Current status of and future strategies for multimodality treatment of unresectable stage III nonsmall cell lung cancer

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ABSTRACT Stage III nonsmall cell lung cancer (NSCLC) encompasses a heterogeneous group of patients, some of whom may be candidates for potentially curative surgery, although for the majority surgery is not an option. Recommended therapy for patients with unresectable stage III disease is concurrent treatment with chemotherapy and thoracic radiotherapy, although even with this dual modality therapy survival remains disappointing. Novel classes of agents including targeted therapies have been shown to improve survival in advanced stage NSCLC, raising the possibility that these agents may have benefits in multimodal therapy when combined with chemoradiotherapy. Here we consider the rationale for combining new agents with chemoradiotherapy and the evidence from clinical studies assessing multimodal strategies for the management of patients with unresectable stage III NSCLC.

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Introduction

Nonsmall cell lung cancer (NSCLC) accounts for the majority (~85%) of cases of lung cancer, which is responsible for an estimated 1.4 million deaths each year [1]. When NSCLC is diagnosed at an early stage, when the tumour is still localised (stage I/II), surgery offers a potential cure. However, local spread or metastasis is often already present at the time of diagnosis, partly accounting for the overall poor prognosis. Patients with distant metastasis or pleural effusion (stage IV) have 2-year survival rates <10% [2] and treatment is palliative using platinum-based chemotherapy doublets, potentially in combination with targeted agents [3, 4].

Stage III disease occupies an intermediate position between resectable stage I–II disease and unresectable stage IV disease, and encompasses a heterogeneous group of patients that vary in terms of prognosis, tumour stage and treatment. Surgical resection is an option for selected patients. Clinical practice on resectability for stage IIIA disease tends to follow national guidelines, but those without mediastinal involvement (TNM (tumour, node, metastasis) staging T3N1M0) are generally considered resectable, while possible resectability in the presence of mediastinal involvement (T1–3N2M0) is the topic of considerable debate, with randomised controlled trials generally showing no significant difference in overall survival compared with radiotherapy/chemoradiotherapy [5–8]. Stage IIIB disease is generally considered unresectable due to the involvement of contralateral nodes, although selected patients with T4N2M0 tumours and single position N2 involvement may be candidates for resection. The combination of chemotherapy and/or radiotherapy with surgery as part of multimodal management is an area of active research and considerable debate [9–11] but is beyond the scope of the current review.

The current standard of care for patients with unresectable stage III NSCLC is concurrent treatment with platinum-based chemotherapy and thoracic radiotherapy [4, 12, 13]. Randomised clinical trials and meta-analyses have generally shown trends in favour of combination chemoradiotherapy compared with radiotherapy alone [14–23], as well as concomitant compared with sequential chemoradiotherapy [24–30]. However, many patients are considered unsuitable for chemoradiotherapy, particularly with concurrent administration, due to poor performance status or the presence of serious comorbidities.

While the data available provide general support for concurrent chemoradiotherapy, many important questions remain. The combination of agents, the total dose delivered and the schedule of administration must all be considered in order to optimise the chemotherapy component, but there are currently insufficient data in all these areas. Both induction and consolidation strategies have been investigated, but neither has demonstrated consistent benefits [26, 31, 32] and attempts to establish an effective maintenance therapy in this setting have so far proved unsuccessful.

There is also a paucity of data regarding the optimal strategy for radiotherapy. Studies have administered different radiation doses according to different schedules [33], including hyperfractionated accelerated radiotherapy [18, 34, 35], but without providing sufficient data to reach firm conclusions. Continuous hyperfractionated accelerated radiotherapy (CHART/CHARTWEL) has failed to show a consistent survival benefit compared with conventional fractionated radiotherapy, when combined with chemotherapy in clinical trials [18, 35, 36] and increases the risk of acute toxicity, particularly oesophagitis [37]. Newer techniques, such as stereotactic, intensity-modulated and image-guided radiotherapy, have not been adequately assessed as a component of multimodal therapy for advanced disease and, as such, conventional fractionated radiotherapy remains the standard treatment. The potential benefit of prophylactic cranial irradiation to prevent brain metastases following chemoradiotherapy for NSCLC also requires further investigation [38].

Recently, advances in our understanding of the molecular pathology of NSCLC have identified new targets and strategies that may complement established therapies. A key challenge is to investigate how these possible new treatments can be best used alongside current modalities to improve outcomes for patients. This narrative review examines the available evidence on a multimodal therapeutic approach with emerging and established treatments.

New strategies in multimodality therapy

There is a pressing need to improve the management of patients with unresectable stage III NSCLC. With current standard treatment, local tumour control is suboptimal, distant metastases are common and long-term survival remains poor [30]. At present, it is not possible to predict which patients will benefit from chemoradiation, although some trials indicate that a response to induction chemotherapy is required in order to benefit from further chemotherapy during radiotherapy [39].

A range of new therapeutic options is currently under investigation as part of a multimodality approach to management of NSCLC, including both novel radiotherapy techniques and new biological agents.

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This raises further questions regarding how emerging treatment options should be used alongside chemoradiotherapy in a rational manner.

New agents: current evidence

A number of new classes of agents have been or are currently being investigated as potential components of multimodality therapy for unresectable stage III NSCLC. With the introduction of new classes of agents that act in different ways and against different targets, the ability to identify those patients most likely to benefit from a particular targeted therapy will be increasingly important. Various oncogenic mutations have been identified as potential molecular biomarkers that can predict the response to targeted therapies, including epidermal growth factor receptor (*EGFR*) mutation status or H-score [40], anaplastic lymphoma kinase (*ALK*) translocation [41, 42] and c-Met amplification [43], and may play an important role in guiding treatment choices for personalised multimodal therapy [44].

