J Korean Soc Ther Radiol Oncol 2004;22(1):1~10

Multidisciplinary Management of the Locally Advanced Unresectable Non-Small Cell Lung Cancer

Kwan Ho Cho, M.D.

Research Institute and Hospital, National Cancer Center, Gyeonggi-do, Korea

Locally advanced (Stage III) non-small cell lung cancer (NSCLC) accounts for approximately one third of all cases of NSCLC. Few patients with locally advanced NSCLC present with disease amenable to curative surgical resection. Historically, these patients were treated with primary thoracic radiation therapy (RT) and had poor long term survival rates, due to both progression of local disease and development of distant metastases.

Over the last two decades, the use of multidisciplinary approach has improved the outcome for patients with locally advanced NSCLC. Combined chemoradiotherapy is the most favored approach for treatment of locally advanced unresectable NSCLC. There are two basic treatment protocols for administering combined chemotherapy and radiation, sequential versus concurrent. The rationale for using chemotherapy is to eliminate subclinical metastatic disease while improving local control. Sequential use of chemotherapy followed by radiotherapy has improved median and long term survival compared to radiation therapy alone. This approach appears to decrease the risk of distant metastases, but local failure rates remain the same as radiation alone.

Concurrent chemoradiotherapy has been studied extensively. The potential advantages of this approach may include sensitization of tumor cells to radiation by the administration of chemotherapy, and reduced overall treatment time compared to sequential therapy; which is known to be important for improving local control in radiation biology. This approach improves survival primarily as a result of improved local control. However, it doesn't seem to decrease the risk of distant metastases probably because concurrent chemoradiation requires dose reductions in chemotherapy due to increased risks of acute morbidity such as acute esophageal toxicity.

Although multidisciplinary therapy has led to improved survival rates compared to radiation therapy alone and has become the new standard of care, the optimal therapy of locally advanced NSCLC continues to evolve. The current issues in the multidisciplinary management of locally advanced NSCLC will be reviewed in this report.

Introduction

More than 10 million new cases of cancer were diagnosed with cancer and 6.2 million were died of cancer around the world in year 2000.[1] It is known that lung cancer is the leading cause of cancer death in the majority of countries. Looking at the cancer statistics, lung cancer is the second most common cancer for both of men and women, but is the most common cause of cancer death in the USA,[2] and so as in Korea.[3] Lung cancer is, therefore, a serious health problem around the world and there is urgent need for effective treatment.

The term of "locally advanced" in non-small cell lung cancer (NSCLC), generally implies stage III disease. The term of "unresectable" usually implies most of stage III disease but some of potentially resectable disease. It is estimated that 30% of NSCLC patients have stage III at initial presentation. Stage

Submitted February 11, 2004
Presented as a plenary lecture at the 6th International Conference of The Asian Clinical Oncology Society (ACOS), June 10-13, 2003, Seoul, Korea
Reprint request to Kwan Ho Cho, Research Institute and Hospital, National Cancer Center, 809 Madu 1-dong, Ilsan-gu, Goyang-si, Gyeonggi-do 411-764, Republic of Korea
Tel: 031)920-1720, Fax: 031)920-0149
E-mail: kwancho@ncc.re.kr

III disease is further subdivided into IIIA and IIIB. Generally, stage IIIA is considered as potentially resectable, while those with stage IIIB is not. Therefore, individuals with stage III comprise a very heterogeneous group of patients with a wide range of prognoses according to disease extent and other important prognostic parameters such as Karnofsky performance status (KPS) and history of body weight loss. For instance, 5 year survival rates among stage III NSCLC patients vary from 30~40% for patients with T3N1 (IIIA) to 5% for those with T4N3 (IIIB). Therefore, pretreatment prognostic factors (stage, KPS, weight loss) can dominate patients' outcome over treatment itself. Hence, treatment effect can be tested only through a well designed phase III randomized trials after a strict stratification for potential prognostic parameters. Looking at the data in the literature, interpretation and comparison of data between even well designed trials is difficult for many reasons. Firstly, there have been several changes in the staging system over time. Secondly, no standards exist regarding the staging work up, extent of surgical resection, the dose and fractionation scheme of radiation therapy, or regimen, doses and combination of chemotherapy. In this review, however, it has been attempted to draw some reasonable conclusions after reviewing well designed randomized trials using multidisciplinary management for locally advanced NSCLC over the last two decades.

