Combining Systemic Therapies with Radiation in Non-small Cell Lung Cancer

Kombinace systematických terapií s radiací u nemalobuněčného karcinomu plic

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Summary

Radiotherapy has been the mainstay of treatment of stage III non-small cell lung cancer patients. In the early 90s, combined treatment with chemotherapy was introduced. In 1995, a meta-analysis showed improved treatment outcome of the sequential use of cisplatin-based chemotherapy and radiotherapy compared to radiotherapy alone. Subsequent randomized studies and two meta-analyses demonstrated that concurrent radiochemotherapy is superior (local control and overall survival) to sequential usage of both method. However, several questions remain unanswered concerning the optimal chemotherapy regimen and radiotherapy doses and techniques in terms of treatment outcome and toxicity profile. Targeted therapies represent a new class of drugs, which interfere with specific molecular targets (typically proteins) playing critical roles in tumor growth and progression. Some combinations appear to be too toxic, such as the vascular epithelial growth factor antibody bevacizumab. The feasibility of adding the epidermal growth factor receptor inhibitor cetuximab has been recently reported for non-small cell lung cancer patients. Strategies to incorporate safely novel antiangiogenic agents into combined-modality therapy in lung cancer are needed. Hopefully, rapid development of molecular oncology will contribute to better patient selection to particular strategies and to treatment optimization. Increasing radiotherapy doses applied according to up-to-date techniques and combinations with new biologicals might lead to further treatment improvements.

Key words

lung neoplasms – chemotherapy – radiotherapy – drug therapy

Souhrn

Radioterapie je hlavní léčebnou modalitou při léčbě III. stadia nemalobuněčného plicního karcinomu. Na počátku 90. let 20. století byla zavedena kombinovaná léčba s chemoterapií. V roce 1995 prokázala metaanalýza zlepšené výsledky léčby při sekvenčním použití chemoterapie a radioterapie založené na cisplatině v porovnání se samotnou radioterapií. Následné randomizované studie a dvě metaanalýzy prokázaly, že současně používaná radiochemoterapie převyšuje sekvenční používání obou metod v celkovém přežití i lokální kontrole onemocnění. Přesto zůstává v rámci výsledků léčby a profilu toxicity nezodpovězeno několik otázek, včetně optimálního režimu chemoterapie a dávky a techniky radioterapie. Cílená léčba představuje novou třídu léčiv, která reagují se specifickými molekulárními cíli (typicky proteiny), které hrají klíčovou roli v růstu nádoru a progresi. Některé kombinace se jeví jako příliš toxické, jako třeba protilátka proti vaskulárnímu epiteliálnímu růstovému faktoru – bevacizumab. Možnost přidání inhibitoru receptoru epidermálního růstového inhibičního faktoru cetuximabu byla nedávno popsána u pacientů s nemalobuněčným karcinomem plic. Jsou zapotřebí vyvinout strategie, jak bezpečně začlenit nová antiangiogenní agens do kombinované terapie u rakoviny plic. Rychlý rozvoj molekulární onkologie snad přispěje k lepšímu výběru pacientů pro jednotlivé strategie a k optimalizaci léčby. K dalšímu zlepšení výsledků léčby může dále vést zvýšení dávek radioterapie, aplikované v souladu s nejnovějšími technikami a v kombinaci s novými biologickými látkami.

Klíčová slova

karcinom plic – chemoterapie – radioterapie – farmakoterapie

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Introduction

Lung cancer is the most common cause of cancer death globally [1]. Most cases of lung cancer occur around the age of 60–70 years [2].

Treatment of non-small cell lung cancer (NSCLC) is challenging in many ways. Until the 1990s, radiotherapy alone was the standard treatment for stages IIIA and IIIB of NSCLC. With the standard dose of 60 Gy in 30 doses, survival rates were extremely poor [3]. Indeed, technical developments allowing the administration of higher radiation doses resulted in strategies to improvetreatment results include increasing doses of radiotherapy and decreasing overall treatment time [4]. For NSCLC, a dose-effect relationship exists: the higher the radiation dose, the greater the probability of tumor control improved local control and OS [5]. The theoretical solution of simply increasing radiation doses to high biologically effective doses, ideally above the threshold of 100 Gy, has been suggested by several groups [6–9]. However, radiation dose escalation does not address the issue of distant or out-of-field relapses. Therefore, a different option is to combine radiotherapy with chemotherapy. The first report on improved OS after adding chemotherapy to radiation was published more than 20 years ago [10]. Over the past decades, concomitant chemotherapy and radiotherapy have become the established treatment for patients with stage III NSCLC. In this review, we present current clinical knowledge on combining available systemic therapies with radiation.

