Chapter 5

Radiation Therapy for Non-Small Cell Lung Cancer in the Twenty-First Century

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Abstract

Lung cancer is the biggest oncologic problem for global health, as it is the most deadly and prevalent pathology after skin cancer. Two million patients are diagnosed every year, and around 80% of them die due to the disease. Radiotherapy has been practiced for decades to treat these patients, but recently, there has been important advances on this treatment on early stages (I and II), as stereotactic radiation therapy is becoming crucial. There has also been an increase on the importance of this treatment on more advanced stages (III), since intensity-modulated radiation therapy has achieved the reduction of undesirable side effects. The performance of stereotactic radiation at metastasis stages on patients with oligometastasis has accomplished great results. Likewise, hypofractionated treatments on polymetastatic patients have increased their quality of life.

Keywords: lung cancer, radiotherapy, IMRT, SBRT

1. Introduction

Lung cancer (LC) is the main cause of oncologic death in the world. It is a very important public health problem, having over two million new cases diagnosed every year in the world and almost 60% of them on undeveloped countries [1].

Rates vary around the world, Europe has the highest (53.5/100 thousand inhabitants) and Africa the lowest (2/100 thousand inhabitants). In Uruguay, sadly, the incidence on men is similar to that on Eastern Europe (50.11/100 thousand inhabitants). However, incidence on

Advances on diagnosis	• Timely diagnosis: screening with low-intensity scanner • Precise staging: PET-CT on lung cancer. Fiber optic bronchoscopy on EBUS
Advances on staging	• New TNM classification • Molecular classification of lung cancer (study of mutation EGFR, ALK, PD-L1, etc.)
Advances on surgical procedures	• Less invasive surgery. Video-assisted thoracoscopic surgery (VATS), video-assisted mediastinoscopic lymphadenectomy (VAMLA), transcervical extended mediastinal lymphadenectomy (TEMNLA)

Advances on systematic treatments	• New chemotherapy drugs
	• Targeted treatments:
	  • Tumors with EGFR gene mutations—ITKS drugs (gefitinib, afatinib, erlotinib)
	  • Tumors with ALK gene changes (crizotinib)
	  • Antiangiogenesis agent (bevacizumab)
	• Immunotherapy: PD-L1 tumors (nivolumab)

Advances on radiotherapy treatment	• Stereotactic body radiation therapy on patients with early tumors, stage I–IIA • Radiosurgery on patients with oligometastasis • Intensity-modulated radiation therapy for stage II and III patients • Breathing control techniques. Four-dimensional computed tomography

Table 1. Advances on diagnosis and treatment of lung cancer.

women is significantly lower (9.95/100 thousand inhabitants), although with a tendency to grow [2]. Even though the incidence and death rate for lung cancer on women is lower than men, it has been acknowledged to be higher than breast cancer in some countries [3].

Usually, lung cancer patients are diagnosed at advanced stages, due to the fact that most of the disease's natural history develops asymptomatically. In these cases, the treatments have not been sufficiently effective, and the death rate remains very high. However, in the last decades, multiple advances have been made, which include diagnosis, assignation of subgroups, surgical treatments, systematic treatments (chemotherapy and targeted therapies), and radiotherapy. All of these facts have helped lung cancer to become the main subject of discussion in recent scientific meetings and oncologic congresses.

In **Table 1**, we will describe the main recent advances on the diagnosis and treatment of lung cancer.

Radiotherapy is the most used treatment for lung cancer patients, because of its role on both early (used exclusively or combined with chemotherapy, process of curative aim) and advanced stages (palliative treatment). It is estimated that 80% of patients with lung cancer diagnosis will receive radiotherapy at some point on their treatment [4, 5].

In this study, we will explain the new advances of radiotherapy on non-small cell lung cancer.

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2. Radiotherapy on the treatment of lung cancer

Nowadays, radiotherapy plays an essential role in every stage of lung cancer treatment. On each of these stages, advances have been made that enhance the results. These advances thanks to better protection of the normal tissues, better definition of the tumors' therapeutic target, that moves normally with breathing, as well as an effective association with different drugs (chemotherapy, targeted drugs, and immunotherapy). In **Table 2**, we will explain the standard treatments and the new advances of radiotherapy according to the different stages of AJCC [6, 7].

Stage	Standard treatment	Advances (advantages)
Stage I–IIA (tumors < 5 cm)	**1.** Surgical resection **2.** Traditional radiotherapy (60–66 Gy/30–33 Fr)	SBRT (1–5 fractions, less death rate, higher local control)
Stage IIB–III (big-sized tumors or with enlarged lymph nodes)	**1.** Surgical resection **2.** 3D-CRT + QT	IMRT VMAT 4DCRT (better tolerance, higher local control, unpleasant side effects reduced)
Stage IV (brain metastasis)	**1.** Surgical resection **2.** Whole brain and spinal cord radiation therapy	Stereotactic radiotherapy (SRT). Stereotactic radiosurgery (SRS) Hippocampus protection in radiotherapy treatment (noninvasive treatment, higher local control, unpleasant side effects reduced)
Stage IV (oligometastasis)	**1.** Chemotherapy **2.** Targeted cancer therapies **3.** Palliative radiotherapy	SBRT on oligometastasis SBRT + immunotherapy (better control on the disease, higher survival rate)

Table 2. Standard radiotherapy treatments and advances on each stage of lung cancer.

3. Advances on the treatment of early LC (stereotactic body radiation therapy, SBRT)

In most countries, the standard treatment for patients with early LC (I–IIA, less than 5 cm size tumors, with absence of nodal involvement) remains to be surgery (lobectomy plus hilar and ipsilateral mediastinal lymph node dissection) [6–12] (**Figure 1**). With this treatment, the 5-year survival rate is between 60–80% for patients at stage I and 30–50% for patients at stage II. For those not apt for surgery, the standard treatment, until a couple years ago, was fractionated radiotherapy for 6–7 weeks, with control rates of 30–70% [13].