Radiation Therapy as a Sole Treatment

Historically, locally advanced NSCLC has been treated with primary thoracic radiation therapy (RT) alone. While this single modality therapy is potentially curative, long term 5 year survival rates are usually 5~10%.[4,8,10,11,13] Patterns of failure reveals both of local and systemic progression. Looking at the literature, durable local control rates with thoracic radiation ranges from 30% to 76% depending on the dose delivered and follow-up duration,[4,5] which appears certainly over- estimated when looking at the data published in recent years. When local control was defined by complete clinical, radiographic, endoscopic, and histologic remission, it was only 17% at 1 year[6] and 8% at 5 years.[7] The possible explanations for over-estimate of local control in the previous studies may result from the difficulties in defining local failure in the previously irradiated lung, and large fraction of patients dying of metastatic disease before local progression. Distant failure rates after radiation alone are approximately 80%.[4]

To improve the outcome with RT, altered fractionated radiotherapy (afRT) has been studies. Phase II dose escalation using hyperfractionated RT(hfRT) was performed by Radiation Therapy Oncology Group (RTOG) and 69.6 Gy delivered 1.2 Gy per fraction, twice a day with interval between two treatments of $\geq$4 hours, appeared to be optimal without causing increased risks of severe pneumonitis.[8] Two year overall survival was 20% which was slightly better than 15% following conventionally fractionated RT. More aggressive treatment using continuous hyperfractionated accelerated RT (CHART) has been studied as a British Multi-center Trial.[9] In this study, CHART of 54 Gy in 36 fractions (1.5 Gy per fraction, three time a day, delivered for 12 consecutive days), was compared with conventionally fractionated RT (cfRT) of 60 Gy delivered in 30 fractions. One and two year survival were 63% and 29% for CHART, and 55% and 20%, respectively; which were not statistically significant. In subgroup analysis for squamous cell carcinoma, CHART was, however, superior to cfRT with 2 year survival of 33% versus 19%, respectively (p=0.004).

In summary, radiotherapy therapy alone sterilizes loco-regional disease only in a small proportion of patients and usually has no impact on occult metastases. Altered fractionation of RT induces modest improvement of short-term survival, but is usually inferior to combined multidisciplinary therapy such as chemo-radiation therapy (CRT) which is being discussed below.

Chemo-radiation (CRT)

There are two basic treatment approaches for administering combined chemotherapy and radiation. One is to administer chemotherapy first followed by radiotherapy sequentially ("Sequential CRT") and the other is to administer chemotherapy and radiotherapy concurrently at the same time ("Concurrent CRT"). There are some practical and hypothetical advantages and disadvantages of each approach; which are summarized in Table 1.

Sequential Chemo-Radiation (sCRT)

Sequential CRT was the first widely utilized combined modality. Potential advantages of this approach may include that the effect of chemotherapy may permit delivery of radiation to a reduced tumor volume and full intensity of chemotherapy can be delivered with less overall toxicity compared to concurrent administration. Potential disadvantages of sequential approach include a prolonged overall treatment time (by delaying RT while CT given), no sensitization of radiation effects on tumor cells by chemotherapy (because CT and RT are to be given separately), and possible accelerated repopulation following CT (the surviving cell following CT can repopulate more rapidly than before); all of which are known to be adversely affecting the local control.

Table 1. Hypothesis, Common Clinical Practice and Outcome of sCRT versus cCRT

	Sequential	Concurrent
Hypothesis:		
Chemosentization of RT	No	Yes
Accelerated repopulation*	Possible	No
Expected effect on:		
Local control	+/−	+
Distant metastases	+/−	+/−
Common clinical practice:		
RT intensity	Maintained	Maintained
CT intensity	Maintained	Reduced
Treatment duration	Longer	Shorter
Observed outcome compared to RT alone:		
Local control	No effect	Better
Distant metastases	Less	No effect
Acute local toxicity	No effect	More

sCRT: sequential chemo-radiation, cCRT: concurrent chemo-radiation, *Accelerated repopulation following chemotherapy

There are several randomized trials demonstrating beneficial effects of sCRT which are summarized in Table 2. The Cancer and Leukemia Group B (CALGB) 8433 trial is the landmark study, comparing sCRT to RT.[10,11] 155 patients with "favorable" (excellent performance (ECOG0-1), minimal weight loss <5% over 3 months, no palpable supraclavicular lymph nodes) stage III NSCLC were randomized. Induction CT consisted of cisplatin (100 mg/m2 on days 1, 8, 15, 22, and 29) and vinblastin (5 mg/m2 on days 1, 8, 15, 22, and 29). RT to a total dose of 60 Gy in 30 fractions was the same in both arms and began on day 50 in sCRT arm. In the initial report, induction CT improved median survival (13.8 vs. 9.7 months, p=0.007) and doubled the long term survival rates with 23% of patients treated with sCRT compared to 11% of those treated with RT alone, prompting early closure of the study.[10] 7 year follow-up confirmed that sCRT improves long term survival rates with 17% vs. 6%, respectively.[11] Other modern cisplatin based induction CT trials have also confirmed the CALGB experience.

