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Non-Small Cell Lung Carcinoma–A Brief Review and Discussion

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SUMMARY

Non-small cell lung carcinoma (NSCLC) is amongst the most commonly diagnosed cancers and grows throughout the tissues of the lung. This report aims to understand the epidemiology, detection methods, and most effective treatment modalities used in stage three-A NSCLC. NSCLC is an advanced type of lung cancer that grows at a slower rate in comparison to others located in lung tissues. NSCLC can be correlated to smoking cigarettes or e-cigarettes and has displayed patterns of familial aggregation. Detection methods such as low-dose spiral computed tomography provide detailed three-dimensional pictures of the chest cavity without exposing the patient to harsh radiation. Radiotherapy gives positive outlook to non-operable patients, specifically high-dose rate brachytherapy. The effects of this treatment have been explored with cell survival curves. Chemotherapy is also an effective treatment, and the chemical structure of the common drug cisplatin has been explored. Understanding the epidemiology, detection methods, and available treatment modalities help to design effective treatment and prevention plans for stage three-A NSCLC.

ABSTRACT

Lung cancer is the development of cancerous cells within the lung tissue and/or the airway that has potential to further spread. The diagnosis of lung cancer is a multifaceted issue requiring innovative approaches, detection technologies and treatments. Understanding lung cancer's epidemiology provides insight into lung cancer's high prevalence. As most are diagnosed at further developed stages, recognizing the associated factors will provide a better understanding of how to approach treatment.[1] Genetic components such as germline mutations and over expression of epidermal growth factor have been analyzed. Advancements in traditional computed tomography (CT) scanning has contributed to an increased survival rate due to the ability to locate tumours in the most discrete locations.[2] Early detection can occur using a spiral CT scan allowing physicians to perceive the lung cavity from multiple perspectives.[3] Early identification of lung cancer is critical in determining the survival of the patient. Treatments for lung cancer that are declared most effective are radiotherapy, chemotherapy, or chemoradiotherapy.[4] Brachytherapy is an emerging form of radiation therapy that provides radiation in the closest proximity. Cisplatin is the standardized agent, analyzed for its efficiency in the treatment of various stages of lung cancer.[5] This discussion will explore the epidemiology, detection methods, and one of many available treatment methods to understand therapies and prevention mechanisms for stage three-A NSCLC.

Keywords: Lung cancer, non-small cell, smoking, brachytherapy, low-dose spiral CT, cisplatin

INTRODUCTION

The development of cancer involves genetic mutations leading to the growth of tumourous masses. Tumour growth is known to be a fast-acting process. As tumours grow and begin to spread, they pose a threat to neighbouring tissues and organs. Based on the 2020 Canadian cancer statistics regarding Canadian cancer patients, the diagnosis of lung cancer is most common.[6] In addition, lung cancer has been seen to be the leading cause of the death of Canadian cancer patients.[6] The high mortality rate associated with lung cancer is reflective of its low survival rate and high diagnosis rate. A reason as to why the reported survival rate is so low may be due to the delay in detecting the cancerous cells. It has been reported that about 50% of Canadians diagnosed with lung cancer have progressed to stage three or four before detection.[6] This report will specifically focus on non-small cell lung carcinoma (NSCLC), which is the most commonly diagnosed type of lung cancer

NSCLC is a type of lung cancer that grows at a slower pace than others located in the tissues of the lung.[7,8] The major subtypes of NSCLC are squamous cell carci-

noma, large cell carcinoma, and adenocarcinoma.[8] Some common symptoms associated with the diagnosis of NSCLC are shortness of breath, chest pain, and fatigue.[7,8] When first diagnosed, NSCLC can be classified under a spectrum of five stages, which assist in gauging the first line of action. These stages have been identified as values spanning from zero to four; where stage zero indicates extremely early detection and stage four is extremely late. If a patient is diagnosed with stage zero NSCLC, it is due to the discovery of cancerous cells along the lining of the air sacs or airway of the lung; little to no spread has occurred at this stage.[9] On the other hand, a patient diagnosed with stage four NSCLC has cancerous cells in various locations in the body (lymph nodes, adrenal gland, brain, liver). This can be classified as distant metastasis.[10] It is known that patients diagnosed with stage four have a very low survival rate.[9] This report includes a brief discussion on the diagnosis of NSCLC in stage three-A. Specifically, the socioeconomic and genetic factors associated with epidemiology, spiral computed tomography scanning as a detection method, brachytherapy as a radiotherapy option with a reference to cell survival curves, and the use of cisplatin as a chemotherapeutic agent have been discussed.

