CONTROVERSIES IN THE LOCAL MANAGEMENT OF LUNG CANCER

EDITED BY: John M. Varlotto and Giulia Veronesi
PUBLISHED IN: Frontiers in Oncology

frontiers Research Topics

frontiers

Frontiers Copyright Statement

© Copyright 2007-2018 Frontiers Media SA. All rights reserved.

All content included on this site, such as text, graphics, logos, button icons, images, video/audio clips, downloads, data compilations and software, is the property of or is licensed to Frontiers Media SA ("Frontiers") or its licensees and/or subcontractors. The copyright in the text of individual articles is the property of their respective authors, subject to a license granted to Frontiers.

The compilation of articles constituting this e-book, wherever published, as well as the compilation of all other content on this site, is the exclusive property of Frontiers. For the conditions for downloading and copying of e-books from Frontiers' website, please see the Terms for Website Use. If purchasing Frontiers e-books from other websites or sources, the conditions of the website concerned apply.

Images and graphics not forming part of user-contributed materials may not be downloaded or copied without permission.

Individual articles may be downloaded and reproduced in accordance with the principles of the CC-BY licence subject to any copyright or other notices. They may not be re-sold as an e-book.

As author or other contributor you grant a CC-BY licence to others to reproduce your articles, including any graphics and third-party materials supplied by you, in accordance with the Conditions for Website Use and subject to any copyright notices which you include in connection with your articles and materials.

All copyright, and all rights therein, are protected by national and international copyright laws.

The above represents a summary only. For the full conditions see the Conditions for Authors and the Conditions for Website Use.

ISSN 1664-8714
ISBN 978-2-88945-561-4
DOI 10.3389/978-2-88945-561-4

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: researchtopics@frontiersin.org

CONTROVERSIES IN THE LOCAL MANAGEMENT OF LUNG CANCER

Topic Editors:
John M. Varlotto, University of Massachusetts, United States
Giulia Veronesi, Humanitas Clinical and Research Center, Italy

Cover image: Magic mine/Shutterstock.com

This special edition of Frontiers in Oncology reviews the current efficacy and limitations of surgical and radiotherapeutic management of lung cancer and provides insight into how local management options may change in the future.

Citation: Varlotto, J. M., Veronesi, G., eds. (2018). Controversies in the Local Management of Lung Cancer. Lausanne: Frontiers Media. doi: 10.3389/978-2-88945-561-4

Table of Contents

CHAPTER 4

THE EFFECTS OF SOCIOECONOMIC VARIABLES ON SURGICAL OUTCOMES

frontiers in Oncology

EDITORIAL
published: 18 June 2018
doi: 10.3389/fonc.2018.00233

Editorial: Controversies in the Local Management of Lung Cancer

John M. Varlotto[1] and Giulia Veronesi[2]*

[1] Department of Radiation Oncology, University of Massachusetts Medical Center, Worcester, MA, United States, [2] Division of Thoracic Surgery, Humanitas Clinical and Research Center, Rozzano, Milan, Italy

Keywords: lung cancer, multi-modality treatment, thoracic surgery, radiation therapy, lung cancer treatment

Editorial on the Research Topic

Controversies in the Local Management of Lung Cancer

At the time we agreed to edit this special edition of Frontiers in early 2017, the immunotherapy revolution was already established in the second-line treatment of metastatic non-small cell lung cancer (NSCLC) (1–4) and even to a select group of patients (those whose tumor cells expressed PD-L1 of ≥50%) (5) in the first-line treatment of metastatic disease. We felt that the summarization and understanding of the strengths and benefits of our local modalities were needed prior to the possible integration of immunotherapy into the treatment paradigms of Stages I–III NSCLC and small cell lung cancer (SCLC).

Three of this issue's 10 article deal with the controversial topic of neo-adjuvant treatment prior to surgery in the management of Stage III lung cancer from the prospective of a multi-disciplinary team (Lewis et al.), a Radiation Oncologist (Sher), and a Thoracic Surgical group (Van et al.). Although no definitive management strategy was recommended as "the way" to manage Stage III NSCLC, each article does a great job of reviewing the current literature, while offering its own unique perspective. The article by Van et al. additionally discusses the rarely investigated topic of salvage surgery.

Four articles dealt with unconventional and/or innovative uses of radiation. Ohri provides a provocative article concerning dose escalation as well as dose de-escalation. Although the idea of dose de-escalation is unpalatable to most Radiation Oncologists, this idea may be considered to be prescient because of the now described synergism between concomitant cytotoxic therapy and immunotherapy in patients with metastatic non-squamous cell NSCLC (6). Kumar et al. offer a pioneering approach to the treatment of Stage III NSCLC which they have labeled quadmodality therapy (concurrent chemo/radiation followed by a stereotactic boost to residual sites of disease, followed by immunotherapy) for the more aggressive treatment of locally advanced lung cancer (Kumar et al.). Both studies, offer different approaches to the hopefully successful integration of immunotherapy with standard chemo/radiation in the near future. Bergsma et al. discuss the rationale and increasingly strong evidence for administering stereotactic body radiation therapy (SBRT) in patients with oligometastatic NSCLC (Bergsma et al.). The work of these investigators and others have led to the NRG LU002 trial that will be investigating the role of SBRT for patients with three or fewer sites of remaining extracranial disease after chemotherapy. Chun et al. have provided a nice review article on heavy ion therapy in the management of NSCLC. Although the recently published prospective randomized trial of passive scattering proton radiation vs intensity-modulated radiation did not reveal any benefit from proton therapy in terms of local failure, radiation pneumonitis, and lung dosimetry, protons resulted in lower heart doses despite larger having larger gross tumor volumes in that trial arm (7). Because heart dose was a strong determinant of overall survival in RTOG 0167's failure to improve outcomes by radiation dose escalation (8), it is hoped that the Bragg–Peak associated with heavy ion therapy will be proven to offer improved local control while limiting normal tissue damage.

OPEN ACCESS

Edited and Reviewed by:
Timothy James Kinsella, Warren Alpert Medical School of Brown University, United States

****Correspondence:***
John M. Varlotto
john.varlotto@umassmemorial.org

Specialty section:
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

Received: *30 May 2018*
Accepted: *06 June 2018*
Published: *18 June 2018*

Citation:
Varlotto JM and Veronesi G (2018) Editorial: Controversies in the Local Management of Lung Cancer. Front. Oncol. 8:233. doi: 10.3389/fonc.2018.00233

The articles by Bloom et al. and Jeremic et al. remind the readers of Frontiers how important local management is to the outcomes of SCLC. Bloom et al. offer a comprehensive review of the literature concerning prophylactic cranial irradiation (PCI) in the management of surgically resectable SCLC. Because the incidence of early-stage SCLC is increasing (9), the review of this topic is very important. Although the authors could not reach a definitive conclusion regarding PCI, it is hoped that NRG CC003 demonstrates that hippocampal sparing allows for effective PCI while limiting harmful neurocognitive sequelae and makes the decision to administer PCI in surgically resectable SCLC an easier one. Jeremic et al. comprehensively review consolidative thoracic radiation in the management of extensive stage SCLC from their pioneering work published in 1999 (10) to the more recent work of Slotman et al. (11). They also discuss the potential merits of different radiation fractionation regimens and the use of sequential vs concomitant chemo/radiation regimens. Furthermore, the authors provide a timely update of the conflicting data (12, 13) in regards to the use of PCI for the treatment of patients with extensive stage SCLC.

Although there are no articles in this edition concerning the benefits and risk of SBRT in comparison to surgical resection for patients with Stage I NSCLC, and past retrospective studies (14, 15) and one small publication of prospective data (16) have suggested equivalency, it is hoped that future studies may shed light on proper patient selection for either of these very effective techniques. Until then, the article by Varlotto et al. sheds needed light on how psychosocial aspects can adversely affect the outcomes of surgically resected NSCLC. These authors demonstrated that not being married and having insurance resulted in lower overall survival/lung cancer-specific survival, increased 90-day mortality and a higher incidence of positive nodes upon resection.

During the last decade surgical treatment of lung cancer changed deeply thanks to the large diffusion of minimally invasive approaches that become the standard approach for early-stage lung cancer (17). Thanks to the introduction of robotic technology, more recently, even selected patients with more advanced disease, even after induction treatment for N2 involvement, have been approached with minimally invasive robotic surgery to reduce surgical trauma, a very important goal in patients with already increased fragility due to systemic treatment (18). Recent publications showed that robotic approach was safe and effective in this subgroup of patients, paving the way to potential changes in the indications of surgical resection in stage III patients, and a rethinking of the better timing for systemic and local treatment (19) with potential advantages to propose minimally invasive surgery upfront for N2 single station disease.

Since our initial agreement to edit this special edition, immunotherapy has continued to radically change the lung cancer landscape. A press release from Merck on April 9, 2018 concerning Keynote-042 demonstrated a superior OS for pembrolizumab (a PD-1 inhibitor) as compared to platinum-based chemotherapy in the first-line setting. The benefit was shown in a population of patients with PD-L1 of $\geq$1% which means that the majority of patients presenting with metastatic NSCLC can benefit from immunotherapy alone as their initial treatment. Furthermore, Keynote 189 (Van et al.) noted an improved overall survival and progression-free survival using combined immunotherapy (pembolizumab) and chemotherapy as compared to chemotherapy alone. Additionally, consolidative durvalumab (a PD-L1 inhibitor) has shown an impressive progression-free survival benefit in patients with stage III lung cancer after the completion of concurrent chemo/radiation (20). We feel that the articles in this special edition can help the readers of Frontiers better understand the strength and limitations of our existing local therapies so that we can better understand how to incorporate immunotherapy in the management of Stage I–III NSCLC and SCLC.

We are very grateful to the tremendous efforts of the fellow authors, the reviewers, and staff at Frontiers for making this special edition possible.

AUTHOR CONTRIBUTIONS

GV and JV both wrote this article.

REFERENCES

1. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* (2015) 373:1627–39. doi:10.1056/NEJMoa1507643
2. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* (2015) 373:123–35. doi:10.1056/NEJMoa1504627
3. Herbst RS, Baas P, Kim D-W, Felip E, Pérez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomized controlled trial. *Lancet* (2016) 387:3540–50. doi:10.1016/S0140-6736(15)01281-7
4. Rittmeyer A, Barlesi F, Watercamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomized controlled trial. *Lancet* (2017) 389:255–65. doi:10.1016/S0140-6736(16)32517-X
5. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* (2016) 375:1823–33. doi:10.1056/NEJMoa1606774
6. Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small cell lung cancer. *N Engl J Med* (2018) 378(22):2078–92. doi:10.1056/NEJMoa1801005
7. Liao Z, Lee JJ, Komaki R, Gomez DR, O'Reilly MS, Fossella FV, et al. Bayesian adaptive randomization trial of passive scattering proton therapy and intensity-modulated photon radiotherapy for locally advanced non-small-cell lung cancer. *J Clin Oncol* (2018). doi:10.1200/JCO.2017.74.0720
8. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* (2015) 16:187–99. doi:10.1016/S1470-2045(14)71207-0
9. Varlotto JM, Recht A, Flickinger JC, Medford-Davis LN, Dyer A-M, DeCamp MM. Lobectomy leads to optimal survival in early-stage small cell lung cancer: a retrospective analysis. *J Thorac Cardiovasc Surg* (2011) 142:538–46. doi:10.1016/j.jtcvs.2010.11.062
10. Jeremic B, Shibamoto Y, Nikolic N, Milicic B, Milisavljevic S, Dagovic A, et al. The role of radiation therapy in the combined modality treatment of patients with extensive disease small-cell lung cancer (ED SCLC): a randomized study. *J Clin Oncol* (1999) 17:2092–9. doi:10.1200/JCO.1999.17.7.2092

11. Slotman BJ, van Tinteren H, Praag JO, Knegjens JL, El Sharouni SY, Hatton M, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. *Lancet* (2015) 385:36–42. doi:10.1016/S0140-6736(14)61085-0
12. Takahashi T, Yamanaka T, Seto T, Harada H, Nokihara H, Saka H, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* (2017) 18:663–71. doi:10.1016/S1470-2045(17)30230-9
13. Slotman B, Faivre-Finn C, Kramer G, Rankin E, Snee M, Hatton M, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* (2007) 357:664–72. doi:10.1056/NEJMoa071780
14. Varlotto JM, Fakiris A, Flickinger JC, Medford-Davis L, Liss A, Shelkey J, et al. Matched-pair and propensity score comparisons of outcomes of patients with clinical stage I non-small cell lung cancer treated with resection of stereotactic radiosurgery. *Cancer* (2013) 119:2683–91. doi:10.1002/cncr.28100
15. Verstegen NE, Oosterhuis JW, Palma DA, Rodrigues G, Lagerwaard FJ, van der Elst A, et al. Stage I-II non-small cell lung cancer treated using either stereotactic ablative radiotherapy(SABR) or lobectomy by video-assisted thoracoscopic surgery(VATS): outcomes of a propensity score-matched analysis. *Ann Oncol* (2013) 24:1543–8. doi:10.1093/annonc/mdt026
16. Chang JY, Senan S, Paul M, Mehran RJ, Louie AV, Balter P, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small cell lung cancer: a pooled analysis of two randomized trials. *Lancet Oncol* (2015) 16:630–7. doi:10.1016/S1470-2045(15)70168-3
17. Yan TD, Cao C, D'Amico TA, Demmy TL, He J, Hansen H, et al. Video-assisted thoracoscopic surgery lobectomy at 20 years: a consensus statement. *Eur J Cardiothorac Surg* (2014) 45:633–9. doi:10.1093/ejcts/ezt463
18. Cerfolio RJ, Ghanim AF, Dylewski M, Veronesi G, Spaggiari L, Park BJ. The long-term survival of robotic lobectomy for non-small cell lung cancer: a multi-institutional study. *J Thorac Cardiovasc Surg* (2018) 155:778–86. doi:10.1016/j.jtcvs.2017.09.016
19. Veronesi G, Park B, Cerfolio R, Dylewski M, Toker A, Fontaine JP, et al. Robotic resection of stage III lung cancer: an international retrospective study. *Eur J Cardiothorac Surg* (2018). doi:10.1093/ejcts/ezy166
20. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* (2017) 377:1919–29. doi:10.1056/NEJMoa1709937

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2018 Varlotto and Veronesi. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

REVIEW
published: 23 January 2018
doi: 10.3389/fonc.2018.00005

Before or After: Evolving Neoadjuvant Approaches to Locally Advanced Non-Small Cell Lung Cancer

Jennifer Lewis[1,2], Erin A. Gillaspie[3], Evan C. Osmundson[4] and Leora Horn[1]*

[1] Division of Hematology/Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, United States, [2] Veterans Health Administration-Tennessee Valley Healthcare System, Geriatric Research Education Clinical Center, HSR&D Center, Nashville, TN, United States, [3] Department of Thoracic Surgery, Vanderbilt University Medical Center, Nashville, TN, United States, [4] Department of Radiation Oncology, Vanderbilt University Medical Center, Nashville, TN, United States

The treatment of patients with stage IIIA (*N2*) non-small cell lung cancer (NSCLC) is one of the most challenging and controversial areas of thoracic oncology. This heterogeneous group is characterized by varying tumor size and location, the potential for involvement of surrounding structures, and ipsilateral mediastinal lymph node spread. Neoadjuvant chemotherapy, administered prior to definitive local therapy, has been found to improve survival in patients with stage IIIA (*N2*) NSCLC. Concurrent chemoradiation has also been evaluated in phase III studies in efforts to improve control of locoregional disease. In certain instances, a tri-modality approach involving concurrent chemoradiation followed by surgery, may offer patients the best chance for cure. In this article, we provide an overview of the trials evaluating neoadjuvant therapy in patients with stage IIIA (*N2*) NSCLC that have resulted in current practice strategies, and we highlight the areas of uncertainty in the management of this challenging disease. We also review the current ongoing research and future directions in the management of stage IIIA (*N2*) NSCLC.

Keywords: neoadjuvant chemotherapy, induction chemotherapy, neoadjuvant chemoradiation, tri-modality, stage IIIA non-small cell lung cancer, mediastinal disease

OPEN ACCESS

Edited by:
John Varlotto, University of Massachusetts Medical School, United States

Reviewed by:
Malcolm M. DeCamp, Feinberg School of Medicine, Northwestern University, United States
Monaliben Patel, University of Massachusetts Medical School, United States

****Correspondence:***
Jennifer Lewis
jennifer.a.lewis@vanderbilt.edu

Specialty section:
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

Received: *01 August 2017*
Accepted: *05 January 2018*
Published: *23 January 2018*

Citation:
Lewis J, Gillaspie EA, Osmundson EC and Horn L (2018) Before or After: Evolving Neoadjuvant Approaches to Locally Advanced Non-Small Cell Lung Cancer. Front. Oncol. 8:5. doi: 10.3389/fonc.2018.00005

INTRODUCTION

An estimated 222,500 new cases of lung cancer are expected in the United States in 2017, of which approximately 80% will be non-small cell lung cancer (NSCLC) (1). Furthermore, approximately 15% of NSCLC cases will present with stage IIIA (*N2*) disease (2). This highly heterogeneous group is characterized by widely variable tumor sizes (sub-centimeter up to 7 cm), possible invasion of local structures, and microscopic or bulky ipsilateral mediastinal or subcarinal lymph node involvement. The degree of mediastinal lymph node involvement has significant prognostic implications. Patients with microscopic involvement have an estimated 5-year overall survival (OS) of 34%. However, OS falls to 11% when more than one lymph node station is involved with microscopic disease and 3–8% for patients with clinical lymph node involvement, seen radiographically, or including multiple stations (3).

Initial staging of lung cancer is performed *clinically* with radiographic studies evaluating the primary tumor size and the presence of enlarged lymph nodes. Such studies may not accurately reflect nodal status since microscopic disease would not be detectable by imaging studies alone.

A pathologic evaluation of the mediastinum with EBUS or mediastinoscopy is paramount to accurate staging, allowing clinicians to determine the optimal strategy in care.

Due to the wide range of presentations within this group, defining the most effective treatment approach has been historically challenging. In the 1970s, the overall cure rate for lung cancer was estimated to be 25% following resection (4). Surgeons at the time noted long-term survivals and an increase in the 5-year survival of up to 30–40% with surgery in a subset of patients with stage IIIA NSCLC with peripheral tumors and microscopic *N*2 disease (5–7). Unfortunately, outcomes were complicated by high rates of locoregional failure and distant recurrence following resection, which led investigators to consider a neoadjuvant treatment strategy for this group of NSCLC patients.

Neoadjuvant, or induction, therapy is defined as therapy administered prior to definitive local treatment (8). Neoadjuvant chemotherapy in patients with early and advanced stage NSCLC was first used in the 1950s, when investigators employed mitomycin C and chromomycin A3 in a "long-term intermittent schedule," in which the first cycle was started prior to surgery (4). A dose of mitomycin C was even "infused directly into the pulmonary vein draining the tumor" during surgery, with the remainder of the cycle delivered post-operatively. Patients then continued on 4-week cycles for up to 3 years after surgery (4). Today, the neoadjuvant therapeutic strategy remains one of the most hotly debated topics among thoracic oncology specialists. The theoretical benefit of neoadjuvant therapy includes earlier treatment of micrometastatic disease, reduction in tumor burden, evaluation of tumor sensitivity *in vivo*, prevention of tumor seeding at the time of surgery, and possible improved compliance with therapy (9). In this article, we will review the literature on the use of neoadjuvant systemic therapy for stage IIIA (*N*2) NSCLC, focusing on phase III trials as well as areas of further research.

NEOADJUVANT CHEMOTHERAPY

The benefit of neoadjuvant chemotherapy was first suggested by multiple single-arm, and later randomized, phase II studies. These trials demonstrated 3-year survival rates as high as 34% and a median survival of up to 23 months in patients with stage IIIA (*N*2) NSCLC treated with neoadjuvant chemotherapy followed by resection, **Table 1** (10–27). As a result, several randomized-controlled trials were designed to evaluate these findings.

The first published randomized-controlled trial was a small, single-institution phase III trial performed at the National Cancer Institute. Patients with stage IIIA NSCLC, biopsy-proven *N*2 disease, were randomized to surgery alone followed by radiation or two cycles of neoadjuvant chemotherapy with cisplatin and etoposide followed by surgery (28). Patients in the chemotherapy arm with a response, defined radiographically by CT, at the time of surgery underwent an additional four cycles of cisplatin and etoposide post-operatively. Patients without a response to neoadjuvant chemotherapy received post-operative radiation to a total dose of 54–60 Gy. Twenty-seven patients were randomized over 4 years, and the median follow-up period for the chemotherapy arm was 29.9 and 34.9 months for the surgery alone arm. The overall response rate to chemotherapy was 62% (8 of 13 patients). There was no significant difference between the rates of R0 resections (85% in each arm) or types of surgical procedures used (pneumonectomy, lobectomy, etc.) in each arm of the study. There were also no post-operative deaths, which was likely attributable to selection bias and the center at which this trial was conducted. There was a trend toward improved survival in patients treated with neoadjuvant chemotherapy, 28.7 versus 15.6 months. In addition, the disease-free interval was longer in the chemotherapy arm (12.7 versus 5.8 months), and the recurrence rate was also lower in the chemotherapy arm (92 versus

TABLE 1 | Neoadjuvant chemotherapy phase II trials.

Reference	Chemotherapy	*N*	*N*2	ORR (% total)	Surgery (% total)	R0 (% surgery)	PCR (% total)	Survival
Martini et al. (10)	MVP	41	41	73	68	75	20	3 years 34%, 3 years 54% (R0),
Vokes et al. (11)	EVP	27	NR	48	15	NR	0	Median 8 months
Pujol et al. (12)	EPI	33	31	70	61	90	15	18 months 30%, median 10 months
Burkes et al. (13)	MVP	39	39	64	56	82	8	3 years 26%, median 19 months
Martini et al. (14)	MVP	136	136	77	84	78	14	3 years 28%, median 19 months; 3 years 41% (R0)
Darwish et al. (15)	PE	46	46	80	72	85	9	2 years 53%, median 25 months
Sugarbaker et al. (16)	VP	74	74	NR	85	37	0	3 years 23%, 3 years 46% (R0)
Elias et al. (17)	P, 5-FU	34	34	65	82	75	18	Median 18 months
van Zandwijk et al.[a] (18)	GP	47	47	70	NS	NS	NS	Median 19 months
Betticher et al. (19)	DP	90	90	66	83	48	16	EFS 15 months, median 33 months
O'Brien et al.[a] (20)	CT	52	52	64	NS	NS	NS	1 year 68%, median 21 months
De Marinis et al. (21)	GTP	49	49	74	59	93	16	1 year 85%, median 23 months
Cappuzzo et al. (22)	GP	129	88	62	31	95	2	1 year 74%, median 19 months
Burkes et al. (23)	MVP or VP	65	65	68	72	75	5	1 year 66%, median 19 months; 5 years 29%
Biesma et al.[a] (24)	DP	46	46	39	NS	NS	NS	1 year 65%, median 16 months
Garrido et al. (25)	GDP	136	69	53	66	69	6	3 years 37%, median 16 months; 5 years 41% (R0)
Chaft et al. (26)	Bev, DP + Bev	50	NR	40	88	82	NR	3 years 64%
Ou et al. (27)	C, Pem, Bev	42	36	42	74	71	NR	1 year 56%, median EFS 15.4 months

Bev, bevacizumab; C, carboplatin; D, docetaxel; EFS, event-free survival; E, etoposide; 5-FU, 5-fluorouracil; G, gemcitabine; I, ifosfamide; M, mitomycin-C; NR, not reported; NS, not significant; ORR, overall response rate P, cisplatin; V, PCR, pathologic complete response; Pem, pemetrexed; T, paclitaxel; vinblastine/vindesine.

[a]*Patients in this trial were randomized to surgery or radiation after induction chemotherapy as part of the EORTC 08941.*

73%) (28). This trial provided preliminary data, but was not conclusive due to its slow rate of accrual and small sample size, an inherent limitation of single-institution trials.

In a second phase III trial, investigators compared neoadjuvant chemotherapy with mitomycin, ifosfamide, and cisplatin every 21 days for three cycles followed by surgery versus surgery alone in 60 patients with stage IIIA NSCLC (29). The trial was terminated early when an interim analysis at 24 months found that neoadjuvant chemotherapy was associated with a significant improvement in median survival, 26 months versus 8 months. Although this was a dramatic improvement, critics point out the higher percentage of patients with tumors harboring KRAS mutations (42 versus 15%), a negative prognostic factor, in the control arm that may have biased the study (8).

A few months later, the results of a similar randomized-controlled trial involving 60 patients with stage IIIA NSCLC were published. This trial compared neoadjuvant chemotherapy with cyclophosphamide, etoposide, and cisplatin for three cycles followed by surgery and an additional three cycles of chemotherapy post-operatively in responders versus surgery alone. Similarly, this study was terminated early when an interim analysis demonstrated that 35% of patients had a radiographic response to neoadjuvant chemotherapy. Moreover, there was an even greater difference in survival with a median survival of 64 months in the chemotherapy arm compared to 11 months in the surgery only arm. The estimated 2- and 3-year survivals were 60 and 56%, respectively, for the patients who received chemotherapy compared to 25 and 15% for those who received surgery alone (30).

A larger randomized phase III trial conducted by the French Thoracic Cooperative Group also evaluated the role of neoadjuvant chemotherapy in patients with NSCLC. This trial randomized 355 patients with stage IB–IIIA to surgery alone or two cycles of induction chemotherapy with mitomycin, ifosfamide, and cisplatin followed by surgery and then two additional cycles of chemotherapy. Patients who were found to have pT3 or pN2 disease received post-operative radiation to a total dose of 60 Gy. Median survival was 37 months in the chemotherapy plus surgery arm compared to 26 months in the surgery alone arm. The 3-year survival (52 versus 41%) also favored the bi-modality treatment approach of neoadjuvant chemotherapy followed by surgery (31).

These four randomized-controlled trials demonstrated a substantial survival advantage, supporting the use of neoadjuvant chemotherapy for patients with stage IIIA NSCLC undergoing surgical resection. Since the publication of these studies, additional trials have been performed. A meta-analysis of 12 randomized studies from 1995 to 2005, some of which used more modern chemotherapy regimens, also suggests a survival advantage for neoadjuvant chemotherapy in NSCLC. However, many of these trials were small and included patients with early stage disease as well as stage IIIA (*N*2) (32). A logical next question would be, what is the best neoadjuvant chemotherapy regimen to use?

NEOADJUVANT CHEMOTHERAPY CHOICE

Many phase II trials have assessed the efficacy of various chemotherapy combinations. Platinum-based neoadjuvant regimens have consistently demonstrated the highest overall response rates ranging from 50 to 70% depending on the combination, **Table 1** (10–27). Phase II studies have also demonstrated increased rates of resection with the use of neoadjuvant platinum-based regimens, albeit with the usual caveats of institutional bias and surgical capabilities at the sites where the trials were conducted (7). Neoadjuvant cisplatin and etoposide with or without radiation is perhaps the most studied regimen as we discuss in the trials below (15, 33–38). However, randomized phase II and phase III studies have also evaluated more modern agents, including cisplatin–vinorelbine, cisplatin–gemcitabine, cisplatin–docetaxel, and cisplatin–pemetrexed (18, 24, 39–41).

