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A population-based comparative effectiveness study of chemoradiation regimens and sequences in stage III non-small cell lung cancer

Jeremy P. Harris[a], Manali I. Patel[b], Billy W. Loo[a,c], Heather A. Wakelee[b,c], Maximilian Diehn[a,c,d,*]

[a] Department of Radiation Oncology, Stanford University School of Medicine, 875 Blake Wilbur Dr, MC 5847, Stanford, CA 94305, United States
[b] Division of Oncology, Department of Medicine, Stanford University School of Medicine, 269 Campus Dr, Stanford, CA 94305, United States
[c] Stanford Cancer Institute, 265 Campus Drive, Ste G2103, Stanford, CA 94305, United States
[d] Institute for Stem Cell Biology and Regenerative Medicine, 265 Campus Drive, 3rd Floor Stanford, CA 94305, United States

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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: 1688 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 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.

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].

* Corresponding author at: Department of Radiation Oncology, Stanford Cancer Institute, and Institute for Stem Cell Biology & Regenerative Medicine, Stanford University School of Medicine, Radiation Oncology, 875 Blake Wilbur Dr., MC 5847, Stanford, CA 94305, United States.
E-mail address: diehn@Stanford.edu (M. Diehn).

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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