

# State of the Art Radiation Therapy for Lung Cancer 2012: A Glimpse of the Future

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# State of the Art Radiation Therapy for Lung Cancer 2012: A Glimpse of the Future

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## Abstract

The prognosis of patients with lung cancer has improved over the past years. Patient selection, optimal sequencing of systemic and local treatments, and better surgical techniques, together with unprecedented improvements in imaging and computer technology and technical advances in radiation therapy planning and delivery has revolutionized radiation therapy in a short period of time. Among the most significant evolutions that have direct implications for daily practice are the more widespread use of stereotactic body radiation for stage I non–small-cell lung cancer (NSCLC), concurrent chemoradiation for stage III NSCLC, the implementation of 4-dimensional computed tomography and positron emission tomography, adaptive radiation therapy strategies, optimizing the timing of chest radiation therapy for limited disease small-cell lung cancer (SCLC) and prophylactic cranial irradiation for extensive disease SCLC. Molecular-based individualized radiation therapy dose prescription, which goes hand in hand with the realization of decision-support systems and the introduction of proton therapy centers give only a glimpse of what the future will bring.

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**Keywords:** Decision support, Individualized, Non–small-cell lung cancer, Radiation therapy, Small-cell lung cancer, Tumor heterogeneity

## Introduction

Lung cancer remains 1 of the most lethal and frequent malignancies in the world.<sup>1</sup> After diagnosis, most patients with non–small-cell lung cancer (NSCLC) or small-cell lung cancer (SCLC) still die of their disease. Nevertheless, survival has slowly been increased, it has been realized that even in the metastatic setting, long-term survivors in selected patients with a few brain or adrenal metastases may be achieved with radical systemic and local treatment.<sup>2</sup> In SCLC, the integration of chemotherapy and thoracic radiation therapy (RT) has

been elucidated and prophylactic cranial irradiation (PCI) has shown to prolong survival in patients with extensive disease (ED) SCLC.

In this review, we will focus on recent advances made in RT. In our view, most significant already for daily practice are the use of stereotactic body radiation (SBRT) also known as stereotactic ablative RT (SABR) for stage I NSCLC,<sup>3</sup> concurrent chemoradiation for stage III NSCLC, the implementation of 4-dimensional (4D) computed tomography (CT) and positron emission tomography (PET), and adaptive RT strategies, the better integration of chest RT and chemotherapy for limited disease (LD) SCLC and PCI for ED SCLC.

## Stereotactic Ablative RT for Stage I NSCLC

In SABR, a few fractions of very high doses of radiation are delivered to small tumors that are located in selected lung regions (eg, those remote from the more susceptible central mediastinal structures such as the main bronchi, large vessels, and the esophagus). It is a new treatment option for early stage NSCLC in inoperable patients. The advantages of SABR compared with conventional irradiation are a short overall treatment time (1-2 weeks) and a high biological effective dose. The possibility to minimize the number of

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treatment sessions is an obvious benefit for medical inoperable patients suffering from cardiopulmonary disease and/or other comorbidities or simply because of their old age. SABR requires highly specialized RT treatment preparation and execution techniques including 4D respiration correlated CT scans and image-guided RT allowing precise patient positioning.

When 54-60 Gy in 3 fractions is delivered to patients with medically inoperable and peripheral located stage I NSCLC, local tumor control rates exceed 85% at 2 years, with approximately 5% subsequent estimated risk of pulmonary complications. For lesions with attachment to or close to the chest wall, the fractionation schedule of SBRT is adapted by delivering 8 fractions (7.5 Gy each), and analogous outcomes as with the 3-fraction regimen have been described.<sup>4</sup> It was demonstrated that a low pretreatment forces expiratory volume and/or diffusion capacity of the lungs for carbon monoxide alone should not be used to exclude patients with NSCLC from treatment with SBRT.<sup>5</sup> Although no phase III trials have been published comparing surgery with SBRT, the introduction of SBRT improved the survival of medically inoperable stage I NSCLC patients in a population-based analysis in The Netherlands.<sup>6</sup>

In the follow-up after treatment of these patients, CT and <sup>18</sup>F-deoxyglucose (FDG)-PET scans appear different after conventional RT, with the development of a mass-like consolidation on CT or persistent FDG uptake being described as long as 3 years and more posttherapy.<sup>7,8</sup>