In general, carboplatin and paclitaxel is an attractive chemotherapy combination for the treatment of NSCLC due to its more favorable toxicity profile. This regimen has been evaluated in the neoadjuvant setting for NSCLC in several clinical trials, including a phase II trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) in patients with stage IIIA (N2) disease. This trial demonstrated a response rate of 64%, median survival of 20.5 months, and an estimated 1-year survival of 68.5% in patients treated with carboplatin and paclitaxel (20). Randomized phase III trials have also employed this regimen, such as the S9900 trial that randomized patients with stage I–IIIA NSCLC to three cycles of neoadjuvant chemotherapy or to surgery alone. Of note, this trial excluded patients with single-station *N*2 disease. The overall response rate to neoadjuvant chemotherapy was 41% and the OS improved from 46 months in the control arm to 74 months in the neoadjuvant chemotherapy arm (42). A large, randomized European phase III trial (NATCH) demonstrated a 53.3% overall response rate for neoadjuvant carboplatin and paclitaxel in patients with early stage NSCLC. Lastly, other chemotherapy combinations utilizing carboplatin have been studied. A small phase II trial found that carboplatin, pemetrexed, and bevacizumab are safe in the neoadjuvant setting with a response rate of 45% and median survival of 37 months (26).

The major advantage of using a neoadjuvant platinum-based chemotherapy is the 12% relative survival benefit or 5% OS improvement in 5 years (41). Another benefit of neoadjuvant chemotherapy is improved compliance. One randomized phase III trial that illustrates this well is the NATCH trial, which compared adjuvant versus neoadjuvant chemotherapy in patients with early stage NSCLC. In this trial, 97% of patients started neoadjuvant chemotherapy and 90% of patients completed neoadjuvant chemotherapy while only 62% started adjuvant chemotherapy and 61% completed adjuvant chemotherapy (43). Perhaps most important, neoadjuvant chemotherapy is not associated with increased post-operative complications or death (44–46).

NEOADJUVANT CHEMOTHERAPY VERSUS NEOADJUVANT CHEMORADIATION

Efforts to improve locoregional control, pathologic response, and resectability led investigators to ask the question of whether the addition of radiation would increase survival compared to induction chemotherapy alone. Several phase II

trials, summarized in **Table 2** (35–38, 47–55), were designed to evaluate the role of neoadjuvant concurrent chemoradiation. Interestingly, five of these studies demonstrated complete pathologic responses of 15–26% and resection rates as high as 80–90%. The results of these studies prompted the development of several randomized phase III trials.

The German Lung Cancer Cooperative Group (GLCCG) was a multi-institutional, randomized phase III trial that enrolled 558 patients with stage IIIA/IIIB NSCLC. The investigators included marginally resectable stage IIIA/IIIB patients, postulating that neoadjuvant treatment could downstage these tumors, rendering them resectable. Patients were randomized to receive either neoadjuvant chemotherapy with cisplatin and etoposide followed by concurrent chemoradiation and resection or neoadjuvant chemotherapy followed by resection and post-operative radiation (33). Neoadjuvant radiation was administered in a hyperfractionated schedule, given twice daily (1.5 Gy per fraction), to a total dose of 45 Gy with weekly carboplatin and vindesine. Notably, all patients in the control arm also received post-operative radiation independent of margin status. A total dose of 54 Gy (1.8 Gy per fraction) was administered in the setting of negative margins (R0 resections) and up to 68.4 Gy if margins were positive or if tumors were deemed unresectable. Responses to neoadjuvant treatment were assessed using CT of the chest, abdomen, and brain. Only patients without disease progression proceeded to concurrent radiation and resection. The primary end point was progression-free survival (PFS) and the secondary endpoints included OS and the proportion of patients undergoing surgery. Of the patients who underwent surgery, the proportions of patients with negative resection margins, complete resections, histopathologic response (tumor regression of >90%), and mediastinal down-staging were evaluated as secondary endpoints. Fifty-four percent of patients in the concurrent chemoradiation arm and 59% of patients in the induction chemotherapy arm underwent resection with 37 and 32% undergoing complete resections in the concurrent chemoradiation arm and induction chemotherapy arm, respectively. There was a significant difference in mediastinal down-staging (*N*2–3 to *N*0–1) ($p = 0.02$) and histopathologic response ($p = <0.0001$), favoring the chemoradiation arm (33). There was no difference in PFS or OS between the two groups even when evaluating only those patients who had a resection. However, compared to patients who underwent an incomplete resection, patients who had a complete resection had longer median, 1-, 3-, and 5-year PFS (median 28.7 versus 21.1 months) and longer OS (median 50.6 versus 20.4 months). More patients who underwent a complete resection were found to have mediastinal down-staging, and this was the only independent predictor of improved PFS and OS on multivariate analysis [HR 2.11 (1.23–3.62), $p = 0.007$] (33). Finally, 35% of patients in both arms of the study underwent a pneumonectomy, and treatment-related mortality was higher among patients who received neoadjuvant chemoradiation (14%) compared to induction chemotherapy (6%) (33).

Since publication of the GLCCG trial, several retrospective and other studies demonstrate a lack of improved survival with the addition of neoadjuvant radiation (56–58). A systematic review and meta-analysis of pooled data from 156 patients with stage IIIA NSCLC from seven randomized and retrospective studies comparing neoadjuvant chemotherapy to neoadjuvant concurrent chemoradiation found no survival benefit with the addition of radiation (HR 0.93, 95% CI: 0.54–1.62, $p = 0.81$) (56). Also, a large, retrospective study of 1076 patients with stage IIIA NSCLC, most with *N*2 disease ($N = 903$), from the National Cancer Database found no difference in survival for patients treated with neoadjuvant chemotherapy compared to neoadjuvant concurrent chemoradiation. However, patients treated with concurrent chemoradiation were found to have decreased residual nodal disease (57). It is important to keep in mind that the studies used in these pooled analyses employed a heterogeneous mix of treatment regimens, some with outdated radiation techniques.

TABLE 2 | Neoadjuvant concurrent chemoradiation phase II trials.

Reference	Chemoradiation	*N*	*N*2	ORR (% total)	Surgery (% total)	R0 (% surgery)	PCR (% total)	Survival
Taylor et al. (47)	P, 5-FU + 40 Gy	64	50	58	61	NR	14	1 year 61%, median 16 months
Pincus et al. (48)	PE, 5-FU + 40 Gy	31	NR	74	39	100	19	2 years 33%, median 15 months
Faber et al. (49)	P, 5-FU or PE, 5-FU + 40 Gy	85	62	NR	71	NR	20	3 years 40%, median 37 months
Recine et al. (50)	PE, 5-FU + 40 Gy	64	NR	84	36	100	14	3 years 30%, median 13 months; 3 years 69% (resection)
Strauss et al. (51)	VP, 5-FU + 30 Gy	41	33	51	61	96	10	1 year 58% median 16 months
Palazzi et al. (35)	PE + 40 Gy	43	21	70	30	92	7	1 year 58%, 2.5 years 21%
Weiden et al. (52)	P, 5-FU + 30 Gy	85	68	56	52	66	9	Median 13 months
Albain et al. (37)	PE + 45 Gy	126	75	59	71	98	15	2 years 37% (*N*2); median 13 months (*N*2)
Favaretto et al. (36)	PE + 51.2 Gy	39	NR	64	51	NR	8	3 years 18%, median 16 months
Choi et al. (53)	VP, 5-FU + 42 Gy	42	42	74	93	87	10	Median 25 months, 5 years 37%
Eberhardt et al. (38)	PE + 45 Gy	94	56	64	66	81	26	Median 20 months (IIIA); 4 years 31% (IIIA) 46% (R0)
Thomas et al. (54)	ICE + 45 Gy	54	25	69	74	85	13	2 years 40%, median 20 months
D'Angelillo et al. (55)	GP + 50.4 Gy	50	29	80	82	88	26	3 years 40%, median 22 months

C, carboplatin; E, etoposide; 5-FU, 5-fluorouracil; G, gemcitabine; I, ifosfamide; NR, not reported; ORR, overall response rate; P, cisplatin; PCR, pathologic complete response; V, vinblastine/vindesine.

One of the most intriguing findings of the GLCCG trial was the increased mediastinal down-staging and histopathologic tumor regression on final pathology in patients who underwent a complete resection after treatment with neoadjuvant chemoradiation compared to chemotherapy. Although the GLCCG did not demonstrate an improvement in OS, a small retrospective analysis of 92 patients with stage IIIA (*N*2) NSCLC found a trend toward improved survival in patients with mediastinal down-staging and had complete resections after neoadjuvant chemotherapy. There was also a 5-year survival benefit for single-station *N*2 compared to multi-station disease discovered at the time of initial mediastinoscopy (37 versus 7% 5-year survival, $p = < 0.005$) (59). Other retrospective studies show improved outcomes in patients with increased nodal clearance after neoadjuvant chemoradiation. One study found increased disease-free survival in patients with mediastinal complete pathologic response after neoadjuvant chemoradiation (58). Another study even found an increase in 5-year survival as high as 47% in patients with a partial or complete nodal pathologic response to chemoradiation (58, 60). Thus, there is evidence that mediastinal down-staging is associated with improved outcomes. In fact, complete nodal pathologic response is widely considered as a surrogate for a favorable prognosis (34, 60).

There is also indirect evidence that neoadjuvant chemoradiation may provide improved outcomes compared to induction chemotherapy followed by resection. The phase III EORTC 08941 (discussed in the Section "Neoadjuvant Tri-modality Therapy") compared induction chemotherapy followed by surgery versus sequential chemotherapy and radiation. Patients who received radiation had a similar OS and PFS with lower morbidity and mortality (2). In unresectable stage III NSCLC, concurrent chemoradiation has been found to be superior to sequential chemotherapy and radiation (61) (discussed in the Section "Sequential versus Concurrent Chemotherapy and Radiation"). Taken together, this suggests that neoadjuvant concurrent chemoradiation may be superior over induction chemotherapy alone followed by surgery. However, we emphasize this comparison has not been adequately addressed in a large phase III trial to date.

The results from the GLCCG trial highlight several key challenges when designing trials for patients with stage IIIA (*N*2) NSCLC. One is the definition of resectability—over 60% of patients had stage IIIB NSCLC (T4*N*2 or *N*3 disease) that is generally considered unresectable. Restaging after neoadjuvant treatment can vary between institutions, and details regarding restaging in the GLCCG are unclear. Reassessment of the mediastinum prior to surgery does not appear to have been performed aside from chest CT. This may have accounted for the higher than expected rate of incomplete resections at the time of surgery. Another challenge in designing trials for patients with stage IIIA (*N*2) NSCLC is the coordination between treatment modalities. Among patients in the GLCCG interventional arm treated with concurrent chemoradiation arm, only 54% ultimately went on to surgery (37% with R0 resection) and the remaining received an additional 24 Gy that was resumed after a 4- to 6-week break for response assessment. It is well documented that prolonged radiotherapy treatment breaks lead to worse outcomes (62, 63). In addition, trials evaluating treatment strategies for patients with stage IIIA (*N*2) NSCLC have been hampered by slow accrual rates, impeding the trials' ability to stay relevant. For example, the radiation techniques used in the GLCCG became outdated over the course of the trial. Neither the hyperfractionated radiation schedule nor the target volumes employed are standard of care at this time (64). Furthermore, all patients in the control neoadjuvant chemotherapy arm received post-operative radiation regardless of pathological nodal involvement, margin status, or extent of resection, a practice that is controversial (65, 66). Finally, many trials evaluating treatment for patients with stage IIIA (*N*2) NSCLC have also been complicated by high pneumonectomy rates, which are associated with worse outcomes (33, 34).

NEOADJUVANT CONCURRENT CHEMOTHERAPY CHOICE

What is the best neoadjuvant chemotherapy regimen to use when treating patients concurrently with radiation? A platinum-based doublet is the recommended regimen. Several combinations with radiation have been evaluated in phase II neoadjuvant trials. As seen in **Table 2** (35–38, 47–55), older cisplatin-containing regimens with 5-fluorouracil, cyclophosphamide, doxorubicin, and vinblastine demonstrate response rates ranging from 50 to 70% and 15–20 month median survival times. Cisplatin and etoposide with radiation has been used extensively in phase II and phase III trials and demonstrates an overall response rate of 60–70% (28, 33–38). This regimen has been preferred among investigators for its manageable outpatient administration and ability to administer an upfront therapeutic-dose concurrently with radiation. Although not evaluated in the neoadjuvant setting, many oncologists use more modern regimens, such as carboplatin/paclitaxel, cisplatin, or carboplatin/pemetrexed, concurrently with radiation. These regimens have been found to have good efficacy and tolerability in the treatment of unresectable NSCLC (67–69). Cisplatin/gemcitabine is a modern, efficacious regimen that has been evaluated in the neoadjuvant setting (55). However, this regimen is highly toxic when combined with radiation and is not commonly used.

Trials evaluating neoadjuvant concurrent chemoradiation with immunotherapy are currently ongoing (nivolumab, pembrolizumab) (70). Because pneumonitis is a known potential side-effect of both immunotherapy and radiotherapy, chemotherapy regimens associated with lower rates of pneumonitis may ultimately become more favorable in this setting. The PROCLAIM trial (69) and a well-conducted Chinese trial (71) that was stratified by factors known to be associated with radiation pneumonitis [percentage of lung volume that receives 20 Gy or more (V20), diffusion capacity of carbon monoxide (DLCO), and gross tumor volume] have shown lower rates of pneumonitis for cisplatin/etoposide versus cisplatin/pemetrexed or carboplatin/paclitaxel. In the PROCLAIM trial, pneumonitis of any grade was significantly higher in the patients treated with cisplatin/pemetrexed versus cisplatin/etoposide (17 versus 10.7%) although there was no difference in Grade 3–4 pneumonitis between treatment arms (69). In the Chinese trial, grade 2 or greater radiation pneumonitis was more frequent in the carboplatin/paclitaxel arm (33.3%)

versus cisplatin/etoposide arm (18.9%), although there were no significant differences in rates of grade 3 or greater pneumonitis between arms (71). Nonetheless, chemotherapy regimens that are less likely to be associated with pneumonitis may become more important in the future if immunotherapy is also incorporated into concurrent chemoradiation treatment plans.

The National Comprehensive Cancer Network issued a provider survey to its members in 2010 and found that approximately 50% of providers use neoadjuvant chemotherapy while the other 50% use neoadjuvant concurrent chemoradiation therapy more often (64). The authors of this paper prefer cisplatin and etoposide with radiation if the patient has a good performance status and no significant comorbidities given its extensive use in clinical trials and the data supporting this regimen.

SEQUENTIAL VERSUS CONCURRENT CHEMOTHERAPY AND RADIATION

Sequential chemotherapy and radiation has been studied extensively in patients with stage III NSCLC. A meta-analysis of seven phase III trials comparing concurrent with sequential chemotherapy and radiation in patients with stage III NSCLC included 1,205 patients, 61% with stage IIIB and 37% with stage IIIA. Median follow-up was 6 years (61). In this pooled analysis, a significant OS benefit (HR 0.84; 95% CI: 0.74, 0.95; $p = 0.004$) was found for patients who were treated with concurrent chemoradiation compared to sequential therapy. The absolute benefit was found to be 5.7% at 3 years and 4.5% at 5 years. There was also a trend toward an improved PFS with a hazard ratio of 0.90 (95% CI: 0.79, 1.01; $p = 0.07$) and a decrease in locoregional progression in the concurrent chemoradiation group (61). There were more toxicities associated with concurrent chemoradiation, particularly esophagitis (61). Nonetheless, sequential chemotherapy and radiation is not routinely considered standard of care for stage IIIA NSCLC, including patients with *N*2 involvement. However, in patients with poorer performance status, who would not tolerate concurrent chemoradiation, sequential therapy is a potential treatment option.

NEOADJUVANT TRI-MODALITY THERAPY

Two multicenter randomized-controlled trials assessed whether resection was necessary following neoadjuvant chemotherapy with or without radiation in patients with stage IIIA NSCLC. EORTC 8941 was a phase III European study that assessed whether surgery is superior to radiation following a radiologic response to induction chemotherapy with a platinum-based regimen in patients with unresectable stage IIIA (N2) disease (2). OS was the primary endpoint. Secondary endpoints included PFS and safety. This trial randomized 332 patients over 10 years. The overall response rate to induction chemotherapy was 61% (2). Compliance among the patients assigned to receive radiation was poor at 55%, with major protocol deviations that included, but were not limited to, inconsistent total radiation dose and/or fractionation schemes, and timing of radiotherapy administration (72). Of the patients who were assigned to undergo surgery, 92% underwent a procedure, but only 50% of patients had a complete resection and 47% of these required a pneumonectomy. PFS and OS were similar in both groups; median PFS was 9 months in the surgery arm versus 11.3 months in the radiation arm and median OS was 16.4 months in the surgery arm versus 17.5 months in the radiation arm. Of the patients who underwent resection, those who had a lobectomy, complete resection, and pathological clearance of the mediastinal lymph nodes did better than those who underwent a pneumonectomy, an incomplete resection, or did not have pathologically clearance in mediastinal lymph nodes. The mortality rate associated with pneumonectomy was 7% compared to 4% overall surgical mortality (2). The strengths of this trial include the large, multicenter population and the requirement for pathological confirmation of *N*2 disease. However, changes in the staging system (PET scan and brain imaging were not performed) may have allowed the inclusion of patients with more advanced disease (64). In addition, the outcome of all patients initially enrolled in the trial is not well described, as only the outcomes of patients who were randomly assigned to therapy are reported. Finally, outdated radiotherapy techniques, slow accrual rate, poor compliance, inconsistency of specialized, thoracic surgeons, and the use of sequential chemotherapy and radiation as definitive therapy in the control arm are potential limitations of this trial (64).

The North American Intergroup 0139 (INT 0139) trial similarly sought to evaluate the potential role of surgery as part of a tri-modality treatment strategy for patients with stage IIIA (*N*2) NSCLC (34). This trial was performed in North America and randomized patients with resectable stage IIIA and pathologically confirmed *N*2 disease to receive either concurrent chemotherapy with cisplatin and etoposide and radiation to 45 Gy followed by resection or concurrent chemotherapy with cisplatin and etoposide and radiation to 45 Gy followed by definitive radiation to 61 Gy, administered in an uninterrupted schedule (29). If patients randomized to the surgery arm did not progress radiographically by CT after completing neoadjuvant chemoradiation, they proceeded to resection. Both groups received two cycles of postoperative chemotherapy with cisplatin and etoposide either after surgery or with completion of definitive radiation. The primary end point was OS, and secondary endpoints were PFS, toxicity, and patterns of failure. The two study arms were well balanced and enrolled 429 patients over 7 years. The majority of patients had biopsy-proven single-station *N*2 lymph node involvement. Of the patients found to be eligible for surgery, 81% underwent thoracotomy, 71% had complete resections, and 55% completed consolidation chemotherapy. Of the patients randomized to definitive radiation, 92% continued radiation without a break in treatment. The median follow-up was 22.5 months. OS did not differ between the two treatment arms, although there was a late trend toward improved OS in the tri-modality treatment arm as well as an increased PFS in the patients treated with tri-modality compared to those who received definitive radiation (12.8 versus 10.5 months). The greatest benefit was seen in patients having a pathologic response (*N*0) at the time of surgery with a median survival of 34.4 months. Fifty-four patients underwent pneumonectomy with a concerning high mortality rate of 26%. The most common grade 3 or 4 toxicity was neutropenia in both

treatment groups. Grade 3 or 4 esophagitis and pneumonitis were more common toxicities in patients who underwent definitive radiation compared to surgical resection (34). The investigators performed an unplanned, exploratory, matched subset analysis that suggested tri-modality therapy could benefit patients if a lobectomy and complete resection are possible. In this population, the median survival time was 33.6 months in the tri-modality group compared with 21.7 months in matched patients treated with definitive concurrent chemoradiation ($p = 0.002$). It remains unclear whether this differs significantly from the 28.7-month median survival of patients with stage III NSCLC randomized to the control arm of the recently published RTOG 0617 trial who were treated with concurrent chemoradiation alone (60 Gy), especially given that 34% had more advanced, stage IIIB disease (73). Although positron emission tomography (PET), which can assist in the detection of regional and distant disease, was not used in the INT 0139 trial, the patient population was otherwise rigorously staged with mediastinoscopy and surgical nodal sampling. Treatment adherence was excellent in both arms with high compliance and resection rates compared to other phase III trials.

Criticisms of INT0139 include the incomplete accrual rate, an underpowered subset analysis suggesting a tri-modality therapy advantage, and a very high mortality rate among patients who underwent pneumonectomy (64). It is also important to point out that the radiation dose administered concurrently with chemotherapy in the surgical arm is considered sub-therapeutic (45 Gy) in the definitive setting, and nearly one in five patients enrolled on this arm did not ultimately undergo thoracotomy. This study, such as the GLCCG trial, highlights the challenges with committing to tri-modality therapy without risking sub-therapeutic treatment or prolonged, detrimental breaks in treatment.

More recently, the results of RTOG 02-29, a phase II trial evaluating therapeutic-dose neoadjuvant chemoradiation in stage III (*N*2 or *N*3, supraclavicular disease excluded) show both the safety and feasibility of delivering neoadjuvant radiotherapy regimens to a dose of 61.2 Gy. In addition to high rates of mediastinal nodal clearance (63%), this regimen eliminates the potential for delivery of sub-therapeutic radiotherapy and/or radiotherapy treatment breaks in patients who do not ultimately undergo complete resection (74).

Despite its limitations, INT0139 represents the strongest evidence to date for the use of tri-modality treatment. Its subset analysis suggests that patients with potentially resectable disease using a lobectomy may benefit from neoadjuvant tri-modality therapy with concurrent chemoradiation followed by surgery. In this setting, two local therapies (radiation and surgery) may downstage microscopic nodal disease prior to resection, leading to improved outcomes. Therefore, early evaluation by a thoracic surgeon is important in order to identify patients with locally advanced NSCLC who may benefit from tri-modality treatment.

TIMING OF SURGERY

A practical concern with a neoadjuvant treatment strategy is the potential for delay of definitive local therapy, which has been associated with worse survival (75). For this reason, it is crucial that patients are evaluated by a thoracic surgeon early, not only to determine resectability but to also allow for timely planning of restaging and resection, ideally within 6 weeks from completion of neoadjuvant therapy. A large, retrospective study of 1,623 patients in the National Cancer Database with stage IIIA NSCLC who were treated with neoadjuvant concurrent chemoradiation from 2004 to 2012 found a statistically significant decline in survival when surgical resection occurred greater than 6 weeks from the completion of neoadjuvant therapy (76). Examining the data more closely, the investigators compared survival times for patients at 0–3, 3–6, 6–9, and 9–12 weeks after completion of neoadjuvant therapy. Although it was *not* statistically significant, there was a trend toward reduced survival when extending surgery to 3–6 weeks compared to 0–3 weeks (45.2 versus 60.7 months, respectively, $p = 0.107$ in multivariate analysis). The survival difference between 0–3 and 6–9 weeks *was* statistically significant ($p = 0.043$ in multivariate analysis). Comparing the survival difference for 3–6 weeks and 6–9 weeks, this was a very small difference (45.2 versus 44.1 months); in fact, the Kaplan–Meier curves for weeks 3–6 and 6–9 touched in some areas (76). Therefore, it may be optimal to plan surgery even earlier than six weeks and closer to 3–4 weeks post-neoadjuvant therapy, assuming patients have recovered from their local therapy.

FUTURE DIRECTIONS

Cytotoxic chemotherapy may not be the only systemic therapy used in future neoadjuvant regimens for stage IIIA NSCLC. Considerable attention has focused on targeted therapy and immune checkpoint inhibitors as potential neoadjuvant therapies for locally advanced NSCLC. A small phase II trial compared erlotinib to carboplatin–gemcitabine in 24 patients with resectable, EGFR mutant, stage IIIA (*N*2) NSCLC and found an overall response of 38% for erlotinib compared to 25% for chemotherapy, although there was no survival benefit for erlotinib (77). In another small, single-arm phase II study, investigators administered erlotinib for 3 weeks prior to surgery in 60 patients with early stage NSCLC. Of note, EGFR testing was obtained on surgical specimens (78). A subset of 15 Asian, female never smokers with non-squamous histology, were analyzed separately as a cohort more likely to harbor an EGFR mutation. The response rate was low overall (5% by RECIST on CT, 27% metabolic response by PET), and 12% of the total population was found to have an EGFR mutation. The response rate increased to 34% in the Asian female subset, 17% of which were found to be EGFR mutated. Furthermore, 23% of patients who underwent resection had more than 50% necrosis at the time of pathology review. Toxicities were tolerable and included rash and diarrhea, which are typical of EGFR tyrosine-kinase inhibitors (78). Additional studies using chemotherapy and/or targeted therapy in the neoadjuvant setting have closed due to poor accrual (79).

As in many areas in oncology today, there are multiple ongoing trials evaluating neoadjuvant immunotherapy, including atezolizumab, pembrolizumab, nivolumab with or without ipilimumab, durvalumab as well as combination checkpoint inhibitors and chemotherapy (79). We will have to await the maturation of these and future clinical trials before determining the role of neoadjuvant targeted therapy and immunotherapy.

Aside from novel therapeutics, other strategies to improve outcomes in patients with stage IIIA (*N*2) are being studied, including the role of PET scan in assessment of response. Fluorine-18 fluorodeoxyglucose (FDG)-PET/CT is a standard of care for the staging of patients initially diagnosed with NSCLC (80). A meta-analysis has shown that increased standardized uptake value (SUV) of the primary tumor is a poor prognostic factor in NSCLC (81). A retrospective review has already shown that patients with stage II NSCLC treated with neoadjuvant chemotherapy who have a greater than 50% reduction in SUV on PET scan demonstrate a trend toward improved survival compared to patients with less than a 50% reduction in SUV (82). A prospective study ($N = 79$), including 25 patients with stage IIIA (*N*2) NSCLC demonstrated that FDG uptake in the mediastinal lymph nodes after three cycles of neoadjuvant chemotherapy was associated with a twofold higher risk of mortality whereas repeat CT was not a predictor of survival (83). In fact, a 35% decrease of FDG uptake after one cycle of neoadjuvant chemotherapy discriminated responders from non-responders (83). Taking these findings further, a recent phase II study assessed the timing of treatment switch to optimize response rates (84). In this phase II study, 40 patients with resectable stage IB to IIIA NSCLC received neoadjuvant chemotherapy with a platinum-based doublet (carboplatin or cisplatin plus gemcitabine or pemetrexed). A PET scan was performed after two cycles. If the SUV decreased by at least 35%, patients continued on the initial chemotherapy regimen, but if the SUV did not decrease by at least 35%, the patients were switched to a different chemotherapy regimen (docetaxel–vinorelbine). Sixty-seven percent of patients who were switched to a different regimen had a metabolic response on subsequent PET scan (84). These studies are small, and PET scan responses as part of the strategy in the neoadjuvant treatment for stage IIIA (*N*2) NSCLC have not been tested in randomized phase III trials. However, we may consider metabolic responses by PET scan after neoadjuvant therapy in the future to prompt changes in systemic regimens.

