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An Economic Analysis of Radiation Therapy Oncology Group 94-10: Cost-Efficacy of Concurrent vs. Sequential Chemoradiotherapy

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Abstract

Background—Cost can be a major issue in therapeutic decision-making, and in particular for patients with locally advanced non-small cell lung cancer (LA-NSCLC).

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Compliance with Ethical Standards

Conflicts of Interest

Walter Curran declares he has no conflicts of interest. Corey Langer declares he has no conflicts of interest. Jean Owen declares she has no conflicts of interest. Rebecca Paulus declares she has no conflicts of interest. Mytheri Bhargavan declares she has no conflicts of interest. Deborah Bruner declares she has no conflicts of interest. Hak Choy declares he has no conflicts of interest. Elizabeth Gore declares she has no conflicts of interest. Ritsuko Komaki declares she has no conflicts of interest. Andre Konski declares he has no conflicts of interest.

Ethical approval

As this study involved patients no animals had been involved in this study. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Informed Consent

All patients who initially participated in this clinical study have given informed consent. All human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in the original study.

Methods—The specific aim of this analysis was to evaluate the costs and outcomes of patients treated on Radiation Therapy Oncology Group (RTOG) 94-10, Medicare Part A and Part B costs from all for patients treated from 1991 to 1996 on RTOG 94-10, a phase III trial showing a survival benefit for concurrent chemoradiation (STD RT) over sequential (RT day 50) chemoradiation in LA-NSCLC with intermediate outcome for concurrent twice daily radiation and chemotherapy (HFX RT). 26-month expected costs for each arm of the trial in 1996 dollars were determined, with Kaplan Meier sampling average estimates of survival probabilities for each month and mean monthly costs. The analysis was performed from a payer's perspective. Incremental cost-effectiveness ratios were calculated comparing RT on day 50 and HFX RT to the STD RT.

Results—Of the 610 patients entered, Medicare cost data and clinical outcomes were available for 92 patients. In this subset, compared to STD RT, RT on day 50 proved less costly but resulted in reduced survival at 1 year. In addition, HFX RT cost slightly more than STD RT but was less effective in this cohort of patients.

Conclusions—In patients with Medicare insurance and with significant toxicity burden, RT on day 50 is the least expensive but also least effective treatment in this subset of patients treated on RTOG 94-10.

Keywords

Lung Cancer; Combination chemotherapy; Induction chemotherapy; Cost-effectiveness; Medicare data

Introduction

Radiation Therapy Oncology Group (RTOG) trial 94-10 showed a survival advantage for concurrent radiation (RT) and chemotherapy with vinblastine and cisplatin over sequential treatment with the same regimen and no advantage for hyperfractionated XRT and concomitant etoposide and cisplatin over the same sequential treatment arm. The study also showed heightened hematologic and esophageal toxicity in both of the concurrent therapy arms. Six hundred and ten patients were randomly assigned in this three-arm phase III trial. Median survival times were 14.6, 17.0 and 15.6 months for patients receiving chemotherapy and then radiotherapy (RT day 50), concurrent chemoradiotherapy (STD RT), and chemotherapy and hyperfractionated radiotherapy (HFX RT), respectively.¹ Patients treated with concurrent chemotherapy and once-daily thoracic radiotherapy also had statistically significantly improved five-year survival rates compared to sequential treatment; no such advantage was observed in the comparison of the HFX RT arm to the RT day 50.¹

Hillner has proposed conditions supporting the inclusion of an economic analysis alongside a clinical trial. RTOG 9410 has a number of factors that would support performing an economic analysis: (1) lung cancer is a common disease; (2) this therapy is easily transferable to the marketplace; (3) the winning therapeutic therapy supersedes other interventions; (4) there are substantial differences in cost and (5) there are substantial differences in acute morbidity.² A number of economic analyses involving the use of different chemotherapy and radiotherapy regimens in the treatment of non-small cell lung

