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Modern Radiotherapy as Part of Combined Modality Treatment in Locally Advanced Non-Small Cell Lung Cancer: Present Status and Future Prospects

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Key Words. Lung cancer • Radiotherapy • IMRT • Stage III • Chemoradiotherapy

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Learning Objectives
After completing this course, the reader will be able to:
1. Employ the current standard of care for stage III NSCLC.
2. Balance the relative merits and risks of IMRT in this disease and position its indication.
3. Advocate the need for further research for improvement in this field.

Abstract
Locally advanced stages account for approximately one third of the incident presentations of non-small cell lung cancer (NSCLC). Optimal treatment in selected patients consists of an integration of chemotherapy and radiation therapy. Both modalities have seen numerous advances in the last decade. This article reviews the current status and outcome of treatment in stage III NSCLC, with special emphasis on the role of novel techniques in radiation treatment, including intensity-modulated radiation therapy. The obstacles for improving local control are identified and the technical progress that aims at removing these obstacles is addressed. The Oncologist 2008;13:700–708

Locally Advanced Non-Small Cell Lung Cancer: Present Status of Treatment and Outcome
More than 80% of the 213,000 incidental cases of lung cancer in the U.S. are of the non-small cell variant—non-small cell lung cancer (NSCLC)—and approximately 37% of these present at diagnosis with locoregional involvement [1]. The latter means that the tumor has spread out of the confines of the lung into the surrounding structures without clinical evidence of dissemination. This extension varies from tumors locally abutting the chest wall, diaphragm, or mediastinum (T3) to frank invasion of the mediastinal tis-
sues and organs (T4) and nodal invasion in either the ipsilateral mediastinal lymph nodes (N2) or the supraclavicular or contralateral mediastinal lymph nodes (N3) [2]. Although some of these extensions are not a formal barrier for radical surgery (e.g., T3N0/1), preferably followed by adjuvant chemo- and/or radiotherapy, most T4 lesions and cases of clinical mediastinal lymph node invasion are considered beyond the limits of immediate surgery. They are referred to as stage III NSCLC and subclassified into IIIA whenever N2 nodes are involved (or T3N1 tumors) and into IIIB whenever any N3 or T4 involvement is present. The surgical–radiological correlation of the mediastinal lymph nodes was recently described [3].

Different techniques are available to ascertain mediastinal (lymph node) invasion: fluorodeoxyglucose positron emission tomography (FDG-PET) scan with or without integrated computed tomography (CT) scan, endoscopic fine-needle aspiration (FNA) biopsies, and surgical techniques such as mediastinoscopy and thoracoscopy. There is overwhelming evidence that PET scanning stages disease in the mediastinum with a higher accuracy than CT, suggesting that the primary use of metabolic information is for mediastinal staging. The currently available data confirm that combined PET–CT scanning is superior to PET scanning alone for T staging [4]. This advantage is largely attributable to the ability of CT to determine tumor extension into adjacent tissue and to accurately measure tumor size. The advantage of combined PET–CT scanning over PET scanning alone for N staging appears to be marginal.

Staging guidelines advise tissue confirmation of FDG-avid lymph nodes if no contraindication for surgery pertains [5]. There is increasing evidence that mediastinal nodal staging by FNA taken under endoscopic ultrasonic guidance through the wall of the esophagus or of the tracheobronchial tree has a similar accuracy to surgical techniques but without their complications, costs, and inconvenience [6, 7].

The overall 5-year survival rate for locally advanced lung cancer is 16% [1]. In the past decade, meta-analyses have gradually shifted the standard of care in selected patients with stage III NSCLC from radical local treatment only, over sequentially administered systemic and locoregional treatments, to the present concurrent chemoradiotherapy [8, 9]. The role of surgery as local treatment following induction chemo(radio)therapy in stage IIIA–N2 NSCLC was recently challenged by two large randomized trials, showing no statistically significant difference in overall survival compared with definitive radiation therapy (RT) [10, 11]. The role of surgery, if any, in stage III NSCLC with clinical nodal involvement is hence to be considered limited [12, 13].

