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A Population-Based Comparative Effectiveness Study of Chemoradiation Regimens and Sequences in Stage III Non-Small Cell Lung Cancer

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Abstract

Objectives—In patients receiving concurrent chemoradiation for locally advanced non-small cell lung cancer (NSCLC), consolidation chemotherapy is frequently given even though several randomized trials have failed to show a benefit. We explored the potential benefits of consolidation chemotherapy using a population-based comparative effectiveness approach.

Materials and Methods—Surveillance, Epidemiology, and End Results-Medicare was used to identify patients with Stage III NSCLC aged ≥65 and diagnosed 2002–2009. We selected patients who received concurrent chemoradiotherapy and determined whether they were (concurrent-consolidation) or were not (concurrent-alone) treated with consolidation chemotherapy. Outcomes were overall and cancer specific survival using a conditional landmark analysis approach.

Results—1,688 patients treated with concurrent-alone or concurrent-consolidation were identified with a median follow up of 29 months. Choice of chemotherapy agents did not correlate with outcome. For concurrent-consolidation versus concurrent-alone, the median overall survival was 21 months versus 18 months, respectively (log-rank p = 0.008) and the median cancer specific survival was 23 months versus 19 months, respectively (log-rank p = 0.03). On multivariate

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Conflict of interest

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analysis, concurrent-consolidation remained associated with improved overall survival (HR 0.85, p = 0.04), and there was a trend for improved cancer specific survival (HR 0.87, p = 0.12). Inverse probability of treatment weighting using propensity scores demonstrated similar findings. Importantly, the benefit of concurrent-consolidation held only for patients treated with carboplatin-taxane but not with cisplatin-etoposide.

Conclusion—Survival outcomes were similar among the five most commonly employed platinum-based doublets. We found that patients receiving cisplatin during radiation do not appear to benefit from additional chemotherapy. However, for patients receiving carboplatin, consolidation chemotherapy was associated with improved overall and cancer specific survival.

Keywords

Non-Small Cell Lung Cancer; Chemoradiation; Comparative Effectiveness Research; Platinum-Doublet Chemotherapy; SEER-Medicare

1. Introduction

For locally advanced non-small-cell lung cancer (NSCLC) patients (i.e. stage IIIA/B), combined modality therapy (chemoradiation) is generally recommended [1]. Studies repeatedly demonstrated the benefit of chemotherapy over radiation alone, as well as the benefit of using a platinum-based agent, typically with a second agent, termed “platinum-based doublet therapy” [1–3]. Chemotherapy can be given in various sequences: before radiation (sequential), during radiation (concurrent-alone), before and during radiation (induction-concurrent), or during and after radiation (concurrent-consolidation). As for radiation therapy, generally treatment is 60–66 Gy in 2 Gy fractions, although hyperfractionated or accelerated courses are also being studied [4].

Controversies remain regarding the optimal choice for the sequence of chemotherapy [1, 5, 6]. Although there are randomized trials showing a lack of efficacy with consolidation after cisplatin-based chemotherapy [7–9], there are no randomized trials studying consolidation after carboplatin-based chemotherapy. Rather, evidence for consolidation after carboplatin-based chemotherapy has been limited to single-arm trials [10]. Using SEER-Medicare, we studied the use of platinum-based doublet therapies as well as chemoradiation sequences among elderly patients in the US.

2. Material and Methods

2.1 Patient Selection

Patients diagnosed with NSCLC from January 2002 to December 2009 were identified using Surveillance, Epidemiology, and End Results (SEER)-Medicare. SEER-Medicare is a linked dataset maintained by the National Cancer Institute and contains data from 17 registries accounting for approximately 28% of the US population [11]. The dataset contains demographic, clinical, pathological, outcomes, and Medicare insurance claims data [12]. Follow up was through December 2010.

The cohort included patients aged ≥65 with pathologically confirmed stage IIIA/B NSCLC. Staging was according to the 3rd edition of the AJCC, as only patients diagnosed since 2004 had documented TNM data [13]. Patients with a malignant pleural effusion were excluded, as they are now classified as stage IV. Patients must have been enrolled in Medicare Parts A and B for 12 months prior to diagnosis until death or censoring, and were excluded for enrollment in a health maintenance organization to ensure Medicare claims completeness and characterize pre-diagnosis comorbidities. Patients with an invalid diagnosis date or who were diagnosed at death were excluded.

2.2 Chemoradiation Definition and Associated Variables

Medicare billing claims were used to determine treatment with chemoradiation within 3 months of diagnosis and to exclude patients with prior resection. Radiation therapy (RT) was categorized as treatment with either intensity modulated (IMRT) or 3D-conformal (3D-CRT) radiation therapy, and required 30–40 daily treatment claims (Supplemental Table 1) [14]. RT facility was categorized as a freestanding center, hospital-based NCI center, or hospital-based non-NCI center. Radiation oncologist density was categorized by quartile, and was determined from the Area Health Resources Files (AHRF) [15]. In the AHRF, regions are divided into health service areas, which are defined as one or more counties with self-contained resources for routine hospital care [16].

