

Current Update on the Management of Locally Advanced Non-small Cell Lung Cancer

Locally advanced NSCLC is a heterogeneous group of bronchogenic malignancies that are traditionally thought to be unresectable without overt distant metastasis or malignant pleural effusion. The mainstay of treatment for this class of diseases until the early 1990s was radiation alone, which resulted in a dismal outcome. The new technologies in radiation therapy (e.g. 3D-CRT) and the shift in paradigm (e.g. omission of ENI) have enabled the dose-escalation, which translated to improved outcome compared to the conventional radiotherapy using 2-D planning. The trials combining chemotherapy with radiotherapy, first sequentially, then concurrently, have changed the standard of care for patients with good functional status to concurrent chemoradiation. Some studies have shown survival benefits to adding consolidative systemic therapy with concurrent chemoradiation. We will outline the development of the current treatment standard of locally advanced NSCLC and present selected topics undergoing active research to forecast the next generation of NSCLC therapy. (*J Lung Cancer* 2006;5(1):1 – 16)

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INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide(1). Roughly 80% of newly diagnosed lung cancers are non-small cell lung cancer (NSCLC) and 35% of NSCLC at diagnosis are locally advanced. Locally advanced NSCLC includes stages IIIA (T3N1 or T1-3N2) and IIIB (T4Nany or TanyN3) and are traditionally considered unresectable. Of these, patients with malignant pleural effusion have particularly poor prognosis and are commonly treated palliatively just as patients with stage IV disease (distant metastasis). The stage III lung cancer patients without "wet disease" (i.e. malignant pleural effusion) are treated with curative intent.

Until the early 1990s, the mainstay care for locally advanced NSCLC was radiotherapy alone, resulting in poor 1, 2, and 5-year survival rates of 40%, 15%, and 5% utilizing a traditional radiation dose and technique(2~5). Based on multiple phase III randomized trials, concurrent chemotherapy with radiotherapy has become the standard of care(6~9). More recently, technological advancements in radiotherapy and novel

chemotherapeutic approaches have shown preliminary data for further improving clinical outcome while minimizing morbidity of therapy.

We will outline the development of the current treatment standard of locally advanced NSCLC and present selected topics undergoing active research to forecast the next generation of NSCLC therapy.

Optimizing Radiation Therapy

Radiation therapy is the primary locoregional modality for locally advanced NSCLC. The relationship between increasing radiation dose with resultant improvements in local control has been well defined(10~15). However, the ability to escalate the dose is limited by the tolerance of adjacent normal structures including the surrounding normal lung parenchyma, spinal cord, heart, and esophagus (Fig. 1). Advancements in the precision of tumor volume definition (e.g. by using PET-CT), better understanding of the patterns of failure (e.g. elimination of elective nodal irradiation), assessment of tumor motion (e.g. gating,

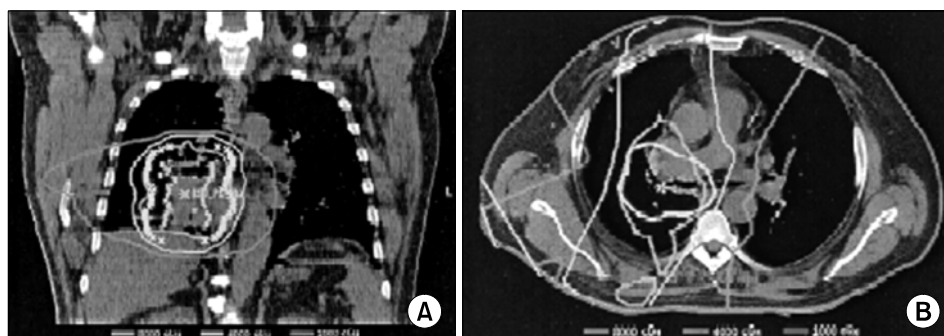


Fig. 1. Three-dimensional treatment plan. (A) Coronal section through isocenter of a typical three-dimensional treatment plan isodose distribution. (B) Axial section at 3.5 cm superior to isocenter for the same patient. The planning target volume is outlined in yellow. The patient had T3 N0 nonsmall cell lung cancer based on disease extension into the right mainstem bronchus. Based on these isodose distributions, the doses were estimated as follows: subcarina, 8,000 cGy; ipsilateral inferior mediastinum, 4,000 cGy; contralateral inferior mediastinum, 1,000 cGy; superior mediastinum and supraclavicular region, 0 Gy.

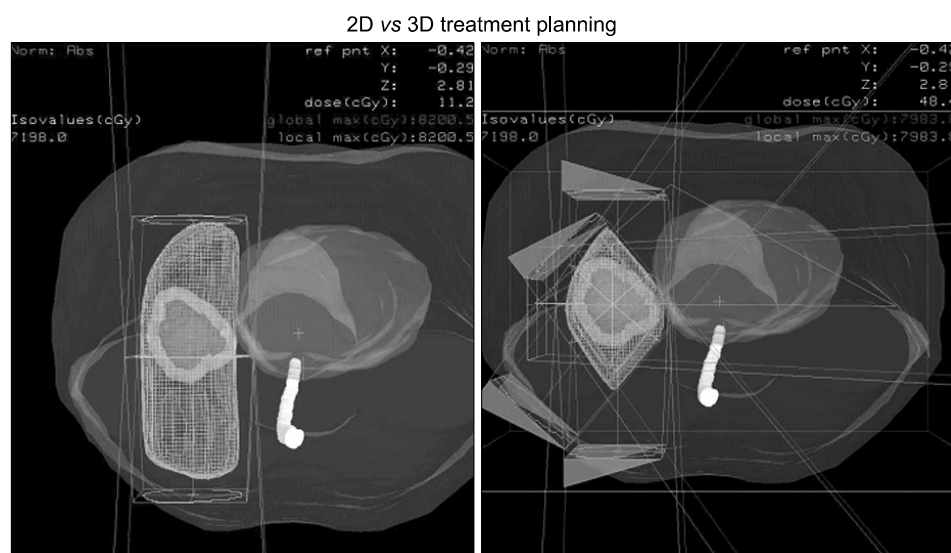


Fig. 2. Compared 2-dimensional radiation treatment planning and 3-dimensional radiation treatment planning.