### Concurrent Chemoradiation for Stage III NSCLC

After the superiority of induction chemotherapy followed by RT over RT alone was shown,<sup>9</sup> several randomized studies and 1 meta-analysis based on updated individual patient data have demonstrated a significant survival gain with concurrent chemoradiation compared with the sequential Schedule 10. The survival at 5 years increased from approximately 10% with sequential chemoradiation to approximately 15% with the concurrent approach. This improved survival has been attributed to improved local tumor control without affecting the incidence of distant metastases.<sup>10</sup> This improved survival is at the expense of a higher incidence of severe (though reversible) esophagitis, occurring in 20%-30% of patients. No increased lung toxicity was observed in the concurrent regimens. The trials all have been performed in the pre-PET era, however, current state of the art staging examinations (brain imaging and FDG-PET scanning) were not performed. For the suboptimal staged patients in these trials, according to current standards, the influence of improved local control positively affected the overall survival. The RT techniques used in the reported trials were essentially 2-dimensional- and sometimes 3-D-based without advanced dose calculation algorithms such as anisotropic analytical algorithm or superposition-convolution that take into account the dose of secondary photons and electrons and adaptive protocols, all of which were not available at the time when these studies were performed. The absolute long-term survival rates are thus likely to be higher in more recent series using modern delivery and verification techniques.

Because of the still high local tumor recurrence rates in nonsurgical series, 2 large phase III studies have addressed the role of surgical resection after induction treatment.<sup>11,12</sup> In the Lung Intergroup

Trial 0139, patients with resectable N2 disease were randomized between surgery and definitive chemoradiation after induction concurrent chemoradiation.<sup>11</sup> In the EORTC (European Organization for Research and Treatment of Cancer) trial, patients with unresectable N2 disease who showed at least a minimal tumor response after 3 cycles of induction chemotherapy were randomized between RT and surgery.<sup>12</sup> Both trials found identical 5-year survival rates in the surgical and the nonsurgical arms: approximately 25% in the Intergroup study (resectable tumors) and 15% in the EORTC trial (unresectable cancers). Although vigorously debated,<sup>13</sup> the results of these 2 randomized trials are in line with previous phase II studies.<sup>14,15</sup> In comparison, patients with resectable N2 disease receiving only chemotherapy followed by surgical resection, several single-institution phase II studies showed 5-year survival rates of approximately 20%, although subgroups may have a better outcome.<sup>16-18</sup>

Also in concurrent chemoradiation it is of utmost importance to avoid treatment delays. In a large series of the Radiation Therapy Oncology Group (RTOG), it was demonstrated that each day of treatment prolongation beyond approximately 6.5 weeks resulted in a 2% decrease of survival.<sup>19</sup> It is therefore logical that the RTOG found a positive association between higher biological RT doses and improved long-term survival rates.<sup>20</sup>

It should also be stressed that concurrent chemotherapy and RT is only safe in patients with no or limited comorbidities, who are relatively young, and have adequate organ functions. In a prospective, population-based study, we estimated that only about 40% of the patients with stage III lung cancer are suitable for the concurrent approach.<sup>21</sup> For the others, sequential chemotherapy and RT remains a reasonable alternative. Moreover, the search for improvements in the RT component of both sequential and concurrent chemo-RT continues. Apart from the combination of targeted drugs and RT and technical advances, altered fractionation schedules that move away from the classic 2 Gy per day, 5 days per week regimen, have been tested.

### Hyperfractionation

The basis of hyperfractionation (HFX) is to exploit the different capacity of cancer cells and late responding normal tissues to recover from sublethal radiation damage, given that the time interval between the 2 fractions is sufficiently long. An adequate interfraction interval is not trivial as the estimated recovery half-time in human tissues is in the order of 4 to 8 hours.<sup>22</sup> That HFX might be useful to improve the therapeutic ratio of RT is based on the difference in fractionation sensitivity between tumors and late-responding tissues. HFX with increased total dose compared with conventional fractionation may thus be an option to improve local control and survival in NSCLC, without increasing the risk of late normal tissue damage.

The combination of HFX with accelerated fractionation, leading to a short overall treatment time, was tested in the CHART (Continuous Hyperfractionated Accelerated Radiotherapy) trial.<sup>23</sup> In this schedule, 54 Gy is delivered in 12 days (3 times 1.5 Gy per day). In a large phase III trial, CHART was compared with the conventional schedule of 60 Gy in 30 fractions.<sup>7</sup> In the CHART arm, the 3-year local tumor control was 17% versus 13% in the conventional arm, with corresponding 3-year survival rates of 20% versus 13% ( $P = .008$ ). The CHART trial supported the hypothesis that accelerated

proliferation of cancer cells is an important reason for treatment failure.