Inhibitors of the EGFR pathway

There is a good theoretical rationale for combining EGFR inhibition with radiotherapy. Upregulation 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 reducing the sensitivity to radiotherapy [45]. Therefore, EGFR inhibitors might have synergistic effects when combined with radiotherapy, sensitising tumours to radiotherapy in addition to direct antiproliferative effects. In terms of scheduling, this argues for EGFR inhibition concurrent with radiotherapy, although preclinical evidence suggests that maintenance EGFR inhibition after radiotherapy may be beneficial in controlling residual disease associated with relatively radioresistant clones [46].

Somatic EGFR mutations are found in 10–20% of Caucasian patients with lung cancer and predominantly involve mutations that cause constitutive activation of the EGFR tyrosine kinase. Tumours with these mutations are highly sensitive to EGFR tyrosine kinase inhibitors (TKIs), which have been shown to be more effective than standard chemotherapy for patients with *EGFR*-mutated NSCLC [47]. Furthermore, NSCLC tumours with tyrosine kinase domain mutations show enhanced sensitivity to radiotherapy [48]. Therefore, multimodality therapy including radiotherapy and a TKI might be particularly beneficial in patients with EGFR-sensitising mutations.

Acquired resistance to targeted therapies is a problem in NSCLC, as in other cancers, and develops in nearly all patients over time. The mechanisms underlying acquired resistance are believed to involve activation of alternative tyrosine kinase pathways, increased angiogenesis and constitutive activation of downstream mediators. Various strategies aimed at overcoming acquired resistance, including combined inhibition of EGFR with a monoclonal antibody and a TKI, have failed. Recently, however, dual targeting of EGFR with a monoclonal antibody (cetuximab) and a pan-ErbB blocker (afatinib) has emerged as a promising approach for patients with NSCLC and acquired resistance to EGFR TKIs [49].

EGFR inhibitors that have been evaluated in combination with radiotherapy or chemoradiotherapy in the treatment of NSCLC include the monoclonal antibody cetuximab and the TKIs gefitinib and erlotinib (table 1). The data are limited but provide some preliminary insights.

Cetuximab

Preclinical data support the rationale for combining radiotherapy with cetuximab, demonstrating synergistic antitumour activity against human squamous cell carcinoma xenografts derived from the head and neck, apparently involving inhibition of post-radiation damage repair and angiogenesis as well as antiproliferative effects [70]. Similarly, in xenografts of human EGFR-overexpressing NSCLC cell lines, the combination of cetuximab and radiotherapy markedly enhanced tumour growth inhibition compared with either modality alone and had similar activity to chemoradiotherapy. The greatest inhibition of tumour growth was seen with triple combination treatment with radiotherapy, cetuximab and chemotherapy, although the differences compared with radiotherapy combined with either cetuximab or chemotherapy were not significant [71].

The effects of adding cetuximab to radiotherapy for treatment of locally advanced squamous cell carcinoma of the head and neck was assessed in a randomised clinical study in which patients received radiotherapy for 6–7 weeks, either alone (n=211) or with cetuximab (n=213; weekly doses of cetuximab 400 $mg \cdot m^{-2}$ concurrent with radiotherapy, followed by seven weekly doses of cetuximab 250 $mg \cdot m^{-2}$). Median overall survival was significantly improved with the combined modality treatment compared with radiotherapy alone (49.0 *versus* 29.3 months, hazard ratio 0.73; p=0.018). The type and incidence of adverse reactions

TABLE 1 Summary of results from clinical trials of targeted agents in combination with radiotherapy/chemoradiotherapy for unresectable stage III nonsmall cell lung cancer (NSCLC)