diaphragmatic immobilization, etc.), and radiation dose distribution/delivery (e.g. 3-D conformal radiotherapy, intensity modulated radiotherapy) should allow us to optimize accurate radiation delivery to the tumor while minimizing the dose to the surrounding normal critical structures. Incorporating these advancements into a combined modality regimen should allow us to escalate dose safely, thereby providing better local control(15~18), ultimately resulting in survival benefits(19~21).

1) Radiation dose

The optimal dose for NSCLC was initially investigated by the RTOG 73-01, which was a four arm randomized controlled trial comparing three different dose levels (40, 50, and 60 Gy) of continuous courses and one 40 Gy split course(22). Among

the continuous course arms, the 60 Gy arm showed the highest clinical/radiographic response rates and the best local control rate. The split course arm showed inferior outcome to the higher dose continuous arms while causing similar number of complications as the 60 Gy arm. Therefore, 60 Gy in conventional fractionation scheme was declared the “standard” dose for comparison. However, even this “standard” resulted in less than satisfactory results with a 5 year overall survival of ~5% (2). Because of the technical limitations of 2D planning and large treatment volumes due to elective nodal irradiation, doses beyond 60 Gy were thought to be too morbid and were not tested.

Arriagada et al. reported only 17% local control based on post-irradiation biopsies following doses of 65 Gy(23). Based

on this data, and the basic principles advocated by Fletcher, it is thought that doses of up to 100 Gy may be required to sterilize the size of tumors frequently treated in locally advanced bronchogenic carcinoma(11).

With the advent of three-dimensional CT-based planning, three-dimensional conformal radiotherapy (3D-CRT), it became possible to escalate the radiation dose beyond that allowed by the conventional methods (Fig. 2). The advantages of 3D treatment planning include the ability to deliver a conformal dose to the tumor volume, delineation of the normal tissues, and thus quantify normal tissue tolerances, and the potential for developing new treatment approaches involving non-coplanar fields in order to dose escalate in an attempt to optimize local control while minimizing the probability of normal tissue complications. Accordingly, several phase I/II radiation dose escalation trials, with or without concurrent chemotherapy, have been performed to determine the maximum tolerated dose (MTD) in this new era of radiation planning and delivery(24~31). These studies have demonstrated that 74~90 Gy can be delivered safely if strict dose-volume limitations are applied to critical structures.

RTOG 93-11(31) was the first multi-institutional study to employ 3D-CRT for lung cancer, and it has successfully escalated dose to 83.8 Gy without concurrent chemotherapy. Another phase I/II trial led by to Radiation Therapy Oncology Group (RTOG 01-17) aims to define the MTD of radiotherapy with concurrent carboplatin and paclitaxel and assess the toxicities and outcomes of this regimen. The study is currently accruing patients to its second phase.

2) Radiation volume

The traditional approach to primary lung irradiation involved the inclusion of the primary tumor and regional nodes including: the ipsilateral hilum, ipsilateral supraclavicular lymph nodes, and bilateral mediastinum with a 2 cm margin regardless of whether they were clinically involved. This technique, called elective nodal irradiation (ENI), is of unproven benefit and can significantly add to the morbidity of thoracic radiation in a population with limited pulmonary reserve(32). A phase I study at University of Michigan treated patients with NSCLC with increasing dose of radiation based on the effective volume of lung irradiated (V_{eff})(28). The escalation of dose up to 92.4 Gy was made possible for select group of patients with omission

of ENI. They saw no obvious negative effect due to exclusion of ENI (e.g. untreated mediastinum as the sole site of first failure) and concluded that the utility of ENI is questionable given our inability to control gross disease and the absence of data to support its benefit.

A retrospective analysis of 171 patients treated with 3D-CRT at Memorial Sloan Kettering Cancer Center, the 2-year actuarial rates of elective nodal control and primary tumor control were 91% and 38% respectively(33). Thus their conclusion was that local control is the biggest challenge in treating patients with radiation therapy and that the omission of ENI did not result in a significant amount of failure in those areas.

Based on the available literature, it appears reasonable to omit elective nodal irradiation given its associated morbidity and the limitations it places on dose escalation. In addition, the primary site of failure remains within the gross tumor volume, and until further improvements are made in controlling regions of known disease, there is probably no need for elective nodal irradiation. It is our policy to include the regional lymph nodes only if they are radiographically involved.

Accounting for respiratory motion of lung cancer is an active area of research. The conventional approach is to contour a margin around the gross tumor volume (GTV) to account for the tumor's internal motion (ITV) (Fig. 3). The disadvantage of this method is the unwanted dose delivered to the normal tissue, leading to complication, thereby limiting dose escalation. There are now a few different approaches to maximize the dose delivery to the tumor while minimizing the normal tissue irradiated. Breath-holding and abdominal compression (often in the context of SBRT) attempt to artificially minimize the tumor motion to provide a stationary target for radiotherapy(34~39). Other approaches let the patient breathe freely and use either respiratory gating(40) or fiducial tracking(41) to deliver the dose to tumor only. Although abdominal compression is the most commonly used method currently, all of these approaches are in their preliminary stages and no one method is accepted as the standard.

