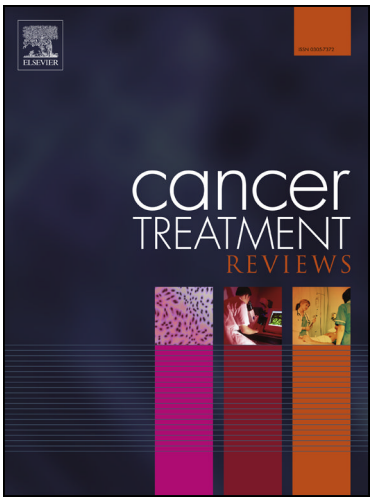

Anti-Tumour Treatment

Consolidation systemic treatment after radiochemotherapy for unresectable stage III non-small cell lung cancer

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Consolidation systemic treatment after radiochemotherapy for unresectable stage III non-small cell lung cancer

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Consolidation systemic treatment after radiochemotherapy for unresectable stage III non-small cell lung cancer

Abstract

The majority of stage III NSCLC patients managed with a combination of radiotherapy and chemotherapy will develop a locoregional or distant relapse. Concomitant radiochemotherapy allows for improved local control but has no impact on extrathoracic recurrences. To ameliorate this inefficiency the concept of consolidation treatment has been put forward, whereby systemically active doses of chemotherapy, targeted therapy or immune therapy are administered after completion of radiochemotherapy. Randomized trials failed to provide support for consolidation treatment using chemotherapy and anti-EGFR therapies. Recently durvalumab, an anti-PD-L1 checkpoint inhibitor, administered as consolidation treatment, was shown to substantially improve progression-free survival. This article critically reviews major studies addressing the role of consolidation systemic therapies following definitive concurrent radiochemotherapy, and discusses prospects for future research.

Highlights

- Concomitant radiochemotherapy is the current standard of care in stage III NSCLC
- Despite therapy, the majority of patients with unresectable stage III NSCLC will relapse
- Consolidation systemic therapies are hoped to improve outcomes
- Consolidation using chemotherapy or EGFR inhibition has been proved ineffective
- Consolidation with PD-1 axis immunotherapy shows impressive activity

Keywords

Locally advanced NSCLC, radiochemotherapy, consolidation therapy, chemotherapy, targeted therapy, immune therapy

Introduction

Maintenance therapy in advanced non-small cell lung cancer (NSCLC) refers to administration of palliative chemotherapy (usually single-agent) beyond 4-6 cycles of platinum doublets. Such therapy is provided with the goal of deferring disease progression, and thereby prolonging symptoms-free and overall survival (OS) [1]. On the other hand, in unresectable stage III NSCLC (regionally advanced disease with a high risk of accompanying occult micrometastases), therapies following concurrent radiochemotherapy are intended to increase systemic control and improve cure, and thus are referred to as *consolidation* treatment. Consolidation chemotherapy (CCT) is typically administered in 2 to 4 cycles [2, 3], whereas consolidation targeted therapy or immunotherapy is continued over longer time [4, 5].

This article critically reviews major studies addressing the role of CCT, targeted therapy and immunotherapy following radical concurrent radiochemotherapy (conRCT), the current standard of care in stage III NSCLC patients. Prospects of consolidation therapy and potential design of future trials investigating current and novel agents will be discussed.

Current standards in stage III unresectable NSCLC

Historically, radiotherapy as a sole therapeutic modality resulted in gloomy survival outcomes in stage III NSCLC patients, with the median OS not exceeding 9–11 months [6, 7]. The addition of induction chemotherapy improved the median OS to 12–14 months [6, 8, 9], and the introduction of conRCT - to approximately 17 months [10]. Nonetheless, five-year survival rates with conRCT remained at the level of merely 10-15% [10].

The current standard of care in unresectable stage III NSCLC patients who are fit includes platinum-based chemotherapy concurrently with curative-dose radiotherapy. This strategy is based on a series of phase III trials that compared conRCT with sequential approach comprising induction chemotherapy followed by radiotherapy [11, 12]. In the pivotal RTOG 9410 study, 610 patients were randomly assigned to radiotherapy (63 Gy in once-daily fractions) delivered concurrently with chemotherapy (cisplatin at 100 mg/m^2 on days 1 and 29 and vinblastine at 5 mg/m^2 weekly for 5 weeks), the same chemotherapy followed by conventionally fractionated radiotherapy (63 Gy in once-daily fractions), or hyperfractionated radiotherapy (69.6 Gy in twice-daily fractions) combined with concomitant chemotherapy [11]. Median OS times in these three groups were 14.6, 17.0, and 15.6 months, respectively. Five-year OS was significantly higher for patients treated with conventionally fractionated conRCT compared with the sequential treatment (16% vs. 10%, respectively; $P = 0.046$), and the five-year OS in the hyperfractionation conCRT arm was of intermediate 13%. Similarly, in the Japanese trial split course radiotherapy of 56 Gy concurrent with two cycles of cisplatin, vindesine and mitomycin resulted in improved OS compared to the same chemotherapy followed by a continuous course of 56 Gy radiotherapy [12]. The metaanalysis of six trials (1205 patients) that compared sequential vs. conRCT showed a significant OS superiority of the latter (HR = 0.84; $P = 0.004$), with an absolute benefit of 5.7% at 3 years and 4.5% at 5 years. Of note, increased OS with conRCT was related to

