

Unresectable stage III non-small-cell lung cancer: Have we made any progress?

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Abstract

Lung cancer is responsible for the most cancer deaths worldwide with an incidence that is still rising. One third of patients have unresectable stage IIIA or stage IIIB disease. The standard of care for locally advanced

disease in patients with good performance status consists of combined modality therapy in particular concurrent chemoradiotherapy. But despite a lot of efforts done in the past, local control and survival of patients with unresectable stage III non-small-cell lung cancer (NSCLC) remains poor. Improving outcomes for patients with unresectable stage III NSCLC has therefore been an area of ongoing research. Research has focused on improving systemic therapy, improving radiation therapy or adding a maintenance therapy to consolidate the initial therapy. Also implementation of newer targeted therapies and immunotherapy has been investigated as well as the option of prophylactic cranial irradiation. This article reviews the latest literature on improving local control and preventing distant metastases. It seems that we have reached a plateau with conventional chemotherapy. Radiotherapy dose escalation did not improve outcome although increasing radiation dose-intensity with new radiotherapy techniques and the use of newer agents, *e.g.*, immunotherapy might be promising. In the future well-designed clinical trials are necessary to prove those promising results.

Key words: Stage III non-small-cell lung carcinoma; Chemoradiotherapy; Induction chemotherapy; Molecular targeted therapy; Consolidation chemotherapy; Dose-escalation; Altered fractionation; Advanced radiotherapy techniques; Prophylactic cranial irradiation

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Core tip: Lung cancer is responsible for the most cancer deaths. One third of patients have unresectable stage IIIA/IIIB disease. Despite a lot of efforts, local control and survival of these patients remains poor. Improving the treatment is therefore one of the biggest challenges in respiratory oncology. This review gives an overview of the important clinical studies that were performed the last decade in the treatment of unresectable stage III non-small-cell lung carcinoma and focuses on improvement of systemic therapy, with the exciting area

of implementation of newer agents (targeted therapy and immunotherapy) and improvement of radiotherapy, including the potential of prophylactic cranial irradiation.

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INTRODUCTION

Lung cancer is responsible for most cancer deaths worldwide with an incidence that is still rising. Non-small-cell lung cancer (NSCLC) accounts for the majority of cases of lung cancer (85%)^[1]. Stage III disease encompasses a heterogeneous group of patients with a variety in tumour size, lymph node location and prognosis for which treatment remains a major challenge. One third of all NSCLC patients have unresectable stage IIIA or stage IIIB disease^[2]. This review will concentrate on the treatment of this group of patients.

The current standard of care for fit patients with unresectable stage III NSCLC is concurrent treatment with platinum-based doublet chemotherapy and radiotherapy^[3], yielding a 5-year overall survival (OS) of 15.1%, which is superior to the sequential approach^[4]. Earlier randomized trials and meta-analyses had already proven that the combination of chemotherapy and radiotherapy, either concurrent or sequential, is superior to radiotherapy alone. During the last decade, strategies to increase survival have focused on improving systemic therapy, radiation therapy or adding a maintenance therapy to consolidate the initial therapy. Numerous trials have therefore investigated different agents, treatment sequences, and radiation schedules and doses.

The purpose of this review is to give an overview of the most important clinical studies that were performed the last decade in the treatment of unresectable stage III NSCLC.

LITERATURE STUDY

A literature search was performed using PubMed, MEDLINE, the Cochrane Database of Systematic Reviews and Science Direct databases since 2005 up to June 2014 with the search term: "stage III", "non-small-cell lung carcinoma/cancer", "locally advanced lung cancer". Guidelines (ESMO, ACCP, NICE, NCCN) were manually searched as well as abstracts of the major conferences since 2005 and the reference sections of selected papers to retrieve relevant publications. Primarily randomized trials, meta-analyses, reviews and practice guidelines were

included. When lacking, additional articles were identified searching for outcomes like progression free survival (PFS), OS and objective response rate (ORR). Non-English articles were excluded.