Chemotherapy was restricted to platinum-based doublet therapy (carboplatin or cisplatin). The second chemotherapy agent that made up the doublet therapy must have started no more than 1 week from the start of the platinum agent (Supplemental Table 1). Sequential was defined as radiation starting 8–45 days after the end of chemotherapy. Concurrent-alone was chemotherapy and radiation starting and ending within 2 weeks of each other. Induction-concurrent was chemotherapy starting more than 2 weeks prior to radiation (but not more than 3 months). Concurrent-consolidation was chemotherapy continuing for more than 2 weeks after radiation, but the next cycle after radiation must have been within 45 days of completion of radiation, and could include starting a new regimen. Similar methods have previously been used to define chemoradiation sequences [17–19].

2.3 Patient Demographic, Clinical, and Diagnostic Variables

Using SEER data, patient demographic data were classified by age, sex, race, marital status, urban setting, area educational attainment (≥4 years of college), and area median income. Geographic area was categorized into West, Midwest, South, and Northeast based on SEER registry. Clinical data were classified by histology, tumor size, and nodal involvement. Using Medicare claims from 12 months prior to diagnosis, a modified Charlson-Deyo comorbidity index and COPD status were determined [20, 21]. Oxygen use was determined from home oxygen supply claims. A proxy performance score (PS) was determined to indicate overall health [14, 22]. PS included hospitalization, skilled nursing or long-term care stay, home health use, and claims for ambulation assistance equipment, bedside commode, or hospital bed.

Diagnostic workup for 3 months before treatment was determined, and included performance of PET, brain imaging, and invasive mediastinal staging. Brain imaging

included magnetic resonance (MRI) and computed tomography (CT). Invasive mediastinal staging included video-assisted thoracoscopic surgery (VATS) mediastinal biopsy, bronchoscopy with nodal biopsy, mediastinoscopy, and mediastinotomy.

2.4 Statistical Analysis

The cohort consisted of the five most commonly used platinum-based doublet agents. Patient treatment was grouped according to 1) chemotherapy agents used (chemoradiation regimen) and 2) chemoradiation sequence. Differences between chemoradiation sequences were assessed using χ^2 tests and Kruskal-Wallis tests. To compare outcomes among patients treated with concurrent-alone or concurrent consolidation, the Kaplan-Meier (KM) method was used to estimate overall survival (OS) and cancer specific survival (CSS). For OS, censoring was at last follow-up, and for CSS non-cancer associated deaths were also censored. Differences in OS and CSS between chemoradiation regimens and sequences were compared with log-rank tests. Multivariate Cox models were adjusted for demographic, clinical, and treatment confounders. Carboplatin-paclitaxel and concurrent-alone were used as references. To account for cases with missing marital status, tumor size, nodal status, or radiation oncologist density, we used multiple imputations with fully conditional specification (20 imputations). Multivariate logistic regressions were used for imputation conditional on all other clinical, demographic, and treatment-related variables in addition to outcome (OS). A secondary complete case analysis was performed.

All patients in the concurrent-consolidation group must have survived long enough to receive additional chemotherapy. To account for this guarantee-time bias, a conditional landmark analysis was used. Only patients surviving more than 45 days after completion of radiation were included. A sensitivity analysis was done using an extended multivariate Cox regression model comparing concurrent-alone to concurrent-consolidation. For this analysis, the chemoradiation sequence was considered a time-varying covariate where patients could enter the concurrent-consolidation group only after completion of radiation. The proportional hazards assumption was evaluated using log-log plots and a time-interaction variable. When this assumption was violated, we used Royston-Parmar flexible parametric models [23]. Model fit was determined using the likelihood ratio.

To adjust for selection bias between patients receiving concurrent-alone and concurrent-consolidation, an inverse probability of treatment weighting (IPTW) analysis was done using propensity scores. A multivariate logistic regression was used to determine the probability of treatment with concurrent-consolidation, conditional on all demographic, clinical, and treatment characteristics. Then a multivariate Cox model was performed with weighting by the inverse of the probability of the treatment received. Subgroup analyses were done with the IPTW method for patients receiving 1) carboplatin-taxane and 2) cisplatin-etoposide. A benefit to concurrent-consolidation was observed with the carboplatin-taxane group only, and so we calculated the power to show the same benefit for the cisplatin-etoposide group [24]. To account for the impact of PET staging, a sensitivity analysis using the IPTW method was performed limited to patients whose workup included PET.

Statistical significance was set at 0.05, and all tests were two-tailed. To adjust for multiple hypotheses comparisons, the method of Benjamini-Hochberg was used [25]. Statistical tests

were performed using SAS (version 9.3, SAS, Cary, North Carolina) and R (version 3.0.2, R Foundation for Statistical Computing, Vienna, Austria).

3. Results

We identified patients with stage III NSCLC diagnosed 2002–2009 who were treated with a platinum-based doublet therapy and radiation (Figure 1). The five most common chemoradiation regimens were: carboplatin-paclitaxel (1,423 patients), cisplatin-etoposide (242 patients), carboplatin-docetaxel (186 patients), carboplatin-etoposide (59 patients), and carboplatin-gemcitabine (33 patients). From 2002 to 2009 cisplatin-etoposide increased from 8% to 17% (Figure 2). The chemoradiation sequences were: concurrent-consolidation (896 patients), concurrent-alone (792 patients), induction-concurrent (140 patients), and sequential (115 patients). During the study period, sequential decreased from 14% to 3% and concurrent-consolidation increased from 35% to 45% (Figure 2). When concurrent-consolidation was given, 176 patients (20%) started a new chemotherapy regimen. The most common new regimen was docetaxel (129 patients) (Supplemental Table 2).

