signs & symptoms**

Some common signs that may be indicative of malignant oral squamous cell carcinomas are erythroplasia and leukoplakia. Leukoplakia is a thickened, white patches inside the mouth that form on the gums, cheeks, bottom of the mouth and on the tongue and these patches can't actually be scraped off. It has not been successfully linked to tobacco however tobacco is considered a big culprit whether someone has indeed smoked, chewed, or dipped it. It is not considered dangerous and normally are benign but some have been signs of early cancer where about 1% may progress to malignancy. Erythroplasia is a mixture of red and white lesions, and they commonly show presence of dysplasia and shown to be cancerous. It is always treated due to its high-risk of malignancy. Both erythroplasia and leukoplakia most frequently occur on the tongue and floor of the mouth and the lower lip (Rivera, 2015). A major danger of oral squamous cell carcinoma is in the early stages, these can go completely unnoticed, and in these stages it is quite painless but could eventually develop a burning sensation or pain when it becomes more advanced. Oral squamous cell carcinoma sometimes presents as an ulcer with fissuring or raised margins or it can present as a non-healing extraction socket or as a cervical lymph node enlargement that’s characterized to be hard and fixed (Markopoulos, 2012). In the case that any of these symptoms manifest, oral squamous
cell carcinoma should be considered if these symptoms last for more than two weeks. Some other signs and symptoms that may indicate oral cancer are:

- Change in voice
- Swelling in jaw
- Sore throat or feeling something is caught in the throat
- Bleeding, pain, numbness in the lip or mouth
- Loose teeth or dentures that no longer fit properly

**How are the Human Papillomavirus and Oral Cancer related?**

The Human Papillomavirus is closely associated with both benign and malignant oral lesions and has been detected in condylomas, focal epithelial hyperplasia, and squamous cell papilloma. HPV positivity is higher in tumors from the oral cavity at 59%, the pharynx with 43%, and larynx at 33% and among those only a small fraction of HPV-infected lesions proceed to a malignant transformation especially those with the HPV subtype of 16 and 18 (Yadav, 2006). The most common types of HPV is HPV 16. It is believed that the viral protein E6 binds to p53 causing its breakdown while E7 reacts with the retinoblastoma protein (pRb) which is considered a tumor suppressor protein inhibiting its function so when these oncopressive molecules are deregulated its results in an irregular cell proliferation and apoptosis my lead to oral cancer. It is current belief that the oral mucosa being with HPV alone would not be enough to induce oral cancer and that there needs to be some exposure a carcinogen agent like benzopyrenes (Markopoulos, 2012).
Diagnosis and the Staging System

The major detriment of the prognosis of oral carcinoma is the risk of metastasis to the lymph nodes, and some important prognostic factors/indicators that affect regional metastasis are the size of the primary tumor, site, stage, depth of the invasion, biological tumor markers, and perineural invasion (how much of the nerve has the cancer surrounded), and patient compliance. The TNM classification of oral squamous cell carcinoma provides a reliable basis for patient prognosis and therapeutic planning. The TNM staging system is used worldwide:

- **T**: size of the primary tumor
- **N**: extent of the regional lymph node involvement
- **M**: Presence of distant metastases

Lymph nodes are assessed for location, number, size, shape, consistency, and fixation; and the nodes are considered malignant if their size is greater than 1 cm and they are hard and fixed. Typically T1-T2 lesions are often associated with a risk of regional metastasis of 10-30%, especially to lymph nodes, and some studies have shown a clear correlation between increasing tumor thickness and an increased risk of cervical metastasis. T3-T4 lesions have a significantly higher risk of regional neck cancer. Although the TMN staging system is used routinely, the technique accurately determines only the size and location of tumor and does not actually predict their metastatic potential so another test is used. The immunohistochemical expression of vascular endothelial growth factor (VEGF)-A and VEGF-C in oral squamous cell carcinoma has been analyzed and
suggested to be associated with the prognosis of patients. VEGF-A expression has significantly revealed to higher tumor stage and invasion grade, while VEGF-C expression was significantly associated with tumor stage, regional lymph node metastasis and invasion grade. Sentinel lymph node (SLN) status has shown to be an excellent predictor of metastatic disease for both melanoma and breast cancer and is now the standard-of-care for oral cancer. Sentinel lymph node utilizes lymphatic mapping to locate and harvest the small group of lymph nodes most likely to harbor metastases, minimizing the invasiveness of the procedure. The concept that goes along with this diagnostic test states that the tumor will spread from the primary site to a single node or group of nodes which are called sentinel nodes before progressing to the remainder of the lymph nodes. The ability for doctors to be able to identify metastases and unpredictable lymphatic drainage patterns is another advantage of having a sentinel lymph node biopsy done. Other methods for diagnosis are computed-tomography (CT) scans, magnetic resonance imaging (MRI) scans, positron emission tomography (PET), ultrasonography, and USG-guided fine-needle aspiration cytology are recommended to give the best neck evaluation in patients with oral carcinoma. Some of these have become routine in screening patients in the recent years and have played an important role in metastasis detection of cervical nodes. CT and MRI scans have specifically become standard methods that are done in most hospitals and can be interpreted by radiologists. Some other diagnostic tests that can be done are the barium swallow where there is a series of X-rays taken of both the esophagus and the stomach where the patient is instructed to swallow barium, which is a silver-white metallic liquid. Barium is used because it coats the esophagus and the x-rays are taken to see if there is any mass that doctors should be concerned about. Another
diagnostic test that can be done is a bone scan which is meant to look for rapidly dividing cells like cancer cells. This procedure is done by having radioactive material injected into a vein and the radioactive material collects in the bones and if there are rapidly dividing cells then it will be picked up on the scan (NIH: National Cancer Institute, 2016). In patients diagnosed with tumors at an advanced stage, there is a high occurrence of invasion to surrounding tissues with lymph node and distant metastasis, usually do not have a very good prognosis and are looking at a low five year survival chance (Noguti et al, 2012).

**Treatment Therapies**

Despite major advances in surgery and chemotherapy achieved in the last few decades, oral cancer is still characterized by poor prognosis and a low survival rate and the mortality rate has actually stayed at 50% (Markopoulos, 2012). Some of the major forms of treatment that are used for oral cancer are surgical resection, radiotherapy, and chemotherapy and each one is used based on what stage the patient is in and whether a combination of these therapies may be used. The whole purpose of being treated is to eliminate the tumor, to restore structure and function of the affected area, and to prevent any further metastasis of the cancer. Sometimes, if the cancer is found in its more advanced stages then the purpose of treatment is to improve the quality of the patient’s life until their death. The approach that is used in treatment will vary from one Oral Maxillofacial Surgeon to another and what therapy is used will depend on their age, their general medical condition, tolerance to treatment, and their lifestyle. Due to the fact that there are a few types of treatment therapies, having a combined therapy regiment such as a surgical resection and then radiotherapy and chemotherapy is mostly used for more
advanced stages whereas as single-modality therapy regiment is used for earlier stages of oral cancer. Currently, surgery-alone is used for early stage where there is no lymph node metastasis or any radiographic evidence of metastasis and neck dissections for detecting neck lymph nodes have become a routine to prevent metastasis. It is widely accepted that more advanced oral tumors can be treated with elective neck dissection as well as radiation and chemotherapy but the management of stage I oral cancer is more controversial. With stage I oral cancer, it’s often treated with a primary tumor resection with clinical follow-up to make sure there hasn’t been a spread of cancer (Noguti et al, 2012). Another common form of treatment is radiotherapy, it’s not commonly used for oral cancer as a single treatment method but it can be unless the tumor site is inoperable (in a risky spot of the oral cavity) or the patient decided to not have surgery, this can be used as a form of palliative treatment in patients who are more terminal. Radiation has some advantages over surgery such as, milder complications following treatment and improved quality of life while surgery of advanced tumors can lead to a possible chance of post-operative death as well as permanent loss of function of oral structures (salivary glands may not function anymore). It is used after surgery to shrink or eliminate any remnants of cancer cells, and the reason why radiotherapy is not used before surgery because it would lead to fibrosis of the tissues, which make the surgical removal of an oral cancer tumor much more difficult. Another form of treatment is chemotherapy, and chemotherapy is a systemic treatment, which is responsible for killing any malignant cells to control the volume of the tumor and to reduce the chances of further metastasis if any. Which is why it is an important form of treatment used for advanced oral squamous cell carcinoma. Over the past few decades, there has been expansion of chemotherapy
drugs used for treatment, such as the introduction of methotrexate, 5-fluorouracil, hydroxyurea, platinum derivatives, anthracyclines, plant alkaloids, and most recently toxoids. Another newer form of treatment is targeted therapies, which target the specific malignant cells and avoid harming healthy cells. Some other advances that have been made but are still in the clinical trial phases are biological therapies which use laboratory-made antibodies and cytokines that help eliminate cancer cells or boost immune function. Another form is virotherapy, where viruses are used as vectors to carry genes into malignant cells in order to disrupt their growth. Gene therapy is another more common form that uses genes to boost immune cell recognition and elimination of cancer cells, or the genes are inserted into cancer cells to increase cytokine production, thus attracting immune cells. One more new form of treatment are cancer vaccines, which stimulate immune function by artificially introducing antigens into the body as prevention for future disease (Noguti et al, 2012).

**Prevention Methods**

The key prevention for many cancers like oral cancer (specifically oral squamous cell carcinoma) is early detection; it is the best possible way to stop it in its tracks. Due to the fact that we know what causes a majority of oral cancers, we can use this knowledge to prevent at least a third of oral cancer occurrences. The best thing, individuals can do to detect oral cancer in its early stages, is to visually examine the oral cavity as well as using this as part of a screening program. Encouraging people to change their lifestyle habits such as smoking or chronic alcohol consumption and impose barriers to triggering factors so people don’t feel the need to use these habits are also important. Education to the general population about oral cancer and how it can be brought about and what can
happen once they have been diagnosed with it (Rivera, 2015). Another form of prevention many people around the world should get is the human papillomavirus vaccine, not just for oral cancer but HPV can also cause most cervical cancer so it is recommended that preteen girls and boys get the HPV vaccine in the three-dose series if they are 11 or 12 years of age. The HPV vaccine is not something that is available to everyone but if one has access to it, it should be utilized (Centers for Disease Control and Prevention, 2016).