IMPROVING SYSTEMIC THERAPY

In the mid-nineties, two meta-analysis reviewing more than 50 trials confirmed the survival benefit of combining platinum-based chemotherapy with radiotherapy over radiotherapy alone in locally advanced unresectable NSCLC^[5,6]. Numerous clinical trials were conducted afterwards to determine the best combination of chemotherapy and radiotherapy and to examine whether concomitant chemoradiotherapy was appropriate in this setting. Systemic chemotherapy is used to achieve two goals: it acts as a radiosensitizing agent to increase the effects of radiotherapy and as a cytotoxic agent to prevent or eradicate distant metastases. A Cochrane meta-analysis comparing concurrent to sequential chemoradiotherapy or radiotherapy alone performed in 2004^[7] was updated in 2010^[8] and confirmed the beneficial results of concurrent therapy seen in 2004 namely a hazard ratio (HR) of 0.74 (95%CI: 0.62-0.89) and a 10% absolute survival benefit at 2 years in favour of the concurrent approach, but at the expense of higher acute oesophageal toxicity. Aupérin *et al.*^[4] in 2010 confirmed these results. In this meta-analysis a significant survival benefit of concurrent therapy was seen (HR = 0.84; $P = 0.004$) with an absolute benefit of 5.7% at 3 years (23.8% vs 18.1%). Here too significantly increased grade 3/4 oesophageal toxicity was reported, but no higher rates of pneumonitis were reported. Despite the higher toxicity, since these publications, concurrent chemoradiotherapy has been accepted as the standard of care. With improved staging, omission of elective node irradiation and more modern radiotherapy techniques, toxicity can be reduced. But also numerous trials have been performed to find more optimal chemotherapy combinations that can further improve the results obtained with the cisplatin-based doublets combined with continuous radiotherapy, as used in the trials included in the meta-analyses. Most commonly used chemotherapy regimens (*e.g.*, platinum/gemcitabin) administered to patients with metastatic disease cannot be safely administered at full doses in combination with radical doses of thoracic radiation because of the risk of pulmonary toxicity. Cisplatin/etoposide concurrent regimens allow the delivery of full doses of chemotherapy compared with third-generation doublets. This is a well-documented regimen with good survival data and acceptable toxicity particular in the control arm of the Hoosier trial^[9]. Another well-known schedule is weekly carboplatin and paclitaxel. However three studies^[10-12] show a lower median survival with the low-dose carboplatin. Until now there have been no randomized studies designed to investigate the optimal

Table 1 Survival data from randomized trials comparing induction chemotherapy followed by concurrent chemoradiation therapy with concurrent chemoradiation therapy alone of chemotherapy followed by radiation therapy alone in non-small-cell lung cancer

Trial	Patients (n)	Schedule	Median survival (mo)	Survival (%)
Vokes <i>et al</i> ^[11]	366	CP × 2 → weekly CP + 66 Gy Weekly CP + 66 Gy	23 19	31 (3 yr) 29
Huber <i>et al</i> ^[16]	214	CP × 2 → weekly P + 60 Gy CP × 2 → 60 Gy	18.7 14.1	33 (3 yr) 14 (3 yr)
Gervais <i>et al</i> ^[14]	584	PVi × 2 → daily C + 66 Gy PVi × 2 → 66 Gy	14 11	- -
Clamon <i>et al</i> ^[13]	283	PVb × 2 → weekly C + 60 Gy PVb × 2 → 60 Gy	13.4 13.5	13 (4 yr) 10
Scagliotti <i>et al</i> ^[15]	89	DC × 2 → D + 60 Gy DC × 2 → 60 Gy	14.9 14	55.8 (1 yr) 58.7

CP: Carboplatin/paclitaxel; P: Paclitaxel; PVi: Cisplatin/vinorelbine; PVb: Cisplatin/vinblastin; DC: Docetaxel/cisplatin; D: Docetaxel.

chemotherapy regimen so no recommendation can be given whether cisplatin/etoposide is better than the combination with vinorelbine or carboplatin and paclitaxel. These regimens are used commonly.

