Chapter 8

General discussion and future directions

The search for optimal management in patients with locally-advanced (stage III) non-small-cell lung cancer (NSCLC) remains a great challenge. In early-stage NSCLC, advances in surgery and stereotactic ablative radiotherapy have lead to recent improvements, even in the sub-group of Dutch patients aged 75 years and older, where the median survival has increased to 24.4 months [1]. However, the majority of patients still present with more advanced stages of disease, where curative-intent treatment options are limited. Survival in stage III NSCLC is modest with a meta-analysis of studies (conducted between 1988 and 2003) reporting a median survival of 18 months [2]. Limited progress is reflected by the improved loco-regional tumor control achieved by administering concurrent chemoradiotherapy (CCRT), which is currently the standard treatment for fit patients presenting with stage III NSCLC [3]. However, rates of distant metastases remain high, and manifest in more than 40% of patients with potentially operable disease [2].

Therefore, stage III NSCLC should be considered as a systemic disease, and important gains may be achieved by developing more effective systemic therapy. We evaluated the combination of cisplatin and epirubicin as induction chemotherapy in a phase II study, and the observed response rates were unsatisfactory. With the growing use of CCRT, new treatment regimens have to be tested for safety and efficacy in both single-modality settings and in combination with radiotherapy, a process that can take many years to accomplish. In comparison to sequential chemoradiotherapy, CCRT is associated with more acute reversible grades III and IV esophageal toxicity (respectively from 4% to 18%) [2]. Similarly, grades III to V pulmonary complications including radiation pneumonitis were observed in 16% of 194 patients treated in the definitive CCRT arm of Intergroup trial 0139 [4].

The role of surgery in stage III NSCLC remains unclear as two phase III trials showed no survival benefit in the treatment arm where surgery was involved after chemo-(radio)therapy [4, 5]. However, patients with proven nodal downstaging after induction CCRT and resectable disease by lobectomy might benefit from resection of residual disease after CCRT [4]. In such a trimodality treatment strategy, delays can occur due to restaging procedures which are performed after 45-50 Gy, a non-radical radiation dose. We showed in our experience that these so-called ‘treatment splits’ can be limited to a few days, but a radical dose of radiotherapy (60 Gy) was not always achieved. It is suggested that a safe resection can be performed after high-dose radiotherapy [6], but there is currently no data from randomized multi-institutional studies to support this strategy.

Applying guideline-specified treatment in populations remains challenging for patients in stage III NSCLC, and this is also reflected in reports of phase III clinical studies. An example is the abovementioned trimodality trial, in which only 79% of patients completed protocol specified radiotherapy to 61 Gy in the definitive CCRT arm [4]. However, survival was not significantly different from the other treatment arm, in which a surgical resection was performed after induction CCRT to 45 Gy. In another multi-institutional trial, patients were randomized between consolidation docetaxel or observation after treatment with CCRT [7]. Of the initial 203 patients, only 147 patients (74%) were eligible for randomization mainly due to reasons of toxicity during CCRT, and finally only 81% received 3 courses of docetaxel in that treatment arm. Updated survival outcomes in the latter study revealed an overall median survival of 21.5 months, and no benefit for consolidation docetaxel. In addition, fit patients aged 70 years or older had similar survival outcomes as younger patients with only higher rates of toxicity [8].

Less than half of Dutch patients under the age of 60 with stage III NSCLC are currently treated with chemoradiotherapy [9]. It has been suggested that more than half of patients with stage III lung cancer in the general population may be ineligible for CCRT because of age or comorbidities, if the patient inclusion criteria applied in clinical trials were to be applied [10]. However, other reports have confirmed the view that elderly stage III NSCLC patients who are fit can achieve similar survival rates with modest toxicity [11, 12]. This approach is also supported by work in this thesis [13]. Although trials specifically designed for elderly can potentially limit excessive treatment toxicity, this may lead to clinicians becoming reluctant to treat older but fit patients without comorbidity using CCRT [14].

