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Chemoradiation for Definitive, Pre-operative, or Post-Operative Therapy of Locally Advanced Non-Small Cell Lung Cancer

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Abstract

Over the last few decades, the integration of chemotherapy and radiation has played a crucial role in the management of locally advanced NSCLC. Locally advanced NSCLC is a very heterogeneous disease. Because of this heterogeneity, advanced NSCLC can be managed in various different ways depending on the bulk of disease, the comorbidities of the patient and the expertise and resources of the treating physicians and facilities. This review describes the evolution of current treatment strategies and predicted future changes for the management of locally advanced NSCLC.

Keywords

Non-small cell lung cancer; locally advanced; stage III; chemoradiotherapy; combined modality; chemoradiation; chemotherapy; radiation

Introduction

Lung Cancer is the leading cause of cancer death in the United States among men and women.(1) More than one third of patients newly diagnosed with non-small cell lung cancer (NSCLC) present with locally advanced, typically unresectable disease. Over the last few decades, the integration of chemotherapy and radiation has played a crucial role in the management of locally advanced NSCLC. Locally advanced NSCLC is a very heterogeneous disease. For example, patients with clinically apparent or bulky N2 disease have survivals ranging from about 3 to 8%.(2–4) In contrast, patients who are discovered to have pathologic N2 disease at the time of surgery have long term-survivals ranging from 10

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to 50%. Because of this heterogeneity, advanced NSCLC can be managed in various different ways depending on the bulk of disease, the comorbidities of the patient and the expertise and resources of the treating physicians and facilities. This review describes the evolution of current treatment strategies and predicted future changes for the management of locally advanced NSCLC.

Definitive chemoradiation

RT alone trials

Prior to the advent of combined modality therapy for unresectable stage III NSCLC, definitive radiation therapy was the primary therapeutic strategy. Beginning in the 1960's, radiation therapy was shown to be superior to supportive care in patients with locally advanced NSCLC.(5) A multi-institutional Veterans Affairs (VA) study compared radiotherapy alone (40–50 Gy) to supportive care among patients with both small cell (SCLC) and NSCLC. Despite numerous limitations such as the inclusion of SCLC, inadequate staging and antiquated radiotherapy techniques, this trial demonstrated a statistically significant survival advantage at one year among patients randomized to the radiotherapy arm (18.2 vs. 13.9%; $p=0.05$). More recent studies have determined that definitive radiotherapy for locally advanced, unresectable NSCLC is associated with an approximate 10 month median survival and a 5-year survival rate of about 5%.(5–7)

The current standard dose of radiation was established in a historic phase III RTOG trial which compared various doses and treatment durations of radiotherapy for medically inoperable NSCLC.(8) In this study, 376 patients were randomized to 40 Gy (split course), 40 Gy (continuous course), 50 Gy, and 60 Gy in 2 Gy fractions. Those who received 60 Gy demonstrated an improvement in intra-thoracic tumor control rates compared to lower doses (67% vs. 58% vs. 56% vs. 48%; $p=0.02$). Furthermore, complete response rates were significantly higher in the groups receiving 50 or 60 Gy (23–24%; $p=0.04$). Importantly, this study also showed that tumor response based on chest X-rays and intra-thoracic tumor control directly correlated with survival. Patients who received 50 Gy and 60 Gy and who were alive at 12 months with local tumor control had a median survival of 23 months in contrast to a median survival 12 months if they had local failure prior to 12 months ($p=0.05$). Those who received 40 Gy had a median survival of 17 months if local control was achieved in the first 12 months, and 12 month median survival if there was local failure by 12 months, respectively ($P=0.008$).

Multiple radiotherapy dose-escalation studies have been performed to evaluate radiotherapy doses more than 60 Gy.(9–11). A phase I dose-escalation study enrolled 104 patients with inoperable stage I – III NSCLC to receive 3D conformal radiation therapy (3D–CRT).(12) This study determined the MTD of 3D–CRT to be 84 Gy.

Another study for patients with stage I–III NSCLC treated 18 patients to doses of 92.4 Gy or 102.9 Gy.(13) Both of these trials permitted neoadjuvant chemotherapy. This study demonstrated that patients with low volume disease could be safely treated to 92.4 or 102.9 Gy with minimal toxicity. The majority of RT dose-escalation trials were modified to chemo-radiotherapy designs once this became a de facto standard.