3) Fractionation

The superiority of continuous daily fractionation over a split course was proven early in RTOG 73-01 as discussed earlier(22). A few studies have since shown benefits of hyper-fractionated radiotherapy (HART) given up to three-times daily

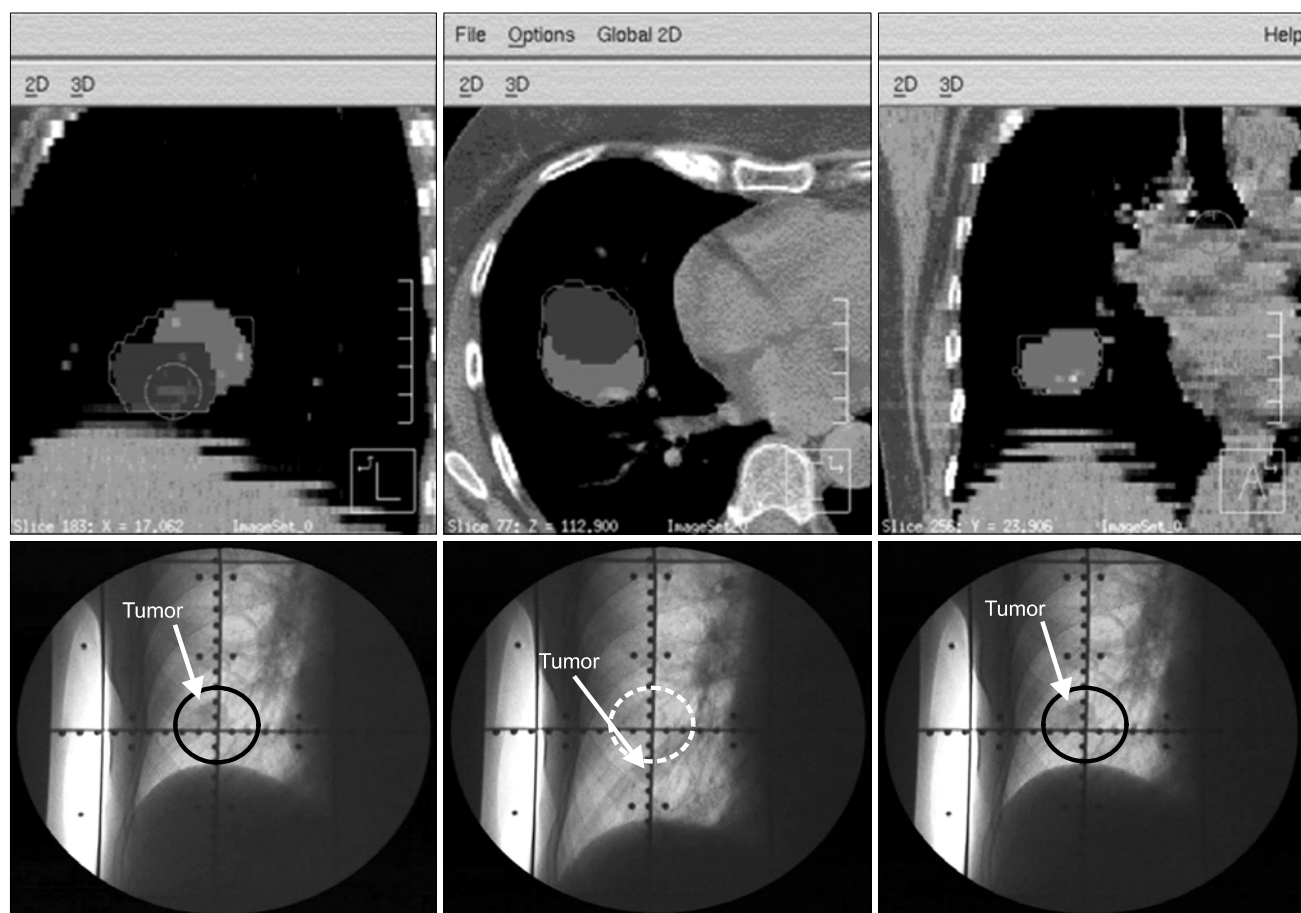


Fig. 3. Tumor is moving by respiration.

over once-daily conventional fractionation(42~44). In particular, the Continuous Hyperfractionated Accelerated Radiotherapy Trial (CHART)(42) showed a significant improvement in the 2 and 3 year survival with hyperfractionated accelerated regimen (three-times daily radiation of 1.5 Gy over 12 consecutive days to the total dose of 54 Gy) over the conventional scheme (60 Gy in 30 daily fractions). This benefit in survival, however, was somewhat offset by an increased incidence of esophagitis (19 vs. 3%), pneumonitis (19 vs. 3%), and transient radiation myelitis (8 vs 0%).

Despite the improvements in survival noted in these trials (not reaching statistical significance in Eastern Cooperative Oncology Group (ECOG) 2597(43) and Intergroup trial(44)) the question of whether HART, which also comes with significantly higher toxicity, should supplant the current standard of daily radiation given concurrently with chemotherapy, has been in question (Table 1).

The RTOG 94-10 trial appears to have settled this debate(7,

45). This trial randomized 610 patients with stage II/III NSCLC to three arms: (A) a sequential chemoradiation arm (SEQ) with cisplatin/vinblastine followed by 60 Gy radiation, (B) a concurrent chemoradiation arm (CON-QD) utilizing the same regimens as SEQ arm, but given concurrently, (C) or a concurrent hyperfractionated chemoradiation arm (CON-BID) using cisplatin/etoposide given concurrently with twice-daily radiation to a total dose of 69.6 Gy. CON-QD arm had a statistically significant improvement over SEQ arms in survival. However there was no significant difference in survival between the CON-BID and SEQ arms. The grade 3~5 acute toxicity, including esophagitis, was highest in the CON-BID arm, and there was a trend towards higher late complications with CON-BID arm.

