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Review Article

New Radiation Therapy Techniques in Non-small Cell Lung Cancer

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Abstract

The evolution to novel teams of treatment with radiations and the design of new techniques for the planning of the therapy of the patients with lung cancer has allowed to find the balance between the toxicities of the organs of risk and the therapeutic dose. The presence of these organs reveille, it can impede the capacity to administer a complete program of radiotherapy. The coming of new teams for the acquisition of more precise images and the development of such advanced techniques as the radiotherapy of modulated intensity (IMRT), Volumetric Modulated Arc Therapy (VMAT) and the Stereotactic Body Radiation (SBRT), they achieve the increment of radiation dose to the tumoral region, it improves the tolerance of the treatment fields, it reduces the dose of radiations to receive for the organs of risk, guaranteeing this way a better objective answer. The objective of the present revision is to promote the knowledge of the new radiotherapy techniques and to foment this way its application in the treatment of the cancer of lung of non-small cells with the purpose of improving the grade of objective answer and the survival of the patients.

Keywords: Lung Cancer; Radiotherapy; Radiotherapy of Modulated Intensity; Organs of Risk

Introduction

Lung cancer (PE) represents a health problem for many countries around the world. Most cases are diagnosed in advanced stages, for which there are no curative treatments; and although there are notable advances in the knowledge of risk factors, pathophysiology, genetic alterations and chemotherapy and radiotherapy treatment, as well as the development of new target therapies, the benefit achieved in terms of long-term survival is little satisfactory. CP is the leading cause of cancer death worldwide [1-3]. It has been estimated that about 2 million cases are diagnosed annually per year worldwide, almost 60% in underdeveloped countries [3,4]. While the incidence and mortality in men is much higher than in women, in some countries, lung cancer mortality in women already exceeds breast cancer [3,5].

In recent decades, multiple advances have been developed:

- In diagnosis,
- In the classification of the different subgroups,
- In surgical treatments,
- In systemic treatments •(chemotherapy and targeted therapies)

- In treatment with radiotherapy

Radiotherapy is the most used treatment in patients with lung cancer, since it has a very important role both in the early stages, used in exclusive form or combined with QT with curative objective, as well as in advanced stages with palliative criteria [3]. Approximately 80% of patients diagnosed with lung cancer will receive treatment with rhadiotherapy at some point in their evolution [3.6,7]. The development of radiotherapy has allowed advances that have improved therapeutic outcomes. These advances have been made through better protection of normal tissues, a better definition of the therapeutic target of these tumors that move normally with breathing and an effective association with different drugs (chemotherapy, targeted drugs and immunotherapy) [3].

Intensity-Modulated Radiotherapy (IMRT) and more recently Volumetric Radiotherapy with Modulated Arcs (VMAT), as well as thoracic extracranial stereotactic radiotherapy (SBRT), have been established as techniques of choice in patients with lung cancer, given the possibility of improving tolerance, mainly limiting the dose delivered to the esophagus and heart. (acute toxicity) and pulmonary parenchyma (late toxicity) [3,8]. The combination of these treatment planning techniques with improvements in volume delimitation such as simulation with a 4D scanner, or so-called image-guided radiotherapy with "conebeam CT" (scanner on the same treatment machine) allows to reduce toxicity and ensure a better distribution of doses in the treatment volumes [3,9].

Development

Lung cancer is the most common malignancy in the world and the leading cause of death in Western countries. The most common variety is non-small cell lung cancer (NSCLC) constituting between 80 and 85% of all lung cancers; the rest belong to the small cell variety (15 - 20%). The diagnosis is most often made in an advanced state. More than 50% of NSCLC cases are diagnosed in patients over 65 years of age. Approximately 54% of patients with this pathology are between 55 and 74 years old and about 27% are diagnosed between 75 and 84 years old [10,11].

