Interdisciplinary multimodality management of stage III nonsmall cell lung cancer

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ABSTRACT   Stage III nonsmall cell lung cancer (NSCLC) comprises about one-third of NSCLC patients and is very heterogeneous with varying and mostly poor prognosis. It is also called "locoregionally or locally advanced disease". Due to its heterogeneity a general schematic management approach is not appropriate. Usually a combination of local therapy (surgery or radiotherapy, depending on functional, technical and oncological operability) with systemic platinum-based doublet chemotherapy and, recently, followed by immune therapy is used. A more aggressive approach of triple agent chemotherapy or two local therapies (surgery and radiotherapy, except for specific indications) has no benefit for overall survival. Until now tumour stage and the general condition of the patient are the most relevant prognostic factors. Characterising the tumour molecularly and immunologically may lead to a more personalised and effective approach. At the moment, after an exact staging and functional evaluation, an interdisciplinary discussion amongst the tumour board is warranted and offers the best management strategy.

Introduction

Locally advanced nonsmall cell lung cancer (NSCLC) is classified according to the TNM staging system as stage III with subclassification into stage IIIA, IIIB and IIIC (TNM 8) [1, 2]. Prognosis for stage III disease has an intermediate position between stage I–II disease and stage IV disease. Overall, the prognosis is poor with failures occurring in the majority of the patients both locally and at distant sites. Therefore, optimal local control as well as systemic treatment are essential. Stage III patients are still a very heterogeneous group ranging from individuals presenting with multiple nodules in the lungs, tumours invading mediastinal structures, unilateral mediastinal lymph nodes and contralateral nodes without a detectable primary tumour. In view of this heterogeneity, this stage clearly needs even more than other stages an interdisciplinary

multimodality approach. This approach is also recommended in international guidelines [3, 4]. One important discussion point within the multidisciplinary tumour board is the question of whether resectable stage III disease in a specific patient has better overall local tumour control with surgery and/or radiotherapy and in which sequence and combination the different modalities should be applied. Also, the possible resulting complications and patient preferences have to be considered. The reason is that when lumping all stage III patients together, the local control and overall survival is similar with only surgery or radiotherapy as the sole local therapy, but that the combination of both results in lower local failure rates without a demonstrated improvement in survival [5]. However, for individual patients, the situation may be different, although this is by no means built on hard data, with the possible exception of superior sulcus tumours. The standard of care for unresectable stage III disease is treatment with radiation therapy and platinum-based chemotherapy. Considerable effort has been directed at attempting to optimise the use of radiotherapy and chemotherapy, but the prognosis remains poor and improvements in survival over the past decade have been limited. The same lack of improvement in survival also applies for resectable disease; the definition of which is also dependent on local expertise, and which can be treated either with surgery or with radiotherapy. In the absence of differences in survival, the most important question in resectable tumours is which local therapy will result in the least short- and long-term toxicity.

With the introduction of targeted therapy and immune-checkpoint inhibitors for the systemic treatment in stage IV and the demonstrated synergism between radiotherapy and immune therapy [6], several studies have combined these agents in the multimodality treatment in stage III, resulting in the new standard of combining immune therapy with concurrent chemotherapy and radiotherapy [7, 8].

Heterogeneity of stage III

Stage III NSCLC is a heterogeneous group of tumours and patients with varying prognosis, tumour and nodal status, and treatment options. These tumours differ widely in their size (T1–4), as well as the extent of local extension and pattern of nodal involvement (N0–N3) (table 1). In the subcategories of lymph node classification there is still a wide variance. For example, the ipsilateral mediastinal lymph node involvement N2 ranges from a single involved lymph node at one level to multiple grossly enlarged lymph nodes already identified by computed tomography. Accordingly the prognosis for patients with stage III disease varies widely, with overall 5-year survival rates for clinical/pathological stage IIIA (TNM 7) of 19%/24% and for stage IIIB (TNM 7) of 7%/9% [9]; although there is considerable variation even within these sub-classes. In the new classification (TNM 8) prognosis varies between a 5-year survival rate of 36%/41% in clinical/pathological stage IIIA, 26%/24% in stage IIIB and 13%/12% in stage IIIC (International Association for the Study of Lung Cancer (IASLC) global database of patients receiving a diagnosis between 1999 and 2010) (table 2) [2]. Resected N2 disease also has a very different prognosis depending on the extent of lymph node involvement [10]. 5-year survival ranges from about 35%, if the lymph node involvement at one level