Radiochemotherapy in locally advanced NSCLC

The strategy of exclusive radiotherapy for locally advanced inoperable NSCLC has been challenged after publication of meta-analysis by the Non-small Cell Lung Cancer Collaborative Group in 1995 [11]. Since than, a combination of chemotherapy and radiotherapy is the recommended treatment in this group of patients. Radiotherapy preceded by (usually) two courses of chemotherapy yielded an improvement of the 2-year overall survival rate (OS) from 21% to 25%. The 5-year survival increased from 6% to 8% provided that the chemotherapy regimen included cisplatin. The effect was explained by a reduction of distant metastases. Until now, this effect of a lower distant metastasis rate was observed in one study only [12]. In this study, Le Chevalier et al. compared radiotherapy alone to chemotherapy and radiotherapy. However, patients with adenocarcinoma were excluded. Since an important proportion of NSCLC patients were not included, results might not be representative. The 2-year survival rate was 14% in radiotherapy alone group and 21% in combined treatment group. The 3-year survival rate was 12% for the combination arm vs. 4% for the radiotherapy arm ($p < 0.02$) and local control was poor in both groups (17% and 15%, resp.). To our knowledge, these results have never been confirmed. Until recently, sequential cisplatin-containing radiochemotherapy has been the standard treatment for inoperable stage IIIA and IIIB disease. Various chemotherapy schedules have been applied, but the treatment outcome did not differ significantly.

Despite this progress, both loco-regional and distant failures are frequent. Over the last 20 years, concomitant use of radiotherapy and chemotherapy have been extensively studied in various malignancies, including NSCLC, rectal cancer, anal cancer and head and neck cancers, and has currently replaced radiotherapy alone in patients with good performance status. This strategy, through superadditive effect, not only improves local tumor control but also increases overall survival [13]. The benefits of concomitant radiochemotherapy include a potential synergism between both modalities and avoiding the delay of radiotherapy. Therefore, there is a rationale for considering concomitant chemo-radiation also in patients with high-risk lung cancer. Attempts to improve the loco-regional control included increasing radiotherapy dose using altered fractionation regiments and combining chemotherapy with radiotherapy. After phase I and phase II studies, the EORTC started a 3-arm phase III trial comparing split-course radiotherapy of 55 Gy using the same radiotherapy scheme, concurrently combined with 30 mg/m^2 cisplatin once a week or 6 mg/m^2 daily [14]. No improvement was seen after treatment with radiotherapy and weekly cisplatin. The 6 mg/m^2 cisplatin daily added to radiotherapy improved OS due to improved control of local disease. The difference was also significant after adjustment for known prognostic factors in a multivariate analysis. There was no effect on the distant metastasis rate, and late toxicity was not increased. These data demonstrated that cisplatin improved the radiotherapy effect by radiosensitization. The most frequently reported acute side effects were nausea and vomiting. In 1992, Trovo et al. [15] also published their randomized phase III study. Three weeks of radiotherapy, to a dose of 45 Gy, were compared to the same radiotherapy dose with the addition of 6 mg/m^2 cisplatin daily. In this study, no significant advantage of the combined treatment over radiation therapy only was found. However, this result may be due to the lower dosage of radiation used in the study (Tab. 1).

All phase III trials were included in a meta-analysis including 12 trials and 1921 patients by Aupérin et al. [16] indicated a 4% survival gain at two years and 2% at five years for concurrent chemoradiation vs. radiotherapy alone, a comparable improvement to that observed with the sequential combination. Even though this meta-analysis was based on individual patient data, it did not allow to accurately define the size of such a potential treatment benefit and the optimal schedule of chemotherapy. The efficacy of concurrent chemoradiotherapy vs. radiotherapy also was compared in a metaanalysis including 14 randomized studies (and 2,393 patients) in 2010 [17]. A Cochrane meta-analysis confirmed these conclusions: concurrent chemoradiotherapy was associated with 14% reduction in the risk of death at two years compared to sequential chemoradiotherapy, and a 7% reduction compared to radiotherapy alone.

If sequential and concurrent radiochemotherapy improved overall survival, so there is another question: which is better? In several trials, improved 1- and 2-year overall survival rates in favor of the concurrent arm were reported [18–23].

Tab. 1. Chemoradiotherapy in locally advanced NSCLC.

