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NONSURGICAL TREATMENT FOR LOCALLY ADVANCED NON–SMALL-CELL LUNG CANCER: GOOD PERFORMANCE STATUS/DEFINITIVE INTENT

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Summary of Literature Review

Introduction

The treatment of inoperable stage III non–small-cell lung cancer (NSCLC) remains a challenge due to high rates of distant metastasis, local recurrence, and toxicity associated with definitive therapy. Radiotherapy (RT) plays a crucial role in the management of lung cancer. However, conventional RT to a dose of 60 Gy is associated with less than 50%–60% local control, and the median survival time is only 15–17 months, with 5-year survival rates of 13%–16% even when concurrent chemotherapy and RT is given [1]. Radiation dose escalation/acceleration has been shown to improve local control and potentially survival in lung cancer in nonrandomized studies. However, the optimal chemoradiation regimen remains unknown. To improve clinical outcome of stage III NSCLC, the Radiation Therapy Oncology Group® (RTOG®) conducted a phase III study (RTOG 0617) [2] to escalate the radiation dose from 60 Gy to 74 Gy with concurrent carboplatin/paclitaxel ± cetuximab. The preliminary data of RTOG 0617 showed that 74 Gy is associated with poorer survival as compared with 60 Gy, although the survival appears improved in both arms based on short-term follow-up compared with the historical RTOG 9410 data. This study raises many questions about the controversial issues of safety and efficacy of dose escalation in stage III NSCLC. The difficulty for dose escalation is toxicity due to tumor proximity to surrounding critical structures. Advanced radiation techniques, such as image-guided radiotherapy (IGRT), optimized intensity-modulated radiation therapy (IMRT), stereotactic ablative RT (SABR, also known as stereotactic body RT), proton therapy [3], and better integration of systemic therapy, particularly molecular marker-guided targeted therapy, [4] are required to further improve the therapeutic ratio.

Heterogeneity Correction

Tissue heterogeneity in the vicinity of the lung has implications on the accuracy of the dose distributions. Dose that would have normally been deposited in the tumor is carried away into the surrounding lung tissue, resulting in potential underdosage of the tumor. The literature is replete with articles demonstrating the need for accurate, "heterogeneity-corrected" dose algorithms in lung cancer planning [5,6]. Consequently, the RTOG has adopted the requirement that algorithms employing heterogeneity corrections be used for treatment planning for both early and locally advanced stage lung cancer [7-9]. To mitigate inaccuracies with dose calculations, it is strongly recommended that algorithms employing accurate heterogeneity correction techniques be utilized for lung cancer treatment planning. Pencil-beam-type algorithms should be avoided [10].

Radiation Therapy Alone: Standard Fractionation

RT alone used to be considered the standard treatment for patients with unresectable and locally advanced NSCLC. The RTOG 7301 trial [11] tried to optimize time/dose scheduling of RT alone for patients with unresectable and locally advanced NSCLC, including those with poor performance status and >5% weight loss. This trial showed that better local control and 2-year survival were achieved by a total dose of 60 Gy in 6 weeks compared to a lower dose of RT alone. Two-year survival rates were 14% among the patients who received 40 Gy

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in 4 weeks with a continuous course and 18% for those who received 50–60 Gy, compared to only 10% among those who received a split course, although this difference was not statistically significant. By 5 years, all dose regimens had a similarly poor survival outcome of <10%. Patients treated with 50–60 Gy with clinical tumor control had a survival rate of 22% in 3 years, compared to 10% if patients failed in the thorax (P=.005). This historical randomized study established the standard radiation dose of 60 Gy in 30 fractions in NSCLC. However, the local control rate is less than 50% in addition to dismal survival using this regimen.

Elective Nodal Irradiation

For many years, the standard RT for NSCLC in the United States was to first deliver 40–50 Gy to the regional lymph nodes (ipsilateral, contralateral, hilar, mediastinal, and occasionally supraclavicular) that showed no evidence of tumor involvement and then deliver additional 20 Gy to the primary tumor through reduced fields. The rationale against the use of elective nodal irradiation is the high rate of local disease recurrence within the previously irradiated tumor and the high risk of distant metastasis and toxicity associated with a large radiation volume. Furthermore, if the gross disease cannot be controlled, there is no point to enlarging the irradiated volumes to include areas that may harbor microscopic disease.

Three major factors have changed since the RTOG 7301 trial established the standard RT for NSCLC: the use of chemotherapy, the advent of 3-D conformal radiation therapy (3-D-CRT), IMRT, and better staging and target delineation with positron emission tomography (PET) and endobronchial ultrasound (EBUS). Emerging clinical data show that omitting prophylactic lymph node irradiation does not reduce the local control rate in patients receiving definitive RT. In these patients, the local recurrence rates in the isolated outside-field (field of RT) have been <8%, particularly in patients with stage I disease and in those who have undergone PET scanning for staging [12-14]. A recent randomized study appeared to support involved-field irradiation approach [15].

Thus, in patients with NSCLC, it is important to deliver adequate doses of radiation to primary tumor and involved nodal or mediastinal areas. Irradiation of other electively treated lymph nodes may not be necessary, particularly in patients whose tumors are staged with computed tomography (CT), PET, and EBUS. Clinical judgment regarding pattern of failure, anatomy, and toxicity need to be considered to decide clinical treatment volume. In addition, if local control and survival continue to improve along with radiation dose escalation techniques, the issue of elective nodal irradiation may need to be revisited in future.

Altered Fractionation and Dose-Escalated Radiation Therapy

Because of the poor 2-year survival and local control with standard radiation doses and fractionation, a randomized dose escalation study was initiated through RTOG 8311. This trial was an attempt to increase local control by using higher total doses while using a twice-daily fractionation regimen to avoid increasing toxicities of late-responding normal tissue [16]. Eight hundred forty patients were treated with 1.2 Gy twice-daily fractionation separated by 4–6 hours. They were randomized to receive minimum total doses of 60 Gy, 64.8 Gy, and 69.6 Gy. After acceptable acute toxicities, 74.4 Gy and 79.2 Gy arms were added. The best arm received 69.6 Gy in 6.5 weeks and showed a 2-year survival rate of 29% for patients with good performance status and <5% weight loss, which was significantly better than the survival rates among patients who received lower doses (P=.02).