Present-day survival figures for selected patients with stage III NSCLC treated with concurrent chemoradiotherapy are on the order of a median survival time of 17 months and a 3-year survival rate of 25%, versus 14 months and 18% with a sequential approach. Factors predictive of outcome are performance status, stage (IIIA/B), weight loss, and pathological downstaging of the mediastinal nodes and/or the tumor with induction treatment. The relapse pattern typically shows that both modalities do not completely control remission of the tumor in 80% of patients, with equal numbers of patients failing intrathoracically, extrathoracically, and both [14]. Improvements in the combined modality outcome should hence come from improvements in local and systemic therapies.

Successful interventions to increase local control with RT include dose escalation, altered fractionation, and integration with concurrent chemotherapy [15]. These interventions increase the tumor cell kill by a variety of mechanisms, inflicting more initial radiation damage and decreasing repair or counteracting the effects of cancer-cell proliferation. We discuss these interventions below.

### Dose Escalation

Conventional thoracic RT administers a boosted 60–63 Gy of radiation in 1.8- to 2.0-Gy fractions on a so-called involved field (IF), where the target volume includes the primary tumor and those lymph nodes assumed to be involved based on their size on a CT scan. This approach requires three-dimensional conformal radiation therapy (3D-CRT), a technique characterized by beam outlines that match the shape of the target volume. Mapping of the IF may be better when using combined FDG-PET–CT scanning or, ideally, by including the results of the above-mentioned endoscopic features, to match as close as possible the actual tumor volume [16]. Several uncontrolled series have now shown that IFRT results in a low incidence of isolated “out-of-field” nodal failures [17]. A randomized clinical trial in stage III NSCLC patients comparing elective field mediastinal nodal irradiation to a dose of 60–64 Gy with IFRT to a dose of 68–74 Gy has been presented [18]. In the IFRT arm, comparable local tumor control (41% versus 49%), a significantly lower incidence of radiation pneumonitis (29% versus 17%), and a superior 3-year survival rate were observed. Only 7% of patients treated with IFRT developed failures in elective nodal regions, supporting the use of IFRT as the standard approach [19].
Altered Fractionation
The Eastern Cancer Oncology Group compared hyperfractionation with standard once-daily fractionation both given concurrently with chemotherapy for NSCLC, and the efficacy benefit did not achieve statistical significance [20]. The trial was closed prematurely because of poor accrual but demonstrated a rather impressive longer median survival time as well as greater 2-year and 3-year survival rates in the recipients of hyperfractionated radiation. Conventional daily 1.8- to 2.0-Gy fractionation nevertheless seems to remain the standard in combination with chemotherapy. Phase I and II studies in selected patients with stage III NSCLC have shown the feasibility of escalating the total dose to 74 Gy, concurrent with chemotherapy [15]. A randomized phase III trial investigating 3D-CRT to 60 Gy versus 74 Gy with concurrent chemotherapy is underway. The recently increased interest in hypofractionation is discussed further.

Integration of Chemotherapy and IFRT
Improvement in the integration of chemotherapy and IFRT is confounded by the presence of numerous associated treatment variables. Among these are the optimal dose, schedule, and regimen of chemotherapy during, preceding, and following RT and the role, if any, of novel biological agents such as monoclonal antibodies or tyrosine kinase inhibitors. The reader is referred to a recent review [15] for an in-depth discussion of this issue.

Modern RT Techniques
Each of the above-mentioned three interventions has the drawback of increasing the rates of radiation pneumonitis and esophagitis, the main radiation dose–limiting toxicity. Pulmonary radiation toxicity depends on various patient, tumor, biological, and treatment factors; among the latter is the mean radiation dose to the lung and the volume of healthy lung exposed above a threshold dose (20 Gy, V20; 30 Gy, V30) [21, 22]. Esophagitis is also primarily related to dosimetric factors, including the length or the circumference of the esophagus irradiated above a threshold dose [23]. The dose–volume–toxicity relationships mean that better dose-localization techniques, like intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), breathing-adapted RT (gating or tracking), particle beam therapy, or a combination of these, can decrease the incidence of toxicity or, alternatively, allow dose escalation, altered fractionation, or chemoradiation. The limited ability of conventional RT to control stage III NSCLC in the thorax puts the focus for dose-localization techniques on increasing local control rather than on decreasing toxicity. Proof-of-principle for these techniques is now being acquired. The early experience with IGRT using the so-called FDG-PET–CT scan painting technique has been reported to result in a low isolated nodal failure rate [24]. Similarly, proton beam therapy permitted higher total doses with concurrent chemotherapy, yet was associated with fewer esophageal reactions than with 3D conformal photon therapy [25]. However, routine use of proton therapy for stage III NSCLC is not yet possible because the installed base of equipment is insufficient. In contrast, photon IMRT equipment is widely available.