HART is a difficult treatment regimen to employ logistically. It is further complicated by the addition of concomitant chemotherapy, which is the standard approach for locally advanced NSCLC. Also, the increased morbidity of this aggressive

Table 1. Multicenter Phase III Randomized Controlled Trials of Altered Fractionated Radiotherapy

Study	Sequence	Patients	RT dose (Gy)	CT	Fraction size (Gy)/Schedule	Local-regional 3 yr (%)	Control 5 yr (%)	Median survival (months)	Overall Survival 3 yr (%)	Survival 5 yr (%)	Toxicity (acute) $\geq$ grade 3 esophagitis
CHART	tidRT	338	54	N/A	1.5 TID	n.r.	n.r.	n.r.	21	n.r.	19
Saunders et al. [34]	qdRT	225	60	N/A	2 QD	n.r.	n.r.	n.r.	13	n.r.	3
ECOG 2597	tidRT	60	57.6	N/A	1.5 TID	n.r.	n.r.	20.3	34	n.r.	25
Belani et al [35]	qdRT	59	64	N/A	2 QD	n.r.	n.r.	14.9	14	n.r.	16
RTOG 9410	CT→qdRT	201	60	CDDP/ vinblastine	2 QD			14.6	n.r.	10	4
Curran et al. [7]	CT+qdRT	201	60	CDDP/ vinblastine	2 QD			17	n.r.	16	23
	CT+bidRT	193	69.6	CDDP/ etoposide	1.2 BID			15.1	n.r.	13	46
Cumulative qdRT		284	60~64	N/A	2 QD			14.9	13.2	n.r.	5.7
Cumulative tidRT		398	54→57.6	N/A	1.5 TID			20.3	23	n.r.	20
Cumulative CT→qdRT		201	60	CDDP/ vinblastine	2 QD			14.6		10	4
Cumulative CT+qdRT		201	60	CDDP/ vinblastine	2 QD			17		16	23
Cumulative CT+bidRT		193	69.6	CDDP/ etoposide	1.2 BID			15.1		13	46

approach, and difficulty of this patient population (predominantly elderly) would have in complying with this regimen preclude its routine use. However, given its superior local control, HART still remains an option for patients who may not be able to tolerate systemic chemotherapy.

Optimizing Combined Modality Therapy

Radiation alone has been the standard of care for locally advanced NSCLC despite the dismal survival data(2). During the early 1990s, the results of multiple randomized phase III studies became known and they shifted the standard to concurrent chemoradiation. We will describe the key trials that led to the evolution of locally advanced NSCLC treatment.

1) Sequential chemoradiation vs. radiation alone

With sequential chemoradiation, the ‘full doses’ of both modalities are delivered without compromise. The rationale behind the sequential combination of chemotherapy and radiation is based on the premise that radiotherapy addresses the locoregional disease while chemotherapy acts systemically to

eradicate micrometastases. Multiple phase III randomized controlled trials have shown survival benefit with the addition of sequential chemotherapy to locoregional radiation(44,46~48). The Cancer and Leukemia Group B (CALGB) 8433 trial randomly assigned 155 patients with clinical stage III NSCLC to a conventionally fractionated course of radiation therapy to a total dose of 60 Gy with or without induction chemotherapy with cisplatin/vinblastine(47). This study showed a statistically significant improvement in the median survival of 13.7 months over 9.6 months with sequential chemoradiation over radiation alone. The 5 year survival rate tripled with combined modality therapy over radiation alone (17% vs. 6%).

The CEBI 138 trial by Le Chevalier et al (also known as IGR or French trial) randomized 353 patients to either a conventionally fractionated course of thoracic radiotherapy to a total dose of 65 Gy or sequential chemoradiation given on a sandwich schedule of 3 monthly cycles of induction chemotherapy consisting of vindesine, cyclophosphamide, cisplatin, and lomustine (VCPC), followed by the same course of thoracic radiotherapy, followed by 3 additional monthly cycles of VCPC (48,49). Again there was a statistically significant benefit in 3

Table 2. Multicenter Phase III Randomized Controlled Trials Comparing Sequential Chemoradiation vs. Radiation Alone

Study	Sequence	Patients	RT dose (Gy)	CT	Local-regional 3 yr (%)	Control 5 yr (%)	Median survival (months)	Overall 3 yr (%)	Survival 5 yr (%)	Toxicity (acute) $\geq$ grade 3
CALGB 8433	qdRT	77	60	N/A	6	5	9.6	6	6	7
Dillman et al. [47]	CT→RT	78	60	CDDP/ vinblastine	18	6	13.7	24	17	3
RTOG 8808	qdRT	152	60	N/A	n.r.	n.r.	11.4	11	5	1
Sause et al. [36]	CT→RT	152	60	CDDP/ vinblastine	n.r.	n.r.	13.8	17	8	1
	bidRT	154	69.9	N/A	n.r.	n.r.	12.3	14	6	3
CEBI 138	qdRT	167	65	N/A	17 (1 yr)	17 (1 yr)	10	4	3	3
Le Chevalier et al. [49]	CT→RT	165	65	VCPC	15 (1 yr)	15 (1 yr)	12	12	6	5
Cumulative QD-RT		396	60~65	N/A	n.r.	n.r.	10.5	7	4.4	3
Cumulative SEQ		395	60~65	See above	n.r.	n.r.	13	16.2	9	3.1
Cumulative BID-RT		154	69.9	N/A	n.r.	n.r.	12.3	14	6	3

year survival rate with sequential chemoradiation over radiation alone (12% vs. 4%) that appeared to be related to the relative risk reduction of distant metastases by 50%.