1. EPIDEMIOLOGY

The frequency of lung cancer diagnosis is a battle the Canadian population has been fighting for several decades. Lung cancer is currently the leading cause of cancer death in Canada, causing approximately 83,300 deaths in 2020.[11] The most common types of lung cancer consist of small cell lung cancer, lung nodules, NSCLC, and mesothelioma.[12]Additionally, rarer forms of lung cancer are seen not to initially develop in the chest cavity but, in other locations of the body known as metastatic cancer development.[12] The Canadian Cancer Society released a report including the 2020 estimated lung cancer statistics that reports the number of new cases and deaths in the Canadian population, along with an estimated five-year survival percentage. They estimated that 15,000 males would be diagnosed, and 11,000 male lung cancer patients would pass away.[13] Further, 14,800 female cases were estimated along with 10,200 female lung cancer related deaths.[13] They estimated the five-year survival rate for males to be 15% in comparison to 22% for females.[13] As previously mentioned, the Canadian population experienced 83,300 deaths due to lung cancer in 2020, a value of approximately 60,000 deaths greater than initially projected.[13] What are the factors that contribute to a mortality rate so substantially different than projected? This review will study both the socioeconomic and genetic factors associated with the diagnosis and mortality of lung cancer amongst the Canadian population.

1.1 Socioeconomic Factors

The World Health Organization (WHO) predicts that the presence of lung cancer on an international spectrum will continue to increase with time due to the significant use of tobacco.[1] Tobacco is seen as one of the primary risk factors associated with the development of lung cancer and many other pulmonary carcinomas as a result of smoking cigarettes.[1] It is often the NSCLC subtype, adenocarcinoma, that has a strong cigarette smoking correlation. The population of tobacco cigarette smoking individuals may be on the decline, but in more recent times there has been a rise in the electronic cigarette (e-cigarette) smoking population, ultimately increasing the risk of developing this deadly disease.[14] Moreover, those who are exposed to second-hand smoke (environmental smoke) are also at a high risk of developing lung cancer.[10] There is no quantity of second-hand smoke that is deemed safe to be around.[10] Second-hand smoke is the primary associated risk factor for the diagnosis of lung cancer in non-smoking individuals.[10] There is a correlation between individuals who smoke and lung cancer diagnosis, although there are other associated risk factors that must be considered. Family history can also contribute to the development of lung cancer. Figure 1 shows a plot of former and current smokers along with the percentage of participants who had quit. An increase in the quitter percentage is apparent through the years of 1999 to 2015 but a decline is observed after 2015.[14] Additionally, the decrease in quitter percentage implies an increase in the current smokers observed in the 2017 data. The study did not clearly dictate the reasons behind why this had occurred, although participants switching to another source of nicotine such as e-cigarettes is a likely observation.[14] This theory is likely as e-cigarettes became more prevalent in Canada between the years of 2015 to 2017 along with Bill S-5 being amended in 2018 permitting for e-cigarettes to contain nicotine.[15]

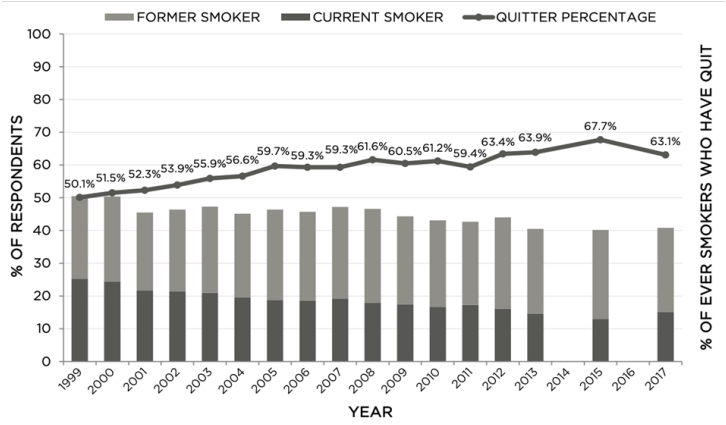

Figure 1. Results of a study conducted by the Centre of Population Health Impact analyzing smoking trends from 1999 to 2017. The percentage of participants who have a history of smoking is

represented by the bars displayed along the x-axis. Dark grey bars represent current smokers and light grey bars represent former smokers. The scatter plot shows the trend of quitter percentage over the years.

1.2 Genetic Factors

Genetic susceptibility to lung cancer remains predominantly elusive, however, there have been various reports on germline mutations associated with lung cancer susceptibility. [16] Particularly in the epidermal growth factor receptor (EGFR) and erb-b2 receptor tyrosine kinase 2 (ERBB2). [16] EGFR is expressed at normal epithelial, neurogenic, and mesenchymal tissue and is a transmembrane receptor tyrosine kinase protein. [17] When EGFR binds to a ligand, it phosphorylates in the intracellular domain, which leads to downstream signal transduction[17]. The over-expression of this gene is associated with NSCLC and is shown to reduce survival and facilitate poor chemosensitivity. [17] In NSCLC, intracellular EGFR overexpression is observed in 43-89% of cases. [17] There has also been evidence that NSCLC shows familial aggregation after tobacco smoking adjustments. [18] There have been linkages to families with aggregation of lung cancer to a region on chromosome 6q23-25. [18] The risk increases 1.51-fold for individuals with first degree relatives that smoke compared to those without a family history of smoking. [19]