The European Organisation for Research and Treatment of Cancer (EORTC) conducted a randomized study for patients with inoperable or unresectable stage II or III NSCLC who were treated by standard RT (60 Gy in 6 weeks) or continuous, hyperfractionated, accelerated RT (CHART). The majority of the patients had squamous cell carcinoma on histology. CHART was given at 1.5 Gy fractions 3 times a day, 7 days/week with at least a 6-hour interfractional interval. The large volume dose was 37.5 Gy in 25 fractions followed by 16.5 Gy in 11 fractions, giving a total dose of 54 Gy. The updated results showed improvement in survival and local control with CHART compared to standard RT (3-year survival rate for CHART treatment was 20% versus 13% with standard RT, and 3-year local control with CHART was 17% versus 12% with standard RT) [17]. More moderate or severe acute dysphagia affected 49% of CHART cases, compared with 19% of those treated conventionally. However, there was no significant difference between the 2 arms in the rate of late complications. Follow-up studies on accelerated fractionation regimens include the recently published CHARTWEL trial, which did not show a survival improvement for 60 Gy given over 2.5 weeks versus 66 Gy standard fractionation in 6.5 weeks [18]. The exact reason for this lack of benefit remains unclear but may relate to the lower fraction of squamous cell cancers, which would benefit most from acceleration, compared to the original CHART trial.

Several studies including recent RTOG trial data analysis with 1,390 patients showed that increased biological effective dose (BED) is associated with improved local control and survival [19,20]. In recent years, image-guided SABR has been shown to achieve higher than 90% local control with promising survival in stage I NSCLC when BED >100 Gy is delivered to target within 3 to 5 fractions [21,22]. With implementation of cutting-edge technologies such as IGRT, 3-D-CRT, IMRT, and proton therapy, a few pilot studies are ongoing to evaluate image-guided proton/photon hypofractionated dose escalation/acceleration with dose up to 60 Gy in 15 fractions in locally advanced disease while respecting normal tissue tolerance without concurrent chemotherapy [23]. The preliminary data appear promising, and a phase III randomized study to compare IGRT 60 Gy in 15 fractions with 60 Gy in 30 fractions in poor performance status patients with stage III NSCLC is ongoing.

Intensity-Modulated Radiation Therapy

Attempts to improve tumor control by dose escalation have been limited by the tolerance of normal tissues, especially lung and esophagus. IMRT has been shown to significantly reduce doses to normal tissues, and it is therefore a promising technique for facilitating safe dose escalation. Concerns exist regarding the application of IMRT to lung tumors, relating to the accurate targeting of a moving lung tumor with IMRT due to interplay effect and the potential increase in the percent lung volume receiving low doses. Data on clinical use of IMRT for lung cancer patients are sparse.

Investigators at MD Anderson Cancer Center generated IMRT plans for 41 stage III NSCLC patients who had been previously treated with 3-D-CRT and found that the IMRT allowed for greater sparing of normal tissues, including heart, lung, and esophagus, with lower probability of lung complications using dosimetric models [24]. A follow-up retrospective report of 151 NSCLC patients treated with IMRT showed an 8% incidence of treatment-related grade 3 or higher pneumonitis at 12 months, compared with 23% for a similar group of 222 patients treated with 3-D-CRT, despite the fact that the IMRT group had a larger mean gross tumor volume [25]. Recent studies also indicated that IMRT reduced esophageal toxicity as compared with 3D-CRT. In addition, clinical implementation of IMRT, 4-D CT simulation, and PET images are associated with improved local control and survival in stage III NSCLC [26]. The Memorial Sloan Kettering Cancer Center experience was reported [27] as follows: 55 patients with stage I-IIIB NSCLC were selected to receive IMRT, mainly due to large tumor size and proximity to critical organs. Doses of 6000–9000 cGy were used, and 76% received chemotherapy. Normal tissue complication probability and f_{dam} lung constraints were used, and inhomogeneity correction was applied. Toxicity was not increased in these patients, and 2-year local control and overall survival rates compared favorably with larger prospective series.

In summary, IMRT has shown promise in dosimetric modeling studies for reducing normal tissue complication probability to allow for dose escalation in lung cancer patients. Early clinical reports of IMRT indicate favorable toxicity profiles and tumor control. IMRT allows integrated dose painting to high-risk regions with minimal increased dose to normal tissues that could translate into improved local control and quality of life [3]. However, motion control and IGRT are required in IMRT, and prospective trials are underway to further evaluate this technology in the clinical setting.

Proton Beam Radiotherapy

Proton therapy has potential dosimetric advantages over photon beam therapy [28]. As therapeutic proton beam radiation becomes more widely available, much interest has been generated in examining the potential benefits of this modality for treating lung cancer. The physical characteristics of the proton beam would seem to allow for greater sparing of normal tissues, although there are also unique concerns about its use for lung tumors due to respiratory motion and low lung parenchymal density.

Prospective and retrospective studies indicated the utility of using protons in locally advanced NSCLC to increase the radiation dose while avoiding normal tissue. Chang et al [29] recently completed a phase II study of 44 patients with stage III NSCLC who received 74 Gy via conventional fractionation (2 Gy per fraction) with weekly concurrent carboplatin and paclitaxel. Despite the very high intensity of this treatment course, no grade 4 or 5 toxicities occurred, and grade 3 toxicities were minimal. Because of the tolerability of this regimen, patients were more likely to complete treatment. The median overall survival duration was 29.4 months, and the overall survival and progression-free survival rates at 2 years were both above 55%. A phase II randomized study to compare proton therapy versus IMRT using 74 Gy with concurrent chemotherapy in stage III NSCLC is ongoing [30].