These findings were validated by the the intergroup trial of RTOG, ECOG, and Southwest Oncology Group (RTOG 88-08, ECOG 4588, SWOG 8892) by Sause et al(44). This was a three arm trial which randomized 452 patients with unresectable NSCLC to one of two radiation alone arms (daily to 60 Gy or twice-daily to 69.6 Gy) or to the third arm of induction cisplatin/vinblastine followed by a daily radiotherapy to 60 Gy, in the same manner as the CALGB 8433 trial(47). Similar to the CALGB trial, there was a statistically significant improvement in median survival seen with sequential chemoradiation therapy over radiation alone.

These three landmark trials consistently demonstrated a significant benefit in survival with the addition of induction chemotherapy over conventional or hyperfractionated radiation alone (Table 2)(44,47,48). As expected, induction chemotherapy appeared to reduce the number of distant relapses which translated into a modest benefit in survival. Based on these studies, sequential chemoradiation became the basis for comparisons in clinical trials of the 1990s.

2) Concurrent vs. sequential chemoradiation

The mechanism of chemotherapeutic radiosensitization is thought to be direct inhibition of radiation-induced damage repair, elimination of radioresistant, chemosensitive clones, or

suppression of inter-fraction tumor repopulation. Concurrent chemoradiation could potentially allow us to address both the distant and locoregional disease simultaneously. Both modalities should act synergistically on tumor clonogens susceptible to either modality, and in a complementary fashion on locoregional clonogens that are susceptible to one or the other (50~52). A number of phase III randomized trials have shown a statistically significant improvement in median survival with the concurrent approach; however, this aggressive strategy has also led to an increase in the incidence and severity of treatment related toxicities(6~9).

The West Japan Lung Cancer Group (WJLCG) randomized 314 patients with locally advanced NSCLC to receive either concurrent or sequential chemoradiation(6). For both arms, the chemotherapy consisted of mitomycin, vindesine, and cisplatin (MVP). The radiotherapy for the concurrent arm was a split course of 56 Gy while it was given continuously in the sequential arm. This trial revealed a statistically significant improvement in median survival (16.5 vs. 13.3 months), 5-year survival (15.8 vs 8.9%), and response rate (84 vs 66%). On further analysis, the survival benefit came from superior local control as evidenced by longer local-failure free survival (30 vs. 11 months). Distant failure rates were similar at approximately 50%, thereby suggesting that the benefits of concurrent chemoradiation is derived from radiosensitization and improved local control. It is noteworthy that the concurrent arm had significant survival benefit despite the fact that the less efficacious split

course was given in that arm.

The RTOG 94-10 was a phase III randomized trial of 610 patients with unresectable stages II/III NSCLC(7,45). As discussed earlier, it attempted to settle two questions by comparing sequential vs. concurrent chemoradiation and daily vs. twice-daily radiation (*see the section on Radiation Fractionation*). There was a statistically significant improvement in median survival (17.0 vs. 14.6 months; $p=0.0038$) and 4 year survival rate (21 vs 12%; $p=0.046$) in the CON-QD arm over the SEQ arm. The incidence of acute grade 3~5 toxicities was significantly higher in the CON-BID and CON-QD arms (67% and 55%, respectively) over that of the SEQ arm of 35%. However the differences in late effects were not statistically significant.

The GLOT-GFPC NPC 95-01 compared sequential vs. concurrent chemoradiation by randomizing 201 patients with unresectable stage III NSCLC. This French trial utilized three

cycles of cisplatin/vinorelbine given either as induction or concurrently with a course of 66 Gy radiation(8). The concurrent arm also received two additional cycles of consolidation chemotherapy with cisplatin/vinorelbine. Although there was an improvement in median survival (16.3 vs. 14.5 months) and four-year survival rate (21 vs. 14%), these were not statistically significant. The study by itself is thought to have been underpowered to detect the survival difference, but taken together with other studies comparing concurrent vs. sequential chemoradiation, it further supports the superiority of concurrent chemoradiation course.

The Czech Republic study by Zatloukal et al was a randomized trial of 102 patients treated with either cisplatin/vinorelbine given either as induction or concurrently with conventionally fractionated thoracic radiotherapy to a total dose of 60 Gy(9). The radiotherapy was begun after the 4th and final

Table 3. Multicenter Phase III Randomized Controlled Trials Comparing Concurrent With Sequential Chemoradiotherapy

Study	Sequence	Patients	RT dose (Gy)	CT	Local-regional 3 yr (%)	Control 5 yr (%)	Median survival (months)	Overall 3 yr (%)	Survival 5 yr (%)	Toxicity (acute) $\geq$ grade 3 esophagitis (%)
West Japan Lung Cancer Group (WJLCG)	CT→qdRT	158	56	MVP	n.r.	n.r.	13.3	15	9	2
Furuse et al. [50]	CT+qdRT	156	56 (split)	MVP	n.r.	n.r.	16.5	22	16	3
RTOG 9410	CT→qdRT	201	60	CDDP/vinblastine	n.r.	n.r.	14.6	n.r.	10	4
Curran et al. [7]	CT+qdRT	201	60	CDDP/vinblastine	n.r.	n.r.	17	n.r.	16	23
	CT+bidRT	193	69.6	CDDP/etoposide	n.r.	n.r.	15.1	n.r.	13	46
GLOT-GFPC NPC 95-01	CT→qdRT	101	66	CDDP/vinorelbine	38	37 (4 yr)	14.5	19	14 (4 yr)	3
Fournel et al. [8]	CT+qdRT→CT	100	66	CDDP/etoposide → CDDP/vinorelbine	57	55 (4 yr)	16.3	25	21 (4 yr)	32
Czech republic study	CT→qdRT	50	60	CDDP/vinorelbine	40%	n.r.	12.9	9.5	n.r.	4
Zatloukal et al. [9]	CT+qdRT	52	60	CDDP/vinorelbine	58%	n.r.	16.6	18.6	n.r.	18
Cumulative SEQ	CT→qdRT	510	56-66				14			3.2
Cumulative CON-QD	CT+qdRT	509	56-66				16.7			18.1
Cumulative CON-BID	CT+bidRT	193	69.6				15.1			46

cycle of chemotherapy in the sequential arm, and during the 2nd cycle in the concurrent arm. There was a significant improvement in median survival (16.6 vs. 12.9 months) and time to progression (11.9 vs. 8.5 months) with the concurrent approach. There was also a significant improvement in overall response rate of 80% vs. 47% with the concurrent approach. However, the concurrent arm was associated with greater toxicity with a significant increase in leukopenia (53% vs 19%), nausea/vomiting (39% vs. 15%), and esophagitis (17.6% vs. 4.2%).