2. METHOD OF DETECTION

In modern-day medicine, the primary focus lies in a detection modem that prioritizes the safety of the patient while still ensuring that they are receiving the highest quality of care. A CT scan provides the physician with highly detailed images of the focus area in order to identify the potential presence of a tumour in both two-dimensional slices and three-dimensional images of the whole organ or cavity. [20]

2.1 Methods Behind CT Scanning

As previously mentioned, both sliced and whole images of the desired area are produced by the CT scanner. With each rotation, the CT develops a two-dimensional image using mathematical techniques. [21] The process to produce these images is facilitated by a rotating x-ray source as shown in Figure 2. The source will rotate in a circular motion around the circumference of the x-ray tube where the patient lays. The x-ray source could possibly be an element of either barium, iodine or gold composed in an aqueous solution. [22] Located in front of the x-ray source is a bowtie filter. This works to alter the incoming frequency of the source by adjusting the angle it is distributed on the patient to create a balance within the exposed photon flux on the detector array. [22] The bowtie filter can be modified in many shapes and sizes depending on the type of image that is desired to be produced. [23] The CT scanner uses fan-beam geometry to emit the radiation allowing for a distributed flux upon the detector array. [23] The linear detector array moves in a circular motion in a 180° displacement of the x-ray source to develop an image as the x-ray source flows through the patient. [24] This setup allows for clear images or slides of the patient to be developed on the technician's computer.

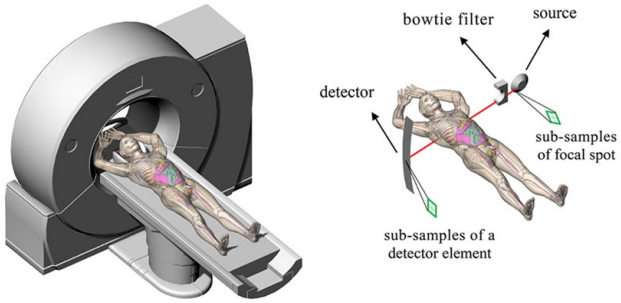

Figure 2. Shown on the left is what the CT scanner looks like on the outside while the image on the right side shows the mechanisms located within the scanner to facilitate the development of the images.[25]

2.2 Low-Dose Spiral CT Scanning

In terms of lung cancer detection, an emerging type of computed tomography (CT) scanning known as low-dose spiral scans has been praised for its ability to provide detailed images of intended locations while emitting far less radiation to the patient. [26] As tumours in the lung can sometimes be difficult to detect, the use of a low-dose spiral CT scanner makes the detection of cancers a far less challenging task. [27] A low-dose spiral CT scan continuously rotates around the patient in a helix shape to develop three-dimensional images of the chest cavity, allowing the physician to observe many different perspectives. [24] Some benefits to using this method include less radiation exposure to the patient and a greater ability to detect tumours in early developmental stages. [28] The low-dose CT scanner provides a lower amount of radiation emission, an average value of 2 mSv in comparison to traditional CT scanning, an average value of 7 mSv. [28] Traditional CT scanning emits approximately three and a half times the amount of radiation putting the patient at greater risk. The traditional CT radiation emittance value is equivalent to two full years of background radiation exposure emitted to the patient at one given time. [29] Although the dose of radiation received from this low-dose CT scanning is higher than traditional chest x-ray scanning, the benefits of undergoing this detection technique outweigh the cons tremendously. [28] The advantages of this scanning technology can be seen in a study conducted by Henschke et al. (1999) which included 1,000 participants who had all declared they are currently smokers. The study concluded with an 85% detection rate for stage one lung cancer discovered using a low-dose spiral CT scan. [30] Low dose CT scanning allows for clear imaging, preventing the need

for multiple scans during the detection process which ultimately reduces radiation exposure.

3. TREATMENT METHODS

In today's day and age, the appropriate technology has been developed to attack cancers that have previously been labeled as incurable. With the knowledge scientists hold today, innovative approaches to treating and potentially curing these kinds of cancers have developed promising solutions. The use of radiotherapy alongside chemotherapy is called chemoradiotherapy and has been known for its effective and safe treatment against cancer.[31] The chemotherapy treatment helps to weaken the cancerous cells, making the radiation therapy the patient is receiving much more effective. Some suggest chemoradiotherapy is one of the most promising treatment plans for those diagnosed with lung cancer, specifically NSCLC.