	Phase	Patients	Induction chemotherapy	Treatment	Overall survival	Progression-free survival	Adverse events	First author [ref.]
EGFR pathway inhibitors								
Cetuximab								
	I	Unresectable stage III NSCLC, PS 0–1 n=12	Platinum-based	Concurrent CTX+RT (68 Gy, 2 Gy per fraction over 7 weeks)			One report each of fatal bronchopneumonia, lethargy (grade 3), skin reaction (grade 2) and pneumonitis (grade 3)	Hughes [50]
	II	Elderly and/or poor PS patients with locally advanced NSCLC n=57		Concurrent CTX+RT (60 Gy, in 30 fractions)	15.1 months	7.2 months	31 patients (~50%) had grade ⩾3 events, mostly rash, fatigue, anorexia, dyspnoea and dysphagia	Jatoi [51]
	II	Unresectable stage III NSCLC, PS 0–1 n=87		Concurrent CTX +RT (63 Gy in 35 fractions) plus chemotherapy (CBP/PTX)	22.7 months 2-year 49%		Haematologic toxicities (grade 4: 20%), oesophagitis (grade 3: 8%), pneumonitis (grade 3/4=7%)	Blumenschein [52]
	II	Unresectable stage III NSCLC n=101		Arm A: Chemotherapy (CBP/PEM)+RT (70 Gy)+PEM consolidation Arm B: CTX+chemotherapy (CBP/PEM)+RT (70 Gy)+PEM consolidation	18-month survival Arm A: 58% Arm B: 54%		No increase in grade ⩾3 toxicities with addition of CTX to chemotherapy, other than skin rash	Govindan [53]
	II	Unresectable stage III NSCLC n=71	DTX+CIS	Concurrent CTX+RT (64 Gy, 2 Gy per fraction over 45 days)	17 months 1-year 66% 2-year 37% 3-year 29%		Incidence of grade 3–4 toxicities, including oesophagitis (1.4%), pneumonitis (4.2%) and rash (4.2%)	Hallqvist [54]
	II	Stage III NSCLC unsuitable for chemoradiotherapy n=30		Concurrent CTX+intensity-modulated RT followed by maintenance CTX for 13 weekk	19.5 months 1-year 67% 2-year 35%	8.5 months	Any grade 3 toxicity 36.7%, pneumonitis 3.3%	Jensen [55]
	II	Unresectable stage III NSCLC n=38		Concurrent CTX +RT (73.5 Gy, 35 fractions over 7 week) consolidation with CTX for 7 weeks and PTX/CBP chemotherapy (three cycles every 3 weeks)	17.1 months	9.3 months	Grade 3–4 rash reported in three patients during concurrent CTX/RT and two patients during consolidation One death due to pneumonitis, possibly related to CTX	Kotsakis [56]
	II	Locally advanced NSCLC n=102		Arm A: concurrent CTX+RT (66 Gy in 24 fractions) plus chemotherapy (CIS) Arm B: Concurrent RT (66 Gy in 24 fractions) plus chemotherapy (CIS)	1-year Arm A: 76% Arm B: 72%	1-year Arm A: 58% Arm B: 49%	Not reported	van den Heuvel [57]
Gefitinib								
	I	Unresectable stage III NSCLC n=23	CBP+IRI+PTX	Concurrent GEF+RT (74 Gy) plus chemotherapy (CBP+PTX)	16 months	9 months	Primary toxicities: grade 3 oesophagitis (19.5%) and cardiac arrhythmia (9.5%)	Stinchcombe [58]
	I	Unresectable stage III NSCLC n=16		Concurrent GEF+RT (70 Gy) plus chemotherapy (escalating doses of DTX: 15–30 $mg \cdot m^{-2} \cdot week^{-1}$)	21 months		Grade 3–4 toxicities: haematologic (27%), oesophageal (27%) and pulmonary (20%) Maximum tolerated DTX dose: 20 $mg \cdot m^{-2} \cdot week^{-1}$	Center [59]
	I	Unresectable stage III NSCLC n=9	GEF	Concurrent GEF+RT (60 Gy in 30 fractions)			Study terminated early after three patients had disease progression (during induction phase for two patients) and two patients developed pulmonary toxicity	Okamoto [60]
	I	Unresectable stage III NSCLC n=14	GEF	Stage 1: GEF+RT (63 Gy); n=5 Stage 2: GEF+RT (63 Gy) plus chemotherapy (CIS)			Stage 1: no dose-limiting toxicity Stage 2: two patients with dose-limiting toxicity (pneumonia, elevated liver enzymes)	Rothschild [61]
	I	Stage III/IV NSCLC n=26		Concurrent GEF or ERL+individualised RT (42–82 Gy)	21.8 months 1-year 57% 2-year 45% 3-year 30%	10.2 months 1-year 42% 2-year 42%	Grade 3–4 adverse events: neutropenia, thrombocytopenia, oesophagitis and pneumonitis, each reported for one patient	Wang [62]

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TABLE 1 Continued

	Phase	Patients	Induction chemotherapy	Treatment	Overall survival	Progression-free survival	Adverse events	First author [ref.]
	II	Unresectable stage III NSCLC n=63	CBP+PTX	Poor risk (⩾5% weight loss and/or PS 2: concurrent GEF+RT (66 Gy in 33 fractions) Good risk (<5% weight loss and PS 0/1: concurrent GEF+RT (66 Gy in 33 fractions) plus chemotherapy (CBP+PTX)	Poor risk: 19.0 months Good risk: 13.0 months	Poor risk: 13.4 months Good risk: 9.2 months	High-grade toxicities comparable with historical chemoradiotherapy data	READY [63]
	III	Unresectable stage III NSCLC n=243		Primary concurrent chemoradiotherapy (61 Gy; CIS+ETO) with DTX consolidation followed by maintenance therapy with either GEF or placebo	GEF: 23 months Placebo: 35 months	GEF: 8.3 months Placebo: 11.7 months	Grade 3–4 toxicities during GEF maintenance: pneumonitis (3%), rash (7%), diarrhoea (7%) and vomiting (3%)	KELLY [64]
Erlotinib								
	I	Unresectable stage III NSCLC n=34	Arm A: none Arm B: CBP+PTX	Arm A: concurrent ERL+RT (66 Gy in 33 fractions) plus chemotherapy (CIS+ETO) Arm B: concurrent ERL+RT (66 Gy in 33 fractions) plus chemotherapy (CBP+PTX)	Arm A: 10.2 months Arm B: 13.7 months	9 months (across both arms)	Grade 3–4 toxicities during concurrent chemoradiotherapy (n Arm A/ n Arm B) Oesophagitis (3/6), leukopenia (9/5), neutropenia (8/3), thrombocytopenia (5/2), vomiting (1/0), diarrhoea (2/0)	CHOONG [65]
	I/II	Stage III NSCLC n=45	BEV+CBP+PTX	Concurrent ERL+BEV+RT (74 Gy) plus chemotherapy (CBP+PTX)	18.4 months	10.2 months	Primary grade 3–4 toxicity: oesophagitis (29%), with one grade 3 tracheo-oesophageal fistula	SOCINSKI [66]
	II	Unresectable stage III NSCLC n=46		Concurrent ERL+RT (63 Gy in 35 fractions) plus chemotherapy (PTX+CBP) followed by PTX+CBP consolidation	25.8 months	13.6 months	Grade 3 toxicities (n): acne (2), oesophagitis (1), pneumonitis (3) No grade 4 toxicity	KOMAKI [67]
Antiangiogenic agents								
Bevacizumab								
	I	Unresectable stage III NSCLC n=29		Concurrent RT (64.8 Gy in 36 fractions) plus chemotherapy (CIS+ETO) followed by consolidation with BEV+DTX	Low-risk: 23 months High risk: 17 months		Adverse events in consolidation phase: two cases of fatal haemoptysis in high-risk stratum; two cases of grade 3 pneumonitis	WOZNIAK [68]
	I/II	Stage III NSCLC n=45	BEV+CBP+PTX	Concurrent ERL+BEV+RT (74 Gy) plus chemotherapy (CBP+PTX)	18.4 months	10.2 months	Primary grade 3–4 toxicity: oesophagitis (29%), with one grade 3 tracheo-oesophageal fistula	SOCINSKI [66]
	II	Unresectable stage III NSCLC n=5		Concurrent BEV+RT (61.2 Gy in 34 fractions) plus chemotherapy (CBP+PEM) followed by consolidation (BEV+CBP+PEM) and maintenance (BEV)	Not assessed due to early trial closure		Trial stopped early when 2 of 5 patients developed trachea-oesophageal fistulae, one of whom died as a result	SPIGEL [69]