Some technical issues unique to proton beam therapy have been discussed. First, proton therapy is more sensitive to motion and anatomy change than photon therapy. 4-D CT-based planning and adaptive RT are required [31].

There is some geometric uncertainty about the range of a given proton beam, and differences in tissue density between tumors and surrounding normal lung tissue can have a profound effect on proton beam planning. In addition, it is challenging to treat lung cancer with complicated anatomy with current passive scattering proton therapy techniques. Intensity-modulated proton therapy (IMPT) will further improve conformity of therapy, but motion uncertainty in that setting is even more profound [32]. A prospective study using IMPT is ongoing.

In summary, due to physical characteristics, protons can spare more normal tissues and may allow further dose escalation/acceleration. However, there are more uncertainties about proton therapy in lung cancer, and much improvement and optimization is still needed. Protons may not be suitable for all lung cancer patients, and proper case selection and proper proton techniques based on motion and anatomy are crucial to improve the therapeutic ratio. Hopefully, larger prospective controlled trials that are underway will clarify the role of proton beam for lung cancer in the near future.

Combined Chemotherapy and Radiation Therapy

Given the poor outcome with RT alone and the high rate of metastatic disease, combined chemotherapy and RT approaches were designed in an attempt to improve outcomes. The Cancer and Leukemia Group B (CALGB) trial [33] randomized 155 patients with stage III NSCLC with good performance status and <5% weight loss who were treated with 2 cycles of vinblastine and cisplatin followed by RT (60 Gy in 6 weeks) or with RT alone (60 Gy in 6 weeks). Patients who were treated by induction chemotherapy followed by RT had a median survival time of 13.8 months (78 patients) compared to 9.7 months for those (77 patients) treated by RT alone. The 2-year survival rate was significantly better among the patients who received combined treatment compared to those who received RT alone, 26% versus 13% (P=.006). The longer follow-up to this study showed that the 5-year survival rate of patients who received combined treatment was 19%, compared to 7% for those who received RT alone.

LeChevalier et al [34] also reported that a phase III randomized study comparing RT alone to combined chemotherapy and RT showed a significant improvement in 3-year survival rate with combined treatment, 12% versus 4% (P=.02). Median survival times were 12 months and 10 months, respectively. However, there was no difference in regard to the local control.

The RTOG 8808 trial [35] randomized 452 patients with stage III NSCLC, good performance status, and <5% weight loss to be treated in 3 arms. Arm 1 received combined chemotherapy and RT. The chemotherapy, using vinblastine and cisplatin, was administered in 2 cycles and was followed by RT with 60 Gy over 6.5 weeks. Patients in the other 2 arms received RT alone, one using 60 Gy of standard fractionation RT in 6 weeks, the other using 69.6 Gy of hyperfractionated (HFX) RT with a fraction size of 1.2 Gy. The median survival time was 13.2 months in the chemotherapy and RT arm compared to 11.4 months among the patients who received standard fractionation RT. The 2-year survival rate was 32% among the patients who received combined treatment versus 19% among the patients who received standard fractionation RT alone (P=.003). The outcome in the HFX RT arm was intermediate between the other 2 arms (mean survival time of 12 months; 2-year overall survival rate of 24%; P=.08 compared to chemotherapy and RT). Five-year survival rates, however, were <10% in all study arms.

The EORTC study [36] showed that daily cisplatin and simultaneous RT significantly improved 2-year survival rates (26% compared to 13%) as compared with the patients who received RT alone (P=.009). However, the RT schedule was not considered optimal as a standard of RT in the United States. The control arm of RT was given 3 Gy in 10 fractions with a 3-week to 4-week break followed by 2.5 Gy in 10 fractions as a boost.

Several meta-analyses have now examined the benefit of adding chemotherapy to radiation for stage IIIA and IIIB NSCLC. The Non-small Cell Lung Cancer Collaborative Group analyzed updated individual patient data from 22 trials including 3,033 patients. The group excluded all trials in which chemotherapy was given only during RT. Five trials used long-term alkylating agents, mainly cyclophosphamide or nitrosourea in combination with methotrexate. Three used vinca alkaloids or etoposide, and 3 used "other" regimens, mostly based on doxorubicin. Eleven trials used chemotherapy regimens containing cisplatin. The group found a significant overall benefit of chemotherapy, which resulted in a 10% reduction in the risk of death, corresponding to absolute benefits of 3% at 2 years and 2% at 5 years. Trials using cisplatin-based chemotherapy gave the strongest evidence in favor of chemotherapy, with absolute benefits of 4% at 2 years and 2% at 5 years [37].

Marino et al [38] performed a meta-analysis of data extracted from published reports of clinical trials evaluating combined radiation plus chemotherapy versus radiation alone for stage IIIA/B NSCLC. Fourteen trials comprising 1,887 patients were analyzed. They found a 30% reduction in mortality at 2 years for cisplatin-based

chemotherapy versus RT alone compared with an 18% reduction in mortality at 2 years for the non–cisplatin-based group. No improvement in survival in either chemotherapy group was seen at 3 or 5 years, compared with radiation alone.

The MAC3-LC Group [39] analyzed individual data from 9 trials (1,764 patients) comparing concurrent chemotherapy and RT with RT alone. Eligible trials used cisplatin-based or carboplatin-based chemotherapy. The hazard ratio of death for the chemotherapy and RT group was 0.89 compared to RT alone, corresponding to an absolute benefit of chemotherapy of 4% at 2 years.

These analyses have provided the evidence that has established combined platinum-based chemotherapy and radiation as the standard of care for the good-performance-status patient with unresectable stage IIIA and IIIB NSCLC and minimal weight loss. Further studies, as described below, have focused on ways to optimize the sequencing of combination therapy as well as techniques of radiation delivery and fractionation.