RTOG 8808 trial randomized 458 patients with the same eligibility criteria as CALGB 8433 to receive conventionally fractionated RT (cfRT) of 60 Gy with or without induction cisplatin and vinblastin.[12] Patients randomized to a third arm received hyperfractonated RT (hfRT) of 69.6 Gy (1.2 Gy twice a day). Median survival was statistically superior (p=0.03) for the combined modality arm (13.8 months) compared to either cfRT arm (11.4 months) or hfRT arm (12.3 months). Final results of this study confirmed an improvement in median survival for CRT, but 5 year survival rates were poor at 8%.[13]

Table 2. Randomized Trials of sCRT versus RT Alone

Trial	CT	RT (Gy)	MS	2YSR (%)	5YSR (%)	p value	References
CALGB 8433	VP	60	13.8		17	0.01	10, 11
		60	9.7		6		
RTOG 8808	VP	60	13.8	31	8	0.03	12, 13
		60	11.4	20	6		
IGR	VCPC	65	12	21		NR	14, 15
		65	10	4			

sCRT: sequential chemo-radiation, RT: radiotherapy, CALGB: Cancer and Leukemia Group B, RTOG: Radiation Therapy Oncology Group, IGR: Institut Gustave-Roussy, CT: chemotherapy, MS: median survival in months, 2YSR: 2 year survival rates, 5YSR: 5 year survival rates, VP: vinblastin, cisplatin, VCPC: vindesine, cyclophosphamide, cisplatin, lomustine, NR: not reported

Le Chevalier et al. reported on a phase III trial in which 353 patients with unresectable locally advanced squamous cell and large cell lung carcinoma were randomized to receive either RT alone (65 Gy in 2.5 Gy fracton) or three monthly cycles of cisplatin-based chemotherapy followed by the same RT.[15] The median survival (12.0 vs. 10.0 months) and 2 year survival rates (21% vs. 14%, p=0.02) were improved for CRT arm. There was a significant decrease in the development of distant metastases (approximately 40% vs. 60% at 24 months) for CRT. A subsequent report revealed that only 8% of patients had continued local control at 5 years.[7] The 5 year survival rates remained poor at 6% and 3%, as results of poor local control on both arms.

In summay, sCRT improved median survival, most likely as a result of decreased rates of distant metastases, but did not seem to improve local control rates. As discussed before, sequential administration of CT might result in a prolonged overall treatment time, no chemo-sensitization effect on RT, and potential accelerated repopulation of surviving tumor cells following CT; all of which are known to adversely affect on local control probability. The 5 year survival rates remained poor at 6~17%.

Table 3. Randomized Trials of cCRT versus RT Alone

Trial	CT	RT (Gy)	MS	2YSR (%)	4YSR (%)	p value	References
EORTC	P (40 mg/week)	55		19			16
	P (6 mg/d)	55		26		*0.009	
		55		13			
Jeremic et al.	CE	69.6	22		23	.02	17
		69.6	14		9		

cCRT: concurrent chemo-radiation, RT: radiotherapy, EORTC: European Organization for Research and Treatment of Cancer, CT: chemotherapy, MS: median survival in months, 2YSR: 2 year survival rates, 4YSR: 4 year survival rates, P: cisplatin, CE: carboplatin, etoposide, *when compared daily cisplatin arm with no chemotherapy arm.

Table 4. Sequential CRT versus Concurrent CRT

Trial	Modality	MS	2YSR (%)	4YSR (%)	p value	References
Furuse et al.	sCRT	13.3	27	10	0.04	18
	cCRT	16.5	35	17		
RTOG 9410	sCRT	14.6	31	12	0.046	19
	cCRT	17.0		21		
	cChfRT	15.2		17		

CRT: chemo-radiation, RTOG: Radiation Therapy Oncology Group, sCRT: sequential chemo-radiation, cCRT: concurrent chemo-radiation, cChfRT: concurrent chemo-hyperfractionated radiotherapy, MS: median survival in months, 2YSR: 2 year survival rates, 4YSR: 4 year survival rates