Dosages: bevacizumab (BEV) dosed at 15 mg·kg^{-1}; cetuximab (CTX) dosed as a 400 mg·m^{-2} loading dose prior to radiotherapy (RT) followed by 250 mg·m^{-2} weekly; erlotinib (ERL) dosed at 150 mg once-daily; and gefitinib (GEF) dosed at 250 mg once-daily. EGFR: epidermal growth factor receptor; PS: performance status; CBP: carboplatin; PTX: paclitaxel; PEM: pemetrexed; DTX: docetaxel; CIS: cisplatin; IRI: irinotecan; ETO: etoposide.

were similar, other than acneiform rash and infusion reactions which occurred more frequently when cetuximab was added to radiotherapy [72].

The results of phase I/II studies combining cetuximab with radiotherapy for stage III NSCLC suggest this is a feasible strategy, with acceptable safety and promising survival data (table 1); overall survival ranged from 15 to 23 months and toxicity appeared no worse than with chemoradiotherapy [50, 51, 54–56]. Recent studies investigating the combination of cetuximab with chemoradiotherapy suggest that this trimodal strategy is at least feasible [52, 53, 57]. In a single arm study (n=87), the median survival of 22.7 months was promising [52]. A randomised study comparing chemoradiotherapy either with or without concurrent cetuximab found no additional survival benefit with cetuximab (18-month survival of 54% and 58%, respectively; n=101). The addition of cetuximab to chemoradiotherapy did not substantially worsen toxicity [53]. Another randomised phase II study recently reported no difference in objective control at 24 weeks with cetuximab compared with concurrent cisplatin and radiotherapy (66 Gy) alone, although long-term disease control and survival data are not yet available [57]. Ongoing studies of cetuximab in combination with radiotherapy or chemoradiotherapy are summarised in table 2.

Gefitinib

Gefitinib increases the radiosensitivity of NSCLC cell lines [73, 74], at least in part by suppressing DNA repair mechanisms [74]. In a prospective study of 26 patients with stage III/IV NSCLC treated with either gefitinib 250 mg or erlotinib 150 mg daily plus concurrent radiotherapy (70 Gy), median overall survival and progression-free survival (PFS) were 10.2 and 21.8 months. Safety was acceptable, with manageable acute skin, haematological, oesophageal and pulmonary toxicities [62]. Another study of concurrent gefitinib and radiotherapy for unresectable stage III NSCLC was terminated after two out of seven patients withdrew following pulmonary toxicity. EGFR-sensitising mutations were detected in two patients, both of whom had a partial response to study treatment and overall survival >5 years. The authors concluded that, while the combination was not worth pursuing in unselected patients, it may warrant further investigation in patients with locally advanced NSCLC and EGFR-sensitising mutations [60].

Clinical studies have also investigated the combination of gefitinib with chemoradiotherapy. Treatment of 23 patients with unresectable stage III disease with two cycles of carboplatin/irinotecan/paclitaxel induction chemotherapy followed by concurrent treatment with gefitinib (250 $mg \cdot day^{-1}$, starting on day 41), chemotherapy (carboplatin/paclitaxel) and three-dimensional conformational radiotherapy (74 Gy) resulted in median overall survival and PFS of 16 and 9 months. The primary grade 3 toxicities were oesophagitis (19.5%) and cardiac arrhythmia (9.5%) [58].

In another study, 16 patients with unresectable stage III NSCLC and good performance status (0–1) were treated concurrently with gefitinib (250 $mg \cdot day^{-1}$) plus three-dimensional conformational radiotherapy (70 Gy) and docetaxel (escalating doses of 15–30 $mg \cdot m^{-2}$ weekly). Patients received consolidation therapy with two cycles of docetaxel 75 $mg \cdot m^{-2}$ and maintenance therapy with gefitinib. Median survival was 21 months and the overall response rate was 46%. However, toxicity was disappointing with relatively high rates of grade 3–4 oesophageal (27%) and pulmonary (20%) toxicities, particularly with higher doses of docetaxel (25 $mg \cdot m^{-2}$) [59]. Dose-limiting toxicities (neutropenic pneumonia and elevated liver enzymes) were also encountered in two out of nine patients in another phase I study of gefitinib administered concurrently with radiotherapy and cisplatin chemotherapy [61].

The phase II CALGB 30106 study (n=63) investigated different multimodal treatment strategies according to the patient's risk level. Poor-risk patients (weight loss ⩾5% and/or performance status 2) were treated with induction chemotherapy followed by concurrent gefitinib and radiotherapy (66 Gy). After induction chemotherapy, good-risk patients (weight loss <5% and performance status 0–1) received gefitinib concurrently with the same radiotherapy and chemotherapy (paclitaxel/carboplatin). Results for the combination of gefitinib with chemoradiotherapy were disappointing and, surprisingly, median overall survival was longer in the poor-risk compared with the good-risk patients (19 months, 95% CI 9.9–28.4 months *versus* 13 months, 95% CI 6.4–25.2 months). There were no survival differences between patients with or without EGFR-sensitising or *KRAS* mutations [63].

Hopes that gefitinib might be an effective option for maintenance therapy after chemoradiotherapy for stage III NSCLC have not been met. In the phase III SWOG S0023 trial, 243 patients received concurrent radiotherapy (61 Gy) and chemotherapy (cisplatin/etoposide) followed by three cycles of consolidation therapy with docetaxel. Patients without disease progression were then randomly assigned to maintenance therapy with gefitinib or placebo. Survival was worse with gefitinib maintenance than with placebo (median survival 23 and 35 months, respectively; p=0.013), with more rapid tumour progression, rather than gefitinib toxicity, apparently accounting for the difference in survival [64].