CONCLUSION

The treatment of patients with stage IIIA (*N*2) NSCLC is complex and requires the expertise of a multidisciplinary thoracic oncology team. Neoadjuvant platinum-based chemotherapy followed by surgery has been found to improve survival in patients with locally advanced NSCLC (28–31). Neoadjuvant chemoradiation improves nodal clearance (33) and is a strong rationale for adding radiation to the neoadjuvant treatment approach. Although improved survival with neoadjuvant chemoradiation followed by resection has not been shown in phase III trials to date (33), these studies have been limited by slow accrual rates, patient selection, outdated radiation techniques, detrimental interruptions in therapy, and high mortality rates associated with pneumonectomy.

The benefit of surgery following neoadjuvant treatment in comparison to definitive concurrent chemoradiation remains unclear based on currently available phase III data. However, there is evidence to suggest that an appropriately selected, rigorously screened subset of stage IIIA patients with *N*2 disease may experience a survival benefit from a tri-modality approach of surgical resection after neoadjuvant concurrent chemoradiation (34). It is critical that a thoracic surgeon evaluates these patients prior to initiating therapy, and if a lobectomy with complete resection (R0) can be performed with reasonable certainty, chemoradiation is a reasonable neoadjuvant option. Similar to induction chemotherapy, chemotherapy in the tri-modality setting should be platinum-based, preferably with cisplatin, although carboplatin is an option in patients who cannot receive cisplatin-containing regimens. Furthermore, care should be taken to minimize interruptions in therapy, even for restaging, which can lead to suboptimal treatment strategies and potentially inferior outcomes.

Finally, targeted therapy and immunotherapy are the major areas of current clinical trial research, and it is expected that accrual rates will improve now that immunotherapy has stolen center stage of neoadjuvant clinical trial design for NSCLC. The results from these trials will hopefully lead to additional systemic options to further improve upon the cure rate for our future patients with stage IIIA (*N*2) NSCLC.

AUTHOR CONTRIBUTIONS

LH and JL are responsible for the conception of the article. JL is responsible for the initial content. JL, LH, EG, and EO are responsible for the intellectual content, critical analysis, and revisions of the manuscript.

ACKNOWLEDGMENTS

This material is based upon the work supported by the Office of Academic Affiliations, Department of Veterans Affairs, VA National Quality Scholars Program, and with resources and the use of facilities at VA Tennessee Valley Healthcare System, Nashville, TN, USA.

REFERENCES

1. American Cancer Soceity. *Cancer Facts & Figures 2017*. Atlanta: American Cancer Society (2017).
2. van Meerbeeck JP, Kramer GW, Van Schil PE, Legrand C, Smit EF, Schramel F, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst* (2007) 99(6):442–50. doi:10.1093/jnci/djk093
3. Andre F, Grunenwald D, Pignon JP, Dujon A, Pujol JL, Brichon PY, et al. Survival of patients with resected N2 non-small-cell lung cancer: evidence for a subclassification and implications. *J Clin Oncol* (2000) 18(16):2981–9. doi:10.1200/JCO.2000.18.16.2981
4. Katsuki H, Shimada K, Koyama A, Okita M, Yamaguchi Y. Long-term intermittent adjuvant chemotherapy for primary, resected lung cancer. *J Thorac Cardiovasc Surg* (1975) 70(4):590–605.
5. Martini N, Flehinger BJ. The role of surgery in N2 lung cancer. *Surg Clin North Am* (1987) 67(5):1037–49. doi:10.1016/S0039-6109(16)44341-0
6. Martini N, Flehinger BJ, Zaman MB, Beattie EJ Jr. Prospective study of 445 lung carcinomas with mediastinal lymph node metastases. *J Thorac Cardiovasc Surg* (1980) 80(3):390–9.

7. Bains MS. Surgical treatment of lung cancer. *Chest* (1991) 100(3):826–37. doi:10.1378/chest.100.3.826
8. Johnson DH, Piantadosi S. Chemotherapy for resectable stage III non-small-cell lung cancer – can that dog hunt? *J Natl Cancer Inst* (1994) 86(9):650–1. doi:10.1093/jnci/86.9.650
9. Farray D, Mirkovic N, Albain KS. Multimodality therapy for stage III non-small-cell lung cancer. *J Clin Oncol* (2005) 23(14):3257–69. doi:10.1200/JCO.2005.03.008
10. Martini N, Kris MG, Gralla RJ, Bains MS, McCormack PM, Kaiser LR, et al. The effects of preoperative chemotherapy on the resectability of non-small cell lung carcinoma with mediastinal lymph node metastases (N2 M0). *Ann Thorac Surg* (1988) 45(4):370–9. doi:10.1016/S0003-4975(98)90007-8
11. Vokes EE, Bitran JD, Hoffman PC, Ferguson MK, Weichselbaum RR, Golomb HM. Neoadjuvant vindesine, etoposide, and cisplatin for locally advanced non-small cell lung cancer. Final report of a phase 2 study. *Chest* (1989) 96(1):110–3.
12. Pujol JL, Rossi JF, Le Chevalier T, Daures JP, Rouanet P, Douillard JY, et al. Pilot study of neoadjuvant ifosfamide, cisplatin, and etoposide in locally advanced non-small cell lung cancer. *Eur J Cancer* (1990) 26(7):798–801. doi:10.1016/0277-5379(90)90155-M
13. Burkes RL, Ginsberg RJ, Shepherd FA, Blackstein ME, Goldberg ME, Waters PF, et al. Induction chemotherapy with mitomycin, vindesine, and cisplatin for stage III unresectable non-small-cell lung cancer: results of the Toronto Phase II Trial. *J Clin Oncol* (1992) 10(4):580–6. doi:10.1200/JCO.1992.10.4.580
14. Martini N, Kris MG, Flehinger BJ, Gralla RJ, Bains MS, Burt ME, et al. Preoperative chemotherapy for stage IIIa (N2) lung cancer: the Sloan-Kettering experience with 136 patients. *Ann Thorac Surg* (1993) 55(6):1365–73; discussion 73–4. doi:10.1016/0003-4975(93)91072-U
15. Darwish S, Minotti V, Crino L, Rossetti R, Maranzano E, Checcaglini F, et al. Neoadjuvant cisplatin and etoposide for stage IIIA (clinical N2) non-small cell lung cancer. *Am J Clin Oncol* (1994) 17(1):64–7. doi:10.1097/00000421-199402000-00014
16. Sugarbaker DJ, Herndon J, Kohman LJ, Krasna MJ, Green MR. Results of cancer and leukemia group B protocol 8935. A multiinstitutional phase II trimodality trial for stage IIIA (N2) non-small-cell lung cancer. Cancer and Leukemia Group B Thoracic Surgery Group. *J Thorac Cardiovasc Surg* (1995) 109(3):473–83; discussion 83–5. doi:10.1016/S0022-5223(95)70278-4
17. Elias AD, Skarin AT, Leong T, Mentzer S, Strauss G, Lynch T, et al. Neoadjuvant therapy for surgically staged IIIA N2 non-small cell lung cancer (NSCLC). *Lung Cancer* (1997) 17(1):147–61. doi:10.1016/S0169-5002(97)00658-2
18. Van Zandwijk N, Smit EF, Kramer GW, Schramel F, Gans S, Festen J, et al. Gemcitabine and cisplatin as induction regimen for patients with biopsy-proven stage IIIA N2 non-small-cell lung cancer: a phase II study of the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group (EORTC 08955). *J Clin Oncol* (2000) 18(14):2658–64. doi:10.1200/JCO.2000.18.14.2658
19. Betticher DC, Hsu Schmitz SF, Totsch M, Hansen E, Joss C, von Briel C, et al. Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of survival in patients with stage IIIA pN2 non-small-cell lung cancer: a multicenter phase II trial. *J Clin Oncol* (2003) 21(9):1752–9. doi:10.1200/JCO.2003.11.040
20. O'Brien ME, Splinter T, Smit EF, Biesma B, Krzakowski M, Tjan-Heijnen VC, et al. Carboplatin and paclitaxel (Taxol) as an induction regimen for patients with biopsy-proven stage IIIA N2 non-small cell lung cancer. an EORTC phase II study (EORTC 08958). *Eur J Cancer* (2003) 39(10):1416–22. doi:10.1016/S0959-8049(03)00319-8
21. De Marinis F, Nelli F, Migliorino MR, Martelli O, Cortesi E, Treggiari S, et al. Gemcitabine, paclitaxel, and cisplatin as induction chemotherapy for patients with biopsy-proven stage IIIA(N2) nonsmall cell lung carcinoma: a phase II multicenter study. *Cancer* (2003) 98(8):1707–15. doi:10.1002/cncr.11662
22. Cappuzzo F, Selvaggi G, Gregorc V, Mazzoni F, Betti M, Rita Migliorino M, et al. Gemcitabine and cisplatin as induction chemotherapy for patients with unresectable stage IIIA-bulky N2 and stage IIIB nonsmall cell lung carcinoma: an Italian Lung Cancer Project Observational Study. *Cancer* (2003) 98(1):128–34. doi:10.1002/cncr.11460
23. Burkes RL, Shepherd FA, Blackstein ME, Goldberg ME, Waters PF, Patterson GA, et al. Induction chemotherapy with mitomycin, vindesine, and cisplatin for stage IIIA (T1-3, N2) unresectable non-small-cell lung cancer: final results of the Toronto phase II trial. *Lung Cancer* (2005) 47(1):103–9. doi:10.1016/j.lungcan.2004.06.004
24. Biesma B, Manegold C, Smit HJ, Willems L, Legrand C, Passioukov A, et al. Docetaxel and cisplatin as induction chemotherapy in patients with pathologically-proven stage IIIA N2 non-small cell lung cancer: a phase II study of the European organization for research and treatment of cancer (EORTC 08984). *Eur J Cancer* (2006) 42(10):1399–406. doi:10.1016/j.ejca.2006.01.049
25. Garrido P, Gonzalez-Larriba JL, Insa A, Provencio M, Torres A, Isla D, et al. Long-term survival associated with complete resection after induction chemotherapy in stage IIIA (N2) and IIIB (T4N0-1) non small-cell lung cancer patients: the Spanish Lung Cancer Group Trial 9901. *J Clin Oncol* (2007) 25(30):4736–42. doi:10.1200/JCO.2007.12.0014
26. Chaft JE, Rusch V, Ginsberg MS, Paik PK, Finley DJ, Kris MG, et al. Phase II trial of neoadjuvant bevacizumab plus chemotherapy and adjuvant bevacizumab in patients with resectable nonsquamous non-small-cell lung cancers. *J Thorac Oncol* (2013) 8(8):1084–90. doi:10.1097/JTO.0b013e31829923ec
27. Ou W, Li N, Wang SY, Li J, Liu QW, Huang QA, et al. Phase 2 trial of neoadjuvant bevacizumab plus pemetrexed and carboplatin in patients with unresectable stage III lung adenocarcinoma (GASTO 1001). *Cancer* (2016) 122(5):740–7. doi:10.1002/cncr.29800
28. Pass HI, Pogrebniak HW, Steinberg SM, Mulshine J, Minna J. Randomized trial of neoadjuvant therapy for lung cancer: interim analysis. *Ann Thorac Surg* (1992) 53(6):992–8. doi:10.1016/0003-4975(92)90373-C
29. Rosell R, Gomez-Codina J, Camps C, Maestre J, Padille J, Canto A, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *N Engl J Med* (1994) 330(3):153–8. doi:10.1056/NEJM199401203300301
30. Roth JA, Fossella F, Komaki R, Ryan MB, Putnam JB Jr, Lee JS, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *J Natl Cancer Inst* (1994) 86(9):673–80. doi:10.1093/jnci/86.9.673
31. Depierre A, Milleron B, Moro-Sibilot D, Chevret S, Quoix E, Lebeau B, et al. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIa non-small-cell lung cancer. *J Clin Oncol* (2002) 20(1):247–53. doi:10.1200/JCO.20.1.247
32. Burdett S, Stewart LA, Rydzewska L. A systematic review and meta-analysis of the literature: chemotherapy and surgery versus surgery alone in non-small cell lung cancer. *J Thorac Oncol* (2006) 1(7):611–21. doi:10.1016/S1556-0864(15)30371-3
33. Thomas M, Rube C, Hoffknecht P, Macha HN, Freitag L, Linder A, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. *Lancet Oncol* (2008) 9(7):636–48. doi:10.1016/S1470-2045(08)70156-6
34. Albain KS, Swann RS, Rusch VW, Turrisi AT III, Shepherd FA, Smith C, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet* (2009) 374(9687):379–86. doi:10.1016/S0140-6736(09)60737-6
35. Palazzi M, Cataldo I, Gramaglia A, De Toma D, Milani F, Ravasi G. Preoperative concomitant cisplatin/VP16 and radiotherapy in stage III non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* (1993) 27(3):621–5. doi:10.1016/0360-3016(93)90388-C
36. Favaretto A, Paccagnella A, Tomio L, Sartori F, Cipriani A, Zuin R, et al. Preoperative chemoradiotherapy in non-small cell lung cancer stage III patients. Feasibility, toxicity and long-term results of a phase II study. *Eur J Cancer* (1996) 32A(12):2064–9. doi:10.1016/S0959-8049(96)00248-1
37. Albain KS, Rusch VW, Crowley JJ, Rice TW, Turrisi AT III, Weick JK, et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. *J Clin Oncol* (1995) 13(8):1880–92. doi:10.1200/JCO.1995.13.8.1880
38. Eberhardt W, Wilke H, Stamatis G, Stuschke M, Harstrick A, Menker H, et al. Preoperative chemotherapy followed by concurrent chemoradiation therapy based on hyperfractionated accelerated radiotherapy and definitive surgery in locally advanced non-small-cell lung cancer: mature results of a phase II trial. *J Clin Oncol* (1998) 16(2):622–34. doi:10.1200/JCO.1998.16.2.622
39. Winton T, Livingston R, Johnson D, Rigas J, Johnston M, Butts C, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med* (2005) 352(25):2589–97. doi:10.1056/NEJMoa043623
40. Kreuter M, Vansteenkiste J, Fischer JR, Eberhardt W, Zabeck H, Kollmeier J, et al. Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine:

the TREAT study. *Ann Oncol* (2013) 24(4):986–92. doi:10.1093/annonc/mds578

41. Gilligan D, Nicolson M, Smith I, Groen H, Dalesio O, Goldstraw P, et al. Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review. *Lancet* (2007) 369(9577):1929–37. doi:10.1016/S0140-6736(07)60714-4
42. Pisters KM, Vallieres E, Crowley JJ, Franklin WA, Bunn PA Jr, Ginsberg RJ, et al. Surgery with or without preoperative paclitaxel and carboplatin in early-stage non-small-cell lung cancer: Southwest Oncology Group Trial S9900, an intergroup, randomized, phase III trial. *J Clin Oncol* (2010) 28(11):1843–9. doi:10.1200/JCO.2009.26.1685
43. Felip E, Rosell R, Maestre JA, Rodriguez-Paniagua JM, Moran T, Astudillo J, et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. *J Clin Oncol* (2010) 28(19):3138–45. doi:10.1200/JCO.2009.27.6204
44. Evans NR III, Li S, Wright CD, Allen MS, Gaissert HA. The impact of induction therapy on morbidity and operative mortality after resection of primary lung cancer. *J Thorac Cardiovasc Surg* (2010) 139(4):991–6.e1–2. doi:10.1016/j.jtcvs.2009.11.070
45. Mansour Z, Kochetkova EA, Ducrocq X, Vasilescu MD, Maxant G, Buggenhout A, et al. Induction chemotherapy does not increase the operative risk of pneumonectomy! *Eur J Cardiothorac Surg* (2007) 31(2):181–5. doi:10.1016/j.ejcts.2006.11.008
46. Stefani A, Alifano M, Bobbio A, Grigoroiu M, Jouni R, Magdeleinat P, et al. Which patients should be operated on after induction chemotherapy for N2 non-small cell lung cancer? Analysis of a 7-year experience in 175 patients. *J Thorac Cardiovasc Surg* (2010) 140(2):356–63. doi:10.1016/j.jtcvs.2010.02.018
47. Taylor SG, Trybula M, Bonomi PD, Faber LP, Lee MS, Reddy S, et al. Simultaneous cisplatin fluorouracil infusion and radiation followed by surgical resection in regionally localized stage III, non-small cell lung cancer. *Ann Thorac Surg* (1987) 43(1):87–91. doi:10.1016/S0003-4975(10)60173-7
48. Pincus M, Reddy S, Lee MS, Bonomi P, Taylor S, Rowland K, et al. Preoperative combined modality therapy for stage III M0 non-small cell lung carcinoma. *Int J Radiat Oncol Biol Phys* (1988) 15(1):189–95. doi:10.1016/0360-3016(88)90365-3
49. Faber LP, Kittle CF, Warren WH, Bonomi PD, Taylor SG, Reddy S, et al. Preoperative chemotherapy and irradiation for stage III non-small cell lung cancer. *Ann Thorac Surg* (1989) 47(5):669–75; discussion 76–7. doi:10.1016/0003-4975(89)90115-X
50. Recine D, Rowland K, Reddy S, Lee MS, Bonomi P, Taylor S, et al. Combined modality therapy for locally advanced non-small cell lung carcinoma. *Cancer* (1990) 66(11):2270–8. doi:10.1002/1097-0142(19901201)66:11<2270::AID-CNCR2820661104>3.0.CO;2-H
51. Strauss GM, Herndon JE, Sherman DD, Mathisen DJ, Carey RW, Choi NC, et al. Neoadjuvant chemotherapy and radiotherapy followed by surgery in stage IIIA non-small-cell carcinoma of the lung: report of a Cancer and Leukemia Group B phase II study. *J Clin Oncol* (1992) 10(8):1237–44. doi:10.1200/JCO.1992.10.8.1237
52. Weiden PL, Piantadosi S. Preoperative chemotherapy (cisplatin and fluorouracil) and radiation therapy in stage III non-small cell lung cancer. A phase 2 study of the LCSG. *Chest* (1994) 106(6 Suppl):344S–7S. doi:10.1378/chest.106.6.344S
53. Choi NC, Carey RW, Daly W, Mathisen D, Wain J, Wright C, et al. Potential impact on survival of improved tumor downstaging and resection rate by preoperative twice-daily radiation and concurrent chemotherapy in stage IIIA non-small-cell lung cancer. *J Clin Oncol* (1997) 15(2):712–22. doi:10.1200/JCO.1997.15.2.712
54. Thomas M, Rube C, Semik M, von Eiff M, Freitag L, Macha HN, et al. Impact of preoperative bimodality induction including twice-daily radiation on tumor regression and survival in stage III non-small-cell lung cancer. *J Clin Oncol* (1999) 17(4):1185. doi:10.1200/JCO.1999.17.4.1185
55. D'Angelillo RM, Trodella L, Ciresa M, Cellini F, Fiore M, Greco C, et al. Multimodality treatment of stage III non-small cell lung cancer: analysis of a phase II trial using preoperative cisplatin and gemcitabine with concurrent radiotherapy. *J Thorac Oncol* (2009) 4(12):1517–23. doi:10.1097/JTO.0b013e3181b9e860
56. Shah AA, Berry MF, Tzao C, Gandhi M, Worni M, Pietrobon R, et al. Induction chemoradiation is not superior to induction chemotherapy alone in stage IIIA lung cancer. *Ann Thorac Surg* (2012) 93(6):1807–12. doi:10.1016/j.athoracsur.2012.03.018
57. Sher DJ, Fidler MJ, Liptay MJ, Koshy M. Comparative effectiveness of neoadjuvant chemoradiotherapy versus chemotherapy alone followed by surgery for patients with stage IIIA non-small cell lung cancer. *Lung Cancer* (2015) 88(3):267–74. doi:10.1016/j.lungcan.2015.03.015
58. Higgins K, Chino JP, Marks LB, Ready N, D'Amico TA, Clough RW, et al. Preoperative chemotherapy versus preoperative chemoradiotherapy for stage III (N2) non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* (2009) 75(5):1462–7. doi:10.1016/j.ijrobp.2009.01.069
59. Decaluwe H, De Leyn P, Vansteenkiste J, Dooms C, Van Raemdonck D, Nafteux P, et al. Surgical multimodality treatment for baseline resectable stage IIIA-N2 non-small cell lung cancer. Degree of mediastinal lymph node involvement and impact on survival. *Eur J Cardiothorac Surg* (2009) 36(3):433–9. doi:10.1016/j.ejcts.2009.04.013
60. Cerfolio RJ, Maniscalco L, Bryant AS. The treatment of patients with stage IIIA non-small cell lung cancer from N2 disease: who returns to the surgical arena and who survives. *Ann Thorac Surg* (2008) 86(3):912–20; discussion 20. doi:10.1016/j.athoracsur.2008.04.073
61. Auperin A, Le Pechoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* (2010) 28(13):2181–90. doi:10.1200/JCO.2009.26.2543
62. Chen M, Jiang GL, Fu XL, Wang LJ, Qian H, Chen GY, et al. The impact of overall treatment time on outcomes in radiation therapy for non-small cell lung cancer. *Lung Cancer* (2000) 28(1):11–9. doi:10.1016/S0169-5002(99)00113-0
63. Bese NS, Hendry J, Jeremic B. Effects of prolongation of overall treatment time due to unplanned interruptions during radiotherapy of different tumor sites and practical methods for compensation. *Int J Radiat Oncol Biol Phys* (2007) 68(3):654–61. doi:10.1016/j.ijrobp.2007.03.010
64. Martins RG, D'Amico TA, Loo BW Jr, Pinder-Schenck M, Borghaei H, Chaft JE, et al. The management of patients with stage IIIA non-small cell lung cancer with N2 mediastinal node involvement. *J Natl Compr Canc Netw* (2012) 10(5):599–613. doi:10.6004/jnccn.2012.0062
65. Douillard JY, Rosell R, De Lena M, Riggi M, Hurteloup P, Mahe MA, et al. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. *Int J Radiat Oncol Biol Phys* (2008) 72(3):695–701. doi:10.1016/j.ijrobp.2008.01.044
66. Burdett S, Rydzewska L, Tierney J, Fisher D, Parmar MK, Arriagada R, et al. Postoperative radiotherapy for non-small cell lung cancer. *Cochrane Database Syst Rev* (2016) 10:CD002142. doi:10.1002/14651858.CD002142.pub4
67. Belani CP, Choy H, Bonomi P, Scott C, Travis P, Haluschak J, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol* (2005) 23(25):5883–91. doi:10.1200/JCO.2005.55.405
68. Ohe Y, Ohashi Y, Kubota K, Tamura T, Nakagawa K, Negoro S, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* (2007) 18(2):317–23. doi:10.1093/annonc/mdl377
69. Senan S, Brade A, Wang LH, Vansteenkiste J, Dakhil S, Biesma B, et al. PROCLAIM: randomized phase III trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol* (2016) 34(9):953–62. doi:10.1200/JCO.2015.64.8824
70. ClinialTrials.gov. (2017). Available from: https://clinicaltrials.gov/ct2/results?cond=NSCLC%2C+Stage+IIIA&term=chemoradiation&cntry=&state=&city=&dist=
71. Liang J, Bi N, Wu S, Chen M, Lv C, Zhao L, et al. Etoposide and cisplatin versus paclitaxel and carboplatin with concurrent thoracic radiotherapy in unresectable stage III non-small cell lung cancer: a multicenter randomized phase III trial. *Ann Oncol* (2017) 28(4):777–83. doi:10.1093/annonc/mdx009

72. Kramer GW, Legrand CL, van Schil P, Uitterhoeve L, Smit EF, Schramel F, et al. Quality assurance of thoracic radiotherapy in EORTC 08941: a randomised trial of surgery versus thoracic radiotherapy in patients with stage IIIA non-small-cell lung cancer (NSCLC) after response to induction chemotherapy. *Eur J Cancer* (2006) 42(10):1391–8. doi:10.1016/j.ejca.2006.01.052
73. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* (2015) 16(2):187–99. doi:10.1016/S1470-2045(14)71207-0
74. Suntharalingam M, Paulus R, Edelman MJ, Krasna M, Burrows W, Gore E, et al. Radiation therapy oncology group protocol 02-29: a phase II trial of neoadjuvant therapy with concurrent chemotherapy and full-dose radiation therapy followed by surgical resection and consolidative therapy for locally advanced non-small cell carcinoma of the lung. *Int J Radiat Oncol Biol Phys* (2012) 84(2):456–63. doi:10.1016/j.ijrobp.2011.11.069
75. Samson P, Crabtree TD, Robinson CG, Morgensztern D, Broderick S, Krupnick AS, et al. Defining the ideal time interval between planned induction therapy and surgery for stage IIIA non-small cell lung cancer. *Ann Thorac Surg* (2017) 103(4):1070–5. doi:10.1016/j.athoracsur.2016.09.053
76. Gao SJ, Corso CD, Wang EH, Blasberg JD, Detterbeck FC, Boffa DJ, et al. Timing of surgery after neoadjuvant chemoradiation in locally advanced non-small cell lung cancer. *J Thorac Oncol* (2017) 12(2):314–22. doi:10.1016/j.jtho.2016.09.122
77. Zhong W, Yang X, Yan H, Zhang X, Su J, Chen Z, et al. Phase II study of biomarker-guided neoadjuvant treatment strategy for IIIA-N2 non-small cell lung cancer based on epidermal growth factor receptor mutation status. *J Hematol Oncol* (2015) 8:54. doi:10.1186/s13045-015-0151-3
78. Schaake EE, Kappers I, Codrington HE, Valdes Olmos RA, Teertstra HJ, van Pel R, et al. Tumor response and toxicity of neoadjuvant erlotinib in patients with early-stage non-small-cell lung cancer. *J Clin Oncol* (2012) 30(22):2731–8. doi:10.1200/JCO.2011.39.4882
79. ClinicalTrials.gov. (2017). Available from: https://www.clinicaltrials.gov/ct2/results?cond=Lung+Cancer+Neoadjuvant&term=&cntry1=&state1=&Search=Search
80. Juweid ME, Cheson BD. Positron-emission tomography and assessment of cancer therapy. *N Engl J Med* (2006) 354(5):496–507. doi:10.1056/NEJMra050276
81. Berghmans T, Dusart M, Paesmans M, Hossein-Foucher C, Buvat I, Castaigne C, et al. Primary tumor standardized uptake value (SUVmax) measured on fluorodeoxyglucose positron emission tomography (FDG-PET) is of prognostic value for survival in non-small cell lung cancer (NSCLC): a systematic review and meta-analysis (MA) by the European Lung Cancer Working Party for the IASLC Lung Cancer Staging Project. *J Thorac Oncol* (2008) 3(1):6–12. doi:10.1097/JTO.0b013e31815e6d6b
82. Bharat AGB, Rusch VW, Bains MS, Rizk NP. Role of PET scan in predicting response to neoadjuvant chemotherapy and long-term outcomes for stage II lung cancer. *ASCO Meet Abstr* (2014) 32(15_suppl):7574. doi:10.1200/jco.2014.32.15_suppl.7574
83. Hoekstra CJ, Stroobants SG, Smit EF, Vansteenkiste J, van Tinteren H, Postmus PE, et al. Prognostic relevance of response evaluation using [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography in patients with locally advanced non-small-cell lung cancer. *J Clin Oncol* (2005) 23(33):8362–70. doi:10.1200/JCO.2005.01.1189
84. Chaft JE, Dunphy M, Naidoo J, Travis WD, Hellmann M, Woo K, et al. Adaptive neoadjuvant chemotherapy guided by (18)F-FDG PET in resectable non-small cell lung cancers: the NEOSCAN trial. *J Thorac Oncol* (2016) 11(4):537–44. doi:10.1016/j.jtho.2015.12.104

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer MP and handling editor declared their shared affiliation.