IMRT is capable of sparing normal structures by the generation of strong dose gradients and concave dose distributions [26–29]. Gradients and concave dose distributions are the keys to delivering high doses to the tumor while keeping the dose and irradiated volume of critical structures like the lung, spinal cord, esophagus, large airways, and vessels below tolerance levels (Fig. 1).

However, dose delivery takes several minutes in IMRT of lung tumors, and blurring of the dose gradients may occur as a result of interference between respiratory motion
4D Techniques

The acquisition of PET and (slow) CT images under shallow breathing leads to motion-distorted images of the patient’s anatomy. Subsequent delineations may take advantage of these images by encompassing the motion in the contours, which obviously overestimate the tumor volume. With the common practice of delivering radiation under shallow breathing, it seems logical to deposit the dose in the motion-encompassing tumor volume to ensure that the prescription dose is reached everywhere in the moving tumor. Because of technical developments in 4D imaging and 4D image-guided delivery, the motion-encompassing volume can be rendered much smaller. These 4D techniques can be classified into three groups: respiratory control [34], gating, and tracking [35]. Respiratory control techniques involve assisted or voluntary pausing of respiration in a selected phase of the respiratory cycle. Irradiation is performed during the respiratory pauses and is turned off when the respiratory motion resumes. Pausing at (deep) inspiration adds the additional benefit of reducing the relative volume of irradiated lung [36]. Gating means enabling irradiation when the motion amplitude coincides with a preselected sector of the respiratory cycle and halting the beam when the respiratory motion travels outside this sector. Tracking involves intentionally moving the irradiating beam so that it follows the movement of the tumor. Each technique requires considerable investments in the chain of imaging, planning, and delivery of IMRT. Acquiring a 4D technique is a must for centers that wish to exploit the full potential of IMRT in stage III NSCLC.

Dose Painting

A central dogma in RT is to strive for dose homogeneity in the PTV. This seems odd because intratumor heterogeneity of radioreponsiveness has been known for decades [37]. Because this heterogeneity cannot be unambiguously imaged for RT-planning purposes, the zeroth order solution was to assume radioreponsiveness to be equal across the tumor volume. For homogeneous radioreponsiveness, radiobiological models show that by applying a homogeneous dose, the highest tumor-control probability (TCP) can be obtained for the lowest energy deposition. Thus, striving for dose homogeneity served the as-low-as-reasonably-achievable principle. However, with precise knowledge of intratumor heterogeneity, the radiobiological models, rather intuitively, show that an inhomogeneous dose allows for obtaining the highest TCP for the lowest energy deposition. New imaging modalities mostly based on PET, functional magnetic resonance imaging, and magnetic resonance spectroscopy now have started to uncover radiobiological information that can then be integrated into IMRT planning [38]. The new concept of “dose painting IMRT”
Aims to exploit inhomogeneous dose distributions adapted to intratumor heterogeneity. Tumor regions of higher radiation resistance may, in the future, be “painted” with an escalated dose while radiation-sensitive regions receive conventional or even de-escalated dose levels. The flow of procedures to accomplish dose painting is drawn in Figure 2. Dose painting techniques lead to highly structured dose distributions. It is self-evident that planning and delivering such dose distributions requires a 4D technique to account for tumor motion or, alternatively, selecting only those patients with minimal tumor motion. To exploit the power of dose-localizing techniques for moving tumors, 4D techniques should be acquired first, with dose painting thereafter.