Induction chemotherapy

To further improve survival, control of micrometastatic disease must be optimised. Therefore induction chemotherapy preceding concurrent therapy has been examined. Randomized controlled trials did however not provide any significant improvement in survival^[11,13-16] (Table 1).

New drugs

Pemetrexed: Cisplatin/etoposide is until now the only regimen that can be given at full systemic dose in concurrent therapy. It has a known, predictable and acceptable side effect profile. More modern doublets with paclitaxel, docetaxel or gemcitabine cannot be given at full doses with concurrent high dose radiotherapy. The antifolate, pemetrexed, can be combined in full dose with thoracic radiotherapy up to 66 Gy. This has been demonstrated in phase I and II trials^[17-20]. Cisplatin with pemetrexed was delivered at full dose concurrently with radiotherapy in the PROCLAIM trial, a randomized phase III trial comparing cisplatin/etoposide with cisplatin/pemetrexed. Unfortunately the phase III trial was stopped because the primary endpoint (improvement of OS) could not be reached.

Targeted therapy

Addition of cetuximab, the monoclonal antibody targeting epidermal growth-factor receptor (EGFR) showed promising results in head and neck cancer better locoregional control and OS compared with radiotherapy alone^[21] and in advanced NSCLC longer OS when cetuximab was added to chemotherapy^[22]. Concurrent cetuximab with radical radiation therapy in stage III NSCLC has shown to be safe with acceptable toxicities^[23-26]. The Cancer and Leukemia Group B (CALGB) 30407^[27] evaluated the OS of patients with

unresectable stage III NSCLC treated with pemetrexed, carboplatin and thoracic radiotherapy with or without cetuximab in a phase II study. Unfortunately the overall response rate (73% without and 71% with cetuximab) and median survival (22.3 mo without vs 18.7 mo with cetuximab) were lower in the cetuximab group. Recently in the RTOG 0617 trial, patients were randomized to standard-dose (60 Gy) or high-dose (74 Gy) radiotherapy. Concurrent chemotherapy included weekly carboplatin and paclitaxel alone or with cetuximab. This RTOG 0617 trial also did not show any significant improvement of OS (18 mo OS with cetuximab 60.8% vs 60.2% without cetuximab; $P = 0.484$; HR = 0.99)^[28]. The radiotherapy related results are discussed later in this review.

When given with radiotherapy, EGFR tyrosine kinase inhibitors (TKIs) act as radiation sensitizer. Phase I and II data showed acceptable toxicity profiles^[29-32] except for a possible higher risk of pulmonary toxicity^[33] but the OS results have been less promising and variable (the latter probably reflecting differences in patients enrolled in the trials). A possible explanation and concern is that concurrent chemotherapy and EGFR TKI may be antagonistic, predominantly in wild-type EGFR^[34]. Further investigation is needed to see if separate administration of chemotherapy and EGFR TKI can overcome this barrier^[32] and to confirm that patients with EGFR mutations have improved outcomes when treated with combined modality treatment including EGFR inhibition by TKIs^[32].

Multi-targeted TKI's and mTOR inhibitors also show promising results in combination with radiation in cell lines acting as radiosensitizers although more clinical evidence is needed regarding efficacy and safety^[35,36].

Very disappointing results were seen in several trials where bevacizumab (the recombinant humanized monoclonal antibody that produces angiogenesis inhibition by inhibiting vascular endothelial growth factor A) was combined with chemoradiation. Preclinical and clinical data suggested that antiangiogenesis therapy and radiotherapy would be additive^[37,38]. Combination of platinum-based therapy with bevacizumab in stage

Table 2 Survival data from phase II and III trials using concurrent chemoradiation therapy followed by consolidation chemotherapy in non-small-cell lung cancer

Trial	Patients (n)	Schedule	Median survival (mo)	Survival (%)
Belani <i>et al</i> ^[10]	92	Weekly CP + 63 Gy → CP × 2	16.3	17 (3 yr)
Albain <i>et al</i> ^[96]	50	PE × 2 + 61 Gy → PE × 2	15	15 (5 yr)
Gandara <i>et al</i> ^[43]	83	PE × 2 + 61 Gy → D × 3	26	29 (5 yr)
Lau <i>et al</i> ^[97]	34	Weekly C + biweekly P + 61 Gy → CP × 2	17	40 (2 yr)
Hanna <i>et al</i> ^[44]	73	PE × 2 + 59.4 Gy → D × 3	21.2	27.1 (3 yr)

CP: Carboplatin/paclitaxel; P: Paclitaxel; PE: Cisplatin/etoposide; D: Docetaxel.