Copyright © 2018 Lewis, Gillaspie, Osmundson and Horn. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

MINI REVIEW
published: 26 October 2017
doi: 10.3389/fonc.2017.00249

Surgical Management of Stage IIIA Non-Small Cell Lung Cancer

Paul E. Van Schil, Lawek Berzenji, Suresh K. Yogeswaran, Jeroen M. Hendriks and Patrick Lauwers*

Department of Thoracic and Vascular Surgery, Antwerp University Hospital and Antwerp University, Antwerp, Belgium

According to the eighth edition of the tumor–node–metastasis classification, stage III non-small cell lung cancer is subdivided into stages IIIA, IIIB, and IIIC. They represent a heterogeneous group of bronchogenic carcinomas with locoregional involvement by extension of the primary tumor and/or ipsilateral or contralateral lymph node involvement. Surgical indications have not been definitely established but, in general, long-term survival is only obtained in those patients in whom a complete resection is obtained. This mini-review mainly focusses on stage IIIA disease comprising patients with locoregionally advanced lung cancers. Different subcategories of N2 involvement exist, which range from unexpected N2 disease after thorough preoperative staging or "surprise" N2, to bulky N2 involvement, mostly treated by chemoradiation, and finally, the intermediate category of potentially resectable N2 disease treated with a combined modality regimen. After induction therapy for preoperative N2 involvement, best surgical results are obtained with proven mediastinal downstaging when a lobectomy is feasible to obtain a microscopic complete resection. However, no definite, universally accepted guidelines exist. A relatively new entity is salvage surgery applied for recurrent disease after full-dose chemoradiation when no other therapeutic options exist. Equally, only a small subset of patients with T4N0-1 disease qualify for surgical resection after thorough discussion within a multidisciplinary tumor board on the condition that a complete resection is feasible. Targeted therapies and immunotherapy have recently become part of our therapeutic armamentarium, and it might be expected that they will be incorporated in current regimens after careful evaluation in randomized clinical trials.

Keywords: lung cancer, stage III, treatment, chemotherapy, radiotherapy, surgery, multimodality therapy, induction therapy

OPEN ACCESS

Edited by:
Giulia Veronesi,
Humanitas Research Hospital, Italy

Reviewed by:
Stephan Bodis,
Kantonsspital Aarau, Switzerland
Eric Chi-ching Ko,
Weill Cornell Medical College, United States

****Correspondence:***
Paul E. Van Schil
paul.van.schil@uza.be

Specialty section:
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

Received: *27 July 2017*
Accepted: *06 October 2017*
Published: *26 October 2017*

Citation:
Van Schil PE, Berzenji L, Yogeswaran SK, Hendriks JM and Lauwers P (2017) Surgical Management of Stage IIIA Non-Small Cell Lung Cancer. Front. Oncol. 7:249. doi: 10.3389/fonc.2017.00249

INTRODUCTION

Precise indications for surgical treatment of stage III non-small cell lung cancer (NSCLC) remain highly controversial although randomized controlled trials have been performed (1). Several reasons account for this ongoing debate. There are several subsets of stage III NSCLC related to the extension of the primary tumor and hilar or mediastinal lymph node involvement (2). Stage III represents an intermediate zone between clearly resectable, early stage disease, and metastatic involvement for which a surgical intervention is only very rarely indicated. There is also a lack of precise definitions that can universally be applied, as, e.g., definition of "resectable" T4 or N2 disease, which is largely dependent on the local expertise (3).

Combined modality therapy is indicated for most patients with stage III NSCLC who have a good performance status but the precise role of surgery, radiotherapy, and chemotherapy within such combined modalities setting has not been firmly established (4). Moreover, with the introduction of targeted agents, and more recently, also immunotherapy, the therapeutic options have clearly expanded. In this mini-review, we mainly focus on stage IIIA with the main emphasis on the contribution of thoracic surgery. Finally, targeted therapies and immunotherapy are mentioned as new therapeutic options that have to be further evaluated, and the relatively new concept of salvage surgery will be highlighted.

T3N1M0 (STAGE IIIA)

T3N1 is relatively rarely encountered in thoracic surgery. Most of these patients are operated for clinical T3 involvement and, incidentally, during the intervention N1 disease is discovered. Every attempt should be made to obtain a complete resection with negative surgical margins (5). In some patients, chest wall resection and reconstruction will be required. Adjuvant chemotherapy is indicated for tumors >5 cm and/or when lymph nodes are involved. In case of microscopic residual disease at the section margins, additional radiotherapy may also be considered after discussion within a multidisciplinary team to decrease the local recurrence rate (6).

T1-3N2M0 (STAGE IIIA–IIIB)

Stage IIIA-N2 remains one of the most controversial areas in thoracic oncology although results of large phase III trials have become available for almost 10 years. N2 involvement represents quite heterogeneous disease entities including unexpected or unforeseen or "surprise" N2 disease, intranodal, and extracapsular invasion, single and multilevel N2 disease, and finally, limited and bulky N2 involvement (7). For this review, we focus on patients with potentially resectable N2 involvement proven by minimally invasive or invasive staging procedures as they represent a highly controversial indication for a surgical intervention. It should already be noted that there is no universally accepted definition of "potentially resectable N2," which largely depends on the specific center and the experience of the involved thoracic surgeon.

Three large randomized trials have been reported at major meetings and published in highly ranked journals but they don't provide a definite answer on optimal management of this disease stage (8–10). In the Intergroup (INT) 0139 and the more recent ESPATUE trial, patients were treated with induction chemoradiation and subsequently randomized between surgery or further radiotherapy. In the ESPATUE phase III trial, the induction therapy was quite complicated and consisted of induction chemotherapy followed by chemoradiation. In the European Organization for Research and Treatment of Cancer (EORTC) 08941 trial, only induction chemotherapy was given followed by surgery or radiotherapy in case of response to chemotherapy, also randomizing those patients with a minor response. In all three trials, overall survival was not different between both arms although in the Intergroup trial progression-free survival was better in the group undergoing surgical resection. In the latter study, mortality of pneumonectomy was unacceptably high, especially for those patients undergoing complex, intrapericardial pneumonectomies. An unplanned subanalysis matched patients undergoing lobectomy after induction chemoradiation to a similar group treated by chemoradiation only. A highly significant survival difference was found favoring the surgical arm (9). This made the authors conclude that there is an advantage for surgical intervention on the condition that a complete resection can be obtained by performing a lobectomy after induction therapy. It should also be noted that the EORTC and Intergroup trial were designed at a time when routine positron emission tomographic scanning was not yet incorporated and that staging by minimally invasive techniques was not available in most participating centers.

Several meta-analyses performed on this subject tried to provide more definite answers, but did not reach similar conclusions. A summary with conclusions is provided in **Table 1**. Two of these meta-analyses should be highlighted. McElnay et al. compared bimodality and trimodality regimens including six trials with a total of 868 patients (11). They concluded that the outcome for the radiotherapy and surgical arms were similar for bimodality regimens, but that there is a 13% survival advantage for surgical intervention within combined trimodality therapy consisting of chemotherapy, radiotherapy, and surgery. This does not reflect a selection bias as in both arms patients qualified for surgical resection. However, the latter difference did not reach statistical significance at the 0.05 level. Conclusions of the most recent meta-analysis including randomized trials that compared surgery with radiotherapy as local treatment modalities were more moderate, stating that there was no difference in overall and progression-free survival between surgery and radiotherapy in the setting of stage III NSCLC (12).

In most studies, it has been clearly demonstrated that downstaging of mediastinal lymph nodes is a major prognostic factor; so, every attempt should be made to thoroughly restage the mediastinum after induction therapy by minimally invasive or invasive techniques before embarking on a major surgical intervention (17–19).

It seems improbable that similar, large-scale phase III trials in patients with N2 disease will still be initiated as currently, many more therapeutic options including targeted therapies and immunotherapy, have become available (20, 21). These newer modalities still have to be evaluated in randomized phase II and phase III trials to determine the optimal combination that provides the best long-term results. As no clear recommendations can be made at the present time, every patient with N2 disease has to be carefully evaluated by a multidisciplinary thoracic oncological team including experienced thoracic surgeons to determine the optimal diagnostic and therapeutic strategy (7).

As there seems to exist a different prognosis between the several N2 subdivisions, it may be logical to make a further distinction, which has been proposed in the seventh edition of the Tumor–Node–Metastasis classification with some modifications in the eighth edition separating involvement of single from multiple nodal zones or stations (22–24). A comparison is provided in **Table 2**. N2 skip metastasis implies that N2 stations are involved by tumor without invasion of the intermediate N1

TABLE 1 | Recent meta-analyses and systematic reviews on stage III non-small cell lung cancer.

Reference	Number of included studies	Number of randomized studies	Total number of patients	Overall survival	Disease-free survival; progression-free survival	Tumor downstaging; pathological complete response; local control	Toxicity
McElnay et al. (11)	6	6	868	– OS was not significantly different between surgery and radiotherapy in bimodality treatment trials [HR = 1.01 (95% CI 0.82–1.23); $p = 0.954$] – OS was not significantly different between surgery and radiotherapy in trimodality treatment trials [HR = 0.87 (95% CI 0.75–1.01); $p = 0.068$] – Overall OS of all trials [HR = 0.92 (95% CI 0.81 to 1.03); $p = 0.157$]			
Pöttgen et al. (12)	6	6	1,322	– OS was not significantly different between surgical and definitive radiotherapy arms [HR = 0.92 (95% CI 0.82–1.04); $p = 0.19$]	– PFS was not significantly different between surgical and definitive radiotherapy arms [HR = 0.91 (95% CI 0.73–1.13); $p = 0.4$]		– Treatment-related toxicity was higher in the surgical arms than the radiotherapy arms [RR = 3.56 (95% CI 1.65–7.72); $p = 0.0005$]
Xu et al. (13)	7	7	1,049	– OS was not significantly different in the surgical group compared to the radical radiotherapy group after neoadjuvant chemotherapy or chemoradiotherapy [HR = 0.95 (95% CI 0.81–1.10); $p = 0.49$]	– PFS was not significantly different in the surgical group – Compared to the radical radiotherapy group after neoadjuvant chemotherapy or chemoradiotherapy [HR = 0.90 (95% CI 0.77–1.05); $p = 0.19$]	– Mediastinal pCR was significantly different in patients who received neoadjuvant chemoradiotherapy prior to surgical resection compared to those who received neoadjuvant chemotherapy [OR = 3.61 (95% CI 1.07–12.15); $p = 0.04$]	
Guo et al. (14)	12	8	2,724	– 5-year OS was significantly different when comparing induction chemoradiotherapy to induction chemotherapy alone prior to surgery [HR = 0.89 (95% CI 0.68–1.19); $p = 0.44$]	– 5-year PFS was not significantly different when comparing induction chemoradiotherapy to induction chemotherapy alone prior to surgery [HR = 0.74 (95% CI 0.43–1.26); $p = 0.26$]	– Induction chemoradiation prior to surgery results in significantly improved downstaging [OR = 0.75 (95% CI, 0.63–0.89); $p = 0.001$], mediastinal pCR [OR = 0.72 (95% CI, 0.60–0.88); $p = 0.001$], and in LC [OR = 0.64 (95% CI, 0.48–0.85); $p = 0.002$] compared with induction chemotherapy alone	
Ren et al. (15)	3	3	1,084	– 2- and 4-year OS were not significantly different when comparing induction treatment plus surgery [RR = 1.00 (95% CI 0.85–1.17); $p = 0.98$] to combined chemoradiotherapy as definitive therapy [RR = 1.13 (95% CI 0.85–1.51); $p = 0.39$]	– PFS was significantly different when comparing induction chemoradiotherapy prior to surgery [RR = 1.78; (95% CI 1.08–2.92); $p = 0.02$] to chemotherapy alone [RR = 1.05 (95% CI 0.61–1.81); $p = 0.86$]		

(*Continued*)

TABLE 1 | Continued

Reference	Number of included studies	Number of randomized studies	Total number of patients	Overall survival	Disease-free survival; progression-free survival	Tumor downstaging; pathological complete response; local control	Toxicity
Shah et al. (16)	7	1	339	– OS was not significantly different when comparing induction chemoradiotherapy to induction chemotherapy alone after meta-analysis of RCTs [HR = 0.93 (95% CI 0.54–1.62), $p = 0.81$] and retrospective studies [HR = 0.77 (95% CI 0.50–1.19), $p = 0.24$]			

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; LC, local control; OR, odds ratio; OS, overall survival; pCR, pathological complete response; PFS, progression-free survival; RCT, randomized controlled trials; RR, relative risk.

TABLE 2 | Subdivisions of N1-3 disease according to the seventh and eighth editions of the Tumor–Node–Metastasis classification (22, 23, 24).

Nodal subdivision	Seventh edition	Eighth edition
N1a	Single N1 zone	Single N1 station
N1b	Multiple N1 zones	Multiple N1 stations
N2a	Single N2 zone	Single N2 station
N2a1	–	Single N2 station (skip metastasis)
N2a2	–	Single N2 station (with N1 involvement)
N2b	Multiple N2 zones	Multiple N2 stations
N3	Contralateral hilar or mediastinal lymph node stations or scalene or supraclavicular lymph nodes	Contralateral hilar or mediastinal lymph node stations or scalene or supraclavicular lymph nodes

stations. Initial analysis for the seventh edition showed that prognosis between involvement of multiple N1 zones and single N2 zone was not different (23). In the eighth edition, the survival curves for N1b and N2a2 overlapped. N2a1 disease even had a better prognosis than N1b, although this difference was not significant (22).

Thoracic surgeons and oncologists are encouraged to submit prospective data to the International Association for the Study of Lung Cancer (IASLC) database to obtain more reliable survival data in larger groups of patients originating from different continents (www.crab.org).

T4N0-1M0 (STAGE IIIA)

T4 disease implies a locally highly aggressive tumor with invasion of critical mediastinal organs or structures as, e.g., esophagus, carina, aorta, or left atrium. By definition, this extension is mostly beyond the limit of potential surgical resectability implying that most patients do not qualify for surgical resection. In these particular cases, it may be quite challenging to obtain a complete R0 resection according to the IASLC definition (5). When lymph nodes are involved, especially, mediastinal N2 stations, two negative prognostic factors are combined resulting in only exceptional 5-year survivors. However, several non-randomized series have shown that, in highly selected patients, long-term survival may be obtained, especially in those patients with good performance status and negative lymph nodes (25). Undoubtedly, these surgical interventions are quite complex, usually involving procedures on large vessels or carina, which require highly skilled thoracic surgeons working in a dedicated environment of a multidisciplinary team composed of medical and radiation oncologists, pulmonary physicians, radiologists, nuclear medicine physicians, pathologists, and intensive-care specialists besides thoracic surgeons. Also a specifically trained nursing and physiotherapy staff is required to detect and treat postoperative complications at an early stage (26). To obtain the best short- and long-term results, these patients should be treated in high-volume thoracic centers (25).

Most reported experience include tumors invading the superior vena cava, left atrium, carina, and intrapericardial

TABLE 3 | Ongoing studies on stage III lung cancer incorporating targeted therapies.

NCT identifier	Status	Study title	Intervention	Phase
NCT01857271	Recruiting	Erlotinib hydrochloride before surgery in treating patients with Stage III non-small cell lung cancer (NSCLC) (EVENT)	Drug: Erlotinib hydrochloride Procedure: therapeutic conventional surgery Other: laboratory biomarker analysis	2
NCT02201992	Recruiting	Crizotinib in treating patients with Stage IB-IIIA NSCLC that has been removed by surgery and ALK fusion mutations (an ALCHEMIST treatment trial)	Drug: Crizotinib Other: laboratory biomarker analysis Other: Placebo	3
NCT02347839	Recruiting	NEoadjuvant Gefitinib followed by surgery and gefiTinib In unresectAble sTage III NSCLC with epidermal growth factor receptor mutations (NEGOTIATE)	Gefitinib-surgery-gefitinib	2

pulmonary vessels whereby 5-year survival rates between 9 and 48% have been reported (25). Whether induction therapy may yield similar results of downstaging as in stage IIIA-N2 disease remains an open question. In some cases, induction chemotherapy or chemoradiation may be helpful for the thoracic surgeon to obtain a subsequent complete resection in order to increase overall and disease-free survival. In a Spanish phase II study, 136 patients with clinical stage IIIA or IIIB disease were treated by induction chemotherapy followed by surgical intervention (27). Complete resection was obtained in 69% of operated patients, or 48% of all assessable patients. Pneumonectomy was necessary in 41% of patients underscoring the extent of the operation that is necessary in these particular cases. Overall mortality was 7.8% and major complications occurred in 30%. In case of complete resection of a T4N0 tumor, an excellent 5-year survival rate of 53% was obtained. However, it should be noted that these were highly selected patients.

A specific category of T4 disease is those patients with ipsilateral tumor nodules in a different lobe than the primary tumor (28). They have an intermediate prognosis between patients with additional tumor nodules in the same lobe and those with distant metastases. It is usually recommended to perform a lobectomy for the largest tumor and a segmentectomy or wide wedge excision for the smallest one, although in some cases, a pneumonectomy may be required. Five-year survival rates of 22% may be obtained in this particular subset of patients (29).

At the present time, no randomized evidence on surgery for T4 disease is available; surely, such evidence will be very difficult to obtain due to the relative scarcity and heterogeneity of this patient population.

TARGETED THERAPIES—IMMUNOTHERAPY

Newer therapeutic options include targeted therapies and immunotherapy. Targeted therapies may be given to patients with specific mutations as epidermal growth factor receptor (EGFR) mutations treated with tyrosine kinase inhibitors. Due to the good results in metastatic NSCLC, immunotherapy is currently also considered for earlier stages of lung cancer. Monoclonal antibodies, such as nivolumab, may stimulate the immune system in different ways and kill tumor cells remaining after surgery and chemotherapy. In a very recently published phase III trial, durvalumab was compared with placebo in patients with unresectable stage III NSCLC who had no evidence of disease progression after two or more cycles of platinum-based chemoradiotherapy (30). Progression-free survival was significantly longer with durvalumab than with placebo. For resectable stage III NSCLC, no randomized evidence is currently available, but there are several ongoing trials incorporating these newer therapeutic options with surgical resection. Recruiting trials incorporating targeted therapies are summarized in **Table 3**.

SALVAGE SURGERY

Salvage surgery is a relatively new concept in thoracic surgery applied to patients with recurrent or progressive disease, when no other therapeutic options are available (31). In the setting of stage III, disease salvage surgery may be indicated in patients who were initially treated by chemoradiation and in whom recurrent or progressive disease is detected at routine follow-up. These interventions should only be performed in highly selected patients who are functionally operable after thorough cardiopulmonary evaluation and be restricted to dedicated centers with a large thoracic surgical experience. In case of respiratory symptoms, fever and raised inflammatory parameters, an infected cavity may be present at the primary tumor site (32). As can be expected, these are technically complex and challenging procedures, especially when a large abscess cavity is present. At the present, time clinical series that have been published on salvage surgery for stage III disease are quite small, but they already show that an acceptable long-term survival may be obtained in patients with good performance status and low cardiopulmonary risk (33).

AUTHOR CONTRIBUTIONS

All authors met following criteria: substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content; and final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Van Schil PE, De Waele M, Hendriks JM, Lauwers PR. Surgical treatment of stage III non-small cell lung cancer. *Eur J Cancer* (2009) 45(Suppl 1):106–12. doi:10.1016/S0959-8049(09)70022-X
2. Eberhardt WE, De Ruysscher D, Weder W, Le Pechoux C, De Leyn P, Hoffmann H, et al. 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer. *Ann Oncol* (2015) 26(8):1573–88. doi:10.1093/annonc/mdv187
3. Van Schil PE. Stage IIIA-N2 non-small-cell lung cancer: from 'surprise' involvement to surgical nightmare. *Eur J Cardiothorac Surg* (2016) 49(6):1613–4. doi:10.1093/ejcts/ezv457
4. Van Schil PE, Yogeswaran K, Hendriks JM, Lauwers P, Faivre-Finn C. Advances in the use of surgery and multimodality treatment for N2 non-small cell lung cancer. *Expert Rev Anticancer Ther* (2017) 17(6):555–61. doi:10.1080/14737140.2017.1319766
5. Rami-Porta R, Wittekind C, Goldstraw P; International Association for the Study of Lung Cancer Staging C. Complete resection in lung cancer surgery: proposed definition. *Lung Cancer* (2005) 49(1):25–33. doi:10.1016/j.lungcan.2005.01.001
6. McCloskey P, Balduyck B, Van Schil PE, Faivre-Finn C, O'Brien M. Radical treatment of non-small cell lung cancer during the last 5 years. *Eur J Cancer* (2013) 49(7):1555–64. doi:10.1016/j.ejca.2012.12.023
7. Vansteenkiste J, Crino L, Dooms C, Douillard JY, Faivre-Finn C, Lim E, et al. 2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up. *Ann Oncol* (2014) 25(8):1462–74. doi:10.1093/annonc/mdu089
8. van Meerbeeck JP, Kramer GW, Van Schil PE, Legrand C, Smit EF, Schramel F, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst* (2007) 99(6):442–50. doi:10.1093/jnci/djk093
9. Albain KS, Swann RS, Rusch VW, Turrisi AT III, Shepherd FA, Smith C, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet* (2009) 374(9687):379–86. doi:10.1016/S0140-6736(09)60737-6
10. Eberhardt WE, Pottgen C, Gauler TC, Friedel G, Veit S, Heinrich V, et al. Phase III study of surgery versus definitive concurrent chemoradiotherapy boost in patients with resectable stage IIIA(N2) and selected IIIB non-small-cell lung cancer after induction chemotherapy and concurrent chemoradiotherapy (ESPATUE). *J Clin Oncol* (2015) 33(35):4194–201. doi:10.1200/JCO.2015.62.6812
11. McElnay PJ, Choong A, Jordan E, Song F, Lim E. Outcome of surgery versus radiotherapy after induction treatment in patients with N2 disease: systematic review and meta-analysis of randomised trials. *Thorax* (2015) 70(8):764–8. doi:10.1136/thoraxjnl-2014-206292
12. Pottgen C, Eberhardt W, Stamatis G, Stuschke M. Definitive radiochemotherapy versus surgery within multimodality treatment in stage III non-small cell lung cancer (NSCLC) – a cumulative meta-analysis of the randomized evidence. *Oncotarget* (2017) 8(25):41670–8. doi:10.18632/oncotarget.16471
13. Xu YP, Li B, Xu XL, Mao WM. Is there a survival benefit in patients with stage IIIA (N2) non-small cell lung cancer receiving neoadjuvant chemotherapy and/or radiotherapy prior to surgical resection: a systematic review and meta-analysis. *Medicine (Baltimore)* (2015) 94(23):e879. doi:10.1097/MD.0000000000000879
14. Guo SX, Jian Y, Chen YL, Cai Y, Zhang QY, Tou FF. Neoadjuvant chemoradiotherapy vesus chemotherapy alone followed by surgery for resectable stage III non-small-cell lung cancer: a meta-analysis. *Sci Rep* (2016) 6:34388. doi:10.1038/srep34388
15. Ren Z, Zhou S, Liu Z, Xu S. Randomized controlled trials of induction treatment and surgery versus combined chemotherapy and radiotherapy in stages IIIA-N2 NSCLC: a systematic review and meta-analysis. *J Thorac Dis* (2015) 7(8):1414–22. doi:10.3978/j.issn.2072-1439.2015.08.14
16. Shah AA, Berry MF, Tzao C, Gandhi M, Worni M, Pietrobon R, et al. Induction chemoradiation is not superior to induction chemotherapy alone in stage IIIA lung cancer. *Ann Thorac Surg* (2012) 93(6):1807–12. doi:10.1016/j.athoracsur.2012.03.018
17. De Leyn P, Dooms C, Kuzdzal J, Lardinois D, Passlick B, Rami-Porta R, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. *Eur J Cardiothorac Surg* (2014) 45(5):787–98. doi:10.1093/ejcts/ezu028
18. Jaklitsch MT, Gu L, Demmy T, Harpole DH, D'Amico TA, McKenna RJ, et al. Prospective phase II trial of preresection thoracoscopic mediastinal restaging after neoadjuvant therapy for IIIA (N2) non-small cell lung cancer: results of CALGB Protocol 39803. *J Thorac Cardiovasc Surg* (2013) 146(1):9–16. doi:10.1016/j.jtcvs.2012.12.069
19. De Waele M, Hendriks J, Lauwers P, Hertoghs M, Carp L, Salgado R, et al. Restaging the mediastinum in non-small cell lung cancer after induction therapy: non-invasive versus invasive procedures. *Acta Chir Belg* (2011) 111(3):161–4. doi:10.1080/00015458.2011.11680728
20. Provencio M, Sanchez A. Therapeutic integration of new molecule-targeted therapies with radiotherapy in lung cancer. *Transl Lung Cancer Res* (2014) 3(2):89–94. doi:10.3978/j.issn.2218-6751.2014.03.06
21. Jabbour SK, Berman AT, Simone CB II. Integrating immunotherapy into chemoradiation regimens for medically inoperable locally advanced non-small cell lung cancer. *Transl Lung Cancer Res* (2017) 6(2):113–8. doi:10.21037/tlcr.2017.04.02
22. Asamura H, Chansky K, Crowley J, Goldstraw P, Rusch VW, Vansteenkiste JF, et al. The International Association for the Study of Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. *J Thorac Oncol* (2015) 10(12):1675–84. doi:10.1097/JTO.0000000000000678
23. Rusch VW, Crowley J, Giroux DJ, Goldstraw P, Im JG, Tsuboi M, et al. The IASLC lung cancer staging project: proposals for the revision of the N descriptors in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* (2007) 2(7):603–12. doi:10.1097/JTO.0b013e31807ec803
24. Rusch VW, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P, et al. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* (2009) 4(5):568–77. doi:10.1097/JTO.0b013e3181a0d82e
25. Reardon ES, Schrump DS. Extended resections of non-small cel lung cancers invading the aorta, pulmonary artery, left atrium, or esophagus: can they be justified? *Thorac Surg Clin* (2014) 24(4):457–64. doi:10.1016/j.thorsurg.2014.07.012
26. Van Schil PE, Hendriks JM, Lauwers P. Focus on treatment complications and optimal management surgery. *Transl Lung Cancer Res* (2014) 3(3):181–6. doi:10.3978/j.issn.2218-6751.2014.06.07
27. Garrido P, Gonzalez-Larriba JL, Insa A, Provencio M, Torres A, Isla D, et al. Long-term survival associated with complete resection after induction chemotherapy in stage IIIA (N2) and IIIB (T4N0-1) non small-cell lung cancer patients: the Spanish Lung Cancer Group Trial 9901. *J Clin Oncol* (2007) 25(30):4736–42. doi:10.1200/JCO.2007.12.0014
28. Detterbeck FC, Bolejack V, Arenberg DA, Crowley J, Donington JS, Franklin WA, et al. The IASLC lung cancer staging project: background data and proposals for the classification of lung cancer with separate tumor nodules in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol* (2016) 11(5):681–92. doi:10.1016/j.jtho.2015.12.114
29. Rami-Porta R, Ball D, Crowley J, Giroux DJ, Jett J, Travis WD, et al. The IASLC lung cancer staging project: proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* (2007) 2(7):593–602. doi:10.1097/JTO.0b013e31807a2f81
30. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* (2017). doi:10.1056/NEJMoa1709937
31. Uramoto H. Current topics on salvage thoracic surgery in patients with primary lung cancer. *Ann Thorac Cardiovasc Surg* (2016) 22(2):65–8. doi:10.5761/atcs.ra.16-00019
32. Shimada Y, Suzuki K, Okada M, Nakayama H, Ito H, Mitsudomi T, et al. Feasibility and efficacy of salvage lung resection after definitive chemoradiation therapy for Stage III non-small-cell lung cancer. *Interact Cardiovasc Thorac Surg* (2016) 23(6):895–901. doi:10.1093/icvts/ivw245

33. Van Breussegem A, Hendriks JM, Lauwers P, Van Schil PE. Salvage surgery after high-dose radiotherapy. *J Thorac Dis* (2017) 9(Suppl 3):S193–200. doi:10.21037/jtd.2017.03.88

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2017 Van Schil, Berzenji, Yogeswaran, Hendriks and Lauwers. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

REVIEW
published: 04 December 2017
doi: 10.3389/fonc.2017.00281

Neoadjuvant Chemoradiotherapy for Stage III Non-Small Cell Lung Cancer

*David J. Sher**

Department of Radiation Oncology, Division of Outcomes and Health Services Research, UT Southwestern Medical Center, Dallas, TX, United States

The local management of stage III non-small cell lung cancer is controversial. Although definitive chemoradiotherapy (CRT) is considered a standard-of-care in the curative management of the disease, inadequate local control outcomes have led to various treatment strategies that incorporate surgical resection. Surgery alone has long been recognized as insufficient for this stage, and thus neoadjuvant strategies have been developed to treat micrometastatic disease and increase the probability of a complete resection. The optimal induction strategy has not yet been defined, however, with arguments favoring either preoperative chemotherapy or CRT. In this article, the data supporting the use of neoadjuvant CRT and the randomized literature comparing the two approaches will be reviewed. The article will conclude with summary comparisons of these induction paradigms.