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Erlotinib

Radiosensitising effects of erlotinib have been demonstrated against a range of human tumour cell lines, including NSCLC. Erlotinib appears to act at multiple levels to enhance radiosensitivity, including induction of cell cycle arrest/senescence and apoptosis, as well as inhibition of cellular repopulation and DNA damage repair [75, 76].

A phase I study evaluated erlotinib alongside two chemoradiotherapy regimens in patients with unresectable stage III NSCLC: 1) erlotinib plus radiotherapy (66 Gy) plus cisplatin/etoposide chemotherapy followed by 3 cycles of docetaxel consolidation; and 2) carboplatin/paclitaxel induction therapy followed by erlotinib plus radiotherapy (66 Gy) plus carboplatin/paclitaxel. The addition of erlotinib to chemoradiotherapy did not appear to increase toxicity but survival was disappointing with both regimens (median survival of 10.2 and 13.7 months) [65].

More recent results from a study in which all 46 patients received erlotinib concurrently with radiotherapy (63 Gy) and chemotherapy (carboplatin/paclitaxel) are more promising. Median overall survival was 25.8 months, with 1-year and 2-year survival rates of 84% and 75%, while PFS was 13.6 months. Toxicity was acceptable, with three reports of grade 3 pneumonitis, two reports of grade 3 acne and one report of grade 3 oesophagitis [67].

Also reported recently were the results of a phase I–II trial which evaluated combining the TKI activity of erlotinib with the antiangiogenic effects of bevacizumab alongside chemoradiotherapy. Patients (n=45) with unresectable stage III NSCLC received induction therapy with carboplatin/paclitaxel and bevacizumab followed by concurrent radiotherapy (74 Gy) and chemotherapy (carboplatin/paclitaxel with bevacizumab and erlotinib). Consolidation therapy with erlotinib and bevacizumab was also planned but proved unfeasible. Median overall survival and PFS were 19 months and 10 months, with objective response rates to induction and overall treatment of 39% and 60%, respectively. Grade 3–4 oesophagitis was reported in 29% of the patients and one patient developed a grade 3 tracheo-oesophageal fistula. The investigators concluded that the multimodal regimen appeared to offer no survival benefit at the cost of a substantial risk of, for example, oesophagitis and so is not recommended [66].

Antiangiogenic agents

Ionising radiation induces the expression of a range of pro-angiogenic factors, including vascular endothelial growth factor (VEGF), and it appears that radiation-induced upregulation of signalling *via* the VEGF receptor (VEGFR) pathway may contribute to radiotherapy failure by enhancing the rate of vascular repair [77]. Sensitisation of tumour cells to radiotherapy has been demonstrated with both monoclonal antibodies directed against VEGFR [78] and VEGFR TKIs [79, 80].

A number of antiangiogenic agents have been or are currently being investigated as potential therapies in the management of NSCLC, including both monoclonal antibodies (*e.g.* bevacizumab) and multi-targeted TKIs (*e.g.* sunitinib, sorafenib and vandetanib).

Bevacizumab

Bevacizumab has been evaluated in combination with chemoradiotherapy for stage III NSCLC, with disappointing results. A trial of bevacizumab combined with radiotherapy and chemotherapy (pemetrexed/carboplatin), followed by consolidation with bevacizumab and pemetrexed/carboplatin, and then bevacizumab maintenance was stopped early when two of the five patients with unresectable NSCLC developed trachea-oesophageal fistulae. High rates of trachea-oesophageal fistulae were seen in a similar trial in patients with small-cell lung cancer [69] and high rates of ulceration and bleeding have been seen when combining bevacizumab with chemoradiotherapy in other tumour types [81, 82].

The risk of fistula formation appears to be particularly related to the combination of bevacizumab with radiotherapy, as similar rates have not been seen in studies in which bevacizumab was administered with chemotherapy only [83]. It seems likely that the risk relates to inhibition of healing of mucosal injury in the radiation field owing to the antiangiogenic effects of bevacuzimab.

Use of bevacizumab as consolidation after, rather than concurrently with, radiotherapy might theoretically reduce toxicity and the risk of fistulation. However, this strategy proved unsuccessful in a recently reported pilot study in which chemoradiotherapy for unresectable stage III NSCLC was followed by consolidation with bevacizumab and docletaxel. Patients were stratified into low- and high-risk strata based on squamous histology, haemoptysis or the presence of tumours with cavitation or near a major blood vessel. Median overall survival was 23 and 17 months for the low- and high-risk patients, respectively. Both strata were closed early, the high-risk group following two cases of fatal haemoptysis and the low-risk group due to slow accrual [68].

TABLE 2 Ongoing clinical trials of targeted agents and active immunotherapies in combination with radiotherapy/chemoradiotherapy for unresectable stage III nonsmall cell lung cancer (NSCLC)