3.1 Radiotherapy

Radiotherapy is a form of cancer treatment that exposes doses of radiation to the cancerous site specifically the tumour. This impacts the growth of cancerous cells making it challenging for cell reproduction. When deciding between different radiotherapeutic approaches to NSCLC, many options present themselves with unique benefits and disadvantages. Brachytherapy is a radiotherapeutic approach that begins with placing a small-sized seed of radioactive matter either locally or directly into the targeted location.[31] The placement is done surgically using a bronchoscope that is put into the mouth and into the bronchi, where the tumour site is located to ensure the radioactive material is as close as possible.[32] The use of a bronchoscope is best for this procedure as it is a thin, flexible device that is equipped with a camera and light fixture, providing medical staff with the ability to see inside the lungs.[33]

A physician may choose HDR-B therapy as it is one of the most effective radiotherapeutic option.[31] This is because the radioactive material travels a small distance to get to the desired site, posing little risk to the neighbouring organs.[31] Most frequently, iridium-192 is used as the radioisotope in this procedure, which has a negative beta decay model (Equation 1).[34] Negative beta decay is present when a neutron transforms into a proton (e), initiating the release of a gamma-ray photon (γ) and an electron antineutrino (υ_e).[35]

$$_{77}^{192}Ir \rightarrow {}_{78}^{192}Pt + \gamma + \upsilon_e + {}_{-1}^{0}e \qquad (1)$$

HBR-B is seen as a valuable asset to the treatment of NSCLC as it provides treatment with the greatest, strongest force. This gives an optimistic outlook for many of these patients having such short life expectancies due to an inoperable tumour. HBR-B is seen as a promising solution due to its short-ranged gamma rays which allow for an increased amount of accuracy.[36] HBR-B's accuracy helps to target the maximum dosage towards the desired region, putting surrounding tissues at less of a risk.[36] HBR-B has been frequently chosen over low-dose-rate brachytherapy by physicians because of its high efficiency and safety rankings. Most often, HBR-B is not the sole treatment option. HBR-B is used simultaneously with external beam radiotherapy (EBT) to provide the patient with a boost in their treatment timeline.[37] Together, both EBT and HBR-B are strong primary treatment plans with a tolerable toxicity emittance for patients diagnosed with NSCLC that are ineligible for surgery. One limitation of pursuing this treatment is its restricted access.[38] Few cancer treatment centers are equipped with the technology to pursue a treatment like this one making physicians think twice about selecting HBR-B.[37]

3.2 Cell Survival Analysis During HBR-B Treatment

Normal tissue and cancerous tissue react very differently to radiation therapy. Radiation therapy damages DNA to the point where a cell cannot divide or multiply, and because tumours grow faster than normal cells, they are the first to be damaged.[39] However, there is a point where normal cells are destroyed much faster than cancerous cells. To define this point, we can utilize a linear-quadratic model and determine the surviving fraction of cells after an absorbed dose, given in Gray (Gy). The ratio of surviving cells is given by the dosage (D) proportional to two coefficients, alpha (α) and beta (β), where α is proportional to D, and β is proportional to (D^2). Our model assumes that normal cells have an α/β ratio of 3, shown in Equation 2, and cancerous cells have an α/β ratio of 10, shown in Equation 3.

$$n(t) = -0.2473t - 0.0824t^2 \qquad (2)$$

$$c(t) = -0.4t - 0.04t^2 \qquad (3)$$

Figure 3 models the relationship of surviving cells versus dose of radiation therapy in Gy. The equal survival ratio, where normal and cancerous cells are equally damaged, occurs at 3.601Gy. At this dose, the ratio of surviving cells is -1.96. It is extremely important that radiation dosages do not surpass this, as normal cells will be destroyed faster than cancerous cells.

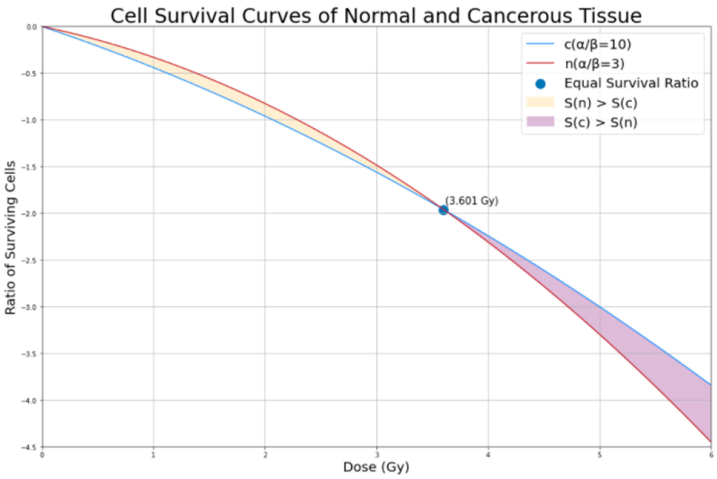

Figure 3. Cell survival curves for normal tissue and cancerous tissue utilizing Equation 2 and 3. The equal survival ration occurs at 3.601Gy. Radiation doses greater than 3.601Gy will destroy more normal tissue than cancerous tissue. This graph was developed using Python 3.