Reference (therapy)	Study type	Patients	Radiotherapy schedule	Systemic therapy	Results
Le Chevalier et al. [12]	phase III n = 353	nonresectable squamous cell and large-cell lung carcinoma; WHO 0–1; stage IIIA or IIIB	the radiation dose was 65 Gy in each group	radiotherapy alone (group A), combined treatment (group B) + chemotherapy included vindesine, cyclophosphamide, cisplatin, and lomustine	2-year OS rate was 14% in group A and 21% in group B; distant metastasis rate was significantly lower in group B; local control was poor in both groups (17% and 15%)
Schaake-Koning et al. [14]	phase III n = 100	inoperable stage I, II, or III; no more than 70 years old; medical contraindications to operation; ECOG 0–2; creatinine clearance min. 70 ml per minute	radiation was administered for 2 weeks in a dose of 3 Gy given 10 times, followed by a rest period of 3 weeks; radiation was again administered for 2 weeks in a dose of 2.5 Gy given 10 times	radiotherapy alone (group A); radiotherapy combined with cisplatin in a dose of 30 mg/m^2, given intravenously on day 1 of each treatment week (group B); radiotherapy with cisplatin in a dose of 6 mg/m^2 daily (group C)	OS was significantly improved in the group C as compared with the group A; OS in group C was 54% at 1 year, 26% at 2 years, and 16% at 3 years, as compared with 46%, 13%, and 2% in group A; OS in group B was intermediate (44%, 19%, and 13%) and not significantly different from OS in either of the other 2 groups, 26% and 28%, resp.
Trovo et al. [15]	phase III n = 173	inoperable stage III	radiotherapy 45 Gy/15 fractions/3 weeks	only radiotherapy (arm A) vs. radiotherapy and daily cisplatin dose 6 mg/m^2 (arm B)	median TTP was 10.6 months for arm A and 14.2 months for arm B; median OS: 10.3 months and 9.97 months; no significant advantage of the combined treatment over radiation therapy only was found
Aupérin et al. [16]	meta-analysis n = 1,764	inoperable stage I, II, III and IV; ECOG 0–3	radiotherapy 45 Gy to 69.6 Gy/15–58 fractions/3–6 weeks	9 randomized studies only radiotherapy (arm A) and radiotherapy with chemotherapy (arm B) (cisplatin daily, cisplatin weekly, carboplatin, cisplatin + etoposide; carboplatin + etoposide)	the hazard ratio (HR) of death in arm B to arm A 0.89; absolute benefit of chemotherapy 4% at 2 years and 2.2% at 5 years; 2- and 5-year OS rates from 21.4% (arm A) to 25.4% (arm B), and from 6.0% (arm A) to 8.2% (arm B)
Rowell et al. [17]	meta-analysis n = 2,393	inoperable stage I, II, III; ECOG 0–3	radiotherapy 45 Gy to 69.6 Gy/15–58 fractions/3–6 weeks	14 randomized studies only radiotherapy (arm A) and radiotherapy with chemotherapy (arm B) (cisplatin daily, cisplatin weekly, carboplatin, cisplatin + etoposide; NR)	reduction in risk of death at 2 years (relative risk – RR 0.93); improvements in 2-year locoregional PFS (RR 0.84) and PFS at any site (RR 0.90); concurrent vs. sequential chemoradiotherapy – significant reduction in the risk of death at 2 years with concurrent treatment (RR 0.86)

Tab. 1 – continuation. Chemoradiotherapy in locally advanced NSCLC.

Reference (therapy)	Study type	Patients	Radiotherapy schedule	Systemic therapy	Results
Aupérin et al. [24]	meta-analysis n = 1,205	inoperable stage I, II, III and IV; ECOG 0–2	radiotherapy 60 and 66 Gy in 2 trial each, and 56 and 48.5 Gy in 1 trial each; in 1 trial the radiotherapy – different in the 2 arms – there was a 10 days split in the concomitant arm; in the 5 trials in the sequential arm, patients randomly assigned to concomitant arm received radiotherapy more frequently than those randomly assigned to the sequential arm	11 randomized studies sequential – cisplatin combined with 1 drug in 4 trials, or with 2 drugs in 2 trials; vinorelbine or gemcitabine were used in 2 trials; concomitant radiochemotherapy arm, cisplatin was used in 5 trials, either on a daily basis as single agent (2 trials) or combined with other drugs every 4 weeks (3 trials); carboplatin administered weekly was used in only 1 trial	OS: significant benefit of concomitant radiochemotherapy (HR 0.84) with an absolute benefit of 5.7% (from 18.1% to 23.8%) at 3 years and 4.5% at 5 years; PFS: significant benefit of concomitant radiochemotherapy HR was 0.90; concomitant treatment decreased locoregional progression (HR 0.77); concomitant radiochemotherapy increased acute esophageal toxicity (grade 3–4) from 4% to 18%
O'Rourke et al. [25] radiotherapy vs. radiotherapy and chemotherapy	meta-analysis n = 2,728	inoperable stage I, II, III; ECOG 0–3	radiotherapy 56 Gy/28 fractions – 70.2 Gy/39 fractions	19 randomized studies vindesine/cisplatin/mitomycin C; cisplatin/vinblastine; cisplatin/vinorelbine; carboplatin/paclitaxel	chemoradiotherapy reduced overall risk of death (HR 0.71) and PFS (HR 0.69); incidence of acute oesophagitis, neutropenia and anaemia were significantly increased with concurrent chemoradiation
O'Rourke et al. [25] sequential radiotherapy and chemotherapy vs. concomitant radiotherapy and chemotherapy	meta-analysis n = 1,024	inoperable stage I, II, III; ECOG 0–3	radiotherapy 56 Gy/28 fractions – 70.2 Gy/39 fractions	6 randomized trials vindesine/cisplatin/mitomycin C; cisplatin/vinblastine; cisplatin/vinorelbine; carboplatin/paclitaxel	OS: significant benefit of concurrent treatment (HR 0.74) with 10% absolute OS benefit at 2 years; more treatment-related deaths (4% vs. 2%) in the concurrent arm without statistical significance (RR 2.02); increased esophagitis with concurrent treatment (RR 4.96)