Altered Fractionation Radiation Therapy Combined with Chemotherapy

The North Central Cancer Treatment Group (NCCTG) conducted a 3-arm phase III randomized trial for patients with unresectable (stage III) NSCLC treated with standard fractionated thoracic RT, accelerated HFX thoracic RT, or HFX RT with concurrent etoposide and cisplatin. The standard fractionation was 60 Gy in 30 fractions over 6 weeks. HFX RT was given in a 1.5 Gy twice-daily fractionation with a 2-week break after the initial 30 Gy in 2 weeks. This HFX RT was given alone or with concurrent cisplatin (30 mg/m^2, days 1–3 and 28–30) and etoposide (100 mg/m^2, days 1–3 and 28–30). The study group analyzed 99 eligible patients out of the 110 patients entered. There was a suggestion of improvement in the rate of freedom from local recurrence and survival for patients with HFX RT with or without chemotherapy compared to standard RT (P=.06 and P=.1, respectively). There was a significant improvement in survival with accelerated and HFX RT (with or without chemotherapy) in the subgroup of patients with non–squamous-cell carcinoma (P=.02). There was no difference in freedom from distant metastasis or survival among the patients who received HFX RT with or without concurrent chemotherapy. This study suggested that the patients with stage III NSCLC treated with accelerated HFX RT with or without chemotherapy may have better freedom from local progression and survival compared to those receiving standard RT, especially for patients with non–squamous-cell carcinoma [40].

The NCCTG next tested concurrent chemotherapy plus once-daily (QD) versus twice-daily (BID) RT [41]. Both arms received cisplatin (30 mg/m^2) and etoposide (100 mg/m^2) on days 1 and 28 concurrent with RT. Grade 3+ nonhematologic toxicity was slightly worse in the twice-daily RT arm. At 2 years there was no difference in local control or overall survival. Subgroup analysis suggested a survival benefit to twice daily in non–squamous-cell histology, similar to previous findings by the NCCTG. This was in contrary to findings from RTOG 9410 (see below) that twice-daily RT improved local control in squamous cancers.

RTOG 9801 [42] was a randomized trial designed to test the hypothesis that the cytoprotectant amifostine would reduce the incidence of esophageal toxicity during concurrent chemotherapy and HFX RT using 3-D-CRT (1.2 Gy BID to 69.6 Gy). The results showed no significant difference in the incidence of the NCI Common Toxicity Criteria grade ≥3 esophagitis (30% versus 34%), although patient-reported swallowing symptoms were significantly less severe with amifostine. No differences in median survival (17.3 months versus 17.9 months) were reported.

Sequential Versus Concurrent Chemotherapy and Radiation Therapy

The West Japan Lung Cancer Group conducted a phase III study to investigate whether concurrent or sequential treatment with RT and chemotherapy improves survival for patients with unresectable stage III NSCLC. In the concurrent arm, chemotherapy consisted of cisplatin (80 mg/m^2 on days 1 and 29), vindesine (3 mg/m^2 on days 1, 8, 29, and 36), and mitomycin (8 mg/m^2 on days 1 and 29). RT began on day 2 at a dose of 28 Gy, 2 Gy fractions, 5 fractions/week for a total of 14 fractions. This was repeated after a rest period of 10 days; the total tumor dose was therefore 56 Gy in 6 weeks. In the sequential arm, the same chemotherapy was given, with RT initiated after completing 2 cycles of chemotherapy. RT consisted of 56 Gy, 2 Gy/fractions, and 5 fractions/week for a total of 28 fractions. Three hundred twenty patients were entered in this study. The response rate for the concurrent arm was significantly higher (84%) compared to the sequential arm (66%) (P=.0002). Median survival time was significantly improved in patients receiving concurrent chemotherapy and RT (16.5 months) compared with those receiving sequential therapy (13.3 months) (P=.04). Two-year and 5-year survival rates in the concurrent group were 34.6% and 15.8%, respectively, compared to 27.4% and 8.9% in the sequential group. Mild suppression was

significantly greater among the patients who received concurrent chemotherapy and RT (P=.0001). There was no significant difference in regard to acute esophagitis between the 2 groups [43].

Fournel et al [44] reported results of the French GLOT-GFPC NPC 95-01 randomized trial. Concurrent chemoradiation patients received etoposide and cisplatin concurrent with 66 Gy of once-daily RT, followed by adjuvant cisplatin/vinorelbine. The sequential arm received induction cisplatin and vinorelbine, followed by the same RT. Survival was better in the concurrent arm, but the difference was not significant.

RTOG 9410 was a 3-arm randomized trial comparing sequential (SEQ) chemotherapy followed by RT (once daily to 63 Gy) with 2 different concurrent chemoradiotherapy regimens. The latter consisted of either concurrent once-daily RT to 63 Gy (CON-QD), or concurrent twice-daily RT to 69.6 Gy (CON-BID). The SEQ and CON-QD arms each included 2 cycles of cisplatin and vinblastine. The CON-BID used 2 cycles of cisplatin and VP-16 based on the experience in RTOG 9204. Acute toxicity was worst in the CON-BID arm. Although time to in-field progression was best in the CON-BID arm, this did not translate into a survival benefit. The best survival times were in the CON-QD arm, which were significantly better than in the SEQ arm (P=.046). Median survival times in the 3 arms were 14.6 months (SEQ), 17 months (CON-QD), and 15.2 months (CON-BID) [1].

Two meta-analyses further support survival advantage of concurrent chemoradiation. A Cochrane meta-analysis demonstrated a significant 14% reduction in the risk of death with concurrent chemoradiation as compared with sequential treatment [45]. The NSCLC Collaborative Group discovered a significant survival advantage with concurrent chemoradiation compared with sequential treatment (hazard ratio: 0.84) with an absolute benefit of 5.7% at 3 years [46].The above data have provided strong support for the use of concurrent, platinum-based chemoradiation as the standard of care for unresectable stage IIIA/B NSCLC patients who have good performance status and minimal weight loss (see Variant 1, Variant 2, Variant 3, and Variant 4).