cancer have been performed and reported. Using the perspective of the Canadian government, Evans et al. found the use of combined modality therapy for patients with stage III non-small cell lung cancer would be cost-effective in terms of life-years gained.³ On the other hand, Thongproasert et al using a Thailand government perspective did not find the combination of carboplatin and paclitaxel to be cost-effective compared to cisplatin and etoposide in the treatment of patients with either stage IIIB or IV non-small cell lung cancer.⁴ The UK's National Institute for Health and Clinical Excellence (NICE) invited Roche to perform an economic analysis of the use of erlotinib in the maintenance treatment of stable patients with non-small cell lung cancer after chemotherapy.⁵ The conclusions of the analysis resulted in NICE declining to recommend the use of this drug in the identified patient population. Using a Markov model, Sher et al. found stereotactic body radiotherapy (SBRT) to be cost effective when compared to three-dimensional conformal radiotherapy (3DCRT) or radiofrequency ablation (RFA) in the treatment of patients with medically inoperable early stage NSCLC.⁶

Therefore the specific aim of this analysis was to compare the cost-effectiveness of 3 different chemoradiotherapy regimens for patients with LA-NSCLC treated on a cooperative group clinical trial using Medicare data.

Material and Methods

RTOG 9410 was a randomized phase III trial evaluating three different chemoradiotherapy regimens in the treatment of locally advanced, non-metastatic non-small cell lung cancer.¹ A standard regimen at the time featured vinblastine 5mg/m² IV bolus weekly for 5 weeks and cisplatin 100mg/m² IV over 30–60 minutes on days 1 & 29 followed by radiotherapy starting on day 50 and delivered to a dose of 63 Gy over 7 weeks at 1.8 Gy/fraction for the first 25 fractions and at 2.0 Gy/fraction for the last 9 fractions. The second arm featured the same chemotherapy regimen and the same radiotherapy was delivered starting day 1 instead of day 50. The third arm of the study featured concurrent oral etoposide 50 mg BID x 10 only on radiotherapy days 1–5, 8–12, 29–33, and 36–40, cisplatin 50 mg/m² IV over 30–60 minutes on days 1, 8, 29 and 36. Patients on this arm received 69.6 Gy over 6 weeks in 58 fractions (1.2 Gy BID separated by at least 6 hours) beginning day 1.

We have previously published our methods for determining costs utilizing Medicare data^{7,8}. Exclusion criteria for this analysis included patients having no RTOG follow-up, patients lacking a Medicare match, patients enrolled in a Medicare HMO, patients entering the trial after January 1997 as they would have little data within the current analysis period, and those for whom we had no claims at all after they entered the trial. The analysis was performed from a government payer or Medicare perspective and included all costs for all providers in all care settings - inpatient, outpatient, skilled nursing facility, home health, hospice, and physicians and other Part B providers. Incremental cost-effective ratios were calculated comparing all three arms of the study. Because Arm 2 led to improved survival, concurrent chemoradiotherapy (STD RT) was chosen as the base case to which the two other arms of the study were compared.

Sensitivity analysis evaluated the effect on expected mean cost using only ICD-9 codes associated with lung cancer and whether patients had a complication (grade 3 or greater). ICD-9 codes used included 162. Non-parametric bootstrap analysis was used to generate 95% confidence intervals on the cost-effectiveness plane and to plot cost-effective acceptability curves.⁹⁻¹² The Institutional Review Boards of the American College of Radiology and Fox Chase Cancer Center approved this study. Approval was also obtained from CMS in accordance with our Data Use Agreement to ensure patients participating in the study could not be identified.

Results

Randomization, inclusion and exclusion criteria used in this analysis are depicted in the CONSORT diagram in Figure 1. Of the original 610 patients entered into RTOG 94-10, 232 were 65 years of age or older or had Medicare as their primary insurance; of these, only 92 met the inclusion criteria. Most patients, included in this analysis, had grade 3 toxicity with 35/38 (92%), 27/28 (96%), and 25/26 (96%) had grade 3 toxicity in the RT day 50, STD RT and HFX RT groups respectively. This is in comparison to the entire study group, where 85%, 91% and 84% experienced grade 3 toxicity respectively in each of the arms.¹ Table 1 shows the pre-treatment characteristics by analysis. As expected, based on the inclusion criteria, patients included in the analysis were significantly older compared to patients not in the analysis, $p<0.0001$. There were more males than females in this analysis group compared to patients not in the analysis, $p=0.035$. Table 2 depicts the toxicity and survival by analysis status. Patients included in the analysis had slightly more hematologic and non-hematologic toxicity compared to patients excluded from the analysis. Patients not in the analysis treated with RT day 50 had significantly greater cardiac toxicity compared to patients in the analysis, $p=0.033$. Patients treated with STD RT included in the analysis had significantly greater worst non-hematological toxicity compared to patients not in the analysis, $p=0.049$. Patient treated with HFX RT in the analysis group had greater leukopenia, worst hematologic and other non-hematologic compared to patients not in the analysis. There was no statistically significant difference in worst overall toxicity between the two groups. There was also no statistically significant difference in overall survival between the groups.

