

Review Article

Hope for progress after 40 years of futility? Novel approaches in the treatment of advanced stage III and IV non-small-cell-lung cancer: Stereotactic body radiation therapy, mediastinal lymphadenectomy, and novel systemic therapy

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Abstract

Non-small-cell lung cancer (NSCLC) remains a leading cause of cancer mortality. The majority of patients present with advanced (stage III-IV) disease. Such patients are treated with a variety of therapies including surgery, radiation, and chemotherapy. Despite decades of work, however, overall survival in this group has been resistant to any substantial improvement. This review briefly details the evolution to the current standard of care for advanced NSCLC, advances in systemic therapy, and novel techniques (stereotactic body radiation therapy [SBRT], and transcervical extended mediastinal lymphadenectomy [TEMLA] or video-assisted mediastinal lymphadenectomy [VAMLA]) that have been used in localized NSCLC. The utility of these techniques in advanced stage therapy and potential methods of combining these novel techniques with systemic therapy to improve survival are discussed.

Keywords: Image-guided radiation therapy, non-small-cell lung cancer, targeted therapy, temla, vaml

INTRODUCTION

Lung cancer remains the leading cause of cancer death with an estimated 221,130 new cases and 156,940 deaths in 2011.^[1] Approximately, 75% of lung cancers are non-small-cell lung cancer (NSCLC) and 15-20% of NSCLC patients are diagnosed with localized disease.^[1] Surgery is the mainstay of

treatment for localized NSCLC with favorable 5-year survival rates of 65-70%.^[2] However, 80-85% of patients present with NSCLC that has spread to mediastinal or supraclavicular lymph nodes (N2 disease, Stage III) or that has spread beyond the lung (metastatic, stage IV.) Such patients, even when they have an excellent performance status and minimal N2 or metastatic disease, often are not candidates for curative surgery and are treated with a combination of chemotherapy and/or radiation therapy.

Although overall survival for all patients with advanced stage III-IV NSCLC remains dismal, new targeted systemic therapies offer hope of prolonged survival in selected patients with advanced NSCLC. Advances in treatment are increasingly providing an individualized approach by

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identifying, targeting, and treating particular genetic and molecular abnormalities in each patient. Some targeted therapies (erlotinib, gefitinib, and crizotinib) are Food and Drug Administration (FDA)-approved either as third-line therapy or for use in metastatic disease. Many ongoing studies are evaluating the role of targeted therapies as first-line agents in select patients with advanced disease. In this new paradigm of individualized therapy, established therapies of surgery, radiation, and chemotherapy must be re-evaluated for their overall efficacy and toxicity so that they can be appropriately intercalated with this new wave of targeted therapies.

FORTY YEARS OF FUTILITY IN THE TREATMENT OF STAGE III-IV NON-SMALL-CELL LUNG CANCER

By definition, survival in patients with stage III NSCLC is superior to those with stage IV disease. Unfortunately, survival with even stage III disease is dismal by any measure and has been remarkably resistant to improvement despite more intensive standard chemotherapy, surgery, and/or radiation therapy.

In the 1970s, the Radiation Therapy Oncology Group (RTOG) performed studies (RTOG 7301 and 7302) with radiation therapy alone for stage III NSCLC. There were high rates (greater than 40%) of both distant and local failures. Five-year overall survival in all groups was less than 10%.^[3] Since then virtually all combinations of chemotherapy, radiation, and surgery have been attempted.^[4-9] In general, the addition of chemotherapy to radiotherapy is associated with statistically significant (but less than 10% in absolute terms) improvement in overall survival. This minimal absolute benefit in survival comes at the expense of a large rise in Grade 3 toxicities [Tables 1 and 2].

Advances in imaging (computed tomography (CT) and positron emission tomography (PET) scanning) and overall staging techniques (bronchoscopy and mediastinoscopy) now exclude many patients with metastatic disease from being misidentified as stage III.^[10-16] Such improvements in the accuracy of staging – via the resulting “Will Rogers phenomenon,” whereby survival in both stage III and IV disease improves because patients with low volume metastatic disease move from stage III to stage IV – should result in some improvement in overall survival. Yet modern trials have failed to produce substantial improvements in long-term survival.^[17-19,49,50] In 2011, the results of RTOG 9410 reaffirmed that concurrent chemotherapy with radiation was superior to sequential therapy, albeit with a 5 year survival of only 16%.^[20]

Furthermore, local control following concurrent

chemoradiation, when post-therapy biopsies were done, is 15%.^[21] Moreover, despite terrible local control and overall survival, toxicity of modern concurrent chemoradiation is extreme with nearly 50% Grade 3 toxicity.^[20]

In select N2 cases with isolated single station N2 disease, surgical cure may be feasible;^[22-28] however, for the remainder of patients with N2 disease, concurrent chemoradiotherapy for 6 weeks is the current standard of care. Escalation of radiotherapy to higher doses over 7.5 weeks has recently shown no improvement in outcome (RTOG 0617 results presented as a late breaking abstract by Jeff Bradley at the American Society for Radiation Oncology (ASTRO) meeting in 2011.)