Taking the results of these studies as a whole (Table 3), there is a consistent improvement in survival with concurrent chemoradiation over a sequential course, directly related to improved locoregional control. Unfortunately, this aggressive approach is also associated with increased toxicity, primarily grade 3~4 esophagitis. The results from these trials established concurrent chemoradiation therapy as the standard for locally advanced NSCLC.

3) Concurrent chemoradiation with induction or consolidation

While the benefits of sequential chemoradiation over radiation alone stems from improved systemic control, the concurrent chemoradiation seems to improve locoregional control over the sequential regimen. A few large phase II/III trials were subsequently performed to utilize both of these aspects by combining concurrent chemoradiation with either induction or consolidation chemotherapy(53~58).

SWOG 9019 was a phase II trial that confirmed the feasibility and long-term survival from full-dose chemotherapy of cisplatin/etoposide given during and after 61 Gy radiotherapy(54). Among 50 patients with pathologically confirmed stage IIIB NSCLC, this treatment strategy resulted in the median survival of 15 months and 3-year survival of 17%. SWOG 9504 was the follow-up study to SWOG 9019 that treated 83 patients with pathologic stage IIIB NSCLC using the similar strategy of concurrent chemoradiation followed by consolidative chemotherapy(55). The only difference in the SWOG 9504 treatment scheme was the use of three cycles of docetaxel instead of two cycles of cisplatin/etoposide for consolidation. The median survival and 3-year survival rate improved to 26 months and 37%, respectively. This regimen was well tolerated with the majority of patients receiving all

three cycles of consolidative chemotherapy. The Hoosier Oncology Group is currently conducting a phase III randomized trial (LUN 01-24) comparing the regimens of SWOG 9019 and 9504.

The CALGB 39801 randomized 366 unresectable stage III NSCLC patients treated with concurrent chemoradiation with carboplatin/paclitaxel to either 2 cycles to full-dose induction with carboplatin/paclitaxel prior to chemoradiation or immediate chemoradiation(57). The survival outcomes (median survival 11.4 to 14.6 months and 1-year survival of 48 to 58%) were similar between the two arms and somewhat inferior to those of other published trials. The study, therefore, did not support the use of induction chemotherapy prior to concurrent chemoradiation.

The American College of Radiology (ACR) 427 trial, better known as LAMP (Locally Advanced Multimodality Protocol), was a phase II trial that randomized 256 patients with unresected stage III NSCLC to one of three arms to determine the optimal sequencing of carboplatin/paclitaxel chemotherapy and daily radiation to 63 Gy(58). The randomization arms were: (A) chemotherapy followed by radiotherapy alone (sequential), (B) chemotherapy followed by concurrent chemoradiation (induction/concurrent), and (C) concurrent chemoradiation followed by chemotherapy (concurrent/consolidation). This trial, first designed in pre-concurrent-chemoradiation era, suffered from poor accrual because of the sequential arm and terminated before enrolling the target number of patients. Nonetheless, it addresses a very important question by being the only large trial directly comparing induction vs. consolidation in the setting of concurrent chemoradiation. With a median follow-up time of 39.6 months, the median overall survival was 13.0, 12.7, and 16.3 months, respectively, favoring the concurrent/consolidation arm. The authors concluded that the concurrent/consolidation scheme offered the best outcome although it was also associated with greater toxicity.

In conclusion, the results of the LAMP and SWOG 9504 trials(55,58) suggest a benefit of consolidation chemotherapy in the setting of concomitant chemoradiation although phase III data are lacking (Table 4).

4) Optimal chemotherapy regimen

Various regimens of chemotherapy have been used with mixed success in the setting of concurrent chemoradiation for

Table 4. Phase II Trials Comparing Induction or Consolidation Chemotherapy With Concurrent Chemoradiotherapy

Study	Sequence	Patients	RT dose (Gy)	CT	Local-regional 3 yr (%)	Control 5 yr (%)	Median survival (months)	Overall survival 3 yr (%)	Survival 5 yr (%)	Toxicity (acute) $\geq$ grade 3 esophagitis (%)
CALGB 39801	CT→CT+qdRT		66	CBGD/ paclitaxel						
Vokes et al. [57]	CT+qdRT		66	CBGD/ paclitaxel						
LAMP	CT→qdRT	201	60	CDDP/ vinblastine	n.r.	n.r.	14.6	n.r.	10	4
Belani et al. [58]	CT+qdRT	201	60	CDDP/ vinblastine	n.r.	n.r.	17	n.r.	16	23
	CT+bidRT	193	69.6	CDDP/ etoposide	n.r.	n.r.	15.1	n.r.	13	46
SWOG 9504	CT→qdRT	101	66	CDDP/ vinorelbine	38	37 (4 yr)	14.5	19	14 (4 yr)	3
Gandara et al. [55]	CT+qdRT→CT	100	66	CDDP/ etoposide → CDDP/ vinorelbine	57	55 (4 yr)	16.3	25	21 (4 yr)	32
Czech Republic Study	CT→qdRT	50	60	CDDP/ vinorelbine	58%	n.r.	12.9	9.5	n.r.	4
Zatloukal et al. [9]	CT+qdRT	52	60	CDDP/ vinorelbine	40%	n.r.	16.6	18.6	n.r.	18
Cumulative SEQ	CT→qdRT	510	56~66				14			3.2
Cumulative CON-QD	CT+qdRT	509	56~66				16.7			18.1
Cumulative CON-BID	CT+bidRT	193	69.6				15.1			46