IMRT – intensity-modulated radiotherapy, KPS – Karnofsky performance status, ECOG – Eastern Cooperative Oncology Group performance status, WHO – World Health Organization performance status, ENI – elective nodal irradiation, OS – overall survival, PFS – progression-free survival, PR – partial remission, CR – complete remission, TTP – time to progresion, NR – not reported

Most of these trials were included in a new meta-analysis based on individual patient data by Aupérin et al. [24] who concluded that concurrent radiochemotherapy yielded superior results compared to sequential combinations. There was a significant benefit of concomitant radiochemotherapy on overall survival (p = 0.004), with an absolute benefit of 5.7% (from 18.1% to 23.8%) at three years and 4.5% at five years. There was no significant difference regarding acute pulmonary toxicity. Concomitant treatment decreased locoregional progression, but concomitant radiochemotherapy increased acute esophageal toxicity (grade 3–4) from 4% to 18%. This improved OS was accomplished because of an improved locoregional control. There were no significant differences between the regimens: single or double high-dose chemotherapy or daily low-dose cisplatin. No differences in distant metastasis rate were observed between the two approaches.

Within a few months, a meta-analysis was published by O'Rourke et al. reporting a 10% absolute survival benefit at two years [25]. Six trials (1,024 patients) of concurrent vs. sequential chemoradiation were included. A significant benefit of concurrent treatment was shown in overall survival (hazard ratio – HR 0.74, 95% CI 0.62–0.89). More treatment-related deaths (4% vs. 2%) were reported in the concurrent arm without statistical significance (relative risk – RR 2.02, 95%

CI 0.90–4.52). There was increased severe esophagitis with concurrent treatment (RR 4.96, 95% CI 2.17–11.37). The most important acute but manageable side effect was esophagitis grade 3 to 4 in 18% of the patients treated with concurrent radiochemotherapy vs. 4% in patients treated with sequential arm.

The role of timing and sequencing of the treatment may also depend on the tumor type, the degree of oxygenation of tumor cells and other biochemical processes occurring during radiation. In clinical practice, a compromise option is the alternation of radiotherapy and chemotherapy, for example by insertion of radiotherapy after 2–3 cycles of chemotherapy. The clinical efficacy of this strategy has, however, not been verified in prospective clinical studies. Concurrent chemoradiation is at present the treatment of choice for patients with locally advanced NSCLC. However, due to its higher toxicity, this combination is mostly restricted to patients in a good general condition, minimal comorbidity and who are relatively young [26–29]. There is a question what proportion of patients would be suitable for concurrent chemoradiation. We found only one report on a population-based study that prospectively evaluated comorbidities in all patients diagnosed with lung cancer, stage III for NSCLC [30]. In this prospective, population-based study, more than half of the patients with stage III NSCLC were not eligible for concurrent chemoradiation on the basis of criteria of age and important comorbidities that were present at diagnosis. Less toxic alternatives are needed for these patients. So, there are arguments for sequential treatment, such as "safe" delivery of full dose of radiotherapy and chemotherapy, but there are also problems like delayed radiotherapy delivery especially in patients' slow recovery from chemotherapy. El Sharouni [31] shows that in the time interval between the end of induction chemotherapy and the start of radiotherapy rapid tumor progression occurs as a result of accelerated tumor cell proliferation: mean tumor doubling times are much shorter than those in not treated tumors. As a consequence, the gain obtained with induction chemotherapy with regard to volume reduction was lost in the waiting time for radiotherapy (chemo-resistant stem cells that persist and can give rise to tumor regrowth). A correlation was observed between the amount of delay and degree of regrowth for percent volume and percent tumor diameter change. A delay between induction chemotherapy and radiotherapy greater than 21 days produced greater increases in percent volume change and percent diameter than lesser delays [32]. Also, a retrospective analysis of a total of 474 patients demonstrates a correlation between prolonged overall radiotherapy treatment time and survival in patients with locally advanced NSCLC, even when concurrent chemotherapy is used [33]. It is recommended to diminishthe time interval between chemo- and radiotherapy to as short as possible.

