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Mechanisms of Metastasis: Analysis on Abdominal Organs and the Effect of Treatment Options

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ABSTRACT

Metastasis is a field of cancer in addition to numerous others that is largely unknown due to lack of advancements in the research and knowledge. It is the leading cause of cancer related deaths and commonly associated with Stage IV cancer. This paper will aim to answer the question of: "How do the different circumstances of metastatic origin, growth, and spread affect the function of abdominal organs and life expectancy in cancer patients as well as how varied treatment options affect tumor spread?" in the style of an empirical review and culmination of research journals. It details numerous studies on metastasis formation, growth, and its effects in the three abdominal organs of the colon/rectum, pancreas, and the stomach. Additionally, it delves into the treatment options for metastasis and how they help or worsen the situation.

Overall, the key factors in tumor spread is the tumor microenvironment which highlights the interactions between healthy and malignant cells. The tumor uses the body's natural processes to manipulate them to its own advantage and metastasize. Tumors secrete various growth factors, the most important being VEGF which is helpful in the processes of acquiring nutrients and oxygen for it to grow and develop. Prior niches are formed which guide the tumors on where to spread depending on the cancer type. For example, in abdominal organ cancers, the liver is the most common site of metastasis which will lead to a pre metastatic niche formed to spread the tumors from these organs to the liver. In abdominal organs specifically, the most common sites of metastasis are the liver, lung, and peritoneum, which indicates proximal metastasis of cancers which originate in that region. Lastly, treatment methods aimed at eliminating the chance of cancer metastasis can lead to a stimulation of metastasis, having the opposite of its intended effect. Ultimately, cancer research is a field which is actively being experienced and studied to make developments and further existing knowledge.

Introduction

Metastasis contributes to the vastly unknown medical problem that is cancer. Part of what makes cancer research incredibly challenging is the growing threat of the tumors metastasizing and spreading throughout the body. As a result, this leads to complications majorly associated with stage four cancer, thus having a significant negative effect on the survival rates and longevity of those affected.

Cancer is the unregulated growth of cells which invade a particular area, causing the formation of tumors. These cancerous cells affect numerous organs, but they present an even more prominent threat if they metastasize. Metastatic cancer occurs when pieces of the original tumor break off and spread to other parts of the body by traveling through the bloodstream and lymphatic vessels. Various articles and experiments have been done to gain a better understanding of the pathways and hormones tumors use to invade and advance through the human body. The information found in studies involving metastatic growth should be further explored to understand how the tumors manipulate and use the body systems to travel and develop in different regions of the body. This knowledge is crucial in finding ways to inhibit the pathways of tumor progression and eventually decelerate metastasis. The severity of the

metastasis such as the rate at which it spreads and the total area which the tumor covers are key indicators of the survival rate and degree of cancer progression.

In this paper, the topics of focus include how different treatment methods of metastatic cancer affect the metastasis of the tumors and the life expectancy, in addition to how the tumors affect specific organs. It will discuss the ways in which the tumors use the body's naturally functioning systems to spread and invade both proximally and distally from its original site. Additionally, it will explore the effect the tumor growth has on organ function, specifically in the abdominal region in organs such as the stomach, pancreas, and the colon/rectum as well as their common metastatic patterns. This study intends to answer the question of: How do the different circumstances of metastatic origin, growth, and spread affect the function of abdominal organs and life expectancy in cancer patients as well as how varied treatment options affect tumor spread?

However, one major limitation related to any cancer related research is the fact that it is a topic which is actively being studied as there still isn't much knowledge as to its specific causes or the factors which influence the severity of its progression. For example, in metastatic cancers, there is much unknown information on which factors influence the distance as to which the tumor spreads away from its origin or which factors affect how quickly the cancer metastasizes. The research we have currently has been able to pinpoint certain proteins and pathways the cancer cells use, but we still don't know the extent to their function or how the tumors have manipulated the body's natural systems. Most research done on this topic focuses on how the tumor spreads to try to find cures and drugs to inhibit the pathways and slow down the cancer progression, increasing the life expectancy. When the cancer reaches stage IV, or the metastatic stage, there is a slim chance of being able to cure the cancer; so the focus is shifted to slowing down and containing the tumor's spread to increase the patient's life span.