Table 5. Induction CT Followed by Concurrent CRT

Trial	Modality	MS	1YSR (%)	4YSR (%)	p value	References
CALGB 9130	iCT+RT			10	NS	20
	iCT+cCRT			13		
RTOG 9204	iCT+cCRT	15.5	65		NS	21
	cChfRT	14.4	58			

CT: chemotherapy, CRT: chemo-radiation, CALGB: Cancer and Leukemia Group B, RTOG: Radiation Therapy Oncology Group, iCT: induction chemotherapy, RT: radiotherapy, cCRT: concurrent chemo-radiation, cChfRT: concurrent chemo-hyperfractionated radiotherapy, MS: median survival in months, 1YSR: 1 year survival rates, 4YSR: 4 year survival rates, NS: not significant

Concurrent Chemo-Radiation (cCRT)

The potential advantages of cCRT include the sensitization of tumor cells to radiation by concurrent administration of chemotherapy, avoidance of accelerated repopulation following initial induction chemotherapy, and reduced overall treatment time compared to sCRT; all of which may contribute an improvement of local control. Potential disadvantages of cCRT include increased morbidity requiring reductions in dose intensity of CT; which may not have any effects on existing occult micro-metastasis (Table 1).

An important European Organization for Research and Treatment of Cancer (EORTC) trial randomized 331 patients with unresectable stage I, II, or III NSCLC to RT alone (55 Gy/ 20 fractions for 6 weeks, 3 Gy$\times$10 fractions for 2 weeks +2 week rest+2.5 Gy$\times$10 fractions for 2 weeks), the same RT with weekly cisplatin (30 mg/m^2), or the same RT with daily cisplatin (6 mg/m^2).[16] The administration of daily cisplatin was shown to significantly improve overall survival (16% vs. 2% at 3 years, p=0.009) and disease free survival (31% vs. 19% at 2 years, p=0.003) compared to RT alone. The survival benefit observed with daily cisplatin was likely due to improved local control as a result of chemo-sensitization of radiation effects on tumor cells. The survival rates with local control at 2 years were 31% with daily cisplatin and 19% with no CT. The weekly cisplatin arm also revealed a trend towards improved survival compared to RT alone, but the difference was not statistically significant.

Jeremic et al. reported on a phase III trial in which 131 patients with stage III NSCLC and KPS$\geq$50% were randomized to receive either hyperfractionated RT (hfRT; 69.6 Gy in 1.2 Gy fracton, twice a day) with or without concurrent low-dose daily CT (carboplatin 50 mg, iv and etoposide 50 mg, po).[17] The cCRT arm demonstrated an improved median survival (MS) (22 vs. 14 months) and an improved 4 year survival (23% vs. 9%, p=0.02). There was also a significant improvement of local relapse free survival (LRFS) for cCRT (42% vs. 19% at 4 years, p=0.015), but was no difference in distant metastases free survival (DMFS) between two arms (38% vs. 42% at 4 years).

In summary, cCRT improved median survival compared to RT alone, and the survival benefits was most likely due to improved local control as a result of chemo-sensitization of radiation effects on tumor cells. However, cCRT did not seem to improve DMFS at the intensity and schedule of CT commonly used in the practice.

Sequential CRT versus Concurrent CRT

The benefit of CRT over RT alone has been demonstrated through numerous randomized trials as described above. The optimal sequencing of the two modalities, sCRT versus cCRT, however, was unknown.

Furuse et al. reported a phase III trial in which 314 patients with unresectable stage III NSCLC were randomized to receive either sCRT or cCRT.[18] Both the response rate (66% vs. 84%, p=0.0002) and the MS (13.3 vs. 16.5 months, p= 0.04) were significantly improved for patients treated with cCRT as compared to sCRT.

The RTOG also compared sCRT with cCRT in a phase III trial.[19] In this trial, 595 patients with unresectable stage II-III NSCLC were randomized to receive sCRT or cCRT or cCRT with hyperfractionated RT regimen (cChfRT). With a median follow up of 40 months, cCRT demonstrated a trend toward improved MS (17 vs. 14.6 months, p=0.08) compared to sCRT. Patients treated with cCThfRT showed a MS of 15.6 months, which was not statistically different from either sCRT or cCRT arm.

In summary, there is some evidence that cCRT is potentially superior to sCRT in terms of median survival benefit. Unlike in most previous cCRT trials using a reduced intensity of CT when combined with RT concurrently, these trials used the full intensity of CT and more toxicity was observed.