Radiation Dose Escalation with Concurrent Chemotherapy

In RTOG 9410, the locoregional failure rate after concurrent chemotherapy and RT at a standard radiation dose of approximately 60 Gy was about 34%–43%. To improve the local control rate, 3 groups (RTOG, the North Central Cancer Treatment Group, and the University of North Carolina) separately performed radiation dose-escalation trials in patients with stage III NSCLC, and their results supported the safety and efficacy of using 74 Gy concurrently with chemotherapy in this population [47-49]. On the basis of promising local control and survival rates and an acceptable toxicity level obtained using 3-D-CRT to a dose of 74 Gy with concurrent chemotherapy, RTOG conducted a phase III study comparing a dose of 60 Gy versus 74 Gy delivered by 3D-CRT or IMRT concurrently with weekly paclitaxel and carboplatin ± antibody against the epidermal growth factor receptor (EGFR) cetuximab in patients with stage IIIA or IIIB NSCLC. Surprisingly the preliminary analysis showed that there was no overall survival improvement in the group randomized to the higher radiation dose [2]. In fact, the survival in the high-dose arm was worse. One interpretation of this outcome is that dose escalation is not oncologically beneficial, but this runs counter to basic biology and a large body of evidence, including prospective phase II and III trials. A competing explanation is that 74 Gy is too toxic when delivered by the photon-based radiation technologies used in current setting of RTOG 0617. It is also possible that 74 Gy is still an inadequate dose (the early-stage NSCLC data suggest the need for BED of 100 Gy in the absence of radiosensitizers, but this dose threshold has not been clearly assessed in the presence of concurrent chemotherapy), and higher biological dose using image-guided hypofractionated RT to reduce total treatment days should be considered. In addition, IGRT and strict quality assurance are crucial to achieve optimal outcome. This puzzling trial result has resulted in much debate, and we hope that these issues are further clarified when the final outcomes are published.

Role of Additional Chemotherapy Before or After Concurrent Chemotherapy and Radiation Therapy

Induction chemotherapy followed by concurrent chemoradiotherapy was proposed as an alternative to concurrent chemoradiotherapy as a way to potentially improve systemic control and survival in patients with unresectable stage III NSCLC. The CALGB recently presented the initial results of trial 39801, in which patients with unresectable stage III disease were randomized to concurrent weekly carboplatin (AUC 2) and paclitaxel (50 mg/m^2) and 66 Gy once-daily RT, versus the same concurrent regimen preceded by 2 cycles of carboplatin (AUC 6) and paclitaxel (200 mg/m^2). A nonsignificant increase in median survival time was seen in the induction arm (14 versus 11.4 months, P=.154), although the survival times in both arms were poor compared with those seen on other recent studies. Significant hematological toxicity was more common on the induction arm, but radiation-related toxicities are similar [50].

A 3-arm study compared sequential chemotherapy/RT, induction chemotherapy followed by concurrent chemoradiotherapy, and concurrent chemoradiotherapy followed by consolidation chemotherapy in stage III NSCLC [51]. The median survival was 16.3 months, 12.7 months, and 13 months in the consolidation arm, the induction arm, and in the sequential arm, respectively. The induction and consolidation arms were associated with greater toxicity, and the incidences of grade 3/4 esophagitis and pulmonary toxicity were highest in the consolidation arm. Although the study was not powered for direct comparison of the 3 treatment arms in terms of survival, the prolonged median survival for concurrent treatment followed by consolidation chemotherapy supports the concept that providing the definitive concurrent chemoradiotherapy up front is the preferred therapeutic approach in stage III NSCLC.

The Southwest Oncology Group (SWOG) reported the results of S9504, a phase II trial in which patients were treated with concurrent CDDP/VP-16 and standard RT (61 Gy). This was followed by 3 cycles of adjuvant docetaxel as consolidation. Results were promising, with a 3-year survival rate of 37% [52]. However, when the addition of adjuvant docetaxel to concurrent CDDP/VP-16 plus RT was compared to CDDP/VP-16 plus RT alone in a randomized trial by the Hoosier Oncology Group, toxicity was higher with docetaxel, without an improvement in survival [53].

In summary, at the present time, combined treatment consisting of RT and chemotherapy has given better 5-year survival rates than RT alone for patients with medically inoperable and surgically unresectable stage III NSCLC. More recent results showed that concurrent chemotherapy combined with RT improved median survival and local control compared to sequential chemotherapy followed by RT. HFX RT and concurrent chemotherapy appears to give better local control, although survival has not been improved significantly. The risk of acute toxicity, especially esophagitis, is increased when HFX RT is combined with concurrent chemotherapy. The role of additional chemotherapy either as induction chemotherapy or consolidative chemotherapy at the completion of chemoradiation has not been well elucidated. Sometimes induction chemotherapy is used when there is high risk of distant metastasis or the disease is too bulky to meet with RT dose-volume constraints. Adjuvant full dose carboplatin/paclitaxel after concurrent RT and weekly low-dose carboplatin/paclitaxel is standard of care, whereas adjuvant chemotherapy after concurrent radiation with cisplatin/etoposide should not be used outside of clinical trials [54].

Personalized Targeted Therapy

Therapeutic decisions in NSCLC are currently based on histology, disease stage, and performance status. However, NSCLC is a heterogeneous disease, and different treatment outcomes have been observed even in the clinical and similar histological features. Given the overall poor results with standard cytotoxic therapies and the number of advances that have been made recently in our understanding of the biology of cancer, a strong interest has emerged in targeting pathways unique to neoplastic cells or tumors. The availability of such targeted biologics requires their use to be matched to tumors of corresponding molecular vulnerability for maximum efficacy. One such example is the EGFR, which can be inhibited by either monoclonal antibodies (eg, cetuximab, panitumumab) or small-molecule tyrosine kinase inhibitors (TKI) (erlotinib, gefitinib, or afatinib). These agents have been tested in conjunction with radiation and chemotherapy in stage III NSCLC, but results have been mixed at best [55-58]. A preliminary report from RTOG 0617 did not find an early survival benefit for cetuximab [59]. These data highlight the need for predictive biomarkers to identify subsets of patients with wild-type EGFR tumors that would benefit from the combination of EGFR-targeted agents with standard chemo/radiation, if those exist. NSCLCs harboring activating mutations in the EGFR, occurring in approximately 10% of patients in the United States, are typically highly responsive to EGFR TKI, at least in the stage IV setting. However, there are little data regarding the incorporation of these inhibitors in patients with stage III EGFR mutation-positive NSCLC. The use of EGFR TKI as an induction regimen prior to standard chemotherapy/radiation in patients with EGFR-mutant NSCLC is under investigation by the RTOG (1306) and elsewhere [60,61]. Similarly, the use of crizotinib as induction for patients with NSCLC driven by fusions of anaplastic lymphoma kinase (ALK) with echinoderm microtubule-associated protein-like 4 (EML4) is being tested by RTOG 1306.