In the Eastern Cooperative Oncology Group trial 2597, patients were randomized after induction chemotherapy to conventional fractionation (64 Gy in 6.5 weeks) or hyperfractionated accelerated radiotherapy (HART) (57.5 Gy in 2.5 weeks).<sup>24</sup> In the experimental arm, patients received 3 fractions of 1.5 Gy per day, 5 days a week. The HART trial closed prematurely after recruiting 144 of the planned 388 patients, because of low patient accrual and logistical issues. The study was therefore underpowered to detect the hypothesized improvement in median survival from 14 to 21 months. The actual observed median survival was 14.9 months after conventional fractionation and 20.3 months after HART ( $P = .28$ ), which is close to the a priori study hypothesis.

A phase II trial investigated induction chemotherapy combined with CHART in locally advanced NSCLC, in which 56 Gy was delivered in 36 fractions in 12 days. Toxicity observed was mild and the median overall survival was 15.7 months.<sup>25</sup>

The CHART regimen, but without irradiation during weekends, is “CHART Weekends Less” or CHARTWEL.<sup>26</sup> In a phase III trial, 406 patients with NSCLC were randomized between RT to 60 Gy/40 fractions in 2.5 weeks (CHARTWEL) or 66 Gy/33 fractions in 6.5 weeks (conventional fractionation; CF). Overall, the outcome after CHARTWEL or CF was not different. The lower total dose in the CHARTWEL arm was compensated by the shorter overall treatment time, confirming a time factor for NSCLC. However, an exploratory analysis showed a significant trend for improved local tumor control after CHARTWEL versus CF with increasing Union Internationale Contre le Cancer (UICC), T or N stage ( $P = .006-.025$ ) and after neoadjuvant chemotherapy (hazard ratio, 0.48; range, 0.26-0.89;  $P = .019$ ). The higher efficacy of CHARTWEL versus CF in advanced stages and after chemotherapy thus provides a basis for further trials on treatment intensification for locally advanced NSCLC. These studies are currently accruing in the United Kingdom.

## Trials of Altered RT Schedules in Lung Cancer

Many randomized phase III trials have been performed in which in 1 arm the RT schedule was different from the standard 2 Gy per day, 5 days per week.<sup>27</sup> When considering all studies, patients being treated with high-dose RT delivered in short treatment times, seem to have the best long-term survival. The results of a meta-analysis based on updated individual patient data are to be awaited.

## Individualized Accelerated RT

The overwhelming majority of trials stratify patients according to the assigned specific radiation doses to different risk groups. As a consequence, an important proportion of patients (eg, those with large tumors or with cancers in the proximity of critical structures such as the spinal cord) will not be able to receive the prescribed dose and be excluded from the study because of normal tissue constraints. Patients with smaller, more conveniently situated cancers will easily attain the prescribed dose without increased risk of toxicity, thus theoretically being undertreated because higher radiation doses could have been but were not given. Ideally one would like to individualize RT doses and deliver the highest possible radiation dose according to

the highest individual achievable radiation dose taking into account the wide diversity in patients with regard to localization, tumor size, and dose-limiting organs at risk. As stated earlier, to overcome repopulation the dose should be delivered in a short overall treatment time. It was estimated that applying such an individualized scheme a gain in tumor control probability of about 25% could be reached compared with a classical scheme of 60 Gy in 2-Gy fractions in 6 weeks.<sup>28</sup> In a phase II trial van Baardwijk et al investigated such an individualized iso-toxic accelerated RT (INDAR) scheme in 166 patients treated with sequential chemoradiation or RT alone.<sup>29</sup> Most patients had bulky, multiple nodal stage N2 or N3 disease. The target volume was defined as the primary tumor and the pretreatment involved lymph nodes on FDG-PET-CT scan. The radiation dose was individually escalated until a dose-limiting normal tissue constraint was reached: a maximal mean lung dose of 19 Gy, a maximal dose of 54 Gy for the spinal cord, and a maximum of 70.2 Gy for centrally located structures, like the main bronchi. The INDAR scheme showed promising results with acceptable toxicity: approximately 20% of acute grade 3 and 2.4% of acute grade 4 toxicity and <5% of grade 3 late toxicity. With a median follow up of 32 months, the median overall survival was 21 months with a 2-year overall survival of 45%. INDAR was subsequently tested in concurrent chemo-RT in a group of 137 patients with stage III NSCLC.<sup>30</sup> A median dose of 65 Gy was given in <5 weeks. Although this scheme showed more acute grade 3 toxicity, this consisted of mainly transient esophagitis. With a median follow-up of 21 months, the estimated median overall survival was 22.3 months. However, more mature results need to be awaited.