Tumor microenvironment

To understand how tumors grow and develop, it is first important to understand the tumor microenvironment. This is the interaction between the malignant, cancer affected cells, and the non-malignant/stromal cells, which are unaffected cells. There are numerous different groups of cells which make up the tumor microenvironment which include, firstly, the malignant cells, cells of the immune system, the tumor vasculature (lymphatic and blood vessels), fibroblasts, adipocytes, and pericytes. Some of these cells indicate good prognosis, while others indicate otherwise. The tumors manipulate these cells by using hormones to attract specific cells, which consequently assist in tumor growth by aiding them in acquiring nutrients and oxygen (Balkwill et al., 2012).

Table 1. Shows the functions and locations of the different cells which make up the tumor microenvironment (Balkwill et al., 2012).

Cell types	Functions
T lymphocytes	Found within and in surrounding mass around the tumor- high numbers of cytotoxic CD8+ memory T cells and $CD4^+$ T helper 1 cells are associated with good prognosis
B lymphocytes	Found in the margin of tumors but more often in the structures adjacent to the tumor site- can inhibit tumor growth by producing antibodies, promoting NK cells and phagocytosis or they can promote tumor growth by producing autoantibodies and tumor growth factors (Yuen et al., 2016)
NK and NKT cells	Innate lymphocytes and are found outside the tumor area- can attack tumor cells directly or can influence function of myeloid

Cell types	Functions
	derived suppressor cells to attack cancer indirectly.
Tumor associated macrophages	TAMs are associated with poor prognosis as they often partner with tumor cells to assist in metastasis and tumor migration and infiltration. They are attracted to the hypoxic parts of the tumors as tumors secrete hormones such as VEGF to attract the TAMs, which contribute largely to tumor angiogenesis.
Myeloid- derived suppressor cells	They are inhibitory immune cells whose phenotypes vary with the tumor environment. Most commonly, they inhibit cytotoxic T cells and change the phenotype of the TAMs to that of a tumor promoting phenotype.
Dendritic cells	Function in antigen processing- have different functions depending on which region of the tumor they reside in In normal tumor regions, they have no effect and are defective, but in hypoxic environments, they are damaged which causes the activation of the immune system and some can suppress T cell functions.
Tumor associated neutrophils	Have both tumor inhibition and progression functions- Can progress tumor growth by promoting angiogenesis, increasing the deterioration of the extracellular matrix, and immune suppression but can also hinder tumor growth by cytokine activation and can eliminate disseminated tumor cells
Cancer associated fibroblasts	They help promote tumor growth by producing growth factors, chemokines, cytokines, ECM components and remodeling enzymes. An increase of them in tumors is seen as an invasive characteristic of the tumor.
Adipocytes	Aid in cancer prognosis by providing fuel in the form of fatty acids to aid in tumor growth and by secreting adipokines to aid in recruitment of tumor cells.
Vascular endothelial cells	Produced by the angiogenic factors- They are the cells which make up the new blood vessels needed for tumor growth
Pericytes	They provide support for the newly forming blood vessels. Low levels of pericytes leads to hypoxia and poor prognosis but higher metastasis as tumors break off to try to find better sources of oxygen and nutrients.
Lymphatic endothelial cells	Found in the growing lymphatic vessels triggered by lymphangiogenesis and aid in tumor progression by altering immune response.