KRAS is the most commonly mutated oncogene in NSCLC, but compared to EGFR and EML4/ALK the development of effective targeted therapies has lagged behind. Whether a KRAS mutation renders the affected tumors more resistant to chemotherapy and radiation therapy remains to be established [62,63]. The presence of somatic KRAS mutation is associated with a lack of sensitivity to EGFR inhibitors [64].

Another example of targeted therapy involves angiogenesis, which can be inhibited with such drugs as bevacizumab, a monoclonal antibody to vascular endothelial growth factor (VEGF). Inhibition of each of these pathways (EGFR and VEGF) has been shown in randomized studies to prolong survival of patients with advanced NSCLC [65,66]. Adjuvant studies are being planned with chemotherapy with or without erlotinib or bevacizumab. However, the incorporation of bevacizumab with radiation is potentially toxic [67].

Future Research Direction: Knowledge-Based Personalized Radiotherapy and Systemic Therapy

Current NSCLC treatment approaches are largely empiric, with minimal improvement in outcome. As we know, not all cancers are created equal. Some cancer cells may be resistant to RT and require a higher BED of RT and some of the patients may not be able to tolerate high doses of RT due to unique genetic and clinical profiles. Conventional 60 to 66 Gy of RT is associated with poor local control and dismal survival. The challenge is to escalate/accelerate dose safely and effectively. Optimizing systemic therapy with RT also plays a crucial role in clinical outcome including local control, survival, and toxicities. There is no magic drug or magic RT modality/technique/regimen that fits all lung cancer patients. Personalized approaches based on tumor genetic makeup that guide systemic therapy as well as knowledge-guided RT dose escalation/acceleration using cutting-edge technologies, such as IGRT, SABR, IMRT, and proton therapy, will likely result in significantly improved survival in these patients. Prospective clinical studies using biomarker-driven therapy in selected patients and personalized RT to maximize local control with dose escalation/acceleration while minimizing toxicities are crucial to improve the therapeutic ratio in NSCLC. These studies, such as molecular marker-based targeted therapy with concurrent chemoradiotherapy and biological PET image-guided dose escalation (RTOG studies), are ongoing.

Summary

- Concurrent chemotherapy and RT remains the standard care for nonsurgical treatment of stage III NSCLC with good performance status.
- Although we should continue to explore radiation dose escalation/acceleration in locally advanced NSCLC, 60 to 66 Gy with concurrent chemotherapy remains the standard regimen in community setting.
- Both 3-D conformal radiotherapy and IMRT are acceptable for treatment of locally advanced NSCLC. Proton therapy may have the potential to further spare critical normal tissues, although more prospective studies are needed.
- Molecular marker-based targeted therapy might have the potential to improve therapeutic ratio in locally advanced NSCLC, but more prospective studies are needed. At this moment, there is no level I evidence to support adding targeted therapy with concurrent chemotherapy/radiotherapy.

Supporting Documents

- ACR Appropriateness Criteria® Overview
- Evidence Table

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Clinical Condition: **Nonsurgical Treatment for Locally Advanced Non–Small-Cell Lung Cancer: Good Performance status/Definitive Intent**

Variant 1: **T2bN3M0 (IIIB): 60-year-old male smoker with NSCLC (adenocarcinoma with mutation in KRAS). Chest CT revealed a 6-cm mass in the right upper and middle lobes and right hilar, subcarinal, and bilateral paratracheal lymphadenopathy. All of these areas were intensely FDG-avid on PET scan. Karnofsky performance status (KPS) >70%, weight loss <5%.**

Treatment	Rating	Comments
Chemotherapy plus RT	9	
External beam RT alone	3	Consider this treatment if patient is unable to tolerate chemotherapy.
Chemotherapy alone	2	
Endobronchial brachytherapy alone	1	
External beam plus brachytherapy	1	
Timing of Chemotherapy with RT (if given)		
Concurrent chemotherapy/RT	9	
Concurrent chemotherapy /RT followed by chemotherapy	7	Consider this timing if using carboplatin/paclitaxel.
Chemotherapy followed by concurrent chemotherapy/RT	5	
RT followed by chemotherapy	3	
External Beam Irradiation		
50–54 Gy at 1.8–2.0 Gy/fraction over 5–6 weeks	2	
54 Gy at 1.5 Gy TID/12 days (CHART) or similar hyperfractionated schedule	3	
59.4–66.6 Gy at 1.8–2.0 Gy/fraction over 6–7.5 weeks	9	
70 Gy at 1.8–2.0 Gy/fraction over 7–8 weeks	No Consensus	There is a lack of level I data between 66 Gy to 70 Gy.
74 Gy in 7.5–8 weeks	3	This is usually not appropriate except for clinical trials.
Treatment Planning Technique		
2-D radiation (AP/PA and/or off-cord obliques)	3	
3-D treatment planning	9	
IMRT	8	This treatment requires respiratory motion management.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Nonsurgical Treatment for Locally Advanced Non–Small-Cell Lung Cancer: Good Performance status/Definitive Intent**

Variant 2: **T3N3M0 (IIIB): 60-year-old patient with NSCLC (squamous-cell cancer). Chest CT showed bilateral paratracheal and subcarinal adenopathy with postobstructive pneumonia due to an endobronchial lesion in the left mainstem bronchus. All of these areas were intensely FDG-avid on PET scan. KPS >70, weight loss <5%.**