locally advanced NSCLC (Table 5). However, paucity of data exists for comparing different chemotherapeutic regimen for locally advanced NSCLC. A few trials to comparing chemotherapeutic regimens were done in the setting of metastatic or “wet” NSCLC(59~67). One hopes to make an inference from these trials to guide the selection chemotherapeutic regimen for locally advanced NSCLC. However, no one chemotherapeutic regimen has emerged as clearly more efficacious than others. Currently, the most commonly used regimen is platinum-based doublet given concurrently with the radiotherapy. The decision to use one particular regimen over others is often made on the basis of secondary factors such as cost, availability, logistical convenience, ease of administration, toxicity profile, and physician’s familiarity.

5) Modulation of chemoradiation toxicity

Concurrent chemoradiation has provided us with a significant survival benefit in locally advanced NSCLC at the cost of

increased toxicity. Radioprotectors are an attractive way to reduce the morbidity associated with combined modality therapy, which should not only reduce the toxicity, but also allow dose-escalation to improve local control and survival. One particular agent, amifostine (WR-2721), has shown significant benefits in preventing xerostomia in the head and neck cancer setting(68). Amifostine is thought to act primarily by scavenging free radicals released during the interaction of ionizing radiation and water. Amifostine theoretically protects normal tissue preferentially, thus increasing the therapeutic window. So far, four phase III randomized studies have been performed with amifostine in the setting of lung cancer and results have been widely conflicting(69~72).

The RTOG 98-01(72) is the largest and most important among them. This was a cooperative group phase III trial which specifically tested the ability of amifostine to reduce esophagitis secondary to concurrent chemoradiation. 243 patients with stages II/III NSCLC treated with induction and concurrent

Table 5. Selected Chemotherapy Schemes in Multicenter Trials Studying Chemoradiation

Study	Patients	RT dose (Gy)	CT	Fraction (Gy)	Size	Median survival (months)	Toxicity (acute) $\geq$ grade 3 esophagitis
RTOG 9410 [7]	CT→qdRT	201	60	CDDP/vinblastine	2 QD	14.6	4
CALGB 8433 [46]	CT→qdRT	78	60	CDDP/vinblastine	2 QD	13.7	3
RTOG 8808 [36]	CT→qdRT	152	60	CDDP/vinblastine	2 QD	13.8	1
CEBI 138 [48]	CT→qdRT	165	65	VCPC	2 QD	12	5
WJLCG [6]	CT→qdRT	158	56	MVP	2 QD	13.3	2
GLOT-GFPC [8]	CT→qdRT	101	66	CDDP/vinorelbine	2 QD	14.5	3
Czech Republic [9]	CT→qdRT	50	60	CDDP/vinorelbine	2 QD	12.9	4
LAMP [58]	CT→qdRT	201	60	CDDP/vinblastine	2 QD	14.6	4
SWOG 9504 [55]	CT→qdRT	101	66	CDDP/vinorelbine	2 QD	14.5	3
RTOG 9410 [7]	CT+qdRT	201	60	CDDP/vinblastine	2 QD	17	23
WJLCG [6]	CT+qdRT	156	56 (split)	MVP	2 QD	16.5	3
GLOT-GFPC [8]	CT+qdRT	100	66	CDDP/etoposide	2 QD	16.3	32
Czech Republic [9]	CT+qdRT	52	60	CDDP/vinorelbine	2 QD	16.6	18
LAMP [58]	CT+qdRT	201	60	CDDP/vinblastine	2 QD	17	23
SWOG 9504 [55]	CT+qdRT	100	66	CDDP/etoposide	2 QD	16.3	32
CALGB 39801 [57]	CT+qdRT	184	66	CBCD/paclitaxel	2 QD	14.1	n.r.
CALGB 8433 [46]	qdRT	77	60	CDDP/vinblastine	2 QD	9.6	7
RTOG 8808 [36]	qdRT	152	60	CDDP/vinblastine	2 QD	11.4	1
CEBI 138 [48]	qdRT	167	65	VCPC	2 QD	10	3
Cumulative	CT→qdRT	1207	56–66		2 QD	13.8	3.3
Cumulative	CT+qdRT	994	56–66		2 QD	16.2	21
Cumulative	qdRT	396	60–65		2 QD	10.5	3

chemotherapy (carboplatin/paclitaxel) with hyperfractionated radiotherapy to 69.6 Gy were randomized to with or without amifostine. There was a significant increase in the rate of nausea/vomiting, cardiovascular toxicity, and infection/febrile neutropenia with amifostine, and no difference in the rate of grade 3–5 esophagitis. Patient subjectively reported improvement in swallowing dysfunction with amifostine, but quality of life (QoL) measures were not statistically different, except improved pain control with amifostine. Amifostine did not impact the treatment compliance or survival.

Other amifostine trials with positive results(69,70) in general had better administration schedule such as more frequent dosing closer to the treatment time. The plausibility of such frequent, strict dosing of this expensive drug in routine clinical setting has not been studied.

Frontiers of NSCLC Research

Although we have made some improvement in treatment of

locally advanced NSCLC in the past two decades, there is still large room for improvement as evidenced by continued poor prognosis. In the following section, we will present the selected topics of current research.

1) Stereotactic body radiotherapy (SBRT) for inoperable stage I lung cancer

One exciting new treatment option for NSCLC is being studied by RTOG 02-36. Based on the favorable single-institution studies and combined analyses that showed promising outcomes for medically inoperable stage I NSCLC, this multi-institutional study attempts to answer whether radiotherapy with high biological dose with limited treatment volume (i.e. SBRT) can achieve satisfactory local control $\geq$ 80% in that select population(73–78). The application of SBRT technique to locally advanced NSCLC, however, is usually prohibitive due to the large treatment volumes that are often necessary.