III B and IV had shown a longer OS in one trial and also higher response rate and longer progression free survival in all other trials^[39-41]. However, the development of tracheoesophageal fistulae has led to early closure of phase II trials combining chemoradiotherapy and bevacizumab in NSCLC and SCLC^[42].

Consolidation therapy

Consolidation chemotherapy: To improve OS in unresectable stage III NSCLC, the strategy of consolidation chemotherapy was investigated. Several phase II studies have assessed the safety and efficacy of concurrent chemoradiotherapy followed by consolidation chemotherapy. The phase II SWOG 9504 trial delivering docetaxel after concurrent chemoradiotherapy with platinum/etoposide showed the most promising median survival (26 mo)^[43]. A phase III trial was therefore performed using the doublet cisplatin/etoposide concurrently with standard dose radiotherapy. Patients with response or stable disease were subsequently randomized to consolidation chemotherapy with docetaxel or best supportive care. Unfortunately there was no difference between the 2 arms [median survival time (MST) 21.2 mo for docetaxel arm and 23.2 mo for observation arm] and moreover there was more toxicity in the group that received docetaxel^[44]. Recently another multinational phase III randomized trial using docetaxel and cisplatin as consolidation chemotherapy after concurrent chemoradiation also did not show an improvement in PFS (8 mo in observation arm vs 9.1 mo in consolidation arm; $P = 0.38$)^[45] (Table 2).

Maintenance targeted therapy

As the EGFR TKIs erlotinib and gefitinib are proven agents in advanced NSCLC in disease progression after chemotherapy and in first-line in patients with activating EGFR mutation positive tumours, maintenance therapy was investigated with gefitinib after concurrent chemoradiotherapy and consolidation docetaxel in the phase III SWOG S0023 trial^[9]. The trial was designed to prospectively evaluate the role of gefitinib in improving OS and PFS in unselected patients. Unfortunately the gefitinib group had significantly worse survival (more rapid tumour progression, same toxicity) (HR = 0.633; 95%CI:

0.44-0.91; $P = 0.013$; median survival times of 23 mo and 35 mo, respectively).

For maintenance with erlotinib a phase III trial investigating erlotinib after concurrent chemoradiotherapy showed no difference in progression-free survival interval^[46].

Also for maintenance with cetuximab no evidence exists to prove benefit in the multimodality treatment of unresectable stage III NSCLC.

Consolidation therapy with the anti-angiogenesis agent bevacizumab was also investigated but because of a high toxicity rate and lack of improvement in OS, no data underscore the further development in stage III treatment^[47,48].

Maintenance immunotherapy

Vaccine therapy: Turning to the potential advantage of adding immunotherapy, promising results were seen in a randomized phase II B trial using a mucin 1 antigen-specific immunotherapy, tecemotide or L-BLP25. The MUC1 glycoprotein is overexpressed and abnormally glycosylated in NSCLC and other cancers. Tecemotide induces a T-cell response to MUC1 and therefore inhibits the abnormal interactions that trigger inappropriate activation of intracellular signalling pathways (promotes growth, proliferation and survival of cancer cells). In the randomized phase II B trial of tecemotide maintenance therapy vs best supportive care, a potential survival benefit was reported in patients with stage III B and IV NSCLC [MST L-BLP25 + best supportive care (BSC) 30.6 mo vs 13.3 mo for BSC only (HR = 0.548; 95%CI: 0.301-0.999)]^[49,50]. In 2010 Butts reported similar survival results [1-year survival rate 82% (95%CI: 66%-98%), 2-year survival rate 64% (95%CI: 44%-84%)] in a single-arm phase II trial investigating tecemotide after chemoradiotherapy^[51]. Because of these promising results, the randomized placebo controlled double-blind phase III START trial was initiated, the results of which have been published recently^[52]. Tecemotide or placebo were given every week for 8 wk to patients with stable disease or objective response after chemoradiotherapy (concurrent vs sequential), and then every 6 wk until disease progression or withdrawal. The primary endpoint was OS. Tecemotide was very well tolerated yet there was no difference in median OS. What was