Treatment	Rating	Comments
Chemotherapy plus RT	9	
External beam RT alone	3	Consider this treatment if patient is unable to tolerate chemotherapy.
Chemotherapy alone	2	
Endobronchial brachytherapy alone	2	
External beam plus brachytherapy	5	Chemotherapy should be added once pneumonia is treated.
Timing of Chemotherapy with RT (if given)		
Concurrent chemotherapy/RT	9	
Concurrent chemotherapy /RT followed by chemotherapy	7	Consider this timing if using carboplatin/paclitaxel.
Chemotherapy followed by concurrent chemotherapy /RT	3	
RT followed by chemotherapy	3	
External Beam Irradiation		
50–54 Gy at 1.8–2.0 Gy/fraction over 5–6 weeks	2	
54 Gy at 1.5 Gy TID/12 days (CHART) or similar hyperfractionated schedule	3	
59.4–66.6 Gy at 1.8–2.0 Gy/fraction over 6–7.5 weeks	9	
70 Gy at 1.8–2.0 Gy/fraction over 7–8 weeks	No Consensus	There is a lack of level I data between 66 Gy to 70 Gy.
74 Gy in 7.5–8 weeks	3	This is usually not appropriate except for clinical trials.
Treatment Planning Technique		
2-D radiation (AP/PA and/or off-cord obliques)	3	
3-D treatment planning	9	
IMRT	8	This treatment requires respiratory motion management.

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Nonsurgical Treatment for Locally Advanced Non–Small-Cell Lung Cancer: Good Performance status/Definitive Intent**

Variant 3: **T4N3M0: 60-year-old man with a history of a few weeks of superior vena caval obstruction. Bronchoscopy revealed extrinsic compression of right upper lobe (RUL). Fine-needle aspiration (FNA) showed undifferentiated large-cell carcinoma. Chest CT showed 6-cm mass in RUL directly invading mediastinum with compression of superior vena cava, 3-cm left paratracheal node, and right pleural effusion too small to tap. KPS >70, weight loss <5%.**

Treatment	Rating	Comments
Chemotherapy plus RT	9	
External beam RT alone	3	Consider this treatment if patient is unable to tolerate chemotherapy.
Chemotherapy alone	2	
Endobronchial brachytherapy alone	1	
External beam plus brachytherapy	1	
Timing of Chemotherapy with RT (if given)		
Concurrent chemotherapy/RT	9	
Concurrent chemotherapy /RT followed by chemotherapy	7	Consider this timing if using carboplatin/paclitaxel.
Chemotherapy followed by concurrent chemotherapy /RT	3	
RT followed by chemotherapy	5	
External Beam Irradiation		
50–54 Gy at 1.8–2.0 Gy/fraction over 5–6 weeks	2	
54 Gy at 1.5 Gy TID/12 days (CHART) or similar hyperfractionated schedule	3	
59.4–66.6 Gy at 1.8–2.0 Gy/fraction over 6–7.5 weeks	9	
70 Gy at 1.8–2.0 Gy/fraction over 7–8 weeks	No Consensus	There is a lack of level I data between 66 Gy to 70 Gy.
74 Gy in 7.5–8 weeks	3	This is usually not appropriate except for clinical trials.
Treatment Planning Technique		
2-D radiation (AP/PA and/or off-cord obliques)	3	
3-D treatment planning	9	
IMRT	8	This treatment requires respiratory motion management.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Nonsurgical Treatment for Locally Advanced Non–Small-Cell Lung Cancer: Good Performance status/Definitive Intent**

Variant 4: **T2aN3M0: 43-year-old woman never-smoker in whom PET/CT showed an FDG-avid 3.5-cm mass in the medial basal segment of the right lower lobe and FDG-avid right infrahilar, subcarinal, right paratracheal, and right supraclavicular lymphadenopathy (all <2 cm). FNA of supraclavicular node revealed adenocarcinoma. A right pleural effusion had mild FDG avidity, but 2 taps were negative. Genetic testing revealed exon 19 deletion mutation in the EGFR. KPS >70, weight loss <5%.**

Treatment	Rating	Comments
Chemotherapy plus RT	9	
External beam RT alone	2	
Chemotherapy alone	3	
Endobronchial brachytherapy alone	1	
External beam plus brachytherapy	1	
Timing of Chemotherapy with RT (if given)		
Concurrent chemotherapy/RT	9	
Concurrent chemotherapy /RT followed by chemotherapy	7	Consider this schedule if using carboplatin/paclitaxel. Encourage patients to enroll in RTOG 1306.
Chemotherapy followed by concurrent chemotherapy /RT	5	
RT followed by chemotherapy	2	
External Beam Irradiation		
50–54 Gy at 1.8–2.0 Gy/fraction over 5–6 weeks	2	
54 Gy at 1.5 Gy TID/12 days (CHART) or similar hyperfractionated schedule	3	
59.4–66.6 Gy at 1.8–2.0 Gy/fraction over 6–7.5 weeks	9	
70 Gy at 1.8–2.0 Gy/fraction over 7–8 weeks	No Consensus	There is a lack of level I data between 66 Gy to 70 Gy.
74 Gy in 7.5–8 weeks	3	This is usually not appropriate except for clinical trials.
Treatment Planning Technique		
2-D radiation (AP/PA and/or off-cord obliques)	2	
3-D treatment planning	9	
IMRT	8	This treatment requires respiratory motion management.