RT dose-escalation with chemotherapy

With the evolution of combined modality approaches for the management of locally advanced NSCLC, several studies have sought to investigate the safety of dose-escalation of radiotherapy with concurrent chemotherapy. A phase I study determined the maximum tolerated dose of radiation to be 74 Gy given with concurrent weekly carboplatin and paclitaxel.(10)

Another dose-escalation study treated patients with induction carboplatin, irinotecan, and paclitaxel followed by concurrent carboplatin and paclitaxel with conformal radiation therapy, achieving doses of 78 to 90 Gy with relatively low toxicities.(14). The Cancer and Leukemia Group B (CALGB) 30105 phase II trial of induction chemotherapy randomized 69 patients to Arm A (induction carboplatin and paclitaxel followed by concurrent weekly carboplatin and paclitaxel and radiotherapy to 74 Gy) or Arm B (induction carboplatin with gemcitabine, followed by concurrent gemcitabine and radiotherapy to 74 Gy).(11) Arm B was closed early due to a high rate of grade 4 and 5 pulmonary toxicity. Compared to historical controls, the median survival of 24.3 months in Arm A was very encouraging.

RTOG 0117 treated 55 patients with carboplatin and paclitaxel with 74 Gy of concurrent radiotherapy.(9) The median survival for all patients was 25.9 months. Furthermore, the toxicity profile was favorable but two grade 5 acute toxicities occurred, with one grade 5 pneumonia and one grade 5 hemoptysis. These encouraging median survival times of 21–37 months paved the way to studying higher doses of radiotherapy in the phase III setting.

More recent phase III studies have attempted to evaluate if higher doses conferred advantages to the standard 60 Gy.(15, 16) A study of involved-field irradiation (IFI) versus elective nodal irradiation (ENI) randomized 200 patients to receive concurrent cisplatin based chemotherapy with either IFI at 68 to 74 Gy or ENI at 60 to 64 Gy.(15) This study demonstrated that patients who received IFI with concurrent chemotherapy had better 5 year local control rates compared to those who received ENI (51 vs. 36%; $p=0.032$). Importantly, radiation pneumonitis rates were also lower among patients who received INI compared to ENI (17 vs. 29%; $p=0.044$).

RTOG 0617 is a multi-institutional 4-arm trial comparing carboplatin plus paclitaxel with or without cetuximab, assigning patients to receive either 60 Gy or 74 Gy of concurrent radiotherapy.(16) Interim results have been presented in abstract form only. The higher dose radiation arms of the study were terminated early after futility analysis did not demonstrate any advantage to 74-Gy. In fact, at interim analysis, there was a significantly inferior survival rate for the high-dose radiotherapy arm (HR 1.45; 95% CI 1.05–2.05; $p=0.02$), speculatively due to increased toxicities, although the principle investigator is currently reviewing these events in greater detail. The standard dose arms of chemotherapy with or without cetuximab remained open and results are pending.

These negative trials all pursued dose-escalation without reducing overall treatment time. It has been well-established that NSCLC is a rapidly-proliferating neoplasm, with a rather short time to accelerating its proliferative response to the initiation of radiotherapy. One approach at overcoming this is through schedule-shortening, either through aggressive accelerated hyper fractionation, or dose-per-fraction intensification. In the phase III randomized UK trial, 536 patients were randomized to CHART (continuous hyper-fractionated accelerated radiotherapy) 1.5 Gy thrice daily for 15 consecutive days to a total dose of 57 Gy versus 60 Gy in 30 fractions, without concurrent chemotherapy.(17) There was an improvement in 2 year overall survival of 29 versus 20% ($p=0.004$) for CHART versus standard fractionation. The benefit was even more pronounced in squamous cell histologies (33 versus 20%, $p=0.0007$). Further, there was a reduction in local control, regional failure, and distant failure with CHART.

This concept of accelerated hyper-fractionation was further corroborated through ECOG 2597 randomized trial of standard radiation versus accelerated hyper-fractionation after induction chemotherapy, a phase III trial where 119 patients received induction carboplatin and paclitaxel for two cycles followed by either standard radiation to 64 Gy at 2 Gy per fraction versus hyper-fractionated accelerated radiotherapy (HART- thrice daily for 12

treatment days) to a dose of 57.6 Gy.(18) The study showed a trend towards improved overall survival with HART (20.3 versus 14.9 months). Though underpowered, the results are intriguing.

Mehta and colleagues described a new concept of dose escalation in NSCLC. Given that NSCLC repopulation is rapid and the cell doubling time is less than 4 days, they proposed a dose per fraction escalation strategy which maintained the number of fractions at 25 treatments, but increased the dose per fraction to help maintain the same risk of pneumonitis, while increasing the local control.(19) This model was later tested clinical in a phase I dose escalation model with the first 46 patients treated reported by Adkison and colleagues.(20) In this study, patients were placed in 1 of 5 dose bins to 25 fractions with doses ranging from 2.28 to 3.22 Gy per fraction. NTD equivalents were between 60 and 100 Gy (with absolute non-corrected doses ranging from 57 to 80.5Gy). No concomitant chemotherapy was delivered, but pre- or post-RT chemotherapy was permitted. Initial toxicity results showed no evidence of grade 3 acute pneumonitis or esophagitis. Early median survival was a promising 18 months with 2 year overall survival of 46.8%. Longer-term data are pending.