Since they were the most commonly employed regimens, we subsequently focused our analyses on patients treated with concurrent-consolidation or concurrent-alone (n = 1,688). Patients receiving concurrent-consolidation were more likely to be younger, married, from an area with more radiation oncologists, diagnosed as N3, staged with a mediastinal procedure, and treated with carboplatin (Table 1). Median follow-up for these patients was 29 months (415 patients). Median OS and CSS did not vary on the basis of chemotherapy regimen (log-rank p = 0.36 and p = 0.63, respectively) (Figure 3). Median OS was 18 months with concurrent-alone treatment and 21 months with concurrent-consolidation (log-rank p = 0.008), and median CSS was 23 months versus 19 months (log-rank p = 0.03).

Multivariate regression models for OS and CSS were performed using parametric Royston-Parmar models, because the proportional hazards assumption was violated. OS did not significantly vary with chemotherapy regimen. With regards to chemoradiation sequence, there was a significant benefit to concurrent-consolidation compared to concurrent-alone (HR 0.85, 95% confidence interval [CI] 0.76–0.95, adjusted p = 0.04) (Table 2). Concurrent-consolidation was also associated with a trend for improved CSS (HR 0.87, 95% CI 0.77–0.98, adjusted p = 0.12). All models demonstrated goodness of fit. Sensitivity analyses using extended Cox regression models similarly showed improved outcomes with concurrent-consolidation compared to concurrent-alone (Supplemental Table 3). A complete case analysis was performed to validate the multiple imputations methods and resulted in similar findings (Supplemental Table 4).

In an IPTW analysis, concurrent-consolidation remained associated with improved OS (HR 0.87, p = 0.01) and a trend for improved CSS (HR 0.89, p = 0.06) compared to concurrent-alone. A subgroup analysis was performed for patients receiving 1) carboplatin-paclitaxel/docetaxel, and 2) cisplatin-etoposide. When a carboplatin-based regimen was used, concurrent-consolidation was significantly associated with improved OS and CSS (Table 3). When cisplatin-etoposide was used, concurrent-consolidation was not associated with a significant difference in OS or CSS. However, there was only a 34% power to detect the

same OS benefit seen with the carboplatin-taxane cohort. Patients receiving cisplatin-etoposide were much more likely than those receiving carboplatin-paclitaxel/docetaxel to switch chemotherapy regimens for consolidation (78% vs 11%, $p < 0.0001$). A sensitivity analysis including only patients who had a diagnostic PET scan demonstrated similar findings with the subgroups (Supplemental Table 5).

4. Discussion

For stage III NSCLC, chemoradiation is the standard treatment for the majority of patients with multi-station or bulky adenopathy. However, no standard chemoradiation regimen or sequence strategy has emerged despite decades of research. We analyzed patients diagnosed 2002–2009 using SEER-Medicare, allowing us to determine the variations in chemoradiation regimens and sequences and perform comparative effectiveness analyses. The most commonly utilized chemotherapy regimens consisted of platinum-based doublet therapies, of which we found carboplatin-paclitaxel to be the most commonly employed, and the most common chemoradiation sequences were concurrent-alone and concurrent-consolidation. Focusing on concurrent-alone and concurrent-consolidation demonstrated there was no significant variation in outcomes with regards to the choice of chemotherapy regimen. As for chemoradiation sequence, we found that concurrent-consolidation treatment was associated with improved OS and a trend for improved CSS compared to concurrent-alone. A significant OS and CSS advantage with concurrent-consolidation was demonstrated for patients treated with carboplatin-based regimens but not cisplatin-etoposide.

With regards to platinum-based chemotherapy in combination with radiation, its use is supported by a large meta-analysis from 52 trials showing a benefit with cisplatin [26]. However, few randomized trials have directly compared chemotherapy regimens [5], and most have not shown a significant benefit of one platinum-based combination over another, including the CALGB 9431 and PROCLAIM studies [27, 28].

A retrospective study of the Veterans Health Administrative Data showed that compared to carboplatin-paclitaxel, there was no advantage with cisplatin-etoposide, although there was increased toxicity [29]. This was also shown in a prior SEER-Medicare study limited to patients receiving concurrent-alone or sequential chemoradiation [30]. Similarly, we did not find any significant outcome difference between the most commonly used platinum-doublet agents compared to carboplatin-paclitaxel when concurrent-alone or concurrent-consolidation are used, suggesting that choice of doublet in this setting does not have a major impact on patient outcome.