As expected, survival with stage IV disease as a group lags survival of stage III disease.^[29,30] Generally, patients are treated with chemotherapy. Traditionally, platinum-based regimens are used, but many other agents such as taxanes, pemetrexed, and gemcitabine are also common. The role of radiation therapy and other modalities in these patients is primarily reserved for palliation of symptoms.

ADVANCES IN SYSTEMIC THERAPY: TARGETED THERAPY

Modern research has developed new therapies that target specific molecular pathways that contribute to carcinogenesis. Several of these therapies have been deployed in the treatment of advanced or metastatic NSCLC. A full discussion of the many targeted therapies currently in human trials is beyond the scope of this review, but recently have been reviewed elsewhere.^[31] The two agents (erlotinib and crizotinib) currently approved as third-line therapy in the USA for patients with advanced NSCLC are briefly discussed.

Erlotinib (Tarceva) and gefitinib (Iressa) are small molecule inhibitors of the endothelial growth factor receptor (EGFR). Erlotinib was approved by the FDA in 2004 for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. The Iressa Pan-Asia Study was a phase III randomized trial which compared gefitinib versus carboplatin/paclitaxel as a first-line treatment in advanced lung adenocarcinomas. Pre-planned subgroup analysis of patients whose tumors expressed EGFR mutations showed significantly longer progression-free survival (PFS) for gefitinib than chemotherapy (hazard ratio 0.48, $P < 0.001$).^[32] In treatment naïve Stage IIIB-IV NSCLC patients with an activating EGFR mutation, the OPTIMAL trial found that erlotinib significantly improved PFS (13.1 vs. 4.6 months) as compared with chemotherapy; hazard ratio 0.16 ($P < 0.001$).^[33] As a result, erlotinib is also

Table 1: Overall survival of trials studying medically inoperable or locally advanced non-small cell lung cancer

Study/author	Year	Study type	Arm 1	Arm 2	RT fraction size	Arm 1 OS (%)	Arm 2 OS (%)
RTOG 7301, Perez ^[3]	1987	RT alone/dose	50 Gy	60 Gy	2 Gy	3 year 10	3 year 15
EORTC, Schaake-Koning ^[17]	1990	RT versus concurrent CRT*	60 Gy split-course	60 Gy split+cisplatin daily	3 Gy	3 year 2	3 year 16
Le Chevalier ^[21]	1991	RT versus sequential CRT/ adjuvant Chemo	65 Gy split-course	VCPC/65 Gy split/ VCPC	2.5 Gy	3 year 5	3 year 11
CALGB 8843, Dillman ^[49]	1990	RT versus sequential CRT	60 Gy	Cisplatin+ vinblastine/60 Gy	2 Gy	5 year 6	5 year 17
RTOG 8808, Sause ^[50]	1996	RT versus sequential CRT**	60 Gy	Cisplatin+vinblastine	2 Gy	5 year 5	5 year 8
RTOG 9410, Curran ^[20]	2011	Sequential versus concurrent CRT***	Cisplatin+ vinblastine/60 Gy	Cisplatin+ vinblastine+60 Gy	2 Gy	5 year 10	5 year 16

RT: Radiotherapy, CRT: Chemoradiotherapy, VCPC: Vindesine, lomustine, cisplatin, cyclophosphamide, *3 arm trial—arm 3 concurrent CRT with cisplatin weekly, 3 year OS 13%, **3 arm trial—arm 3: hyperfractionated RT alone 69.6 Gy at 1.2 Gy BID, 5 year OS 6%, ***3 arm trial—arm 3: concurrent chemo-RT with carboplatin/etoposide and hyperfractionated RT 69.6 Gy at 1.2 Gy BID, 5 year OS 13%, RTOG: Radiation therapy oncology group, CALGB: Cancer and leukemia group B, EORTC: European organisation for research and treatment of cancer, OS: Overall survival, BID: Twice daily

Table 2: Reported grade 3 or higher toxicities in trials comparing radiotherapy alone versus combined chemoradiotherapy

Study/author	Year	Study type	Most frequent toxicity	Arm 1 toxicity %	Arm 2 toxicity %	Arm 3 toxicity %
EORTC, Schaake-Koning ^[17]	1990	RT alone versus concurrent CRT (daily cisplatin) versus concurrent CRT (weekly cisplatin)	Nausea/Vomiting	2	22	19
CALGB 8843, Dillman ^[49]	1990	RT alone versus sequential CRT	Neutropenic infection	3	7	N/A
RTOG 9410, Curran ^[20]	2011	Sequential CRT versus Concurrent CRT versus Concurrent CRT with HFRT	Granulocytopenia	77	81	53
			Esophagitis	4	22	45
			Late pulmonary	14	13	17

HFRT: Hyper-fractionated RT, NR: Not reported, CALGB: Cancer and leukemia group B, RTOG: Radiation therapy oncology group

recommended as first-line therapy in patients with advanced, recurrent, or metastatic non-squamous NSCLC who have known activating EGFR mutation.