Induction Chemotherapy (iCT) Followed by Concurrent Chemo-Radiation (cCRT)

The combined modality treatment either of sCRT or cCRT, demonstrated survival benefit as shown above. Consequently, it appeared to be reasonable to examine the efficacy of combination of two strategies using induction chemotherapy followed by cCRT. Hypothetical advantages of this approach may include not only improved DMFS by administration of induction CT in full intensity, but also improved local control by concurrent administration of chemo-radiation.

CALGB 9130 trial randomized 283 patients to determine whether the administration of carboplatin (weekly 100 mg/m2) concurrently with radiation treatment improves survival in patients with inoperable stage III NSCLC. All patients received induction cisplatin and vinblastin, and 60 Gy of cfRT.[20] There was no difference in overall survival or progression free survival at 4 years between two arms. Concurrent administration of carboplatin during the course of RT did not impact on disease control or survival at the dose and schedule used in the study.

RTOG 9204 phase II trial randomized 162 patients with locally advanced inoperable NSCLC to receive iCT (two cycles of vinblastin and cisplatin) followed by cCRT (63 Gy in 35 fractions and concurrent cisplatin of 75 mg/m2 at days 50, 71, 92) or cChfRT (69.6 Gy in 58 fractions of 1.2 Gy bid, for 6 weeks with 2 cycles of DDP 50 mg/M2 i.v. days 1 and 8, and oral VP-16 50 mg b.i.d. during the first 10 days of RT).[21] At 1 year, 31.7% of patients had in-field progression on iCT+cCRT arm compared to 19.8% on cChfRT arm (p=0.042), but overall progression-free survival rates were nearly identical; 50 and 49%, respectively, at 12 months. One-year and median survivals were 65% and 15.5 months on iCT +cCRT arm compared to 58% and 14.4 months on cChfRT.

In summary, the data available at present did not prove the hypothetical advantages of combining both strategies using iCT followed by cCRT. This strategy might cause more severe hematologic toxicity compared to cCRT with no iCT (this will be discussed later). However, further study with refinement of regimen is warranted to prove the benefit.

Morbidity of Treatment

In locally advanced NSCLC, combined modality therapy improves disease control at the cost of increased morbidity. "More aggressive" treatment causes more toxicity with no exception. The sequential addition of chemotherapy increases the rates of nausea, vomiting, and acute hematologic toxicity, without increased rates of esophagitis or pneumonitis.[7,10~12,14] Chemotherapy administered concurrently with RT usually increases the rate of non-hematologic toxicity, particularly esophagitis, without increasing late effects.[16,18,19] Concurrent CT may increase acute hematologic toxicity, but does not increase the risk of septic death. Concurrent chemotherapy combined with more aggressive RT using hyperfractionated regimen increase the acute and late esophageal and pulmonary toxicities compared to conventionally fractionated regimen with lower total dose.[19,21,22] Fig. 1 depicts treatment related morbidity per treatment modalities.

Conclusions

Over the past two decades, many trials of multidisciplinary treatment have been conducted for patients with locally advanced unresectable NSCLC. The use of combined modality therapy primarily with chemo-radiation has demonstrated a modest, but reproducible survival benefit compared to single modality therapy (Fig. 2). As shown on the figure, the median survival increased from approximately 10 months with RT alone to 20 months with the most aggressive CRT. However,

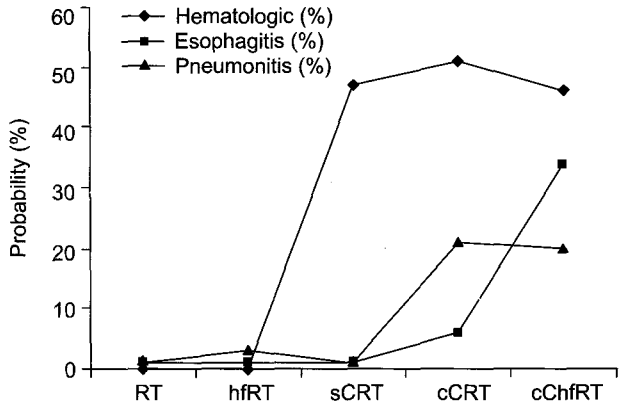

Fig. 1. Treatment related morbidity.