better locoregional control (HR, 0.77; *P* = 0.01); but not to decreased distant progression (HR = 1.04; *P* = 0.69) (10).

Accelerated radiotherapy, i.e. radiotherapy delivered in a shorter overall treatment time by increasing daily dose to 2.6–3 Gy, led to an absolute benefit of 2.5% in 5-year OS and is increasingly used [13]. In turn escalating the radiotherapy dose up to 74 Gy within conRCT did not improve survival of stage III NSCLC patients**,** and the dose of 60-66 Gy in 2 Gy fractions remains the standard management within conRCT [14].

Two most commonly used chemotherapy combinations within conRCT include cisplatin (50 mg/m^2 on days 1, 8, 29 and 36) plus etoposide (50 mg/m^2 on days 1–5, 29–33), or weekly carboplatin (AUC 2) and paclitaxel (45–50 mg/m^2 weekly), or alternatively - combinations of cisplatin or carboplatin with vinorelbine or pemetrexed [3, 14-16]. The cumulative dose of cisplatin administered within conRCT regimens usually does not exceed 200 mg/m^2, and is expected to exert radiosensitizing rather than systemically relevant cytotoxic effect. Indeed, in the preoperative and postoperative settings in early NSCLC, the dose of cisplatin that has been proven effective in reducing metastatic spread and increasing OS was usually above 300 mg/m^2 (3-4 cycles) [17-20]. The relatively low cumulative doses of cytotoxic agents used in conRCT trials, in the context of likely higher micrometastatic burden in stage III disease, may have been among the reasons why this treatment did not improve the control of extrathoracic disease [10]. In fact, the vast majority of recurrences following conRCT occur at distant sites, presumably owing to the common presence of micrometastatic disease at presentation [11, 12, 21].

Consequently, attempts at increasing the doses of chemotherapy in combination with radiation have been made. For example, in the phase III French NPC 95-01 trial, induction chemotherapy (three cycles of cisplatin and vinorelbine) followed by radiotherapy (66 Gy in 33 fractions) was compared with the same dose radiotherapy administered concurrently with two cycles of cisplatin plus etoposide [16]. In order to balance the dose of cisplatin between the arms, the conCRT was followed by two additional cycles of chemotherapy [16]. Although not statistically significant, this trial favored conRCT approach also at the background of more intensive chemotherapy exposure. Of note, 16 toxic deaths were reported in this study, including six (5.6%) in the sequential arm and 10 (9.5%) in the concurrent arm. Six of the fatal cases were due to febrile aplasia, possibly suggesting excessive doses of cytotoxic agents used in this trial.

Several trials assessed the role of induction chemotherapy preceding conRCT, but none showed superiority of this approach over conRCT alone [21-23]. As a result this strategy has not been further developed.

Consolidation chemotherapy (CCT)

A high frequency of sub-clinical micrometastases in stage III NSCLC, which are poorly controlled with conRCT, led to the development of consolidation chemotherapy (CCT) concept, i.e. continuation of chemotherapy after completion of conRCT.

In 2001 the Southwest Oncology Group (SWOG) reported the results of a single-arm, phase II SWOG 9504 study that investigated CCT comprising 3 cycles of docetaxel after conRCT [24]. This strategy was intended to both, increase exposure to systemically active doses of chemotherapy, and counteract potential intrinsic resistance to cisplatin or etoposide by adding a drug with a different mechanism of action. The impressive median progression-free survival (PFS) of 16 months and OS of 26 months suggested a benefit from this approach and resulted in its wide implementation in clinical practice.

Disappointingly, the subsequent Hosier Oncology Group (HOG) LUN 01-24 phase III trial, that used the same concurrent and consolidation regimens, did not confirm superiority of this strategy over standard management [2]. In this study, patients were randomized to 3 cycles of docetaxel (75 mg/m^2 every 3 weeks) or observation after radiotherapy (59.4 Gy in 33 fractions) combined with cisplatin (50 mg/m^2 on days 1, 8, 29 and 36) and etoposide (50 mg/m^2 on days 1–5, 29–33). Initially, 230 patients were to be registered and 210 randomly assigned. The study was prematurely terminated as a result of futility analysis after the initial 203 patients were entered and 147 randomized. At the final analysis the median OS in the consolidation and observation arms was 24.2 and 26.1 months, respectively (P = 0.75) [2]. Consolidation induced considerable toxicity including grade 3 to 5 febrile neutropenia in 11% of patients and pneumonitis in 9.6%; 29% of patients were hospitalized during docetaxel (vs. 8.1% in the observation arm), and 5.5% died due to toxicity in the docetaxel arm vs. 0% in the control arm.