Conclusion

In conclusion, oral cancer is a deadly disease when diagnosed in more advanced stages of metastasis and when detected much later can decrease an individual’s likelihood of surviving past five years. Oral cancer is a type of cancer that is easily preventable if the general population is made aware of the risk factors like alcohol and tobacco use. Even though medical science has come quite far in treating oral cancer, there is still much to be done in finding more effective treatment methods that increase an individual’s survival past five years.
Neuroblastomas: The Clinical Enigma of Pediatric Oncology

Neuroblastomas are considered highly malignant tumors and are the most common extracranial solid tumors of childhood (Schilling and McCann, 2011). Essentially, neuroblastomas are tumors that grow from neural crests (the precursor of the spinal cord) that eventually make up the sympathetic nervous system. The tumor can grow in the sympathetic ganglia, adrenal medulla, and many other sites. The average diagnosis age is 17-18 months since most neuroblastoma tumors are a disease of developing tissues (Losty & Mullassery, 2015). However, the behavior of the tumor varies from case-to-case based on the patient’s age, stage, histology, and biology. This tumor represents a group of tumors that account for 7% of all childhood malignancies and accounts for 15% of all deaths in the pediatric population (Tomlinson and Kline, 2010). About 30% of patients present symptoms in the first year of life, and 96% of patients present before the age of ten years old (Losty & Mullassery, 2015). Neuroblastomas affect boys at a higher rate than girls, as well as being more prevalent in Caucasian children compared to occurrence rates in black children (Tomlinson and Kline, 2010). This accounts for 9-12 million who are diagnosed with neuroblastoma tumors (Losty & Mullassery, 2015). The occurrence pattern of neuroblastoma tumors are sporadic, however there seems to be a small group of neuroblastoma cases in which 1-2% of them are familial (Tomlinson & Kline, 2010). The cases that are familial follow an autosomal dominant pattern of inheritance (Losty & Mullassery, 2015). One aspect that sets neuroblastomas apart from other types of cancer is the environment does not play nearly as significant of a role in its development and progression. There has been some correlation with intrauterine exposure to agents such as alcohol, medications, and
maternal use of hair coloring has been a hypothesis for researchers, but has not yet been proven. However, as more research is done on neuroblastomas this may change and we will hopefully be able to decipher if there is indeed a correlation between the occurrences of neuroblastomas and environmental factors.

The Significance of Genetics

Neuroblastomas are unique tumors for many reasons, but one of them is that its occurrence is mainly linked to a child’s genetic make-up. To date, no environmental influences or parental exposures seem to significantly impact the occurrence rates. Neuroblastomas usually appear sporadically, but about 1-2% of cases have a family history (Weinstein, Katzenstein, & Cohn, 2003). Molecular risk factors previously identified in primary neuroblastomas include the amplification of the MYCN oncogene, mutations of the ALK receptor, allelic deletions in the 1p,3p, 11q chromosomal regions and chromosomal gain of 17q. In 1983, the amplification of the MYCN oncogene was one of genes shown to be of prognostic value in pediatric oncology and it has remained a marker of high-risk patients (Modak & Cheung, 2010). The systemic search for genomic alterations using whole genome sequencing has shown that neuroblastomas have an extraordinarily low genetic complexity, with significant mutations in the ALK genes.

Activating anaplastic lymphoma kinase (ALK) mutations occurs in about 8% of all primary tumors and virtually all hereditary neuroblastomas (Schramm et al. 2015). The ALK gene helps provide the instructions for making the ALK receptor tyrosine kinase which is part of a family of proteins called receptor tyrosine kinase (rtk). The specific function of the ALK receptor tyrosine kinase is unknown; however, it is believed that it plays a role in the development and regulation of nerve cells (Genetics Home...
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Reference: Your Guide to Understanding Genetic Conditions, 2017) (b). The ALK gene playing a role in the proliferation of nerve cells explains why a neuroblastoma tumor would appear in the case that the ALK gene is mutated. The majority of primary neuroblastomas are triploid/near triploid (55%) which contains 55-80 chromosomes. The patients who have near-triploid tumors have a more favorable clinical and biological prognostic factors as well as excellent survival rates compared to patients with a near-diploid or near tetraploid tumors (Davidoff, 2012). In patients younger than 18 months with metastatic disease near diploid DNA content is usually predictive of a poor outcome (Losty & Mullassery, 2015).

Another genetic risk factor is the amplification of MYCN gene. The MYCN gene gives instruction on how to make a protein that plays a crucial role in the formation of tissues and organs during embryonic development. The MYCN gene belongs to a class of genes called oncogenes, so when they end up becoming mutated this has the potential for normal cells to become cancerous. When studies were done on the MYCN gene to understand its function better, it was shown that the gene is important in producing the protein crucial in the development of limbs, heart, kidneys, nervous system, digestive system, and lungs (Genetics Home Reference: Your Guide to Understanding Genetic Conditions, 2017) (a). Similar to the ALK gene, if there is a mutation in the MYCN gene it would make sense for an infant to be diagnosed with a neuroblastoma since both play an important role in the development of the nervous system and nerve cells.

Another genetic risk factor is allelic deletions and insertions in certain regions of chromosomes. Specific areas of deletion result in different outcomes; these deletions vary in size so there could be a larger region of the chromosome that can potentially be
affected. In regards to the evolution of neuroblastoma tumors, loss of genetic material is a frequent occurrence. It is believed that regions of the chromosome that experience a loss of heterozygosity (LOH) may harbor tumor suppressor genes (similar to p53 or pRb). Loss of heterozygosity (LOH) on the long arm of chromosome 11 is seen in 35-45% of neuroblastoma tumors and this is considered another negative prognostic marker (this is one region that is thought to have a tumor suppressor gene) (Tomlinson & Kline, 2010). Both gains and losses of genetic material are commonly detected in neuroblastomas cell lines and primary tumors (Weinstein, Katzenstein, & Cohn, 2003). Unbalanced deletion of 11q is inversely related to MYCN amplification, yet is strongly associated with other high risk features (Davidoff, 2012). Deletion of the long arm chromosome 11 (11q) also appears to be common in neuroblastoma being present in about 40% of neuroblastoma cases (Davidoff, 2012). Aggressive tumor behaviors with poorer outcomes are associated with deletions at the specific chromosomal region of 1p36.3 or 11q23, and with unbalanced gain of the long arm of chromosome 17 (Losty & Mullassery, 2015). Then with patients who have deletions of 1p generally also have an MYCN amplification end up having a poor survival outcome. A deletion of the 1p chromosome is considered an independent prognostic factor for children who are generally on the younger end of the spectrum and where deletions on the shortest arm of chromosome 1(1p36) are seen frequently in advanced cases of neuroblastomas (Tomlinson & Kline, 2010). In terms of genetic loss of 1p, there is a strong correlation between those high risk neuroblastoma patients with an older age of diagnosis, metastatic disease, MYCN amplification, and a patient with an unfavorable outcome (Davidoff, 2012). When early karyotype analyses have been done on neuroblastoma-derived cell lines, the analyses showed there to be
frequent deletions on the short arm 1p chromosome. There has not been a particular gene that has been identified on chromosome 1p that is a tumor suppressor gene, one gene called CHD5 has been the strongest candidate as a tumor suppressor gene that has been deleted from 1p36.31 in some neuroblastomas that have been analyzed (Davidoff, 2012). Through studies that have been done on the genetics of neuroblastoma cells, it is bringing scientists and doctors closer to figuring out how best to cure a young patient with a neuroblastomas tumor.

**Clinical Manifestations of Neuroblastomas**

It is no secret among health care professionals that neuroblastoma tumors are well noted for their broad spectrum on clinical behavior as well as being life threatening in their rapid progression (Mullassery et al. 2014). Neuroblastoma tumors have often been described as being enigmatic, meaning they are difficult to interpret and can be quite mysterious and unpredictable because of the way its associate with contrasting patterns of clinical behavior that have the ability to be life-threatening in their progression to ganglioneuroblastomas or ganglioneuroma to a pretty spontaneous regression (Mullassery et al. 2014). Regardless of the fact that there have been certain subsets of patient who have had improved treatment outcomes over the last few decades, there have been children with high-risk neuroblastoma tumors that continue to have a poor long-term survival where the outcome is less than a 40% long-term survival (Losty & Mullassery, 2015). The behavior of a neuroblastoma tumor is dependent upon the site of the primary tumor, as well as the extent of metastasis, and the presence of paraneoplastic syndromes (rare disorders that alter a patient’s immune system). There are nonspecific symptoms that a patient may experience such as pain and malaise, which can be present in the early
stage of the disease process (Losty & Mull sassery, 2015). In some cases where the tumor is localized to one area of the body, the patient may be asymptomatic (in a majority of cases they are), and those patients who are symptomatic will present with clear systemic symptoms like bone pain and fever; they also have more specific symptoms that are specific to neuroblastoma tumors (Weinstein, Katzenstein, & Cohn, 2003). Some of those specific symptoms are:

- Abdominal Pain and distention, nausea, vomiting, distention. The etiology is due to a possible abdominal tumor.
- "Blueberry muffin" skin lesions. The etiology is due to the tumor involving the skin and this symptom is normally exhibited in infants.
- Anorexia and weight loss. The etiology behind this is there could be a midline tumor.
- Horner's Syndrome, which encompasses ipsilateral ptosis, miosis, and anhidrosis. The etiology behind this is the presence of high thoracic and cervical tumors, which leads to a compromise of the descending sympathetic nerve tracks.
- Respiratory distress. The etiology is extensive liver involvement that occurs in infants with stage IV disease or pleural effusions that cause respiratory distress.
- Proptosis, periorbital ecchymosis, which are essentially "raccoon eyes". The etiology is there could be involvement of a periorbital tumor.
- Anemia, thrombocytopenia, and frequent infections. The etiology is due to a disruption in the bone marrow.
- Hypertension. The etiology may be related to a renal vascular compression.
• Limp or leg pain. The etiology behind this condition is metastatic bone disease.
• Decreased motion in the legs, muscle weakness, bowel or bladder disturbances.
  The etiology causing this symptom is a possible spinal or paraspinal disease.
• Weakness or paraplegia. The etiology causing this is a compression of the spinal
cord caused by dumbbell tumors.
• Watery diarrhea and failure to thrive. The etiology is vasoactive intestinal
  peptide (VIP) secretion (paraneoplastic syndrome).
• Ataxia, rapid eye movements, and irregular muscle movements. The etiology
  behind this condition is opsoclonus-myoclonus ataxia (OMA) syndrome which
  is considered a paraneoplastic syndrome.