TABLE 1 The TNM staging system, version 8, demonstrating the heterogeneity of stage III

T/M and label	Description	N0	N1	N2	N3
T1					
T1a	⩽1 cm	I A1	II B	III A	III B
T1b	>1–2 cm	I A2	II B	III A	III B
T1c	>2–3 cm	I A3	II B	III A	III B
T2					
T2a	Central, visceral and pleura	I B	II B	III A	III B
	>3–4 m	I B	II B	III A	III B
T2b	>4–5 cm	II A	II B	III A	III B
T3	>5–7 cm	II B	III A	III B	III C
	Invasive	II B	III A	III B	III C
	Satellite	II B	III A	III B	III C
T4	>7 cm	III A	III A	III B	III C
	Invasive	III A	III A	III B	III C
	Ipsilateral nodes	III A	III A	III B	III C
M1					
M1a	Contralateral nodes	IV A	IV A	IV A	IV A
	Pleura disseminated	IV A	IV A	IV A	IV A
M1b	Single	IV A	IV A	IV A	IV A
M1c	Multi	IV B	IV B	IV B	IV B

Modified from [1].

TABLE 2 5-year survival rates of the different stages: average overall survival in the International Association for the Study of Lung Cancer (IASLC) global database of patients receiving a diagnosis between 1999 and 2010

	Clinical stage	Pathological stage
I A1	92	90
I A2	83	85
I A3	77	80
I B	68	73
II A	60	65
II B	53	56
III A	36	41
III B	26	24
III C	13	12
IV A	10	
IV B	0	

Data from [2], modified from [1].

is only detected by pathology after resection, to about 5% if the ipsilateral mediastinal lymph node involvement at several levels has already been suspected with computed tomography (bulky disease).

In addition, in patients treated with chemoradiotherapy, the volume of the tumour and the extent of lymph node involvement determine the overall survival [11].

The heterogeneity of stage III is a major issue and we can only make progress if we evaluate the different subtypes separately.

Relevance of histological subtypes and molecular features

In stage IV NSCLC, the chemotherapy regimen is partly based on the histologic tumour type [12]. However, in stage III NSCLC, the PROCLAIM phase III trial failed to demonstrate a different survival in patients with stage III adenocarcinoma when concurrently treated with radiotherapy and cisplatin-etoposide or cisplatin-pemetrexed [13]. This contrasts with the superior overall survival in stage IV adenocarcinoma treated with a platinum-pemetrexed doublet. In advanced disease, molecular characterisation, at least in non-squamous histology, is mandatory and offers the option of targeted therapy [14, 15]. Therefore, accurate determination of the histologic subtype of lung cancer is mandatory in stage IV. It is not yet clear for stage III [16, 17]. In resected pulmonary carcinomas, histology can provide additional prognostic information beyond TNM staging; until now without therapeutic consequences. For pulmonary adenocarcinoma, comprehensive histologic subtyping, as established by the 2011 IASLC/American Thoracic Society/European Respiratory Society multidisciplinary classification [18] and included in the 2015 World Health Organisation classification of lung tumours [19], has been shown to have prognostic relevance independent of tumour stage. The predominant histologic subtype in resected lung adenocarcinoma correlated with overall and disease-free survival in several studies from different countries and even seems to predict benefit from adjuvant chemotherapy in a subset of patients re-evaluated in adjuvant chemotherapy trials [20]. Whether or not the predominant histologic subtype of pulmonary adenocarcinoma evaluated in biopsy specimens carries the same prognostic and predictive significance as shown for tumour resections has yet to be proven. For stereotactic body radiotherapy of the lung there is some hint that the subtype determined from core biopsies is relevant for treatment response and failure patterns [21]. As even small percentages of micropapillary and solid patterns seem to have prognostic impact [22, 23], the detection of any amount of these high-grade patterns in biopsy specimens should have prognostic relevance as well, but sampling error remains a major drawback especially in biopsies with small tumour volumes included [24]. Regarding pulmonary squamous cell carcinoma, no international consensus has been reached on a tumour grading system that adds prognostic information independent of tumour stage, although promising proposals exist [25, 26].