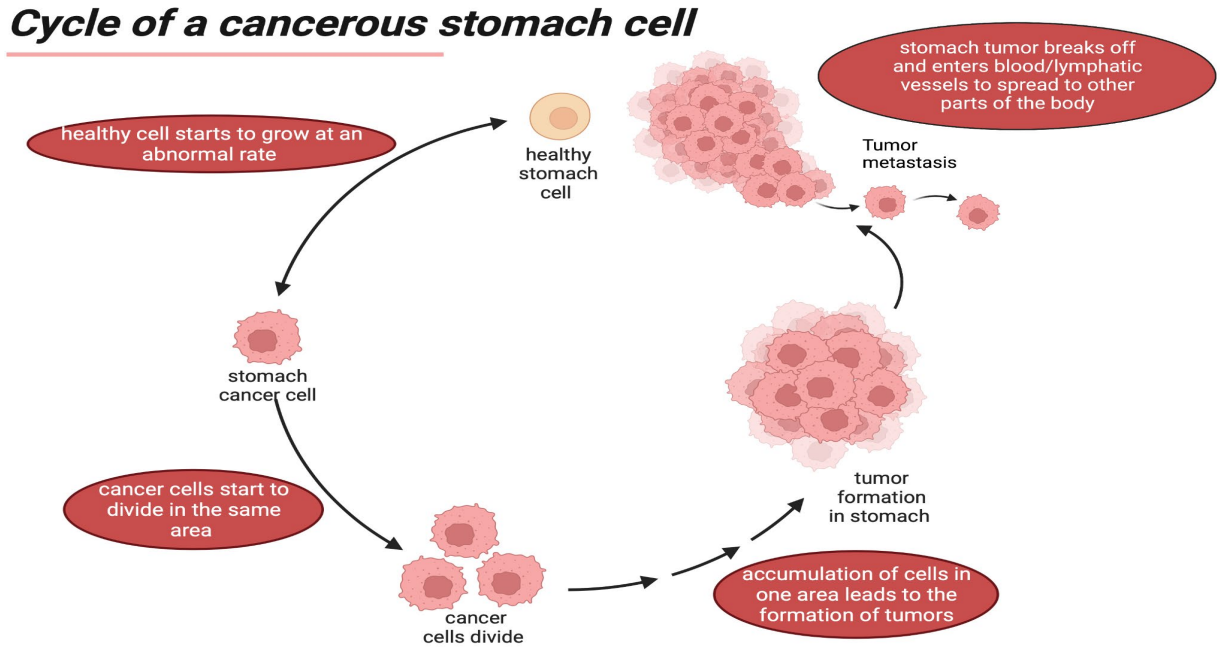

Figure 1. Cycle of a cancerous stomach cell from start to metastasis. Created using biorender.com

Tumor Growth and Spread

As tumors start to develop in size, they require nutrients and sources from the environment such as oxygen from the blood in the blood vessels to grow past 1-2 mm. The tumor grows and develops by using the cells which make up the tumor microenvironment to stimulate three main processes: angiogenesis/lymphangiogenesis, epithelial-mesenchymal transition, and pre-metastatic niche formation. By stimulating these processes, the tumor is able to use the body's mechanisms and pathways to attain the necessary nutrients needed for it to progress.

The tumors start to secrete growth factors, which trigger angiogenesis and lymphangiogenesis to increase the amount of blood and lymphatic vessels in and around the tumor, allowing it to acquire more surface area. Angiogenesis is the formation of new blood vessels. Similarly, lymphangiogenesis is the formation of new lymphatic vessels from preexisting ones. Both processes are controlled primarily by the family of vascular endothelial growth factors, also known as VEGF (Carmeliet, 2005). The VEGF family of hormones are synthesized into proteins to activate the specific pathways unique to stimulate angiogenesis and lymphangiogenesis. To start the synthesis of lymphatic vessel production, the tumors secrete VEGFC/D which bind to their receptor, VEGFR-3. Correspondingly, it secretes VEGFA/C/D which bind to activate the receptor VEGFR-2, which triggers the production of additional blood vessels. While VEGFR-2 and VEGFR-3 are responsible for two different pathways, research has shown that VEGFR-3 is more prominent in tumor metastasis when compared to other receptors, because there is a higher lymphatic vessel density in metastatic tumors. (Matsumoto et al., 2013)