There are two types of paraneoplastic syndromes that a child with neuroblastoma tumors
may present with, Opsoclonus-myoclonus Ataxia (OMA) and Secretion of Vasoactive
Intestinal Peptide (VIP), which watery diarrhea (Tomlinson & Kline, 2010). OMA
syndrome consists of random eye movements, myoclonic jerking movements, and
cerebellar ataxia. OMA occurs in about 2-4% of neuroblastoma patients. There is
speculation that this came about due to the production of anti-neural antibodies that end
up cross-reacting with the neural cells in the cerebellum or other regions of the brain.
What is nice about OMA syndrome is that patients who present with this syndrome end
up having a lower-stage development. The downside to this syndrome is that a majority
(70-80%) of children end up suffering some form of long-term neurological &
developmental deficits (Tomlinson & Kline, 2010). Secretion of Vasoactive Intestinal
Peptide (VIP) causes intractable diarrhea which is actually a rare presentation that is
brought about when the tumor secretes VIP; the symptoms normally disappear with or
even after the tumor is surgically resected. The prognosis of a child with VIP-associated neuroblastoma tumors have a more favorable prognosis since it can be fixed through surgical resection (Tomlinson & Kline, 2010). This is what makes neuroblastoma tumors so deadly; they can end up in any region of the body due to its origin of growth. Thoracic tumors may present as an "incidentaloma" on a chest radiography or with symptoms related to spinal cord compression with an intraspinal extension. In other cases, a patient may have an abdominal neuroblastoma where it causes organ compression that could cause constipation or urinary retention (Losty & Mullassery, 2015). Tumors have the ability to infiltrate local structures and eventually surround important nerves, or vital vessels such as the coeliac artery axis; they will also metastasize to regional lymph nodes and if it goes far enough it will go into the bone marrow (Losty and Mullassery, 2015). This is what makes neuroblastoma tumors such a clinical enigma, they could end up anywhere and it depends on the individual patient and their circumstances. The cases may be similar but not exactly the same. To identify how far the tumor has metastasized, it is staged for both clinicians and surgeons.

**How are Neuroblastomas Staged?**

Neuroblastomas, similar to any other type of cancer have a staging system based on certain criteria. The International Neuroblastoma Staging System was first described in 1988 and was eventually revised in 1993. The International Neuroblastoma Staging System (INSS) is a surgicopathologic staging system that is dependent upon the completeness of resection of the primary tumor, an assessment of the ipsilateral and contralateral lymph nodes, and the relation of the primary tumor to the midline (Davidoff, 2012). The International Neuroblastoma Staging System is meant for low-grade tumors;
In the case that there is extensive involvement of the liver, skin, and possibly bone marrow means the neuroblastoma is a stage IV. The risk is classified based on clinical features like stage, age, and biological factors to determine risk stratification (low, intermediate, or high). The expertise and aggressiveness of the surgeon is a big influence on how treatment progresses, as well as the tumor stage, lymph node sampling (done randomly) (Davidoff, 2012). Staging of a neuroblastoma tumor is based on such:

- **Stage I**: Localized tumor with gross total resection, with or without microscopic residual disease.
- **Stage IIA**: Localized tumor with incomplete gross total resection, lymph nodes are negative.
- **Stage IIB**: Localized tumor, with or without gross total resection, with ipsilateral positive nodes.
- **Stage III**: Unresectable unilateral tumor, which crosses the midline, or unilateral tumor with contralateral regional lymph node involvement.
- **Stage IV**: Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, and other organ sites.
- **Stage IVS**: Localized primary tumor (included I, IIA, IIB), with dissemination limited to skin, liver, and/or bone marrow. The child is less than 12 months (Tomlinson & Kline, 2010).

Based off the staging criteria, it helps determine the risk classification of low-risk, intermediate risk, or high-risk. For low-risk patients, this means that surgical resection and observation is all that is needed to be done. This group of patients usually includes those who are stage I, II, and sometimes IVS in case they have no MYCN amplification.
Neuroblastomas do have the ability to spontaneously regress or differentiate and sometimes these patients may receive radiation or chemotherapy. These patients often present with OMA tumors who have favorable outcomes but still require treatment for the OMA symptoms. Treatment usually entails intravenous gamma globulin, steroids, adrenocorticotropic hormone, and chemotherapy (Tomlinson and Kline, 2010). These patients also normally have a favorable histology result where there is no MYCN amplification (Davidoff, 2012).

Patients who have an intermediate-risk are staged at IIA and IIB where there is no MYCN amplification and the tumor has been resected less than 50% (Davidoff, 2012). The age range for these patients ranges from 0-12 years of age. These patients normally undergo both surgery and neoadjunct chemotherapy. What is special about this group is the patient can be staged at II, III, IV, and IVS; it just depends on that individual patient’s biology. Patients normally receive moderate intensity carboplatin, etoposide, cyclophosphamide, and doxorubicin. In recent years, there has been a trend to decrease the amount of chemotherapy given to patients, and the purpose of this was to tailor the amount of therapy based on the biology and how the tumor responded (Tomlinson & Kline, 2010). In the case that the primary tumor is assessed by the surgeon and declares it is unresectable, a diagnostic biopsy is taken and then chemotherapy is initiated (Davidoff, 2012). Surgery can be done after numerous cycles of chemotherapy, in the case that a patient is symptomatic they are given radiation therapy. However, with radiation therapy, there is a high risk of organ damage (Davidoff, 2012).

Lastly, there is high-risk where the patients are classified as stage IV and normally with poor biological features (Tomlinson & Kline, 2010). Normally, the patient
will have MYCN amplified tumors. With these patients, it is controversial on whether surgical resection is the best option; in cases that surgery is one it is meant to improve local tumor control and increased overall survival. Surgical patients also receive a stem cell transplant along with high-dose chemotherapy, and total body irradiation may be beneficial as well (Davidoff, 2012).

**Diagnostics of a Neuroblastoma**

The diagnosis of a neuroblastoma makes the world of a difference for a patient and their family. Normally, diagnosing a patient requires diagnostic imaging, laboratory, and pathology. The information obtained from the imaging and biopsy results helps physicians determine the risk stratification based on both the clinical stage and biological factors (Tomlinson & Kline, 2010). Obtaining an adequate tissue sample, it is done through an open surgical biopsy but it can be done through a minimally invasive image-guided procedure; it normally depends on the surgeon’s preference. Multiple bone marrow biopsies and aspirates are also taken to determine the stage of metastasis (Losty & Mullassery, 2015). In terms of imaging, CT scans are the most common image taken to evaluate tumors of the mediastinum, abdomen, and pelvis; the risk classification is also determined through CT scans. Another diagnostic tool used is an MRI, which can be considered superior in investigating how extensive paraspinal and intraspinal tumors may present as. Bone scans are also important, and used to determine the presence of skeletal metastases. Metaiodobenzylguanidine (MIDBG) scans are another special diagnostic tool done where a tracer is used that concentrates granules of neuroblastoma cells and is helpful in identifying metastases. MIDBG imaging has been positive in over 90% of neuroblastoma tumors. Another scan used is PET-CT scans which are used to track a
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patient’s response to treatment, especially in cases where MIDBG scans couldn’t be used (Tomlinson & Kline, 2010).

Another diagnostic tool/test that can be done is a Catecholamine test using the patient’s blood and urine, which are used in diagnosing catecholamine-secreting tumors like those found in the adrenal medulla. The urine test is used to assist in diagnosing neuroblastomas. Increased levels can be indicative of neuroblastomas (Leeuwen, Poelheuis-Leth, & Bladth, 2013). Another test that can be done is metanephrines, which are used to assist in diagnosed cancer of the adrenal medulla. Metanephrines are the inactive metabolites of both epinephrine and norepinephrine. Increased levels of metanephrines can be indicative of a neuroblastoma, ganglioneuroma, pheochromocytoma, or even severe stress. Lastly, neuroblastomas can be diagnosed through a urine test used for the diagnosis of pheochromocytoma, neuroblastoma, or ganglioblastoma. Vanillymandelic acid is another major metabolite of epinephrine and norepinephrine. Elevated levels are marked by an excess of catecholamine’s (Leeuwen, Poelhuis-Leth, & Bladth, 2013). Through these diagnostic tests and scans, they can help a physician diagnose a patient with a neuroblastoma and decide the appropriate treatment.

Treatments Used Today

When treatment for cancer is thought of, it is usually surgery, chemotherapy, radiation therapy, and in some cases like neuroblastoma treatments there are options like myeloablative chemotherapy with autologous stem cell stem transplants, differentiation therapy, and more recently immunotherapy. One form of treatment is surgery, it is used to resect the primary tumor which is important to decrease the number of tumor cells
present so they respond better to chemotherapy increases the degree of complete excision and it helps decrease surgical complication (Tomlinson & Kline, 2010). Most localized tumors with favorable biological characteristics respond well to a surgical tumor resection. When neuroblastomas reoccur locally, surgery can be used, but with rare metastatic reoccurrences chemotherapy and radiation therapy are implemented (Losty & Mullassery, 2015).

Another common method of treatment is the use of chemotherapy, and this can be used in conjunction with surgery, radiation therapy, or other methods of treatment. Chemotherapy regimens are intense with the goal of shrinking the primary tumor, which can help facilitate surgical resection and as a result control the metastasis of the tumor (Tomlinson & Kline, 2010). Most induction regimen use different combinations of anthracyclines, platinum based compounds, etoposide, microtubule inactivating agents, alkylating agents, cisplatin, carboplatin, doxorubicin, and ifosfamide. Cyclophosphamide and topotecan have been used successfully in relapses for a few years (Tomlinson & Kline, 2010). With low-risk patients, only surgical resection and observation are necessary unless there are organ-threatening symptoms at the time of diagnosis. Patients who have an intermediate risk will receive chemotherapy to halt tumor progression or shrink it in hopes that it gets small enough for surgeons to resect it. Patients that are high-risk, usually do receive carboplatin, etoposide, cyclophosphamide, doxorubicin, and vincristine. High-risk patients also receive myeloablative chemotherapy, which wipes out the tumor as well as the normal bone marrow, which is followed by bone marrow transplantation. Chemotherapy for high-risk patients is divided into three phases: induction of remission, consolidation of remission, and maintenance phase. The induction
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of remission is where chemotherapy is administered in hopes of killing all cancer cells. Then the consolidation of remission phase is meant to sustain remission. Lastly, is the maintenance phase is when the patient is given low doses of chemotherapy to prolong the remission (Losty & Mullassery, 2015).