Therefore, despite encouraging phase I and phase II results for dose escalation of radiotherapy, this has yet to be confirmed in the phase III setting and thus, 60 Gy remains the standard radiotherapy dose for concurrent chemoradiotherapy for locally advanced NSCLC.

Sequential chemoradiotherapy

A pivotal trial that introduced the use of chemotherapy with radiotherapy as a standard of care in locally advanced NSCLC was the Cancer and Leukemia Group B (CALGB) 8433 trial.(21) 155 patients with stage III NSCLC were randomized to vinblastine weekly for 5 weeks, and cisplatin on day 1 and day 29 followed by 60 Gy of radiotherapy or to 60 Gy alone. The median survival for the sequential arm was 13.8 months compared to 9.7 months for the radiotherapy alone arm ($P=0.0066$). Additionally, the 1, 2, and 3-year survival rates in the sequential chemoradiotherapy group were 55, 26, and 23%, respectively, compared to 40, 13, and 11% in the radiotherapy alone arm. A 7-year update of this trial confirmed durable survival advantage for sequential chemoradiotherapy ($p=0.012$). (6) Survival rates for chemoradiotherapy at 5 and 7 years in were 17 and 13%, respectively compared to 6% and 6% in the radiotherapy alone arm.

Another RTOG trial evaluated the addition of chemotherapy to radiotherapy and to also evaluate hyper-fractionated radiotherapy as a method to dose escalate with similar late side effects.(7, 22) This trial confirmed the results of the CALGB trial demonstrating that induction chemotherapy followed by standard dose radiotherapy resulted in a survival advantage compared to radiotherapy alone with a median survival of 13.2 months and 5-year survival of 8% compared to a median survival of 11.4 months and a 5-year survival of 5% in the standard dose radiotherapy arm ($p=0.04$).

The NSCLC Collaborative Group performed a meta-analysis to evaluate the role of chemotherapy with radiotherapy using individual patient data on 9,387 patients from 52 randomized trials.(23) Twenty-two trials included 3033 patients that evaluated radiotherapy versus radiotherapy in addition to various chemotherapy regimens. Overall, the addition of chemotherapy to radiotherapy for locally advanced disease conferred a survival advantage ($HR=0.90$; $p=0.006$), and surprisingly, this benefit was almost solely from a reduction in local relapse without a significant impact on distant metastatic disease. Additionally, among there was a survival advantage for cisplatin based chemotherapy (compared to non-cisplatin regimens) with hazard ratio of 0.87 ($p=0.005$). The results of this meta-analysis, along with

the two primary phase III trials set the standard that sequential chemoradiotherapy is superior to radiotherapy alone for locally advanced, surgically unresectable NSCLC.

Concomitant chemoradiotherapy

Multiple phase III studies have demonstrated an advantage of concurrent chemoradiation therapy over sequential chemoradiation and this is currently the standard of care (table 1). The West Japan Lung Cancer group performed a phase III trial with 320 patients comparing concurrent cisplatin, vindesine, and mitomycin with a planned split course of radiation to a total of 56 Gy, versus the same chemotherapy delivered sequentially prior to continuous course of 56 Gy of radiation.(24) Concurrent therapy conferred a survival advantage over sequential therapy with a median survival of 16.5 vs. 13.3 mos. ($p=0.04$) and 5-year survival of 17.9 versus 7.1%, respectively.

The RTOG 9410 trial involving 610 patients also demonstrated a survival advantage for concurrent over sequential chemoradiation.(25) Patients were assigned to one of three treatment arms. Arm 1 received sequential cisplatin and vinblastine for 5 weeks followed by 63 Gy ($n=203$), arm 2 received concurrent cisplatin and vinblastine with 63 Gy ($n=204$), and arm 3 received concurrent cisplatin and oral etoposide with hyper-fractionated radiotherapy to 69.6 Gy ($n=203$). Five-year survival rates were significantly higher for arm 2 compared to arm 1 (HR for death = 0.812; 95% CI 0.663–0.996; $p=0.046$), but not for arm 3 versus arm 2 (HR for death = 0.925; 95% CI 0.752–1.138; $p=0.46$). The lack of benefit from arm 3 may have been related to the regimen being too toxic leading to treatment breaks. The rates of grade 3 and higher esophagitis were 4, 22, and 45% for arms 1–3, respectively ($P<0.001$) (table 2). Based on these results, concurrent chemoradiotherapy has become the standard therapy for fit patients with locally advanced, unresectable lung cancer.