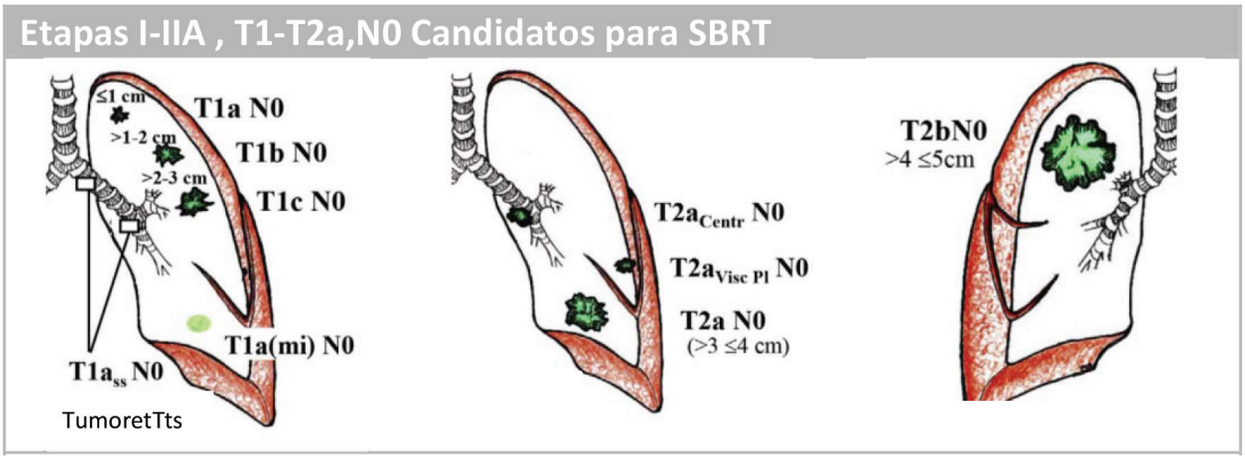

Figure 1. SBRT indications according to the stages of TNM UICC 8th edition (I–IIA).

In the last decade, a new technique has been developed, called stereotactic body radiation therapy (SBRT). After being used in malignant and benign intracranial injuries, it was extended to other physical wounds. SBRT consists of the delivery of extremely high doses of radiation, in little fractions, but with a precise delimitation of the treatment's targets. This technique has the potential of accomplishing similar results to those obtained with surgery but with very low morbidity and mortality rates. It is performed on an outpatient basis and in 1–5 fractions of 1 h each, during approximately a week. In **Figure 2**, it is clearly illustrated the difference between three-dimensional radiation therapy (3D-CRT) and SBRT in the distribution of doses.

This technique was first used for treating lung cancer in 1995, and the results obtained so far have been very encouraging [14]. In the past years, an increasing number of papers showing similar results to those obtained with surgery have been published. This has coined the concept of "conservatory lung cancer treatment," similar to what happened with breast cancer in the 1980s [15]. Nowadays, not only is this technique the most adequate to LC patients that are not candidates to surgery, but it is also considered by some authors as a second "Gold Standard" [16]. Recently, on a revision of the participant centers in the elaboration of the NCCN (National Comprehensive Cancer Network) Guidelines, the existence of a wide variation in the local treatment of these patients was proved, which confirms a clear lack of level I evidence to decide which treatment, surgery or SBRT, is the most adequate [17].

Around the same time, various studies that prove how important of a role does the low-intensity scanner plays in the early diagnose of lung cancer have been published [18]. In most clinical guidelines, there is a clear indication and a precise group of patients who are benefited from this screening study; therefore, we hope that in our country, as well as in the rest of Latin America, this procedure will become usual so that we can treat more patients at an early stage of the disease. The upcoming situation will determine a challenge for the health authorities, so an outpatient treatment of one to five applications with almost no death rate is perceived as utterly interesting [19, 20].

The SBRT has permitted an increase in the number of patients who are treated with a curative aim, and the undesired effect rates are very low (especially pneumonitis, 3–6%), even for those patients whose lung function is compromised, compared to radiotherapy in its three dimensions [21–24].

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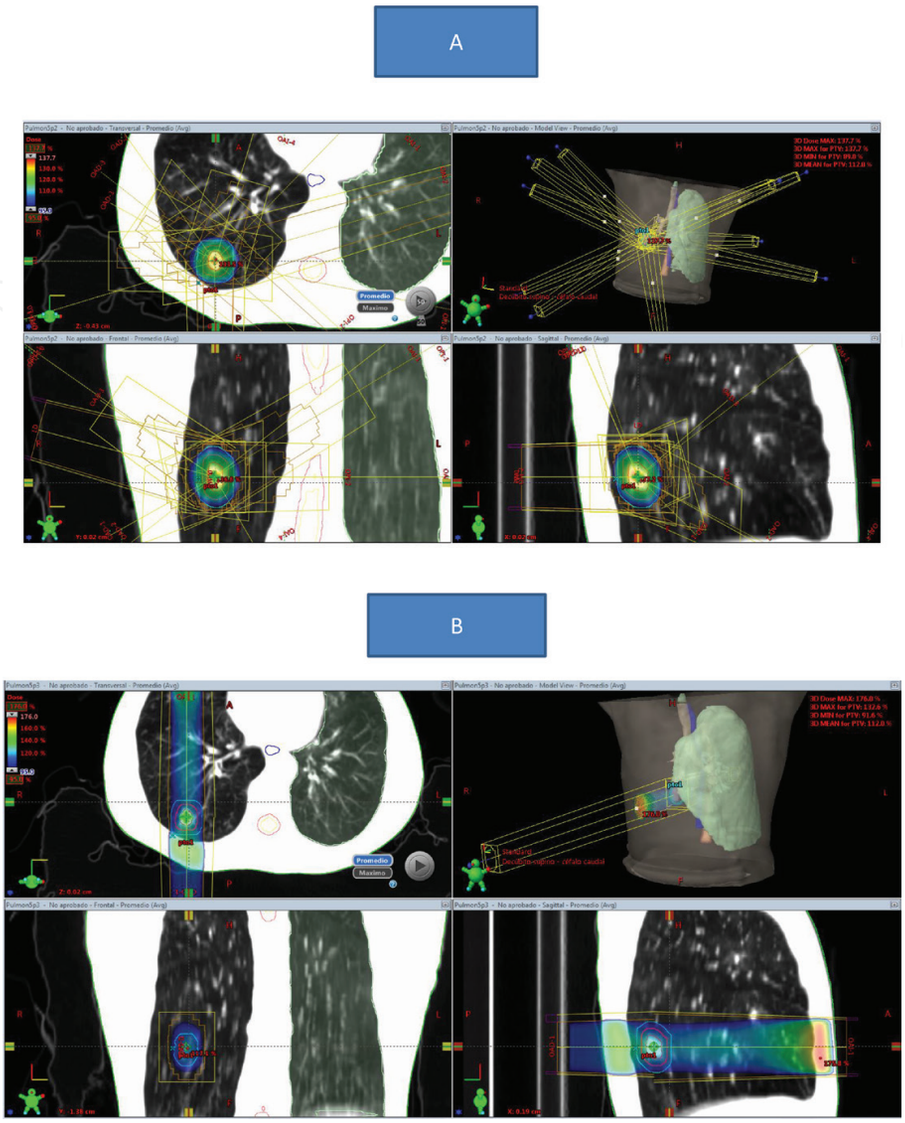