To date, these and other characteristics do not change the management of the patient in stage III NSCLC, but in order to get further knowledge they should be evaluated prospectively in a consequent manner.

Immune features in stage III NSCLC

In stage IV of NSCLC, immune checkpoint inhibition depending among others on programmed death-ligand (PD-L1) expression and tumour mutational burden has improved prognosis and reawakened

interest into the immune mechanisms in lung cancer. Especially for stage III NSCLC the knowledge about immune defence and tumour stroma interactions is limited. Immunohistochemistry, partly in combination with multispectral imaging, provides some insight into the tumour stroma interaction [27]. As in other tumours one can categorise the immune activity as "inflamed" and "non-inflamed" tumours. There are data analysing tumour infiltrating lymphocytes in resected NSCLC which suggest a better survival with intense lymphocytic infiltration [28]. An analysis of published literature with the goal of evaluating subsets of tumour infiltrating lymphocytes and prognosis in patients with lung cancer suggests that high levels of CD3 + and CD8+ T-cells correlated with improved survival, but higher stromal Foxp3 levels may be detrimental [29]. There seem to be differences in resected tumours between stage I/II and III, as well between histologic tumour types especially regarding squamous and adenocarcinoma [30]. Multispectral assessment of CD8 and PD-L1 has a clear correlation with clinical outcome [31] and might have some predictive relevance in stage III NSCLC patients receiving chemoradiotherapy [32]. Neutrophil-lymphocyte ratio is a measure of systemic inflammation and was a prognostic factor for overall survival in a retrospective review of 276 patients with stage III NSCLC treated with definitive chemoradiation with or without surgery [33]. It could potentially also be an indicator of inflammatory response to radiotherapy or chemotherapy.

In the PACIFIC study, the beneficial effect of durvalumab, administered after concurrent chemoradiotherapy, was mainly observed in the PD-L1 positive subset, although these claims should be regarded as exploratory [7, 8]. PD-L1 staining was indeed only performed in about 75% of patients and the correlation with progression-free and overall survival was based on a non-predefined subgroup of patients, of which some were very small and not corrected for imbalances. In stage IV, PD-L1 staining is only partly predictive. Other markers like tumour mutational burden and the tumour-infiltrating lymphocytes are of additional relevance. Usually there are only small biopsies in chemoradiotherapy settings which limit the analyses and interpretation. Nevertheless, the European Medicines Agency labelling for durvalumab in stage III NSCLC is based on PD-L1 expression. Therefore, it is important to obtain histology of these patients as PD-L1 staining on cytological material is feasible, but not yet widely standardised for routine implementation. Also, for PD-L1 expression on histological material, standardisation and quality assurance is very important.

In our opinion we need further prospective data in resectable and non-resectable stage III NSCLC regarding the relevance of systemic and local immune features regarding prognostic and predictive relevance.

Treatment modalities

The main local treatment modalities for patients with NSCLC in stage III are surgery and radiotherapy. As the leading site of relapse is outside the thorax, systemic treatment is usually combined with these treatments (figure 1).
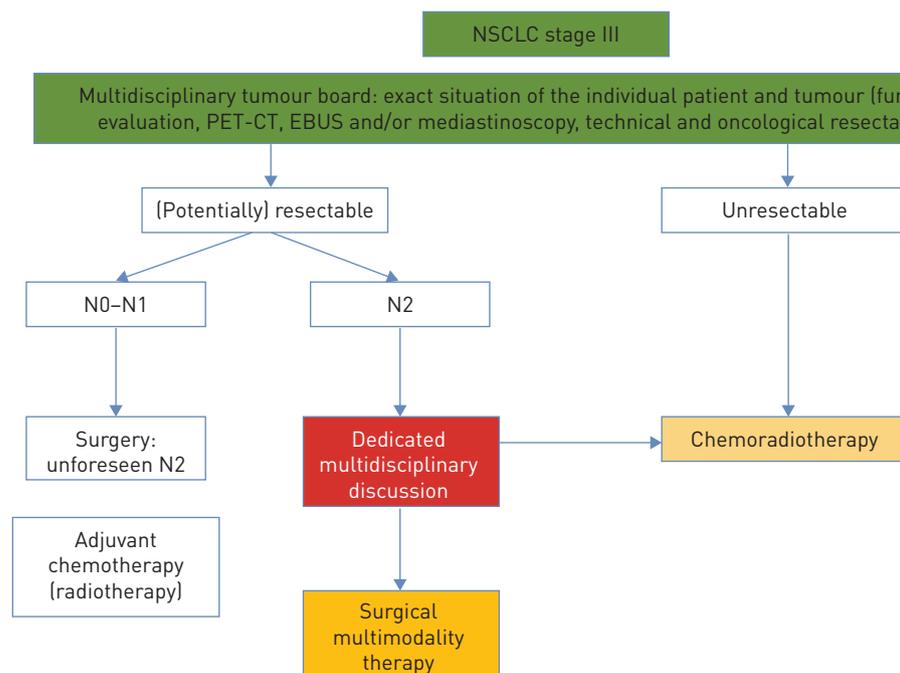