Crizotinib (Xalkori) is a small molecule inhibitor that targets anaplastic lymphoma kinase (ALK) fusion gene. In 2011, crizotinib was approved by the FDA for patients with locally advanced or metastatic NSCLC and are positive for the ALK gene rearrangement. Early results of phase I trials are extremely promising. Initial treatments in patients with prior treatment for ALK rearranged NSCLC demonstrate a 57% response rate and 72% 6-month PFS.^[34] Follow-up in these patients demonstrates that crizotinib significantly increased survival as compared with other second-line NSCLC treatment (2 year overall survival 55% vs. 12%; hazard ratio 0.36 $P = 0.004$).^[35]

STEREOTACTIC BODY RADIATION THERAPY (SBRT)

SBRT is a different way of delivering radiation therapy than conventionally fractionated radiation as discussed above for stage III lung cancer. Lung SBRT uses very tight margins with image guidance to precisely deliver high doses (10-34 Gy) of radiation in 1-5 treatments over 1-14 days maximum. By comparison, conventional radiation delivers higher doses (60-70 Gy) using smaller doses (1.8-2.5 Gy) over 30

or more treatments.

STEREOTACTIC BODY RADIATION THERAPY FOR EARLY STAGE, MEDICALLY INOPERABLE LUNG CANCER

Timmerman *et al.*, carried out a prospective, phase II, 70-patient trial using SBRT to doses of 60-66 Gy in three fractions over 1-2 weeks. With a median follow-up of 17.5 months, the 3-month major response rate was 60%. Kaplan–Meier local control at 2 years was 95%. Median overall survival was 32.6 months and 2-year overall survival was 54.7%. Among patients experiencing toxicity, the median time to observation was 10.5 months. Grades 3-5 toxicity occurred in a total of 14 patients. Six patients died as a consequence of treatment-related toxicity. Tumors with volume of more than 10 mL had an eight-fold risk of high-grade toxicity compared with smaller tumors ($P = 0.017$).^[36]

These data^[36,37] lead to the RTOG multi-institutional prospective trial of SBRT in 2004 (RTOG study 0236). This study enrolled 59 medically inoperable patients with peripherally located, node negative NSCLC measuring 5 cm or less. Patients received 60 Gy (3 × 20 Gy fractions) over 10-14 days. The median overall survival was 48.1 months and 3-year disease-free and overall survival was 48.3% and 55.8%, respectively. One patient had primary

tumor failure and 11 patients had distant failure. Grades 3–4 adverse events were reported in nine patients.^[38]

On the strength of these results and superiority to the results of conventional radiation in similar populations,^[39] SBRT is now standard of care medically inoperable patients. An ongoing national study is currently comparing SBRT versus surgery in medically operable patients (RTOG 1021/ACOSOG Z4099).

STEREOTACTIC BODY RADIATION THERAPY DOSE AND FRACTIONATION

Though the superiority of SBRT over conventional fractionation is accepted for early stage medically inoperable patients, the optimal dose and fractionation are not known. The three-fraction approach to a total of 54–60 Gy described can have considerable toxicity. Alternate fractionation scheme (1, 4, and 5) treatments are in wide use. Hof *et al.*, reported outcomes in 42 patients with stage I or II NSCLC treated with single-fraction SBRT (dose range: 19–30 Gy). Overall local tumor control at 36 months was 68%, but control was significantly improved in patients who received 26–30 Gy when compared to those who received less than 26 Gy.^[40] Others have studied single-dose SBRT for lung tumors (both primary lung tumors and metastases). With median follow-up intervals of 12–18 months, local control was greater than 90%.^[38,39] In both studies, single-fraction SBRT was well tolerated.

Open studies are currently enrolling patients to evaluate single-fraction SBRT to multiple fraction regimens. A multi-institutional study (RTOG 0915, now closed to accrual) is a phase II study comparing single-fraction (34 Gy) to multiple fractions (48 Gy in four fractions).