Figure 2. (A) Dose distribution and treatment beam on lung cancer T1bc (2.1 mm) N0 M0 treated with SBRT. (B) Same case, with radiotherapy planning conformed of 3D. Note the difference and volume of the treated lung.

Recently, Stenan et al. have analyzed the advantages and disadvantages of both surgery and SBRT that are explained in **Table 3** [20].

To date, there are various retrospective studies that demonstrate tumor control rates higher than 80%, with morbidity and mortality rates at a minimum (**Table 4**). A recent revision at SEER (Surveillance, Epidemiology, and End Results Program) by Yale University's group was published by Yu et al. It includes a group of patients over age 67, treated between 2007 and 2009 with LC at an early stage [30]. More than 1000 patients were checked, 367 treated with SBRT and 711 treated with surgery. The acute toxicity (0–1 month) was 7.9% for SBRT and 54.9% for surgery ($p < 0.001$). At 24 months, the difference in toxicity was not that significative (69% against 73.9% $p = 0.31$). The IRR of toxicity for SBRT against surgery was 0.74 (95% CI of 0.64–0.87). The mortality rate was lower for SBRT (23.3% vs. 40.1% $p < 0.001$). The main complications carried by surgery in this study were, besides the pain caused to the patient, IAM, cardiac arrhythmias, TVP, PTE, and pneumonia that are not registered at surgical operations. Every patient that was subjected to surgery needed a hospitalization of at least 3 days in case no complications occurred.

Surgery (lobectomy + hilum and mediastinal lymphadenectomy)	SRBT
Advantages: • Definite pathological diagnosis • Allows the diagnosis of lymph node involvement, which is redundant for selecting patients for adjuvant treatment	Advantages: • Five-year survival rate of 90% • Outpatient treatment • Lung function and quality of life are preserved • Minimal morbidity, almost no mortality
Disadvantages: • Procedure of high morbidity and mortality • Invasive procedure on patients who frequently suffer from associated comorbidities	Disadvantages: • No definitive pathological verification. Local fibrosis for RT may conceal a local recurrence

Table 3. Advantages and disadvantages of SBRT and surgery on patients with lung cancer at early stages (I and IIA).

Initially, the selected patients had tumors at a peripheral level, due to the fact that, at first, the analysis of the side effects seemed to be more important on the central injury [31–33]. Even at RTOG's (Radiation Therapy Oncology Group) team, there was a denominated zone of exclusion called "no fly zone." However, this restriction is not that strong anymore, owing to the fact that the fractionation must be adjusted and the restrictions of the organs at risk maintained within the established limits [34]. In the first studies where some patients with central tumors were included, some cases of high toxicity at a long run were described [35, 36]. Nevertheless, in most recent publications, where the number of fractions is higher and the doses for each one are slightly reduced, similar results to those from peripheral tumors are obtained. **Table 5** presents in detail works that include patients with central tumors [37–42]. Baba et al. made a revision of 20 studies on more than 500 patients with central injuries treated with SBRT. The toxicity levels III and IV were 8.6% and the death rate of the treatment was 2%, a bit higher than those patients with peripheral tumors. The 3-year local control rate was 60–100% and the survival rate was 50–75% [43].

Study	No. of patients	Treatment	Result	Drawbacks
Brown et al. [25]	59	15–67 Gy on 1–5 Fr	Five-year survival rate, free from disease, of 90%	Pneumonitis G3, 7%
Negata et al. [26]	104	12 Gy on 1–14 Fr	Three-year survival rate, free of progression, of 70%	Dyspnea G3, 9% Pneumonitis, 7% Pain, 2%
Onishi et al. [27]	257	30–84 Gy on 1–14 Fr	Five-year survival rate of 84%	Lung complications G3, 5.4% Esophageal complications, 1%
Senthi et al. [28]	676	3–8 Fr (54–60 Gy)	Five-year survival rate of 89%	No significant drawbacks
Ven der Voort et al. [29]	70	12–15 Gy × 3 Fr	Two-year survival rate of 92%	Late toxicity G3, 10%

Table 4. Initial retrospective studies. Fragmentation and results. SRBT on patients with lung cancer on stages I and IIA.

Author	No. of patients	Tumor characteristics	Dosage	Local control	Survival rate
Chang et al. [27]	27	48% T1–T2 52% recurrence	40–50 Gy/5 Fr	3 patients (40 Gy)	
Milano et al. [38]	53	66% T1–T2 36% NSCLC with metastasis	20–55 Gy/1–18 Fr	73% to 3 years	72% to 2 years (T1–T2)
Haasbeek et al. [39]	63	No T1–T3	60 Gy/8 Fr	92.5% to 5 years	DFS 71% SR 49.7%
Rowe et al. [40]	47	59% T1–T2 41% NSCLC	50 Gy/4 Fr	Two local failures	PFS 24% to 2 years
Oshiro et al. [41]	21	95% recurrence of NSCLC	25–39 Gy/1–10 Fr	60% to 2 years	SR 62.2% to 2 years
Unger et al. [42]	20	85% NSCLC with metastasis	30–40 Gy/5 Fr	63% to 1 year	SR 54% to 2 years

Table 5. SBRT results on patients with non-small cell lung cancer (NSCLC) with focal injuries.