of interest, however, was the improvement of 10.2 mo in median OS in the concurrent chemoradiotherapy subgroup treated with tecemotide. In contrast there was no benefit in the group treated with sequential chemoradiation. It remains to date unclear what explains this difference: is it the heterogeneity in patient population between the groups of concurrent chemoradiation and sequential chemoradiation (e.g., performance status, tumour size)? The START trial threw a new light on the treatment of unresectable stage III NSCLC and especially on the possible effect of immunotherapy in multimodality treatment. Another phase II trial administering GV 1001, a telomerase peptide vaccine, after chemoradiotherapy, also demonstrated improved PFS and significantly improved OS in immune responders^[53] and therefore a phase III study is planned. Unfortunately the START II trial designed to further investigate the potential benefit of tecemotide in maintenance after concurrent chemoradiation, will not be conducted because the pharmaceutical company is allocating resources to other immunotherapy strategies.

Checkpoint inhibitors: Promising results have been reported with the checkpoint inhibitors targeting cytotoxic T-lymphocyte-associated antigen 4 and the programmed death-1 pathway with achievement of durable clinical responses with manageable toxicity in advanced NSCLC and also in previously heavily treated lung cancer patients. Moreover recently there have been indications that combination of radiation treatment and immune checkpoint modulators could be beneficial in the treatment of malignant processes. Several investigators have shown the systemic effects of radiation therapy due to radiation-enhanced antitumoral immune responses^[54,55]. The oxidative stress induced by radiation, augments the antigenicity of the irradiated tumor cells, more activating signals for dendritic cells become available. Dendritic cells produce neoantigens and together antitumoral immunity is induced even at sublethal doses of radiotherapy. This is called the immunomodulatory effect of radiation. Because of this mechanism cancer cells are efficiently recognized by the immune system and cleared. For this reason radiation could augment the antitumor immune responses elicited by checkpoint immunomodulators anti-CTLA-4 and anti-PD-L1^[56]. Trials are currently ongoing evaluating the effect of checkpoint inhibitors in locally advanced unresectable stage III NSCLC following completion of treatment with chemoradiotherapy and no evidence of tumour progression (ClinicalTrials.gov Identifier NCT02125461).

IMPROVING RADIOTHERAPY

With the current standard treatment of chemotherapy delivered concurrently with continuous radiotherapy up to a dose of 60 Gy over 6 wk, 2-year loco-regional control rate of 20%-44% has been reported^[4,57,58]. As

the meta-analysis of Aupérin highlighted^[4], superior OS is related to better locoregional control. Therefore strategies that focus on improving local control by optimising radiotherapy may potentially enhance OS outcomes.