STEREOTACTIC BODY RADIATION THERAPY FOR CENTRAL LESIONS

Timmerman *et al.*, found that patients treated for peripheral lung tumors had 2-year freedom from severe toxicity of 83% compared with only 54% for patients with central tumors.^[36] However, further follow-up eliminated the statistical significance of this difference. Grades 3–5 toxicity occurred in five of 48 patients with peripheral lung tumors (10.4%) and in six of 22 patients (27.3%) with central tumors ($P = 0.088$).^[41] Despite this eventual disappearance of the statistically significant difference between central and peripheral tumor treatment toxicity, the fear of central irradiation had already become established. Prior to publication of the update results, RTOG 0813 was launched as a phase I-II study evaluating a variety of multi-fraction

regimens and doses for central lesions. This ongoing trial continues to accrue patients.

ADVANCEMENTS IN SURGICAL STAGING: TRANSCERVICAL EXTENDED MEDIASTINAL LYMPHADENECTOMY (TEMLA)/ VIDEO-ASSISTED MEDIASTINAL LYMPHADENECTOMY (VAMLA)

Assessment of mediastinal lymph nodes is critical to the staging of NSCLC. A variety of approaches are used, including radiographic (CT, and PET/CT), endoscopic (endobronchial/endoesophageal ultrasound (EBUS/EUS) guided biopsies,) and surgical (mediastinoscopy). Several reviews and meta-analyses can be found in the literature attempting to quantify the sensitivities and specificities of each of these approaches.^[42] To date, the gold standard has been considered to be surgical staging with cervical mediastinoscopy with lymph nodes sampled from select paratracheal (level 2, 4) and subcarinal (level 7) lymph node stations.

In 2005, Zielinski *et al.*, described a novel approach to surgical staging of the mediastinum, a TEMLA.^[43] The TEMLA procedure includes a 5–8 cm collar incision in the neck, elevation of the sternal manubrium with a special retractor, bilateral visualization of the laryngeal recurrent and vagus nerves, and dissection of all mediastinal nodal stations except for the pulmonary ligament nodes (station 9). VAMLA uses a video-assisted technique in lieu of the special retractor.

Recently, Dr. Zielinski presented data at the World Conference on Lung Cancer 2011 comparing surgical staging with TEMLA versus endoscopic staging with EBUS/EUS. The sensitivity of TEMLA for primary staging was 98.6%, compared with 88.9% for EBUS/EUS. The specificity of TEMLA was 100% versus 98.7% with EBUS/EUS. The negative predictive value (NPV) of TEMLA was 99.7% and the positive predictive value (PPV) was 100% versus a NPV of 84.1% and PPV of 99.1% for EBUS/EUS. Such impressive NPV and PPV have led some in the thoracic surgery field to declare TEMLA (or VAMLA), the new gold standard for mediastinal staging.^[44,45]

Of note, a variety of other advancements in surgical techniques including video-assisted thoracic surgery (VATS) have been made and allow the resection of early stage disease in less-fit patients than previously considered possible.^[46] Moreover, it may be possible to extend these techniques to more advanced patients.^[47] VATS literature and outcomes are fully reviewed elsewhere.^[48]

FUTURE WORK

In the context of the low survivals and high toxicities shown in Table 1, it is clear that more work is needed to craft multi-modal therapy that seeks to improve survival and mitigate toxicity. Future trials should focus on assessing the feasibility and toxicity of combining the therapies as described in this review for advanced stage (III/IV) NSCLC. In theory, TEMPLA/VAMLA could be used to assess and clear the mediastinum of metastatic disease followed by SBRT or surgery to treat the primary lesion, with targeted chemotherapy to follow. SBRT may also be deployed in the adjuvant setting to areas of high risk in the mediastinum or primary location following surgery. Selection of the chemotherapeutic agent (s) could be based on the medical oncologist (s) assessment of the patient's performance status, in addition to screening for EGFR, ALK, and other gene mutations. Clinical trials – a necessity given the potential toxicity of combining these novel and potentially toxic therapies which have thus far been used mostly in patients with more limited stages of NSCLC – utilizing these principles are currently under design and development in a variety of institutions including our own.

CONCLUSION

For advanced disease (Stage III), the current standard of care of concurrent chemotherapy and radiation has produced disappointing results with high toxicities. Novel-targeted chemotherapeutic agents have recently been developed with promising results for select patients with specific molecular mutations. SBRT has been shown to have excellent local control with acceptable toxicity for peripheral early stage NSCLC in medically inoperable patients. Ongoing trials continue to look at refining dose and fractionation schedules. TEMPLA/VAMLA has the ability to improve the detection and staging of true mediastinal disease not otherwise detectable by other surgical, endoscopic, or radiographic means. These recent advances should be evaluated further in combination, to assess whether improvements in survival can be achieved while limiting the toxicity associated with NSCLC treatments.

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