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Trial/Author	*N*	*Years*	*Induction Chemotherapy*	*Concurrent Chemotherapy*	*Consolidation Chemotherapy*	*RT Dose*	*Dose/Fx*	*Locoregional Recurrence*	*Grade 3-5 Pneumonitis*	*Grade 3-5 Esophagitis*	*Median OS*	*3-year OS*
RTOG 9410 Curran et al [1]	204	'94-'98	–	cisplatin Q 4 wks etoposide Q 4 wks	–	60.0 Gy	2.0 Gy	34% (5-year)		26%	17 months	29%
	195	'94-'98	–	cisplatin Q 4 wks etoposide Q 4 wks	–	69.6 Gy	1.2 Gy BID	33% (5-year)			15 months	
NCCTG 94 24 52 Schild et al [41]	117	'94-'99	–	cisplatin Q 4 wks etoposide Q 4 wks	–	60.0 Gy	2.0 Gy	48% (3-year)	11%	20%	14 months	25%
RTOG 9309 Albain et al [68]	194	'94-'01	–	cisplatin Q 4 wks etoposide Q 4 wks	cisplatin Q 4 wks etoposide Q 4 wks	61.0 Gy	1.8-2.0 Gy	22% (crude)	16%	23%	22 months	33%
SWOG 9504 Gandara et al [52]	83	'96-'98	–	cisplatin Q 4 wks etoposide Q 4 wks	docetaxel Q 3 wks	61.0 Gy	1.8-2.0 Gy	47% (crude)	7%	17%	26 months	37%
UNC Stinchcombe et al [69]	62	'96-'99	carboplatin Q 3 wks paclitaxel Q 3 wks	carboplatin Q wk paclitaxel Q wk	–	60.0-74.0 Gy	2.0 Gy	34% (crude)	0%	8%	25 months	38%
GLOT Fournel et al [44]	102	'96-'00	–	cisplatin Q 4 wks etoposide Q 4 wks	cisplatin Q 4 wks vinorelbine Q wk	66.0 Gy	2.0 Gy	53% (crude)	5%	32%	16 months	25%
China Yuan et al [15]	98	'97-'01	–	cisplatin Q 3 wks etoposide Q 3 wks RT started cycle 2	cisplatin Q 3 wks etoposide Q 3 wks	68.0-74.0 Gy	1.8-2.0 Gy	44% (3-year)	1%	4%	20 months	29%
Czech Republic Zatloukal et al [70]	52	'97-'01	–	cisplatin Q 4 wks vinorelbine Q wk RT started cycle 2	cisplatin Q 4 wks vinorelbine Q wk	60.0 Gy	2.0 Gy	62% (3-year)	4%	18%	17 months	19%
LAMP Belani et al [51]	92	'98-'01	–	carboplatin Q wk paclitaxel Q wk	carboplatin Q 3 wks paclitaxel Q 3 wks	63.0 Gy	1.8-2.0 Gy		16%	28%	16 months	17%
	74	'98-'01	carboplatin Q 3 wks paclitaxel Q 3 wks	carboplatin Q wk paclitaxel Q wk	–	63.0 Gy	1.8-2.0 Gy		4%	19%	13 months	15%
BROCAT Huber et al [71]	99	'97-'02	carboplatin Q 3 wks paclitaxel Q 3 wks	paclitaxel Q wk	–	60.0-66.0 Gy	2.0 Gy		1%	13%	19 months	19%
CALGB 39801 Vokes et al [50]	184	'98-'02	carboplatin Q 3 wks paclitaxel Q 3 wks	carboplatin Q wk paclitaxel Q wk	–	66.0 Gy	2.0 Gy	36% (crude)	10%	28%	14 months	23%
	182	'98-'02	–	carboplatin Q wk paclitaxel Q wk	–	66.0 Gy	2.0 Gy	36% (crude)	4%	30%	12 months	19%
RTOG 9801 Movsas et al [57]	243	'98-'02	carboplatin Q 3 wks paclitaxel Q 3 wks	carboplatin Q wk paclitaxel Q wk ± amifostine 4×/wk	–	69.6 Gy	1.2 Gy BID	49% (4-year)	11%	32%	18 months	27%
EORTC 08972 Belderbos et al [72]	80	'99-'03	–	cisplatin Q day	–	66.0 Gy	2.75 Gy	46% (crude)	18%	17%	17 months	29%
Meta-analysis Aupérin et al [46]	603	'88-'03	various	various	various	48.5-66.0 Gy	2.0-3.0 Gy	28% (3-year)		18%	14 months	24%
NCCTG N0028 Schild et al [47]	13	'02-'04	–	carboplatin Q wk paclitaxel Q wk	carboplatin Q 3 wks paclitaxel Q 3 wks	70.0-78.0 Gy	2.0 Gy		23%		28 months	

Trial/Author	*N*	*Years*	*Induction Chemotherapy*	*Concurrent Chemotherapy*	*Consolidation Chemotherapy*	*RT Dose*	*Dose/Fx*	*Locoregional Recurrence*	*Grade 3-5 Pneumonitis*	*Grade 3-5 Esophagitis*	*Median OS*	*3-year OS*
CALGB 30105 Socinski et al [73]	43	'02-'04	carboplatin Q 3 wks paclitaxel Q 3 wks	carboplatin Q wk paclitaxel Q wk	–	74.0 Gy	2.0 Gy		16%	16%	24 months	37%
SWOG S0023 Kelly et al [56]	125	'01-'05	–	cisplatin Q 4 wks etoposide Q 4 wks	docetaxel Q 3 wks	61.0 Gy	1.8-2.0 Gy		7%	13%	35 months	45%
HOG Hanna et al [53]	73	'02-'06	–	cisplatin Q 4 wks etoposide Q 4 wks	docetaxel Q 3 wks	59.4 Gy	1.8 Gy		10%	17%	21 months	27%
	74	'02-'06	–	cisplatin Q 4 wks etoposide Q 4 wks	–	59.4 Gy	1.8 Gy		1%	17%	23 months	26%
RTOG 0324 Blumenschein et al [55]	87	'04-'05	–	carboplatin Q wk paclitaxel Q wk cetuximab Q wk	carboplatin Q 3 wks paclitaxel Q 3 wks cetuximab Q wk	63.0 Gy	1.8 Gy		7%	8%	23 months	
RTOG 0117 Bradley et al [74]	44	'03-'07	–	carboplatin Q wk paclitaxel Q wk	optional: carboplatin Q 3 wks paclitaxel Q 3 wks	74.0 Gy	2.0 Gy	48% (crude)	23%		22 months	