FIGURE 1 Principal management of patients with nonsmall cell lung cancer (NSCLC) in stage III. PET-CT: positron emission tomography-computed tomography; EBUS: endobronchial ultrasound.

Radiotherapy

Concurrent treatment with platinum-based chemotherapy and thoracic radiotherapy (CCRT) is the current standard of care for patients with unresectable stage III NSCLC and recently the addition of durvalumab for 12 months after completion of CCRT. Randomised clinical trials favour the combination chemoradiotherapy compared with radiotherapy alone [34–43]. This is also the case for concomitant chemoradiotherapy compared with sequential chemoradiotherapy [44–47]. Meta-analyses of individual patient data from these studies indicate moderate but statistically significant improvements in overall survival with chemoradiotherapy *versus* radiotherapy alone (HR 0.89; p=0.02) and with concomitant *versus* sequential chemoradiotherapy (HR 0.84; p=0.004) [48, 49]. In concurrent chemoradiotherapy there is an increased risk of acute, but not late, irreversible oesophageal toxicity compared with both sequential treatment and radiotherapy alone and not for pneumonitis. However, many patients are considered unsuitable for chemoradiotherapy due to poor performance status or the presence of serious comorbidities [50].

Increasing the amount of chemotherapy over two cycles as additional induction or consolidation therapy until now did not demonstrate an advantage in progression-free and overall survival in randomised trials [51–54].

Regarding systemic treatment with PD-L1 inhibition, PACIFIC is the first randomised trial which demonstrated a benefit in progression-free survival after simultaneous chemoradiotherapy with consolidation therapy using durvalumab [7, 8]. It was 16.8 months (95% CI 13.0–18.1) with durvalumab *versus* 5.6 months (95% CI 4.6–7.8) with placebo (stratified HR for disease progression or death 0.52; 95% CI 0.42–0.65; p<0.001). Grade 3 or 4 adverse events occurred in 29.9% of the patients who received durvalumab and 26.1% of those who received placebo; the most common adverse event of grade 3 or 4 was pneumonia (4.4% and 3.8%, respectively). A total of 15.4% of patients in the durvalumab group and 9.8% of those in the placebo group discontinued the study drug because of adverse events. Durvalumab also significantly prolonged overall survival, as compared with placebo (stratified HR for death 0.68; 99.73% CI 0.47–0.997; p=0.0025) [8]. Unfortunately, there are some deficits in the trial regarding, for example, the exact staging and re-staging methods and the treatment in recurrence.

The optimal strategy for radiotherapy is still under investigation. Studies have administered different radiation doses and fractions according to different schedules, including hyperfractionated accelerated radiotherapy [55–58]. In the non-concurrent setting, shortening the overall treatment time of radiotherapy led to a significant increase in 5-year overall survival [59]. In concurrent chemoradiotherapy, no regimen has been shown to be superior to 60 Gy delivered in 30 daily fractions of 2 Gy [60–62]. Dose escalation >60 Gy in 30 daily fractions by adding 2 Gy fractions up to 74 Gy was detrimental for survival.

Whereas prophylactic cranial irradiation has been shown to improve survival in patients with small cell lung cancer and is a standard therapy, at least for patients with non-metastatic small cell lung cancer in complete remission [63], this is not clear for NSCLC [64–66]. Brain metastases are a common cause of relapse in patients with NSCLC, but although randomised trials consistently showed a reduction in the incidence of brain metastasis by using prophylactic cranial irradiation, this has not been translated into a gain in overall survival until now.