The journal CA CANCER J CLIN (for its acronym in English) has published in 2019 the study of incidence and mortality worldwide GLOBOCAN 2018. According to this, the incidence of cancer in the world in 2018 was 18.1 million new cases, and there were 9.6 million deaths from cancer [12]. The lung was the most frequent location (2 093 876) followed by breast (2 088 849) and prostate (1 276 106). Lung cancer once again confirmed to be the deadliest, causing 1.7 million deaths in the same year [13].

In the United States, according to the American Cancer Society, malignant lung tumor is second in incidence (not including skin cancer), only behind prostatic malignancies in men and breast malignancies in women [14,15]. Approximately 13% of newly diagnosed cancers correspond to lung cancer. The number of new cases for 2015 was 221,200 (115,610 in men and 105,590 in women) and the estimated number of deaths from this disease was 158,040 (86,380 men and 71,660 women) [10]. Only 17.4% of lung cancer patients remain alive 5 years after diagnosis. There, more inhabitants die each year from lung cancer than from colon, breast and prostate cancer combined [15]. The growing trend in the incidence of lung cancer in most Western countries has been much more pronounced among women, undoubtedly in relation to changes in smoking habits. With these data, the American Cancer Society concludes that in the United States one in 13 men and one in 16 women (smokers or not) developed lung cancer throughout their lives [16].

In Cuba, according to the statistical yearbook of the Ministry of Public Health (MINSAP), 4,987 new cases of lung cancer (3,188 men and 1,799 women) were diagnosed in 2015 and 5,613 inhabitants (3,534 men and 2,079 women) died from this same cause in 2018. It was the leading cause of death from malignant tumors for both sexes in that year [17].

The World Health Organization (WHO) classification updated in 2015 brings important changes since 2004 [18]. More than 95% of lung cancers can fall into four main histological types:

- Non-small cell carcinoma
- Large cell carcinoma
- Small cell lung carcinoma
- Neuroendocrine tumors

For therapeutic, histological and biological behavioral purposes, malignant pulmonary epithelial tumors have been classified into two large groups. Small cell or microcytic carcinomas (SCLC) (15 - 25%) and non-small cell or non-small cell charminomas (NSCLC) (75 - 85% of the total), which mainly include squamous cell car-

cinoma (25%), adenocarcinoma (40%) and large cell carcinoma (10%) [19]. A new proposal for a classification for adenocarcinomas (19) was published in 2011.

Knowing the stage of the disease allows you to decide on treatment, know its prognosis and communicate comparable final results between different institutions and doctors. The TNM system (Tumor, Nodes and Distant Metastasis) was proposed by Pierre Denoix in 1946. This system allows patients to be grouped into stages within which prognosis and treatment are similar [20,21].

The symptoms will depend on the location of the tumor, that is, if they are central, patients have a cough that does not respond to treatment, mucopurulent expectoration, hemoptysis, dyspnea and wheezing; if they are peripheral, inspiratory chest pain and dysphonia. Other symptoms will depend on the presence of metastases and paraneoplastic affectations [22].

The therapeutic strategy of lung cancer includes treatment with surgery, radiotherapy and systemic treatment (chemotherapy, molecular targets, immunotherapy, etc.). Of these, complete surgical resection is the most likely to be cured. In potentially resectable patients in whom surgery is not possible due to high risk of morbidity and mortality, radiotherapy with radical intent in its different modalities may be a therapeutic alternative. The surgical option in patients considered to be at high operative risk becomes in some cases a challenge [23].

Surgery is the recommended therapeutic modality for patients with clinical stages (CD) I and II, so it is imperative that they be evaluated by a chest surgeon with training in oncology or by a surgical oncologist with chest training, to determine their resectability. Surgery is considered the best treatment alternative for early-stage NSCLC [24]. Despite complete resection, survival of patients with NSCLC remains poor, with an expectation of 67% to five years for stage I, which drops to 23% in patients with mediastinal node metastasi, where distant recurrence is the leading cause of death [24]. In patients with stage IA, complementary treatment is usually not offered after surgery. However, those with positive margins should be reoperated, or in case of refusal of reoperation, receive chemotherapy or adjuvant radiotherapy.