One of the last conventional treatment methods is radiation therapy. Neuroblastomas are actually radiosensitive, so radiation therapy is used in cases where it is absolutely necessary, for example, in the case there might be organ damage. In cases where the primary tumor cannot be completely resected, and there are locally involved lymph nodes, radiation therapy is implemented. When radiation has been delivered to a primary tumor, regardless of the surgical resection has the ability to decrease the local relapse in high-risk tumors (Tomlinson & Kline, 2010). Radiation therapy is not normally advised for low-risk tumors and is reserved for patients with progressive clinical deterioration despite use of both surgery and chemotherapy. Radiation therapy is also contraindicated in patients who have intraspinal tumors because it can lead to gross vertebral damage and a possibility of causing severe scoliosis, but it can be used for patients who are experiencing symptomatic spinal cord compression (Losty & Mullassery, 2015).

Hope for the Future?

Since neuroblastomas are one of those few types of cancers that can become resistant to some that can become resistant to some forms of treatment, it’s so important to continue doing research in order to find other methods of treatment to avoid the issue
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of resistance. A few types of treatment that are being developed are immunotherapy, aurora A kinase inhibition, TRK inhibition, and immunotoxin therapy.

Immunotherapy is a great approach for a more effective and beneficial treatment to combat this tumor since it is a multi-drug resistant tumor. It's essentially targeted immunotherapy, which exploits the tumor selectively and has minimal cross-resistance as well as overlapping toxicities with chemotherapy (Losty & Mullassery, 2015). A suitable target for immunotherapy is Disialoganglioside (GD2) because the antigen is expressed at a high density in a majority of neuroblastoma tumors (Losty & Mullassery, 2015). This form of therapy is being implemented more and more but has not been used nearly as frequently as chemotherapy or surgical resections.

Another form of treatment is aurora A kinase inhibition. Aurora A kinase is a serine/threonine kinase that is expressed in all actively dividing cells and is a crucial part of the cell cycle progression. It also can be overexpressed in a few types of tumors such as neuroblastomas where most likely serves is as an oncogene. Since aurora A kinase plays an important role in mitosis, inhibiting aurora A kinase may be a broadly effective treatment for the types of cancers that overexpresses aurora A kinase. MLN 8237 is a selective and reversible molecule inhibitor for aurora A kinase that was effective against a panel of neuroblastoma xenografts that was above and beyond standard agents used (Davidoff, 2012). This form of treatment could be effective against not only neuroblastoma tumors but also other types of tumors.

The next type of treatment is called tyrosine kinase (TRK) inhibition. Neuotrophins and their TRK receptors are extremely crucial in the development of the
sympathetic nervous system and have been used in the pathogenesis of neuroblastomas.

Three receptor-ligand pairs have been identified and they are called TRK A, B, and C. TRK A is the primary receptor for the nerve growth factor, it seems to mediate the differentiation of developing neurons (or neuroblastomas) in the presence of NGF ligand and apoptosis in the absence of NGF (Davidoff, 2012). A high TRK A expression is associated with favorable tumor biology and a good outcome and has inversely correlated with MYCN amplification. TRK B is the primary receptor of brain-derived neurotrophic factor and has been exhibited in 40% of neuroblastoma tumors and normally in advanced stages of neuroblastomas. Similar in TRKC, which is a receptor for neurotrophin-3, which is expressed in about 25% of neuroblastomas and is strongly associated with the expression of TRK A. Even though the exact function of the TRK receptors in neuroblastoma tumors isn’t known, it still remains a form of treatment that can be quite promising (Davidoff, 2012).

Lastly, is immunotoxin therapy. The purpose of immunotoxin therapy (IT) is that it targets the tumor cell surface receptor and is considered a supplementary treatment approach. There were studies done at the University of Shanghai where the purpose was to detect for the expression of epidermal growth factor receptor (EGFR) in neuroblastoma cell lines and tissues, and to explore if IT therapy can be used to treat refractory neuroblastomas (Zheng et al. 2016). The results revealed there was a consistency and widespread expression of EGFR in both neuroblastoma cell lines and tissue samples that suggest that is it possible to develop future treatments by targeting EGFR. Due to the fact that neuroblastomas can build a drug resistance, it may render normal therapy methods no longer effective in the future (Zheng et al. 2016). Another downside to normal
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conventional methods of treatment is there is a significant amount of drugs that still remain in the body long after treatment is initiated and this can cause chronic organ failure as well as secondary tumors. New methods of treatment like Immunotoxin therapy (IT) can increase tumor clearance and reduce the side effects of toxic drugs (Zheng et al. 2016). Targeted therapy can be a very promising therapy for refractory tumors and this can also be used for the treatment of lung cancer, ovarian carcinomas, breast cancer, and melanoma. Simply, more studies and clinical trials need to be implemented on this type of therapy in order to warrant if this can be used in the future when conventional methods aren’t useful.

Conclusion

In conclusion, neuroblastomas are considered deadly when gone undiagnosed, so as healthcare providers it is important to not jump to conclusions when diagnosing a patient and to look at all the diagnostic tests. When that is not done, that’s when the patient suffers. There have been great leaps in learning more about neuroblastomas that we would not have known about a decade ago, especially in terms of their genetic make-up. This goes to show that research needs to be continued so we can fill in the pieces of what we do not know about neuroblastomas. Hopefully, as we conduct more research we will find more effective methods of treatment for our pediatric population.

Henrietta Lacks: Do the ends justify the means?

Consent, permission, respecting a patient’s space has become such a crucial aspect in medicine. Asking the patient before we take their vital signs or simply if they want their medication. Imagine a physician at a prestigious hospital, stealing your cells
and not bothering to tell you what he was planning to do with them, let alone knowing they were being taken in the first place. Sadly, this is exactly what happened to Henrietta Lacks. This paper will discuss the background of who Henrietta Lacks was, what happened to her after being diagnosed with cervical cancer and the treatment she received, what makes the HeLa cells so special, how they affected the progression of cancer treatment and overall modern medicine, why this case was ethically and morally wrong on the part of the doctors at John's Hopkins Hospital, then lastly discuss where the Lacks family is today and with this case and some new ethical issues they faced in the previous years.

Who was Henrietta Lacks?

Henrietta Lacks was born, Loretta Pleasant on August 1, 1920 to Eliza Lacks Pleasant and Johnny Pleasant and had eight older siblings. When Henrietta was only four years old, her mother Eliza died giving birth to her tenth child in 1924. Sadly, Henrietta's father Johnny did not have the patience nor the ability to take care of his ten children so he ended up taking them back to his home of Clover, Virginia where his family still lived. The children ended up being split up amongst the relatives where Henrietta ended up living with her grandfather, Tommy Lacks. Henrietta went to school up to sixth-grade until she stopped going to school. When she was 20 years old, she ended up marrying her cousin David (nicknamed 'Day'), whom she grew up with at the age of 25 years old. They ended up having five children together: Deborah Lacks, Elsie Lacks, David Lacks, Jr., Joseph Lacks, and Lawrence Lacks (Skloot, 2010).
Henrietta's Diagnosis

About one year before Henrietta passed away, she gave birth to a normal, healthy infant and six weeks later her cervix was perfectly normal. Then three months later, she presented herself to the clinic with a two to three centimeter cervical tumor to the doctors at John’s Hopkin’s Hospital. On February 1, 1951, the 30-year old Henrietta came to the Gynecology Clinic at the Johns Hopkins Hospital in Baltimore, Maryland. She came to the clinic because she was experiencing symptoms of spotting in between her normal menstrual periods (Lucey, Nelson-Rees, & Hutchins, 2009). Dr. Howard Jones, M.D. was the gynecologist who was treating Henrietta. When Henrietta described the pain, bleeding and the fact that she knew there was something wrong with the neck of her womb, Dr. Jones was confused by her description of her symptoms until he actually did the physical exam (Skloot, 2010). During the examination, her cervix was examined and Dr. Jones found a raised, smooth, glistening, and purple lesion that was less than an inch in size (Lucey, Nelson-Rees, & Hutchins, 2009). According to Dr. Jones, he had never seen anything like it and described it as looking, “shiny, and purple and very delicate looking” (Skloot, 2010). The lesion looked like it was confined to the cervix and appeared to be different from typical carcinomas. A sexually transmitted disease test was negative, Dr. Jones took a few samples of the lump on Henrietta’s cervix and then told her to go home. Dr. Jones explained that he was shocked that Henrietta had a full term birth because he noticed in her history that there was no note made about the lump at her six week return visit. Dr. Jones came to the conclusion that either the doctors missed this during her last exam or the tumor was growing at an extremely dangerous rate (Skloot, 2010). After a few days, Dr. Jones got Henrietta’s biopsy from the pathology lab and the
tissue sample came back as: Epidermoid carcinoma of the cervix, stage 1. A majority of cervical cancers are carcinomas which grow from the epithelial cells that cover the cervix and protect its surface. That day when Henrietta came to the hospital to hear her diagnosis, Dr. Jones and his boss Richard Wesley TeLinde were debating over what qualified as “cervical cancer” and how it should be treated (Skloot, 2010). What Henrietta did not know at the time of her stays at the hospital, was her cells were actually growing in the lab (Skloot, 2010).