In conclusion, ideally patients with non-resectable stage III NSCLC should be treated in clinical trials. Outside of clinical trials for fit patients with non-resectable stage III concurrent radiochemotherapy with two cycles of cisplatinum combined with vinorelbin, pemetrexed or etoposide in our opinion is standard of care and can be followed by durvalumab in tumours which express PD-L1.

Surgery

Whereas large tumours without mediastinal lymph node involvement are usually resected, if possible, the possible role of surgery in the management of patients with stage IIIA disease with mediastinal involvement (T1–3N2M0) is the topic of considerable debate [5, 67]. Randomised controlled trials have generally found no significant difference in overall survival when surgery was compared with radiotherapy/chemoradiotherapy for stage IIIA-N2 disease. However, a significant improvement in progression-free survival was seen with surgery *versus* chemoradiotherapy in one study and, in an exploratory analysis of the same study, overall survival was improved compared with chemoradiotherapy in patients who underwent lobectomy, but not pneumonectomy. This observation was not found in recent series, which also showed a lesser surgical mortality [68–70].

A number of factors are discussed in favour of a surgical approach, including single- *versus* multi-zone mediastinal involvement, mediastinal downstaging in response to induction chemotherapy, technical and of course functional resectability, taking into account the patient performance status including assessments of lung function, cardiac risk and exercise capacity, but all of these parameters are merely prognostic and not predictive factors.

Two recent meta-analyses reviewed the current evidence from randomised trials addressing the role of surgery in patients with N2 disease as part of bimodality and trimodality treatment. [71, 72]. MCELNAY *et al.* [71] specifically addressed the key question: should surgery be considered as part of multimodality treatment for patients with resectable lung cancer and ipsilateral mediastinal nodal disease? These systematic reviews and meta-analyses included data from six trials with a total of 868 patients. In four trials, patients received induction chemotherapy [73–76] and in two trials patients received induction chemoradiotherapy [77, 78]. The authors found no important differences in overall survival in patients randomised to surgery as part of bimodality treatment and improved overall survival in patients randomised to surgery as part of trimodality treatment in their meta-analyses. The second cumulative meta-analyses by PÖTTGEN *et al.* [72] reviewed randomised evidence of radiochemotherapy *versus* surgery within multimodality treatment in stage III NSCLC in general. Because they did not exclusively address N2 disease in their review they also included data from the ESPATUE trial [68] which comprised both patients with IIIA (N2) and IIIB (N3) disease. Besides that, they reviewed the same studies as MCELNAY *et al.* [71] with one exception. They excluded the Medical Research Council trial [76] from their analysis due to relevant treatment cross-over (only four out of 24 patients were finally resected in the surgical arm). Including data from the ESPATUE trial, PÖTTGEN *et al.* [72] found no significant different overall survival in patients with locally advanced NSCLC after induction treatment and surgery compared with those receiving definitive radiochemotherapy. Therefore, they came to a somewhat more nuanced conclusion saying that both induction therapy followed by surgery or definitive radiochemotherapy represent valuable curative treatment options for patients with stage III NSCLC, and that the individual treatment choice deserves careful interdisciplinary evaluation and counselling. In ESPATUE [68] and SAKK [69, 70] combining surgery with radiotherapy approximately halved the rate of local recurrences compared to surgery or radiotherapy alone.

Arguments in favour of surgery in patients with resectable disease are bulky, necrotic tumours, which are difficult to control with radiotherapy and which may lead to the formation of a lung abscess, and multiple nodules in the same lobe. The combination of preoperative concurrent chemotherapy and radiotherapy followed by surgery should be considered where local control is especially important for quality of life, such as with invasion of the brachial plexus in superior sulcus tumours (the so-called Pancoast tumours).

Finally, it should be stressed that tumours that are not resectable at diagnosis do not become resectable after any induction treatment.