Two recent meta-analyses re-demonstrated an advantage to concurrent chemoradiotherapy over sequential chemoradiotherapy.(26, 27) In an updated Cochrane meta-analysis, five clinical trials which included 937 participants showed a significant benefit in overall survival (H.R. 0.74; 95% CI 0.62–0.89) and in two-year survival (RR 0.87; 95% CI 0.78–0.97) for those receiving concurrent versus sequential chemoradiotherapy. This translated into an absolute 2-year survival advantage of 10%.

A second meta-analysis was performed by the NSCLC Collaborative Group which included 6 trials and individual patient data for 1,205 patients who were randomized to concomitant versus sequential chemoradiotherapy. This meta-analysis demonstrated a similar advantage for overall survival for patients receiving concomitant over sequential therapy (HR, 0.84; 95% CI 0.74–0.95; $p=0.004$). The analysis also showed a benefit for concurrent chemoradiotherapy in terms of loco-regional progression (HR, 0.77; CI 0.62 to 0.95; $p=0.01$) but not for distant progression (HR, 1.04; 95% CI 0.86 to 1.25; $p=0.69$). These data suggest that the survival advantage for concurrent chemoradiotherapy results from the improved loco-regional control achieved with concurrent chemoradiotherapy.

Despite improvements in loco-regional control, rates of distant metastatic failures in patients who receive either concurrent or sequential chemoradiotherapy is similar at around 35% to 40%.(25, 28) Unfortunately, phase III studies to evaluate the role of induction chemotherapy or consolidation chemotherapy after concurrent chemoradiotherapy have not demonstrated improvements by the addition of induction or consolidation chemotherapy.(29, 30) This paves the way for future studies to work towards improving loco-regional control in locally advanced NSCLC, and to also address death due to distant metastatic disease.

Toxicity of chemoradiotherapy

Compared to radiotherapy alone, concurrent chemoradiotherapy is associated with higher rates of treatment related morbidity.(27) In a systematic review, treatment related morbidity and mortality was evaluated for 19 randomized studies where patients received either concurrent chemoradiotherapy or radiotherapy alone. There was a numerically higher rate of treatment related deaths in the concurrent chemoradiotherapy arm compared to radiotherapy alone (RR 1.38; 95% CI 0.51 to 3.72) but this is not statistically significant. There were, however, statistically significant higher rates of acute grade 3 or worse esophagitis (RR 1.76; 95% CI 1.34 to 2.31), neutropenia (RR 3.53; 95% CI 1.84 to 6.77), and anemia (RR 4.17; 95% CI 1.13 to 15.35) for concurrent chemoradiotherapy compared to radiotherapy alone.

This systematic review also compared treatment related morbidity and mortality for concurrent versus sequential chemoradiotherapy.(27) Again, there were numerically (4% vs. 2%) higher rates of treatment related mortality for the concurrent versus sequential chemoradiotherapy groups but this was not statistically significant (RR 2.02; 95% CI 0.90 to 4.52). There were also higher rates of grade 3 or higher esophagitis in the concurrent group (RR 4.96; 95% CI 2.17 to 11.37). There were not significant differences in hematologic toxicity between those receiving concurrent versus sequential chemoradiotherapy.

Pre-operative chemoradiation therapy

Because many patients experience loco-regional failure with current approaches, tri-modality therapy with neoadjuvant chemoradiation followed by surgery has been investigated. Multiple phase II studies have suggested a survival advantage for the addition of surgery to induction chemotherapy or chemoradiotherapy.(31–34)

In a phase III study of 524 patients, the surgical arm received 3 cycles of cisplatin and etoposide followed by concurrent chemoradiotherapy using carboplatin, vindesine, and hyper-fractionated radiotherapy, followed by surgery.(35) Patients who had a positive margin at the time of surgery were offered adjuvant radiotherapy. The control group was given 3 cycles of cisplatin and etoposide followed by surgery and then radiotherapy. While there was a significant improvement in mediastinal down-staging and pathologic response in the intervention group there was no significant difference in median progression free survival (PFS) (9.5 mos. vs. 10 mos.; $p=0.87$) or overall survival (OS) (median OS 15.7 mos. vs. 17.6 mos.; $p=0.97$).