Table 6 describes the recommended treatment schemes for SBRT according to NCCN's Clinical Guidelines. It also details the differences between the doses for each fraction on central and peripheral tumors [9].

To date, it has not been published any randomized study that compares surgery to SBRT on patients eligible for surgery, so the recommendations are based on retrospective works or on a series of cases which mainly include noncandidate patients due to their comorbidity. Mahmood et al. revised 19 works where high-risk surgery patients were submitted to suboptimal resection (sublobar or wedge resection) or SBRT [44]. In this revision, it was proved a local control of 90% with SBRT, similar results to those obtained with lobectomy on patients with low risk but very much superior to the results obtained with suboptimal surgery. The rate of local recurrence was 4% for SBRT and 20% for surgery ($p = 0.07$).

Most of the results obtained with SBRT on patients with low surgical risk come from information given by patients who rejected surgery. To date at least three different studies have been published that add a total of 260 cases. In these, the local control rate was 93% for T1 and 73%

Doses	No. of fractions	Indication
25–34 Gy	1	Small (<2 cm) peripheral tumors. More than 2 cm between chest wall
45–60 Gy	3	Small peripheral tumors. Less than 2 cm between the chest wall
48–50 Gy	4	Central or peripheral tumors, smaller than 4–5 cm, and less than 1 cm between the chest wall
50–55 Gy	5	Central or peripheral tumors less than 1 cm between the chest wall
60–70 Gy	8–10	Central tumors

Table 6. Fractioning on SBRT. Modified from NCCN [7].

for T2. The 5-year survival rate was 72 and 62%, respectively, and the local and distant recurrence rate was 20% [45–47].

Zheng et al. published a meta-analysis in 2014 that includes every study published on non-small cell lung cancer's treatment between 2000 and 2012 [48]. Forty publications regarding SBRT are included, from which 30 were retrospective (4800 patients) and 23 on surgery. The average age was 74 years old for SBRT and 66 years old for surgery. The 1-year survival rate was 83.4% against 92.5%, 2-year survival rate was 56.6% against 77%, and 5-year survival rate was 41.2% against 66.1%. These results seemed to show a slight advantage for surgery patients. Nevertheless, when the operable patients are studied and the data are organized by age, the chance of survival and nonrecurrence is similar. These prove that the selection of treatments depends on the patients' age; the youngers are usually treated with surgery and the older with SBRT.

To compare these two procedures directly, some randomized works have been developed, among them, the "STAR" protocol, directed by MD Anderson's team; the "ROSEL" protocol, directed by a Dutch and German team; and, lastly, one by RTOG [46, 49, 50]. All of them include patients with non-small cell lung cancer at stage I and tried to compare standard surgery, lobectomy, and lymphoganglionar hilar-mediastinal dissection with SBRT. The three studies were finished before time due to the difficulty in the inclusion of the patients, most of them rejected the randomization to evaluate both treatments, of which none was better than the other, but one implied a surgical intervention that the other did not. Chang et al. analyzed patients who were included in two of these frustrated protocols, they were randomized, and the results were published as a whole [51, 52]. Only 58 patients were included (31 for SBRT and 27 for surgery), the average follow-up was 40.2 months, and the 3-year survival rate was 95% for SBRT and 79% for surgery ($p = 0.54$). In the group conformed by patients on SBRT, 10% (three individuals) presented some type of minimal adverse effect (chest pain 10%, dyspnea or cough 6%, and only one patient presented rib fracture). On the other hand, in the group conformed by those who were treated with surgery, one patient passed owing to complications during surgery (4%), and 44% (12 patients) presented some complications regarding G3-4 (RTOG's Toxicity Scale). This author concludes that even though the quantity of patients is low and requires more complex work, the SBRT is a clear valid option for treating non-small cell lung cancer patients at an early stage. Other authors who reanalyzed the results obtained by these three studies wonder whether the failure of inclusion of patients maintains the question or if it is an answer by itself.

Rusthoven et al. proposed that these results prove that similar changes to those occurred to breast cancer's conservatory treatments during the 1980s will happen to non-small cell lung cancer's treatments. It could be compared as well to localized and low-risk prostate cancer, where radiotherapy and surgery are valid alternatives with very little difference between them, even though there are no randomized works that compare them directly [53, 54]. This situation in concern with the implementation of the low-intensity scanner on risk groups will absolutely change the epidemiology, so a higher number of patients with lung cancer will be treated with a curative aim at the radiotherapy units.

Nowadays, there are various works in course: the RTOG 013 that analyzes a dose escalation on focal tumors, smaller than 5 cm; the RTOG 0915 that compares different treatment schemes, 34Gy/1 fraction against 48 Gy in 4 fractions; the VALOR (Veterans Affair Lung Cancer Surgery Or Stereotactic Radiotherapy) protocol from the USA; and the SABRTooth in the UK that tries to answer various current questions [55, 56].

Finally, studies have begun to question the necessity of a histological confirmation previous to SBRT on patients with a suspicious lump on their lung and at high risk. In this sense, for those who are submitted to lung cancer screening with a low-intensity scanner (older than 50–55 years old, younger than 74, and tobacco use exceeding 30 pack-years) and are as well discovered a suspicious lung lump and submitted to surgery, many authors do not perform a histological confirmation before the thoracotomy, due to the fact that the probability of malignancy is higher than 65% and also the complication rate from the needle biopsy is high [57]. The importance of this situation increases for those patients who are SBRT candidates, as they usually have higher comorbidity rates [58, 59]. Therefore, in recent publications, the necessity of previous biopsy to SBRT is analyzed. The performance of algorithms that employ at least two serial scans to evaluate the evolution of the patient, added to the use of PET-CT, benefits the achievement of a high positive predictive factor. Recent studies show that the long-term survival results from patients treated with SBRT with or without the previous biopsy are similar, contrary to the popular belief that one may hope a higher survival rate for those not confirmed for inclusion in this group without an oncologic pathology [60].