Mean Medicare costs were \$7318 for RT day 50, \$9,032 for STD RT, and \$10,772 for HFX RT. In this subset analysis, patients receiving STD RT had the best survival, followed by patients receiving HFX RT treatment with patients having RT day 50. Table 3 shows the incremental cost effectiveness ratio comparing RT day 50 and HFX RT to STD RT. The discounted survival is greatest in the STD RT group and lowest in the RT day 50 group. Patients receiving RT day 50 had the lowest expected mean cost while patients receiving HFX RT had the highest expected mean cost. We compared RT day 50 and HFX RT to STD RT as this is currently how the majority of therapy for non-small cell lung cancer is currently given. Calculating the incremental cost effectiveness in this fashion results in a negative ICER ratio for HFX RT treatment since survival is poorer and cost higher. In contrast, we note a positive ICER ratio comparing RT day 50 to STD RT since both survival is inferior and costs are lower resulting in a double negative with a positive result. Figure 2 shows the results on the ICER plane comparing HFX RT to STD RT. The mean ICER line extends

from the origin through quadrant II signifying the comparator treatment was both less effective and more costly when compared to the standard treatment. The 95% confidence ellipses cross both axis indicating that the results are not statistically significant. This occurs because of the small number of cases and small differences seen between the two groups and because the trial was not powered to show differences in cost-effectiveness between the two arms. Figure 3 depicts the results on the ICER plane comparing RT day 50 RT to STD RT. The mean ICER line extends from the origin to quadrant III signifying a treatment that is less expensive but also less effective. Once again the 95% confidence ellipses cross both axes indicating no statistical difference in the cost effectiveness between the treatments.

Patients having grade 3 complications had higher costs as one would expect. Average payment by Medicare was \$26,293, \$41,241, and \$45,683 for patients receiving RT day 50, STD RT, and HFX RT, respectively.

Discussion

This study evaluated the cost-effectiveness in a subset of patients with Medicare insurance on one of three treatment regimens for locally advanced non-small lung cancer tested in a phase III clinical trial. The least costly treatment, calculated as expected mean costs (cancer treatment + complication treatment), also resulted in worse survival for those patients. This resulted in a “favorable” cost-effectiveness ratio below \$50,000/life-year but not a result patients or physicians would want to choose. A question that cannot be readily answered is why this treatment proved less costly when compared to the other treatments. The patients in this group had the lowest median survival time of all of the groups, but also the least toxicity. Was the treatment less expensive because these patients died earlier and thus could not consume additional healthcare resources? Or did the lower costs stem from fewer toxicities and therefore reduced costs in managing side effects? HFX RT treatment on the other hand was more costly and less effective. The patients treated in this group had more hematologic toxicity, when compared to patients not in the analysis.

This study has a number of limitations. The study was not powered to detect a difference in cost-effectiveness. Because of the reliance on Medicare data, the numbers in all three arms meeting the cost-effectiveness inclusion criteria were small. We have previously shown the number of patients needed to power a trial to show a difference in cost-effectiveness is different from patient numbers needed to show a clinical difference.⁷ However, partnering economic analyses alongside clinical trials does provide benefits. The marginal cost of collecting economic data from claims history is small relative to trying to develop a prospective study collecting both clinical outcomes and economic resource utilization. In addition, formal quality of life and utility measurement was not performed, limiting our ability to perform quality-adjusted survival for use in a cost-utility analysis. This would have been helpful given the differences in toxicity experienced by patients between the treatment arms.