The Intergroup 0139 Phase III trial randomized patients to one of two groups.(36) Group one ($n=202$) received cisplatin and etoposide concurrently with 45 Gy of radiotherapy followed by surgical resection for patients who did not have progressive disease. Group 2 ($n=194$) received cisplatin and etoposide concurrently with radiotherapy (61 Gy) without surgical resection. Although progression free survival (PFS) was improved for group 1 versus group 2 (12.8 mos. vs. 10.5 mos., $p=0.017$), there was no difference in overall survival (OS) between group 1 and 2 (23.6 mos. vs. 22.2 mos., $p=0.24$). Based on an unplanned subset analysis, patients who received a lobectomy after chemoradiation therapy, OS was superior compared to the chemoradiotherapy alone group (median survival 33.6 mos. vs. 21.7 mos.; $p=0.002$). Based on these results, tri-modality therapy for locally advanced NSCLC remains controversial but can be considered by centers with experience in this treatment approach for selected patients, especially with the clear desire to avoid pneumonectomy. RTOG 0229 and the currently accruing RTOG 0839 have demonstrated low mortality rates for experienced surgeons after full dose chemoradiation. This approach appears to increase the pN0 rate in the multi-institutional setting although has not been tested in the phase III setting.

Adjuvant radiation therapy or chemoradiotherapy

Recent clinical trials using adjuvant platinum-based chemotherapy have shown significant improvements in survival for patients with resected NSCLC, and the majority of the benefit appears to be in resected stage II and stage III NSCLC. The Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis evaluated individual patient data from the largest clinical trials of adjuvant chemotherapy and included 4584 patients, showing a significant improvement in survival with the addition of chemotherapy for stage II (HR 0.83; 95% CI 0.73–0.95) and stage III (HR 0.83; 95% CI 0.72–0.94).(37) For patients with stage IB resected lung NSCLC, there was not a significant improvement in survival (HR 0.93; 95% CI 0.78–1.10). In contrast, the JBR 10 trial randomized 482 patients with resected stage IB or II NSCLC to either surgery alone or surgery with adjuvant vinorelbine plus cisplatin. In an exploratory Cox-regression analysis, this study demonstrated a trend towards improved survival in stage IB tumors more than 4 cm (HR 0.66; 95% CI 0.39–1.14; $p=0.13$).(38) At present, adjuvant chemotherapy in resected lung cancer has become the mainstay of therapy for resected stage II, III, and in some stage IB NSCLC.

Because a significant proportion of surgically resected patients with NSCLC also experience local failure, adjuvant radiation therapy has also been studied to improve loco-regional failure rates. In patients who were considered “high risk” based on the number of involved lymph nodes and the level of mediastinal lymph node involvement, retrospective studies have suggested there may be a survival advantage for the use of adjuvant radiation therapy. (39) Randomized trials, however, have not confirmed these findings. Subsequent meta-analyses were performed to improve the power of detecting significant survival differences in these small clinical trials. The Lung Cancer Study Group published a randomized trial of 210 patients with N1 or N2 disease to observation or PORT which was powered to demonstrate an improvement in local regional control. This study did demonstrate an improvement in local control, although there was no improvement in overall survival.(40)

The PORT meta-analysis identified 9 randomized controlled trials with data from 2128 subjects who had completely resected stage I to IIIA NSCLC.(41) Postoperative radiation doses varied between trials and ranged from 30–60 Gy and the majority of patients had stage II or III NSCLC. This meta-analysis demonstrated that postoperative radiotherapy appeared to have a detrimental effect with a hazard ratio for death of 1.21 (95% CI 1.08–1.34, $P=.001$). Local recurrence-free survival and distant recurrence-free survival also favored the surgery alone arm. The PORT meta-analysis has been criticized for a number of reasons primarily related to the techniques utilized dating back into the 1960’s. The best example of these antiquated techniques is the French trial which made up 35% of the patient population in the analysis.(42) This trial demonstrated the highest rate of death related to inter-current disease (35%). This trial used the largest field size including a large part of the heart and lung while additionally delivering the highest dose of radiotherapy (60 Gy), and allowed the use of Cobalt radiotherapy. In addition this trial also demonstrated a higher inter-current death rate related to higher doses per fraction. Over the last 2 decades, the use of more conventional total doses, dose per fractions and smaller target volumes, the rates of intercurrent disease and treatment related morbidity has decreased substantially.(43–45)