As for the importance of consolidation therapy, prior studies have found conflicting results. A single-arm study of concurrent-consolidation using cisplatin-etoposide during RT and docetaxel consolidation resulted in a promising median survival of 26 months (compared to 15 months of a historical comparison of concurrent-alone) [31]. However, a subsequent randomized trial by Hanna was prematurely terminated for futility [7]. Additionally, there was no benefit to consolidation chemotherapy found in the GILT study using cisplatin-vinorelbine or a South Korean trial using cisplatin-docetaxel [8, 9]. Finally, this lack of

benefit of consolidation therapy was shown in a meta-analysis of 41 trials by Tsujino [10]. On the contrary, our study demonstrated improved outcomes with concurrent-consolidation.

Notably, our results were dominated by carboplatin-containing regimens, as 83% of patients received carboplatin-paclitaxel/docetaxel. On subgroup analysis, we found a benefit of concurrent-consolidation for patients treated with carboplatin-paclitaxel/docetaxel, but not with cisplatin-etoposide. Although this study was not adequately powered to detect a similar benefit to concurrent-consolidation in the cisplatin-etoposide cohort, finding no significant difference to concurrent-alone is consistent with the cisplatin-based trials reported by Hanna, Flentje, and Ahn. As for the meta-analysis by Tsujino, all 3 of the randomized trials employed cisplatin, and there was not a separate analysis limited to the carboplatin trials. The benefit we found with concurrent-consolidation using carboplatin may be explained by the fact that carboplatin is typically employed at lower doses during radiation due to toxicity concerns and only given at higher “systemic” doses during consolidation [29, 32, 33]. In contrast, cisplatin is used at “systemic” doses during radiotherapy [7–9, 27–29, 31, 32, 34, 35]. Thus, consolidation chemotherapy in patients receiving carboplatin regimens is likely needed to achieve similar sterilization of micrometastatic disease as can be attained when cisplatin-containing regimens are used with concurrent-alone.

In addition to the strengths compared to prior studies outlined above, our study also had several limitations, including that it is retrospective and relies on Medicare claims and SEER reporting. It is not possible to determine the selection criteria physicians used for a particular chemoradiation regimen or sequence. Thus there is a potential concern for selection bias, which could affect outcomes. To minimize this bias, we controlled for a modified Charlson comorbidity score as well as a proxy for performance status [19]. We are also unable to determine exact radiation dosimetric, targeting, and motion management techniques. However, to mitigate radiotherapy variation, treatment was limited to IMRT or 3D-CRT and models were adjusted for treatment year. Furthermore, we included only patients with 30–40 daily radiation treatment claims, as prior studies have shown that treatment with at least ~60 Gy results in improved survival [36, 37].

5. Conclusions

In summary, using SEER-Medicare we found that for patients with locally advanced NSCLC undergoing definitive chemoradiation survival outcomes are similar for carboplatin- or cisplatin-containing regimens, as long as consolidation chemotherapy is given for patients receiving carboplatin. Our data therefore support a personalized approach to use of consolidation chemotherapy based on the choice of drugs given during radiation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the Applied Research Program, NCI; the

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Abbreviations

IMRT	intensity-modulated radiation therapy
3D-CRT	3-dimensional conformal radiation therapy
PET	positron emission tomography
NCI	National Cancer Institute

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Highlights

- Chemoradiation is used to treat many patients with stage III NSCLC.
- Carboplatin- and cisplatin-containing regimens resulted in similar outcomes.
- Consolidation chemotherapy after concurrent chemoradiation improved survival.
- Consolidation chemotherapy only benefited patients treated with carboplatin.
- When using carboplatin, consolidation chemotherapy should be considered.