Targeted therapies and radiotherapy in locally advanced NSCLC

Targeted therapies represent a new class of drugs, which interfere with specific molecular targets (typically proteins) playing critical roles in tumor growth and progression. The approved targeted therapies in lung cancer include erlotinib, gefitinib (a small-molecule tyrosine kinase inhibitors) and bevacizumab (a monoclonal anti-VEGF antibody). The accepted dogma is that antiangiogenic therapy destroys or blocks the function of tumor-associated vessels to deprive the tumor of oxygen and nutrients, thereby inhibiting tumor growth. Numerous preclinical studies indicated synergistic activity of various antiangiogenic or antivascular therapies with single-dose or fractionated radiotherapy in human and murine tumors [34,35]. However, since multiple variables contribute to the sensitivity of tumors to radiation or antiangiogenic treatment, the most effective way of their combining is virtually unknown [36,37]. Blocking survival signaling in endothelial cells after irradiation seems to increase the radiation response considerably [38]. Moreover, sensitization of endothelial cells just before exposure to radiation may be the most effective way to improve response of tumor cells to radiation [39,40]. On the other hand, induction of hypoxia via blood vessel damage may potentially induce radioprotection of the tumor. A logical and clearly proven premise for optimal multimodality therapy is therefore necessary for efficient translation of promising preclinical strategies into clinical applications. Many new biologicals have entered the therapeutic domain; several were combined with concurrent RCT regimens. Some combinations appear to be too toxic, such as the vascular epithelial growth factor antibody bevacizumab [41]. Also, the use of bevacizumab and erlotinib is not recommended given the lack of an efficacy signal and the substantial risk of esophageal toxicity (Tab. 2) [42].

Erlotinib and gefitinib are small molecule inhibitors that reversibly target tyrosine kinase activity of the epidermal growth factor receptor (EGFR). EGFR is overexpressed and/or mutated in many cancer types, and its activation triggers pathways involved in cell growth and proliferation. Early clinical studies with gefitinib showed promising efficacy and mild toxicity in patients with advanced NSCLC. In clonogenic *in vitro* survival experiments, gefitinib had significant radiosensitizing effects on NSCLC cell lines [43]. Gefitinib enhances radioresponse of NSCLC cells by suppressing cellular DNA repair capacity. But in unselected population, gefitinib did not improve OS [44]. The trial from the National Cancer Institute of Canada Clinical Trials Group showed that erlotinib monotherapy prolonged OS in patients with advanced NSCLC who had progressed after standard chemotherapy [45], and erlotinib is approved in this setting. Interestingly, EGFR expression does not seem to correlate with response to EGFR inhibitors but a recent analysis of data from this trial indicated that EGFR mutations and high copy number are predictive of response to erlotinib [46]. In addition, EGFR fluorescence *in situ* hybridization score was a significant predictive marker of differential survival benefit of erlotinib. Erlotinib-induced apoptosis was augmented by radiation in cells with very high expression of HER1/EGFRonly. In conclusion, high

HER1/EGFR expression may result in a high degree of radiosensitization with erlotinib combined with radiation [47]. A strong rationale may exist for combining erlotinib with radiotherapy. Erlotinib helps disrupt cell growth pathways and enhances the sensitivity of cells to the effects of radiotherapy [48–50]. It is also possible that radiotherapy enhances the effectiveness of erlotinib by cytoreducing the tumor and creating a hypoxic environment [51]. Several studies in NSCLC were conducted to evaluate erlotinib in combination with radiotherapy. A prospective phase II study found that radiotherapy and concurrent erlotinib used in the treatment of patients with unresectable NSCLC shows promis-

Tab. 2. Targeted therapies and radiotherapy in locally advanced NSCLC.