The next process is epithelial-mesenchymal transition, which is the transformation of epithelial cells to mesenchymal ones. The process of forming tissues and organs begins with a single layer of epithelial cells. These cells are what's known as apical base polar, meaning that they have an apical membrane, which faces the outside of the lumen, and a basolateral membrane which faces the opposing side, away from the lumen. (Purohit et al., 2021) Both of the membranes are connected by specialized junctions, but the most important one being adherens. Adherens are responsible for aiding in lateral cell adhesions between epithelial cell sheets. Contrastingly, mesenchymal cells have a front- back polarity and are much less likely to make direct contact with other mesenchymal cells. Unlike epithelial

cells, mesenchymal cells can invade through the extracellular matrix individually, whereas epithelial cells can only move in sheets due to the adherens. This previous characteristic of mesenchymal cells is crucial in understanding why the tumors stimulate this process. A majority of human tumors originate from epithelial cells, which as mentioned earlier, can't break off because of the various junctions. In order for the tumor to break off and travel to other parts of the body to metastasize, they must lose their adhesion to surrounding cells and gain mobility. This is done by converting the epithelial cells to mesenchymal ones, which gives the tumor cells mobility to allow it to break off and travel to invade other regions (Yang & Weinberg, 2008).

Lastly, pre metastatic niche formation is a topic of increased study amongst cancer researchers as it could provide reasons as to why tumors are more likely to spread to certain organs. These niches are the environment and its conditions in a secondary organ which make it more favorable as a target for the metastasis of a primary tumor. The pre metastatic niche consists mainly of resident cells, recruited bone marrow derived cells, soluble factors, and extracellular vesicles. Out of these cells, the recruited bone marrow derived cells, also known as BMDCs, are the most abundant and important in the niche formation. In a research experiment done on mice, it was observed that prior to tumor injection, BMDCs were observed in small quantities around the lung; after tumor implantation but before the tumor cells arrived, a higher count of BMDCs were observed in alveoli and the terminal bronchioles, which were the most common sites for future metastasis. By understanding the causes of the niche formation, it will be possible to find the causes behind the patterns of metastatic spread (Wang et al., 2019).