Keywords: lung cancer, radiation therapy, neoadjuvant therapy, combined modality therapy, stage III non-small cell lung cancer

OPEN ACCESS

Edited by:
John Varlotto, University of Massachusetts Medical School, United States

Reviewed by:
Vivek Verma, University of Nebraska Medical Center, United States
Joel S. Greenberger, University of Pittsburgh Medical Center, United States

***Correspondence:**
David J. Sher
david.sher@utsouthwestern.edu

Specialty section:
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

Received: *02 August 2017*
Accepted: *06 November 2017*
Published: *04 December 2017*

Citation:
Sher DJ (2017) Neoadjuvant Chemoradiotherapy for Stage III Non-Small Cell Lung Cancer. Front. Oncol. 7:281. doi: 10.3389/fonc.2017.00281

INTRODUCTION

Although it is well-known that the successful treatment of stage III non-small cell lung cancer (NSCLC) is compromised by a high risk of micrometastatic disease, obtaining locoregional control has also long bedeviled local therapists. In the classic RTOG 73-01 study of radiation dose escalation in NSCLC, Perez et al. showed that the ultimate intrathoracic failure risks for squamous cell carcinoma and adenocarcinoma were 80 and 65%, respectively (1).

Additional non-invasive efforts to improve locoregional control first centered on altered fractionation approaches, and while there were some modest successes (2), none were paradigm shifting. The most important therapeutic change in the management of the disease arose from a series of landmark trials of chemotherapy. First, sequential chemotherapy and radiotherapy (RT) were shown to improve overall survival over RT alone (3), and then randomized trials of concurrent chemoradiotherapy (CRT) confirmed that concomitant treatment was clearly superior to single modality radiation treatment (4). The next generation of randomized studies showed that concurrent was superior to sequential delivery of chemotherapy, with the mode of improvement through superior locoregional control (5).

Yet despite this elegant progression of clinical investigation, definitive RT-based regimens still resulted in inadequate thoracic control rates. For example, the concurrent CRT arm of the RTOG 9410 trial, which helped to establish definitive CRT as a standard-of-care, still resulted in a crude thoracic failure risk of 45% (6). A more modern study of definitive CRT using the now favored carboplatin–paclitaxel regimen with 66 Gy resulted in a crude local failure risk of 36% (7). After multiple retrospective studies of radiation dose escalation, the definitive RTOG 0617 study randomized patients between 60 and 74 Gy of CRT, finding no difference in locoregional control or survival between the arms (8). Despite modern RT planning and near uniform PET-CT staging, the

2-year local failure risk was 30.7 and 38.6% for the 60 and 74 Gy arms, respectively. Given these humbling results, there have been longstanding efforts to integrate surgical resection into the curative paradigm of operable patients. The underlying concept is that surgical extirpation of potentially radioresistant disease would provide improved thoracic control that may translate into an overall survival benefit. In this article, the key prospective data that motivate treatment with preoperative CRT will be reviewed. Studies of preoperative chemotherapy versus upfront surgery will not be the subject of this review.

SWOG 8805

The viability of preoperative CRT was shown in SWOG 8805, which was a multi-institutional phase II trial of induction CRT followed by anatomic resection (9). In this study, 126 patients with either N2 or N3 nodal disease and/or T4 primary lesions were treated with induction RT to 45 Gy with two concurrent cycles of etoposide–cisplatin. Patients with a complete resection and negative mediastinum were subsequently observed, and the remaining patients were treated with two additional cycles and consolidation RT to 59.4 Gy. Four patients experienced an early death (two treatment related), and 10 patients experienced progression of disease; 4 additional patients were ineligible for surgery.

Eleven percent of the remaining cohort had unresectable disease at thoracotomy. A pathologic complete response (pCR) was seen in 21% of resected patients, and 56% of patients with initial mediastinal nodal assessment experienced clearance of disease. Out of the entire initial cohort of 126 patients, there were a total of 25 first locoregional progressions (including synchronous metastases), resulting in a crude failure risk of 20%. The 3-year OS for patients with N2 disease at diagnosis was only 24%. However, among all patients with pathologically proven mediastinal adenopathy at diagnosis, the 3-year survival in patients with mediastinal nodal pCR versus not was 41 vs. 11% ($p = 0.003$), highlighting a consistent theme through the induction literature; namely, that patients with mediastinal clearance experience dramatically improved survival in comparison to those who do not.

The toxicity of trimodality therapy was not trivial. A total of 49 and 13% of patients experienced a grade 3 or grade 4 toxicity, respectively. Out of the 32 non-cancer related deaths, 13 were attributed to treatment, 8 of which were in the postoperative period. Six of these deaths were in patients who underwent a pneumonectomy, some of the initial data showing that the physiologic stress of post-CRT pneumonectomy may be profound.

ALTERNATIVE DOSE-FRACTIONATION REGIMENS

Because mediastinal pCR rates appear so closely linked to outcome, attempts have been made to increase mediastinal clearance through radiation dose intensification. For example, in a large phase II trial for patients with stage III NSCLC, investigators in Germany delivered four cycles of induction chemotherapy followed by 45 Gy in 3 weeks (1.5 Gy twice per day, BID) with concurrent carboplatin–paclitaxel, with surgery after radiation therapy (10). As opposed to most studies of trimodality therapy, this study cohort did not mandate operability at diagnosis. Of the 84 patients (out of 120) who were ultimately resectable, 58 (48% of the entire cohort) were completely resectable. The 30-day mortality was only 3%, but it was 11% (4 deaths) among the 36 patients who underwent pneumonectomy. The 5-year overall survival for all patients was 21.7% at 5 years, with the outcomes improving to 32.3% for individuals with stage IIIA disease; this latter number is quite favorable in comparison to most series for this stage. Patients with nodal pCR ($n = 30$, 25% of entire cohort, 52% of patients who underwent complete resection) experienced a superb 5-year survival probability of 53.3%, although interestingly there was no significant difference between patients with ypN1 and ypN2 disease (38.5 and 30.8%, respectively).

From a total dose perspective, RTOG 0229 was a multi-institutional prospective study that treated patients with CRT to a total dose of 61.2 Gy with subsequent surgery, essentially a curative dose even without subsequent surgery (11). Out of the 57 initial patients, 56 were eligible for resection and 37 patients ultimately underwent surgery. Most of the patients who did not go to surgery had unresectable or metastatic disease, or were medically inoperable. Forty-three patients had post-RT mediastinal sampling (either at surgery or mediastinoscopy), and 27 patients (63%) experienced mediastinal clearance. The 2-year progression-free and overall survival probabilities were 33 and 54%, respectively. Patients with mediastinal clearance had a 2-year survival probability of 67%, which rose to 75% if they underwent surgical resection. There was only one postoperative death and 14% incidence of grade 3 postoperative pulmonary complications. The survival outcomes for the whole cohort are encouraging, although one cannot discount selection bias for the favorable overall survival results. This result appears to be reproducible, as a small RTOG randomized phase II study using induction CRT (60 Gy) with or without panitumumab—powered to see an improvement in mediastinal clearance—ended up with a similar probability of downstaging (68.2%) in the control arm (12). Yet although this higher dose appears to be to tolerable, the mediastinal CR rate (63–68%) is not so much greater than the comparable rate from SWOG 8805, which used 45 Gy.

Indeed, one must remember that favorable biology is a potent confounder of the relationship between mediastinal clearance and survival. Patients with responsive disease will have improved survival no matter how they are treated, as well as improved mediastinal sterilization rates: aiming to improve mediastinal downstaging with intensified local therapy in this population will only translate into a marginal, if any, improvement in survival.

INTERGROUP 0139

Uncertainty about the utility of surgical resection after CRT led to the critical Intergroup 0139 trial, which compared the induction paradigm of SWOG 8805 with definitive CRT (61 Gy) for approximately 400 patients with pN2 stage IIIA NSCLC (13). Both arms received concurrent etoposide and cisplatin. Although the study was designed to answer whether trimodality therapy is superior,

the results have been used to support treatment with either treatment approach. With a median follow-up of 69.3 months for surviving patients, there was no significant difference in overall survival [hazard ratio (HR) 0.87, $p = 0.24$, with the 5-year survival probabilities of 27 versus 20% favoring surgery]. Progression-free survival was significantly better for patients in the surgery arm, doubling from 11 to 22% at 5 years. The patterns-of-failure analysis suggested that primary tumor control was the sole oncologic benefit from resection, as it significantly reduced the local-only relapses (22 vs. 10%).

One of the salient findings from the trial, though, revolved around treatment-related mortality, as 14 patients (out of 54, 26%) died after pneumonectomy, most of whom ($n = 11$) had a right-sided pneumonectomy, resulting in a mortality rate of 40% in this subset. This result prompted the authors to perform an unplanned subset analysis, matching patients who underwent a lobectomy with patients in the definitive CRT arm, and similarly matching individuals who underwent a pneumonectomy with patients in the CRT arm. As expected, among patients in the lobectomy comparison, surgery was associated with significantly improved overall survival (36 vs. 18% at 5 years, $p = 0.002$), whereas there was no significant difference in the pneumonectomy comparison. This result has led to the problematic and flawed interpretation that if patients are able to undergo a lobectomy (or if they are converted to a lobectomy with induction treatment), then they will gain a survival benefit from the resection.

The issue with this conclusion is that patients were not stratified by proposed surgery, and thus not only unknown confounders could have biased this comparison, but also obviously known confounders would prevent a legitimate comparison. The included surgical patients did well by virtue of their receipt of surgery after induction, and potentially very well as shown by the ability to undergo a lobectomy rather than a more involved operation. Indeed, only 71% of analyzed surgical patients underwent a complete resection, so by definition patients in the completely resected lobectomy "cohort" were more favorable than the comparison RT patients, in which there was no post-treatment selection. The comparison was the proverbial apples-to-oranges analysis, although unfortunately a popular conclusion from the paper is that patients who may undergo a lobectomy should be treated with trimodality therapy. Nevertheless, a safer and more statistically grounded assessment is that trimodality therapy improved progression-free survival in comparison to definitive CRT, a result that preserved its place as a potentially viable treatment approach for patients expected to tolerate the aggressive therapy.

ESPATUE

While the Intergroup study provided motivation for continuing to explore trimodality therapy, the unexpected post-surgical mortality risk significantly dampened enthusiasm for the approach. There is a second multi-institutional randomized study of definitive CRT versus trimodality therapy that provides additional information on these two treatments (14). In this German study, patients with IIIA (N2) and selected IIIB NSCLC were all given three cycles of induction chemotherapy with cisplatin and paclitaxel, and non-progressors were all treated with hyperfractionated CRT (45 Gy in 30 twice-daily fractions). Patients were re-assessed for operability during the last week of RT, and those eligible for surgery were randomized between completing RT (additional 20–26 Gy in daily fractions) and surgical resection.

Although the study was closed early, 246 patients were enrolled, and after the serial treatments 161 patients were randomized. Seventy (out of 81) of the surgical patients went to resection, of whom 66 had an R0 resection. A total of 5 (7%) patients experienced a grade 5 toxicity after surgery, but only one death was following pneumonectomy. After a median follow-up of 78 months, there were no differences in progression-free (35 vs. 32% favoring CRT) or overall (40 vs. 44% favoring surgery) survival. Unfortunately, the patterns-of-failure were not reported.

This trial differs from the Intergroup study in several ways. First and perhaps most important, patients were selected for response (or progression) prior to randomization. Thus, the cohort who made it to randomization were responding to treatment, so perhaps they were more likely to respond to RT as well. Second, the vast majority of patients underwent pre-treatment PET staging, so individuals with previously occult metastatic disease were not included in the study, increasing the likelihood of seeing a survival advantage with improved local therapy. And yet, there was no difference in overall survival.

What can we conclude from these two phase III studies? One straightforward answer is that there is no obvious winner, but for patients who may not tolerate anatomic surgical resection—a non-trivial if not large percentage of the population—definitive CRT is the obvious treatment of choice. On the other hand, the Intergroup study suggests that without first selecting patients with induction therapy, progression-free survival is improved following surgical resection *via* improved local/primary control. Thus, for high performing patients who are at greatest risk for local first progression, trimodality therapy may be reasonable.

COMPARING INDUCTION CHEMOTHERAPY WITH INDUCTION CRT

There is a long history of trials comparing induction chemotherapy followed by surgery with surgery alone, with the majority of those trials showing an overall survival advantage with neoadjuvant systemic treatment (15). Two phase III randomized trials have, thus, asked the natural question of whether preoperative CRT provides any additional benefit to preoperative chemotherapy alone. In the first study, the German Lung Cancer Cooperative Group treated over 500 patients with induction chemotherapy, with non-progressors then randomized between preoperative hyperfractionated CRT (45 Gy in 3 weeks) followed by surgery, or immediate surgery, with postoperative RT (54–68 Gy) (16). Out of the original 279 patients assigned to CRT, 231 finished induction chemotherapy, 208 started CRT, and 142 patients underwent surgery (54% of original cohort). A total of 279 patients were assigned induction chemotherapy alone, of whom 230 patients finished chemotherapy, and 154 patients underwent surgery (59% of original cohort). From

a toxicity perspective, patients receiving CRT experienced significantly increased grade 3 or higher hematologic toxicity (10 vs. 1%) and esophagitis (19 vs. 4%), but less pneumonitis (1 vs. 7%). There were no significant differences in surgical mortality, although numerical trends favored preoperative chemotherapy alone (9 vs. 5%) overall surgical mortality, with mortality after pneumonectomy doubled (14 vs. 6%).

Essentially every surrogate endpoint favored preoperative CRT, with more patients undergoing complete resection (75 vs. 60%, $p = 0.0008$), nodal downstaging to N0-1 (46 vs. 29%, $p = 0.02$), and histopathologic response greater than 90% (60 vs. 20%, $p < 0.0001$). As expected, patients undergoing a complete resection experienced superior survival, as did individuals with mediastinal downstaging. Despite these results, though there were no differences in progression-free or overall survival, or in the patterns-of-failure.

An important question is why such clear pathologic differences did not translate into improved overall survival with CRT. One possible explanation is simply that the superior responses in CRT are due to the increased time between the start of induction therapy and pathologic evaluation, and the chemotherapy cohort would have had an increased pCR rate if more time had transpired. Another relevant hypothesis is that pathologic response largely reflects micrometastatic sensitivity to chemotherapy. Although radiation therapy increases the local pathologic response by adding an additional cytotoxic therapy, the prognostic information is largely held in the chemotherapy response, which is obviously unchanged given that both arms received the same systemically active chemotherapy. Since any chemoresistant disease is ultimately removed by surgery, and then followed by radiation therapy, there would be no expected locoregional control differences in the two arms. These two explanations are important considerations as one tries to interpret the strengths and weaknesses of the two treatment paradigms.

The second trial was smaller cooperative group study perform by SAKK (Swiss Group for Clinical Cancer Research), and the results generally echoed the German study (17). In this study, operable stage IIIA/N2 patients were treated with three cycles of induction cisplatin and docetaxel, and non-progressors received either underwent immediate surgery or RT alone (44 Gy in 22 daily fractions) followed by surgery. An additional difference between these two trials is that postoperative RT was only delivered for an R1 or R2 resection (16% of patients in total). Although this study benefited from utilized a third-generation induction doublet, toxicity from induction chemotherapy was high—45% of patients in the RT arm and 60% in the chemotherapy arm developed a grade 3 or 4 toxic effect. In part likely due to the absence of concurrent chemotherapy, toxicity with RT was mild, with only 9 total grade 3 events. The addition of preoperative RT did not increase the risk of postoperative complications or mortality, the latter of which was quite low (3%) and only seen in the chemotherapy-alone patients.

Patients treated with trimodality therapy were more likely to have an objective response (61 vs. 44%), but that was the only statistical difference between the arms. There were clear numerical benefits in resection score and nodal downstaging (e.g., mediastinal clearance in 64 versus 53% of patients), but no comparisons were statistically significant. There were no statistically significant differences in event-free survival, overall survival, or patterns-of-failure, although the latter were not clearly specified. Overall survival outcomes were favorable, with median overall survival times of 37.1 and 26.2 months for induction chemotherapy and radiation and chemotherapy alone, respectively, with 5-year overall survival of approximately 40%.

It is important to remember, though, that patients were operable and generally had low-bulk disease. Moreover, what the authors term the "chemoradiation" arm was actually sequential therapy and is far removed from conventional preoperative combined modality therapy. Since it has been long established that radiation alone is an unimpactful neoadjuvant strategy (18), it is difficult to translate these results into routine practice. The study was also underpowered to compare these two treatments in a relatively favorable patient population, with just over 100 patients per arm: expecting a 50% increase in median survival with the addition of preoperative radiation therapy alone is not a reasonable assumption.

DETERMINING THE OPTIMAL NEOADJUVANT APPROACH

In order to determine the optimal treatment paradigm for a given patient, one must first recognize the unclear benefits of adding surgical resection to stage III NSCLC. Two large phase III trials have failed to show a consistent oncologic benefit to resection over CRT alone, and postoperative morbidity—before even considering mortality—is not trivial and potentially quite life-altering for patients. Patients in whom there is any legitimate question of surgical fitness should not be considered for bi- or trimodality therapy incorporating surgery.

For the relatively small subset of patients who clearly have operable disease and are straightforward operative candidates, the treatment options are more debatable. Certainly definitive CRT is a viable and possibly always the correct approach. Yet the Intergroup study is convincing that tolerable surgical resection reduces the probability of local failure, and there are certainly clinical scenarios in stage III NSCLC in which primary tumor recurrence is the greatest risk for the patient. For example, patients with large primaries and limited mediastinal disease will often fall into this category.

Once the idea of introducing surgery is entertained, which neoadjuvant approach is best? It is clear from the literature that there is no significant overall survival benefit with induction CRT over chemotherapy alone. And while there is often more concern over postoperative morbidity following combined treatment, the recent data from Europe should allay most fears about a meaningful increase in complications, provided there is surgeon and institutional experience in surgery following induction treatment. In addition, if the surgical technique needed to achieve an R0 resection is so complicated that radiation treatment may significant complicate the procedure, then resection probably is not such a good idea!

So the treatment recommendations ultimately hinge on physician and patient preferences. Favoring chemotherapy alone is the

recognition that many patients who ultimately go to resection can be spared any RT, provided there is a complete resection. There is certainly some value in omitting RT. Moreover, novel (or at least more active) chemotherapy agents may be easily delivered without concurrent RT, so patients may benefit from histology-directed agents rather than a regimen that is compatible with radiation treatment. Yet it is completely unclear whether the chosen chemotherapy doublet is that impactful in the non-metastatic setting.

On the other hand, a major risk of preoperative chemotherapy alone is the possibility that surgery becomes infeasible for whatever reason, and then the patient requires definitive CRT for an opportunity for cure. This scenario is not uncommon. In the German randomized study, which did not screen for operability, only 59% of patients ultimately went to surgery. That number was substantially higher in the SAKK trial, which only included operable stage IIIA patients, but even still 10% of patients did not make it to the operative room, and 8% of operated patients had gross residual disease. For those individuals who then need definitive CRT, they will have already received induction chemotherapy, which has been shown not to improve outcomes relative to definitive CRT (7), and their tolerability of treatment will likely be altered due to their recent exposure to systemic therapy.

By contrast, initiating CRT preserves all definitive treatment options without creating the possibility of delivering ultimately fruitless systemic therapy. Such treatment also will clearly increase the pathologic response, but in fairness, as mentioned above, the implications of this improvement relative to chemotherapy alone are still questionable. Although 45 Gy should be considered the standard induction dose based on Intergroup 0139, stopping at 45 Gy and then hoping the surgeon still considers the case operable is always anxiety-producing, because if surgery is not ultimately performed, the patient has received inadequate local therapy.

Instead, regardless of the preoperative likelihood that the patient will go to surgery, my preference is to deliver radical dose CRT to 60 Gy, which has been shown to be tolerable in a multi-institutional setting, and then selectively choose patients for resection. This minimizes the possibility of delivering insufficient local therapy—especially when patients are marginally operable—while providing the opportunity for subsequent surgery in the appropriate situation.

From an academic standpoint, patient scenarios can be divided into four groups based on tumor and nodal response. Patients who theoretically have a complete primary and nodal response do not need surgery, as the marginal gain in local control will be outweighed by toxicity. Patients with progressive or persistent primary and nodal disease do not need surgery, as the prognosis is too poor to warrant the risks of resection. Patients with persistent mediastinal disease but a complete primary response do not need surgery, as the risk of metastasis outweighs the very small improvement in local control. Finally, patients with a mediastinal response but persistent local disease may very well gain from resection, as micrometastastic disease may have been sterilized by chemotherapy but the local treatment has not fully responded. It is this latter cohort, defined by imaging and ideally mediastinal evaluation, for whom the therapeutic ratio favors trimodality therapy. Unfortunately, patients cannot be easily placed into one of these "boxes," as restaging modalities are insufficiently accurate to determine local and nodal response (19, 20), but this basic paradigm roughly guides how we can think about intensified local therapy in this disease.

THE FUTURE

One can divide future progress on this question to be divided into evolutionary versus revolutionary innovations. With time, more genomic and radiomic predictors of locoregional and distant control may be developed, providing either pre-treatment or mid-treatment information on the expected outcomes. Such prognostic information could provide valuable non-invasive information on the likelihood of the clearing the mediastinum or obtaining primary tumor control prior to deciding on surgery. Such technology would be a welcome innovation but would likely not meaningfully raise the proverbial tail of the survival curve, which has largely plateaued. A more revolutionary step would be the introduction of novel systemic therapies that more effectively control micrometastatic disease, raising the impact of improved locoregional control. Of course, such chemotherapy may also reduce local progression, minimizing the benefit of surgical resection. For example, there was a recent announcement that a phase III randomized trial of adjuvant durvalumab, an immunotherapy drug that blocks PD-L1 (programmed death-ligand 1), improved progression-free survival in stage III patients treated with definitive CRT (21). The future integration of surgical resection into stage III NSCLC may grow or shrink, depending on how these exciting therapies influence the disease course.