To sum up, we could say that patients with localized lung cancer, T1 and T2, without lymph node involvement, conform a growing group due to the implementation of screening studies. Radiotherapy with SBRT technique is one of the electable treatments, with encouraging results and a low morbidity and mortality rate.

4. Advances on the treatment of advanced local nonmetastatic non-small cell lung cancer: stages II and III

4.1. Intensity-modulated radiotherapy (IMRT)

4.1.1. Volumetric arc therapy (VMAT)

The standard treatment for patients with locally advanced NSCLC, on stages II and III, is surgery. For those who are not eligible for it, the preferred treatment is combined chemotherapy and radiotherapy [9, 61]. The most used drugs are explained in **Table 7**, but the analysis of the different schemes is beyond the scope of this paper.

Chemotherapy schemes combined with radiotherapy, recommended by NCCN
Cisplatin 50 mg/m^2 days 1, 8, 29, and 36 + etoposide 50 mg/m^2 days 1–5, 29–33
Cisplatin 100 mg/m^2 days 1 and 29 + vinblastine 5 mg/m^2/weekly × 5
Carboplatin AUC 5 day 1 + pemetrexed 500 mg/m^2 day 1 every 21 days × 4 cycles (nonsquamous cancer)
Cisplatin 75 mg/m^2 day 1 + pemetrexed 500 mg/m^2 day 1 every 21 days × 3 cycles (nonsquamous cancer) ± 4 cycles of pemetrexed 500 mg/m^2
Paclitaxel 45–50 mg/m^2 weekly + carboplatin AUC 2 ± 2 additional cycles of paclitaxel 200 mg/m^2 and carboplatin AUC 6

Table 7. Schemes and drugs used on combined radiotherapy and chemotherapy on patients with non-small cell lung cancer.

Radiotherapy is typically delivered in 30–35 fractions, five times a week until reaching a total dose of 60–66 Gy [62–64]. Distant metastases are the main cause of failure on the treatment, but 45% of the patients also present a persistence or local failure [64]. SBRT is not feasible for this group of patients due to its volume.

For these patients, intensity-modulated radiotherapy (IMRT) and, more recently, volumetric arc therapy (VMAT) have been established as electable techniques, due to its possibility to improve tolerance, fundamentally by limiting the doses delivered to the esophagus (acute toxicity) and to the lung parenchyma (late toxicity) [65] (**Figure 3**).

The combination of these treatment planning techniques added to the improvements on the delimitation of volumes like scanner simulation on 4D, or the guided RT with images with cone beam CT (a scanner in the same machine of treatment), allows to decrease the toxicity and ensure a better distribution of doses on the treatment's volumes [66].

Various studies that compare the different treatments, more precisely 3D-CRT (radiotherapy conformed in three dimensions) vs. IMRT or VMAT*(VMAT, sophisticated RT IMRT technique characterized for the use of at least one dynamic arc that allows the quick delivery of doses on irregular volumes), clearly show the advantages of the modern techniques in terms of the medium dose on a healthy lung, lung V20, dose on the spinal cord, and dose on the esophagus and heart [67, 68]. These modern techniques have spread very quickly to most of the centers of reference. Most of the clinical comparisons between IMRT and 3DCRT are retrospective studies from separate institutions, with the limitations entailed to that notion [66]. An analysis from the National Cancer Database from the USA shows that, with the use of 3DCRT or IMRT, an improvement on the survival rate is obtained, compared to 2D techniques [69]. However, when we compare the 3D with IMRT in a separate way, the differences are not so clear. On an analysis of the subgroups on patients at T3 and T4, the differences on favor to IMRT are more evident [70].

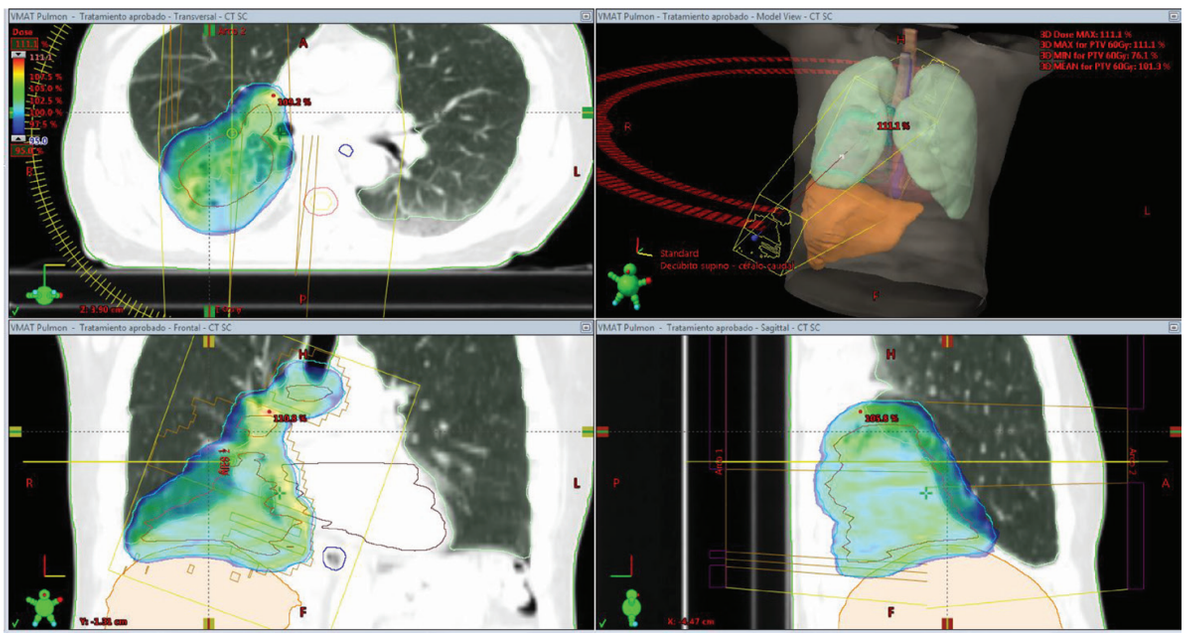

Figure 3. IMRT. Volumes of treatment with IMRT-VMAT on a patient with lung cancer diagnosis T3 N1 M.