There are a number of factors that may have contributed to the negative outcomes of this study. Due to slower accrual and a dropout rate of 27% vs. the projected 10% after conRCT phase, the statistical power of the study decreased to 80%. Moreover, there was an imbalance between the study arms with almost 20% more patients having poor pulmonary reserve in the docetaxel arm. Although borderline significant (p=0.066) this difference revealed that the patients administered docetaxel may have had larger disease volume or more advanced chronic obstructive pulmonary disease, both of which are known to negatively impact survival [25]. It is therefore not clear whether a 5.5% treatment-related death rate in the CCT arm was due to docetaxel toxicity or due to pulmonary complications of conRCT. Furthermore, PET/CT staging was used in 71% of patients in the control arm vs. 59% in the CCT arm. This imbalance may have led to inclusion of more asymptomatic stage IV patients into the docetaxel arm. With only 30 events in this group, such imbalances may have increased the likelihood of the false negative study outcome. Hence, the results of this study can be viewed as inconclusive rather than definitive.

In the Korean KCSG-LU05-04 phase III trial, 437 patients were administered low-dose cisplatin (20 mg/m^2) and docetaxel (20 mg/m^2) weekly for 6 weeks, concurrently with radiation (66 Gy in 33 fractions) [26]. The study treatment assignments included three cycles of consolidation cisplatin and docetaxel (35 mg/m^2 each, every 3 weeks) or observation. Of the 209 patients assigned to consolidation therapy, only 143 (68%) actually received this treatment, with 88 patients (42%) completing three planned cycles. The median OS in the intent-to-treat analysis was 20.6 and 21.8 months in the observation and consolidation arms, respectively (HR, 0.91; P = 0.44). CCT was associated with higher rate of grade 3 and 4 neutropenia (6.9% vs. 2.6% in control arm), and slightly increased non-hematologic toxicity. The main shortcoming of this trial concerned its design, whereby the patients were assigned to CCT or placebo before the

initiation of conRCT. As a result, approximately a third of patients assigned to CCT did not even start the treatment due to progression, death or incomplete recovery from the adverse effects of conRCT. In this study, the same drug combination was used during conRCT and consolidation phases. It is not known whether the low dose chemotherapy during conRCT does not induce chemoresistance that might offset the effect of subsequently administered systemic doses of the same drug. PET/CT was mandated for staging in all cases except for in T4 disease, and was performed in 92% of the patients.

The most recent phase III randomized GILT trial did not provide a clear evidence for the clinical benefit of CCT either [27]. In this study, conRCT included radiotherapy (66 Gy in 33 fractions) combined with cisplatin (20 mg/m^2 on days 1–4 and 29–32) and oral vinorelbine (50 mg/m^2 on days 1, 8 and 15, and 29, 36 and 43). A total of 279 patients were enrolled, 201 of whom (72%) were randomized to either CCT (two cycles of cisplatin 80 mg/m^2 and oral vinorelbine on days 1 and 8; cycle 1: 60 mg/m^2, cycle 2: 80 mg/m^2, 3 weeks apart) or observation. During CCT, 19% of patients with stable disease converted to partial response, vs. 3.7% in the observation arm (P = 0.12). The median OS from randomization after conRCT was 20.8 months in the consolidation arm and 18.5 months in the control arm, and the four-year survival rates in the CCT and control arms were 25% and 21%, respectively (P = 0.51). Grade 3 leukopenia occurred in 26% of patients in the CCT arm vs. 0% in the control arm. The GILT trial protocol did not mandate PET/CT for staging, and again a considerable proportion of asymptomatic stage IV patients may have been enrolled in this study. Also in this study the same cytotoxic agents were used during conRCT and consolidation phases, which might raise concerns about potential induction of chemoresistance.

A pooled analysis of data from randomized clinical trials investigating the role of CCT (a total of 1707 and 1772 patients who did and did not receive CCT following conRCT, respectively) failed to demonstrate survival benefit related to the addition of CCT (median OS of 19.0 and 17.9 months, respectively; HR = 0.98; 95% CI 0.8–1.13; P = 0.76) [28]. However, this analysis included conRCT trials utilizing variable intensities of chemotherapy, which has been indicated as a potentially confounding factor [29]. Interestingly, the pooled analysis detected incremental improvement of survival according to periods in which trials were performed, likely reflecting increasingly meticulous initial staging. Several smaller phase I and II studies investigating the role of consolidation therapies after conRCT were summarized in detail elsewhere [30].