Dose escalation

A meta-analysis of six trials of concurrent chemoradiotherapy showed better local control and survival with increased dose of radiation^[57]. These findings laid the base for performing several prospective phase I / II cooperative group studies^[59-61]. These trials all showed encouraging OS results and manageable side effects with total radiotherapy doses up to 74 Gy in 2 Gy fractions. Because of these favourable results, the randomized phase III RTOG 0617 trial^[62] was launched to compare the standard-dose (SD: 60 Gy) vs high-dose (HD: 74 Gy) radiotherapy, both delivered in 2 Gy daily fractions. Unfortunately, 74 Gy did not prove superior in terms of OS, even more so, there was a trend towards lower 1-year survival in the 74 Gy arm [MST 28.7 mo (SD) vs 19.5 mo (HD); 18 mo OS rates 66.9% (SD) vs 53.9% (HD)] concluding that prolonging conventionally fractionated radiotherapy for dose escalation was not sufficient to create a better local tumour control. Although there is no clear evidence of higher toxicity in the 74 Gy arms, the percentage of grade V toxicity was higher when combining 74 Gy to chemotherapy and cetuximab. It has been unclear why the results of previous phase I - II trials did not translate into better outcome in the randomized trial, nor what might have caused this inferior outcome. The phase I - II studies might have been biased by a more favourable patient selection (more restrictive dose constraints enrolling patients with limited tumour burdens, first trial with use of FDG PET-CT imaging for staging). A possible explanation for the inferior outcome that was put forward was that in patients with larger tumours, the dose to the target might have been compromised in order to meet the dose constraints on the organs at risk. The RTOG performed a very detailed analysis of the quality aspects of the delivered radiotherapy that was published very recently^[63]. The poorer outcome of the 74 Gy arm seems to be the result of a combination of factors: concurrent therapy was more difficult to complete, there was more non-compliance to radiotherapy planning, planning target volume coverage was poorer, there were more treatment-related deaths and higher doses on the heart. Further analyses will be performed to investigate the effect of the heart dose-volume on overall survival.

Altered fractionation

While extending the overall treatment time (OTT) is not the way to go to enhance efficacy, counteracting tumour repopulation by increasing the dose intensity and/or accelerating the OTT is presumably a better approach. A meta-analysis of Mauguén^[64] showed a

significant OS benefit from modified (accelerated or hyperfractionated, *i.e.*, different smaller fractions per day) radiotherapy in patients with locally advanced, nonmetastatic NSCLC. In the past continuous hyperfractionated accelerated radiotherapy (CHART) showed promising results. Both phase III trials of Saunders *et al.*^[65] [54 Gy/1.5 Gy TID (three times daily) in 12 d] and Belani *et al.*^[66] (57.6 Gy/1.5 Gy TID for 2.5 wk except for the weekend) showed a significant better OS and median survival with accelerated radiotherapy. Saunders *et al.*^[65] showed an improvement in 2-year survival of 9% (20% to 29%) and Belani *et al.*^[66] showed an improvement in MST from 14.9 mo to 20.3 mo. This could not be confirmed by the randomized phase III CHARTWEL trial (60 Gy in 40 fractions for 2.5 wk except for the weekend)^[67]. These experiences have not widely translated into clinical practice, partly because of practical reasons (treatment with radiotherapy several times a day is difficult to implement), but also because greater toxicity in combination with chemotherapy remains an important challenge.

A shortened OTT can also be achieved by administration of a higher daily dose (hypofractionated radiotherapy). In a retrospective study of Pemberton^[68], a hypofractionated radiotherapy schedule (55 Gy in 2.75 Gy daily fractions) appeared as promising as CHART. Another retrospective trial of Amini *et al.*^[69] concluded that accelerated hypofractionated radiotherapy (ACRT, 45 Gy in 15 fractions over 3 wk) showed significantly lower toxicity profiles in elderly receiving only radiotherapy compared to standard radiotherapy (60 Gy or more). Mehta *et al.*^[70] developed a dose per fraction escalation schedule in NSCLC using advanced radiotherapy delivery technologies. This strategy was used by Donato *et al.*^[71] in the context of combined (induction, sequential and concurrent) chemo-radiotherapy and showed that hypofractionated radiotherapy could be safely administered with or without chemotherapy. Outcomes (local tumour control and survival) were comparable with prospective data from phase II trials^[72,73]. These promising results were confirmed in the meta-analysis of Manguen^[64], which was based on individual patient data from phase III trials. Higher 5-year OS rates [OS absolute benefit of 2.5% at 5 years (8.3% to 10.8%)] were seen in patients treated with a non-concurrent schedule but at the expense of transient acute oesophagitis. In non-concurrent setting, accelerated radiotherapy (*e.g.*, 66 Gy in 24 fractions) is therefore recommended in the ESMO guidelines^[3].

Advanced radiotherapy techniques

The face of radiotherapy for lung cancer has changed by the introduction of advanced techniques allowing to conforming the delivered dose to the target volume better, thus translating into reduced rates of radiation-associated toxicity.