At the VU University Medical Center, CCRT for stage III NSCLC was routinely implemented in 2003. Analysis of our results outside clinical trials showed a median overall survival of 18 months, with acceptable toxicity, including a rate of fatal complications in 4.5% of patients, and grade III radiation pneumonitis in 7.9% [13]. A sub-group analysis revealed favorable median survivals in small volume tumors (of 27 months) and in those with a performance score of 0 (36.6 months). Forty percent of patients were unable to receive a dose of 60 Gy or higher during this period (2003 to 2008), mainly as normal organ constraints could not be met as the technique of intensity-modulated radiotherapy (IMRT) was unavailable for treating bulky tumors, or tumors with supraclavicular nodal metastases.

One example of the latter is a 56-patient with a right-sided superior sulcus tumor where the planning target volume was 1197 cc (T4N2M0, stage IIIB NSCLC). The patient was treated in 2006 with CCRT, consisting of an induction cycle consisting of cisplatin-gemcitabine, followed by 2 courses of cisplatin-etoposide concurrent with thoracic radiotherapy to 50 Gy, in once-daily fractions of 2 Gy. **Figure 1** shows diagnostic and follow-up CT-scans. The patient was deemed medically inoperable as he developed an arterial thrombosis during CCRT. Despite the large size and extensive mediastinal lymph node involvement (N2), this patient is alive with no signs of disease recurrence more than 5 years after start of treatment. This case illustrates the principle that CCRT is an effective treatment, which can be curative even in patients who are unable to receive the radiotherapy doses in the range of 60-66 Gy.

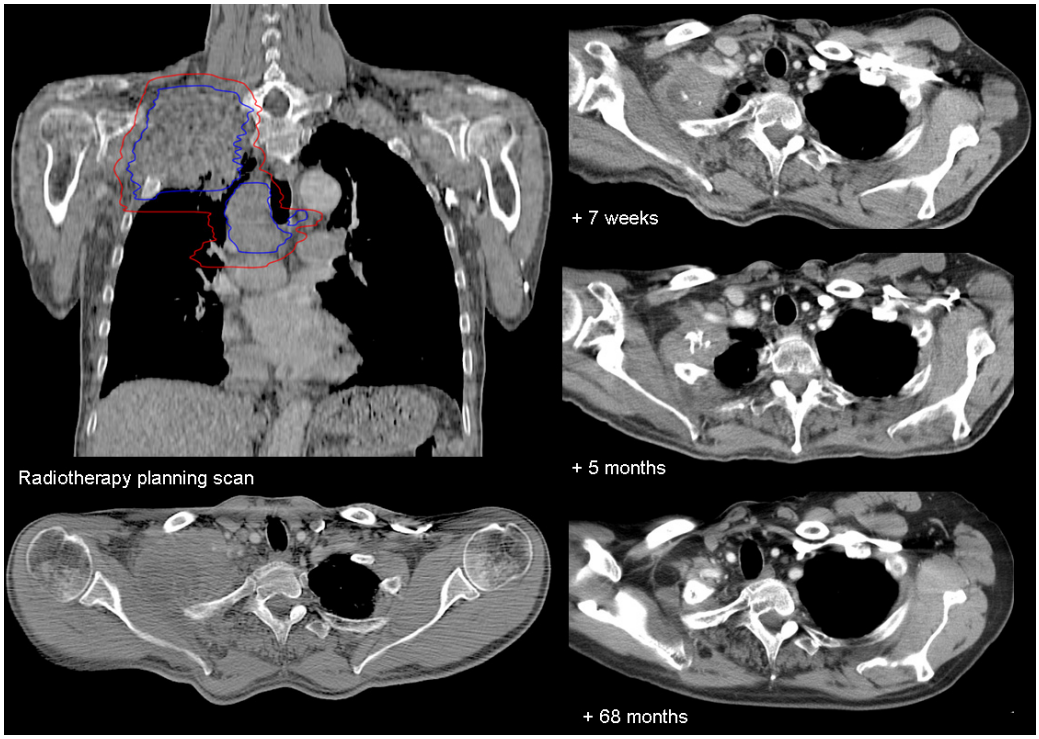

Figure 1. Patient with a superior sulcus tumor (T4N2M0) treated with definitive CCRT to 50 Gy (2006).