In conclusion, in most patients there is no need to combine two local treatment modalities when it comes to overall survival. When local tumour control is extremely important, *e.g.* in case of invasion of the brachial plexus, the combination of surgery and radiotherapy is recommended and will lead to the highest chance of permanent local tumour control. Likewise, bulky, necrotic tumours especially with abscedation or with multiple cancer foci in the same lobe are better treated with surgery with or without radiotherapy. Smaller tumours with multiple nodal involvement can achieve high local cure rates with chemotherapy and radiotherapy alone. These considerations which are discussed in the multidisciplinary tumour board are outlined in table 3.

TABLE 3 Considerations in the multidisciplinary tumour board for the various local treatment options in stage III nonsmall cell lung cancer

Resection as primary local treatment
  Adequate pulmonary and cardiovascular function
  Tumours without multi-zone mediastinal lymph node involvement
  Bulky, necrotic tumours with possible complications
  Multiple nodules in the same lobe
  Adequate technical operability, no pneumonectomy necessary
  Local experience and outcome date
  Patient's preferences
Radiotherapy as primary local treatment
  Not adequately resectable disease
  Reasonable dose affections of lung and heart
  (Small) tumours with multiple mediastinal lymph node involvement
  Local experience and outcome date
  Patient's preferences
Radiotherapy and surgery
  Local tumour control is very important
  Locally invasive tumours with slim possible resection margins (*e.g.* superior sulcus tumours)

Systemic treatment

As in stage IV disease [79], both in the adjuvant/neoadjuvant as well as in the chemoradiotherapy setting, a combination of platinum-based chemotherapy with a second chemotherapeutic agent is used.

In the setting of chemoradiotherapy three major combinations are used. In North America cisplatin and etoposide or carboplatin and paclitaxel are usually applied, in Europe cisplatin and vinorelbine as well as cisplatin and etoposide are often used. There is only one randomised phase II trial which compared different combinations [80]. In this trial, a combination of induction chemotherapy with concurrent chemoradiotherapy was chosen for patients with NSCLC in stage III. The combinations which were compared were vinorelbine+cisplatin, paclitaxel+cisplatin and gemcitabine+cisplatin. In this setting efficacy was comparable, but regarding toxicity vinorelbine+cisplatin was the preferable regimen. Other direct comparisons between the combinations in the setting of chemoradiotherapy are lacking. Furthermore, on a more individualised approach including patient features, tumour characteristics like histology (squamous and non-squamous histology) and molecular patterns (driver mutations, *e.g.* in epidermal growth factor receptor (EGFR), EML4-ALK, *etc.*) are missing. If an unselected approach is chosen you may even get detrimental effects like worse survival with adjuvant gefitinib after CCRT in unselected patients [81].

In combination with surgery, either as a neoadjuvant or adjuvant approach, the most valid data are with cisplatin in combination with a taxane or, especially in the adjuvant situation, vinorelbine. There are not enough comparative data to choose the neoadjuvant or the adjuvant approach as the best option. The Spanish NATCH trial made a direct comparison of both approaches with surgery alone in a limited number of patients [82]. Under these conditions no significant difference in survival between these two approaches was found. When one looks at the other randomised phase III trials there is, in comparison to surgery alone with both approaches, a comparative survival benefit with similar toxicity [83]. In the adjuvant setting four cycles of chemotherapy are used, in the neoadjuvant setting three to four cycles are mostly used.

In conclusion, systemic therapy is an essential part of the treatment plan for patients with stage III NSCLC. Outside of clinical trials in non-resectable patients concurrent chemotherapy with two cycles of cisplatin and vinorelbine, pemetrexed (non-squamous NSCLC) or etoposide (plus adjuvant durvalumab) is used. In resectable disease neoadjuvant and adjuvant approaches are probably equivalent. But until now data for individualising systemic therapy in stage III NSCLC are largely lacking and are needed.

Work in progress

With current standard treatment, even local tumour control is suboptimal and distant metastases are common. Recurrences are often both local and at distant sites, and long-term survival remains poor. At the moment, parameters that are associated with a worse outcome are the tumour and nodal volume and the number of affected nodal stations. However, as these are prognostic factors, this knowledge will not lead to a better survival option. Therefore, molecular work-up of the tumour and immunophenotyping the tumour and its microenvironment are active fields of research. Translational and clinical trials try to integrate immunotherapeutic approaches in the perioperative setting and with chemoradiotherapy. Also targeted therapies have to be adequately included in the multimodality treatment. Stereotactic radiotherapy has to be evaluated as a component of multimodality treatment approaches especially for more advanced disease.