An analysis of the Surveillance, Epidemiology, and End Results (SEER) database was performed on patients with stage II or stage III NSCLC who underwent a lobectomy or pneumonectomy between 1988 and 2002.(46) The purpose of this analysis was to explore if more modern treatment methods of radiation therapy had a positive impact as opposed to those observed in the PORT meta-analysis. 7,465 patients who received PORT or observation after surgical resection were included. In contrast to the PORT meta-analysis, multivariate analysis of the SEER analysis did not demonstrate a significant impact on overall survival by the use of PORT (HR = 1.048; 95% CI, 0.987 to 1.113; $P=.1269$). This

lack of detriment may be a result of less heart disease related deaths.(47) However, on a subset analysis, there was a significant detriment to survival in patients with N0 (HR=1.1176; 95% CI 1.005 to 1.376; P=0.0435) or N1 (HR=1.097; 95% CI, 1.015 to 1.186; P=0.0196) disease. Interestingly this analysis did show a significant improvement in survival for patients who had N2 nodal disease and received PORT radiotherapy after surgery (HR=0.855; 95% CI, 0.762 to 0.959; P = 0.0077). Questions remain regarding the use of PORT following surgery, particularly in the era of adjuvant chemotherapy, but N2 patients should be considered for PORT.

The question becomes whether improvements in local control can improve survival in the post-operative setting when chemotherapy is increasing survival presumably by decreasing distant metastatic disease. In a German phase II trial using induction Docetaxel and Cisplatin prior to surgery for pathologic N2 disease, 45 of 75 patients went on to develop local regional failure suggesting chemotherapy alone is inadequate for local control in this setting.(48) In a retrospective analysis of patients treated on the ANITA trial, Douillard demonstrated that the addition of PORT following chemotherapy improved the 5 year survival from 34 to 47% for patients with N2 disease.(49, 50) The use of PORT on this trial was not randomized but was allowed based on institution preference. PORT was delivered in a sequential fashion following chemotherapy on this trial. The CALGB tried to conduct a phase III for patients with N2 disease where patients received 4 cycles of carboplatin and paclitaxel and were then randomized to receive PORT or observation. This trial closed early in 2000 due to poor accrual although based on the 40 patients that were accrued the median failure free survival favored those who received PORT (25.9 vs. 15.6 months). Currently the French are accruing to a phase III study led by Le Pechoux called Lung Adjuvant Radiotherapy Trial (Lung ART). In the United States, NCCN guidelines suggest PORT for those with N2 disease found at the time of surgery.(51)

Future Directions

Future directions for the management of locally advanced NSCLC include the incorporation of newer technology, improved radiotherapy techniques, minimization of toxicity, decreasing the risk of distant metastatic disease, and more individualized therapies such as histological based approaches and therapies guided towards newly discovered molecular targets.

PET scan

Positron Emission Tomography (PET) has led to more accurate staging of NSCLC. PET sensitivity and specificity to detect distant metastatic disease, is significantly higher than CT in NSCLC.(52) PET imaging may also have value as a therapeutic planning and selection tool in the management of locally advanced NSCLC. PET scans may have an important role in aiding radiotherapy planning. PET has been shown to decrease variability between radiation oncologists in planning tumor contours and target volumes.(53, 54) The role of FDG-PET for radiation planning for clinical stage III NSCLC was evaluated in one study where it was hypothesized that the incorporation of PET could decrease the radiation doses to surrounding normal organs.(55) Twenty-one consecutive patients with clinical stage N2M0 or N3M0 NSCLC and SCLC underwent CT scan and PET/CT scan and radiotherapy treatment plans were generated. Nodal tumor volumes were lower in PET-CT planning compared to CT-planning (9.9 ± 4.0 vs. 13.7 ± 3.8 cm³; p=0.011). Additionally, doses of radiation could be safely increased from 56.0 ± 5.4 Gy with CT-planning to 71.0 ± 13.7 Gy with PET-CT planning, without increased modeled toxicity to the lung, esophagus, and spinal cord (p=0.038).

In some novel clinical trials, boosting of residual PET-avid disease detected in the middle of chemoradiotherapy is being pursued to increase dose to potentially treatment-resistant disease; novel tracers to dose escalate treatment to hypoxic and/or hyper-proliferative portions of the tumor are also being evaluated.(56, 57) RTOG 1106/American College of Radiology Imaging Network (ACRIN) 6607 trial is a randomized phase II study that plans to enroll 138 patients and evaluates an adaptive approach to radiation therapy based on a mid-treatment FDG-PET scan.(58) The control arm will have a mid-treatment FDG-PET scan, but the radiation therapy will stay the same based on the original plan prior to initiation of treatment. In addition, a baseline PET scan will be obtained in all subjects using a novel radio-tracer (18F) Fluoromisonidazole (FMISO) to measure hypoxia and to correlate this with outcomes.