The introduction of FDG PET-CT has not only resulted in better patient selection by a better detection of extra-thoracic disease, but for radiotherapy planning, FDG PET-CT offers the potential of better target delineation. It allows distinguishing atelectasis from malignant tissue and to differentiate involved from uninvolved nodes, necessary for selective node irradiation. Both advantages translate into reduced treatment volumes, hence, lower radiation-induced toxicity^[74].

Intensity-modulated radiotherapy (IMRT) has improved the conformality of radiotherapy by modulating the intensity profile of the radiation beam. IMRT has been shown to decrease mean lung dose (MLD), V_{lung20} (percentile volume of total lung receiving 20 Gy) and maximal spinal cord dose compared to 3-dimensional conformal radiotherapy (3DCRT)^[75]. This again yields the potential of delivering higher doses to the target volume while sparing the organs at risk or conversely delivering the same target dose with lower organs at risk doses. There are until now no prospective data comparing the efficacy and safety of IMRT to 3DCRT. Retrospective data comparing the outcome of patients treated with concurrent chemoradiation either with IMRT/4DCT (4-dimensional-CT, taking respiratory motion into account) or 3DCRT, show less acute and late pulmonary and oesophageal toxicity and a median survival of 21.6 mo^[75-77]. There is a phase II randomized trial ongoing to investigate pulmonary toxicity and loco-regional progression in patients treated with concurrent chemo-radiotherapy and IMRT/4DCT/IGRT (image guided radiotherapy), vs 3DCRT (ClinicalTrials.gov Identifier: NCT00520702). IGRT has been optimized by the use of cone-beam CT that acquires 3-dimensional images of the patient pre-treatment allowing evaluation of the patient's anatomy in the treatment position.

Another interesting technique is adaptive radiotherapy (AR), which uses changes in tumour volume (*e.g.*, using CT or FDG-PET imaging during therapy) to adjust the radiotherapy treatment plan during therapy. It has been facilitated by the adoption of daily image guidance. In planning studies, this technique has demonstrated a significant reduction of the GTV (gross tumour volume) during treatment, with consequently a lower dose delivered to the organs at risk^[78,79]. Ongoing trials are investigating the impact of this technique (ClinicalTrials.gov Identifier: NCT01507428).

A last interesting approach is to deliver the highest possible radiation dose to every individual patient: individualised accelerated radiotherapy (INDAR). In the Mastro clinic, this strategy is used with selective nodal irradiation based on FDG PET CT and accelerated radiotherapy in order to increase the biological effectiveness^[80]. Each individual patient receives the highest possible biological radiation dose with the best therapeutic ratio based on his/her specific tumour and anatomical constraints. INDAR is not only feasible with

radiotherapy alone or with sequential chemoradiation, resulting in acceptable toxicity and promising survival rates that come close to results of concurrent chemoradiation schedules^[81], but in the concurrent approach as well. Recently published results of a phase II trial with INDAR in concurrent chemoradiation show acceptable toxicity and very promising 2 year OS reaching 52.4%^[82].

Proton therapy

Proton therapy is of interest because it could further improve the therapeutic ratio for NSCLC through even better dose-conformality and reduction of the integral dose delivered to normal tissues, thus allowing dose escalation. This is mediated by the characteristic properties of protons: low doses upon tissue penetration, maximal dose deposition towards the end of the beam's path and finite range with minimal dose beyond the tumour.

Preliminary results of an ongoing phase II trial of concurrent CRT show a median survival of 24.9 mo and low rates of grade 3 pneumonitis (2%), and oesophagitis (11%)^[83]. Sejpal *et al.*^[84] retrospectively analyzed toxicity of concurrent platinum-based chemotherapy with proton therapy and showed lower rates of pneumonitis and oesophagitis compared to 3DCRT or IMRT, even if the latter were delivered at lower total doses.