Some Dutch centers have applied CCRT by using radiotherapy concurrent with daily doses of cisplatin of 6 mg/m^2 as radiosensitizer (as opposed to chemotherapy doses showing systemic disease activity), resulting in a median survival of 16.5 months [15]. The use of daily low-dose cisplatin has not been shown effective in decreasing systemic relapses [16]. Additional selection criteria applied in the abovementioned study, for example selection using the criteria that less than 12 cm of esophagus was permitted in the tumor volume (boost fields), makes this strategy not suitable to fit patients with stage III NSCLC who should receive adequate doses of systemic chemotherapy for a disease where more than half of all patients develop distant disease as the first manifestation of disease progression [5, 15]. Other Dutch centers have attempted to increase survival by using an individualized radiotherapy dose based on normal tissue constraints, in conjunction with sequential chemotherapy in only 50% of stage III tumors. One such study reported mature results in stage IIIA and IIIB NSCLC, reporting a median survival of 17.2 and 16.2 months, respectively [17]. In this study, almost 50% of patients had recurrence of disease after median follow-up of 31.6 months.

The application of CCRT increases rates of both hematologic and non-hematologic toxicity, and acute esophagitis continues to be a problem, even with modern radiation techniques. In our experience, 28% of patients needed tube feeding (grade III) [13]. It is important that patients have adequate intake during/after CCRT, while malnutrition can have a detrimental effect on treatment outcomes [18]. In our experience using trimodality therapy, we found that malnutrition has a negative influence on prognosis in overweight patients, which indicates even more that all patients need sufficient intake despite toxicities as nausea/vomiting and radiation esophagitis. Of 187 stage III NSCLC patients in a large RTOG study who were treated in the concurrent arm with cisplatin-etoposide to 60 Gy, grade III and IV esophagitis developed in respectively 42% and 3% [19]. However, after a median follow-up of 11 years, late esophageal toxicity was limited to only 6 patients (4%).

Radiation pneumonitis is a dose-limiting toxicity, and 15 to 40% of NSCLC patients undergoing CCRT experience symptomatic radiation pneumonitis [20]. An individual patient data meta-analysis of 836 patients treated with CCRT in Europe, North America and Asia, found that 30% of patients had symptomatic radiation pneumonitis with fatal event in 2% [21]. Furthermore, patients above the age of 65 receiving CCRT with carboplatin-paclitaxel had a risk of more than 50% to suffer from radiation pneumonitis. Finally, more than 2Gy-fractionation, V_{20} and lower-lobe tumors predicted for grade V radiation pneumonitis.

Asymptomatic changes in lung density are more commonly observed, and our work revealed that lung regions receiving a threshold dose of more than 30 Gy changed significantly in lung density starting from 3 months after CCRT [22]. Monitoring such changes could be helpful when evaluating the combination of radiotherapy with new agents.

Although the toxicity of CCRT is acceptable given the otherwise dismal prognosis, identifying patients who are at high risk for treatment-related toxicity is important given the modest survival gains achieved. One example are patients presenting with a cavitating primary tumors described in Chapter 7, which led to the development of high-grade infectious lung toxicity. It can be hypothesized that the combination of myelosuppression by chemotherapy and radiation effects on a cavitated tumor will lead to colonization and bacteraemia of the cavitation, which is very difficult to tackle with antibiotics. Therefore, surgery with induction- or postadjuvant chemotherapy might be a better strategy for these patients. Another option would be the application of weekly low-dose chemotherapy to prevent severe myelosupression in these cases.