Another strategy to further individualize radiation treatment is to develop an assay to predict toxicity of organs at risk. This might be based on biomarkers like cytokines interleukin-6 or transforming growth factor- $\beta$ 1, or image-based. However data are still limited,<sup>31,32</sup> and cannot be implemented in daily practice yet. Nomograms based on clinical and other parameters offer already now a practical way to define risk groups with reasonable accuracy.<sup>33,34</sup>

## Radiation Therapy Target Determination

As the accuracy of FDG-PET is higher than CT for the staging of mediastinal lymph nodes, the incorporation of PET in the treatment planning process of RT has received a lot of attention. In many theoretic studies in NSCLC, the use of PET has resulted in smaller radiation fields which may lead to fewer side effects or to the possibility of radiation dose-escalation with the aim to improve local tumor control.<sup>35,36</sup> Prospective studies indeed showed that selective mediastinal node irradiation based on FDG-PET scans did not lead to higher isolated nodal recurrences.<sup>37,38</sup>

Another important feature to support FDG-PET integration in RT planning, is that it reduces the variability of tumor delineation among radiation oncologists<sup>39-41</sup> and even allows for automatic tumor delineation where the computer provides radiation oncologists with delineations that can be edited.<sup>42</sup> The latter is very important, for the resolution of clinical PET scanners is approximately 5-7 mm, edges are blurred, and movements interfere significantly with PET signals. 4D-PET-CT scans may therefore become another step forward in tumor target delineation.

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It is highly likely that FDG-PET could help identify therapy-resistant areas within the tumor that could be eradicated if a higher radiation dose was given and hence lead to a better local control and survival.<sup>43,44</sup> Dose escalation on the high FDG-PET area within the tumor is currently pursued in ongoing trials.

### Strategies to Deal With a Moving Lung Tumor

A conventional planning CT scan consists of images without time information from the moving lung tumor and anatomy of the patient pretreatment. This 3-D planning CT scan is an arbitrary snapshot of the anatomy at a random moment of the breathing phase. During treatment, the patient is breathing freely, which results in a tumor position uncertainty. To overcome this tumor position uncertainty several strategies are currently introduced:

(1) Gated RT; the tumor is irradiated only during a part of the breathing cycle (gating window). During gated RT, the respiration is measured externally by respiration sensors (eg, skin markers or belt) and/or internally using fluoroscopy<sup>45,46</sup> to determine when the beam should be on and off. Gated treatment is mostly performed with patients free-breathing,<sup>46</sup> however, breath-hold irradiation<sup>47</sup> is also possible. Gating is generally performed in exhalation, because the exhale respiration phase is more reproducible and takes longer than inspiration.

(2) Tumor tracking (irradiating the tumor dynamically with a moving beam)<sup>48</sup> results in similar target volumes as gating. This technique is still under development at various centers and not applied in a routine setting.

(3) The use of a midventilation (MidV) planning CT scan for treatment planning increases geometrical accuracy. The MidV CT scan represents the tumor in its time-averaged position over the respiratory cycle.<sup>49</sup> Using this MidV planning CT scan, the systematic deviation from its average position due to breathing motion can be reduced to nearly 0, permitting a significant reduction of the treatment margin needed to correct for tumor motion.

However, with all scenarios described above, one has to be careful with baseline differences of the tumor position during the course of treatment. Such a difference might be tackled using image-guided or adaptive RT (see further).