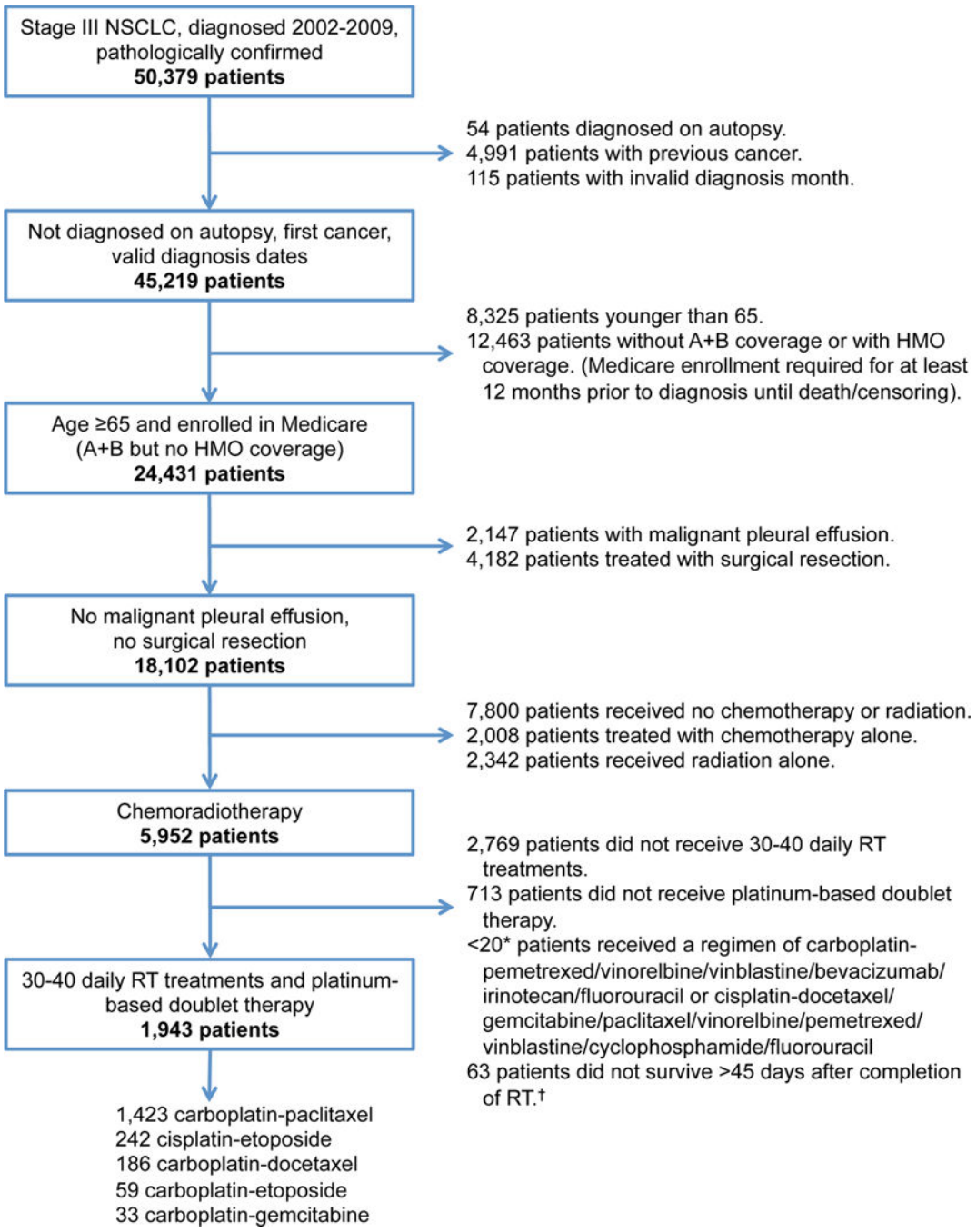

Figure 1. Cohort of patients treated with chemoradiation for stage IIIA/B non-small-cell lung cancer identified from SEER-Medicare diagnosed 2002–2009

The cohort selection of patients identified using SEER-Medicare data. * Exact figures <11 not specified to protect patient identity. † These patients were included in the extended Cox regression model.

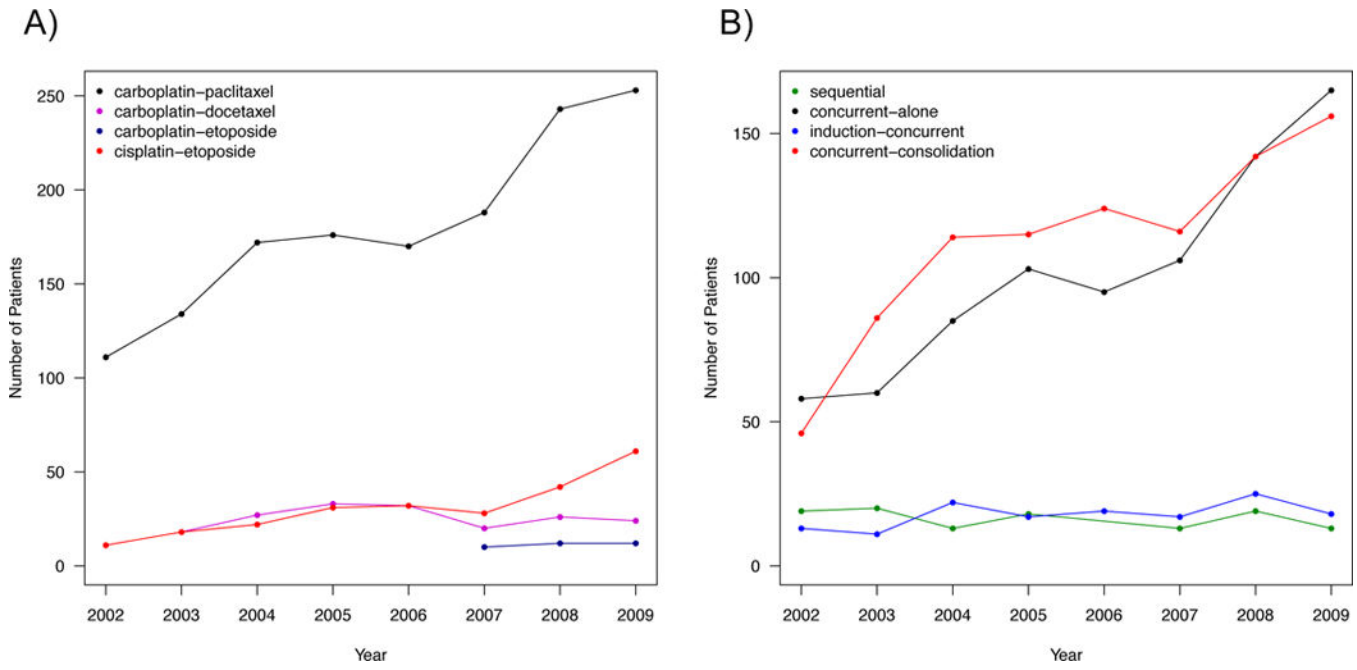

Figure 2. The use of chemoradiation regimens and sequences for stage III non-small-cell lung cancer over time

Prevalence of: a) the most commonly employed platinum-based chemoradiation regimens and b) chemoradiation sequences used from 2002–2009 for stage III NSCLC. Data points representing <11 patients not shown to protect patient identity.