2) Molecular targeted combined modality therapy

Molecular targeted therapy is a novel strategy borne from our mounting understanding of the underlying pathways and key molecules involved in tumor growth and progression. Theoretically, the specificity of molecular targeted therapy should improve the therapeutic window by affecting the tumor cells and sparing normal cells. Epidermal growth factor receptor (EGFR) is an important mediator of growth-factor signaling pathways that affect normal cell proliferation, motility, adhesion, and survival as well as angiogenesis. EGFR is highly expressed in many solid tumors, and there have been reports correlating high expression of EGFR with poor prognosis(79, 80).

Gefitinib (Iressa, ZD 1839; AstraZeneca), an inhibitor of EGFR tyrosine kinase activity, was the first targeted agent to be approved for advanced NSCLC. Two phase II trials, IDEAL 1(81) and IDEAL 2(82), showed that gefitinib had anti-tumor activity as a 2nd or 3rd line therapy. However, in two large phase III trials looking at gefitinib as a first line therapy, INTACT 1(83) and INTACT 2(84), the results have been largely disappointing.

Another drug that is showing some promise for targeted molecular therapy is cetuximab (Erbix, C225; ImClone Systems Inc.). It is a chimeric antibody to IgG₁ subclass with five-fold greater affinity than the murine monoclonal antibody. It works by blocking the binding of EGF to EGFR and TGF α and suppressing the downstream activity. Recently reported preliminary results of a phase III randomized trial shows that cetuximab offered statistically significant overall and median survival when combined with concurrent chemoradiation for head and neck cancer(85). The efficacy of cetuximab for stage III NSCLC in combination with chemoradiation consisting of carboplatin/paclitaxel with daily fractionated radiotherapy is being studied by RTOG 03-24 phase II study. The study has completed planned accrual and is awaiting maturation.

3) Integration of molecular imaging

While CT and magnetic resonance imaging (MRI) have become routine diagnostic modalities used for the management of lung cancer, significant advances have been made in functional and molecular imaging modalities. Positron emission tomography (PET), most often with 18-fluorodeoxyglucose (FDG), is being used in multiple facets of lung cancer

management. It can aid in evaluating solitary pulmonary nodule (SPN)(86-88), staging of lung cancer(89~91), and restaging after neoadjuvant therapy(92,93).

Additional information acquired from PET scans often alter the treatment plan for radiation by either by omission of biologically inactive nodule/ atelectasis or by inclusion otherwise-occult tumor. Small studies have shown that the radiation portals are changed significantly in 36 to 62% of patients when PET scans are utilized routinely(94~97). RTOG is planning a multi-institution study (RTOG 05-15) to compare NSCLC gross tumor volume definitions with or without FDG-PET fusion.

The need to evaluate the patient's response to first-line therapy is greater now that more options, which can be very toxic and costly, for second-line therapy exist. Several studies have shown the role of FDG-PET in assessing response to chemotherapy or radiation therapy(98~101). The American College of Radiology Imaging Network (ACRIN), in a joint-effort with RTOG, is conducting a multi-institution non-randomized study (ACRIN 6668 / RTOG 0235) to determine the utility of FDG-PET for locally advanced NSCLC. The study recently opened and is in its accrual phase.

CONCLUSION

Locally advanced NSCLC is a heterogeneous group of bronchogenic malignancies that are traditionally thought to be unresectable without overt distant metastasis or malignant pleural effusion. The mainstay of treatment for this class of diseases until the early 1990s was radiation alone, which resulted in a dismal outcome(2). The new technologies in radiation therapy (e.g. 3D-CRT) and the shift in paradigm (e.g. omission of ENI) have enabled the dose-escalation(24~31,32) which translated to improved outcome compared to the conventional radiotherapy using 2-D planning.

The trials combining chemotherapy with radiotherapy, first sequentially(44,46~48), then concurrently(6~9), have changed the standard of care for patients with good functional status to concurrent chemoradiation. Some studies have shown survival benefits to adding consolidative systemic therapy with concurrent chemoradiation(55,58).

It is still unclear what the optimal combination, dose, and schedule is for locally advanced NSCLC. Platinum-based

doublet regimens are most commonly used for chemotherapy although the choice is not based on a phase III randomized trial data. Molecular targeted therapy holds the promise of specificity beyond any systemic chemotherapeutic regimen, but again further work is necessary to determine its utility as a first-line therapy for locally advanced NSCLC.

Exciting new research for NSCLC is now possible largely owing to advances in technology and molecular biology such as image guided stereotactic body radiotherapy for early stage inoperable disease, use of molecular therapy for better targeting tumors, and incorporation of functional imaging. However, investigations introduced in this article are by no means comprehensive. For example, active research is being done to evaluate the role of prophylactic cranial irradiation (PCI) in NSCLC.

Lastly, one should continue to be reminded that cigarette smoking continues to be overwhelmingly dominant cause of lung cancer. Public health policy, especially one targeting to educate the adolescents on the harms of tobacco smoking, will have a bigger impact on lung cancer mortality than any scientific research.

The old Korean adage "With dust you can build a mountain" rings true in the approach to locally advanced NSCLC. Over the span of 25 years we have seen a slow, incremental, but significant improvement in the 5-year survival from 5% with radiation alone in the early 1980s(2) to around 20% with concurrent chemoradiation with consolidative therapy(55). Admittedly, there is vast room for improvement, but the future holds promise with greater understanding of the underlying mechanisms of lung cancer, continued advancement of technology, and innovative treatment approaches to lead the way.

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