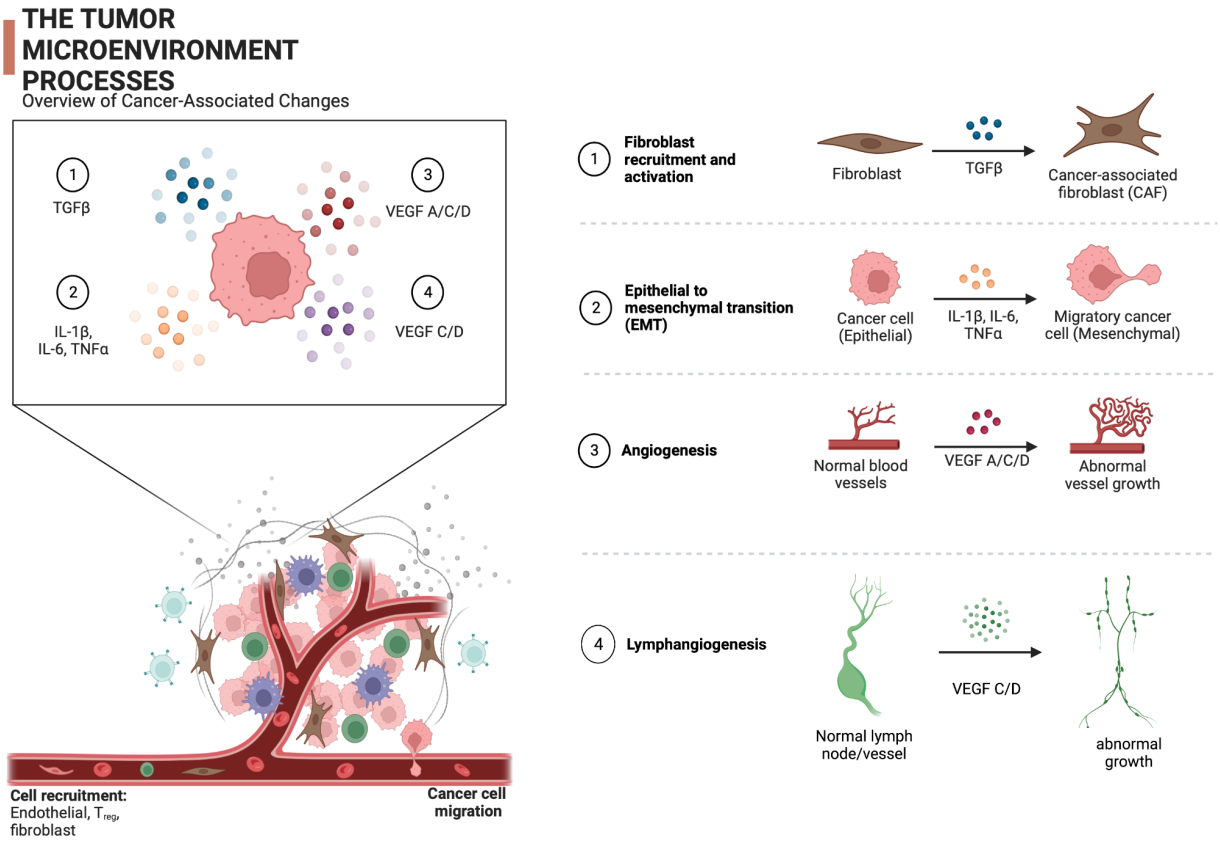

Figure 2. The tumor microenvironment processes. Created using biorender.com

Common Metastatic Patterns

The most commonly targeted organs for metastasis include the liver, lung, bone, and the brain, which can be seen in the diagram below. There is also a notable trend among cancers which originated in the abdominal organs as the most common sites for metastasis were the liver, lung, and peritoneum. Most cancer types are more likely to metastasize to these specific organs, but there are some organs which are not common sites of metastasis such as the skin, ovaries, and the spleen. The distance of metastatic spread has two main factors, "intrinsic ones such as the ability of the cancer cells to interact with the environment which allow them to cross physical barriers, survive in distant sites, engage with a distinct organ specific cell type, and eventually overtake the host tissue," and extrinsic ones "enabling cancer cell access to organs, such as circulation patterns and vascular wall accessibility"(Obenauf & Massagué, 2015). The tumor microenvironment also has a major influence on the common metastatic organ patterns, as seen in the pre metastatic niche formation of different organs. Additionally, cancerous cells express certain factors such as proteins or other molecules which trigger the start of multiple pathways, thus allowing the cancer cells to infiltrate the body's systems.

When looking specifically at bone metastasis, bone cells called osteoblasts are known to secrete factors which include CXCL12, RANKL, OPN, and BMPs, which attract cancer cells into the bone marrow. CXCL12 and IGF1 are known to trigger the transduction of the P13K-AKT pathway, which is responsible for increasing the survival of cancer cells in strenuous environments. Other factors which are also expressed by tumor cells such as the EGF receptor ligand epiregulin and the metalloproteinases MMP1 and MMP2, aid in helping the cancerous cells pass through the blood vessels to invade the lung and metastasize.

In lung metastasis, cancer cells, specifically breast cancer and melanoma cells, express multiple proteins and molecules such as SPARC, ANGPTL4, AND cANGPTL4, which enhance the endothelial to mesenchymal cell transition, further speeding up the process of metastasis. Other factors which are also expressed by tumor cells such as the EGF receptor ligand epiregulin and the metalloproteinases MMP1 and MMP2, aid in helping the cancerous cells pass through the blood vessels to invade the lung and metastasize.

The liver is the most common site of metastasis in tumors, mainly in the abdominal region. The organs in that region are a part of the Enterohepatic circulation, which is a "process whereby a drug in the liver is secreted into the bile, stored in the gallbladder, and subsequently released into the small intestine, where the drug can be reabsorbed back into circulation and subsequently returned to the liver"(Science Direct , 2017). Due to this process within the abdominal organs, the tumors which break off and travel in those pathways of circulation, reach the liver first, and get stuck there, which lead them to grow and develop there (Obenauf & Massagué, 2015).

Table 2. Shows the common metastasis sites of different types of cancers (National Cancer Institute, 2020).