### Intensity Modulated RT

Intensity modulated RT (IMRT) requires a treatment planning that is almost entirely computerized, and represents a major change in the way RT treatments are planned.<sup>50</sup> IMRT is a technical improvement of 3-D conformal RT by applying nonuniform (modulated) radiation intensity over the treatment fields. IMRT has enabled larger tumor volumes to be irradiated to a radical dose (because of a steeper dose fall-off). Schwarz et al<sup>51</sup> analyzed IMRT dose distributions in the organs at risk and compared the results with conventional conformal RT techniques in 10 lung cancer patients participating in a dose escalation trial. The constraints used for the organs at risk were the same as the constraints used in a dose escalation trial using 3-D conformal RT. Schwarz concluded that the IMRT technique together with the acceptance of dose heterogeneity within the target volume allowed further increase of radiation dose, especially in patients with mediastinal involve-

ment of their lung cancer (patients with large and concave tumors). Using IMRT a dose escalation of 20%-35% compared with 3-D conformal RT was achieved.<sup>51</sup>

### Image-Guided RT

For the irradiation of lung cancer geometrical uncertainties like patient setup variation, organ motion, and delineation variation must be kept as low as possible.

Modern linear accelerators equipped with multileaf collimators and in-room imaging options have enabled the delivery of more accurate irradiation. The multileaf collimators are used to automatically create individualized treatment fields and the in-room imaging options facilitate image-guided RT (IGRT): in IGRT images of the patient acquired just before a treatment fraction are used to measure or estimate the position of the patient's anatomy at a given time to ensure correct placement of the radiation treatment beams. IGRT considerably increases the precision of RT as lung tumors move during treatment and change between treatment fractions because of tumor shrinkage and radiation-induced pulmonary changes.

Because of the high level of accuracy reached using IGRT delivery the margins around the tumor can be reduced and we can safely irradiate to higher doses the lung tumor and pathologic lymph nodes. IGRT can be performed using:

(1) Electronic portal imaging devices (EPIDs) that image the radiation that has passed through the patient (megavolt imaging). The EPID can be used to reduce setup errors to monitor target position during radiation delivery by acquiring megavoltage CT scans.<sup>52,53</sup>

(2) Kilovoltage or MV x-ray tubes and detectors that image the patient can be used for pre- or posttreatment cone beam CT acquisition, provide superior tumor visualization compared with MV imaging. For real time tumor tracking images radio-opaque markers are particularly useful. These radio-opaque markers should be implanted into or near the tumor. Verification of tumor motion at the time of treatment may be performed using 4D cone beam CT scanning.<sup>53</sup>

(3) Optical monitoring of a point (or points) on the patient surface gives real-time information. The optical signals can be used to monitor respiration and patient motion for respiratory gated RT, and also be combined with kV or MV imaging data to estimate internal target positions.<sup>54</sup>

(4) Magnetic resonance imaging is a newer modality for in-room imaging for lung tumors under development by several groups.

Several authors have studied interfraction patient setup errors and reported 4-mm systematic and 3-mm random errors (1 SD). Setup correction protocols have been developed to reduce these patient setup errors. Using simple off-line correction protocols (imaging approximately one-third of the fractions), the systematic error can be reduced by a factor 2 to 3.

More recently, considerable day-to-day variation of the tumor relative to the bony anatomy (baseline shifts) were observed.<sup>55,56</sup> Tumor visualization or accurate surrogates are required to correct for these baseline shifts. In the absence of such corrections, the application of gated treatment delivery is not recommended.

The type of correction strategy applied to reduce geometrical uncertainties needs to be in balance between workload and precision



and depend on the fractionation scheme prescribed. For conventional fractionation using a large number of fractions, a less precise correction strategy is generally considered adequate.

### Adaptive RT

Computed tomography image-guided (either cone-beam or conventional CT) RT, allows repetitive imaging of the anatomy in 3-D during the 5 to 6 weeks of a radiation course. During the course of treatment, tumor progression or regression may be seen as well as other anatomical changes within the thorax requiring replanning and/or treatment adaptation. In a study by Schaake et al<sup>57</sup> anatomic changes during conventional RT with curative intent was quantified. In this study, 114 consecutive lung cancer patients were included, treated with conventional RT with a dose of 45-88 Gy over 5-6 weeks for cT1N0 to cT4N3 NSCLC. Patients received repetitive cone-beam CT scans for an off-line setup correction protocol. The tumor volume was delineated on the planning CT and the cone-beam CT each treatment week. The occurrence or resolution of atelectasis, and pleural effusion were scored qualitatively. In one-third of the lung cancer patients, tumor regression was seen over the 5-6 week course of conventional treatment. Forty-seven patients (41%) manifested considerable anatomical changes in at least 1 of the categories. Further research is needed to monitor anatomical changes during treatment and quantify whether the delivered dose meets the treatment intent.