In this respect, on a recent study on the protocol of the dose escalation for RTOG 0617, where patients treated with IMRT and 3DCRT are included, it can be concluded that, although the patients treated with IMRT had a PTV (Planning Treatment Volume) of 15% more and a higher percentage of stage IIIB tumors, the G3 pneumonitis rate was cut from 7.9 to 3.5%. Moreover, the group treated with IMRT presented a larger number of patients who were able to receive consolidated chemotherapy and reported lower cases of impaired quality of life [67]. This paper shows as well that patients treated on larger centers, where IMRT is used more frequently on treatments, have a higher 2-year survival rate (10% more).

Currently, a group of investigators is analyzing the possibility of delivering a higher dose on zones that are most metabolically active, detected by the PET-CT with [18] fluorodeoxyglucose, with IMRT techniques. These protocols that are based on the metabolic activity are positively correlated with areas where developing a recurrence or lack of control is more frequent [66].

5. Strategies for the handling of breathing movements

5.1. 4DCT

An important challenge for lung cancer radiotherapy treatment is the management of the physiological movements related to breathing. The lung tumors move during the breathing, especially those closer to the diaphragmatic cupolas. Usually, to ensure the adequate dose delivery to the tumor, a margin is left around it. For tumors that move, this procedure presents some particular characteristics. For example, caudal skull movement is higher than latero-lateral and anteroposterior movement.

Four-dimensional computed tomography (4DCT) is a technique that allows the user to characterize and quantify the injury's movement during breathing (**Figures 4** and **5**). It is essential for more sophisticated radiotherapy techniques such as SBRT, IMRT, or VMAT, where great precision is needed, as it allows to reduce the geographical miss (parts of the injury remains outside the treatment's range) and the volume of the healthy tissue surrounding the tumor [71].

With images obtained by 4DCT and the precise knowledge of the tumor's movement, we could make advances in many senses [72]:

1. Determine a margin around the tumor according to the movement, usually denominated ITV (internal tumor volume).
2. Operate instruments that attempt to reduce the breathing movement (abdominal compressor).
3. Use techniques that allow to perform the treatment during breathing, at a certain stage called gating.
4. Operate radiotherapy robotic equipment that moves synchronized with breathing, "real time tumor tracking" (CyberKnife).

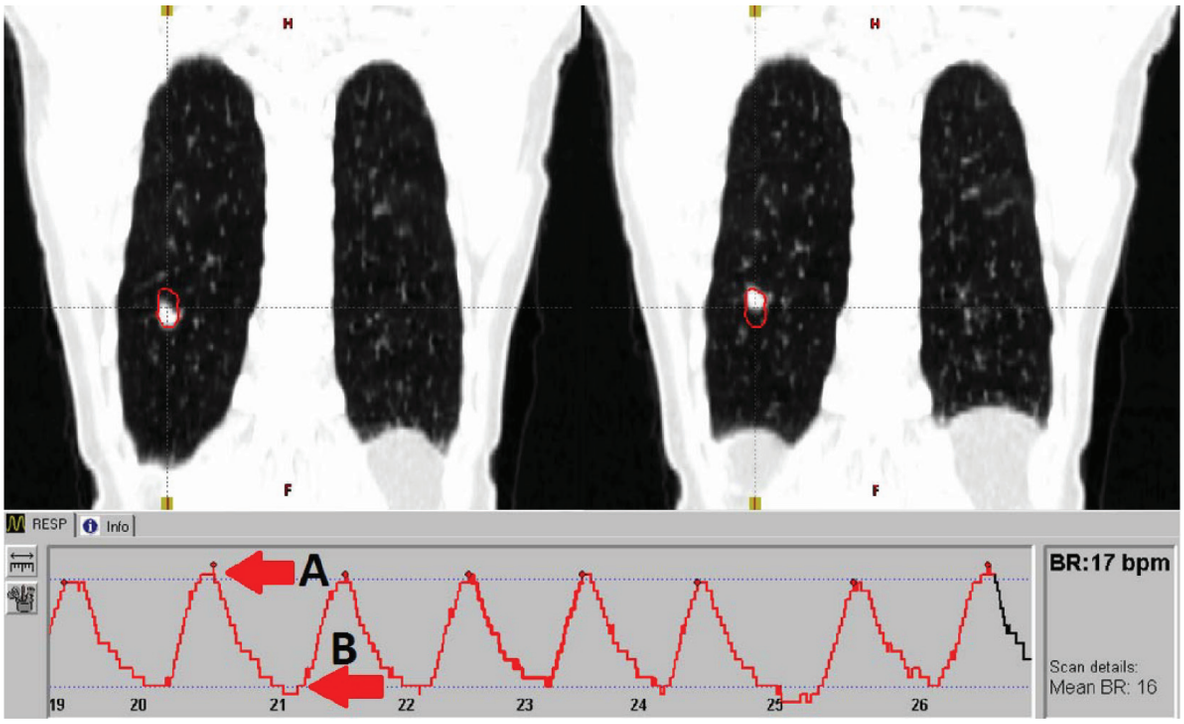

Figure 4. A 4DCT, appreciated on synchronized reconstructions with breathing signal (red curve on the bottom edge). The top left image corresponds to movement of the tumor at inhalation (reconstruction of the images on point A of the breathing signal). The top right image corresponds to the movement of the tumor at exhalation (reconstruction of images on point B of the breathing signal).