Cancer type	Main sites of metastasis
Bladder	Bone, liver, lung
Breast	Bone, liver, lung, brain
Colon	**Liver, lung, peritoneum**
Kidney	Adrenal gland, bone, brain, liver, lung
Lung	Adrenal gland, bone, brain, liver, other lung
Melanoma	Bone, brain, liver, lung, skin, muscle
Ovary	Liver, lung, peritoneum

Cancer type	Main sites of metastasis
Pancreas	**Liver, lung, peritoneum**
Prostate	Adrenal gland, bone, liver, lung
Rectal	**Liver, lung, peritoneum**
Stomach	**Liver, lung, peritoneum**
Thyroid	Bone, liver, lung
Uterus	Liver, lung, peritoneum, bone, vagina

Metastatic patterns in organs in the abdominal region

Pancreas

Pancreatic cancer is one of the deadliest cancers with one of the poorest prognosis; “According to the latest data, a total of 55,440 patients were newly diagnosed with pancreatic cancer, and 44,330 people died from the disease in the United States. In contrast, other cancer types had increases in survival rates, whereas pancreatic cancer survival rates went down” (Ren et al., 2018). This is because most diagnoses are during the latter stages, when the cancer has metastasized to other organs, so the chance of survival is extremely low, and most patients are given between a few months to years to live.

At the pancreatic cancer sites, severe fibrosis, which is caused by a stiff extracellular matrix, leads to stiff stromal cells which causes an “increase in angiogenesis, hypoxia, and compromises anti-tumor immunity” (Piersma et al., 2020). The stiffness, known as Desmoplasia, of the extracellular matrix leads to the tightening of the cytoskeleton, which is a favorable environment for tumor growth. Since the ECM isn't made up of elastic fibers, while the fibers are rearranging, the strands become tighter and tighter, which impacts cell cell communication by decreasing the possibility of long-range communication. This allows the tumor to grow without any growth factors due to a lack of cell communication, thus making this environment favorable for tumor growth.

Colon and rectum

Colorectal cancer is one of the most common cancers in the world and the second deadliest. It ranks “third in terms of incidence (10.2% of all cancer cases worldwide) and second in mortality (9.2% of all cancer mortality) in the world” (Bray, 2018, as cited in Kow, 2019). The most common metastatic site is the liver, and distant metastasis is common multiple years after initial diagnosis. Colorectal cancers have one of the highest rates of recurrence of cancer in the form of distant metastasis.

When the colorectal cancer tumor breaks off of the initial diagnosed area, it travels through the bloodstream in the hepatic veins, which is filtered by the liver, making it the primary and most common site of metastasis. The tumors use the myeloid derived cells, neutrophils, Kupffer cells, and hepatic setallic cells from the pre metastatic niches to spread to the liver. Additionally, for the tumors to grow beyond a certain size, they need oxygen and nutrients which they receive through angiogenesis, which results in an increased amount of vascularization.