Despite the lack of level I evidence, CCT has been consistently included in the design of trials for unresectable locally advanced disease. For example, recently published PROCLAIM study that investigated the efficacy of combining pemetrexed with radiation [3] and RTOG 0617 trial, evaluating a higher dose of radiation and/or addition of cetuximab to standard treatment [14], mandated at least two cycles of CCT. The use of four cycles of CCT is an extrapolation of beneficial effect of the same number of chemotherapy cycles in the postoperative setting. Since the elective nodal irradiation is not routinely used in modern definitive radiotherapy protocols, the provision of four rather than two cycles of CCT seems prudent, considering the regional control.

Although conRCT was associated with considerable toxicity, the large majority of patients in CCT trials were able to continue chemotherapy beyond that already received [2, 4, 31]. However, CCT after modern conRCT does not seem to incur unmanageable

toxicity, as evidenced by RTOG 0617 or PROCLAIM studies [3, 14]. The gruesome 5.5% of treatment related death rate in the LUN 01-24 trial might be partially accounted for by the use of elective mediastinal irradiation. Likewise, in the KCSG-LU05-04 study, the use of elective mediastinal fields may have added to the relatively high mortality rate of 10% in the CCT arm during conRCT phase [26]. This particular finding may have also been associated with the use of cisplatin and docetaxel, a doublet possibly excessively toxic if used concurrently with radiation. In the GILT trial [27], where only tumor-involved areas were irradiated, the toxic death rate was only 1.1%, and grade 3-4 pneumonitis occurred in 2% of patients, as compared to 9.6% and 7% in the LUN-1 trial [2] and SWOG S0023 trial [4], respectively. Finally, the addition of two chemotherapy cycles appears to increase primarily hematological toxicity. For example, in the GILT trial, CCT with cisplatin and vinorelbine doubled the rates of grade 3 and 4 leukopenia and neutropenia noted during conRCT phase.

Consolidation targeted therapy

The introduction of anti-EGFR drugs into palliative treatment of NSCLC spurred an interest in this class of agents as consolidation after conRCT in unresectable stage III patients [32, 33] The SWOG 0023 trial investigated the role of an EGFR tyrosine kinase inhibitor, gefitinib, in addition to conRCT and consolidation docetaxel [4]. Patients whose disease did not progress were randomly assigned to gefitinib 250 mg daily or placebo until disease progression, intolerable toxicity or the end of 5 years. Unexpectedly, the addition of gefitinib resulted in inferior results compared to placebo (median OS of 23 and 35 months, respectively; P = 0.013). The reasons for the apparently worse outcome in the gefinitib arm remain unclear. The baseline patient characteristics were well balanced between the study arms and there were no significant treatment interactions. Decreased survival in the gefitinib arm did not seem to be a result of toxicity, as there was only a 2% toxic death rate. It has been hypothesized that radiation therapy might have altered EGFR signaling and conferred gefitinib resistance. Of note, this study did not incorporate testing for activating *EGFR* mutations, now routinely applied to select patients to EGFR tyrosine kinase inhibitors, and poststudy treatments were not captured. Discouraging results of this study slowed down further development of EGFR inhibition in the consolidation setting.

Cetuximab, an anti-EGFR antibody, administered during conRCT and subsequently combined with docetaxel as consolidation, was investigated in the phase III RTOG 0617 study [14]. This trial, with 2x2 factorial design, randomized patients to radiotherapy at a dose of 60 Gy or 74 Gy concurrently with carboplatin and paclitaxel in weekly radiosensitizing doses, followed by consolidation with two cycles of the same cytotoxic drugs in full systemic doses. Second randomization assigned patients to cetuximab or placebo concurrently with conRCT and CCT. After the median follow-up of 22.9 months, there was no benefit of EGFR blockade (median OS 25 months and 24 months in experimental and control arms, respectively; P = 0.58).

Attempts to incorporate anti-angiogenic agents to CCT in stage III NSCLC were also unsuccessful. A phase I trial evaluated the safety of three cycles of consolidation with docetaxel (75 mg/m^2) and bevacizumab (15 mg/kg) after conRCT including cisplatin 50 mg/m^2 on days 1, 8, 29 and 36, etoposide 50 mg/m^2 on days 1 to 5 and 29 to 33 and radiotherapy (65 Gy in 36 fractions) [34]. After 2 cycles of consolidation, two episodes of

fatal hemoptysis occurred among 21 patients that were assessable for toxicity. The use of bevacizumab in combination with conRCT treatments was earlier demonstrated to trigger tracheo-eosophageal fistulae formation [35]. In consequence, anti-angiogenic agents are currently not recommended as an addition to CCT regimens.