From this model we were able to determine the optimal dose, where there is the greatest amount of surviving normal tissue and least amount of cancerous tissue. The optimal dose is 1.8Gy and can be displayed by number of treatments to determine when cancerous cells are destroyed. Figure 4 assumes a starting point of 10^8 cells and shows the number of surviving cells decrease as number of treatments increase. Normal tissue persists as the greater number of surviving cells until treatment seven, where cancerous cells have a higher survival rate. At this point, normal tissues are depleted at greater quantities than cancerous tissues and the treatment becomes toxic.

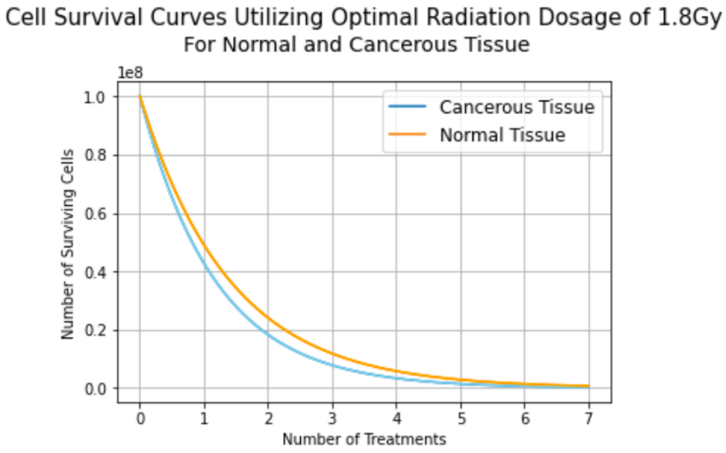

Figure 4. Normal and cancerous tissue undergoing radiation therapy of 1.8Gy displayed over a number of treatments. This model assumes a starting point of 10^8 cells. This graph was developed using Python 3.

3.3 Chemotherapy

Chemotherapy is often used in combination with other techniques such as surgery and radiation to treat stage three-A NSCLC. The chemotherapeutic drug this review is focusing on is cisplatin, often combined with an alternate drug such as gemcitabine or paclitaxel to reduce drug toxicity and drug resistance.[5,40] For stage three-A NSCLC patients, chemotherapy and surgery are used if they cannot be given radiation. Stage-three-B and three-C patients may be given chemotherapy if they are too unwell to undergo chemoradiotherapy or radiation therapy.[40] Cisplatin is considered an irritant and causes inflammation to the vein it is administered in.[5] It also may have harsh side effects such as nausea, vomiting, kidney toxicity, low blood count, ototoxicity, and blood culture abnormalities.[5] Cisplatin can be used to treat carcinomas, germ cell tumours, lymphomas, and sarcomas.[5] Cisplatin is composed of a doubly charged platinum ion surrounded by four ligands as seen in Figure 5.[5] The chloride ligands on the right form leaving groups, allowing the ion to form bonds with DNA bases, and the ligands on the left form stronger interactions with the platinum ion.[5] Carboplatin is a less toxic, yet very similar drug to cisplatin.[41] It differs from cisplatin by containing bidentate dicarboxylate ligand instead of the chloride ligands.[5] This reduces DNA reactivity and induces slower kinetics.[5]

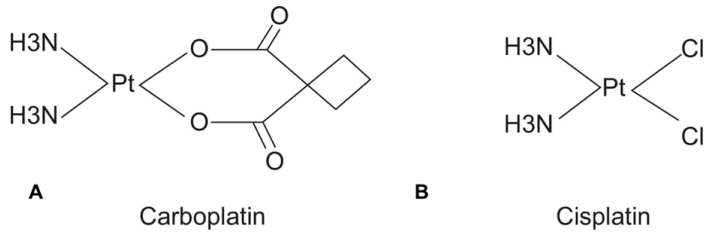

Figure 5. Showing the chemical structure of (A) carboplatin with bidentate dicarboxylate ligands and (B) cisplatin with chloride ligands.[41]

Cisplatin applies cytotoxic effects by forming DNA adducts including mono, inter, and intrastrand cisplatin DNA cross-links that affect the cell cycle at S, G1, or G2-M phase.[42] It becomes active once it enters the cell, and the chloride atoms on the right ligands are displaced by H_2O molecules.[5] The products of this displacement are electrophiles which bind to the N7 reactive center on purine residues.[5] This causes DNA damage and the 1,2-intrastrand crosslink, which is primarily responsible for stimulating this bondage, resulting in apoptosis by preventing the cell from repairing and replicating itself.[42] The adducts between 1,2-intrastrand and purine residues represent 90% of all adducts.[5] The increased metabolic activity and mitochondrial malfunction prompts cancerous cells to display high oxygen species reactivity.[5] Oxidative stress is the most prominent mechanism for cisplatin toxicity