CONCLUSION

Although it is debatable whether surgical resection plays any role in stage III NSCLC, if one pursues a preoperative paradigm, either induction CRT or chemotherapy alone are viable treatment approaches. The strengths and weaknesses of both approaches have been detailed above, and from a practical, "real-world" perspective, a strong argument has been made to favor the incorporation of RT into the neoadjuvant program. Regardless of the final treatment, however, central to treatment success is close coordination between medical, radiation, and surgical oncologists. Collaboration and open dialog are critical to ensure the safest and most efficacious treatment in this challenging patient population.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

REFERENCES

1. Perez CA, Pajak TF, Rubin P, Simpson JR, Mohiuddin M, Brady LW, et al. Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. *Cancer* (1987) 59:1874–81.
2. Ramroth J, Cutter DJ, Darby SC, Higgins GS, McGale P, Partridge M, et al. Dose and fractionation in radiation therapy of curative intent for non-small cell lung cancer: meta-analysis of randomized trials. *Int J Radiat Oncol Biol Phys* (2016) 96:736–47. doi:10.1016/j.ijrobp.2016.07.022
3. Dillman RO, Seagren SL, Propert KJ, Guerra J, Eaton WL, Perry MC, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. *N Engl J Med* (1990) 323:940–5. doi:10.1056/NEJM199010043231403
4. Schaake-Koning C, van den Bogaert W, Dalesio O, Festen J, Hoogenhout J, van Houtte P, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N Engl J Med* (1992) 326:524–30. doi:10.1056/NEJM199202203260805
5. Auperin A, Le Pechoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* (2010) 28:2181–90. doi:10.1200/JCO.2009.26.2543
6. Curran WJ Jr, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst* (2011) 103:1452–60. doi:10.1093/jnci/djr325
7. Vokes EE, Herndon JE II, Kelley MJ, Cicchetti MG, Ramnath N, Neill H, et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: cancer and leukemia group B. *J Clin Oncol* (2007) 25:1698–704. doi:10.1200/JCO.2006.07.3569
8. Brown F. Vaccines. *Curr Opin Immunol* (1989) 2:392–6. doi:10.1016/0952-7915(89)90147-7
9. Albain KS, Rusch VW, Crowley JJ, Rice TW, Turrisi AT III, Weick JK, et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. *J Clin Oncol* (1995) 13:1880–92. doi:10.1200/JCO.1995.13.8.1880
10. Eberhardt W, Wilke H, Stamatis G, Stuschke M, Harstrick A, Menker H, et al. Preoperative chemotherapy followed by concurrent chemoradiation therapy based on hyperfractionated accelerated radiotherapy and definitive surgery in locally advanced non-small-cell lung cancer: mature results of a phase II trial. *J Clin Oncol* (1998) 16:622–34. doi:10.1200/JCO.1998.16.2.622
11. Suntharalingam M, Paulus R, Edelman MJ, Krasna M, Burrows W, Gore E, et al. Radiation therapy oncology group protocol 02–29: a phase II trial of neoadjuvant therapy with concurrent chemotherapy and full-dose radiation therapy followed by surgical resection and consolidative therapy for locally advanced non-small cell carcinoma of the lung. *Int J Radiat Oncol Biol Phys* (2012) 84:456–63. doi:10.1016/j.ijrobp.2011.11.069
12. Edelman MJ, Hu C, Le QT, Donington JS, D'Souza WD, Dicker AP, et al. Randomized phase II study of preoperative chemoradiotherapy ± panitumumab followed by consolidation chemotherapy in potentially operable locally advanced (stage IIIa, N2+) non-small cell lung cancer: NRG oncology RTOG 0839. *J Thorac Oncol* (2017) 12:1413–20. doi:10.1016/j.jtho.2017.06.007
13. Albain KS, Swann RS, Rusch VW, Turrisi AT III, Shepherd FA, Smith C, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet* (2009) 374:379–86. doi:10.1016/S0140-6736(09)60737-6
14. Eberhardt WE, Pottgen C, Gauler TC, Friedel G, Veit S, Heinrich V, et al. Phase III study of surgery versus definitive concurrent chemoradiotherapy boost in patients with resectable stage IIIA(N2) and selected IIIB non-small-cell lung cancer after induction chemotherapy and concurrent chemoradiotherapy (ESPATUE). *J Clin Oncol* (2015) 33:4194–201. doi:10.1200/JCO.2015.62.6812
15. NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. *Lancet* (2014) 383:1561–71. doi:10.1016/S0140-6736(13)62159-5
16. Thomas M, Rube C, Hoffknecht P, Macha HN, Freitag L, Linder A, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. *Lancet Oncol* (2008) 9:636–48. doi:10.1016/S1470-2045(08)70156-6
17. Pless M, Stupp R, Ris HB, Stahel RA, Weder W, Thierstein S, et al. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. *Lancet* (2015) 386:1049–56. doi:10.1016/S0140-6736(15)60294-X
18. Johnstone DW, Byhardt RW, Ettinger D, Scott CB. Phase III study comparing chemotherapy and radiotherapy with preoperative chemotherapy and surgical resection in patients with non-small-cell lung cancer with spread to mediastinal lymph nodes (N2); final report of RTOG 89-01. Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* (2002) 54:365–9. doi:10.1016/S0360-3016(02)02943-7
19. Arnett AL, Packard AT, Mara K, Mansfield AS, Wigle DA, Haddock MG, et al. FDG-PET parameters as predictors of pathologic response and nodal clearance in patients with stage III non-small cell lung cancer receiving neoadjuvant chemoradiation and surgery. *Pract Radiat Oncol* (2017) 7(6):e531–41. doi:10.1016/j.prro.2017.04.013
20. Ripley RT, Suzuki K, Tan KS, Adusumilli PS, Huang J, Park BJ, et al. Postinduction positron emission tomography assessment of N2 nodes is not associated with ypN2 disease or overall survival in stage IIIA non-small cell lung cancer. *J Thorac Cardiovasc Surg* (2016) 151:969–77, 979.e1–3. doi:10.1016/j.jtcvs.2015.09.127
21. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* (2017) 377(20):1919–29. doi:10.1056/NEJMoa1709937

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2017 Sher. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

REVIEW
published: 21 September 2017
doi: 10.3389/fonc.2017.00205

Radiotherapy Dosing for Locally Advanced Non-Small Cell Lung Carcinoma: "MTD" or "ALARA"?

Nitin Ohri[1,2]*

[1] Radiation Oncology, Albert Einstein College of Medicine, The Bronx, NY, United States, [2] Radiation Oncology, Montefiore Medical Center, The Bronx, NY, United States

Locally advanced non-small cell lung cancer (LA-NSCLC) is typically treated with thoracic radiotherapy, often in combination with cytotoxic chemotherapy. Despite tremendous advances in the evaluation, treatment techniques, and supportive care measures provided to LA-NSCLC patients, local disease progression and distant metastases frequently develop following definitive therapy. A recent landmark randomized trial demonstrated that radiotherapy dose escalation may reduce survival rates, highlighting our poor understanding of the effects of thoracic radiotherapy for LA-NSCLC. Here, we present rationale for further studies of radiotherapy dose escalation as well as arguments for exploring relatively low radiotherapy doses for LA-NSCLC.

Keywords: locally advanced NSCLC, radiotherapy, dose–response relationship, radiation, chemoradiotherapy, lung cancer

OPEN ACCESS

Edited by:
John Varlotto, University of Massachusetts Medical Center, United States

Reviewed by:
Michael T. Milano, University of Rochester, United States
Ronald Charles McGarry, University of Kentucky HealthCare, United States

***Correspondence:**
Nitin Ohri
ohri.nitin@gmail.com

Specialty section:
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

Received: *08 August 2017*
Accepted: *23 August 2017*
Published: *21 September 2017*

Citation:
Ohri N (2017) Radiotherapy Dosing for Locally Advanced Non-Small Cell Lung Carcinoma: "MTD" or "ALARA"? Front. Oncol. 7:205. doi: 10.3389/fonc.2017.00205

BACKGROUND

Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality in the United States and worldwide, causing over one million deaths each year (1). Approximately one-third of NSCLC patients are diagnosed with locally advanced disease, which may be defined as stage III disease or unresectable stage II disease (2). For locally advanced non-small cell lung cancer (LA-NSCLC), the standard treatment approach is conventionally fractionated (1.8–2.0 Gy/day) radiotherapy to a dose of approximately 60–66 Gy with concurrent, platinum-based chemotherapy. This treatment approach yields median survival times of only 16–30 months. Randomized trials have tested changes or additions to systemic therapy (3–7), radiotherapy dose escalation (6), and the addition of surgical resection (8) but have failed to improve overall survival for this patient population.

In this review, we will focus on the question of radiotherapy dosing for LA-NSCLC. Dozens of trials have sought to identify the optimal dosing schedule through modifications of the total radiotherapy dose, the daily radiotherapy dose, and treatment frequency (9, 10). However, tremendous uncertainty persists regarding the optimal radiotherapy regimen for LA-NSCLC. As an infinite number of radiotherapy schedules could be an envisioned, we will simplify our discussion by considering two opposing viewpoints: "maximum tolerated dose" (MTD) and "as low as reasonably achievable" (ALARA).

Maximum tolerated dose is defined by the National Cancer Institute as follows: "The highest dose of a drug or treatment that does not cause unacceptable side effects. The MTD is determined in clinical trials by testing increasing doses on different groups of people until the highest dose with acceptable side effects is found." (11) The United States Nuclear Regulatory Commission states that "ALARA is an acronym for *as low as (is) reasonably achievable*, which means making every

reasonable effort to maintain exposures to ionizing radiation as far below the dose limits as practical, consistent with the purpose for which the licensed activity is undertaken…" (12) ALARA is most often used in the context of environmental or occupational radiation exposure. For the purposes of this exercise, we will consider ALARA to represent the delivery of the lowest possible radiotherapy dose for LA-NSCLC that does not compromise local disease control probability.

FACT: DISEASE PROGRESSION FOLLOWING CHEMORADIOTHERAPY FOR LA-NSCLC IS COMMON

Supporting MTD

Chemoradiotherapy for LA-NSCLC yields local control rates of only 40–66% (6, 13–17). At least 75% of LA-NSCLC patients will succumb to their disease (6). While distant disease progression is a competing risk for LA-NSCLC that may theoretically detract from the importance of local control, there is high-level evidence that improving local control will directly improve survival rates. In a meta-analysis of six randomized trials comparing concurrent chemoradiotherapy to sequential chemoradiotherapy, the use of concurrent chemoradiotherapy increased the 5-year locoregional control rate by 6% at 5 years and improved the overall survival rate by 5% at 5 years, without reducing the frequency of distant metastasis (18). Thus, there seems to be a nearly 1:1 ratio linking locoregional disease control and overall survival in LA-NSCLC. This may be compared with the 4:1 ratio that has been established in the treatment of breast cancer with postoperative radiotherapy (19). The importance of local control in LA-NSCLC may become even more important in the future, as novel and more effective systemic therapy (20–22) may be incorporated into the management of LA-NSCLC (23) and attenuate the competing risk of distant metastasis.

Radiotherapy dose escalation or intensification using altered fractionation has been shown to improve disease control in cancers of the prostate (24) and head and neck (25). Altered radiotherapy fractionation for LA-NSCLC has also been shown to improve outcomes to some extent in large, randomized clinical trials (26). Established radiobiological principles indicate that intensified radiotherapy is required to sterilize lung tumors, where hypoxia and accelerated repopulation contribute to radioresistance (27). For early stage lung cancer, hypofractionated stereotactic body radiotherapy (SBRT) yields excellent control rates, particularly when high biologically effective doses are delivered (28, 29). Advances in radiotherapy treatment planning and delivery should be leveraged in a similar fashion to safely deliver curative radiotherapy doses for LA-NSCLC. While RTOG 0617 demonstrated that radiotherapy dose escalation applied to large volumes using conventional fractionation does not improve outcomes in LA-NSCLC (6), more innovative strategies to intensify radiotherapy using adaptive planning (30), SBRT boost (31), and particle therapy (32, 33) must be explored to improve outcomes for patients with LA-NSCLC.

Supporting ALARA

Distant metastasis occurs within two years in the majority of LA-NSCLC patients who are treated with concurrent chemoradiotherapy with definitive intent (6). Thoracic radiotherapy, which can cause profound acute (34, 35) and subacute (36, 37) toxicities in a dose-dependent fashion, should therefore be administered cautiously in this patient population. The current "standard" schedule of 60 Gy in 30 fractions was established approximately 40 years ago in a landmark randomized trial (38). 60 Gy was chosen over 50 Gy because 60 Gy yielded slightly better (but not statistically significantly superior) outcomes with respect to overall survival and local disease control. The relevance of these findings to current practice, where LA-NSCLC patients are treated with vastly more advanced techniques and typically receive concurrent chemotherapy, is unclear.

Several retrospective studies demonstrated strong associations between radiotherapy dose and overall survival duration, including in patients receiving concurrent chemotherapy (39, 40). In light of the results of RTOG 0617, however, it appears likely that those associations are attributable to selection biases (e.g., treating smaller volume disease with higher doses) or advances in treatment techniques (41) and systemic therapy (42) that took place during the era when non-randomized dose escalation trials were performed. Notably, RTOG 0617 (6) and several other trials where chemoradiotherapy was intensified using altered radiotherapy fractionation (9, 10) failed to demonstrate that local disease control or overall survival is improved with more aggressive radiotherapy. Meta-analyses strongly suggest that radiotherapy intensification may be beneficial when radiotherapy is delivered without chemotherapy but has not improved outcomes in the setting of concurrent chemotherapy (9, 10). The ability to control LA-NSCLC with chemoradiotherapy may more closely be related to tumor biology (43) and disease burden (44) than with radiotherapy dose. One may therefore argue that clinical trials should seek to define the lowest radiotherapy dose that can be used to treat LA-NSCLC without meaningfully compromising the likelihood of local disease control. An adaptive study design, such as the time-to-event continual reassessment model (45) could be could be ideal for defining a "minimum tolerated dose" in this setting. Based on analyzes of recurrence patterns demonstrating that local disease progression typically occurs in regions with large initial disease burden (46), a dose-painting approach may be implemented to reduce the dose delivered to small tumors and lymph nodes. In the rare cases where isolated thoracic disease progression occurs, salvage treatment options such as SBRT may yield excellent rates of disease control with acceptable toxicity rates (47).

FACT: SERIOUS COMPLICATION RATES FOLLOWING THORACIC RADIOTHERAPY FOR LA-NSCLC ARE LOW

Supporting MTD

The elimination of elective nodal irradiation (48), advances in imaging and target delineation (49), and advances in treatment techniques have significantly reduced the toxicity profile

of thoracic irradiation (50). Two dose escalation studies demonstrated that treatment with 74 Gy in 37 daily fractions with concurrent carboplatin and paclitaxel is safe (51, 52), leading to the use of that regimen in the experimental arm of RTOG 0617. In RTOG 0617, rates of severe (grade ≥ 3) toxicities were essentially equal across the control (60 Gy) and experimental (74 Gy) arms, demonstrating that modern treatment techniques and evidence-based constraints can be implemented to allow the safe delivery of dose-escalated thoracic radiotherapy. Complication rates may be expected to decline in future trials, as intensity-modulated radiotherapy and particle radiotherapy are increasingly being implemented for the treatment of LA-NSCLC (32, 53). Esophagitis is one important acute complication of thoracic radiotherapy that occurs in a dose-dependent fashion (6, 34). With modern treatment techniques and supportive care measures, however, most patients can complete radiotherapy without a treatment break (54).

Supporting ALARA

Evolving evidence reveals that thoracic irradiation can have profound consequences that were previously not appreciated. Two examples are provided below. As these risks emerge in a dose-dependent fashion, it is imperative that we examine the relationship between radiotherapy dosing and outcomes in LA-NSCLC rigorously and without bias and implement the lowest dose required to achieve local disease control.

Across the field of Oncology, patient-reported outcomes (PROs) have emerged as a key tool for assessing individual patients as well as in evaluating novel treatment strategies. PROs may be particularly revealing in the setting of LA-NSCLC, where patients' health status may be compromised by underlying comorbidities, disease burden, and treatment toxicity. In a key secondary analysis of RTOG 0617, treatment with 74 Gy rather than 60 Gy dramatically increased the risk of meaningful quality of life decline at 3 months (55). Baseline quality of life scores were also found to be significant predictors of overall survival on multivariable analyses. The "safety" of high-dose thoracic radiotherapy should be reexamined using PROs. Existing data indicate that patient-reported toxicity rates will differ dramatically from clinician-scored adverse event rates (56), particularly in the setting of dose-escalated radiotherapy.

A growing body of literature indicates that minimizing cardiac irradiation should be a goal in planning thoracic radiotherapy. Recent publications have demonstrated a strong association between cardiac irradiation and both cardiac events (36, 37, 57, 58) and all-cause mortality (6). The risks of cardiac irradiation may be highest in subjects with comorbid conditions such as existing heart disease (36, 37) or a smoking history (58), which are common in NSCLC patients. Somewhat surprisingly, these effects have been seen within a few years of radiotherapy delivery (6, 36, 37, 57) and in populations with high risk of cancer-specific mortality (6, 36, 37). In retrospect, this is consistent with previous analyses demonstrating that excessive (59) or unnecessary (60) mediastinal irradiation for lung cancer can meaningfully reduce survival rates. Thoracic irradiation may directly lead to coronary artery stenosis (61) and may also impair patients' immune systems (62).

FACT: SYSTEMIC THERAPY FOR NSCLC IS EVOLVING RAPIDLY

Supporting MTD

Targeted therapy and immunotherapy are revolutionizing the management of advanced NSCLC (20, 63). As these agents are incorporated into the management of LA-NSCLC (23, 64), one may expect the rate of distant metastasis to improve significantly. This could magnify the importance of achieving durable local disease control with effective radiotherapy. If induction therapy is utilized to reduce target volumes before delivery of thoracic radiotherapy, dose escalation with conventional or even stereotactic radiotherapy techniques would be particularly appealing.

Immunotherapy may be an ideal partner for high-dose radiotherapy. Radiotherapy may enhance tumor antigen presentation, increase cytokine production, and modulate the tumor microenvironment, promoting antitumor immunity (65, 66). Numerous preclinical studies (67, 68) and case reports (68–71) have demonstrated that there may be synergy between radiotherapy and immunotherapy. These effects may be maximized by employing "ablative" radiotherapy schedules, avoiding prolonged treatment courses, minimizing incidental irradiation of regional lymph nodes and other organs, and utilization of heavy ion radiotherapy (72, 73).

Supporting ALARA

For appropriately selected patients with advanced NSCLC, targeted therapy (74) or immunotherapy (20) yields far higher response rates and more durable disease control than cytotoxic chemotherapy. If similar responses are seen in LA-NSCLC, relatively low radiotherapy doses may be required to provide high rates of local disease control. On a patient level, tumor characterization and molecular subtyping will be facilitated by liquid biopsies (75). Functional imaging (46, 76) and radiomic analyses (77, 78) will also aid in identifying patients and specific tumors or lymph nodes where disease is likely to be controlled without receiving high radiotherapy doses. It is imperative that radiation oncologists continuously reassess the relationship between radiotherapy dose and local disease control, as NSCLC is increasingly understood represent a mosaic of heterogeneous diseases rather than a single disorder. At the same time, novel systemic agents may unexpectedly modulate the toxicity profile of thoracic radiotherapy (79, 80) such that modest radiotherapy doses optimize the risk/benefit ratio of thoracic irradiation for LA-NSCLC. Therefore, the relationship between radiotherapy doses and toxicity risk must also be reassessed frequently, preferably in trials designed to account for subacute and delayed adverse events (81).

CONCLUSION

Decades of clinical trials have not changed in the "standard" radiotherapy dosing for LA-NSCLC. However, it remains unlikely that current practices yield optimal results, and it is impossible to believe that a single dosing regimen should be administered to every patient with LA-NSCLC. The effects of radiotherapy dosing on both disease control probability and complication probability

must be reassessed as new systemic treatment options emerge and as new subtypes of NSCLC are recognized. PROs may provide more meaningful information that physician-scored toxicity rates and should be incorporated into all NSCLC trials.

AUTHOR CONTRIBUTIONS

The lead author (NO) was responsible for designing and writing this review article.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* (2011) 61:69–90. doi:10.3322/caac.20107
2. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC lung cancer staging project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. *J Thorac Oncol* (2007) 2:706–14. doi:10.1097/JTO.0b013e31812f3c1a
3. Vokes EE, Herndon JE, Kelley MJ, Cicchetti MG, Ramnath N, Neill H, et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III non-small-cell lung cancer: cancer and leukemia group B. *J Clin Oncol* (2007) 25:1698. doi:10.1200/JCO.2006.07.3569
4. Hanna N, Neubauer M, Yiannoutsos C, McGarry R, Arseneau J, Ansari R, et al. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. *J Clin Oncol* (2008) 26:5755–60. doi:10.1200/JCO.2008.17.7840
5. Kelly K, Chansky K, Gaspar LE, Albain KS, Jett J, Ung YC, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. *J Clin Oncol* (2008) 26:2450–6. doi:10.1200/JCO.2007.14.4824
6. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* (2015) 16:187–99. doi:10.1016/S1470-2045(14)71207-0
7. Senan S, Brade A, Wang L-H, Vansteenkiste J, Dakhil S, Biesma B, et al. PROCLAIM: randomized phase III trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol* (2016) 34:953–62. doi:10.1200/JCO.2015.64.8824
8. Albain KS, Swann RS, Rusch VW, Turrisi AT 3rd, Shepherd FA, Smith C, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet* (2009) 374:379–86. doi:10.1016/S0140-6736(09)60737-6
9. Yamoah K, Showalter TN, Ohri N. Radiation therapy intensification for solid tumors: a systematic review of randomized trials. *Int J Radiat Oncol Biol Phys* (2015) 93:737–45. doi:10.1016/j.ijrobp.2015.07.2284
10. Ramroth J, Cutter DJ, Darby SC, Higgins GS, McGale P, Partridge M, et al. Dose and fractionation in radiation therapy of curative intent for non-small cell lung cancer: meta-analysis of randomized trials. *Int J Radiat Oncol Biol Phys* (2016) 96:736–47. doi:10.1016/j.ijrobp.2016.07.022
11. National Cancer Institute. *NCI Dictionary of Cancer Terms*. (2017).
12. United States Nuclear Regulatory Commission. *ALARA*. (2017).
13. Belani CP, Choy H, Bonomi P, Scott C, Travis P, Haluschak J, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol* (2005) 23:5883–91. doi:10.1200/JCO.2005.55.405
14. Fournel P, Robinet G, Thomas P, Souquet PJ, Léna H, Vergnenégre A, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Francais de Pneumo-Cancérologie NPC 95-01 study. *J Clin Oncol* (2005) 23:5910. doi:10.1200/JCO.2005.03.070
15. Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* (1999) 17:2692. doi:10.1200/JCO.1999.17.9.2692
16. Zatloukal P, Petruzelka L, Zemanova M, Havel L, Janku F, Judas L, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. *Lung Cancer* (2004) 46:87–98. doi:10.1016/j.lungcan.2004.03.004
17. Curran WJ Jr, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst* (2011) 103:1452–60. doi:10.1093/jnci/djr325
18. Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* (2010) 28:2181–90. doi:10.1200/JCO.2009.26.2543
19. Group EBCTC. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* (2006) 366:2087–106. doi:10.1016/S0140-6736(05)67887-7
20. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* (2016) 375:1823–33. doi:10.1056/NEJMoa1606774
21. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* (2015) 373:1627–39. doi:10.1056/NEJMoa1507643
22. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* (2015) 373:123–35. doi:10.1056/NEJMoa1504627
23. Gerber DE, Urbanic JJ, Langer C, Hu C, Chang IF, Lu B, et al. Treatment design and rationale for a randomized trial of cisplatin and etoposide plus thoracic radiotherapy followed by nivolumab or placebo for locally advanced non-small-cell lung cancer (RTOG 3505). *Clin Lung Cancer* (2017) 18:333–9. doi:10.1016/j.cllc.2016.10.009
24. Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. *Int J Radiat Oncol Biol Phys* (2009) 74:1405–18. doi:10.1016/j.ijrobp.2008.10.091
25. Pignon JP, le Maître A, Maillard E, Bourhis J, Group M-NC. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol* (2009) 92:4–14. doi:10.1016/j.radonc.2009.04.014
26. Mauguen A, Le Péchoux C, Saunders MI, Schild SE, Turrisi AT, Baumann M, et al. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. *J Clin Oncol* (2012) 30:2788–97. doi:10.1200/JCO.2012.41.6677
27. Bazan JG, Le Q-T, Zips D. *Radiobiology of Lung Cancer. Iaslc Thoracic Oncology E-Book*. (2017). 330 p.
28. Onishi H, Araki T, Shirato H, Nagata Y, Hiraoka M, Gomi K, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma. *Cancer* (2004) 101:1623–31. doi:10.1002/cncr.20539
29. Ohri N, Werner-Wasik M, Grills IS, Belderbos J, Hope A, Yan D, et al. Modeling local control after hypofractionated stereotactic body radiation therapy for stage I non-small cell lung cancer: a report from the elekta collaborative lung research group. *Int J Radiat Oncol Biol Phys* (2012) 84:e379–84. doi:10.1016/j.ijrobp.2012.04.040
30. Kong F-M, Ten Haken RK, Schipper M, Frey KA, Hayman J, Gross M, et al. Effect of midtreatment PET/CT-adapted radiation therapy with concurrent chemotherapy in patients with locally advanced non-small-cell lung cancer: a phase 2 clinical trial. *JAMA Oncol* (2017). doi:10.1001/jamaoncol.2017.0982
31. McGarry R, Feddock J. A prospective study of SBRT boost to residual disease in stage III NSCLC: updated results. *Int J Radiat Oncol Biol Phys* (2014) 90:S651. doi:10.1016/j.ijrobp.2014.05.1925