Improving combined modality treatment

The complexity of CCRT and treatment-related risks could lead to low rates of compliance with this approach, particularly in view of a growing proportion of elderly patients with stage III NSCLC. The involvement of expert multidisciplinary teams may be one way to identify and treat eligible patients with CCRT, and to avoid both inadequate and inappropriate treatments. The importance of treating lung cancer patients in experienced centers was emphasized in a Dutch analysis of treatment patterns and outcomes in 13,744 stage III NSCLC patients diagnosed between 2000 and 2006 [23]. Significant differences were seen between hospitals (and regions) in the utilization of chemoradiotherapy, which lead to differences in survival rates for these patients. Similarly, a report on 239 inoperable locally-advanced NSCLC patients who underwent chemoradiotherapy in 2 RTOG trials showed that centers treating 5 or more patients achieved a more than doubling in 2- and 3- year survival rates, when compared to centers enrolling less than 5 patients [24]. Similar findings relating quality of chemoradiotherapy plans with outcomes have also been reported for head and neck tumors [25].

Improved radiotherapy delivery

Modern radiation techniques have become more widely available, including 3-Dimensional (3D) conformal radiotherapy, 4-Dimensional (4D) CT scans to incorporate tumor motion, and IMRT [26]. Such techniques can be used to deliver optimal doses to the planning target volume, while preventing high dose in the organs at risk, i.e. myelum, heart and normal lung tissue. Radiation dose escalation would be a logical step to try to improve loco-regional control, since CCRT with mostly 2-Dimensional radiation techniques in the range 48.5-66 Gy leads to a locoregional progression rate of 28.9% after 5 years [2]. A study of 1356 NSCLC patients who underwent chemoradiotherapy in 7 RTOG studies, found a 5-year locoregional failure rate of 52% and 5-year survival of 15%, but multivariate analysis suggested that higher biologically effective doses (BED) were associated with improved loco-regional control and survival [27]. However, a phase III trial in stage III NSCLC patients randomizing between 60 or 74 Gy with or without cetuximab in CCRT using IMRT was partly terminated in June 2011 as the arm with higher dose showed no survival benefit compared to the standard 60 Gy arm, with 1-year survival rates of respectively 70.4% and 81% [28]. A full analysis of the study data is awaited.

Intensity-modulated radiotherapy (IMRT)

A retrospective study of long-term outcomes of IMRT combined with 4D-CT planning suggest reasons for optimism [29]. Of a total 165 patients, including 82% who underwent CCRT with median dose of 66 Gy, grade III or higher pneumonitis at 12 months developed in only 14% of patients. IMRT restricts the V_{20} and V_5, which are both parameters considered as predictors of radiation pneumonitis. Our recent comparative study of 5 thoracic radiation techniques, namely 3D-conformal, full IMRT, hybrid IMRT, full volumetric modulated arc therapy (RapidArc™) and hybrid RapidArc™), revealed that the 2 hybrid delivery techniques were superior for treating large tumors averaging 779 cm^3, with respect to tumor coverage, avoidance of hotspots, reduction in lung doses and delivery times [30]**.** Current treatment planning objectives used at the VU University Medical Center are summarized in **Table 1**. The planning parameter associated with lung toxicity (V_{20}) for both hybrid techniques was 30%, and the V_5 for the controlateral lung was 36%.

Table 1. Current treatment planning objectives in stage III NSCLC [30], VUmc 2012

PTV $V_{95\%}$	>97%
PTV $V_{107\%}$	<5%
Total body $V_{107\%}$	<10 cm^3
Spinal cord D_{max}	<50 Gy
Total lung V_{20}	<35%
Contralateral lung V_5	<50%

PTV, planning target volume

V_N, volume receiving at least N (% or Gy) of radiation dose

D_{max}, maximum dose

A case illustrating the impact of improvements in radiotherapy techniques is that of a 63 year-old patient who presented in 2009 with a T3N3M0 NSCLC in the right upper lobe with pathological contralateral supraclavicular lymph nodes. **Figure 2** shows the extent of tumor, with a planning target volume of 736 cc. At initial presentation, delivery of a dose higher than 55 Gy was not feasible due to the need to limit spinal cord doses to 48 Gy. After molecular diagnostics showed a mutation for epidermal growth factor receptor (EGFR) exon 19, she was treated with erlotinib until such time that locoregional progession was diagnosed in 2011. At that stage, availability of IMRT delivery using RapidArc™, led to her being treated with CCRT to 66 Gy, in 33 once-daily fractions of 2 Gy.