and can cause damage to cellular proteins, lipids, and DNA, which lead to fatal lesions.[5] The mitochondria becomes damaged, mostly from the oxidative stress due to cisplatin losing its sulfhydryl group and taking in calcium, which reduces membrane potential.[5] Resistance of cancer cells to cisplatin chemotherapy after the first round of therapy is mediated by microRNAs creating a resistivity and sensitivity to the drug.[44] The stimulation of nuclear factor erythroid 2-related factor 2 (Nrf2) protects cancer cells from cytotoxic impacts by translocating to the nucleus, binding to antioxidant response element, and upregulating antioxidant and detoxifying enzymes.[43] Researchers are continuously looking for strategies to inhibit cisplatin resistance. This includes altering drug delivery platforms and exploring nano- and microcarriers.[43]

CONCLUSION

With extensive research and advancements through epidemiological lenses, detection methods, and treatment modalities, we can efficiently design treatment and prevention plans that benefit the general population. Lung cancer epidemiology includes determinants, distribution, incidence rates and frequency of this disease. The study of the associated epidemiology of lung cancer provides an understanding behind the factors which contribute to its high incidence and mortality rates observed today on an international scale. It is critical to acknowledge the trends this disease currently possesses in addition to predisposing risks and other causes, in an attempt to decrease future incidence. It has been concluded that there is a contributing genetic component alongside the diagnosis of lung cancer within a family.[18] With this, it becomes challenging to develop a sole cure for a disease that has associated mutations which are very unpredictable. Further, it has been concluded that the 6q23-25 chromosome has been studied for its linkages between lung cancer diagnosis within the family tree making it a crucial factor to analyze in determining the genetic susceptibility for lung cancer.[18]

Lung cancer begins with localized tumour growth that can become metastatic as the severity of cancer increases. With this, it is extremely important to ensure that the first approach in the detection process is as clear and informative as possible to prevent the development of a worsened condition and ultimately, further spread. An effective imaging technique is spiral CT scanning, where both two-dimensional and three-dimensional images are produced, providing physicians with multiple perspectives of both the whole chest cavity and individual cross sections.[24] In the present day, this imaging technique has come to be extremely common as it allows for conclusions to be developed in a timely manner, preventing delay in the treatment process.

As most of the lung cancer cases diagnosed are late stages, it is extremely crucial that treatment plans are developed for each unique patient situation.[1] Both radiotherapy and chemotherapy have been seen as effective treatment options. Although, the most effective treatment is known as a combination between both radiotherapy and chemotherapy, a term coined chemoradiotherapy[4]. Brachytherapy is known to be the most precise in issuing radiation to the desired location within the body.[1] Inserting radioactive material near or embedded into the cancerous site prevents any unnecessary exposure to neighbouring tissues and organs.[31] Chemotherapy has been acknowledged for its abilities in the treatment of lung cancer, specifically the use of the drug cisplatin that can tremendously limit the reproduction of cancerous cells.[40] Many medical advancements have been made throughout this past century involving both treatment plans and associated technology which have contributed to lower incidence rates. Although, there still lie many unanswered questions about the most effective treatment guidelines that apply to every patient.

Lung cancer holds a significant risk to those with a history of smoking both traditional and electronic cigarettes. Knowing this, the importance of a treatment which is less harmful to neighbouring organs and tissues such as HBR-B is critical in mitigating the associated treatment impacts. Moreover, the use of cisplatin is most effective as a treatment when combined with radiotherapy. Further research into pharmacotherapeutic approaches to the treatment of lung cancer are strongly encouraged. Despite the complexity lung cancer holds, medical advancements in the long-term care and treatment of this disease have been very effective and will continue to decrease the observed incidence and mortality rates.

APPENDIX

Using the Keywords, Lung Cancer, Non-Small Cell, Smoking, Brachytherapy, Low-dose Spiral CT, Cisplatin, the authors were able to locate articles to compose this piece. National Center for Biotechnology Information's MeSH database was the primary database for our search. Through this database the selection of many subheadings also helped to refine our search. Each manuscript used in this piece was read by both authors to validate its relevance to this topic and strength in the science community. Taking an interdisciplinary approach to this review was of primary focus. Incorporating the disciplines of Life Science, Physics, Chemistry, Epidemiology and Mathematics to strengthen our understanding of NSCLC was our primary goal.

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REFERENCES

(1) Dela Cruz CS, Tanoue LT, Matthay RA. Lung cancer: epidemiology, etiology, and prevention. Clin Chest Med. 2011 Dec;32(4):605–44.

(2) Purandare NC, Rangarajan V. Imaging of lung cancer: Implications on staging and management. Indian J Radiol Imaging. 2015;25(2):109–20.