32. Higgins KA, O'Connell K, Liu Y, Gillespie TW, McDonald MW, Pillai RN, et al. National cancer database analysis of proton versus photon radiation therapy in non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* (2017) 97:128–37. doi:10.1016/j.ijrobp.2016.10.001
33. Shirai K, Kawashima M, Saitoh J-I, Abe T, Fukata K, Shigeta Y, et al. Clinical outcomes using carbon-ion radiotherapy and dose-volume histogram comparison between carbon-ion radiotherapy and photon therapy for T2b-4N0M0 non-small cell lung cancer – a pilot study. *PLoS One* (2017) 12:e0175589. doi:10.1371/journal.pone.0175589
34. Palma DA, Senan S, Oberije C, Belderbos J, de Dios NR, Bradley JD, et al. Predicting esophagitis after chemoradiation therapy for non-small cell lung cancer: an individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys* (2013) 87:690–6. doi:10.1016/j.ijrobp.2013.07.029
35. Bar-Ad V, Ohri N, Werner-Wasik M. Esophagitis, treatment-related toxicity in non-small cell lung cancer. *Rev Recent Clin Trials* (2012) 7:31–5. doi:10.2174/157488712799363235
36. Wang K, Eblan MJ, Deal AM, Lipner M, Zagar TM, Wang Y, et al. Cardiac toxicity after radiotherapy for stage III non-small-cell lung cancer: pooled analysis of dose-escalation trials delivering 70 to 90 Gy. *J Clin Oncol* (2017) 35:1387–94. doi:10.1200/JCO.2016.70.0229
37. Dess RT, Sun Y, Matuszak MM, Sun G, Soni PD, Bazzi L, et al. Cardiac events after radiation therapy: combined analysis of prospective multicenter trials for locally advanced non-small-cell lung cancer. *J Clin Oncol* (2017) 35:1395–402. doi:10.1200/JCO.2016.71.6142
38. Perez CA, Stanley K, Rubin P, Kramer S, Brady L, Perez-Tamayo R, et al. A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lung. Preliminary report by the Radiation Therapy Oncology Group. *Cancer* (1980) 45:2744–53. doi:10.1002/1097-0142(19800601)45:11<2744::AID-CNCR2820451108>3.0.CO;2-U
39. Machtay M, Bae K, Movsas B, Paulus R, Gore EM, Komaki R, et al. Higher biologically effective dose of radiotherapy is associated with improved outcomes for locally advanced non-small cell lung carcinoma treated with chemoradiation: an analysis of the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* (2012) 82:425–34. doi:10.1016/j.ijrobp.2010.09.004
40. Brower JV, Amini A, Chen S, Hullett CR, Kimple RJ, Wojcieszynski AP, et al. Improved survival with dose-escalated radiotherapy in stage III non-small-cell lung cancer: analysis of the National Cancer Database. *Ann Oncol* (2016) 27:1887–94. doi:10.1093/annonc/mdw276
41. Liao ZX, Komaki RR, Thames HD, Liu HH, Tucker SL, Mohan R, et al. Influence of technologic advances on outcomes in patients with unresectable, locally advanced non-small-cell lung cancer receiving concomitant chemoradiotherapy. *Int J Radiat Oncol Biol Phys* (2010) 76:775–81. doi:10.1016/j.ijrobp.2009.02.032
42. Zhou C, Wu Y-L, Chen G, Feng J, Liu X-Q, Wang C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* (2011) 12:735–42. doi:10.1016/S1470-2045(11)70184-X
43. Scott JG, Berglund A, Schell MJ, Mihaylov I, Fulp WJ, Yue B, et al. A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study. *Lancet Oncol* (2017) 18:202–11. doi:10.1016/S1470-2045(16)30648-9
44. Ohri N, Duan F, Machtay M, Gorelick JJ, Snyder BS, Alavi A, et al. Pretreatment FDG-PET metrics in stage III non-small cell lung cancer: ACRIN 6668/RTOG 0235. *J Natl Cancer Inst* (2015) 107:djv004. doi:10.1093/jnci/djv004
45. Iasonos A, O'Quigley J. Adaptive dose-finding studies: a review of model-guided phase I clinical trials. *J Clin Oncol* (2014) 32:2505–11. doi:10.1200/JCO.2013.54.6051
46. Ohri N, Bodner WR, Halmos B, Cheng H, Perez-Soler R, Keller SM, et al. 18 F-fluorodeoxyglucose/positron emission tomography predicts patterns of failure after definitive chemoradiation therapy for locally advanced non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* (2017) 97:372–80. doi:10.1016/j.ijrobp.2016.10.031
47. Amendola BE, Amendola MA, Perez N, Wu X, Suarez JB. Local failure after primary radiotherapy in lung cancer: is there a role for SBRT? *Rep Pract Oncol Radiother* (2015) 20:440–5. doi:10.1016/j.rpor.2015.08.001
48. Yuan S, Sun X, Li M, Yu J, Ren R, Yu Y, et al. A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for inoperable stage III nonsmall cell lung cancer. *Am J Clin Oncol* (2007) 30:239–44. doi:10.1097/01.coc.0000256691.27796.24
49. Bradley J, Bae K, Choi N, Forster K, Siegel BA, Brunetti J, et al. A phase II comparative study of gross tumor volume definition with or without PET/CT fusion in dosimetric planning for non-small-cell lung cancer (NSCLC): primary analysis of Radiation Therapy Oncology Group (RTOG) 0515. *Int J Radiat Oncol Biol Phys* (2012) 82(435–41):e1. doi:10.1016/j.ijrobp.2010.09.033
50. Chun SG, Hu C, Choy H, Komaki RU, Timmerman RD, Schild SE, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: a secondary analysis of the NRG oncology RTOG 0617 randomized clinical trial. *J Clin Oncol* (2017) 35:56–62. doi:10.1200/JCO.2016.69.1378
51. Schild SE, Hillman SL, Tan AD, Ross HJ, McGinnis WL, Garces YA, et al. Long-term results of a trial of concurrent chemotherapy and escalating doses of radiation for unresectable non-small cell lung cancer: NCCTG N0028 (alliance). *J Thorac Oncol* (2017) 12:697–703. doi:10.1016/j.jtho.2016.12.021
52. Bradley J, Graham M, Suzanne S, Byhardt R, Govindan R, Fowler J, et al. Phase I results of RTOG L-0117; a phase I/II dose intensification study using 3DCRT and concurrent chemotherapy for patients with inoperable NSCLC. *J Clin Oncol* (2005) 23:7063–7063. doi:10.1200/jco.2005.23.16_suppl.7063
53. Shirvani SM, Jiang J, Gomez DR, Chang JY, Buchholz TA, Smith BD. Intensity modulated radiotherapy for stage III non-small cell lung cancer in the United States: predictors of use and association with toxicities. *Lung Cancer* (2013) 82:252–9. doi:10.1016/j.lungcan.2013.08.015
54. McMillan MT, Ojerholm E, Verma V, Higgins KA, Singhal S, Predina JD, et al. Radiotherapy treatment time and overall survival in locally advanced non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* (2017) 98:1142–52. doi:10.1016/j.ijrobp.2017.04.004
55. Movsas B, Hu C, Sloan J, Bradley J, Komaki R, Masters G, et al. Quality of life analysis of a radiation dose-escalation study of patients with non-small-cell lung cancer: a secondary analysis of the radiation therapy oncology group 0617 randomized clinical trial. *JAMA Oncol* (2016) 2:359–67. doi:10.1001/jamaoncol.2015.3969
56. Fogh S, Deshmukh S, Berk LB, Dueck AC, Roof K, Yacoub S, et al. A randomized phase II trial of prophylactic manuka honey for the reduction of chemoradiation therapy induced esophagitis during the treatment of lung cancer: results of trial. *Int J Radiat Oncol Biol Phys* (2017) 97:786–96. doi:10.1016/j.ijrobp.2016.11.022
57. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* (2013) 368:987–98. doi:10.1056/NEJMoa1209825
58. Taylor C, Correa C, Duane FK, Aznar MC, Anderson SJ, Bergh J, et al. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. *J Clin Oncol* (2017) 35:1641–9. doi:10.1200/JCO.2016.72.0722
59. Machtay M, Lee JH, Shrager JB, Kaiser LR, Glatstein E. Risk of death from intercurrent disease is not excessively increased by modern postoperative radiotherapy for high-risk resected non-small-cell lung carcinoma. *J Clin Oncol* (2001) 19:3912–7. doi:10.1200/JCO.2001.19.19.3912
60. Group PM-AT. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. *Lancet* (1998) 352:257–63. doi:10.1016/S0140-6736(98)06341-7
61. Nilsson G, Holmberg L, Garmo H, Duvernoy O, Sjögren I, Lagerqvist B, et al. Distribution of coronary artery stenosis after radiation for breast cancer. *J Clin Oncol* (2011) 30:380–6. doi:10.1200/JCO.2011.34.5900
62. Tang C, Liao Z, Gomez D, Levy L, Zhuang Y, Gebremichael RA, et al. Lymphopenia association with gross tumor volume and lung V5 and its effects on non-small cell lung cancer patient outcomes. *Int J Radiat Oncol Biol Phys* (2014) 89:1084–91. doi:10.1016/j.ijrobp.2014.04.025
63. Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med* (2017) 376:629–40. doi:10.1056/NEJMoa1612674
64. Xing L, Wu G, Wang L, Li J-C, Wang J, Yuan Z, et al. A multicenter, randomized, open-label, phase II trial of erlotinib versus etoposide plus cisplatin

with concurrent radiotherapy in unresectable stage III non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) activating mutation. *Am Soc Clin Oncol* (2017) 35(15 Suppl):8531. doi:10.1200/JCO.2017.35.15_suppl.8531
65. Bernstein MB, Krishnan S, Hodge JW, Chang JY. Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach? *Nat Rev Clin Oncol* (2016) 13:516–24. doi:10.1038/nrclinonc.2016.30
66. Formenti SC, Demaria S. Combining radiotherapy and cancer immunotherapy: a paradigm shift. *J Natl Cancer Inst* (2013) 105:256–65. doi:10.1093/jnci/djs629
67. Chakravarty PK, Alfieri A, Thomas EK, Beri V, Tanaka KE, Vikram B, et al. Flt3-ligand administration after radiation therapy prolongs survival in a murine model of metastatic lung cancer. *Cancer Res* (1999) 59:6028–32.
68. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, McKenna C, Jones S, Cheadle EJ, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. *Cancer Res* (2014) 74:5458–68. doi:10.1158/0008-5472.CAN-14-1258
69. Postow MA, Callahan MK, Barker CA, Yamada Y, Yuan J, Kitano S, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. *N Engl J Med* (2012) 366:925–31. doi:10.1056/NEJMoa1112824
70. Golden EB, Demaria S, Schiff PB, Chachoua A, Formenti SC. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. *Cancer Immunol Res* (2013) 1:365–72. doi:10.1158/2326-6066.CIR-13-0115
71. Hiniker SM, Chen DS, Reddy S, Chang DT, Jones JC, Mollick JA, et al. A systemic complete response of metastatic melanoma to local radiation and immunotherapy. *Transl Oncol* (2012) 5:404–7. doi:10.1593/tlo.12280
72. Durante M, Brenner DJ, Formenti SC. Does heavy ion therapy work through the immune system? *Int J Radiat Oncol Biol Phys* (2016) 96:934–6. doi:10.1016/j.ijrobp.2016.08.037
73. Hodge JW, Guha C, Neefjes J, Gulley JL. Synergizing radiation therapy and immunotherapy for curing incurable cancers: opportunities and challenges. *Oncology (Williston Park)* (2008) 22:1064–70.
74. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* (2012) 13:239–46. doi:10.1016/S1470-2045(11)70393-X
75. Crowley E, Di Nicolantonio F, Loupakis F, Bardelli A. Liquid biopsy: monitoring cancer-genetics in the blood. *Nat Rev Clin Oncol* (2013) 10:472–84. doi:10.1038/nrclinonc.2013.110
76. Meng X, Loo BW, Ma L, Murphy JD, Sun X, Yu J, et al. Molecular imaging with 11C-PD153035 PET/CT predicts survival in non-small cell lung cancer treated with EGFR-TKI: a pilot study. *J Nucl Med* (2011) 52:1573–9. doi:10.2967/jnumed.111.092874
77. Ohri N, Duan F, Snyder BS, Wei B, Machtay M, Alavi A, et al. Pretreatment 18F-FDG PET textural features in locally advanced non-small cell lung cancer: secondary analysis of ACRIN 6668/RTOG 0235. *J Nucl Med* (2016) 57:842–8. doi:10.2967/jnumed.115.166934
78. Aerts HJ, Velazquez ER, Leijenaar RT, Parmar C, Grossmann P, Cavalho S, et al. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. *Nat Commun* (2014) 5:4006. doi:10.1038/ncomms5006
79. Shibaki R, Akamatsu H, Fujimoto M, Koh Y, Yamamoto N. Nivolumab induced radiation recall pneumonitis after two years of radiotherapy. *Ann Oncol* (2017) 28:1404–5. doi:10.1093/annonc/mdx115
80. Flaum N, Lorigan P, Whitfield GA, Hawkins RE, Pinkham MB. Integrating radiation therapy with emerging systemic therapies: lessons from a patient with cerebral radionecrosis, spinal cord myelopathy, and radiation pneumonitis. *Pract Radiat Oncol* (2016) 6:110–3. doi:10.1016/j.prro.2015.10.008
81. Bezjak A, Paulus R, Gaspar L, Timmerman R, Straube W, Ryan W, et al. Primary study endpoint analysis for NRG Oncology/RTOG 0813 trial of stereotactic body radiation therapy (SBRT) for centrally located non-small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* (2016) 1:5–6. doi:10.1016/j.ijrobp.2015.10.040

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2017 Ohri. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

REVIEW
published: 04 September 2017
doi: 10.3389/fonc.2017.00197

Emerging Therapies for Stage III Non-Small Cell Lung Cancer: Stereotactic Body Radiation Therapy and Immunotherapy

*Sameera S. Kumar[1], Kristin A. Higgins[2] and Ronald C. McGarry[1]**

[1] Department of Radiation Medicine, University of Kentucky, Lexington, KY, United States, [2] Department of Radiation Oncology, Winship Cancer Institute of Emory University, The Emory Clinic, Atlanta, GA, United States

The current standard of care for locally advanced non-small cell lung cancer (NSCLC) includes radiation, chemotherapy, and surgery in certain individualized cases. In unresectable NSCLC, chemoradiation has been the standard of care for the past three decades. Local and distant failure remains high in this group of patients, so dose escalation has been studied in both single institution and national clinical trials. Though initial studies showed a benefit to dose escalation, phase III studies examining dose escalation using standard fractionation or hyperfractionation have failed to show a benefit. Over the last 17 years, stereotactic body radiation therapy (SBRT) has shown a high degree of safety and local control for stage I lung cancers and other localized malignancies. More recently, phase I/II studies using SBRT for dose escalation after conventional chemoradiation in locally advanced NSCLC have been promising with good apparent safety. Immunotherapy also offers opportunities to address distant disease and preclinical data suggest immunotherapy in tandem with SBRT may be a rational way to induce an "abscopal effect" although there are little clinical data as yet. By building on the proven concept of conventional chemoradiation for patients with locally advanced NSCLC with a subsequent radiation dose intensification to residual disease with SBRT concurrent with immunotherapy, we hope address the issues of metastatic and local failures. This "quadmodality" approach is still in its infancy but appears to be a safe and rational approach to the improving the outcome of NSCLC therapy.

Keywords: stereotactic body radiation therapy, immunotherapy, radiation therapy, non-small cell lung cancer, stage III

OPEN ACCESS

Edited by:
John Varlotto, University of Massachusetts Medical Center, United States

Reviewed by:
Eric Chi-ching Ko, Weill Cornell Medical College, United States
Nitin Ohri, Albert Einstein College of Medicine, United States

****Correspondence:***
Ronald C. McGarry
ronald.mcgarry@uky.edu

Specialty section:
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

Received: *31 July 2017*
Accepted: *17 August 2017*
Published: *04 September 2017*

Citation:
Kumar SS, Higgins KA and McGarry RC (2017) Emerging Therapies for Stage III Non-Small Cell Lung Cancer: Stereotactic Body Radiation Therapy and Immunotherapy. Front. Oncol. 7:197. doi: 10.3389/fonc.2017.00197

CHEMORADIATION IN STAGE III NON-SMALL CELL LUNG CANCER (NSCLC)

One hundred years ago, lung cancer was a rare malignancy (1). Lung cancer today is the leading cause of cancer death in the United States, with over 158,000 estimated deaths in 2016 (2). Forty percent of these patients present with locally advanced disease (3). Approximately 80–90% of newly diagnosed lung cancers are classified as NSCLC, primarily consisting of adenocarcinoma, squamous cell carcinoma, or large cell carcinoma histologies. Historically, surgery has been the gold standard for newly diagnosed NSCLC with early-stage resectable disease, resulting in 5-year overall survival

rates (OS) of 50–70%. However, for patients with more locally advanced NSCLC, 5-year OS after treatment with definitive radiation therapy and concurrent chemotherapy remains modest, at approximately 15–20% (4). Prior to the advent of cytotoxic chemotherapy, lung cancer at all stages was treated surgically or by radiation alone (5, 6). TNM staging was introduced in 1974 and it helped shape the way lung cancer was managed. Stage III lung cancer, though heterogeneous in its classification, includes non-metastatic but locally advanced disease with involvement of N1–N3 nodal stations and/or T3 and T4 primaries. Presently, stage III lung cancer is managed with a combination of chemotherapy, radiation therapy, and sometimes surgery but the two major challenges in improving outcomes of the treatment of this disease remain local control and metastatic spread.

CHEMORADIOTHERAPY (CRT) DOSE ISSUES

Multiple studies have examined the issue of the optimal dose of radiotherapy in NSCLC but are complicated by the heterogeneity of the disease itself in terms of size and location of the primary tumor, number and size of involved lymph nodes, and the patient's comorbidities, all of which limit the treatment tolerability and risks. Delivery of tumoricidal doses to the primary tumor and involved lymph nodes is balanced by treatment-related toxicities, namely esophagitis, pneumonitis, and cardiac injury.

An early dose-finding study by the Radiation Therapy Oncology Group (RTOG) 7301 study was conducted from 1973 to 1978 and studied four different doses and schedules: 40 Gy split course, 40 Gy continuously, 50 Gy, and 60 Gy. All doses were given in 2 Gy fractions. The optimal dose was determined to be 60 Gy (7).

Further improvements in survival were sought by the incorporation of chemotherapy. The Cancer and Leukemia Group B 8433 study solidified chemotherapy's importance in the treatment of locally advanced lung cancer. In this phase III study, 155 patients with stage III NSCLC were randomized to receive 60 Gy in 30 fractions or induction chemotherapy consisting of two cycles of cisplatin and vinblastine followed by 60 Gy in 30 fractions. Both median OS (13.8 versus 9.7 months) and 3-year OS were improved in the CRT arm (23 versus 11%) (8). Likewise, a European Organisation for Research and Treatment of Cancer study showed a benefit to concurrent CRT by randomizing patients to split-course radiotherapy alone to a dose of 55 Gy, split-course radiotherapy plus low-dose daily cisplatin, and split-course radiotherapy plus higher dose weekly cisplatin. The most salient differences were seen between concurrent daily CRT and radiation alone with the 3-year OS for CRT being 16 versus 2% for radiotherapy alone. This difference was thought to be due to an improvement in local control, as the 2-year local control in the daily CRT arm was 31 versus 19% in the radiotherapy alone arm (9).

Only one phase III trial has compared the traditional standard of 60 Gy to a modestly escalated dose regimen of 74 Gy. Based on the results of RTOG 0117 suggesting that 74 Gy represented a maximum tolerated dose of CRT for most patients, RTOG 0617 compared 60 versus 74 Gy both combined with weekly carboplatin and paclitaxel. In this four-arm study, a second randomization of cetuximab versus observation was also studied. Unfortunately an interim analysis showed that the 74 Gy arm had increased risk of death, with a median survival of 20 months for patients receiving 74 Gy versus 29 months for patients receiving 60 Gy, leading to early termination of the study (10). There was no benefit to local control. Of note, the 60 Gy arm had the highest median survival demonstrated within a phase III trial for this patient population. On multivariate analysis, increased dose to the heart, represented as heart V5 and V30 (the percent volume receiving $\geq$5 and $\geq$30 Gy, respectively), maximum esophagitis grade, planning target volume, and radiation dose (74 Gy) were all shown to negatively impact overall survival. There were no statistically significant differences in $\geq$grade 3 toxic effects between the groups; however, heart-specific toxicities were not assessed in this trial. Ultimately this underlines the difficulty of dose escalation with conventional radiation therapy fractionation techniques in the general population of patients with stage III NSCLC, opening the door for new strategies to improve outcomes for locally advanced disease. Often the argument is put forth that surgery is the ultimate form of local control and indeed 5-year local control rates for locally advanced NSCLC after CRT have been reported as low as 15%, but at least some of this is possibly biased by the selection of more resectable patients receiving surgery (11). Improving local control of the primary lesion in NSCLC does influence overall survival, as demonstrated by a meta-analysis of concurrent CRT versus sequential chemotherapy and radiation (12). Thus, if radiation techniques could be optimized and local control improved, one could expect to see improvement in long-term patient survival.

INDIVIDUALIZED CRT

Since most dose-escalation studies have produced problematic results in relatively unselected patients, can escalated radiation doses safely be delivered to patients by adaptive radiotherapy either during or after conventional radiotherapy? Additionally, in an era of intense research into molecular markers and innovative systemic therapies, how can combination strategies best be utilized to improve both local control and risk of metastasis?

Radiation Therapy Oncology Group 9311 was an early multi-center dose-escalation trial of 179 patients which used radiotherapy alone (13). The treatment was individualized based on the volume of lung receiving 20 Gy or more (V20). Those with a V20 less than 25% were dose-escalated to 90.3 Gy. Those with a V20 of 25–36% were dose-escalated to 83.8 Gy. Both schemes were performed at 2.15 Gy per fraction. Two treatment-related deaths occurred in the 90.3 arm and this dose was labeled as too toxic. Elective nodal coverage was not allowed, but still the isolated nodal failure rate was less than 10%. For the group with a V20 less than 25%, 83.8 Gy was found to be safe and for the group with a V20 of 25–36% 77.4 Gy was found to be safe.

More recently Kong et al. reported results of a phase II study of mid-treatment positron emission tomography-computed tomography (PET/CT) adapted radiotherapy with concurrent chemotherapy (14). Briefly, in this study, 43 patients with

unresectable stage II–III NSCLC received radiotherapy with doses individualized for an allowable mean lung boost dose of up to 20 Gy which would produce a risk of pneumonitis up to 17.5%. Radiation was delivered in 30 fractions with all patients receiving 2.1–2.85 Gy/fraction for the initial dose up to approximately 50 Gy EQD2 with the adaptive phase of the treatment of 2.85–5.0 Gy/fraction for a total radiation dose of up to 86 Gy in an attempt to deliver >100 Gy BED_{10}. Weekly carboplatin and paclitaxel were given concurrently. After a median follow-up of 47 months, the 2-year infield and overall local regional tumor controls were 82 and 62%, respectively; and median OS was 25%. Overall these results are consistent with most other stage III studies. This promising strategy of mid-treatment PET with dose escalation is currently being evaluated in the RTOG 1106 randomized trial, which recently completed accrual. Though local control has improved with these trials, metastatic disease still remains an important site of failure.

Stereotactic body radiation therapy (SBRT) has changed the standard of care for early-stage lung cancer, and data are emerging showing applicability to the stage III NSCLC population. The evidence for a role of SBRT in the stage III lung cancer population is summarized within this review.

BIOLOGICALLY EFFECTIVE DOSE (BED) AND SBRT

The success of SBRT treatments in early-stage NSCLC likely reflects the radiobiologic properties of high radiation doses. Higher radiation doses result in exponential increases in cell kill, and may also have an ablative effect on tumor vascularity and stroma (15, 16). A method of dose modeling based on the linear quadratic model of cell killing, referred to as the BED, takes into account the radiation dose per fraction and the inherent radiation response of a particular tissue (17). As derived from linear quadratic curves, mathematically two different dose and fractionation schemes can be compared theoretically for tumor control probability. An important assumption of this model is referred to as the α/β ratio, simplistically thought of as the ratio of cell killing based on single hit and multi-hit kinetics that leads to local control of a cancer mass (primarily from cell culture experiments, animal data and clinical observation). Nevertheless, tumor control probabilities are more complicated than a simple mathematical statement since tissues are complicated structures with underlying vasculature, stroma, and tumor cells, all of which interact (18). Many of the α/β assumptions are, therefore, also based on long clinical observation of tumor control and normal tissue toxicities. The BED equation can be expressed as $BED = nd(1 + d/\alpha/\beta)$ where n = the number of fractions, d = the dose/fraction, and α/β = alpha-beta ratio. Often early-reacting tissues/tumor cells are considered to have an α/β of approximately 10 whereas late reacting tissues are assigned an α/β of approximately 3. Based on these assumptions, Martel et al. constructed a mathematical model which predicted that in NSCLC a dose 84 Gy must be achieved for a local progression-free survival (PFS) of greater than 30 months (19). A retrospective study found that the doses of at least 70 Gy at 1.8–2 Gy per fraction provided better local control and survival for tumors less than 100 cc (20). Using 2 Gy fractions, a dose of 70 Gy has a BED of 84 Gy.

Based on the success of Gamma Knife treatment of brain lesions, extremely hypofractionated extracranial stereotactic radiotherapy programs began in the 1990s and are commonly known as SBRT or stereotactic ablative radiation therapy. SBRT treatments, because of the high dose per fraction, are able to achieve a much higher BED to localized volumes than conventional radiation delivered at 2 Gy/fraction. Multiple studies have demonstrated that a higher BED is correlated with improved local control and survival (21–24). Onishi et al. have shown that in early-stage lung cancer, superior local control and survival are achieved with treatment regimens that reach a BED of 100 Gy or greater (21). Specifically in lung cancer, SBRT delivers a high dose per fraction, with robust immobilization that minimizes intra-fraction motion and tumor-related internal motion, allowing for overall reduction in size of treatment volumes and overall treatment time.

In the seminal clinical reports by Blomgren and Lax, the philosophy and treatment parameters for the hypofractionated highly conformal treatment of localized disease that we use today were elucidated (25). In an *ad hoc* manner, they treated a number of different sites of localized disease most notably early-stage lung cancers settling on a dose of 60 Gy in three fractions of 20 Gy each with excellent local control and minimal toxicity. Their studies defined the parameters required for safe and precise delivery that we utilize in SBRT delivery today. Presciently, they speculated that "this new technique may also be used for delivering boost doses with a high precision after conventional radiation therapy" (26).

SBRT CLINICAL TRIALS IN EARLY-STAGE LUNG CANCER

In an effort to better define SBRT doses for localized disease, Timmerman et al. performed a phase I-II dose-escalation study for SBRT to the primary tumor in patients with stage I NSCLC using the concept derived from Swedish studies (27). Inhomogeneity corrections to correct for lung density were not performed. Separate cohorts of patients were followed with the dose-escalation ending at 60 Gy in 20 Gy fractions with no dose-limiting toxicity. Termination of the dose escalation for these smaller tumors was based on modeling of cell kill. For larger tumors (up to 7.0 cm) a dose-limiting toxicity (pneumonitis) was reached at 72 Gy in 24 Gy fractions. This experience laid the groundwork for further national clinical trials evaluating SBRT as a therapy for medically inoperable early-stage NSCLC, and ultimately changed the standard of care for these patients. Currently, SBRT is defined as 1–5 treatments of high-dose radiation delivered to tumors, typically measuring up to 7 cm, with registration of the patient's anatomy to a 3-D coordinate system either physical or within the planning system. SBRT is considered an ablative treatment intended to disrupt cellular clonogenicity, and lead to cell death. Robust immobilization, control of internal organ and tumor motion, sharp dose gradients, and high dose per fraction (≥600 cGy) for five or fewer fractions have been considered to define SBRT.

The first North American prospective cooperative group clinical trial evaluating SBRT, RTOG 0236 began accrual in 2004 and only allowed "peripherally located" tumors as defined by being outside 2 cm of the proximal bronchial tree or mediastinum (commonly referred to as the "no fly" zone). This study accrued 59 patients, treated with 18 Gy × 3 (total 54 Gy with heterogeneity corrections) to the primary tumor, and demonstrated 3-year local control (involved tumor and primary lobe) of 91% for patients with T1-2, N0 medically inoperable lung cancer (28). Three-year local–regional control was 87%, and distant failure rate was 22%. Overall survival was 56%. Results from longer follow-up have shown higher rates of local failure, primarily due to intralobar recurrences, with 5-year local recurrence rates of 20% (29). Importantly, these clinical outcomes are far better than historical studies treating medically inoperable early-stage lung cancer with conventionally fractionated radiation (2 Gy/fraction), with dismal local control of the primary tumor of 50% or less (30). Grade 3 and higher adverse events occurred in approximately 15% of patients enrolled in RTOG 0236.

For centrally located tumors, RTOG 0813 was a phase I-II study for T1-2, N0 medically inoperable lung cancer 5 cm or less in size, centrally located within or touching the 2 cm bronchial tree "no fly" zone. The primary endpoint was to establish the optimal SBRT dose for centrally located tumors. With dose cohorts of 10 Gy × 5, 10.5 Gy × 5, 11 Gy × 5, 11.5 Gy × 5, and 12 Gy × 5, it was found that the highest dose cohort had a 7% probability of a dose-limiting toxicity (31). RTOG 0915 was a randomized phase II study designed to test 34 Gy × 1 versus 12 Gy × 4 for non-centrally located tumors, with a primary endpoint of determination of the regimen with the lowest rates of protocol specified adverse events at 1 year. One year adverse events were 10% for the 34 Gy arm, and 13% for the 48 Gy arm (32).

It thus appears that there are multiple hypofractionated schemes that are acceptable using SBRT techniques to achieve high degrees of local control but they all have one thing in common: BED > 100.

SBRT TOXICITY

Though grade 3–5 toxicities with SBRT are overall low, Timmerman et al. retrospectively found in the initial single institution phase II study that 20–22 Gy × 3 was overly toxic for tumor in a central location, defined as within 2 cm from the proximal bronchial tree. In this phase II study, 2-year freedom from severe toxicity was 83% in patients with peripheral tumors and 54% for patients with central tumors (33). A separate single institution study recently showed a 3.7% fatal toxicity rate for SBRT with central tumors, with tumors abutting the proximal bronchial tree having significantly more grade 3+ adverse events (31 versus 7%) (34).

This suggests that tumor location with regards to the potential for late toxicity attributable to SBRT may be important as described above, but the RTOG 0813 SBRT dose-escalation study shows that central tumors may be safely treated to significant SBRT doses (31). As data and experience accumulates, dose-limiting organs within the hilum and mediastinum are becoming better defined and with care, SBRT can be utilized to treat "central" tumors safely.