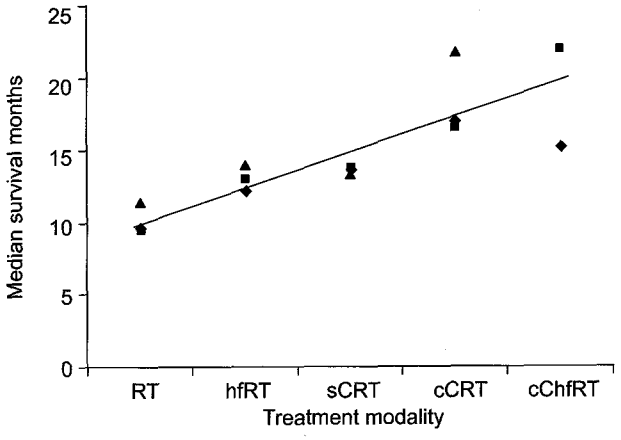

Fig. 2. Treatment modality vs. median survival.

these survival figures are still far from satisfaction. In addition, it is also embarrassing that long term survival data are still scanty even in previously mentioned well designed randomized protocol studies. With more aggressive treatment, it is well recognized that a short term delay of progression is possible without improving ultimate outcome since short term follow-up may not detect late recurrence. Therefore, an improvement of median survival may not be necessarily translated into a long term 5 year survival benefit. Long term follow-up is, therefore, critical to determine the ultimate outcome of treatment. Besides, the best therapeutic regimen remains unknown. The research should be continued to improve local control and decrease distant metastases.

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국문초록

수술 불가능한 국소 진행 비소세포성 폐암의 집합적 요법

국립암센터

조관호

비소세포성 폐암에서 국소 진행성 병변(병기 3)이 3분의 1을 차지한다. 이 중 완전 절제가 가능한 소수의 환자를 제외하고 대부분의 환자에서 근치적 방사선치료가 전통적으로 시행되어 왔다. 하지만 근치적 방사선치료 후 장기 생존율은 극히 불량하고, 대개의 경우 원격 전이 또는 국소 재발로 사망하게 된다.

지난 20년간, 집합적 요법으로 국소 진행성 비소세포성 폐암 치료효과의 향상이 있었다. 그중 화학방사선요법이 가장 흔히 사용되었고, 화학요법과 방사선치료를 병용하는 순서에 따라 다음 두 가지 기본적 방법이 있다. 즉, 순차적 요법과 동시 요법이 그것이다.

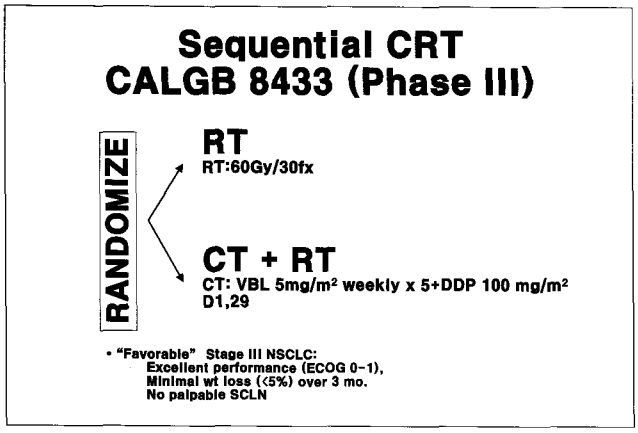
순차적 병용 요법은 유도 화학요법 완료 후 방사선 치료를 진행하는 순서로 주로 시행되었다. 근거로는 방사선 치료 전 유도 화학요법 사용 으로 종양의 크기를 줄여 국소제어율을 높이고, 보이지 않는 미세 전이 병변을 제거하여 원격 전이를 감소시키는 데 있다. 방사선 단독 치료와 비교하여 순차적 화학방사선요법으로 중앙생존기간과 장기생존율의 향상을 보고한 여러 연구가 있다. 재발 양상을 분석한 보고에 따르면, 방사선치료 단독과 비교하여 순차적 병용요법이 원격전이율은 감소시키나, 국소 재발률에는 영향이 없었다.

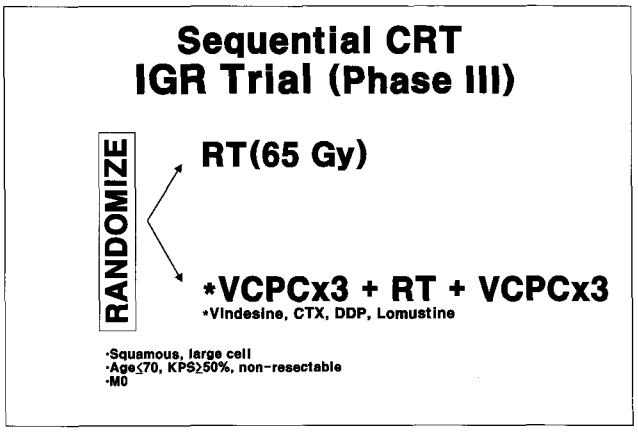
화학요법과 방사선치료를 동시 시행하는 동시병용요법에 대한 많은 보고가 있다. 근거로는 화학요법을 방사선과 동시 투여함으로써 화학요법에 의한 종양세포 방사선 감작효과를 기대할 수 있고, 순차적요법과 비교하여 전체 치료기간을 단축하여 국소제어율을 향상시킬 수 있다. 기대했던 대로 동시 병용요법 후 국소 제어율 향상과 이로 인한 생존율 증가가 관찰되었다. 하지만 방사선 치료 단독과 비교하여 원격 전이율에는 차이가 없었고, 이는 급성 부작용, 특히 급성 식도염 위험을 줄이기 위해 대다수의 연구에서 관찰되듯이 화학요법의 강도를 줄인 때문으로 생각된다.