Dose Intensity

Local control rates in the range of 70%–100% have been reported for stage I–II NSCLC patients with a variety of schedules, with the common principles being (a) fraction sizes of 6–30 Gy, (b) fraction numbers of 1–10, and (c) short overall treatment times of 3 weeks to the time needed to deliver a single fraction (Table 1). The dose intensity of these schedules is substantially higher than the 60–70 Gy delivered in 30–40 fractions over 6–7 weeks commonly given for stage III NSCLC. Explanations for the apparently much higher local control rates reported for the dose-intensive schedules than for conventional fractionation include reduced repopulation by short overall treatment times or low α/β tumor values, which is a signature of a high damage-repair capacity between small radiation fractions [39]. Tumor response mediated by the effects of large fraction sizes on the neovasculature [40] may be an alternative explanation for the favorable results of the dose-intensive schedules in stage I–II patients. The spectacular results in early-stage NSCLC are hypothesis-generating for phase I–II studies using high dose intensities in stage III NSCLC. Such trials should be conducted with extreme care. In the lung, as well as in other tumor sites, large-fraction doses are well tolerated only when they are applied to relatively small volumes. Even when delivered to small volumes, radiographic changes consistent with bronchial or vascular damage are common and increase with fraction dose [33]. Regional differences in tolerance to large fractions have been demonstrated in the thorax. Using three fractions of 20–22 Gy, patients treated for tumors in the peripheral lung had a 2-year
freedom from severe toxicity rate of 83%, compared with only 54% for patients with central tumors [42]. Schedules applying total doses around 60 Gy in 6- to 10-Gy fractions seem to also be safe for central tumors [43], but the critical volume of application is unknown.

With the frequent occurrence of large tumor volumes and the central location in stage III NSCLC, high dose intensity may seem impractical unless the volume and the regional fraction size are simultaneously controlled. This would mean the delivery of a smaller fraction size to the PTV subvolume nearby or inside the mediastinum than to the subvolume in the peripheral lung. Dose-painting IMRT is capable of meeting such objectives and may render dose-intensive schedules tolerable in stage III NSCLC.

**PUBLISHED RESULTS OF IMRT IN NSCLC**

IMRT has found widespread use, but the published clinical data for NSCLC are scarce. As of January 2008, only two clinical studies were published as full papers [44, 45]. A case series by Yom et al. [44] retrospectively reported on 68 NSCLC cases treated with IMRT and concurrent chemotherapy. Pulmonary toxicity was compared in 222 similar patients treated with 3D conventional RT. They found significantly lower levels of grade 3 or greater treatment-related pneumonitis at 12 months in the IMRT group (8% versus 32%). In contrast, Holloway et al. [45] reported on a phase I dose-escalation study of PET–CT scan guided IMRT with respiratory gating, employing accelerated fractionation with induction chemotherapy. That study was halted because one of the five patients enrolled in the study developed lethal pneumonitis at a dose of 84 Gy in 35 fractions. The authors pointed to the pre-existing deficient lung function in the deceased patient, the combination of RT and chemotherapy, the influence of respiratory gating on the relation between V20 and the probability of radiation pneumonitis, and the hypofractionated high-dose radiation regime (84 Gy in 35 fractions of 2.4 Gy each) as possible factors contributing to the severe complication. In addition, erroneous dose computation, underestimating the dose to the lung, was likely to be a contributing factor [46].

Although challenges of dose computation in the lung and at interfaces between the lung and higher density tissues for IMRT plan optimization have been adequately addressed, data on the use of IMRT to improve local control in stage III lung cancer remain scarce for other reasons discussed before, like large target volumes, uncertainties related to breathing [47], and relapses in the high-dose area at conventionally fractionated doses reaching up to 104 Gy [48]. Now we are in an era in which 4D RT and dose painting with IMRT offer the prospect for stage III NSCLC of using the dose-intensive schedules that have revolutionized local control rates in stage I–II NSCLC.