A Treatment Experience at Johns Hopkins Hospital

For the community of African Americans living in Baltimore at this time, Johns Hopkins was the only major hospital that would treat African Americans and this was not Henrietta's ideal choice, but because it was the closest hospital, it was her only option (Skloot, 2010). As Henrietta was going though radium treatments, there was no recorded record of her having any side effects, however the doctors were not listening to Henrietta during her treatment when she complained of abdominal discomfort. At one point, Henrietta asked her doctors when she would be better so she could have more kids, but what the doctors failed to tell her was that the radium treatments would render her infertile. When she was told this, she said she would have rather not been treated at all. Back then, African Americans did not question a white's professional judgement and it seemed that Henrietta was not any different because she did not seem to question Dr. Jones. Amongst doctors, there was an understanding that doctors should not confuse the patients and even in some cases, they would not give their patients a diagnosis. Dr. Howard Jones claimed that the treatment that Henrietta received was the same as a white patient and that she got the standard biopsy, radium, and radiation treatment (Skloot,
2010). However, according to studies, it has been shown that African American patients were actually hospitalized later and treated in later stages of their disease compared to white patients that were treated much sooner. In terms of pain medication, African Americans got less and had a higher mortality rate. Henrietta went back several times complaining of the same discomfort that turned into a bilateral ache but the doctors wrote in her chart that she had no complaints. About three weeks later, Henrietta came back to the hospital complaining of abdominal pain and being unable to urinate, due to how severe the pain was, she could not walk and the doctors had to catheterize her in order to empty her bladder; promptly they sent her home after emptying her bladder (Skloot, 2010). Another three days later, Henrietta came back to the hospital where she was still complaining of abdominal pain, when palpated the doctors felt a strong, hard mass. They took an x-ray, which revealed a tumor that was attached to her pelvic wall that caused a nearly complete blockage of the urethra. Which then prompted them to declare the tumor as inoperable (surgery cannot be done) (Skloot, 2010). In a matter of a few weeks, the doctors went from declaring her “healthy” to calling her “chronically ill” and “obviously in pain”. Henrietta could not walk at this point was still coming back to the hospital for treatments that doctors insisted on because they still thought she could be cured regardless of the fact that the cancer was progressing at a rapidly dangerous rate. Each day, the radiation doses were increased quite drastically and they did this in hopes that it would shrink the tumors and ease the pain but it caused Henrietta’s skin to turn black and progressively turn blacker, and her pain only got much worse. Henrietta ended up being admitted on August 8th, and the doctors reported that Henrietta was complaining bitterly of pain and seemed miserable. Once she was checked in, a nurse took her blood and
labeled her vial “colored” in the case she would need a blood transfusion. The doctors tried to help her pain by giving her Demerol which did not work, they then tried giving her morphine but that was not enough for her. At one point, the doctors tried injecting alcohol into her spine, but this failed as well. At one point, it seemed that tumors were appearing daily on her lymph nodes, hip bones, labia, and she had a fever of 105° F. Henrietta was constantly nauseated and she claimed she vomited everything she ate. Eventually the doctors decided to stop the radiation therapy and accepted defeat that there was nothing they could do (Skloot, 2010). Henrietta Lacks passed away on October 4th, 1951 at 12:51 am at the age of 31 years old (Lucey, Nelson-Rees, & Hutchins, 2009).

After they lost their wife and mother, David Lacks abandoned their children and their daughter Deborah ended up being abused by a relative, her son Joe ended up in prison and her other daughter had epilepsy and was sent to a state hospital where she died at the age of 15 years old. For the Lacks family, the HeLa cells were the essence of their lost mother they never got to know (Shah, 2010).

**What She Never Knew**

During her treatment, there was great deal that the doctors neglected to tell both Henrietta and her family. It stated by Dr. Howard Jones taking a sample of her cervical cancer without asking her and sending it to the lab for more than having a diagnosis drawn from it. After Henrietta was sent home that day after giving a sample of her cells, that is when her cells started growing successfully in the lab (Skloot, 2010). Eventually, the cells were growing so fast that they has to be moved from one tube, to four separate tubes, than into six tubes. George Gey was the cell biologist who propagated her cells into an immortalized human cell line. Eventually, George Gey went onto television
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proclaiming that he found a way to “conquer cancer” in which he showed a pint-sized bottle containing Henrietta’s cells. He went on to explain that he and his team may have the ability to stop cancer because of these cells and said that this will help them learn a way that cancer cells can be completely wiped out. At no point during the interview did Gey say where the cells came from or who the donor of the cells was. Gey began sending Henrietta’s cells to scientists all over the country to cancer researchers in Texas, India, New York, Amsterdam, and Chile all to do cancer research on them (Skloot, 2010).

During her fight with cervical cancer, a doctor took more cervical cancer cells at the request of George Gey just so he could see if those cells would grow like the first sample. At this point, Henrietta was so sick to the point that her body had become so contaminated with toxins that are normally flushed from the body through urinating; but when the lab tried to culture the cells, they ended up dying almost instantly. Unlike the syphilis study in Tuskegee, Alabama, violating Lacks’ privacy did not seem to harm Henrietta physically (Shah, 2010). Henrietta was never told any of this while she was alive, and the doctors at Johns Hopkins did not seem to care to tell any members of the Lacks family. No one clearly cared enough to tell the family what the cells did for modern medicine until the recent decade.

Why are the HeLa cells special?

Dr. George Gey, M.D. was the director of the laboratory of Johns Hopkins Hospital and he focused his research on tissue culture, and later cancer, endocrinology, and virology. While at Hopkins, Dr. Gey and his colleagues were conducting their research by collecting cervical cancer tissue samples from surgical procedures. When Dr. Gey collected Henrietta’s samples, they were placed into a cell culture using a roller-tube
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technique where the cells grew robustly compared to previous cell samples that failed (Lucey, Nelson-Rees, & Hutchins, 2009). About 20 years later, the diagnosis of Henrietta Lacks’ was revisited, and it was revised to her having a very aggressive adenocarcinoma, of the cervix that was clearly very malignant with a very rapid clinical deterioration. What made Henrietta’s cells so special had been a question many people pondered. In recent years, it was shown that the HeLa cells contained the human papillomavirus (HPV) 18 DNA which has been linked to changes seen in microRNA expression. HPV18 has been linked to extremely aggressive adenocarcinomas which explain why Dr. Gey and his colleagues were surprised by the prolific growth of the HeLa cells in the culture (Lucey, Nelson-Rees, & Hutchins, 2009). The cells were extremely valuable because their ability to proliferate so rapidly allowed scientists to perform experiments that were not “ethically” possible. The cells were cut apart and exposed them to various toxins, radiation, and infection; the ultimate goal was to expose the cells to drugs hoping that they would kill the malignant cells without killing the normal cells. Scientists studied their immune suppression and cancer growth by injecting HeLa cells into immune-compromised rats, which grew malignant tumors extremely similar to the tumors Henrietta possessed. Then if the cells died, then it did not matter to the scientists because they could continue to use the immortal cell line (Skloot, 2010). After all the constant experimentation on Henrietta’s cells over the past 65 years, it resulted in the development of the polio vaccine, drugs for leukemia, influenza, hemophilia, Parkinson’s disease, as well as furthering our knowledge of cancer and genetics (Shah, 2010). In those 65 years since Henrietta’s passing, about 20 tons of her cell line have been reproduced and distributed worldwide for research (Epstein, 2016).
What Happened to the Family of Henrietta Lacks

For a woman who gave so much to modern medicine and science, it would be a hope that the family of Henrietta Lacks would be taken care of in some way. Sadly, this was not the case at all. Her daughter, Deborah has been the most vocal on the topic of her mother and the wrong that Hopkins did by not obtaining consent from Henrietta when she was alive as well as never telling them what became of their mother’s cells. Deborah has talked so much and has been stressed that she got the point where she did not want to talk about her mother anymore. Whenever Deborah went to her doctor’s appointments she would tell the staff that her mother was HeLa and how they would get excited telling her that her cells helped make blood pressure medication, antidepressant pills, the polio vaccine, and even the nuclear bomb. Deborah always thought it was strange that the family of someone who contributed so much to medicine and science cannot afford to see doctors. On the other hand, Rebecca is also happy that her mother’s cells contributed so much to man-kind because it helped the lives of so many people and that she thinks her mother would have been happy to help (Skloot, 2010). Now, it is a question of why the family hasn’t been given the respect and peace that they deserve after so much they have dealt with in the last 65 years.

Another Ethical Battle?

After the last few decades, the Lacks family still had to deal with, and face problems from the science community. For several decades, Henrietta’s family had absolutely no clue about the HeLa cell line or its genetic linkage to Henrietta or themselves. On March 11, 2013 a team of researchers from the European Molecular
Biology Laboratory (EMBL) that was led by Lars Steinmetz who published an article about the genomic characteristics of one of the HeLa cell line strains. The EMBL then posted the entire genome sequence online assuming for it to be a source to aid other researchers and they did not expect nearly half the backlash they received. There were numerous questions raised about publishing the genome sequence of the HeLa cell line, because even though its DNA has mutated immensely over the past 60 years, the data did offer some genomic information about Henrietta and her living family members (Greely & Cho, 2013). The EMBL apologized for any distress and removed the sequence data from the internet and offered to work with the Lacks family to find ways to make this potentially scientifically valuable information, but also protect the family and respecting Henrietta (Greely & Cho, 2013). The director of the NIH, Francis Collins was trying to help make up for the decades of dishonesty to the Lacks family. Director Collins met with the Lacks family to discuss options of what should be done with the genomic data. This was the first time in a long time that researchers were explaining to the family what was actually going on. Collins mentioned that the Lacks family members told him how disturbing it had been to learn about the HeLa cells decades after she had passed away. Of course, the family drilled Director Collins with questions regarding how her cells were used and about the genetic sequence. Collins told the family that they might have identified the genetic change that made Henrietta's cancer so aggressive. Eventually, the NIH put the family in touch with experts in clinical genetics who told them what health information can be learned from the genomes and they offered to help members of the Lacks family sequence their own genome and then interpret them. Collins did not pressure the family to publish her genome sequence but he did explain the reality that the
organization were willing to leave the work unpublished; however, the information could not be kept away too long because there were 400 genomes worth of HeLa data already available to the public so they could not stop other scientists around the world from sequencing her cell line. The family raised a question about financial compensation, but Director Collins said this was not possible but he reassured the family that other people could not actually profit off patenting a genetic test for cancer based on HeLa cell mutation because the U.S. Supreme Court had ruled in 2013 that unmodified genes could not be patented (Callaway, 2013). A HeLa Genome Data Access Working Group was established to review requests to use the data, making recommendations to the Advisory Committee to the Director and the NIH Director. The group consisted of three scientists, two family members of the Lacks family, and one bioethicist. It was agreed and implemented that specific acknowledgments to Henrietta Lacks and her family would be made. As a result, on August 7th, 2013, the U.S National Institute of Health (NIH) announced that they reached in agreement with the descendants of Henrietta Lacks concerning further use of the HeLa cell line (Greely & Cho, 2013). This was considered a reasonable compromise to make for an extreme conflict between researchers needing a broad availability of data and legitimate privacy and autonomy interests regarding the people who are providing biological sources. Sadly, the agreement is not completely enforceable because the Director of the NIH has the only power over the organization so one can only hope that the NIH will abide to the agreement out of respect for the Lacks family and Henrietta's memory (Greely & Cho, 2013).
**What can be learned from the Henrietta Lacks' story?**