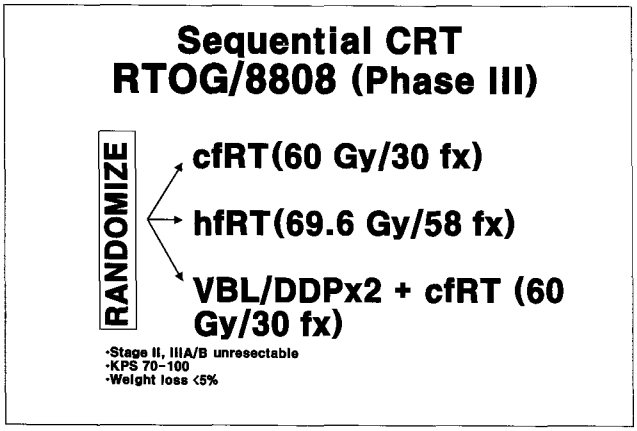
상기한 바와 같이 집합적 치료가 방사선 단독 요법과 비교하여 생존율의 향상에 기여하였고, 현재 새 표준 치료로 정착되었으나, 이의 치료효과는 아직도 실망스러우며, 최적 치료 개발을 위한 연구는 계속되어야 한다. 본 보고에서 국소 진행 비소세포성 폐암에서 집합적 치료에 대한 현 논점을 검토하고자 한다.