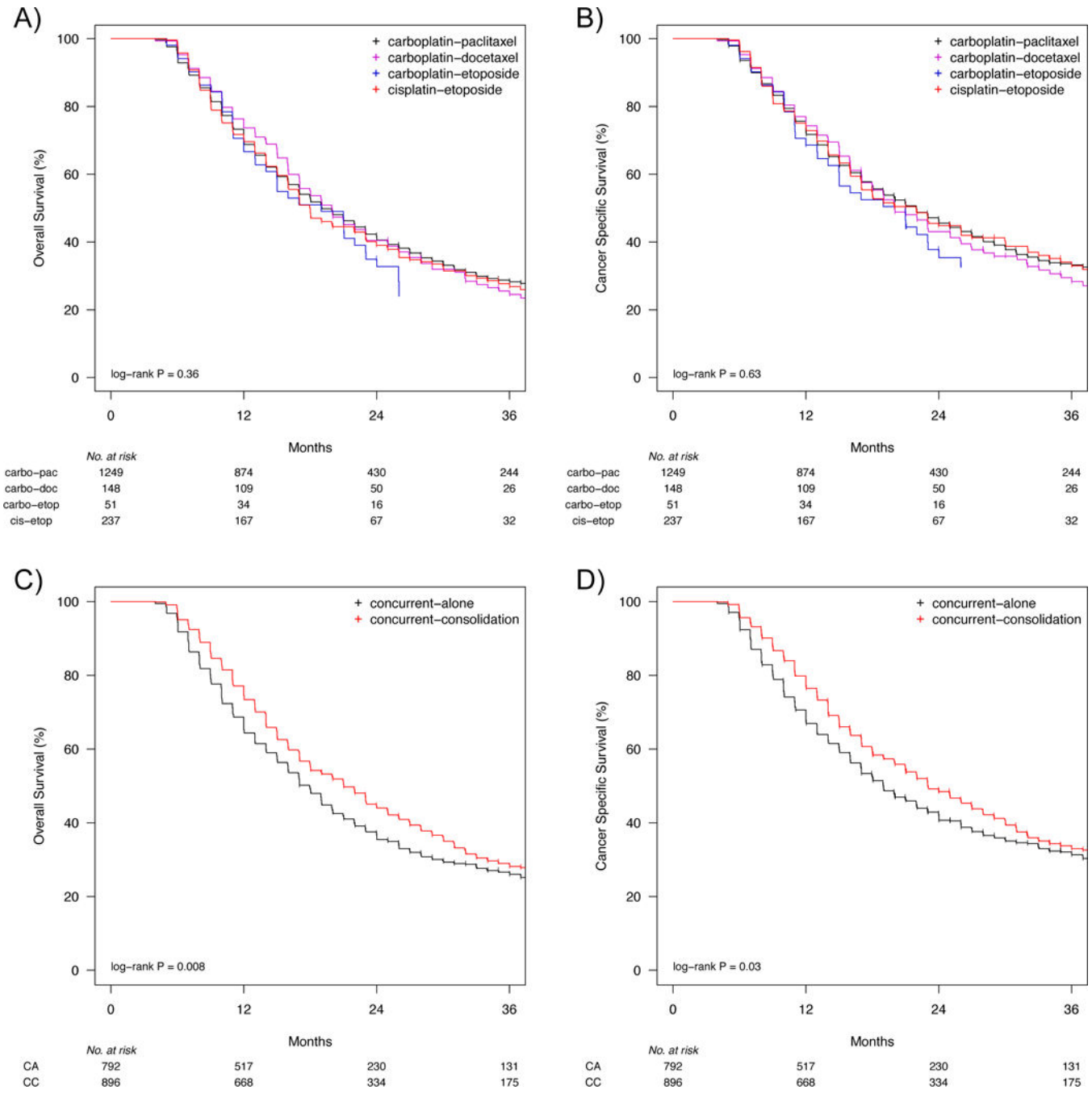

Figure 3. Survival analysis of patients with stage III non-small-cell lung cancer treated with concurrent-alone or concurrent-consolidation chemoradiation by regimen and sequence

a) OS and b) CSS did not vary by chemotherapy regimen for patients treated with chemoradiation. Concurrent-consolidation resulted in improved outcomes compared to concurrent-alone, with c) a median OS of 21 months versus 18 months, and d) a median CSS of 23 months versus 19 months. Median follow up was 29 months, and curves are truncated at 36 months. Data is not shown where n < 11 to protect patient identity.

Table 1

Differences of demographic, clinical, and treatment characteristics of patients with stage III NSCLC by chemoradiation sequence.