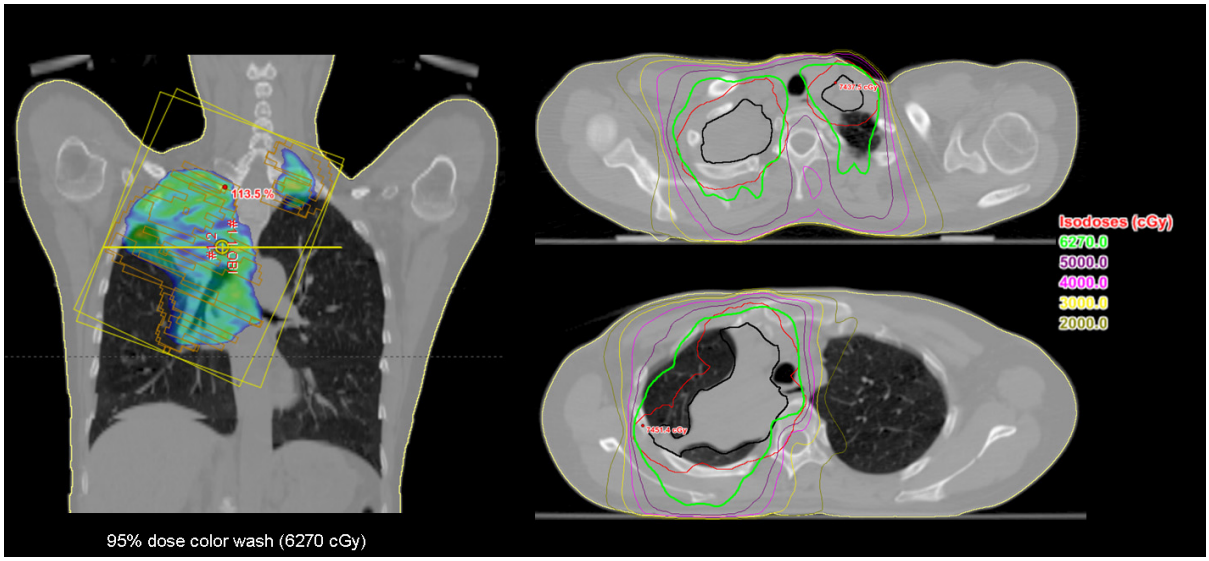

Figure 2. Patient treated with CCRT to 66 Gy with IMRT using RapidArc™ (2011).

Proton radiotherapy

Another investigational treatment option is the use of proton radiotherapy, which is theoretically superior to photon radiotherapy in terms of dose distribution. However, current studies do not confirm its potential value, for example in prostate cancer [31, 32]. In stage III NSCLC, a single-institution phase II study applying CCRT with proton radiotherapy to 74 Gy in 44 patients, reported a median overall survival of 29.4 months [33]. Median V_{20} en V_5 were respectively 25.7% and 32.8%, despite the fact that 50% of patients had T3-4 tumors, and 77.3% had N2-3 disease. Despite the encouraging survival outcomes, 20.5% of patients developed locoregional disease recurrence, and 43.2% developed distant metastases. The last illustrates the need for improvements in systemic therapy for NSCLC. Applying proton radiotherapy in moving targets such as lung tumors can only be successful if it is carried out with the same modern techniques as in photon therapy, for example image guidance [34].

Prophylactic cranial irradiation

Brain metastases are a major site of distant failure in patients with stage III NSCLC, and more than 75% of recurrences occur within 2 years of diagnosis [35]. Prophylactic cranial irradiation (PCI) could potentially eradicate micro-metastases which are not targeted by systemic therapy. In small-cell lung cancer, PCI is part of standard of treatment in both limited- and extensive stage disease as it improves survival [36, 37]. Initial results of a phase III trial randomizing stage III NSCLC patients after radical therapy to PCI or observation, showed no difference in disease-free survival nor in overall survival, although fewer brain metastases occurred in the PCI group (n=163) at 1-year follow-up [38]. However, this study was closed early because of slow accrual. The role for PCI in stage III NSCLC is still unclear.