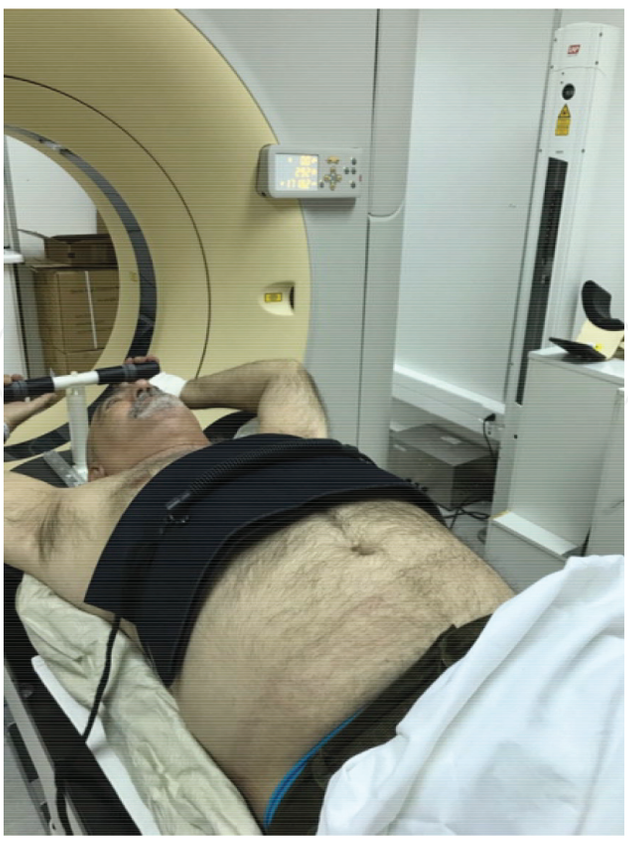

Figure 5. Device used to quantify the breathing movement on 4D scanner.

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5.2. Gating

On this technique, radiotherapy is practiced on a specific stage of the breathing cycle, usually exhalation, and stops irradiating at the next stage, leaving the tumor out of the irradiation area. It requires the adequate technology, collaboration from the patient, and training, so that the cycle remains harmonious and stable [73, 74]. The election of one or another method depends on each case's preference and access.

6. Stereotactic radiotherapy on brain metastasis and hippocampus protection

Approximately 20% of non-small cell lung cancer patients develop brain metastasis, and as in small cell lung cancer, prophylactic cerebral irradiation is sometimes recommended [75]. This percentage increases as staging studies are performed on asymptomatic patients, also when the systematic disease's control is increased with new therapeutic means, such as chemotherapy or targeted drugs. Brain metastasis' prognosis varies based on the patient's age, overall health, the size and number of the metastasis, and the systematic control (or not) of the disease [76, 77]. The standard treatment for patients with multiple metastases used to be, until recently, whole brain radiotherapy, which achieved an average of 4- to 8-month survival.

On a group of patients with good prognosis, a limited number of injuries, young, overall healthy, and with a relatively controlled systematic disease, the most aggressive metastasis treatment, either surgery or radiosurgery, obtains an improvement on the survival rate as well as on the quality of life [78, 79].

Radiosurgery for patients with brain metastasis must only be considered for those whose injuries are not bigger than 3 cm. It consists of delivering only one fraction of radiation with high doses and highest precision (1 mm). To date, there are no randomized studies that compare radiosurgery to surgery, although it is believed that the second should be saved for bigger injuries, while radiosurgery is recommended when the metastases are multiple.

Even though the addition of whole brain radiotherapy benefits the raise of neurocognitive alterations, it is not clear if it also improves the local disease control on patients undergoing radiosurgery [80, 81].

Despite what was discussed before, for some patients who present a larger number of metastasis, whole brain treatment cannot be avoided. Some preclinical studies proposed that the neurocognitive deleterious effects are partly caused by the irradiation of the neuronal stem cells, located on the lateral ventricles' subventricular zone and also on the hippocampus and the dentate gyrus (both related to memory). These structures can be protected with the implementation of IMRT, which has proved to decrease the decay of memory to 7%, compared to a previous 30% [82, 83].

7. Radiotherapy on oligometastasis

As we mentioned before, a large number of patients present metastasis at the time of their diagnosis or during the evolution of the disease [84]. They receive a poor prognosis; however,

those who present a limited number of injuries (for some authors up to six), seem to have a less aggressive behavior and a better prognosis [85]. This group of patients suffers from oligometastasis and could be benefitted from a more aggressive local treatment [9]. Just as a group of patients with hepatic metastases from colorectal cancer has been established, there is also a group of lung cancer patients who are benefited from a local control of the metastasis. In this sense, SBRT, as previously mentioned, is a noninvasive treatment with little undesirable effects. It has been successfully practiced, having controlled an 80% of the metastasis [86].

Recently, Iyengar et al. published the results of a randomized study that compares radiotherapy on the primary tumor and metastasis (less than six) to combined chemotherapy against only chemotherapy. These prove there is a difference in the progression-free survival (PFS) of 9.7 against 3.5 months, respectively ($p < 0.01$). This difference is also extremely higher than that found on different chemotherapy schedules [87].

Other authors have also proved that the use of targeted drugs (erlotinib) added to SBRT for patients with oligometastasis raises the PFS and the survival rate in relation to controls [88].

Certainly, big changes are occurring on the traditional concepts regarding this field and patients with metastasis. In the near future, enormous advances are expected to be underway on the field of combining radiotherapy with immunotherapy.

8. Radioimmunotherapy

For many years, radiotherapy has been known to be related to tumor immunotherapy, even the abscopal effect, also known as bystander, was descripted 30 years ago. This effect refers to the radiation's impact outside the irradiated area, when a tumor injury is treated with radiotherapy and another injury outside the irradiated area is reduced or disappears [89–91]. Ten years ago, Formetti et al. related the bystander effect to immunity [92].

Nowadays it is known that the traditional paradigm that stated that the damage caused by radiation was exclusively due to the effects on the irradiated cells' DNA has become more complex. Radiation causes a series of effects on the cells (tumors or not): inflammation, chain activation, and complex metabolic steps [93]. A bigger number of inhibitors, signal transduction, related to DNA's damage reparation have been described. These present a tremendous opportunity to be used as interesting targets in new forms of treatments.