	Phase	Patients	Estimated enrolment n	Treatment	Primary outcomes	Location (centres n)	Trial identifier (primary completion date)
EGFR pathway inhibitors							
Cetuximab							
	II	Unresectable, locally advanced stage II/III NSCLC	27	Concurrent CTX and RT	PFS	USA (1)	NCT00673738 (March 2013)
	II	Unresectable, locally advanced stage III NSCLC	62	Arm A: induction chemotherapy (CIS+DTX) followed by concurrent CTX, chemotherapy (CIS+VNB) and RT (66 Gy) Arm B: induction chemotherapy (CIS+DTX) followed by concurrent CTX, chemotherapy (CIS+ETO) and RT (66 Gy)	Safety	France (1)	NCT00985855 (September 2012)
	II	Stage III NSCLC	100	Concurrent CTX, chemotherapy (PEM+CIS) and RT (66 Gy)	Disease-control rate	France (38)	NCT01102231 (June 2013)
	III	Unresectable stage III NSCLC	500	Arm A: standard-dose RT (60 Gy) and concurrent and consolidation chemotherapy (PTX+CBP) Arm B: high-dose RT (74 Gy) and concurrent and consolidation chemotherapy (PTX+CBP) Arm C: standard-dose RT and concurrent and consolidation chemotherapy (PTX+CBP+CTX) Arm D: high-dose RT and concurrent and consolidation chemotherapy (PTX+CBP+CTX)	OS	USA and Canada (213)	NCT00533949 (May 2014)
Gefitinib	II	Unresectable stage III NSCLC EGFR mutation positive	30	Concurrent GEF and RT (60–66 Gy)	Response rate	China (6)	NCT01391260 (July 2017)#
Erlotinib							
	I/II	Stage III NSCLC	50	Arm A: concurrent BEV, chemotherapy (PTX+CBP) and RT Arm B: concurrent ERL, BEV, chemotherapy (PTX+CBP) and RT Arm C: concurrent ERL (higher doses), BEV, chemotherapy (PTX+CBP) and RT	Maximum tolerated ERL dose Safety	USA (3)	NCT00280150 (January 2016)
	II	Unresectable stage III or stage IV NSCLC	25	Concurrent ERL and RT followed by ERL maintenance therapy	PFS	USA (2)	NCT00983307 (October 2013)#
	II	Unresectable stage III NSCLC	48	Concurrent ERL, chemotherapy (PTX+CBP) and RT (63 Gy)	Time to disease progression	USA (1)	NCT00563784 (May 2014)
	II	Stage III NSCLC	50	Concurrent ERL and RT (60–70 Gy)	Disease progression	China (1)	NCT00973310 (October 2015)#
	II	Unresectable stage III NSCLC, EGFR mutation positive	75	Concurrent ERL and RT (60–70 Gy)	Response rate, safety	China (1)	NCT01091376 (March 2013)#
	II	Unresectable stage III NSCLC	76	Induction chemotherapy (PTX+CBP) followed by concurrent ERL and RT	OS	USA (99)	NCT00553462 (January 2014)
	II	Unresectable stage III NSCLC, EGFR mutation positive	100	Arm A: concurrent ERL and RT (60–66 Gy) Arm B: concurrent chemotherapy (CIS+ETO) and RT (60–66 Gy)	PFS	China (14)	NCT01714908 (October 2017)
	II	Unresectable stage III NSCLC	212	Arm A: induction therapy with ERL followed by concurrent ERL and RT (60 Gy) and then consolidation ERL Arm B: induction therapy with ERL followed by concurrent chemotherapy (IRI+CIS) and RT (60 Gy) followed by ERL maintenance on recurrence Arm C: induction chemotherapy (IRI+CIS) followed by concurrent chemotherapy (IRI+CIS) and RT (60 Gy) Arm D: concurrent chemotherapy (IRI+CIS) and RT (60 Gy) followed by consolidation chemotherapy (IRI+CIS)	Response rate	South Korea (1)	NCT00620269 (March 2015)
	III	Unresectable stage III NSCLC	380	Arm A: concurrent chemotherapy (DTX+CBP) and RT followed by ERL maintenance Arm B: concurrent chemotherapy (DTX+CBP) and RT followed by placebo maintenance	PFS	USA (65)	NCT00153803 (December 2012)

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TABLE 2 Continued

	Phase	Patients	Estimated enrolment n	Treatment	Primary outcomes	Location (centres n)	Trial identifier (primary completion date)
Antiangiogenic agents							
Bevacizumab							
	I/II	Stage III NSCLC	50	Arm A: concurrent BEV, chemotherapy (PTX+CBP) and RT Arm B: concurrent ERL, BEV, chemotherapy (PTX+CBP) and RT Arm C: concurrent ERL (higher doses), BEV, chemotherapy (PTX+CBP) and RT	Maximum tolerated ERL dose, safety	USA (3)	NCT00280150 (January 2016)
	I/II	Unresectable stage III NSCLC	182	Arm A: concurrent chemotherapy (CIS+ETO) and RT Arm B: concurrent BEV (on days 15, 36, 57), chemotherapy (CIS+ETO) and RT Arm C: concurrent BEV (on days 1, 22, 43), chemotherapy (CIS+ETO) and RT Consolidation therapy (BEV+DTX) in all arms	Haemorrhage rates	USA (36)	NCT00334815 (June 2013)
	II	Unresectable stage III NSCLC	55	Concurrent chemotherapy (PTX+CBP) and RT followed by consolidation chemotherapy (PTX+CBP) and maintenance therapy with BEV+L-BLP25	Safety	USA (88)	NCT00828009 (January 2016)
mTOR inhibitors							
Everolimus	I	Unresectable stage II or stage IV NSCLC	36	Concurrent everolimus (10, 20 and 50 mg) and RT (66 Gy), followed by consolidation chemotherapy (CIS+navelbine)	Safety	France (1)	NCT01167530 (July 2014)
COX-2 inhibitors							
Celecoxib	II	Unresectable stage III NSCLC	100	Arm A: concurrent chemotherapy (CIS+ETO) and RT Arm B: concurrent celecoxib, chemotherapy (CIS+ETO) and RT	OS	China (1)	NCT01503385 (December 2014)
Active immunotherapies							
L-BLP25 (mucin-1)							
	I/II	Unresectable stage III NSCLC	168	Arm A: maintenance therapy with L-BLP25 following chemoradiotherapy (platinum-based+RT $\geqslant$50 Gy) Arm B: maintenance therapy with placebo following chemoradiotherapy (platinum-based+RT $\geqslant$50 Gy)	OS	Japan (4)	NCT00960115 (December 2014)
	II	Unresectable stage III NSCLC	55	Concurrent chemotherapy (PTX+CBP) and RT followed by consolidation chemotherapy (PTX+CBP) and maintenance therapy with BEV+L-BLP25	Safety	USA (88)	NCT00828009 (January 2016)
	III	Unresectable stage III NSCLC	420	Arm A: maintenance therapy with L-BLP25 following chemoradiotherapy (platinum-based+RT $\geqslant$50 Gy) Arm B: maintenance therapy with placebo following chemoradiotherapy (platinum-based+RT $\geqslant$50 Gy)	OS	China, Hong Kong, Singapore, South Korea, Taiwan (43)	NCT01015443 (September 2015)
	III	Unresectable stage III NSCLC	1514	Arm A: maintenance therapy with L-BLP25 following chemoradiotherapy (platinum-based+RT $\geqslant$50 Gy) Arm B: Maintenance therapy with placebo following chemoradiotherapy (platinum-based+RT $\geqslant$50 Gy)	OS	Global (295)	NCT00409188 (February 2013)
Mucin-1 100mer peptide	I/II	Stage I–IV NSCLC	30	Maintenance therapy with mucin-1 100mer vaccine following standard-of-care primary treatment according to disease stage (concurrent chemoradiotherapy for unresectable stage III NSCLC)	Immunologic response	USA (1)	NCT01720836 (November 2017)
GV1001 (telomerase)	III	Unresectable stage III NSCLC	600	Arm A: maintenance therapy with GV1001 following chemoradiotherapy (platinum-based doublet+RT $\leqslant$66 Gy) Arm B: maintenance therapy with placebo following chemoradiotherapy (platinum-based doublet+RT $\leqslant$66 Gy)	OS	N/S	NCT01579188 (May 2016)