EGFR and other driver mutations in combination with radiotherapy

There is a good preclinical rationale for combining EGFR inhibition with radiotherapy [84–90]. Up-regulation of signalling through the EGFR pathway is implicated in various pro-oncogenic processes, including cell proliferation, invasion, survival and angiogenesis. EGFR is frequently overexpressed in patients with NSCLC (~30–80% of patients) and ionising radiation activates EGFR signalling by cancer cells potentially limiting the sensitivity to radiotherapy. Therefore, EGFR inhibitors might, independent of the mutation status, have synergistic effects when combined with radiotherapy, sensitising tumours to radiotherapy in addition to direct anti-proliferative effects. Until now the clinical data with tyrosine kinase inhibitors (TKIs) are inconclusive [91]. Unfortunately, the RTOG0617 phase III trial did not show a beneficial effect of adding cetuximab to CCRT [61, 62].

Activating somatic EGFR mutations are found in 10–20% of Caucasian patients with lung cancer. They cause constitutive activation of the EGFR tyrosine kinase. Tumours with these mutations are highly sensitive to EGFR TKI, which have been shown to be more effective than standard chemotherapy for patients with EGFR-mutated NSCLC [14]. Furthermore, NSCLC tumours with tyrosine kinase domain mutations show enhanced sensitivity to radiotherapy. Therefore, multimodality therapy including radiotherapy and a TKI might be particularly beneficial in patients with EGFR-sensitising mutations.

However, thus far, the addition of gefitinib or erlotinib has not led to an improved survival and may even be harmful.

In the adjuvant setting, two trials in Caucasian patients were primarily performed in unselected patients where there was no benefit [81, 92]. In one trial there was only a small percentage of patients with activating mutations and no benefit was found in this subgroup. In the other trial, the subgroup with active EGFR mutation was somewhat larger. A not statistically significant advantage for the EGFR inhibition was found, which did not result in an overall survival benefit. In a recent Chinese randomised trial in patients with activating mutation an advantage in progression-free survival could be found [17]. Overall survival data are not yet published.

Several smaller trials with EGFR tyrosine kinase inhibitors and radiotherapy in unselected patients have been reported with mixed results and usually enhanced pulmonary toxicity [93–95]. Due to the lack of specific data in stage III, chemoradiotherapy is usually also performed in patients with activating mutations reserving the TKI for the systemic relapse.

Other interventions at the molecular level in combination with thoracic radiotherapy were only done in small clinical trials. Therefore, there is uncertainty regarding safety in such combinations.

Antiangiogenic agents and thoracic radiotherapy

There are preclinical data showing that ionising radiation induces the expression of a range of pro-angiogenic factors, including vascular endothelial growth factor (VEGF). Radiation-induced up-regulation of signalling *via* the VEGF receptor (VEGFR) pathway may contribute to radiotherapy failure by enhancing the rate of vascular repair. Also the sensitisation of tumour cells to radiotherapy has been shown with both monoclonal antibodies directed against VEGFR and VEGFR-TKIs. Clinically, however, this concept was not further developed with bevacizumab as there were complications with bleeding and fistulas, especially in central tumours [96]. If the TKIs could be used, has to be evaluated. But phase I studies suggest that the risk of bleeding is also high.

Immune modulation

Even in a localised tumour the tumour stroma interaction and the status of the immune system is important. In stage IV disease the introduction of immune-checkpoint inhibitors has changed the systemic treatment. In second-line treatment, PD1/PD-L1 inhibitors are more beneficial than docetaxel [97–100]. But even in first-line, pembrolizumab is more efficacious than standard chemotherapy if >50% of the tumours express PD-L1 [101]. Knowing the phenotypes of inflamed and non-inflamed tumours in the resected material could lead to a specific adjuvant therapy with PD1/PD-L1 inhibition. At the moment this approach is under investigation, but neoadjuvant approaches are also being tested [102]. Radiotherapy induces an inflammatory response and an upregulation of PD-L1 expression [103]. As discussed previously the addition of durvalumab to radiochemotherapy improved progression-free and overall survival. Furthermore, PD1/PD-L1 inhibitors in various combinations are studied in the context of chemoradiotherapy in clinical trials. Trials with vaccination in combination with radiotherapy or radio chemotherapy or surgery are, despite initial promising results, until now negative [104–107]. Perhaps the additional combination with PD1/PD-L1 inhibition will be efficacious. Of course the side-effect pattern has to be considered, especially the possible interaction of radiation pneumonitis and autoimmune reactions of the lung to PD1/PD-L1 inhibition.