Consolidation immunotherapy

Another concept to improve generally poor outcomes in unresectable stage III NSCLC patients is consolidation immunotherapy. One of the largest clinical trials, START, assessed the efficacy of tecemotide (Stimuvax, L-BLP25) [36]. This liposomal vaccine is capable of inducing a T-cell response to MUC1, a glycoprotein antigen over-expressed by lung cancer cells. The study randomly assigned 1513 patients to either tecemotide or placebo. Injections were given every week for 8 weeks, and then every 6 weeks until disease progression or withdrawal. Cyclophosphamide or saline was given once before the first administration of tecemotide and placebo, respectively. The vaccination did not improve outcome in comparison to placebo, with median OS times of 25.8 vs. 22.4 months, respectively (P = 0.11). Exploratory analyses indicated that this type of immunotherapy might be more active in patients after concurrent rather than sequential chemoradiation, and in patients with higher plasma levels of soluble MUC1 and antinuclear antibodies [37].

The unprecedented activity of checkpoint inhibitors (CPIs) in advanced NSCLC [38-42] prompted their assessment in the combined treatment of unresectable stage III patients. The rationale for combining CPIs with radiotherapy is supported by an observation that ionizing radiation upregulates the programmed death 1 (PD-1) pathway [43], resulting in T-cell exhaustion [44]. Although upregulation of PD-1 ligand (PD-L1) may ameliorate some of the radiation-induced toxicities, it has also the potential to weaken radiation-induced antitumor immunity [45]. Combination of PD-1 pathway inhibition with radiotherapy might therefore enhance antitumor immune response [46]. Radiation delivered to the primary tumor is also thought to trigger the abscopal effect, i.e. mounting the systemic anti-tumor immune response through release of tumor antigens from radiation induced cellular damage [47, 48]. Preclinical studies showed that this effect may be potentiated by PD-1 blockade [49].

The recent phase III PACIFIC trial assessed consolidation immunotherapy using durvalumab, an anti-PD-L1 antibody [5]. In this study, 709 stage III patients with disease controlled after radiotherapy (60-66 Gy in 30-33 fractions) and at least 2 cycles of concomitant platinum-based chemotherapy were randomized to either 12 months of placebo or durvalumab. The median PFS from randomization was 16.8 months with durvalumab vs. 5.6 months with placebo (stratified HR for disease progression or death, 0.52; $P < 0.001$). The PFS of 5.6 months in the placebo arm of this study may be viewed as relatively short. For example, in a comparable patient cohort in the RTOG 0617 trial, PFS in the control conRCT arm was 11.8 months. However, PFS in this trial was calculated from the initiation of conRCT. The 12-month PFS rate with durvalumab was 56% vs. 35% with placebo, and the 18-month PFS rates were 44% and 27%, respectively. Grade 3-4 toxicities occurred in 30% and 26% of patients in the durvalumab and placebo arms, respectively. Immune-mediated adverse events of any grade, regardless of cause, were reported in both groups in 24% and 8.1% of patients, respectively, but there were relatively few severe immune-related adverse effects. A

total of 15.4% and 9.8% of patients in both groups, respectively, discontinued study treatment because of adverse events [5]. Based on these results, durvalumab is now recommended by NCCN as a consolidation strategy in locally advanced NSCLC.

The success of consolidation immunotherapy in the PACIFIC study fostered interest in combining CPIs concurrently with standard treatments for stage III NSCLC patients. Multiple ongoing concurrent radioimunotherapy and radiochemoimmunotherapy trials are anticipated to determine the optimal sequencing of immunotherapy in treatment combinations with curative intent. It is likely that other PD-1 axis inhibitors will result in a similar magnitude of benefit as durvalumab, i.e. about 15-20% increase in PFS rates. Nevertheless, despite this progress, the majority of stage III NSCLC patients will still require more effective treatments. For example, in the durvalumab arm of the PACIFIC study, within a year almost a half of the patients succumbed to progression within radiation fields or at distant sites [5].