Conventional external radiotherapy (RT) consists of the administration of ionizing radiation capable of eliminating neoplastic cells by irreversibly damaging the DNA molecule. This modality was considered until a few years ago, as the treatment of choice in inoperable patients with early-stage NSCLC. This therapy achieves survivals of 20-35% to 3 years, with local failure rates of 40-60% [24-26]. This is mainly because with conventional radiotherapy there is a very high risk of toxicity when the equivalent biological dose (BED) of approximately 80 Gy is exceeded, a dose still suboptimal for the eradication of the disease in most patients [24-26].

Extracranial thoracic stereotactic radiation therapy (SBRT) offers better results in both disease control and prevention of therapy-related toxicities. The treatment of choice for inoperable patients with early-stage NSCLC has gone from being conventional external RT to SBRT, and this is stated in the clinical practice guidelines of the NCCN and ESMO since 2013 [24]. This technique also called ablative stereotactic RT (SABR) is a non-invasive outpatient procedure, used to deliver high doses of highly conformal radiation to relatively small extracranial targets. SBRT requires a high level of knowledge of the technique and strict quality control since high doses of RT are administered in each fraction (more than 8 Gy) with a high level of precision; a loss of accuracy in its administration would cause drastic changes in the possibility of cure and in the probabilities of toxicity [24]. Se carries out by means of state-of-the-art technology that allows the localization of the volume to be treated taking into account the mobility of the tumour, and the administration of high doses to the target volume with rapid dose drop, thus protecting adjacent healthy organs [24]. SBRT has the potential to achieve results similar to surgery, but very low morbidity and mortality, is done on an outpatient basis and in 1 to 5 fractions of 1 hour at a time, for about a week [3].

Intensity-modulated radiotherapy (IMRT) has generated great interest since its introduction into clinical practice in the late 90s, and represents one of the greatest technical innovations in modern radiotherapy. Es an advanced formed three-dimensional treatment, which is capable of generating an irradiation beam of non-uniform intensity: it optimally assigns different "weights" to small subdivisions of the beams called "rays" or "beamlets" [27]. The possibility of manipulating the intensity of each individual "ray" within each beam, allows great control over the flow of the radiation, achieving an optimal distribution of dosis. The biggest advantage of IMRT is its ability to produce a greater conformation of the dose distribution (i.e. that the dose is adapted in a more precise

way to the three-dimensional shape of the area we want to treat) than with conventional 3-D treatments [27]. In addition to the ability to achieve a highly conformal treatment, there is a high dose gradient (sharp dose drops around the target volume), this means that doses in nearby risk organs can be greatly reduced.

For this reason, IMRT has the greatest clinical impact on treatments that require a large conformation or a strong dose gradient between areas to be treated and organs at risk [27]. The appropriate clinical application of this technology requires careful consideration of issues related to dose heterogeneity and the different dose-fraction resulting, as well as the long-term relevance of areas treated with low doses without forgetting the uncertainties related to lung positioning and mobility during treatment.

Conclusion

Currently, radiotherapy plays an important role throughout all stages of patients with lung cancer and in each of them there have been several advances that have improved the results in terms of objective response and survival of patients. These advances have allowed a better protection of normal tissues, a better definition of the therapeutic target of these tumors that move normally with respiration and a more effective association with different drugs.

Authors' Statement

The signatories declare to be authors of the manuscript New Radiotherapy Techniques in Non-Small Cell Lung Cancer. This has not been submitted or published in any other journal

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Ethical Aspects

This work was authorized by the ethics committee of the Miguel Enríquez General Clinical Surgical Teaching Hospital. Havana. Cuba

Conflicts of Interest

The authors declare that there is no conflict of interest.

Contribution of the Authors

Rubén Alexander Elzaurdín Mora and Noralys Lara Fernández: Bibliographic review, preparation of the article and final review.

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