Recently, it has been proven that high doses of radiation, like those used on SBRT, cause various immunomodulating effects, similar to those on vaccines [93]. It has been established, for example, that performing a combination of radiotherapy and antibodies to treat some antigens associated with T cytotoxic lymphocytes like CTLA-4 (which suppresses its activity) results on a regression of the tumors that are not included in the volumes of radiation, producing the bystander effect [94].

The basic mechanisms used on radiotherapy to interact with the immune system are extremely complex and only partially known. The damage produced by radiotherapy when used on high doses, like SBRT, happens on the intra-tumor blood vessels. Changes on the membrane-spanning

molecule and the release of soluble mediators have been discovered, so that the dendritic cells are stimulated, which also causes the stimulation of the T lymphocytes [92]. Radiotherapy induces multiple immunological changes, such as the tumor cell's death, thanks to the ionizing radiation, the overregulation of immunogenic surface markers like MHC-1, and discharge of danger signals or cytokine such as TNF-alfa. It also induces immunological death via calreticulin and other reticulins, simultaneously to the tumor DNA's exit and ATP, just as HMGB1 (high mobility group box 1 protein). These proteins are associated with chromatin and seem to have a big impact on the triggering of immune response through the incentive of dendritic cells. It has also been described the arrival of immunocompetent cells like cytotoxic T lymphocytes or the raise of tumor antigens from dendritic cells, the transformation of macrophages activated by M1 or M2, and the overregulation of surface antigen such as PD-L1 and other endless events [95] (**Figure 6**).

However, these effects get complex when the usual effects on traditional radiotherapy treatment are studied, when low doses are used on big volumes. The effects may be different on these treatments and also counterproductive from an immunological perspective, because of the possible implementation of other mediators (e.g., TGF-β), added to the phenotypic alteration of macrophages that are infiltrative tumors (M2 to M1). These would explain the nonstimulation of immunological effects contemplated on high doses and small volumes, which is clearly evidenced on immunosuppressive effects of radiotherapy on low doses and small volumes.

Therefore, this interaction of radiotherapy with different immunomodulating molecules is being thoroughly studied. Various teams are working on the combination of SBRT and immunotherapy, which is one of the most advantageous treatments for different tumors, lung cancer among them [96–99].

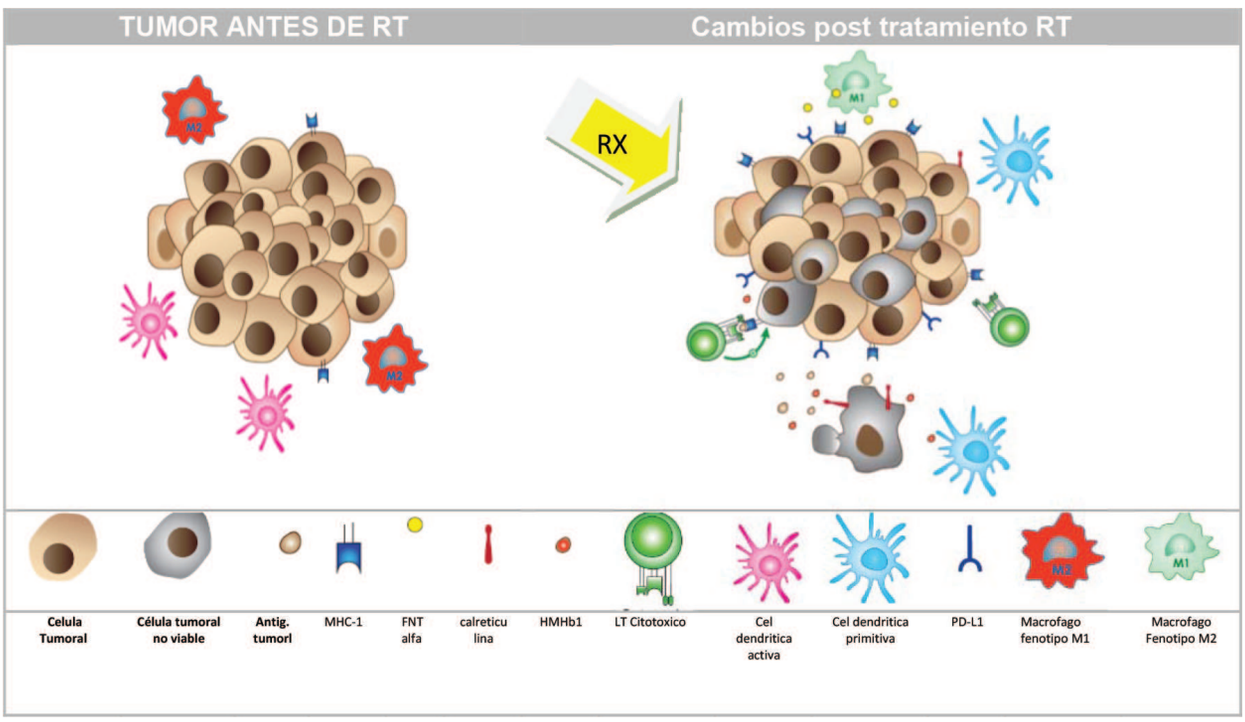

Figure 6. Molecular and cell effects that occur after the application of high doses of radiotherapy.

9. Conclusion

Certainly, radiotherapy still plays an important role on lung cancer treatment. In recent years, new sophisticated techniques have been developed and propelled themselves into different stages of the treatment. SBRT is a valid mean for treating patients with located tumors, as it presents surprising results and minimal side effects. This technique has been implemented on groups of patients suffering from oligometastasis and has showed great improvements on the survival rate. As previously mentioned, Iyengar et al. presented on the last ASTRO congress, September of 2017, an even higher survival rate of 3.5–9.7 with the addition of SBRT on patients suffering from oligometastasis. This kind of improvement has hardly been found on other new drugs for chemotherapy.

Lastly, we have begun to understand the molecular mechanisms triggered by radiotherapy with high doses, as the involved molecules are more familiar. These studies are the beginning of a new treatment, the combination of SBRT and immunotherapy.

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