**CONCLUSION**

The optimal treatment of locally advanced NSCLC is by itself a moving target. There is a strong conviction that modern RT as part of a multimodality approach in stage III patients will further improve outcome. The last decade has

<table>
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<th>Study</th>
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<th>Dose (Gy) per fraction</th>
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<th>Biological equivalent dose (Gy)</th>
<th>Local control rate (%)</th>
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<td>Onimaru et al. [52]</td>
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Abbreviations: NA, not available; NSCLC, non-small cell lung cancer.
seen the advent of several novel radiation techniques that are likely to improve local control by the delivery of higher radiation doses to smaller volumes, allowing for less toxicity. These techniques are not mutually exclusive, but instead are complementary to each other. Further implementation of these techniques needs well-designed clinical trials in appropriately selected patients and taking into account as many of the different variables present and options available. Opinions differ as to whether these advances should all be confirmed by randomized trials or whether adequately sized-matched case–control studies will provide sufficient evidence. We must, however, ensure that evolution equals progress. Our patients deserve this dedication.

APPENDIX: EXAMPLE OF A COMMONLY USED PROCEDURE FOR TARGET DELINEATION

Patient Positioning and Image Acquisition
Imaging for planning consists of an FDG-PET scan and a CT scan executed on an integrated PET–CT scanner with the patient lying on a flat couch in the supine position, with the arms alongside the body and using a neck support and a knee rest. The patient is instructed to breathe quietly. Two sets of adjacent 2- to 5-mm CT slices are acquired (120 kV, 250 mAs). The first set, acquired without i.v. contrast, is used for dose computations. The second set, acquired with i.v. contrast, is used for delineation of target volumes and organs-at-risk (OAR). For the PET scan, 0.1 mCi (3.7 MBq) of FDG/kg is injected i.v. and the emission acquisition (5 minutes/bed position) starts 50 minutes later.

Target Volumes
Gross Tumor Volume
The gross tumor volume (GTV) is delineated using a two-step procedure (Fig. 3). The first step involves an automatic or manual delineation of the primary tumor and the pathological lymph nodes using the FDG-PET scan. The PET scan is acquired during quiet breathing and contains internal motion. The second step uses the information from both imaging modalities. The PET-delineated GTV is adapted where the CT scan information is considered contributive. The lung window setting is used to define the edge between the lung tissue and tumor; mediastinal window settings are

Figure 3. The preliminary GTV (red) contour, based on the PET scan (B), is overlaid on the CT scan (A). Adaptation of the preliminary PET-based contour, using the CT scan, yields the GTV (displayed in rose).
Abbreviations: CT, computed tomography; GTV, gross tumor volume; PET, positron emission tomography; PTV, planning target volume.

Figure 4. Isodose distribution on transverse (A) and coronal (B) sections. The gross tumor volume is delineated in red; the planning target volume is delineated in blue.
selected to define the edge of the tumor and mediastinal tissues.

**Clinical Target Volume**

Elective nodal irradiation is not prescribed. The clinical target volume (CTV) includes the GTV and microscopic extensions. The CTV results from a 5- to 8-mm [58] expansion of the GTV with restrictions on the expansion at anatomical boundaries like air cavities or normal-appearing structures like bone, cartilage, or vessels.

**PTV**

Image acquisition during quiet breathing ensures inclusion of respiratory motion in the GTV and the CTV. A 3- to 5-mm margin for setup error is added to the CTV to create the PTV.

**OAR**

The following OAR are usually delineated: the spinal cord, lungs, esophagus, and heart. The liver and left and right kidney are delineated for tumors close to the diaphragm and if oblique beam directions are used that could traverse these organs.

**Planning Aim**

IMRT is an optimization process performed by computers. The planning aim is predefined for the PTV and OAR. Optimization means that the computer searches for beams and intensity modulations to obtain a dose distribution that approaches as close as possible all planning aims. Plan evaluation includes the study of the optimized dose distribution by a variety of tools, including slice-by-slice inspection of dose-distribution plots overlaid on the CT scan (Fig. 4).

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**AUTHOR CONTRIBUTIONS**

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Final approval of manuscript: Jan P. van Meerbeeck, Sabine Meersschout, Rebecca De Pauw, Indira Madani, Wilfried De Neve

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