Characteristic	Concurrent-alone n=792	Concurrent-consolidation n=896	Induction-Concurrent n=140	Sequential n=115	P	P*
Chemoradiation regimen						
Carboplatin-paclitaxel	595	654	99	75	<.0001	0.0005
Carboplatin-docetaxel	48	100	21	17		
Carboplatin-gemcitabine	<11	<11	<20	<20		
Carboplatin-etoposide	19	>22	<11	<11		
Cisplatin-etoposide	128	>99	<11	<11		
Age						
Median	74	72	73	74	<.0001	<.0001
Gender						
Male	427	504	75	59	0.64	0.35
Female	365	392	65	56		
Race						
White	685	764	129	104	0.16	0.15
Black	57	76	<11	<11		
Hispanic	28	20	<11	<11		
Other	22	36	<11	<11		
Marital status						
Unmarried	324	315	53	35	0.03	0.003
Married	456	549	>73	>66		
Unknown	12	32	<11	<11		
Year of diagnosis						
2002	54	46	13	18	0.0009	0.18
2003	58	85	11	18		
2004	82	113	21	13		
2005	99	115	17	17		
2006	94	124	19	<11		
2007	106	116	17	11		

Characteristic	Concurrent-alone n=792	Concurrent-consolidation n=896	Induction-Concurrent n=140	Sequential n=115	P	P*
2008	138	141	25	>9		
2009	161	156	17	12		
Geographic region						
West	258	280	51	34	0.10	0.80
Midwest	151	170	20	12		
South	212	235	36	29		
Northeast	171	211	33	40		
Urban region						
Urban	701	793	128	>97	0.36	1.00
Rural	91	103	12	<11		
Educational attainment of area (≥4 years college)						
1st quartile	199	231	28	22	0.26	0.92
2nd quartile	199	230	34	27		
3rd quartile	197	225	41	25		
4th quartile	197	210	37	41		
Median income of area						
1st quartile	198	237	29	21	0.26	0.66
2nd quartile	210	217	34	24		
3rd quartile	197	218	41	31		
4th quartile	187	224	36	39		
Modified Charlson comorbidity						
0	511	563	98	66	0.69	0.85
1	196	231	29	35		
2	51	65	<11	<11		
≥3	34	37	<11	<11		
Performance score proxy						
0	723	827	>121	>98	0.47	0.14
1	42	52	<11	<11		
≥2	27	17	<11	<11		
COPD						

Characteristic	Concurrent-alone n=792	Concurrent-consolidation n=896	Induction-Concurrent n=140	Sequential n=115	P	P*
No	512	590	106	70	0.05	0.61
Yes	280	306	34	45		
Home oxygen use						
No	727	838	>122	103	0.26	0.19
Yes	65	58	<11	12		
Tumor size						
≤2 cm	66	77	15	11	0.33	0.16
2.1–3 cm	114	119	20	12		
3.1–5 cm	247	269	38	32		
5.1–7 cm	153	151	28	25		
≥7 cm	75	121	22	11		
Unknown	137	159	17	24		
Nodal status						
N0	115	107	16	11	0.14	0.02
N1	37	>20	<11	<11		
N2	511	570	88	>69		
N3	117	180	>20	18		
Unknown	12	<11	<11	<11		
Histology						
Adenocarcinoma	214	265	51	35	0.35	0.51
Squamous cell	303	330	51	39		
Other	275	301	38	41		
Diagnostic PET done						
No	425	503	93	89	<.0001	0.33
Yes	367	393	47	26		
Brain CT/MR done						
No	295	313	61	72	<.0001	0.33
Yes	497	583	79	43		
Invasive mediastinal imaging performed						
No	629	671	116	89	0.06	0.03

Characteristic	Concurrent-alone n=792	Concurrent-consolidation n=896	Induction-Concurrent n=140	Sequential n=115	P	P*
Yes	163	225	24	26		
Radiation type						
IMRT	110	97	17	15	0.29	0.06
3D-CRT	682	799	123	100		
Radiation facility type						
Freestanding center	198	206	32	36	0.12	0.48
Hospital-based center	219	268	47	21		
Hospital-based NCI center	375	422	61	58		
Area radiation oncologist density	179	222	36	22		
1st quartile					0.006	0.0009
2nd quartile	180	162	27	22		
3rd quartile	164	177	35	34		
4th quartile	162	246	28	>17		
Unknown	107	89	14	<11		

*P value represents concurrent-alone versus concurrent-consolidation. Exact figures not specified in some cells to protect patient identity.

Table 2

Comparison of overall survival (OS) and cancer specific survival (CSS) by treatment, clinical, and demographic covariates for patients with stage III NSCLC treated with chemoradiation. Hazard ratios are determined from multivariate Royston-Parmar flexible parametric models.