Reference (therapy)	Study type	Patients	Radiotherapy schedule	Systemic therapy	Results
Spigel et al. [33] bevacizumab	phase II n = 29 (small cel) n = 5 non-small cell	NSCLC trial included patients with unresectable stage III non-squamous without pleural or pericardial effusions; ECOG 0–1	radiotherapy began with cycle 3, at a dose of 1.8 Gy/day to a total of 61.2 Gy	induction treatment included: carboplatin AUC = 5, pemetrexed 500 mg/m^2, and bevacizumab 15 mg/kg; consolidative therapy with carboplatin AUC = 6, pemetrexed 500 mg/m^2, and bevacizumab 15 mg/kg; patients received maintenance bevacizumab 15 mg/kg every 3 weeks for 9 cycles with restaging every 3 months	the trial's primary PFS end point could not be assessed due to early trial closure becouse of toxicity; the objective response rate was 88%; 2 patients developed tracheoesophageal fistulae, prompting early study closure; both patients developed esophageal toxicity during chemoradiotherapy and bevacizumab treatment
Socinski et al. [34] bevacizumab	phase I/II n = 45	medically inoperable or unresectable, WHO 0–1; stage IIIA or IIIB	conformal radiation therapy to 74 Gy	induction chemotherapy (carboplatin AUC 6, paclitaxel 225 mg/m^2, and bevacizumab 15 mg/kg followed by concurrent chemotherapy (carboplatin AUC 2 and paclitaxel 45 mg/m^2 weekly with bevacizumab 10 mg/kg in the phase I portion, cohort 1 received no erlotinib, whereas cohorts 2 and 3 received erlotinib at 100 and 150 mg, resp.; consolidation therapy with erlotinib (150 mg daily) and bevacizumab (15 mg/kg every 3 weeks) 3 to 6 weeks later for 6 cycles	the objective response rates to induction and overall treatment were 39% and 60%; median PFS 10.2 months; median OS 18.4 months
Kelly et al. [36] gefitinib	phase III n = 243	inoperable stage IIIA or IIIB without pleural or pericardial effusions; ECOG 0–1	initial field received 1.8 Gy/day for 5 weeks for a dose of 45 Gy; an additional radiation boost to gross disease with 2 Gy/day to 16 Gy was delivered without a break; the total radiation dose received was 61 Gy	concurrent cisplatin and etoposide with thoracic radiation; cisplatin 50 mg/m^2 with etoposide 50 mg/m^2; 4 to 8 weeks after completion of radiation, patients without progressive disease received 3 cycles of docetaxel 75 mg/m^2; 3 to 6 weeks after docetaxel, patients received gefitinib 500 mg or placebo orally, once a day for 5 years or until disease progression or intolerable toxicity; later gefitinib was amended to the 250 mg/day	median OS time was 23 months for gefitinib (n = 118) and 35 months for placebo; the toxic death rate was 2% with gefitinib compared with 0% for placebo

Tab. 2 – continuation. Targeted therapies and radiotherapy in locally advanced NSCLC.

Reference (therapy)	Study type	Patients	Radiotherapy schedule	Systemic therapy	Results
Martinez et al. [44] erlotinib	phase II n = 23	unresectable stage I–IIIA, not suitable to receive chemotherapy, ECOG 0–2	66 Gy in 33 fractions during 6 weeks	radiotherapy and placebo (arm A) or concomitant erlotinib 150 mg/day po maintained for 6 months (arm B)	esophagitis 40% in arm A and 23% in arm B, (no grade 3–4); radiodermitis 50% in arm A (no grade 3–4 observed) and 8% in arm B, being grade 3; pneumonitis 20% in arm A (10% grade 3) and 8% in arm B (no grade 3–4 observed); main toxicities related to erlotinib were skin rash (61.5%) and diarrhea (23%); response rate in arm A was 55.5% and 83.3% in arm B; disease progression is documented in 22.2% in arm A and 16.7% in arm B
Jensen et al. [49] cetuximab	phase II n = 30	not candidates for concomitant chemoradiation (or refused), KPS at least 70, 1 of 2 trials with mandatory PET; stage IIIA or IIIB, no malignant pleural effusion	IMRT trial, 66 Gy in 33 daily fractions of 2 Gy, ENI to 50 Gy (or 40 depending on lung dose)	cetuximab followed by 13 weekly consolidation cycles	median OS 19.6 months, median PFS 8.5 months, 63% PR, no CR
Jatoi et al. [48] cetuximab	phase II n = 58	not candidates for concomitant chemoradiation, either age ≥ 65 years with ECOG 0–2 or younger but ECOG 2; stage IIIA or IIIB, no pleural effusion	RT 60 Gy in 30 daily fractions of 2 Gy, ENI to ipsilateral hilar and mediastinal nodes (44 Gy)	cetuximab 400 mg/m$^{(2)}$ i.v. on day 1 followed by weekly cetuximab 250 mg/m$^{(2)}$ i.v. with concomitant radiation	median OS 15.1 months, median PFS 7.2 months, 26% PR, no CR
Hallqvist et al. [50] cetuximab	phase II n = 71	medically inoperable or unresectable, WHO 0–1; stage IIIA or IIIB, no pleural effusion with positive cytology	radiotherapy 68 Gy in 34 daily fractions of 2 Gy, no ENI	2 cycles of induction cisplatin/docetaxel, cetuximab starting 1 week before radiotherapy	median OS 17 months, PFS NR, 16% PR and 7% CR at 12 months (NR at earlier time points), patterns of failure: 31% distant only, 23% local only, 7% regional only, 11% combinations of these
Hughes et al. [51] cetuximab	phase II n = 12	inoperable, WHO 0–1; stage IIIA or B, no pleural effusion	radiotherapy 64 Gy in 32 fractions of 2 Gy, in 4 cases ENI to ipsilateral hilar and mediastinal nodes (50 Gy)	up to 4 cycles (median 3) of platinum-based induction chemotherapy, cetuximab starting 1 week before radiotherapy	median OS NR, PFS NR, 58% PR, no CR

Tab. 2 – continuation. Targeted therapies and radiotherapy in locally advanced NSCLC.