Trials identified as ongoing based on a search of clinicaltrials.gov (accessed December 4, 2012) using the name of the targeted agent, ''radiotherapy'' and NSCLC, excluding entries not in patients with stage III NSCLC and/or not verified since January 2010. Dosages: cetuximab (CTX) dosed as a 400 mg·m^{-2} loading dose prior to radiotherapy (RT), followed by 250 mg·m^{-2} weekly; erlotinib (ERL) dosed at 150 mg once-daily; gefitinib (GEF) dosed at 250 mg once-daily. EGFR: epidermal growth factor receptor; mTOR: mammalian target of rapamycin; COX-2: cyclooxygenase-2; PFS: progression-free survival; CIS: cisplatin; DTX: docetaxel; VNB: vinorelbine; ETO: etoposide; PEM: pemetrexed; PTX: paclitaxel; CBP: carboplatin; OS: overall survival; BEV: bevacizumab; IRI: irinotecan. #: date for completion of study rather than primary outcome measure.

Consequently, it appears that bevacizumab is not suitable for use alongside radiotherapy. Furthermore, the results urge caution when investigating other antiangiogenic agents in combination with radiotherapy or chemoradiotherapy, particularly when planning scheduling and dosing.

Multi-targeted TKIs

Currently, there are no clinical data on the use of small molecule VEGFR TKIs in combination with radiotherapy or chemoradiotherapy for stage III NSCLC, although preclinical findings provide some support for the strategy. Radiosensitising effects of vandetanib, a TKI that inhibits both the VEGFR and EGFR pathways, have been demonstrated in an orthotopic mouse model of NSCLC. Tumour dissemination into the chest wall was common in the orthotopically injected mice, as it is in patients with NSCLC. Combination therapy with vandetanib and radiotherapy markedly reduced tumour dissemination into the thoracic wall and was more effective than either modality alone or the combination of paclitaxel with radiotherapy [84]. Vandetanib also has radiosensitising effects on head and neck carcinoma cell lines and xenografts [85–87].

Sunitinib inhibits signalling through both the platelet-derived growth factor receptor (PDGFR) and VEGFR pathways and has been shown to increase the sensitivity of a human pancreatic carcinoma cell line to radiation damage. Adding sunitinib to radiation delayed tumour growth by 30 days, compared with just 6 days with sunitinib alone and 10 days with radiation alone [88]. Another dual PDGFR/VEGFR TKI sorafenib did not appear to affect the radiosensitivity of a human colorectal cancer cell line, but tumour growth of xenografts was substantially slower with the combination of sorafenib and radiation compared with either modality alone [89].

mTOR inhibitors

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase that plays an important role in regulating various basic cellular functions, including cell growth and proliferation and DNA repair. Combining the mTOR inhibitor everolimus with radiation resulted in synergistic antitumour effects in a xenograft model of human NSCLC, reducing the mean tumour volume by 73% compared with control, a significantly greater reduction than with either everolimus alone (38%; $p<0.001$) or radiation alone (52%; $p=0.015$) [90]. Addition of the mTOR inhibitor everolimus to radiation treatment has also been shown to enhance radiation damage to colon and pancreatic cancer cell lines and improved tumour control *in vivo* [91]. The radiosensitising effects of mTOR inhibitors appear to operate primarily on the vascular endothelium [91, 92]. Radiation recall syndrome may be a concern when combining mTOR inhibitors with radiotherapy, based on cases in which patients received mTOR inhibitors (everolimus or temsirolimus) as part of combination therapy following radiotherapy for breast, prostate or ovarian cancer [93].

Cyclo-oxygenase inhibitors

Selective cyclo-oxygenase (COX)-2 inhibition has been shown to increase the sensitivity of lung cancer cell lines to both radiation [94–96] and various chemotherapeutic agents including docetaxel and irinocetan [97]. The combination of the COX-2 inhibitor celecoxib with radiotherapy appears to be a feasible strategy in patients with NSCLC. Safety was acceptable in a phase I study including a cohort of patients with locally advanced NSCLC who received celecoxib at doses up to 800 $mg \cdot day^{-1}$ concurrent with palliative radiotherapy (45 Gy). The main toxicities were grade 1–2 nausea and oesophagitis [98]. In a phase I–II trial, 18 patients with unresectable stage IIA or stage III NSCLC and poor performance status (performance status 2 and/or >5% weight loss) received celecoxib (400–800 $mg \cdot day^{-1}$) concurrently with radiotherapy (45 Gy in 15 fractions or 60–66 Gy in 30–33 fractions), followed by maintenance therapy with celecoxib. Median survival was 10 months and 1- and 2-year survival rates were 44% and 22%. Toxicity was comparable to that typical of radiotherapy alone [99].