Future prospects

With the new consolidation treatment options in sight, there is still a need for refining the indications for consolidation therapies in stage III NSCLC. On the one hand, reliable prognostic biomarkers might select patients with high risk of occult disease persistent after conRCT, who are most likely to benefit from consolidation approaches. Owing to scarcity of tissue specimens from diagnostic biopsies, liquid biopsy may be particularly appropriate in this clinical context. A recent report showed the possibility of tracking lung cancer temporal evolution with the use of bespoke assays interrogating the blood plasma for the presence of tumor specific mutations, which correlated with the existence of active disease [50]. These markers, however, require the knowledge of the mutational composition of the primary tumor and therefore may not always be applicable to stage III patients. The most recent development is a cancer personalized profiling (CAPP-seq) technique that allows for plasma analysis of a panel of mutations, with both driving and unknown functional impact [51]. This method was shown to detect molecular residual disease in 53% (17/32) of NSCLC patients who had undergone radical treatment [51]. With a caveat of a small series of patients, this approach demonstrated an impressive 100% specificity in reference to healthy controls, and 96% specificity in regard to patients who did not develop recurrence. These results, however, pertain to the blood samples obtained within 4 months after completion of conRCT. The sensitivity and specificity of this assay will need to be confirmed at earlier time points, e.g. 4-6 weeks after completions of local treatment, when decision on a possible use of consolidation therapy is taken.

Higher efficacy of consolidation treatment may also be achieved by virtue of validated predictive biomarkers that could indicate the sensitivity to specific systemic therapies. Tissue PD-L1 expression analyzed by immunohistochemistry is a predictor of pembrolizumab efficacy in advanced setting [41], although it is less predictive for nivolumab and atezolizumab [39, 42]. In the PACIFIC trial, the PD-L1 expression was not clearly associated with the efficacy of durvalumab, albeit the group with expression over 25% had the highest benefit [5]. Additionally, there are controversies around the definition of the test positivity thresholds, and the type of antibodies used for immunohistochemistry [52-54]. Other metrics predictive of response to CPIs are under development, including HLA class I genotyping [55] or tumor mutational burden (TMB)

[56]. TMB, defined as the total number of somatic missense mutations present in tumor, was shown to correlate with response to the first line nivolumab [57]. In an exploratory analysis, whereby patients were divided into groups with low, medium and high TMB, the high TMB cohort appeared to benefit from nivolumab, whereas in the low TMB cohort anti-PD-L1 treatment resulted in inferior outcomes in comparison to chemotherapy. Most recently, serum TMB level was demonstrated to predict the efficacy of atezolizumab [58]. Hence, if optimized and validated in prospective clinical studies, TMB may become a clinically useful predictive marker of response to CPIs [59]. The CCT could then be revisited in prospective trials enrolling the low TMB patients, whereas CPI-based consolidation might be tested in the high-TMB subsets (Figure 1).

Conclusions

ConRCT remains the backbone of treatment in stage III NSCLC. Phase III trials that specifically investigated the role of CCT after conRCT failed to provide evidence for clinical benefit of this approach. Nonetheless, using two to four cycles of CCT is still a common practice and has been employed as a control arm in some contemporary trials investigating new therapies.

The futility of CCT in clinical trials may have been due to several factors, such as relative chemoresistance of NSLCS micrometastatic disease following conRCT, possibly high residual micrometastatic burden and, in particular, faulty initial staging. Indeed, most clinical trials have not mandated PET/CT and brain MR staging to exclude asymptomatic stage IV disease. As a consequence, up to a third of the patients enrolled without PET staging may have been initially beyond curative measures [60], thus diluting potential benefit from CCT. Furthermore, none of the trials included stratification according to PET/CT staging. Future investigations will need to take into account PET/CT derived metrics, such as metabolically active tumor volume, in order to assure proper balancing of study arms in terms of disease burden and radiotherapy induced-toxicity. The use of elective nodal irradiation, which is not routinely practiced in stage III NSCLC, may have added to the reported toxicity of CCT.

Clinical trials using consolidating anti-EGFR therapies have been unsuccessful. However, targeted therapies still represent a viable consolidation option, provided validated criteria to select responsive patients are strictly applied in future clinical trials.

Immune therapy using PD-1 pathway inhibition currently represents the most promising option for consolidation after conRCT, although the OS data from PACIFIC trial are yet unknown, and the absolute PFS benefit should be weighed against the immune-specific side effects and considerable costs. Therapy using immune checkpoint inhibitors may further be refined by individualized patient selection, and optimizing the dose and schedule.

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Author contributions

Marcin Skrzypski: Conception, design and planning of the study. Analysis of the data and interpreting the results. Drafting of manuscript and critically reviewing and revising the manuscript for important intellectual content.

Jacek Jassem: Conception, design and planning of the study. Analysis of the data and interpreting the results. Drafting of manuscript and critically reviewing and revising the manuscript for important intellectual content.

Both authors approved the final version of the manuscript.

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Legend to Figure 1.