Reference (therapy)	Study type	Patients	Radiotherapy schedule	Systemic therapy	Results
Blumenschein et al. [52] cetuximab	phase II n = 87	inoperable, Zubrod 0–1; stage IIIA or B, weigh loss < 5%, FEV1 ≥ 1.2 l	radiotherapy 63 Gy in 35 fractions of 1.8 Gy, ENI to ipsilateral hilar and mediastinal nodes (45 Gy)	cetuximab week 1–17, weekly carboplatin/paclitaxel during radiotherapy followed by 2 cycles consolidation carboplatin/paclitaxel	median OS 22.7 months, median TTP around 14–15 months, 29% CR, 33% PR
Govindan et al. [53] cetuximab	phase II n = 101	inoperable, ECOG 0–1, 1 of 2 trials with mandatory PET; stage IIIA or B, no pleural effusion, weight loss ≤ 10%	70 Gy in 35 fractions of 2 Gy, no ENI	cetuximab (7 weeks) plus 4 cycles carboplatin/pemetrexed vs. chemotherapy without cetuximab (n = 48), afterwards 4 cycles of pemetrexed	median OS 25.2 months, median failure-free survival 12.3 months, 4% CR, 68% PR

IMRT – intensity-modulated radiotherapy, KPS – Karnofsky performance status, ECOG – Eastern Cooperative Oncology Group performance status, WHO – World Health Organization performance status, ENI – elective nodal irradiation, OS – overall survival, PFS – progression-free survival, PR – partial remission, CR – complete remission, TTP – time to progresion, NR – not reported

ing results without an increase in toxicity [52]. Adverse events related to radiotherapy included esophagitis, radiation dermatitis, and pneumonitis. The addition of erlotinib to radiotherapy did not appear to increase radiotherapy associated toxicities. Erlotinib-related adverse events included mild to moderate skin rash (61.5%) and diarrhea (23%). The RR was 55.5% in the radiotherapy-alone arm compared with 83.3% in the erlotinib arm. The Cancer and Leukemia Group B is conducting a phase II trial, CALGB 30605, of paclitaxel followed by radiotherapy and erlotinib in patients with unresectable stage III NSCLC. The study is evaluating induction chemotherapy consisting of paclitaxel and carboplatin. Patients with no disease progression outside the planned radiation field will continue to receive concurrent erlotinib and radiotherapy. Results from current studies are eagerly awaited.

Several drugs interfering with the EGFR signaling pathway have been developed e. g. cetuximab (a human-murine chimeric IgG1 monoclonal antibody that binds to the extracellular region of the EGFR). Under experimental laboratory conditions in animal models, cetuximab increases tumor radiocurability (fractionated and single dose irradiation) [53,54]. The feasibility of adding the epidermal growth factor receptor inhibitor cetuximab has been recently reported for NSCLC patients [55]. We found a few phase II clinical trials of cetuximab combined with radiotherapy for NSCLC. Two of them have combined radiotherapy and cetuximab without any chemotherapy in patients who are not candidates for chemoradiation [56,57]. Combined radioimmunotherapy with cetuximab was safe and feasible, especially in elderly patients with multiple comorbidities. Another study included patients with inoperable stage III disease and good performance status after induction chemotherapy [58,59]. Induction chemotherapy followed by concurrent cetuximab and radiotherapy to 68 Gy was clearly feasible with promising OS. Toxicity, like pneumonitis and esophagitis was low compared to most schedules with concurrent chemotherapy. The last study published by Radiation Therapy Oncology Group (RTOG) was a phase II study of chemoradiotherapy with carboplatin and paclitaxel plus cetuximab in patients with stage III NSCLC [60]. The combination of cetuximab with CRT is feasible and shows promising activity. The overall survival achieved with this regimen was longer than any previously reported by the Radiation Therapy Oncology Group with median survival 22.7 months, and 24-month overall survival – 49.3%. The second trial in this category with several important differences (mandatory PET, higher radiation dose of 70 Gy, only seven weeks of cetuximab concomitant to radiotherapy, chemotherapy with carboplatin and pemetrexed) was done [61]. Median OS was 25.2 months and failure-free survival 12.3 months.