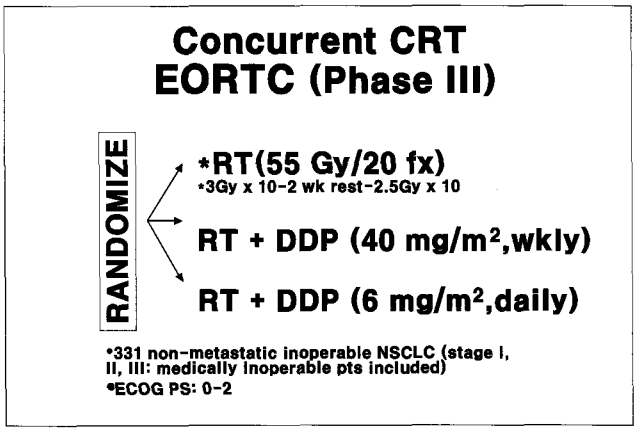
Appendix

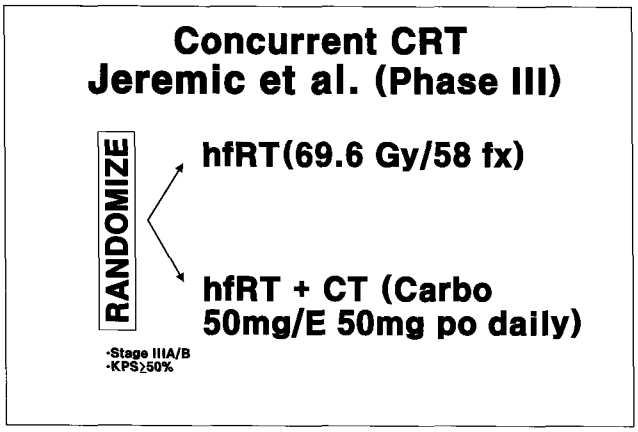
Protocol Schema

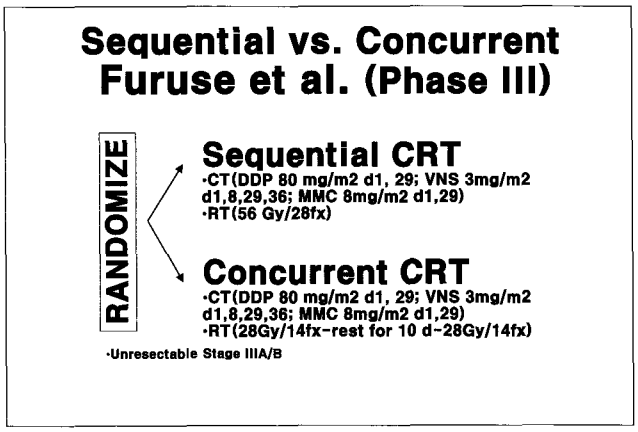


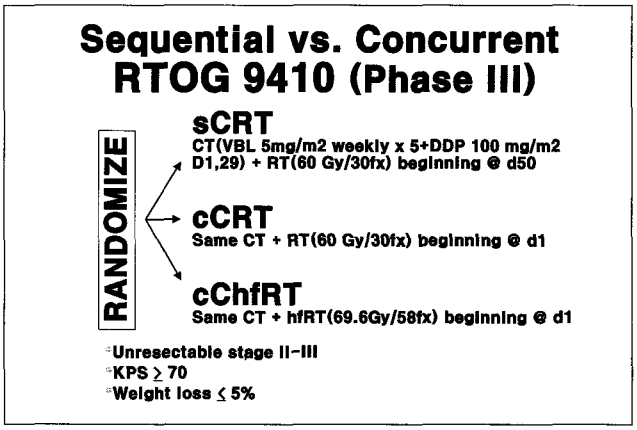


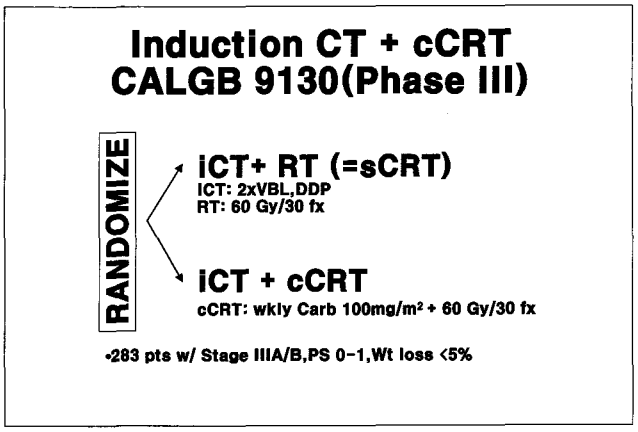


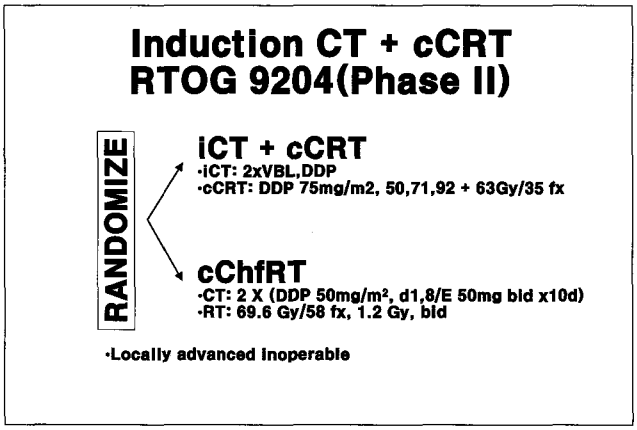







Sequential vs. Concurrent
RTOG 9410 (Phase III)
RANDOMIZE
sCRT
CT(VBL 5mg/m2 weekly x 5+DDP 100 mg/m2 D1,29) + RT(60 Gy/30fx) beginning @ d50
cCRT
Same CT + RT(60 Gy/30fx) beginning @ d1
cChfRT
Same CT + hfRT(69.6Gy/58fx) beginning @ d1
Unresectable stage II-III
KPS ≥ 70
Weight loss ≤ 5%


Induction CT + cCRT
CALGB 9130(Phase III)
RANDOMIZE
ICT+ RT (=sCRT)
ICT: 2xVBL,DDP
RT: 60 Gy/30 fx
ICT + cCRT
cCRT: wkly Carb 100mg/m² + 60 Gy/30 fx
•283 pts w/ Stage IIIA/B,PS 0-1,Wt loss <5%


Induction CT + cCRT
RTOG 9204(Phase II)
RANDOMIZE
ICT + cCRT
•ICT: 2xVBL,DDP
•cCRT: DDP 75mg/m2, 50,71,92 + 63Gy/35 fx
cChfRT
•CT: 2 X (DDP 50mg/m², d1,8/E 50mg bid x10d)
•RT: 69.6 Gy/58 fx, 1.2 Gy, bid
•Locally advanced inoperable