Targeted therapies with radiation

Histology based approaches

In advanced and metastatic NSCLC it has become more evident in the last decade that histology plays a crucial role and that therapies are often guided by the histology. For example, in a phase III study comparing cisplatin plus pemetrexed compared to cisplatin plus gemcitabine for advanced NSCLC, a pre-planned analysis by histology demonstrated improved efficacy of cisplatin plus pemetrexed over cisplatin plus gemcitabine for non-squamous histologies.(59) Conversely, there appeared to be improved efficacy of cisplatin plus gemcitabine for squamous cell NSCLC. There are also significant data, that sensitivity to pemetrexed may be inversely related to the thymidylate synthase activity in a tumor.(60, 61) The increased expression of thymidylate synthase in squamous cell carcinomas relative to adenocarcinomas may partially explain the variation in response to pemetrexed by histology. As a result, newer studies for locally advanced surgically unresectable NSCLC have started to investigate therapies based on histology.

One large ongoing trial is the PROCLAIM trial, a Phase III Study of Pemetrexed, cisplatin, and radiation therapy followed by consolidation pemetrexed versus etoposide, cisplatin, and radiation therapy (66 Gy) followed by consolidation cytotoxic chemotherapy of choice in locally advanced stage III NSCLC other than predominantly squamous cell histology.(62) Six-hundred patients with locally advanced NSCLC and an ECOG PS 0–1 will be randomized between the two arms.

Epidermal Growth Factor Receptor (EGFR)

The discovery of molecular targets, such as the epidermal growth factor receptor (EGFR) or EGFR mutations has been crucial for the development of more “targeted” and “individualized” therapies for patients with NSCLC. In the advanced or metastatic NSCLC setting, molecularly targeted strategies are encouraging and investigators are starting to test targeted therapies in earlier stages of the disease.

Cetuximab

Although specific kinase-domain activating mutations are relatively uncommon, EGFR over-expression, using the H-score is observed in numerous NSCLCs and its activation leading to signal transduction and cell proliferation and has been identified as a poor prognostic factor.(63) Additionally, radiation therapy can lead to increased EGFR expression and inhibiting EGFR signaling has been shown to enhance radiation effects.(64, 65)

Cetuximab, a monoclonal antibody to EGFR, has been shown to improve overall survival (HR 0.74; p=0.03) and progression free survival (HR 0.70; p=0.006) for patients with

locally advanced head and neck cancer compared to radiotherapy alone.(66) The First-Line Erbitux in Lung Cancer (FLEX) trial randomized 1125 patients with EGFR expressing advanced tumors to cisplatin, vinorelbine, and cetuximab versus cisplatin and vinorelbine and demonstrated a modest improvement in survival for the cetuximab arm (HR 0.871; 95% CI 0.762–0.996; $p=0.044$).(67) Cetuximab was therefore combined with concurrent chemoradiotherapy.(68) RTOG 0324 enrolled 93 patients to receive concurrent carboplatin, paclitaxel, and cetuximab with radiotherapy. This study resulted in a promising median survival of 22.7 months, providing the rationale to study this regimen in the phase III (16, 69) RTOG 0617 trial, a four arm study comparing standard versus high dose radiotherapy and with or without Cetuximab, on a standard chemotherapy platform. The cetuximab results are pending.

Erlotinib and gefitinib

In the past 5 years, the discovery of EGFR activating mutations has been revolutionary to better understanding NSCLC. Activating mutations in the tyrosine kinase domain of the EGFR receptor predict response to erlotinib and gefitinib, the two orally available tyrosine kinase inhibitors of EGFR which have conferred survival benefit in the second and third-line management of advanced NSCLC.(70–73) These two agents have also demonstrated activity as in-vitro radiation sensitizers in NSCLC cell lines.(74, 75) Phase I and phase II studies combining erlotinib or gefitinib with chemoradiotherapy have been performed and have had varying results and median overall survivals ranging between 13–26 months.(76, 77) However, in these studies, patients were not selected by clinical or molecular criteria such as EGFR expression or EGFR mutational analysis.

The role of TKIs in locally advanced disease is also controversial particularly after the results of Southwest Oncology Group S0023 (SWOG S0023) were reported.(78, 79) This was a phase III clinical trial with a planned accrual of 840 patients who had unresectable stage IIIA or IIIB NSCLC. All patients were to receive concurrent cisplatin and etoposide with concurrent radiation to the thorax, followed by 3 cycles of consolidative docetaxel, and then randomized to gefitinib or placebo daily until disease progression, toxicity, or death. However, this trial was closed prematurely after an unplanned interim analysis demonstrated statistically significant worse outcomes for patients who were randomized to the gefitinib arm. There was a trend towards an inferior median PFS for patients who received gefitinib vs. placebo, 8.3 vs. 11.7 months, ($p=.17$). An even more concerning finding was the inferior median survival for patients who received gefitinib compared to placebo (23 and 35 months, respectively, $p=.013$). These results in a patient population that is not selected for histology or EGFR mutation status are concerning and future studies in this setting, even in a population enriched for EGFR mutated tumors, should proceed with caution.