Until now, no definite data can be reported. Further basic research and appropriately designed clinical studies are clearly needed to optimize scheduling of combined radiation and molecular targeted therapies. The results of the published clinical trials (one of them was a phase III study) suggest that larger randomized trials are warranted. It is very important to include the right patient population, especially patients with the right genetics/mutations for these clinical trials.

Conclusions

Patients with stage III disease differ with regard to primary tumor volume and

proximity/infiltration of surrounding structures, extent of lymphatic spread, cancer biology, and host factors such as age, cardiopulmonary function and other comorbidity. Treatment recommendations have to take into account these differences and stratify patients according to technical resectability, ability to tolerate high-dose radiotherapy and chemotherapy, and many more. Many patients with inoperable stage III disease are candidates for combined modality chemo- and radiotherapy. In conclusion, after two decades of mainly sequentially combined treatment, concurrent radiochemotherapy is nowadays the standard treatment of locally advanced NSCLC. However, there are some doubts.

Firstly, it should be realized that the trial data were collected in a period before routine staging with FDG-PET and MRI of the brain. The routine use of these tests definitely changed the population of patients enrolled in radiochemotherapy.

Secondly, the other topics for future research are RCT with more sophisticated radiotherapy techniques allowing possibly higher tumor doses and/or lower toxicities in surrounding healthy tissues. For patients with larger tumor volumes, possibilities to increase the radiation dose were limited by normal tissue constraints (esophagus and spinal cord). Conventionally fractionated radiotherapy for stage I NSCLC has shown inferior outcomes than surgery, and these results are linked to insufficient radiation doses. After the impact of radiotherapy dose for lung cancer was established, a number of trials were structured in the quest for better local control and overall survival by either dose escalation or shortening the total treatment time through conventional/altered fractionation, even in combination with chemotherapy. The delivery of 60 Gy resulted in a 5-year survival rate of 38% for patients with primary tumors less than 2 cm in size, 22% for tumors 2–3 cm in size, 5% for tumors 3–4 cm in size, and 0% for larger tumors [62]. Based on biological and statistical modelling of tumor responses to various radiation dose levels, it has been shown that doses as high as 80 to 90 Gy ensure a progression-free survival rate of 50% [63]. The majority of studies concluded that patients receiving higher radiation doses have better treatment outcomes [64,65].

New technical advances in the application of radiotherapy enhanced the ability of targeted treatment and sparing of normal tissues, making high BED studies possible. Intensity-modulated radiotherapy (IMRT) has the potential benefit to further increase the dose that can be safely prescribed in lung cancer patients due to a better conformity index [66–68]. In Stereotactic Radiation Therapy (SABR), high doses per limited number of fractions are used, although the actual biologically equivalent dose (BED) for the eradication is not yet completely understood [69]. When a sufficient dose (BED ≥ 100 Gy) is used, it has been noted in most clinical studies that the success rate of local control is over 90%. In particular, the surprising results of the RTOG 0617 trial [70] drove attention to the importance of adverse effects, once again emphasizing that future research should focus on quality of life.

Thirdly, in most of these studies, authors did not include factors such as histological type, age, comorbid conditions into their analyses. Since the incidence of NSCLC is high among elderly patients and many of them have history of smoking, the majority of these patients have severe comorbidities. Therefore, aggressive combined modality treatment might be contraindicated or poorly tolerated. However, age is not an independent prognostic factor in stage III and IV NSCLC, and epidemiological studies show that, with increasing age, the percentage of people treated with chemotherapy decreases [71–73]. Elderly patients with marginal renal function (creatinine clearance < 70 mL/min) or marginal cardiac function are eligible for administration of daily low-dose cisplatin, while administration of full-dose chemotherapy is often contraindicated. Combination of concurrent daily cisplatin with radiation appears to be a good alternative, especially in these elderly, frail patients [74,75]. Also, preclinical studies on RCT support the use of daily administration for optimal radiosensitizing effects [76]. This approach, delivered in a short overall treatment time, is suitable for both the elderly and for patients with comorbidities. It also offers the opportunity to combine concomitant radiochemotherapy with new agents. Existing data concerning targeted therapies in conjunction with radiotherapy are inconsistent and do not allow for firm conclusions. The optimal timing of the administration of radiotherapy and EGFR kinase inhibitors has yet to be determined. Strategies to safely incorporate novel antiangiogenic agents into combined-modality therapy in lung cancer are needed. Studies using targeted therapies, in particular addressing their optimal integration with radiotherapy, are still in their infancy. Rapid development of molecular oncology will hopefully contribute to better patient selection to particular strategies and to treatment optimization.

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