(3) Paranjpe DV, Bergin CJ. Spiral CT of the lungs: optimal technique and resolution compared with conventional CT. AJR Am J Roentgenol. 1994 Mar;162(3):561–7.

(4) Conibear J. Rationale for concurrent chemoradiotherapy for patients with stage III non-small-cell lung cancer. Br J Cancer. 2020 Dec 1;123(S1):10–7.

(5) Dasari S, Tchounwou P. Cisplatin in cancer therapy: Molecular mechanisms of action. 2014;740(5):364–78.

(6) Government of Canada. The Daily — Canadian cancer statistics, 2020 [Internet]. 2020 [cited 2021 Mar 31]. Available from: https://www150.statcan.gc.ca/n1/daily-quotidien/200922/dq200922b-eng.htm

(7) Government of Canada. What is Lung Cancer [Internet]. Lung Cancer. 2019. Available from: https://www.canada.ca/en/public-health/services/chronic-diseases/cancer/lung-cancer.html

(8) National Institute of Biomedical Imaging and Bioengineering (NIBIB). Computed Tomography (CT) [Internet]. n.d. [cited 2021 Mar 7]. Available from: https://www.nibib.nih.gov/science-education/science-topics/computed-tomography-ct

(9) Detterbeck F, Boffa D, Kim A, Tanoue L. The Eighth Edition Lung Cancer Stage Classification. Chest Journal. 2017 Jan;151(1):193–203.

(10) Brown KG. Lung Cancer and Environmental Tobacco Smoke: Occupational Risk to Nonsmokers. Environmental Health Perspectives. 1999 Dec;107:885.

(11) Brenner DR, Weir HK, Demers AA, Ellison LF, Louzado C, Shaw A, et al. Projected estimates of cancer in Canada in 2020. CMAJ. 2020 Mar 2;192(9):E199–205.

(12) John Hopkins Medicine. Lung Cancer Types | Johns Hopkins Medicine [Internet]. n.d. [cited 2021 Mar 31]. Available from:https://www.hopkinsmedicine.org/health/conditions-and-diseases/lung-cancer/lung-cancer-types

(13) Canadian Cancer Society. Lung cancer statistics - Canadian Cancer Society [Internet]. n.d. [cited 2021 Mar 31]. Available from: https://www.cancer.ca/en/cancer-information/cancer-type/lung/statistics/?region=pe

(14) Reid JL, Hammond D, Tariq U, Burkhalter R, Rynard VL, Douglas O. Tobacco Use in Canada: Patterns and Trends, 2019 Edition. 2019;(2019 Edition):118.

(15) Government of Canada H. Bill S-5, an Act to amend the Tobacco Act and the Non-smokers' Health Act and to make consequential amendments to other Acts: An Overview [Internet]. 2017 [cited 2022 Jan 14]. Available from: https://www.canada.ca/en/health-canada/programs/consultation-regulation-vaping-products/s5-overview-regulate-vaping-products.html

(16) Lu S, Yu Y, Li Z, Ding Y, Shao Y, Jian H. EGFR and ERBB2 Germline Mutations in Chinese Lung Cancer Patients and Their Roles in Genetic Susceptibility to Cancer. Journal of Thoracic Oncology. 2019;14(4):732–6.

(17) Bethune G, Bethune D, Ridgway N, Xu Z. Epidermal growth factor receptor (EGFR) in lung cancer: an overview and update. Journal of Thoracic Disease. 2010;2(1):48–51.

(18) Musolf A, Simpson C, Andrade M, Mandal D, Gaba C, Yang P, et al. Familial Lung Cancer: A Brief History from the Earliest Work to the Most Recent Studies. 2017;8(1).

(19) Coté M, Liu M, Bonassi S, Zhang Z-F, Etzel C. Increased risk of lung cancer in individuals with a family history of the disease: A pooled analysis from the International Lung Cancer Consortium. 2012;48(13):1957–68

(20) Jacques S, Christe B. Healthcare technology basics. In: Introduction to Clinical Engineering [Internet]. Elsevier; 2020 [cited 2022 Jan 14]. p. 21–50. Available from: https://doi.org/10.1016/B978-0-12-818103-4.00002-8

(21) National Institute of Biomedical Imaging and Bioengineering (NIBIB). Computed Tomography (CT) [Internet]. n.d. [cited 2021 Mar 7]. Available from: https://www.nibib.nih.gov/science-education/science-topics/computed-tomography-ct

(22) FitzGerald PF, Colborn RE, Edic PM, Lambert JW, Torres AS, Bonitatibus PJ, et al. CT Image Contrast of High-Z Elements: Phantom Imaging Studies and Clinical Implications. Radiology. 2015 Sep 10;278(3):723–33.

(23) Liu F, Yang Q, Cong W, Wang G. Dynamic bowtie filter for cone-beam/multi-slice CT. PLoS One. 2014;9(7):e103054.