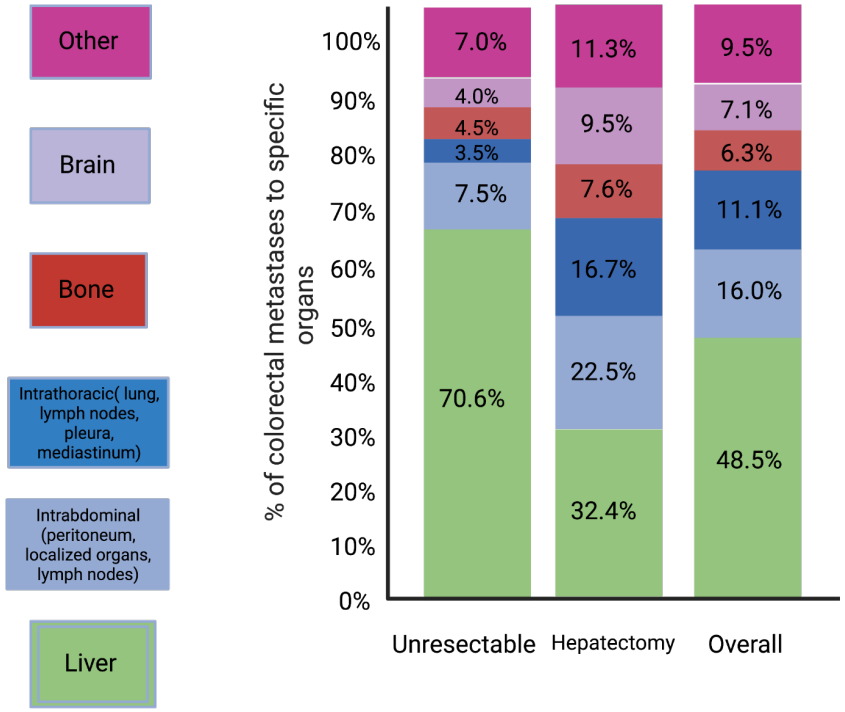

Figure 3. Shows the organ metastasis patterns in colorectal cancers (Ren et al., 2018). Created with BioRender.com

Stomach

Stomach cancer, otherwise known as gastric cancer, is the fifth most common and one of the leading cancers that cause mortality. In 2012, there were 952,000 cases diagnosed, resulting in an estimated 723,000 annual deaths" (McQuire, 2016, as cited in Wang et al., 2021). The most common site of metastasis is the lymph nodes with much research being done on the mechanisms of which the cancer tumor metastasizes to both proximal and distant lymph nodes. The Tumor, node, metastasis system has been used to diagnose gastric cancer as the extent to which the lymph nodes are targeted by metastasis indicates the prognosis of the individual (Aurello et al., 2007). The process of gastric cancer lymph node metastasis has been difficult to understand due to the varied results obtained from experiments. However, recent studies have found the involvement of the RhoA pathway in the migration of a certain growth phenotype in gastric tumors, which has yet to be explored.