Another limitation of this study is that the study population may not be representative of the general population as a whole.¹³ The population in this study by definition was Medicare “age”; they were older and may have had greater toxicities at baseline and during the course

of treatment compared to a younger population. There was, however, no statistical difference in overall survival between patients in the analysis and patients not in the analysis; nor was there any statistically significant difference in overall toxicity between these two groups. However, almost all of the patients enrolled on this study had Grade 3 toxicity which would result in higher costs. Patients included in the study had greater hematologic and non-hematologic toxicity compared to patients excluded from the analysis. Patients experiencing toxicity had higher costs compared to patients without toxicity so extrapolation to the general population could be problematic. Because Medicare does not typically include younger patients, we cannot address whether the expected mean cost of care might have been different in a younger population compared to those who were analyzed.

The potential advantages of collecting economic data alongside clinical trials have been well documented.^{14–18} The opportunity to collect these data may improve as healthcare reform potentially changes how payments are made. Different procedures may need to be instituted if global payments are made by diagnosis as opposed to our current practice. This may be similar to the global payments made to payers for Medicare HMO patients. Ideally cost data will need to be collected for the entire population, not just those on Medicare. To collect the appropriate data, more resources will need to be expended from a societal perspective rather than a payer perspective; this would account for other factors that could contribute to higher overall resource utilization such as time off from work and loss of productivity, indices that are not currently collected in most clinical trials.

Conclusion

This cost-effectiveness study based on the phase III clinical trial RTOG 9410 showed the least costly treatment also yielded the worse outcome among Medicare patients with a high burden of toxicity. What is not known, however, is whether poor survival in the “losing arm” resulted in a reduction in resource consumption? Economic analysis may be affected in the future as healthcare reform changes how reimbursement is made both to hospitals and physicians.

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Figure 1.
CONSORT Diagram of RTOG 9410

Figure 2.
HFX RT vs STD RT Day 1 \$ per year of survival

Figure 3.
RT Day 50 vs STD RT Day 1 \$s per year of survival

Table 1**Pretreatment Characteristics By Analysis Inclusion Status**

	Excluded from Analysis (n=503)	Included in Analysis (n=92)
Treatment Arm		
RT ON DAY 50	163 (32.4%)	38 (41.3%)
STD RT/DAY 1	173 (34.4%)	28 (30.4%)
HFX RT/DAY 1	167 (33.2%)	26 (28.3%)
Age (years)		
Median	60	69
Min - Max	33 – 79	49 – 80
Q1 – Q3	53 – 66	66 – 72
Gender		
Male	314 (62.4%)	68 (73.9%)
Female	189 (37.6%)	24 (26.1%)
Race		
White	431 (85.7%)	82 (89.1%)
Hispanic	6 (1.2%)	1 (1.1%)
Black	51 (10.1%)	9 (9.8%)
Asian	10 (2.0%)	0 (0.0%)
American Indian	2 (0.4%)	0 (0.0%)
Other	3 (0.6%)	0 (0.0%)
Stage		
Stage I	1 (0.2%)	1 (1.1%)
Stage II	10 (2.0%)	3 (3.3%)
Stage IIIA	203 (40.6%)	41 (44.6%)
Stage IIIB	286 (57.2%)	47 (51.1%)
Histology		
Squamous	191 (38.0%)	39 (42.4%)
Adenocarcinoma	158 (31.4%)	24 (26.1%)
Large cell	65 (12.9%)	15 (16.3%)
Combined squamous/adenocarcinoma	12 (2.4%)	0 (0.0%)
Carcinoma NOS	71 (14.1%)	13 (14.1%)
Other	6 (1.2%)	1 (1.1%)

Q1 = first quartile; Q3 = third quartile.