There are many lessons to be learned from this medical case. First, as healthcare professionals we should be aware of seeking consent from our patients in big cases similar to Henrietta’s where tissue samples were taken and then grown. Then there are smaller tasks like taking vital signs where consent is still needed. It is extremely crucial to ask consent of your patient out of respect for them. Another lesson that can be learned is providing equal treatment and care for all patients regardless of their skin color not just in theory, but in actual practice. Even though Jim Crow Laws have been done away with, as a society these racial ideas are still very much prevalent for anyone who is not Caucasian. As a whole, health disparities are still in existence and there are still groups of the population that do not benefit from the same health status compared to other racial groups (Dimaano & Spigner, 2017). Just because it is the 21st century, it does not always mean such archaic beliefs have disappeared; we need to be vigilant to make sure these same unethical mistakes do not occur.

**Conclusion**

In conclusion, despite the color of Henrietta Lacks’ skin she still deserved the same attention and treatment that any white individual would have gotten. Sadly, due to the civil rights issues of the time it most likely played a part in her rapid deterioration and eventual passing. Whether doctors could have done anything to cure her with the medicine they had, is an answer we may never know. As the medical field moves forward, we should let Henrietta’s story serve as a reminder of how every single patient we treat deserves our utmost care and attention without any hesitation in regards to what
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color of skin they have or their standing in society. It also serves as a reminder that we as healthcare professionals are there to serve the patient and that their consent to treatment is always a priority.
A Centuries old Controversy: Physician Assisted Suicide and Euthanasia

Some may assume that this ethical debate of Euthanasia & Physician Assisted Suicide is a modern day issue, however; this controversy of life and death can be traced all the way back to the ancient times. In this research paper, what physician assisted suicide is will be explained, some history behind the issue, the laws that are currently in place, arguments against physician assisted suicide, the arguments that are in support of physician assisted suicide, the opinions of both physicians and nurses, the famous physician assisted suicide cases we as a society have heard about, why someone would choose physician assisted suicide over palliative care, and why the physician assisted suicide is so crucial as of today.

What is Physician Assisted Suicide?

The idea of physician assisted suicide and euthanasia has been an issue for centuries and has divided people. The best way to understand the topic better is by understanding what physician assisted suicide entails. In physician assisted suicide, the physician provides the terminally ill patient with the means to cause death, and the ultimate decision to end their life is the patients’ (Miller & Truog, 2012). The term “Euthanasia” means “a good death” and has actually been used for centuries to describe this ethical controversy. In the original medical use, euthanasia implied that the duty of a physician is meant to assure that his patients died as peacefully and comfortably that could be provided at the time (Jonsen, Siegler, & Winslade 2010). Universally, euthanasia is considered a form of homicide even if it may not be punished with the same magnitude as others (Yount, 2007). There are three types of euthanasia; one is voluntary
euthanasia which is described as situations where the patient consciously and deliberately requests death. Nonvoluntary euthanasia is where a patient was incapacitated and has made no formal request for death, which has been criticized by all commenters. Involuntary euthanasia is a situation in which patients were killed against their wishes, this was actually practiced as a policy in Nazi medicine and has been rightfully condemned by all the commenters (Jonsen, Siegler, & Winslade, 2010). Another term associated with physician assisted suicide as well as palliative care is palliative sedation which is when there is a monitored use of medications that are intended to induce a state of decreased or absent awareness to help relieve the burden of otherwise unbearable suffering in a way that is ethically acceptable for the patient, family, and healthcare providers (De Lima et al., 2016).

**History**

As it was previously mentioned, physician assisted suicide and euthanasia have had centuries long history that many assumed was decades old. There has been some historical evidence that has suggested that numerous ancient cultures were tolerable of assisted suicide and euthanasia. An example of this is the ancient Greeks and Romans who actually drank lethal poison to end their lives when faced with debilitating injury, life-limiting illness or unbearable pain. The ancient Romans not only tolerated assisted suicide but was widely accepted if an individual was faced with this dilemma (Haerens, 2015). What made the Romans so different from how our society deals with assisted suicide was that they did not punish people who attempted suicide (McDougall & Brown, 2008). In some Greek-city-states, suicide was also quite common to end one’s life; in the Greek city-states, poison was used for suicide and assisted suicide was done by the city
magistrates. During the era, the ancient Greeks were the civilization that came up with the term “Euthanasia” which means, “a good death”. Even though there was acceptance of the practice, there was also a fair amount of opposition from major names such as the Greek philosopher Aristotle. Aristotle went as far as calling it a “cowardly death” and an offence against the state. Aside from Aristotle, Hippocrates was a well-known physician of the time who spoke explicitly against the practice of euthanasia in his oath, “I will give no deadly medicine to any one if asked, nor suggest any counsel” (Haerens, 2015).

Because of the Hippocratic Oath, physicians still take the same oath “to do no harm”, there remains a strong opposition to euthanasia in the medical community even if some individual health care professionals support it under particular circumstances.

Religion has played a role in whether individuals in society have accepted or rejected euthanasia and physician assisted suicide. In a number of religions, physicians were explicitly prohibited from having a role in taking any life. Suffering was viewed as the wages for sin and a way for the individual to pay for their wrongdoings. Even with the spread of Christianity and Islam in the later centuries, they helped to reinforce the opposition to euthanasia. Both religions forbade the practice, mainly for moral grounds, deeming life to be sacred and suicide in any form to be forbidden (Haerens, 2015).

During the middle ages, with the widespread of death and suffering that was caused by the bubonic plague and other horrendous disease outbreaks that actually led some theologians and philosophers to justify euthanasia in special circumstances, which led society to rethink how they confronted the process of dying. During the mid-nineteenth century, advances in our medical understanding and technology spurred another need to look at euthanasia and physician assisted suicide from a different perspective once more.
Some medical ethicists believed that it was acceptable to use morphine and chloroform as pain management for those individuals that are terminally ill to help euthanize them in order to help manage their pain. During the late nineteenth century, there was a euthanasia movement that actually occurred during the development of the modern hospital system. During this time, a prominent activist and educator by the name of Felix Adler who was the first American to argue in the favor of patients who were suffering from a chronic illness and unbearable pain, had the right to end their life if they felt it was necessary. Adler did regard it as ethical for a physician to play their role in a patients’ death. In the 1970s, the euthanasia movement really gained steam when there was the emergence of the death with dignity movement (Haerens, 2015). About a decade later in 1980, a British American journalist by the name of Derek Humphrey founded the Hemlock Society, which served the purpose of providing people with information on suicide and assisted dying for people who were terminally ill. The society also supported the legislation to permit physician-assisted suicide in particular circumstances. The reason why Humphrey started the Hemlock Society was due to the fact that his wife, Jean had died from a prolonged and painful death from terminal cancer (Haerens, 2015).

**Laws currently in place**

Another important aspect in understanding physician assisted suicide is what the law instructs for each state. Legislation to legalize euthanasia and physician assisted were introduced in the state legislatures of Ohio and Iowa back in 1906, but both proposals failed after fierce debates over the morality and scope of the legislation (Haerens, 2015). Oregon was the first state to pass legislation in 1994 to allow physician assisted dying in limited circumstances (Jonsen, Siegler, & Winslade, 2010). The Oregon Death with
Dignity Act allows for terminally ill patients to request in writing a dose of medication to commit suicide with the help of a consenting physician. However, the law was not implemented until 1997 due to some legal challenges, which consisted of a case being heard by the United States Supreme Court that allowed for the law to remain in place (Haerens, 2015). Then about eleven years later, the state of Washington passed a similar initiative to allow for physician assisted suicide, again, under specific circumstances (Haerens, 2015). Overall, in the United States, 37 states have laws that made assisted suicide with three states (Alabama, Massachusetts, and West Virginia) that prohibit assisted suicide by common law. The states of New York, North Carolina, Utah, and Wyoming have no specific laws regarding assisted suicide, may not recognize common law, or are otherwise unclear on the legality of assisted suicide. In total, six states have legalized physician assisted suicide (ProCon.org, 2017).

California

California has is an extremely diverse in socioeconomic status, race/ethnicity, language, and cultural background and actually has the greatest number of adults living with a disability in the United States (Petrillo et al., 2017). The Californian law includes safeguards, yet the healthcare providers will face practical and ethical issues implementing physician assisted death that are not addressed by the law (Petrillo et al., 2017). In California, the ABX2-12 End of Life Option Act was signed into law on October 5, 2015. In order for a patient to be eligible, they must be at least 18 years or older; be a resident of California; Must be capable of making and communicating health care decisions for him/herself; diagnosed with a terminal illness that will lead to death within six months; and lastly, they must be physically and mentally capable of self-
administering the aid-in-dying drug (ProCon.org, 2017). The patient’s physician must be licensed in the same state as the patient and have a current US Drug Enforcement Administration (USDEA) certificate. The diagnosis made by the physician must include a terminal illness with six months or less to live. The diagnosis must be certified by a consulting physician, who must either confirm or deny that the patient is mentally competent to make and communicate health care decisions. In the case that a physician determines that the patient is not mentally competent, they must be referred for a psychological examination. The physician overseeing case for the patient is obligated to inform the patient of the alternatives, such as palliative care, hospice care, and pain management options. When the patient is ready to go through the process, they must make an oral request to their physician, then there has to be a 15 day waiting period, then the patient is required to make a second oral request to their physician and then make a written request to the physician (ProCon.org, 2017). A miscellaneous aspect of the California law is that pharmacists are also protected from prosecution for filling aid-in-dying prescriptions (ProCon.org, 2017).