(24) White KS. Invited article: Helical/spiral CT scanning: a pediatric radiology perspective. Pediatr Radiol. 1996 Jan 1;26(1):5–14.

(25) Samei E, Harrawood B, Sharma S, Kapadia A, Segars WP. DukeSim: A Realistic, Rapid, and Scanner-Specific Simulation Framework in Computed Tomography – EMBS [Internet]. 2018 [cited 2021 Mar 28]. Available from: https://www.embs.org/tmi/articles/dukesim-a-realistic-rapid-and-scanner-specific-simulation-framework-in-computed-tomography/

(26) Marshall HM, Bowman RV, Yang IA, Fong KM, Berg CD. Screening for lung cancer with low-dose computed tomography: a review of current status. J Thorac Dis. 2013 Oct;5 Suppl 5:S524-539.

(27) Banerjee S. Multi-slice/helical computed tomography for lung cancer screening. Issues Emerg Health Technol. 2003 Jun;(48):1–4.

(28) Larke FJ, Kruger RL, Cagnon CH, Flynn MJ, McNitt-Gray MM, Wu X, et al. Estimated Radiation Dose Associated With Low-Dose Chest CT of Average-Size Participants in the National Lung Screening Trial. American Journal of Roentgenology. 2011 Nov;197(5):1165–9.

(29) Yu L, Liu X, Leng S, Kofler JM, Ramirez-Giraldo JC, Qu M, et al. Radiation dose reduction in computed tomography: techniques and future perspective. Imaging Med. 2009 Oct;1(1):65–84.

(30) Henschke C, McCauley D, Yankelevitz D, Naidich D, McGuinness G, Miettinen O, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. 1999;354(9173):99–105.

(31) Thomadsen B, Miller R. Brachytherapy Physics. In: Comprehensive Biomedical Physics [Internet]. Elsevier; 2014 [cited 2022 Jan 18]. p. 315–81. Available from: https://doi.org/10.1016/B978-0-444-53632-7.00926-6

(32) Paradis TJ, Dixon J, Tieu BH. The role of bronchoscopy in the diagnosis of airway disease. J Thorac Dis. 2016 Dec;8(12):3826–37.

(33) Vachani A, Sterman DH. Bronchoscopy. In: Clinical Respiratory Medicine [Internet]. Elsevier; 2008 [cited 2022 Jan 18]. p. 177–96. Available from: https://doi.org/10.1016/B978-032304825-5.10012-1

(34) Pouliot J, Beaulieu L. Modern Principles of Brachytherapy Physics. In: Leibel and Phillips Textbook of Radiation Oncology [Internet]. Elsevier; 2010 [cited 2022 Jan 18]. p. 224–44. Available from: https://doi.org/10.1016/B978-1-4160-5897-7.00013-5

(35) Kónya J, Nagy NM. Radioactive Decay. In: Nuclear and Radiochemistry [Internet]. Elsevier; 2018 [cited 2022 Jan 18]. p. 49–84. Available from: https://doi.org/10.1016/B978-0-12-813643-0.00004-4

(36) Chargari C, Deutsch E, Blanchard P, Gouy S, Martelli H, Guérin F, et al. Brachytherapy: An overview for clinicians. CA Cancer J Clin. 2019 Sep;69(5):386–401.

(37) Rochet N, Hauswald H, Stoiber EM, Hensley FW, Becker HD, Debus J, et al. Primary radiotherapy with endobronchial high-dose-rate brachytherapy boost for inoperable lung cancer: long-term results. Tumori. 2013 Apr;99(2):183–90.

(38) Aygun C, Weiner S, Scariato A, Spearman D, Stark L. Treatment of non-small cell lung cancer with external beam radiotherapy and high dose rate brachytherapy. International Journal of Radiation Oncology*Biology*Physics. 1992 Jan 1;23(1):127–32.

(39) Baskar R, Lee KA, Yeo R, Yeoh K-W. Cancer and radiation therapy: current advances and future directions. Int J Med Sci. 2012;9(3):193–9.

(40) Hanna N, Neubauer M, Yiannoutsos C, McGarry R, Arseneau J, Ansari R, et al. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. J Clin Oncol. 2008 Dec 10;26(35):5755–60.

(41) Fonseca de Sousa G, Wlodarczyk S, Monteiro G. Carboplatin: molecular mechanisms of action associated with chemoresistance. 2014;50(4).

(42) Aldossary SA. Review on Pharmacology of Cisplatin: Clinical Use, Toxicity and Mechanism of Resistance of Cisplatin. Biomed Pharmacol J. 2019 Mar 28;12(1):07–15.

(43) Ashrafizadeh M, Zarrabi A, Hushmandi K, Hashemi F, Moghadam ER, Owrang M, et al. Lung cancer cells and their sensitivity/resistance to cisplatin chemotherapy: Role of microRNAs and upstream mediators. Cellular Signalling. 2021 Feb;78:109871.

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