Proposed outline for future trials of consolidation systemic therapy in unresectable stage III non small cell lung cancer

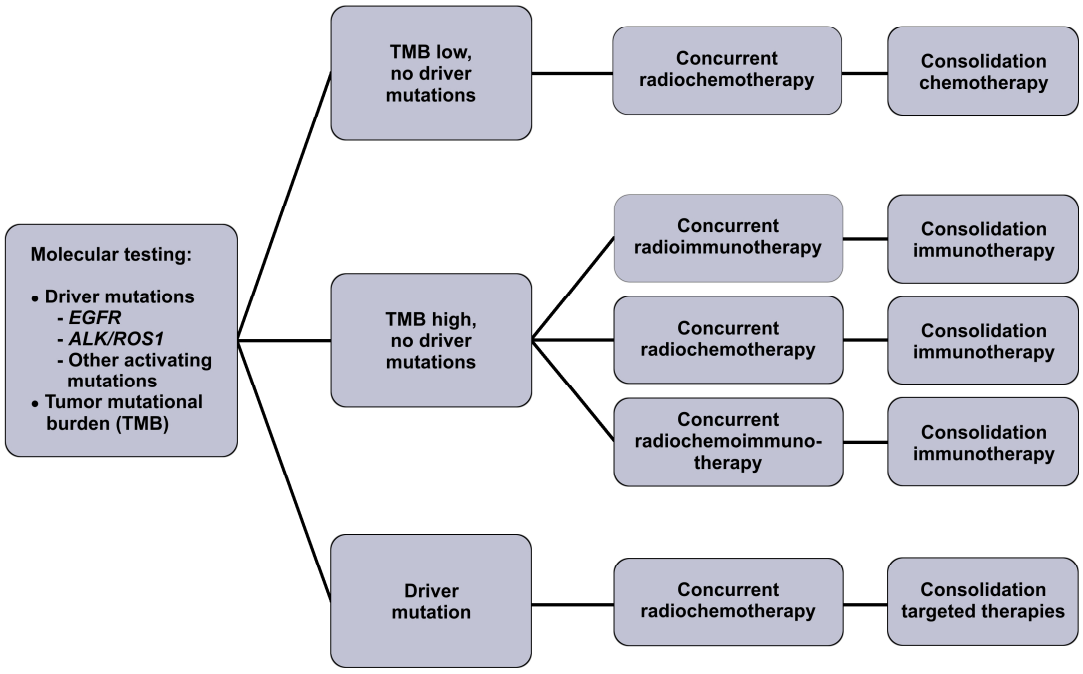

Table 1. Major phase III trials of consolidation therapies following concurrent radiochemotherapy in unresectable stage III NSCLC patients

Study	ConRCT schedule	Consolidation treatment	Main study outcomes	Comments
LUN 01-24 Hanna et al. [3]	59.4 Gy plus cisplatin 50 mg/m^2 d. 1, 8; etoposide 50 mg/m^2 d. 1–5; 2 cycles q. 4 weeks	Docetaxel 75 mg/m^2; 3 cycles q. 3 weeks; vs. no consolidation	• Median OS in CCT and control arms 24.2 vs. 26.1 months, respectively (P = 0.88); • G 3-5 infections 11% vs. 0%, respectively. • G 3-5 pneumonitis 9.6% vs. 1.4%, respectively. • Treatment related deaths 5.5% vs. 0%, respectively	• PET/CT staging not mandated; 34% of the patients not staged with PET/CT • CCT initiated with ECOG 0-2 (the percentage of ECOG 2 not reported). • Large radiotherapy fields (elective irradiation of the mediastinum) • Large margins of 2-3 cm used to expand gross tumor volumes and clinical treatment volumes • Prophylactic granulocyte colony-stimulating factor support allowed during consolidation chemotherapy • FEV1 $\geq$ 1 L required; more patients in the control compared to the docetaxel arm with FEV1 $\geq$ 2 L (59% vs. 41%, respectively; P = .066)
GILT Flentje et al. [31]	66 Gy plus cisplatin 20 mg/m^2 d. 1-4; vinorelbin (oral) 50 mg/m^2; d. 1, 8, 15; 2 cycles q. 4 weeks	Cisplatin 80 mg/m^2 d. 1; vinorelbine (oral) 60-80 mg/m^2 d. 1, 8; 3 cycles q. 3 weeks; vs. no consolidation	• Median OS in CCT and control arms 20.8 vs. 18.5 months, respectively (P = 0.87) • G2 pneumonitis: 2.2% vs 3.5%, respectively; no G3 pneumonitis • G3-4 neutropenia 22% vs. 11%, respectively • Febrile neutropenia 1.4 % vs. 1.0 %, respectively • Two toxic deaths during CCT and three in the control arm	• PET/CT staging not mandated, its use for staging not reported. • Limited radiotherapy fields (elective nodal irradiation of mediastinum not allowed) • FEV1 > 1.5 L required • CCT initiated if ECOG 0-1 (minimum Karnofsky score 80%)