**Colorado**

Colorado became the sixth state with legal physician assisted death in 2016 (Petrillo et al., 2017). With Colorado, signing the physician assisted suicide into law was more recent. On November 8, 2016 the Proposition 106: End of Life Options Act was voted on and then implemented and took effect in January 2017 (ProCon.org, 2017). In order for a patient to be eligible, they must be a resident of Colorado, must be 18 years or older, are capable or making and communicating health care decisions for him/her and has made the request voluntarily, and lastly the physician’s diagnosis must include a
terminal illness that will lead to death within sixth months (ProCon.org, 2017). For the physician, they must follow protocol in order to participate in their patient’s assisted suicide. The physician must include a terminal illness with sixth months or less to live and that the patient is mentally capable of making an informed decision and making the decision voluntarily. The physician must also request that the patient demonstrate that they are a resident of Colorado; and the patient must also be referred to a consulting physician who could confirm the patient’s diagnosis and competency. Once this is done, the physician must discuss with the patient their medical diagnosis and prognosis to explore any feasible alternatives or additional treatment, along with the risks of taking aid-in-dying medication, and that a patient may fill the aid-in-dying medication prescription but may choose to not use it (ProCon.org, 2017). Part of the mental competency component require, the physician to refer their patient to a licensed mental health professional. Next, the physician must request that the patient notify their next of kin about the prescription request. For the patient, they must make their first request to their physician orally, and then wait 15 days to then make their second oral request, which is then followed by a written request to their physician (ProCon.org, 2017).

**Washington D.C.**

Washington D.C. has also legalized physician-assisted with the DC ACT 21-577 Death with Dignity Act of 2016, which was signed into law on December 19, 2016 (ProCon.org, 2017). Similar to California and Colorado, a patient must be at least 18 years or older, be a resident of the District of Columbia, capable of making and communicating health care decisions for themselves. The patient must be diagnosed with a terminal illness that will lead to death within sixth months. In order for the physician to
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do their job within the legal limits, they must be licensed within the District of Columbia; the diagnosis must be confirmed by a consulting physician, certifies that the patient is mentally competent to communicate their health care decisions. In the case that either physician concludes that the patient’s judgment is impaired, then the patient must be referred for a psychological evaluation. Lastly, the physician must inform the patient of alternatives such as palliative care, hospice care, and pain management options. Again, similar to the states of California and Colorado; the patient’s first request to their physician must be done orally, then a written request to the physician before the second oral request with at least 48 hours before the medication gets dispensed. That second oral request to the physician should be made at least 15 days after the first oral request. The D.C. laws are subject to Congressional oversight, and when the Death with Dignity Act of 2016 was submitted to Congress for a 30-day review on January 6, 2017. Representative Brad Wenstrup of Ohio (Republican) and Senator James Lankford of Oklahoma (Republican) submitted their disapproval resolutions to the House and Senate on January 12, 2017 that would eventually do away with the law. However, the resolutions did not come up for a full vote of the House or Senate within the 30 working days which led to the law being put into effect on February 18, 2017 (ProCon.org, 2017).

Montana

In Montana, the law was passed on December 31, 2009 through the Montana Supreme Court in Baxter v. Montana. A patient is required to be a resident of Montana. However, there is no set age limit as well as there being no requirement in the number of months until the patient’s expected death. There are also no requirements in the number and type of requests made by the physician (ProCon.org, 2017). Although there is no
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state law on assisted dying in Montana, the state Supreme Court ruled that there is no law prohibiting a physician to assist a patient in dying and cannot be prosecuted under state law (Haerens, 2015).

Oregon

Oregon passed Ballot Measure 16, which allows for terminally ill adults to obtain prescription for a lethal drug, which is what we know as the Death with Dignity Act that was signed into law on November 8, 1994. The Death with Dignity Act states that an adult who is capable, is a resident of Oregon, and has been determined by their attending physician and consulting physician to be suffering from a terminal disease, and who has voluntarily expressed their wish to die, may make a written request for the purpose of ending their life in a humane and dignified manner (ProCon.org, 2017).

Washington

On November 4, 2008, Washington passed the Initiative 1000: Death with Dignity Act which states that an adult who is competent, is a resident of Washington state and has been determined by the attending physician and consulting physician to be suffering from a terminal disease, and who has voluntarily expressed their wish to die. They may make a written request for medication that the patient may self-administer to end his/her life in a humane and dignified manner (ProCon.org, 2017). The goal of the law is meant to help give control back to the terminally ill and allow them to die with dignity. In the state of Washington, it is required that the patient is a resident, be at least the age of 18 or older. The patient must have sixth months or less until expected death.
The patient must make two oral requests to their physician that are at least 15 days apart, and they must make one written request (ProCon.org, 2017).

**Arguments against Physician Assisted Suicide**

Throughout the world, physicians are trained to provide care and preserve life. Physicians take the Hippocratic Oath which states, “I will give no deadly medicine to anyone if asked nor suggest any such counsel”; this professional code of ethics for physicians have clarified that ending life is not part of the task of a physician (De Lima et al., 2016). This ancient prohibitions seems directly aimed at physician assisted death suicide contemporary organized medicine reaffirms this tradition of rejecting physician assisted suicide (Jonsen, Siegler, & Winslade, 2010).

The American Medical Association (AMA) rejects physician assisted suicide as something that is “fundamentally incompatible with the physicians role as a healer and because it would be difficult or impossible to control and would pose serious societal risks” (Luper, 2016). The AMA condemns the practice of euthanasia as conducted by physicians for these reasons as well and adds, by way of clarifying the serious risks at hand, that euthanasia could be readily by extended to incompetent patients and other vulnerable populations (Luper, 2016). The dedication of the medical profession to the welfare of patients and to the promotion of health might be seriously undermined in the eyes of the public and of patients by the participation of physicians in the death of the very ill, even of those who request it (Jonsen, Siegler, & Winslade, 2010). It is not uncommon for patients with advanced incurable disease to express a desire to hasten their death (Hospice and Palliative Nurses Association, 2011). Another opponent to physician
assisted suicide is the American College of Physicians that particularly does not support any legalization of the practice. They make the point that, the practice might undermine patient trust and will distract from the reform in end-of-life care and because of the risk of discrimination against vulnerable populations which include the elderly and disabled (Jonsen, Siegler, & Winslade, 2010).

Many religions have also prohibited the act of physician assisted suicide stating that the consent of the individual is still considered an act of homicide. Many religions also consider the “indirect” involvement of a physician as a prescribed alone as equally wrong (Jonsen, Siegler, & Winslade, 2010). By making the practice more available, it may bring subtle coercion for individuals who feel that their compromised health may feel they are a burden (Jonsen, Siegler, & Winslade, 2010). According to Dr. Jason Karlawish, MD, of the University of Pennsylvania Center for Bioethics’ Assisted Suicide Consensus Panel, and coauthor of the Annals of Internal Medicine (AIM) article, “The problem is that physician assisted suicide requires skills that the average physician does not have, and should not have. We physicians should be able to treat those who are dying, relieving their pain and symptoms, but not helping them skill themselves” (Farella, 2000, p. 2). An article written by the Annals of Internal Medicine (AIM) states that physician assisted suicide violates physicians’ professional integrity and suggests that other disciplines such as nursing may be more capable of leading assisted suicide efforts (Farella, 2000). A number of problems have emerged due to the debate of physician assisted suicide, such as financial pressures where at least twice, the Oregon health department told that cancer patients that it would fund assisted suicide but not expensive
drugs for their treatments and this fact fuels fears that bureaucracies might use assisted
suicide as a form of cost-cutting (Cook, 2014).

Related to depression in the elderly population, it could be a result of elder abuse. In more than 80% of cases there were no independent witnesses of the elder abuse and this is a clear recipe for elder abuse by the people with a financial agenda in that elderly individual’s death (Cook, 2014). Another issue that might change an individual’s mind in regards to going though with physician assisted suicide is that some terminal illnesses do not actually terminate. There has been close examination of the statistics reveal that some patients have lived for as long as three years after receiving their lethal prescription (Cook, 2014). There are many factors to consider for an individual if they believe that they must go through with physician assisted suicide.

**Arguments in support of Physician Assisted Suicide**

The discussion of aid in dying is difficult because it does indeed evoke medical, emotional, and spiritual issues that were discussed earlier (Novelli & Banerjee, 2017). According to consumer polling, almost 75 percent of American adults believe individuals with a serious illness should be allowed to terminate their lives (Novelli & Banerjee, 2017). Autonomous individuals have moral authority over their lives; patients who are dying should be allowed the means to control the time and manner of their death with assistance from competent clinicians. No individual should be required to bear disproportionate burdens of pain and suffering, and those who relieve them of such burdens at their request, are acting ethically, that is out of compassion and respect for autonomy (Jonsen, Siegler, & Winslade, 2010). In some cases, pain and disability are the
result of medical interventions and treatment being successful but extending life to an unacceptable quality. The individuals who have affected the therapy outcome should be permitted to respect of the patient’s desire to no longer bear the poor quality of life. Just as patients may refuse artificial nutrition and hydration to hasten their death, one might argue that physician assisted suicide accomplishes the same goal. The Hippocratic oath, which prohibits the “giving of poisons” is outdated, because medicine could never have anticipated the ability to prolong dying to the extent is has today (Jonsen, Siegler, & Winslade, 2010).

Arguments in favor of euthanasia and physician assisted suicide are focused on relieving intolerable suffering. A small percentage of severely ill or dying patients experience excruciating suffering despite all the best efforts to palliate, as a result, ending their life may the only option to end their suffering. A request for patient autonomy is crucial for those who decide to utilize physician assisted suicide is often related to the patient’s own perception of a loss of control (De Lima et al., 2016). It is correct that direct administration of a lethal drug constitutes an act of homicide (Jonsen, Siegler, & Winslade, 2010). However, prescription of drugs that the terminally ill patient can take at their own will removes the physician as the agent of the patient’s death. The decision and the action of ending their life still remains in the patient’s control (Jonsen, Siegler, & Winslade, 2010). Physician participation is a proper medical response out of respect for patient autonomy and of their patient’s evaluation of their quality of life (Jonsen, Siegler, & Winslade, 2010). With a majority of controversial issues like physician assisted suicide, there will always be a radical group and should not be ignored. Some radical supporters of physician assisted suicide constantly test these limits by helping people die
outside of the approved legal guidelines. It is naïve to assume that a law will put an end to secret euthanasia, as many have predicted (Cook, 2014).