Higher capital investments and operational costs of proton centres compared to photon therapy however still preclude wide access to proton therapy and therefore also hamper wide-spread investigation^[85]. Another challenge for proton therapy in the treatment of pulmonary malignancies, due to the protons' finite range, is the respiratory tumour motion and size variability during radiotherapy which could lead to target miss or delivery of higher doses to the normal tissue^[86]. In this respect, a study of Mohan *et al.*^[87] showed inferior conformality of proton therapy compared to IMRT in highly irregular tumours. Therefore further research is ongoing - and warranted - to assess the feasibility, safety and efficacy and value for money of proton radiotherapy in stage III NSCLC.

PROPHYLACTIC CRANIAL IRRADIATION

Brain metastases in patients with NSCLC are one of the most frequent sites of progression in previously treated locally advanced NSCLC^[88]. Brain metastases moreover have a profound impact on survival and quality of life. Studies have shown that prophylactic cranial irradiation (PCI) is successful in decreasing the incidence of brain metastases but there is no proven survival advantage nor advantage in disease free survival^[37,89]. There is still a trial ongoing comparing PCI to observation in stage III NSCLC (ClinicalTrials.gov Identifier: NCT01282437).

POOR-RISK PATIENTS

It is important to mention that poor-risk factors influence the choice of treatment and the outcome in locally advanced NSCLC. The risk factors include age, performance status, comorbidities and weight loss^[90]. It has been seen moreover that lung cancer incidence is strongly related to age, with the highest incidence rates being in older men and women. In the United Kingdom, *e.g.*, between 2009 and 2011, an average of more than four in ten cases were diagnosed in men and women aged 75 years and over underlining the importance of treatment according to age (cancer-researchuk.org). In advanced NSCLC advanced age alone has not been shown to influence response or survival with therapy^[91]. In unresected stage III NSCLC it has been shown that despite toxicity, radiotherapy alone may improve the outcomes of elderly patients^[92]. After concurrent chemoradiotherapy fit older patients have increased hematologic toxicity but renal toxicity, pulmonary toxicity, oesophagitis differed between trials. These patients do seem to have the same survival benefit though studies only included small amounts of elderly patients, mostly having good performance status and few comorbidities, and were not designed to make these conclusions for age-specific subgroups^[93-95]. In conclusion fit elderly might benefit from concurrent chemoradiotherapy but there is a great need to develop trials including an important number of older patients with certain comorbidities and poorer performance status to develop tolerable combinations of systemic therapy with radiotherapy. Also there is a need to develop an applicable geriatric assessment tool to select the right patient for the right therapy.

CONCLUSION

Despite a lot of efforts done over the last decade, local control and survival of patients with unresectable stage III NSCLC remains poor. Improving the treatment is therefore one of the biggest challenges in respiratory oncology. Staging has improved tremendously with FDG PET-CT and endobronchial ultrasound and this probably has contributed to improved outcomes in recent trials. But the improvement in radiotherapy techniques in the last decade will undoubtedly improve the therapeutic ratio and prognosis for the patients with unresectable stage III NSCLC. Dose escalation with conventional fractionation recently showed no promising results, but further research needs to be done towards altered fractionation schedules, individualised radiotherapy and proton therapy. What we are also still missing are trials investigating how the knowledge on radiation biology can help to improve patient selection and outcomes. In the context of systemic therapy, it seems that we have reached a plateau with conventional chemotherapy. The results

of targeted therapy concurrent with chemoradiation were so far not promising. Further investigation is needed to see if separate administration of chemotherapy and EGFR TKI can improve outcome and to confirm that patients with EGFR mutations have improved outcomes when treated with combined modality treatment including EGFR inhibition by TKIs. Newer agents such as multi-targeted TKIs and mTOR inhibitors should also be further investigated to confirm promising results *in vitro* when combined with radiation. The promising results of the START trial with the tumour vaccine tecemotide, threw a new light on the treatment of unresectable stage III NSCLC and especially on the effect of immunotherapy in multimodality treatment. To finalise the last decade it has become more clear that individual treatment protocols considering for instance age, health status, EGFR mutations, tumor size variability, *etc.*, have to be used to reach better results.

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