Specific patient groups
Elderly patients

Overall elderly patients are not included in enough clinical trials. Therefore, our knowledge to this patient group is limited. Regarding surgery there is not a relevant limitation as long as the patients have no functional limitation, especially in lung and cardiovascular function, which exceeds the norms given in the guidelines [108].

The risk–benefit ratio of adjuvant chemotherapy in the elderly is, due to a lack of relevant data, difficult to estimate. For example, in the LACE meta-analyses the median age was 59 years in the chemotherapy arm and 60 years in the control arm with 95th percentiles of 72 and 71 years, respectively [109]. In the subgroup analysis of patients aged ⩾70 years an advantage in overall or disease-free survival could not be demonstrated. Also, radiochemotherapy data from randomised trials are sparse for elderly patients. For example, in the meta-analysis comparing concomitant *versus* sequential chemoradiotherapy, 13% in the concomitant arm and 19% in the sequential arm were aged ⩾70 years, the median age was 62 and 62.4 years, respectively, with a range of 79–82 years [49]. A pooled analysis of US National Cancer Institute Cooperative Group studies of concurrent chemoradiotherapy in elderly patients (⩾70 years) suggests a worse overall survival, more toxicity, and a higher rate of death during treatment [110].

Like surgery, radiotherapy alone is probably not limited by age if the functional limits are observed [108].

For chemoradiotherapy there is no clear hint on relevant negative effects of age in the subgroup analyses of the meta-analyses. But of course one has to have in mind that probably only fit elderly patients without contraindications to chemotherapy were included.

Patients with poor performance status

In the LACE meta-analysis, a small group of patients with an Eastern Cooperative Oncology Group performance status of 2 were included. In the subgroup analysis for this group no adjuvant chemotherapy was better than adjuvant chemotherapy regarding overall survival [109]. Patients with poor performance status should not receive adjuvant chemotherapy.

For example, in the meta-analysis comparing concomitant *versus* sequential chemoradiotherapy, 2% in the concomitant arm and 1% in the sequential arm had a performance status of 2 [49]. There is no good evidence of chemoradiotherapy being of benefit in patients with poor performance status.

Interdisciplinary multimodality treatment approach

The overall prognosis in stage III disease is rather poor with a high rate of systemic relapses. This rate varies according to the exact tumour extent and location, its histology, molecular characteristics and the immunologic situation. This setting in the individual patient can only be evaluated by a multidisciplinary team characterising the situation as a whole and planning the treatment. The outcome can be improved by adequately combining local treatments with systemic treatment concepts. Especially in N2 disease there is an overlap between surgical approaches and radiotherapy, both combined with systemic therapy. This decision is also dependent on the specific experience and the outcome in the individual centre and the preferences of the patient. Furthermore, sequencing and timing in combining these methods is relevant for the outcome of the individual patient. Overall, stage III NSCLC is the situation where interdisciplinary management is of upmost importance. There is some evidence for lung cancer in general (including stage III) that a multidisciplinary team improves various aspects of management and probably survival [111–115]. Specifically stage III is examined in a single centre study. This trial shows, for example, an improvement in mediastinal staging, unsuspected N2 disease and there is a hint for improved survival [116]. The approach to these patients varies largely and needs better evidence-based harmonisation [117]. Integrating new knowledge and new treatment strategies such as targeted therapy and immunotherapy in the management of patients in the various settings of stage III can also only be done in an interdisciplinary trial context.

Conclusions

Patients with NSCLC in stage III disease have a rather poor prognosis. Both local treatment, as well as systemic therapy, has to be optimised. Stage III disease is a heterogenous group of tumours. The outcome varies greatly and strongly depends on a good inter- and multidisciplinary strategy, involving radiologists, nuclear medicine, pathologists, molecular biology, respiratory physicians, oncology, radiotherapy and surgery. Adequately stratified interdisciplinary trials have to integrate new systemic approaches such as targeted therapy and immunotherapy.

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