There are still limited data on the role of erlotinib or gefitinib in locally advanced NSCLC in patients who have an EGFR mutation or are selected by molecular criteria. One retrospective analysis hypothesized that EGFR mutations may confer sensitivity to radiotherapy because lower rates of local relapse were observed in patients with and EGFR mutation versus EGFR wild-type (17.8% vs. 41.7%; $p=0.005$).(80)

Furthermore, in the setting of advanced NSCLC, other molecular targets such as the EML4-ALK translocation have been discovered which is predictive of response to an oral small-molecule inhibitor of the ALK tyrosine kinase, crizotinib.(81) There are in fact two proposed prospective trials through RTOG and the Alliance for Clinical Trials cooperative group that will randomize patients with either an EGFR mutation or an EML4-ALK translocation to upfront erlotinib or crizotinib, respectively, followed by concurrent chemoradiation therapy.(82) The control arm in each study will treat patients with standard

chemoradiotherapy alone. Other molecular mutations such as ROS1, RET, and KRAS are also the focus of ongoing clinical investigation using targeted therapies.(83, 84)

The Biomarker-integrated Approaches of Targeted therapy for Lung Cancer Elimination (BATTLE) trial was an innovative study for pre-treated patients with advanced NSCLC.(85) It was the first study to randomize 255 patients based on biopsy-mandated biomarker results to erlotinib, sorafenib, vandetanib, or erlotinib plus bexarotene based on real-time biomarker analyses. This study's most notable accomplishment was to demonstrate the feasibility of a more personalized approach to treating lung cancer and performing clinical trials using molecularly based stratification and randomization. Targeting driver mutations such as EGFR mutations or EML4-ALK translocations, or adapting therapy based on molecular targets is a promising and feasible approach to personalize therapy in advanced NSCLC and the treatment of locally advanced NSCLC may similarly evolve.

Conclusion

Lung cancer remains the most common cause of cancer death in the United States and many patients present with locally advanced disease. Current and future studies focus on improving local and distant failures for patients using combined modality approaches, improved systemic agents, and individualizing therapeutics with an emphasis on molecular genotyping. Although combined modality therapies have resulted in improved survival for patients presenting with locally advanced disease, outcomes still remain poor and there is tremendous potential for improvement.

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Table 1.0

Concurrent chemoradiation trials – phase III trials, meta-analysis

Study	N	Treatment	Long-term survival Concurrent vs. sequential	p-value
Furuse 1999	320	Cisplatin Vindesine Mitomycin Concurrent 56 Gy XRT Vs. Cisplatin Vindesine Mitomycin Sequential 56 Gy XRT	5 yr. 15.8% 8.9%	0.03998
Zatloukal 2003	102	Cisplatin Vinorelbine Concurrent 60 Gy XRT Vs. Cisplatin Vinorelbine Sequential 60 Gy XRT	3 yr. 18.6% 9.5%	0.023
Fournel NPC 95-01 2005	212	Cisplatin Etoposide Concurrent 66 Gy Consolidation cisplatin + vinorelbine Vs. Cisplatin Vinorelbine Sequential 66 Gy	4 yr. 20.7% 14.2%	0.24
Curran RTOG 9410 2011	577	Arm 1 Cisplatin Vinblastine Sequential 60 Gy XRT Arm 2 Cisplatin Vinblastine Concurrent 60 Gy XRT Arm 3 Cisplatin Etoposide Concurrent BID 69.6 Gy XRT	5 yr. 10% 16% 13%	0.046
Auperin Meta-analysis 2010	1205	Concurrent Vs. Sequential	23.8% 18.1%	0.004

Table 2.0

Concurrent chemoradiotherapy toxicity tables

Study	Toxicity (grade 3 or 4)	Sequential	Concurrent			P-value
Furuse	Anemia	33%	10%			<0.0001
	Leukopenia	77%	99%			<0.0001
	Thrombocytopenia	23%	53%			<0.0001
Zatloukal	Leukopenia	19%	53%			0.009
	Nausea and vomiting	15%	39%			0.044
Fournel	Neutropenia	88%	77%			0.05
	Esophagitis	3%	32%			<0.0001
Curran		Arm 1	Arm 2	Arm 3		
	Esophagitis	4%	22%	45%	P<0.001	
	Leukopenia	29%	42%	36%	Not reported	
	Thrombocytopenia	3%	5%	9%	Not reported	
Auperin (meta-analysis)	Esophagitis	4%	18%			P<0.001