### Timing of Chest RT for LD-SCLC

Many phase III studies have investigated the timing of chest radiation in LD-SCLC (reviewed in Fried et al,<sup>58</sup> and Pijls-Johannesma et al<sup>59</sup>). When all studies were considered, the delivery of early versus late thoracic irradiation did not influence the survival. However, when the most active chemotherapy regimen (platinum-based) was administered concomitantly with chest RT, long-term survival was increased at the expense of a higher incidence of severe, though transient esophagitis. At 5 years, the survival was significantly higher when chest RT was given early (ie, within 30 days after the initiation of chemotherapy), representing a 5-year survival rate of 20.2% for early versus 13.8% for late thoracic RT. In a pivotal phase III study,<sup>60</sup> decreasing the overall treatment time of chest RT from 5 weeks (2 Gy once per day) to 3 weeks (1.5 Gy twice per day), while keeping the total radiation dose to 45 Gy, increased the 5-year survival from 16% to 26%.

Early, concurrent chemotherapy with accelerated radiation may result in approximately 20%-30% grade 3 acute esophagitis, which contrasts with approximately 15% in early, concurrent, nonaccelerated RT and approximately 5% in sequential schedules. Interestingly, lung toxicity appeared not to be influenced by the timing of RT.

It has been hypothesized<sup>61</sup> that accelerated repopulation is triggered by the first dose of any effective cytotoxic agent and that in order to obtain local tumor control, the last tumor clonogen should be killed by the last irradiation. It follows from these 2 assumptions that the long-term tumor cell survival should decrease with increasing time between the start of any treatment to the end of RT (SER). A meta-analysis of published data showed superior long-term survival if the SER was kept to less than 30 days in LD-SCLC.<sup>61</sup>

These results are consistent with accelerated proliferation of tumor clonogens triggered by RT and or chemotherapy. As expected, accelerated treatments also cause more toxicity in rapidly proliferating tissues such as the esophageal mucosa.

In conclusion, for limited-stage small cell lung cancer, current evidence supports the early administration of thoracic RT with concurrent cisplatin and etoposide chemotherapy.

In the only prospective study that was specifically designed to selectively irradiate CT enlarged nodal areas in limited disease SCLC, in 11% of the patients, isolated nodal failures were observed.<sup>62</sup> Because of the higher staging accuracy of FDG-PET also in SCLC, a prospective study in which the nodal target volume was defined on the basis of FDG-PET was performed.<sup>63</sup> Only 2 patients out of 60 patients included (3%) developed isolated nodal failures. Because of the reduced target volume irradiated after FDG-PET treatment preparation compared with elective nodal irradiation the incidence of severe esophagitis can be reduced, even in these often high-volume tumors.<sup>63</sup> These findings were subsequently confirmed in an American retrospective study.<sup>64</sup>

### Prophylactic Cranial Irradiation for ED-SCLC

Prophylactic cranial irradiation is standard treatment in stage I-III SCLC, but its role in stage IV has only recently been studied in randomized studies.

In patients with ED-SCLC who had any response to chemotherapy, PCI was compared with no PCI in a prospective, randomized study.<sup>65</sup> Patients in the PCI group had a lower risk of symptomatic brain metastases. The cumulative risk of symptomatic brain metastases within 1 year was 14.6% in the irradiation group (95% confidence interval [CI], 8.3-20.9) and 40.4% in the control group (95% CI, 32.1-48.6). Irradiation was associated with an increase in median disease-free survival from 12.0 to 14.7 weeks and in median overall survival from 5.4 to 6.7 months after randomization. The 1-year survival rate was 27.1% (95% CI, 19.4-35.5) in the PCI group and 13.3% (95% CI, 8.1-19.9) in the control group. Irradiation had side effects, especially fatigue but did not seem to have a clinically significant effect on global health status, although the long-term toxicity was not examined.

### Conclusions

Beside undisputable advances in systemic treatment and improved surgical techniques, RT has further improved. Among the most significant evolution that have direct influence in standard practice are the more wide-spread use of SABR for stage I NSCLC, concurrent chemoradiation for stage III NSCLC, the timing of chest RT for LD SCLC and PCI for ED-SCLC, which all contributed to the better survival of patients with lung cancer. The respiration correlated 4D CT treatment planning, IMRT and image-guided techniques like cone beam CT scanning open a completely new episode of high geometrical precision RT, which may be further improved with new beam qualities such as proton therapy.<sup>66</sup>

### Disclosure

None declared.

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