Failure patterns after chemoradiotherapy

A retrospective study using RTOG data from chemoradiotherapy trials in 1390 NSCLC patients suggested that loco-regional control is strongly associated with survival [39]. However, the high incidence of distant metastases soon after treatment for stage III NSCLC remains an important issue to address, even in the era of staging PET scans. Some authors suggest that locally-advanced lung cancer should be broadly considered as a systemic disease, as staging methods have yet to be sensitive enough to visualize small metastases that cannot

be diagnosed at present [40]. The former view is that fit patients with stage III and IV lung cancer are not that different as one would expect based on the TNM staging system.

Improvements in systemic chemotherapy

The American College of Chest Physicians Society (ACCP) published guidelines in 2007, which stated that patients with stage III NSCLC and a good performance status (0 to 2) should receive platinum-based combination chemoradiotherapy as primary treatment [3]**.** The optimal systemic treatment when applying CCRT is unclear, but generally used regimen are cisplatin-etoposide or carboplatin-paclitaxel [41].

Pemetrexed, a folate antimetabolite, has been shown equally effective in combination with cisplatin compared to cisplatin-gemcitabin in stage IV NSCLC [42]**.** Remarkably, patients with non-squamous cell carcinoma had the most benefit. A phase III trial (PROCLAIM) is currently underway to compare radiotherapy with concurrent cisplatin-pemetrexed or cisplatin-etoposide in stage III non-squamous cell patients [43]. Both arms also include consolidation chemotherapy.

Targeted therapies

New medicines are in development which aim to target on specific tumor characteristics or driver mutations in NSCLC [44]. Current approaches that improve the effect of radiotherapy include hypoxia modifiers, antiangiogenic agents, epidermal growth factor receptor (EGFR) inhibitors, IGF-1 inhibitors and P13K/Akt inhibitors [45].

Monoclonal antibodies as EGFR tyrosine-kinase inhibitors (TKI) are tested in stage III NSCLC, for example maintenance gefitinib or observation after CCRT and consolidation docetaxel [46]. Patients in the treatment arm had lower survival rates compared to the observation arm, respectively 23 versus 35 months, and the authors stated that the main cause was progression of disease, and not treatment toxicity.

Cetuximab is another monoclonal antibody directed against EGFR, with radiosensitizing properties. A phase II trial in stage III NSCLC patients showed its feasibility when combining with CCRT (carboplatin-paclitaxel) [47]. The earlier mentioned RTOG phase III trial comparing radiation doses of 60 Gy or 74 Gy will also investigate the outcomes of cetuximab versus observation [28].

The antiangiogenic agent bevacizumab has been tested for safety in a phase I trial concurrently with radiotherapy in stage III NSCLC [48]. This study was terminated after treating 6 patients because of the observed pulmonary toxicity (grade ≥II radiation pneumonitis in 4 patients), and the authors concluded that only sequential administration of these agents should be investigated in further studies.

Molecular or biological imaging

PET tracers are able to distinguish metabolic rates in different parts of tumors, revealing locations where radiation therapy will not have sufficient effect in the current dose standards, and where most likely a recurrence will develop after treatment. These biological images allow for prescription of non-uniform dose distributions to the tumor volume or 'dose painting'. A phase II dose-escalation trial is currently ongoing using a radiation boost to the entire primary tumor (arm A) or to the region in the tumor where high FDG uptake (>50% SUVmax) is present (arm B) [49]. Planning results already showed that in the majority of patients, dose escalation can be achieved to at least 72 Gy, considering predefined normal tissue constraints.

Conclusion

The increasing complexity of combined modality treatment in stage III (locally-advanced) NSCLC has led to improvements in cure rates, with modest gains in survival. Highly motivated patients and good supportive care are necessary as hematologic toxicities and esophagitis are common. Long-term survival still remains poor, a finding determined not only by the cancer itself, but also by the smoking-related comorbidity in patients with NSCLC [50].

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