KCSG-LU05-04 Ahn et al. [25]	66 Gy plus cisplatin 20 mg/m^2 and docetaxel 20 mg/m^2; both weekly x 6	Cisplatin 35 mg/m^2 d. 1, 8; docetaxel 35 mg/m^2 d. 1, 8; 3 cycles vs. no consolidation	• Median OS in CCT and control arms: 21.8 vs. 20.6 months, respectively (P = 0.44) • G3-4 neutropenia 6.9% vs. 2.9%, respectively • G 3-4 pneumonitis 1.2% in both arms • All grade pneumonitis 13.3% vs. 5.8%, respectively • Overall treatment related mortality 2.9% during the consolidation phase	• PET/CT staging mandated except for T4 disease; 92% staged with PET/CT • Only 42% of patients received all three planned cycles of CCT, and 54% completed at least two cycles • Large radiotherapy fields (elective irradiation of mediastinum) • FEV1 $\geq$ 0.8 L required; 70% of patients with FEV1 > 2L • Stage IIIB tended to be more prevalent in consolidation vs. observation arm (80% vs. 74%, respectively; P=0.16)
SWOG 0023 Kelly et al. [4]	61 Gy plus cisplatin 50 mg/m^2 d 1, 8; etoposide 50 mg/m^2 d. 1–5; 2 cycles q. 4 weeks	Docetaxel 75 mg/m^2 3 cycles q. 3 weeks, followed by gefitinib orally 500 mg or placebo for 5 years	• Median OS in gefitinib and placebo arms 23 months vs. 35 months, respectively (P = 0.013) • G 3-5 pneumonitis after conRCT followed by docetaxel in 7% of patients, including six deaths (1%) • Neutropenia in 53% of patients (19% G 3, 33% G 4) during consolidation docetaxel • G 3-4 pneumonitis in 3% of patients administered consolidation gefitinib • Treatment discontinuation within the first 6 months in 52% and 44% of patients in the gefitinib and placebo arms, respectively (P = 0.23); mainly due to progression • The overall toxic death rate 2% for conRCT, 4% for docetaxel, 2% for gefitinib and 0% for placebo	• PET/CT not mandated, unknown percentage of patients staged with PET/CT • ECOG 0-1 patients eligible for enrollment • Large radiotherapy fields (elective irradiation of mediastinum) • Gefitinib treatment initiated 3-6 weeks after completion of CCT (or conRC); thus group subjected to consolidation was enriched for patients with slower proliferating disease (excluded those who progressed after conRCT or CCT)
START Butts et al. [36, 37]	60-63 Gy plus at least two cycles of platinum	Tecemotide (preceded by cyclophophamide	• Median OS in tecemotide and placebo arms: 25.8 vs. 22.4 months, respectively (P = 0.11)	• PET/CT not mandated; 16-34% of patients staged with PET/CT, depending on a study arm • Both sequential and conRCT allowed

	containing chemotherapy (various regimens)	300 mg/m^2 3 days earlier); weekly for 8 weeks; consolidation q. 6 weeks until progression vs. placebo	• Subset analysis suggested the benefit of tecemotide in patients administered conRCT (HR 0.78; *P* = 0.016) • No toxicity concerns in relation to tecemotide	• No data on the type of radiotherapy fields
PACIFIC Antonia et al. [5]	54-66 Gy plus at least two cycles of platinum containing chemotherapy (various regimens)	Durvalumab 10 mg/kg; vs. placebo q. 2 weeks for 12 months	• Median PFS in durvalumab and placebo arms: 16.8 vs. 5.6 months, respectively (*P*<0.001) • G 3-4 pneumonitis 3.4% vs. 2.6%, respectively. • Treatment discontinued due to pneumonitis in 6.3% vs. 4.3% of patients, respectively	• PET/CT not mandated; the use of PET/CT for staging not reported • No information on the type of radiotherapy fields • Patients commenced consolidation therapy 1-42 days after completion of conRCT • PFS not related to the initial PD-L1 levels

Legend: ConRCT, concurrent radiochemotherapy; CCT, consolidation chemotherapy; OS, overall survival; PFS, progression-free survival

Conflict of interest

Marcin Skrzypski: travel grants from BMS, Roche and Boehringer.

Jacek Jassem: consulting personal fees from AstraZeneca, Boehringer, BMS, Celgene, G1 Therapeutics, Merck, Pfizer, Pierre Fabre, Roche, Abbvie and Eisai.

Highlights

- Concomitant radiochemotherapy is the current standard of care in stage III NSCLC
- Despite therapy, the majority of patients with unresectable stage III NSCLC will relapse
- Consolidation systemic therapies are hoped to improve outcomes
- Consolidation using chemotherapy or EGFR inhibition has been proved ineffective
- Consolidation with PD-1 axis immunotherapy shows impressive activity