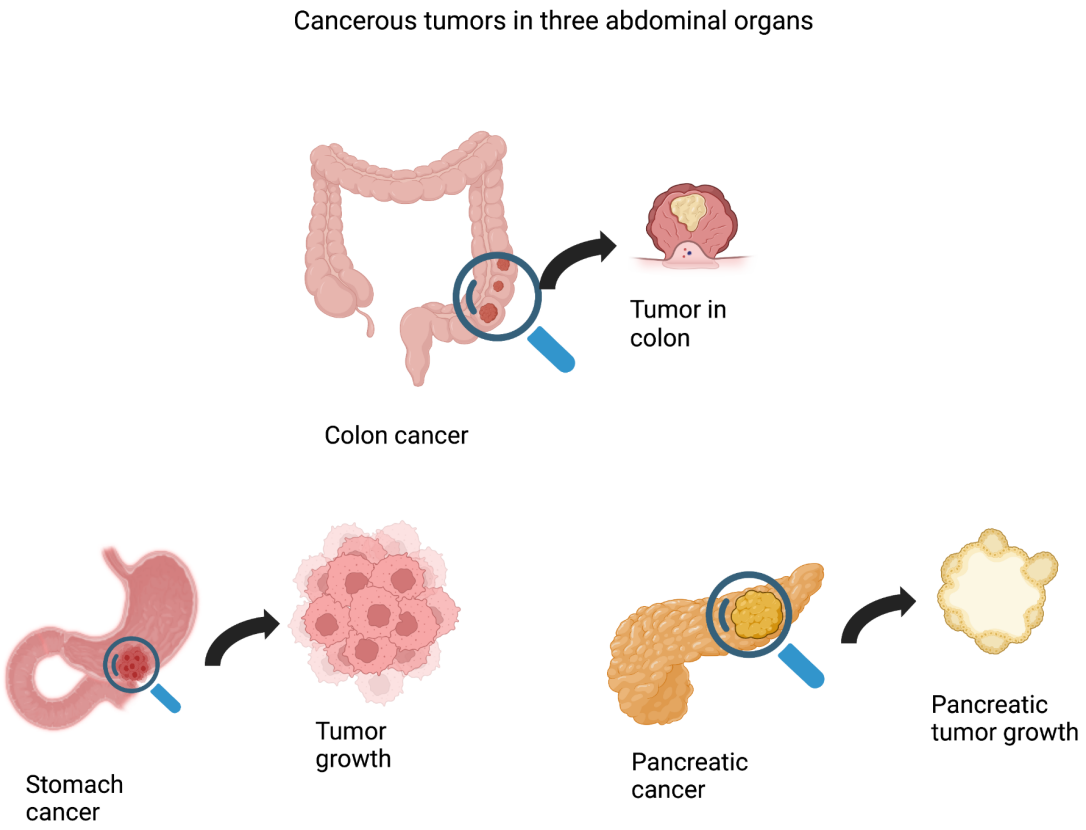

Figure 4: Cancerous tumors in the four main abdominal organs. Created using BioRender.com

Effects of different treatment options

Multiple treatment options have been tested to determine its effects on cancer spread and elimination. However, most of these have resulted in a stimulation of metastatic growth. In diagnosis, necrosis and apoptosis are key indicators of metastasis. This is seen in two pathways: the lack of blood supply leads to necrosis which leads to metastasis or a troubled environment stimulates apoptosis and an immune reaction which also leads to metastasis. The relationship between necrosis and metastasis implies that cell death stimulates the growth and spread of cancer tumors. Similarly, apoptosis is programmed cell death and the proteins associated with it can stimulate breast cancer metastasis if not taken at suitable conditions.

Similarly, immune reaction and inflammation triggers metastasis because the inflammation presents a danger to the tumor cells, causing it to escape in tense situations. After it escapes, it spreads to the other parts of the body. Lastly, the facilitation of blood flow can trigger greater metastasis because the increased blood circulation provides ways for the tumors to flow in the bloodstream, allowing metastasis. However, decreasing angiogenesis and blood circulation can also cause metastasis as it would deprive the cells from their required nutrients, resulting in the tumors metastasizing to search for nutrients (Wang et al., 2015).

One interesting study was conducted on whether knowing the metastatic origin site would have an impact on the treatment of cancer patients. This is known commonly as The Cancer of Unknown Primary or CUP. To test this, researchers studied cancer records from the Swedish Cancer Registry and focused on eight of the most common metastatic cancers: Liver, lung, breast, stomach, bladder, prostate, pancreatic, and colorectal cancers. Overall, it was observed that patients with CUP had poorer survival rates compared to cancers of known primaries with the exceptions

of liver, pancreatic, and stomach cancers, which exhibited great survival rates as CUPs. Metastatic lung cancer showed similar survival rates for both cancers of known and unknown primaries.

The poorer survival rates of patients with CUPs may be because of human intervention. Due to prior attempts to get rid of the cancer, the cells developed adaptations to the environment and previous procedures to make themselves undetectable, making it hard to pinpoint the origin of the cancer and thus, allowing it to spread at a greater rate until it is uncontainable. By mutating numerous times, the cancer cells are able to develop immunity to certain treatments, allowing them to thrive in the body's environment. (Riihimäki et al., 2013).

Conclusion

Overall, this paper intended to answer the question of: How do the different circumstances of metastatic origin, growth, and spread affect the function of abdominal organs and life expectancy in cancer patients as well as how varied treatment options affect tumor spread? It discussed the characteristics of the tumors which enable it to spread beyond its primary site and infiltrate other organs both proximally and distally through growth factors, cell cell transitions, pre metastatic niches, and vessel formation which are all methods used by tumors to metastasize. It details the ways in which the tumors affect the abdominal organs of the stomach, colon/rectum, and the pancreas as they all metastasize the most often to the liver, which indicates proximal metastases. Lastly, it covers the effect of certain treatments on the rate of metastatic spread as they create an environment favorable to the environment.

Since cancer is still being studied and the information we know is continually expanding, it is still quite difficult to find answers to all the questions that these studies imply.To understand more about metastatic cancers, we need to understand why certain patterns or tendencies are the way that they are and what underlying factors influence them. As we experiment and test more, we will be able to answer more questions which provide a segway to an array of them.

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