	OS			CSS		
	Hazard Ratio	**P**	**Adjusted P***	**Hazard Ratio**	**P**	**Adjusted P***
Chemoradiation sequence						
Concurrent-alone	Reference			Reference		
Concurrent-consolidation	0.85	0.006	0.04	0.87	0.03	0.12
Chemoradiation regimen						
Carboplatin-paclitaxel	Reference			Reference		
Cisplatin-etoposide	1.07	0.40	0.63	1.04	0.68	0.88
Carboplatin-docetaxel	1.02	0.88	0.94	1.04	0.75	0.88
Carboplatin-etoposide	1.28	0.12	0.36	1.29	0.13	0.36
Carboplatin-gemcitabine	1.92	0.27	0.48	1.36	0.67	0.88
Age	1.01	0.06	0.24	1.01	0.03	0.12
Gender						
Male	Reference			Reference		
Female	0.92	0.17	0.38	0.96	0.59	0.87
Race						
White	Reference			Reference		
Black	0.91	0.45	0.64	0.88	0.32	0.61
Hispanic	0.82	0.27	0.48	0.93	0.69	0.88
Other	0.96	0.78	0.94	0.98	0.89	0.94
Marital status						
Unmarried	Reference			Reference		
Married	1.09	0.19	0.40	1.15	0.05	0.16
Educational attainment of area (≥4 years college)						
1st quartile	Reference			Reference		
2nd quartile	0.96	0.67	0.90	0.97	0.76	0.88
3rd quartile	0.95	0.58	0.81	0.96	0.71	0.88
4th quartile	1.05	0.69	0.90	1.03	0.78	0.88

	OS			CSS		
	Hazard Ratio	**P**	**Adjusted P***	**Hazard Ratio**	**P**	**Adjusted P***
Median income of area						
1st quartile	Reference			Reference		
2nd quartile	1.11	0.20	0.41	1.13	0.19	0.43
3rd quartile	1.21	0.05	0.22	1.27	0.020	0.11
4th quartile	1.03	0.82	0.94	1.07	0.59	0.87
Modified Charlson comorbidity						
0	Reference			Reference		
1	1.10	0.16	0.38	1.06	0.43	0.75
2	1.17	0.17	0.38	1.08	0.53	0.87
≥3	1.17	0.29	0.49	1.21	0.22	0.48
Performance score proxy						
0	Reference			Reference		
1	0.98	0.90	0.94	0.98	0.91	0.94
≥2	1.04	0.84	0.94	1.13	0.56	0.87
COPD						
No	Reference			Reference		
Yes	1.00	0.95	0.97	1.04	0.62	0.88
Home oxygen use						
No	Reference			Reference		
Yes	1.17	0.17	0.38	1.01	0.92	0.94
Tumor size						
≤2 cm	Reference			Reference		
2.1–3 cm	1.02	0.85	0.94	1.05	0.70	0.88
3.1–5 cm	1.26	0.040	0.22	1.33	0.020	0.11
5.1–7 cm	1.17	0.21	0.42	1.20	0.16	0.39
≥7 cm	1.57	0.0006	0.007	1.66	0.0004	0.005
Nodal status						
N0	Reference			Reference		
N1	1.30	0.11	0.36	1.37	0.06	0.20
N2	1.18	0.06	0.24	1.14	0.17	0.39

	OS			CSS		
	Hazard Ratio	**P**	**Adjusted P***	**Hazard Ratio**	**P**	**Adjusted P***
N3	1.35	0.005	0.04	1.37	0.007	0.05
Histology						
Adenocarcinoma	Reference			Reference		
Squamous cell	1.02	0.76	0.94	0.98	0.77	0.88
Other	0.99	0.88	0.94	1.00	0.99	0.99
Diagnostic PET done						
No	Reference			Reference		
Yes	0.90	0.08	0.30	0.85	0.02	0.11
Brain CT/MR done						
No	Reference			Reference		
Yes	1.09	0.15	0.38	1.05	0.45	0.76
Invasive mediastinal staging performed						
No	Reference			Reference		
Yes	0.84	0.01	0.08	0.85	0.03	0.12
Radiation type						
IMRT	Reference			Reference		
3D-CRT	0.93	0.42	0.91	0.91	0.33	0.61
Radiation facility type						
Freestanding center	Reference			Reference		
Hospital-based center	1.06	0.44	0.64	1.09	0.29	0.60
Hospital-based NCI center	0.94	0.36	0.59	0.99	0.91	0.94
Area radiation oncologist density						
1st quartile	Reference			Reference		
2nd quartile	1.00	0.97	0.97	0.91	0.34	0.61
3rd quartile	0.90	0.26	0.48	0.86	0.12	0.35
4th quartile	0.88	0.16	0.38	0.81	0.03	0.12

*Benjamini-Hochberg adjusted p values.

Abbreviations: HR = hazard ratio; 3D-CRT = 3-dimensional conformal radiation therapy; IMRT = intensity-modulated radiation therapy; ET = positron emission tomography; NCI = National Cancer Institute.

Table 3

Subgroup analysis comparing concurrent-consolidation to concurrent-alone for patients treated with a carboplatin- or cisplatin-based chemotherapy regimen during the concurrent phase of chemoradiation. Hazard ratios for overall survival (OS) and cancer-specific survival (CSS) were determined from inverse probability of treatment weighting analysis, with a hazard ratio <1 representing a benefit with concurrent-consolidation. Propensity scores were used to represent probability of treatment.

	OS			CSS		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**
Carboplatin-paclitaxel/docetaxel	0.83	(0.73–0.95)	0.006	0.85	(0.74–0.98)	0.02
Cisplatin-etoposide	0.91	(0.60–1.40)	0.67	0.89	(0.57–1.41)	0.63