A phase II trial of celecoxib (800 $mg \cdot day^{-1}$) with concurrent paclitaxel/cisplatin chemoradiotherapy followed by celecoxib maintenance was stopped early due to a disappointing overall response rate. Out of 14 patients, one patient had a complete response and five patients had a partial response, resulting in an overall objective response rate of 42.9%. Complete and partial responses were seen only in patients with robust reductions in the major metabolite of prostaglandin in the first 5 days after starting celecoxib treatment, suggesting that this may provide a biomarker for response to COX-2 inhibition in NSCLC. The main toxicities of the multimodal therapy were pulmonary and gastrointestinal, with one case of high-grade (≥ 3) pneumonitis and two cases of high-grade dysphagia/oesophagitis/odynophagia [100].

Active immunotherapy

A number of active immunotherapies (therapeutic cancer vaccines) are under investigation in NSCLC. These include an allogeneic vaccine derived from irradiated NSCLC cell lines (belagenpumatucel-L),

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protein-specific vaccines (human recombinant epidermal growth factor, purified melanoma-associated antigen (MAGE)-A3 recombinant protein and telomerase) and mucin-1 targeting antigen-specific cancer immunotherapies (L-BLP25 and TG4010) [101]. Each immunotherapy differs in its mechanism of antigenic stimulus, although many incorporate immunoadjuvant to potentiate the immune response [101]. Examples include L-BLP25, administered with the adjuvant monophosphoryl lipid A, which is currently being investigated following primary chemoradiotherapy for unresectable NSCLC in the phase III START (Stimulating Targeted Antigenic Responses To NSCLC) study (table 2) [102], and MAGE-A3 with AS02B as an adjuvant, following complete resection of stage IB, II or IIIA NSCLC in the phase III MAGRIT (MAGE-A3 as Adjuvant, Non-Small Cell Lung Cancer Immunotherapy) trial [103]. As adjuvants have potent immunostimulatory effects, it is important to consider the combined effects of administering immunoadjuvant alongside other therapies in the context of multimodality regimens.

There are currently no clinical data on the concurrent use of active immunotherapy with radiotherapy. However, clinical trials in other tumour types, including prostate cancer [104] and glioblastoma [105], provide a proof of principle. Irradiation of tumours induces a cascade of pro-immunogenic effects involving both the innate and adaptive immune responses [106–108] and preliminary evidence suggests radiotherapy might enhance the effects of immunotherapy with L-BLP25 [102].

Conclusions

Rational, evidence-based decision making in the treatment of unresectable stage III NSCLC is a challenge, given that critical questions regarding optimisation of each of the individual modalities remain unanswered. Furthermore, the areas of uncertainty multiply when the different modalities are combined together and new agents are introduced into the therapeutic armamentarium.

While chemotherapy concurrent with radiation therapy is now the standard-of-care for unresectable stage III NSCLC, no single regimen can be considered as standard. Ongoing studies continue to try and determine the optimal combinations of chemotherapeutic agents, the most effective technique for delivering radiotherapy and the ideal schedules for administering radiotherapy alongside chemotherapy.

Targeted therapies have shown some initial promise in multimodality therapy, but robust evidence of consistent benefits in unresectable stage III NSCLC remain lacking. Consequently, they currently have no indication in routine practice in this setting and further investigations are needed.

Increasing attention is focused on personalising therapy, taking into account various factors including patient-related characteristics, tumour histology, treatment history and the presence of comorbidities. With the introduction of targeted therapies that act through discrete molecular pathways, the use of biomarkers to predict those patients most likely to benefit from a particular therapy is an active area of research. The best characterised and most useful of these biomarkers is currently *EGFR* mutation status, but other markers, such as *KRAS* mutations and *ALK* translocations, may also prove valuable in guiding treatment decisions.

In order to improve the management of patients with unresectable stage III NSCLC, a number of key questions remain. In our opinion, these include the development of prognostic biomarkers, where the emphasis should be upon identifying candidates for higher intensities of systemic therapy, in the context of chemoradiotherapy regimens. In addition, a greater appreciation of the interactions between radiotherapy and systemic therapy, and the biological consequences of combining these two modalities at different intensities, is required. A primary focus of future research should include the use of near *in vivo* models to develop a ''molecular signature'' for unresectable stage III tumours. This would facilitate the treatment of tumours according to molecular status and, through the use of repeated biopsies, allow therapy to be adapted according to early treatment responses. These steps should ultimately allow personalised and flexible treatment regimens to become a reality for an increasing number of patients. Organ co-culture systems more closely model the multicell, three-dimensional tumour environment and can be used to differentiate the effects of combining radiotherapy with systemic treatments on malignant and non-malignant tissue [109]. These *in vitro* approaches should be included in the assessment of all new systemic agents.

With regards to priorities for clinical studies, the EGFR TKIs gefitinib and erlotinib, and the ALK inhibitor crizotinib are already used in the treatment of stage IV NSCLC patients. A first step could be to initiate phase I–II trials in which patients with appropriate genetic alterations receive the systemic agent as induction therapy and then concurrent chemoradiotherapy. The experience gained from these studies, including molecular analysis of follow-up biopsies, and clinical results, including morphological and metabolic imaging, could then be used in the design of phase III studies. Further steps in developing multimodal treatment will depend on the results of these investigations.

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