Table 2

Toxicity and Survival By Analysis Inclusion Status

Toxicity	Excluded from Analysis			Included in Analysis		
	RT ON DAY 50 (n=163)	STD RT/DAY 1 (n=173)	HFX RT/DAY 1 (n=167)	RT ON DAY 50 (n=38)	STD RT/DAY 1 (n=28)	HFX RT/DAY 1 (n=26)
Chemotherapy and acute radiotherapy toxicities, No. (%)	Grade 3-5	Grade 3-5	Grade 3-5	Grade 3-5	Grade 3-5	Grade 3-5
Granulocytopenia	123 (75)	136 (79)	87 (52)	31 (82)	26 (93)	15 (58)
Leukopenia	90 (55)	142 (82)	110 (66)	24 (63)	25 (89)	23 (88)
Thrombocytopenia	6 (4)	17 (10)	25 (15)	3 (8)	1 (4)	6 (23)
Worst hematological	128 (79)	146 (84)	114 (68)	32 (84)	26 (93)	24 (92)
Pulmonary	14 (9)	6 (3)	6 (4)	4 (11)	2 (7)	0 (0)
Esophagus	4 (3)	37 (22)	74 (44)	3 (8)	10 (36)	14 (54)
Cardiac	1 (1)	1 (1)	5 (3)	2 (5)	0 (0)	2 (8)
Mucositis	2 (1)	20 (12)	37 (22)	1 (3)	4 (14)	9 (35)
Nausea/Vomiting	25 (15)	35 (20)	44 (26)	4 (11)	9 (32)	4 (15)
Anemia	11 (7)	19 (11)	30 (18)	4 (11)	5 (18)	7 (27)
Other nonhematological	25 (15)	40 (23)	39 (23)	9 (24)	5 (18)	15 (58)
Worst nonhematological	54 (33)	89 (51)	110 (66)	16 (42)	20 (71)	20 (77)
Worst overall toxicity	135 (83)	154 (89)	138 (83)	34 (89)	27 (96)	25 (96)
Late radiotherapy toxicities, No. (%)	Grade 3-5	Grade 3-5	Grade 3-5	Grade 3-5	Grade 3-5	Grade 3-5
Granulocytopenia	1 (1)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Leukopenia	1 (1)	1 (1)	0 (0)	0 (0)	1 (4)	0 (0)
Thrombocytopenia	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Worst hematological	3 (2)	1 (1)	2 (1)	0 (0)	1 (4)	0 (0)
Pulmonary	20 (13)	20 (12)	25 (15)	6 (17)	3 (11)	4 (16)
Esophagus	1 (1)	4 (2)	7 (4)	0 (0)	1 (4)	0 (0)
Cardiac	1 (1)	2 (1)	7 (4)	0 (0)	2 (7)	0 (0)
Mucositis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nausea/Vomiting	0 (0)	0 (0)	0 (0)	1 (3)	1 (4)	0 (0)
Anemia	1 (1)	0 (0)	3 (2)	0 (0)	1 (4)	0 (0)

	Excluded from Analysis			Included in Analysis		
	RT ON DAY 50 (n=163)	STD RT/DAY 1 (n=173)	HFX RT/DAY 1 (n=167)	RT ON DAY 50 (n=38)	STD RT/DAY 1 (n=28)	HFX RT/DAY 1 (n=26)
Other nonhematological	1 (1)	7 (4)	5 (3)	1 (3)	3 (11)	0 (0)
Worst nonhematological	24 (15)	28 (16)	35 (21)	7 (18)	7 (25)	4 (15)
Worst overall toxicity	27 (17)	29 (17)	36 (22)	7 (18)	8 (29)	4 (15)
Overall Survival Rates						
1 year	60.1%	60.7%	59.9%	47.4%	71.4%	65.4%
2 year	33.1%	36.2%	31.7%	26.3%	42.9%	30.8%
3 year	18.4%	25.7%	22.2%	15.8%	35.7%	19.2%
4 year	12.3%	19.3%	15.6%	10.5%	32.1%	19.2%
5 year	10.4%	15.7%	13.1%	7.9%	21.4%	11.5%
Median (Years)	1.3	1.2	1.3	0.9	1.7	1.3
(95% CI)	(1.1, 1.6)	(1.1, 1.7)	(1.0, 1.5)	(0.6, 1.4)	(1.0, 3.1)	(1.0, 1.7)

Table 3

Incremental Cost-effectiveness comparing induction chemotherapy and hyperfractionated radiotherapy to standard chemoradiation

Treatment Arm	Expected Mean 26-Month Cost	Discounted Survival (Years)	Overall Survival ICER (\$/LY)
STD RT/DAY 1	\$42,522	2.55	
RT ON DAY 50	\$25,515	1.51	\$16,387
HFX RT	\$44,250	1.91	\$-2,708