**Opinion of Nurses**

Due to the intimacy that characterizes the nurse-patient relationship, nurses who care for terminally ill patients encounter ethically challenging issues, such as requests for assistance in prematurely ending life. A request from a terminally ill patient to hasten death represents a clinical, ethical, and legal dilemma for nurses (Hospice and Palliative Nurses Association, 2011). When the law was implemented, the assumption was the physicians would be the first ones to explore physician assisted suicide with patients, but in actuality, nurses are normally the ones in the life of fire. Patients often feel nurses understand their wishes for good quality of life and good quality of death (Farella, 2000). Much of the nurses’ roles lie behind the scenes before the drama of physician assisted suicide unfolds (Farella, 2000). Even when nurses support physician assisted suicide, they might not understand how they feel until they are faced with it. A nurse, Lynda Moses, RN, BSN said, “Although I support the patient’s right to die, I’m always saddened by the fact that some people don’t choose to live.” Lynda Moses was relieved when her patient died of natural causes shortly before he was to take his own life. She realized just how uncomfortable she was about physician assisted suicide even though she did believe in it. She also reported that “have no problem caring for patients after they’ve taken a lethal dose of medication–I just don’t want to be there when they do” (Farella, 2000, p. 2).
Nurses need to consider their comfort with the idea that some of their patients may choose to accelerate their dying process (Hospice and Palliative Nurses Association, 2011). In the case that assisted dying is legal in the state that a nurse practices, they must decide whether their own moral and ethical value system does or does not allow them to be involved in providing care to a patient who has made the choice to end their life through assisted dying (Hospice and Palliative Nurses Association, 2011). “Many RNs believe that to intentionally assist in dying is to participate in killing. They see it as disrespect for life and something that prohibited by law, our nursing code of ethics, and our practice guidelines” said Judith Kennedy Schwarz, RN, MSN, doctoral candidate, division of nursing, New York University, and a consultant in nursing ethics and expert in the subject of assisted dying (Farella, 2000, p. 3). Of the 441 nurses surveyed, 30% reported receiving requests for lethal drugs in the previous year, and 25% of nurses reported receiving requests for lethal injections, with 1% of nurses admitting to helping a patient commit suicide (Farella, 2000). 70% of nurses lacked detailed on the policies and procedures adopted, by their healthcare facilities in handling patients request for physician assisted death (Madujibeya & Villaren, 2015). The American Nurses Association (ANA) states that the nurse is prohibited from participating in assisted death and should provide interventions to relieve pain and suffering of the dying patient, even if they may hasten death. According to the ANA Code of Ethics for Nurses, nurses may not act with the sole’ intent of ending a patient’s life even though such action may be motivated by compassion, respect for patient autonomy, and quality of life considerations. The Hospice and Palliative Nurses Association (HPNA) acknowledges that disagreement exists regarding assisted dying but maintains their position that HPNA
does not support legalization of assisted dying (Hospice and Palliative Nurses Association, 2011). As more states pass laws supported assisted death, nurses will be faced with choices regarding the provision of information and caring for the patient and family (Hospice and Palliative Nurses Association, 2011). Education is an important tool that health care organizations and clinics can use to prepare staff and reduce distress; providers should be taught about the basic aspects of the law and local policy (Petrillo et al., 2017).

**Palliative Care**

A more popular alternative to physician assisted suicide is palliative care. According to the World Health Organization (WHO), palliative care is defined as “an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual” (De Lima et al., 2016). The basics of palliative care include symptom control, psychological and spiritual well-being, and care of the family; fit the goal of helping patients to live with dignity until their death (De Lima et al. 2016). Assisted dying proposals all have a common factor, and it is their physical pain. However, palliative care has advanced so much in the recent years that a majority of all pain can be controlled. What might seem unbearable may be due to incompetent medical care. If so, death may seem like a heavy penalty for choosing a bad physician (Cook, 2014). The International Association for Hospice and Palliative Care (IAHPC) is an organization that has a formal relationship with the World Health Organization (WHO). the IAHPC serves as an advisor and observer to the relevant
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discussion and expert committees (De Lima et al., 2016). The IAHPC believes that no country or state should consider the legalization of euthanasia or physician assisted suicide until it ensures universal access to palliative care services as well as appropriate medications including opioids for pain and dyspnea. The IAHPC also makes the point that withholding or withdrawing ineffective, futile, burdensome, and unnecessary life prolonging procedures or treatments does not constitute euthanasia or physician assisted suicide because it is not intended to hasten death, but rather indicate their acceptance of death as a natural consequence of the underlying disease progression (De Lima et al., 2016).

Adequate palliative care delivery requires four major components according to the WHO palliative care public health strategy are: adequate health care policies; education of health providers, legislators and the public in general; availability of medications; and implementation of services in all levels of care (De Lima et al., 2016). Studies have indicated that patient’s relief is at an increased risk for suicide and quickened death (DeLima et al., 2016). Many individuals living in rural areas of California communities lack access to palliative care, whereas in Oregon and Washington palliative care is more accessible where nearly all patients who use physician assisted suicide are also enrolled in hospice care (Petrillo et al., 2017). Patients may even ask their physicians about physician assisted dying because of their unmet psychosocial, physical or spiritual needs; therefore it is necessary to make palliative care more accessible and to educate the public about it (Petrillo et al., 2017). Part of palliative care consists of symptom and pain management. WHO has included a number of medications, including opioids (morphine, oxycodone, and hydromorphone) for pain treatment and palliative care. The reported
consumption of opioids to the International Narcotics Control Board (INCB) has been used as an indicator of access to palliative care where high-income countries consume 90% of opioid analgesics. Access to these medications is extremely inadequate and more than 80% of the legitimate global need for opioids for medical purposes is unmet (De Lima et al., 2016). Palliative care is a feasible option for those who are terminally ill to help make their situation more bearable.

**Brittany Maynard**

Through the spread of stories like Brittany Maynard’s, who was a 29-year-old diagnosed with a terminal brain cancer called a glioblastoma; her case has helped bring awareness to the numerous options to those individuals who are terminal and approaching death (Novelli & Banerjee, 2017). Brittany had recently gotten married and was contemplating having children with her husband, until she started having awful headaches that would not go away and she received the diagnosis of a grade two astrocytoma (brain cancer) and promptly after having a partial craniotomy and a partial resection of her temporal lobe. Eventually, the cancer came back and was a grade four astrocytoma, which is known as a glioblastoma (Hoffman, 2014). When Brittany Maynard received the diagnosis of terminal brain cancer, she made the decision to end her life by taking a lethal dose of barbiturates (Armstrong, 2014). Brittany worried about waiting too long that her seizures would leave her incapable of making decisions (NBC News, 2014). Maynard made a decision based on the full context of her values and knowledge. Her death was tragic, but she could not avoid it, she could only control its course and timing and therefore minimize her own suffering. Brittany and her husband Daniel went to the extent of moving from their home in California to Oregon to take
advantage of the state allowing assisted suicide (Armstrong, 2014). When the news reached the Catholic Church, they denounced Brittany’s choice and Pope Francis went as far as calling assisted suicide “playing with life and a sin against the creator”. Leaders of the Catholic Church and many other religions see life as not your own but god’s or society’s and hold that we have a moral duty to stay alive regardless, even if you face unspeakable suffering and death due to a terminal illness (Armstrong, 2014). Brittany said, “I want to see all Americans have access to the same healthcare rights” (NBC News, 2014). “I think until anyone has walked a mile in my shoes and know what they are facing and has felt the bone splitting headaches that I get sometimes, or the seizures, or the inability to speak, or the moments where I’m looking at my husband’s face and I can’t think of his name…” Brittany had every intention to die with dignity (CBS This Morning, 2014). According to Art Chaplan, A Bioethicist from NYU Langone Medical Center said, “Jack Kevorkian scared people, he was almost the fanatic. Brittany, she’s young, articulate, she doesn’t frighten anyone and she’s saying I want my choice, and I’d like other people to have a choice like me” (NBC News, 2014). Her death has helped to reframe the debate of physician assisted suicide (NBC News, 2014) and as the legalization debate continues, her story will always be one society thinks back on.

Conclusion

From centuries ago to modern day, physician assisted suicide and euthanasia has played a role in our society whether we have noticed it or not. It is an important topic of debate that is clearly important as of today and will continue to be as we struggle with the ethical question of legalization of assisted suicide in other states in the USA. As a country that preaches equality, it should extend to healthcare rights in that every
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American has a right to decide the best path for them, in the circumstance that they do become terminally ill. It is also important to educate our physicians and nurses on physician assisted suicide in the case that when a patient asks about it, they will be ready to educate and provide the best care. In that manner, by educating our healthcare providers it will give them a chance to decipher their stance on the issue but to still respect the autonomy of their patient above all.

Discussion

Cancer treatment has come a long way in the last century that many healthcare professionals from the past would have only dreamed of; and yet, physicians and scientists are constantly learning more about the various types of cancers and how they are caused, discovering new forms of treatment, and therapy.

Learning more about these types of cancers and how they are caused aides us as healthcare professionals to find new forms of cancer treatment. With this comes the question of whether patients want to pursue a treatment when they are terminal or the newer treatments and potentially risk their lives trying to stay alive and compromising their quality of life. Ultimately, it is the patient’s decision and always should be. A cancer patient should be free to decide the type of treatment they want to try, if they feel it may be time to accept that they have exhausted all their potential treatments, then they should consider exploring the possibilities of palliative care or physician assisted suicide. In the case, that a patient chooses physician assisted suicide after exploring all options than they are decisions should be respected by their nurses and physicians even if they fundamentally disagree.
Patient autonomy plays a big role in cancer treatment and medicine as a whole. Comparing what Henrietta Lacks went through for her treatment that she was not even fully aware of, and what patients like Brittany Maynard have dealt with goes to show that patient autonomy needs to be respected regardless of our own personal beliefs. It has constantly been a question between quality of life and quantity for most cancer patients and as a profession; nurses have the privilege of providing cancer patients with the best quality of life on their terms.
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