Nonetheless, a large body of literature is accumulating confirming that SBRT treatment is well tolerated and safe in patients who are medically inoperable with early-stage lung cancer and produces excellent results. The question of applying SBRT to a stage III population with centrally located mediastinal lymph nodes as well as primary tumors remains pertinent. The studies summarized below describe the experience of SBRT in the locally advanced, stage III patient population.

DOSE-ESCALATED HYPOFRACTIONATED RADIATION (SBRT) IN STAGE III NSCLC

Investigators at the University of Kentucky completed a prospective study evaluating the feasibility of conventional CRT followed by a SBRT boost to the primary tumor as a method to dose escalate in patients with residual disease following CRT (35). In this study, patients with stage IIIA and IIIB NSCLC received CRT (median dose of 59.4 Gy) followed by a whole body fluorodeoxyglucose-positron emission tomography (FDG-PET) scan 1 month after treatment. Eighty-nine percent of patients received concurrent, platinum-based chemotherapy during CRT. Patients were eligible for SBRT if they had evidence of residual disease at the primary tumor location that was ≤5 cm in greatest dimension. Patients with progressive metastatic disease, contralateral lung disease or residual disease in the hilum or mediastinum were not eligible (defined as SUV ≥ 2). SBRT doses were 6.5 × 3 for centrally located primary tumors, and 10 Gy × 2 for non-central tumors. With these dose schemas, the cumulative BED10 to the primary tumor was 110 Gy for non-central tumors and 102 Gy for centrally located tumors. Sixty-two patients were screened, and 37 patients were ultimately eligible and enrolled. Approximately 31% of patients screened had new metastatic disease and an additional 31% had persistent nodal disease on post-treatment FDG-PET. The primary endpoint of this study was to assess the proportion of patients who developed ≥grade 3 radiation pneumonitis, according to the RTOG acute and late radiation morbidity scoring criteria. Overall, 11.4% of patients experienced radiation pneumonitis consistent with rates found in most studies of conventional CRT suggesting no increase risk with the SBRT boost. Two patients developed fatal pulmonary hemorrhage felt to be possibly related to treatment but careful analysis showed that these cases were more likely to have been related to squamous cell cavitary recurrences involving the hilum (36). Statistically there were no differences dosimetrically between patients who developed a fatal hemorrhage from those who did not. Local recurrence remained the most significant predictor. The central structures including the bronchial walls, pulmonary arteries, and aorta were contoured and the individual doses delivered to these structures were compared as well as the location of the PTV to the hilum. This small series of patients suggested that it is prudent to restrict the maximum radiation dose to the pulmonary artery to less than 185 Gy cumulative BED_3, and to less than 120 Gy BED_3 for the 5 cc volume; as well as limiting the maximum dose to the bronchial wall to less than 175 Gy BED_3. The equivalent dose on a per fraction basis would be equivalent to limiting each of these structures to less than 700 cGy per fraction times 3, or 900 cGy

per fraction times 2 for the boost, assuming that the patient has previously received between 60 and 66 Gy using standard fractionation. The most recently reported long-term follow-up of this study shows a crude local control rate of 78%. Median overall survival was 25 months. There were no significant late toxicities seen within the study population (37).

Second, a recent phase I study by Higgins et al. (in press) evaluated the optimal SBRT dose after 44 Gy CRT. Inclusion criteria included stage IIIA or IIIB NSCLC, with a primary tumor of 8 cm or less and no N1 or N2 nodal station >5 cm in maximum dimension. This multi-institution phase I study enrolled 15 patients, and dose-escalated a SBRT boost according to the following dose cohorts: 9 Gy × 2, 10 Gy × 2, 6 Gy × 5, 7 Gy × 5. Patients received 44 Gy with weekly carboplatin and paclitaxel, and then underwent a second computed tomography (CT) simulation after 40 Gy was delivered. The SBRT boost was then planned to encompass all residual primary and nodal disease as seen on the planning CT simulation. This volume was then dose-escalated according to the dose assignment of the patient. The maximum tolerated dose was determined to be 6 Gy × 5. There was one treatment-related grade 5 toxicity at this dose level, and 10 Gy × 2 is felt to be the most optimal SBRT boost dose, as no grade 3 or higher toxicities were seen in patients treated within the dose cohort. For all patients, actuarial local regional control at 3 years was 59%, and 3-year overall survival was 39% (38).

In an additional phase I study by Hepel et al., 12 patients with stage III NSCLC who had a primary tumor volume <120 cc (approximately 6.0 cm) and nodal disease volumes <60 cc received CRT to a dose of 50.4 Gy in 28 fractions (39). The study used a dose-escalation design to identify the maximum tolerated dose. SBRT dose was escalated from 16 Gy in two fractions to 28 Gy in two fractions in 2 Gy/fraction increments, resulting in four potential dose cohorts. The endpoint was dose-limiting toxicity occurring within 4 weeks of SBRT. A standard phase I cohort design was used. SBRT cohort doses started at 800 cGy × 2 fractions and escalated by 200 cGy/fraction to a final dose of 1,400 cGy × 2 for a total SBRT boost of 28 Gy. No early grade 3–5 toxicities were noted and at a median follow-up of 16 months, 1 year local–regional control was 78% with 100% at ≥24 Gy. Overall survival at one year was 67%. One late fatal pulmonary hemorrhage was noted and it was determined that the patient's 4 cc proximal bronchial-vascular tree dose was substantially higher than all patients reported at 30.2 Gy for the SBRT boost and 73.5 Gy for the total treatment. A total BED computation was not available to assess all patient doses.

It is clear from these studies and RTOG 0813, contouring of at risk structures and applied dose constraints (see above estimates) particularly for the pulmonary vasculature need to be respected in the treatment plan.

IMMUNOTHERAPY IN NSCLC

The use of immunotherapy in NSCLC is rapidly burgeoning. Early vaccine trials and trials with interferon therapy for those who were suffering from NSCLC have been largely negative and led to the hypothesis that NSCLC was believed to be largely non-immunogenic. Clearly, the immune response must be tightly controlled to prevent rampant autoimmunity. Multiple mechanisms to regulate immune responses have been shown to exist including innate tolerance to self-antigens, a network of both B and T suppressor cells and more recently elucidation of molecular regulatory mechanisms including checkpoint inhibitors. Immune checkpoint inhibitors have shown some promise in modulating the tumor microenvironment so that evasion of the immune system is more difficult.

Surveillance and destruction of tumor cells is postulated to be effected by the immune system and the vanguard of early tumor control may be the natural killer cell although its full role is yet to be elucidated. Once a tumor is established, control may be mediated by activated T-lymphocytes including CD4+ and CD8+ cells. The CTLA-4 and programmed death ligand 1 (PD-1) pathways are two T-cell inhibitory pathways that may modulate immune responses to lung antigens in the presence of an increasing burden of malignant cells possibly in an effort to prevent damage to host normal tissues. Inadvertently this may result in suppression of the immune system favoring tumor cell survival and growth. A CTLA-4 monoclonal antibody which is currently in use is ipilimumab, currently indicated in the treatment of melanoma. The PD-1 receptor ligands include PD-L1 and PD-L2. Nivolumab and pembrolizumab are two PD-1 inhibitors which have been FDA approved for clinical use in lung cancer.

Several seminal trials suggested the utility of blocking the PD inhibitory pathway by monoclonal antibodies to harness the immune system in control of NSCLC. The Checkmate 057 phase III clinical trial randomized 582 patients with non-squamous metastatic NSCLC who had progressed during or after platinum-based chemotherapy to salvage docetaxel chemotherapy or nivolumab. Median OS was longer in the nivolumab group (12.2 versus 9.4 months). Patients with even <10%, but greater than 1% PD-L1 expression showed a benefit with nivolumab over docetaxel (40). A second study, Checkmate 017, studied 272 patients with metastatic squamous cell NSCLC who progressed through platinum-based first-line chemotherapy. Those who received nivolumab had a median OS of 9.2 months versus those who received docetaxel, with a median OS of only 6.0 months (41). The use of nivolumab as a first-line agent was explored in the phase III Checkmate 026 trial in which 541 patients with previously untreated metastatic NSCLC with at least 1% PD-L1 expression were randomized to nivolumab or standard-of-care platinum doublet chemotherapy. Both PFS and OS were not significantly different between the two arms (42).

The KEYNOTE-010 trial enrolled over 1,000 patients with previously treated advanced NSCLC with at least 1% PD-L1 expression. They were randomized to two different doses of pembrolizumab or docetaxel. Median OS was 10.4 months with 2 mg/kg of pembrolizumab, 12.7 months with 10 mg/kg of pembrolizumab, and 8.5 months with docetaxel, which was statistically significant. An even greater survival benefit was seen in those with >50% tumor PD-L1 expression: 14.9 months with 2 mg/kg of pembrolizumab, 17.3 months with 10 mg/kg of pembrolizumab, and 8.2 months with docetaxel, which was also statistically significant (43). As a first-line therapy, the phase III KEYNOTE 024 trial explored the use of pembrolizumab in advanced NSCLC with at least 50% PD-L1 staining versus

cytotoxic chemotherapy, which was up to the discretion of the treating physician. Only 30% of the patients had the required 50% or greater PD-L1 staining tumors. In those patients, pembrolizumab was seen to significantly increase the 6-month OS (80.2 versus 72.4%) (44).

PD-L1 reactive monoclonal antibodies are currently being explored in NSCLC. Atezolizumab is one such IgG1 agonist to PD-L1. In the OAK trial, 1,225 patients with advanced NSCLC were randomized to salvage chemotherapy with docetaxel or atezolizumab. Greater OS was seen with atezolizumab regardless of PD-L1 expression (13.8 versus 9.6 months) (45).

To date, there are only limited data from phase III trials regarding immunotherapy for stage III NSCLC. The phase III START trial enrolled 1,514 patients with stage III NSCLC who had received CRT and had not progressed within 1–3 months. Patients were randomized to either placebo or tecemotide, an anti-MUC-1 immunotherapy designed to stimulate a T-cell response against the MUC-1 protein. There was no OS difference between the placebo group and the tecemotide group, except in a subgroup receiving concurrent CRT. In this case, the tecemotide group did have an improved OS (46), suggesting a possible synergistic interaction between the radiation and the drug. Belagenpumatucel-L is a tumor vaccine of four allogeneic NSCLC cell lines. In a phase III trial, 270 stage III or IV patients who were treated with platinum-based chemotherapy and who had not progressed were randomized to receive placebo or belagenpumatucel-L. There were no differences in OS or PFS between the two arms (47). A killed *Mycobacterium vaccae* named SRL172 was the subject of a phase III clinical trial published in 2004. A total of 419 patients were treated with 6 cycles of mitomycin, vinblastine and cisplatin or carboplatin with or without monthly administration of SRL172. There were no differences in overall survival, but patients in the SRL172 arm reported better quality of life (48). A meta-analysis of 20 trials by Zhou et al. found an OS benefit to immune checkpoint inhibitors and therapeutic vaccine (49).

RATIONALE FOR THE USE OF IMMUNOTHERAPY WITH RADIOTHERAPY

Immunogenic cell death is a postulated mechanism of radiation injury. Classically it is thought that the immune system must recognize either foreign (e.g., viruses) or mutated antigens on tumor cells to initiate an immunostimulatory response. Thus far, no simple antigen has been identified since in many ways, cancer cells are "self." Roszik et al. found a significant relationship between the predicted tumor mutation load and clinical benefit from ipilimumab, T-cell therapy, and pembrolizumab suggesting mutated proteins or DNA-protein complexes may be immunostimulatory (50). Unlike conventional apoptosis, when due to an immunogenic cell death apoptosis causes a release of molecules which may lead to an inflammatory or augmented immune response (51, 52). Damaged cells produce damage-associated molecular patterns which lead to uptake and subsequent presentation of tumor antigen by dendritic cells. Radiation has been shown to release or upregulate immune and tumor-related molecules such as major histocompatibility complex, tumor markers, adhesion molecules, cytokines, and many others (53). Single doses of 15–25 Gy induced strong T-cell responses, but these immune responses were dampened by the use of fractionated radiation or chemotherapy (54). Unfortunately, since lymphocytes are so radiosensitive, only a low integral dose is needed to kill any surrounding tumor lymphocytes. There is some evidence that ablative radiation fraction sizes (at least 6 Gy) or high linear energy transfer radiation causes increased release of immunogenic antigens. Mouse studies have shown evidence of the abscopal effect after use of large fractions (55, 56). A paper by Lugade et al. looked at 15 Gy in a single fraction versus 15 Gy in 5 fractions of 3 Gy in in a mouse melanoma model. They found that both fraction sizes lead to tumor-infiltrating lymphocytes that were capable of lysing tumor cell targets, but that the larger fraction size produced better results (57). A strong antitumor immunogenic response was observed in mouse models after being treated with a carbon ion beam. This resulted in fewer contralateral squamous cell tumors, which is thought to be due to an immune-mediated abscopal effect (58). Strictly defined, the abscopal effect is the resulting shrinkage or disappearance of metastatic deposits following treatment of the primary tumor mass. Clinically the abscopal effect is rarely seen, with fewer than 50 documented cases in the literature (59). Barid et al. propose that this is because while radiotherapy provides available antigen, it does not provide the necessary co-stimulation of T cells or cytokine release (60). Thus, this presents an opportunity for the combined use of radiotherapy and immunotherapy.

Both laboratory and clinical evidence exist regarding the advantage of combined radiotherapy and immunotherapy. In a murine model of metastasis, squamous cell carcinoma cell lines were inoculated into the mouse thigh typically requiring $\geq 10^6$ tumor cells to ensure tumor growth. Most of these cells die and release tumor lysis products which may bias treatment results. Mice were treated with a single 6 Gy dose of carbon ions and 36 h later treated with α-galactosylceramide-pulsed dendritic cells. Compared to the untreated control mice, these mice developed significantly fewer pulmonary metastases (61). Intravenous administration of isolated dendritic cells with either carbon beam therapy or photon beam therapy was compared in a murine model. Both types of irradiation produced an antimetastatic effect, but carbon ions did so at a lower BED (62). Sharabi et al. examined the effect of SBRT in murine melanoma or breast cancer and found that the effect of radiation was enhanced in the presence of a PD-1 inhibitor or regulatory T-cell depletion (63). Some studies suggest that an immune-mediated abscopal effect is increased with fractionated radiotherapy using large fractions in addition to a CTLA-4 inhibitor as opposed to single-dose radiotherapy (64). Indeed, further mouse studies confirmed that fractionation using "medium-sized doses" (7.5 Gy per fraction) provided both low numbers of regulatory T-cells and the best control of the tumor (65).

Clinical studies also show encouraging results of the use of combined radiation and immunotherapy. Abscopal effects in humans after SBRT with or without immunotherapy have been reported in both renal cell carcinoma and melanoma (66–68). The KEYNOTE-001 study predated the KEYNOTE-010 study. KEYNOTE-001 was a phase I clinical trial which enrolled 495

patients with advanced NSCLC. They were treated with pembrolizumab at doses of 10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks. The objective response rate was found to be 19.4% and OS was 12 months. In patients with at least 50% expression of PD-L1 median overall survival was not reached. It was deemed to have an acceptable side effect profile and the most common side effects included fatigue, itching, and decreased appetite (69). An analysis of the trial was done and showed that in 97 patients who had prior radiation PFS and overall survival were significantly longer, especially for those who received extracranial radiotherapy (70). In the PACIFIC study, a phase III study for stage III unresectable lung cancer, patients in the experimental arm received chemoradiation followed by durvalumab for 12 months. In a preliminary report, Astra Zeneca suggests an improvement in PFS in the immunotherapy arm was seen, however, these data have yet to be presented (71). Currently, there are several ongoing clinical trials investigating the use of immunotherapy with radiotherapy. These trials include agents such as cancer vaccines, CTLA-4 inhibitors, PD-1 inhibitors, and PD-L1 inhibitors (**Table 1**). This table was generated by searching the ClinicalTrials.gov database with search terms such as "radiation," "chemoradiation," "thoracic RT," and several variations. The results were then manually filtered for the inclusion of Immunotherapy.

SUMMARY

Treatment of locally advanced lung cancer has not made great strides since the 1990s when cytotoxic chemotherapy was combined with radiation. The two major stumbling blocks to improvements in survival of these patients are local control and distant metastasis. It is clear that SBRT for stage I NSCLC is one of the most important treatment advancements in decades with excellent outcomes of high local tumor control and survival with low toxicity.

Cytotoxic chemotherapy remains an important modality in more advanced disease but has reached a point where major improvements are unlikely and despite systemic therapy, metastatic disease is a prominent cause of death in locally advanced NSCLC patients.

We need more innovative approaches to management of this disease. Evidence is accumulating that dose escalation of radiotherapy improves local control of much of the microscopic and gross disease in the chest. Since dose escalation by conventional radiation delivery has been compromised by toxicity, the careful delivery of hypofractionated radiation therapy (SBRT) to the sites of gross disease should improve local control by ablating any residual viable cancer cells. The initial studies of SBRT boost while small, show this approach is safe and feasible, but the impact of this approach on survival in the management of stage II-III awaits larger studies.

The sequencing and combination of this "quadmodality" approach is still being explored. In the Phase I/II studies described above, concurrent chemoradiation to a dose of 44–60 Gy was used which was followed by an SBRT boost. The trials showed favorable toxicity profiles using this approach. Fractionated chemoradiation promotes immunotolerence through the killing of lymphocytes by the chemotherapy and radiation therapy, but SBRT has been shown to induce strong T-cell responses. Thus ideally the patient would undergo concurrent chemoradiation to a dose of 44–60 Gy, have an approximately 2-week break to allow for SBRT treatment planning and recovering from leukopenia, then get an SBRT boost. In order to capitalize on the immunostimulatory effects of the SBRT, the immunotherapy should be administered soon (within 1 week) of the SBRT boost. Cranial stereotactic radiosurgery with concurrent immunotherapy appears to be well tolerated, but data on lung SBRT and concurrent immunotherapy is still developing. Theoretically, there could be an increased risk for toxicity, especially induced auto-immune effects, due to this quadmodality approach. Indeed, the SBRT boost followed by immunotherapy may prime the immune system to attack not only tumor cells but normal tissue as well.

From a metastatic viewpoint, immunotherapy is an exciting option that is still in its infancy. There are adequate early and non-clinical data suggesting that hypofractionated radiation and immunomodulation may be synergistic. Thus, a more cogent approach to trials addressing both local control and metastatic

TABLE 1 | Active clinical trials involving the use of both radiotherapy and immunotherapy such as cancer vaccines, CTLA-4 inhibitors, PD-1 inhibitors, and PD-L1 inhibitors in Stage III non-small cell lung cancer (NSCLC).

NCT Number	Title	Recruitment	Study results	Phase	Enrollment
NCT02987998	Neoadjuvant chemoradiation plus pembrolizumab followed by consolidation pembrolizumab in NSCLC	Recruiting	No results available	Phase 1	20
NCT02662634	A safety and feasibility study of AGS-003-LNG for the treatment of stage 3 NSCLC	Recruiting	No results available	Phase 2	20
NCT02434081	NIvolumab consolidation with standard first-line chemotherapy and radiotherapy in locally advanced stage IIIA/B non-small cell lung carcinoma	Recruiting	No results available	Phase 2	43
NCT02318771	Radiation therapy and MK-3475 for patients with recurrent/metastatic head and neck cancer, renal cell cancer, melanoma, and lung cancer	Recruiting	No results available	Phase 1	40
NCT02621398	Pembrolizumab, paclitaxel, carboplatin, and radiation therapy in treating patients with stage II-IIIB NSCLC	Recruiting	No results available	Phase 1	30
NCT02768558	Cisplatin and etoposide plus radiation followed By nivolumab/placebo for locally advanced NSCLC	Recruiting	No results available	Phase 3	660
NCT02125461	A global study to assess the effects of MEDI4736 following concurrent chemoradiation in patients with stage III unresectable NSCLC (PACIFIC)	Ongoing, but not recruiting	Active, not recruiting	Phase 3	713

disease may become "quadmodality" and include combining chemotherapy, conventionally fractionated radiation therapy, immunotherapy and SBRT dose intensification to ablate the residual primary tumor mass. Given the continued devastating effect of lung cancer on the world, such trials need to be developed promptly.

AUTHOR CONTRIBUTIONS

Contributors who meet fewer than all four of these criteria for authorship should not be listed as authors, but they should be acknowledged: substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content; and final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (SK, KH, and RM).

ACKNOWLEDGMENTS

The University of Kentucky Markey Cancer Center's Research Communications Office assisted with manuscript preparation.

REFERENCES

1. Adler I. *Primary Malignant Growths of the Lungs and Bronchi: A Pathological and Clinical Study*. New York: Longmans, Green (1912).
2. Cancer Facts & Figures 2016. American Cancer Society. Available at: https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2016.html (accessed June 19, 2017).
3. Chen VW, Ruiz BA, Hsieh M-C, Wu X-C, Ries LAG, Lewis DR. Analysis of stage and clinical/prognostic factors for lung cancer from SEER registries: AJCC staging and collaborative stage data collection system. *Cancer* (2014) 120(Suppl 23):3781–92. doi:10.1002/cncr.29045
4. Curran WJ, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst* (2011) 103:1452–60. doi:10.1093/jnci/djr325
5. Davies HM. Recent advances in the surgery of the lung and pleura. *Br J Surg* (1913) 1:228–58. doi:10.1002/bjs.1800010211
6. Brunn H. Surgical principles underlying one-stage lobectomy. *Arch Surg* (1929) 18:490–515. doi:10.1001/archsurg.1929.04420020312020
7. Perez CA, Pajak TF, Rubin P, Simpson JR, Mohiuddin M, Brady LW, et al. Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. *Cancer* (1987) 59:1874–81. doi:10.1002/1097-0142(19870601)59:11<1874::AID-CNCR2820591106>3.0.CO;2-Z
8. Dillman RO, Seagren SL, Propert KJ, Guerra J, Eaton WL, Perry MC, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. *N Engl J Med* (1990) 323:940–5. doi:10.1056/NEJM199010043231403
9. Schaake-Koning C, van den Bogaert W, Dalesio O, Festen J, Hoogenhout J, van Houtte P, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N Engl J Med* (1992) 326:524–30. doi:10.1056/NEJM199202203260805
10. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* (2015) 16:187–99. doi:10.1016/S1470-2045(14)71207-0
11. Le Chevalier T, Arriagada R, Quoix E, Ruffie P, Martin M, Tarayre M, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: first analysis of a randomized trial in 353 patients. *J Natl Cancer Inst* (1991) 83:417–23. doi:10.1093/jnci/83.6.417
12. Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* (2010) 28:2181–90. doi:10.1200/JCO.2009.26.2543
13. Bradley J, Graham MV, Winter K, Purdy JA, Komaki R, Roa WH, et al. Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. *Int J Radiat Oncol Biol Phys* (2005) 61:318–28. doi:10.1016/j.ijrobp.2004.06.260
14. Kong F-M, Ten Haken RK, Schipper M, Frey KA, Hayman J, Gross M, et al. Effect of midtreatment PET/CT-adapted radiation therapy with concurrent chemotherapy in patients with locally advanced non-small-cell lung cancer: a phase 2 clinical trial. *JAMA Oncol* (2017). doi:10.1001/jamaoncol.2017.0982
15. Garcia-Barros M, Paris F, Cordon-Cardo C, Lyden D, Rafii S, Haimovitz-Friedman A, et al. Tumor response to radiotherapy regulated by endothelial cell apoptosis. *Science* (2003) 300:1155–9. doi:10.1126/science.1082504
16. Szeifert GT, Atteberry DS, Kondziolka D, Levivier M, Lunsford LD. Cerebral metastases pathology after radiosurgery: a multicenter study. *Cancer* (2006) 106:2672–81. doi:10.1002/cncr.21946
17. Fowler JF. 21 years of biologically effective dose. *Br J Radiol* (2010) 83:554–68. doi:10.1259/bjr/31372149
18. Chan R, Sethi P, Jyoti A, McGarry R, Upreti M. Investigating the radioresistant properties of lung cancer stem cells in the context of the tumor microenvironment. *Radiat Res* (2016) 185:169–81. doi:10.1667/RR14285.1
19. Martel MK, Ten Haken RK, Hazuka MB, Kessler ML, Strawderman M, Turrisi AT, et al. Estimation of tumor control probability model parameters from 3-D dose distributions of non-small cell lung cancer patients. *Lung Cancer* (1999) 24:31–7. doi:10.1016/S0169-5002(99)00019-7
20. Willner J, Baier K, Caragiani E, Tschammler A, Flentje M. Dose, volume, and tumor control prediction in primary radiotherapy of non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* (2002) 52:382–9. doi:10.1016/S0360-3016(01)01823-5
21. Onishi H, Araki T, Shirato H, Nagata Y, Hiraoka M, Gomi K, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. *Cancer* (2004) 101:1623–31. doi:10.1002/cncr.20539
22. Machtay M, Bae K, Movsas B, Paulus R, Gore EM, Komaki R, et al. Higher biologically effective dose of radiotherapy is associated with improved outcomes for locally advanced non-small cell lung carcinoma treated with chemoradiation: an analysis of the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* (2012) 82:425–34. doi:10.1016/j.ijrobp.2010.09.004
23. Bradley JD, Moughan J, Graham MV, Byhardt R, Govindan R, Fowler J, et al. A phase I/II radiation dose escalation study with concurrent chemotherapy for patients with inoperable stages I to III non-small-cell lung cancer: phase I results of RTOG 0117. *Int J Radiat Oncol Biol Phys* (2010) 77:367–72. doi:10.1016/j.ijrobp.2009.04.029
24. Socinski MA, Blackstock AW, Bogart JA, Wang X, Munley M, Rosenman J, et al. Randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and dose-escalated thoracic conformal radiotherapy (74 Gy) in stage III non-small-cell lung cancer: CALGB 30105. *J Clin Oncol* (2008) 26:2457–63. doi:10.1200/JCO.2007.14.7371
25. Lax I, Blomgren H, Näslund I, Svanström R. Stereotactic radiotherapy of malignancies in the abdomen. Methodological aspects. *Acta Oncol* (1994) 33:677–83. doi:10.3109/02841869409121782
26. Blomgren H, Lax I, Näslund I, Svanström R. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator: clinical experience of the first thirty-one patients. *Acta Oncol* (1995) 34:861–70. doi:10.3109/02841869509127197
27. Timmerman R, Papiez L, McGarry R, Likes L, DesRosiers C, Frost S, et al. Extracranial stereotactic radioablation: results of a phase I study in medically

inoperable stage I non-small cell lung cancer. *Chest* (2003) 124:1946–55. doi:10.1378/chest.124.5.1946
28. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* (2010) 303:1070–6. doi:10.1001/jama.2010.261
29. Timmerman RD, Hu C, Michalski J, Straube W, Galvin J, Johnstone D, et al. Long-term results of RTOG 0236: a phase II trial of stereotactic body radiation therapy (SBRT) in the treatment of patients with medically inoperable stage I non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* (2014) 90:S30. doi:10.1016/j.ijrobp.2014.05.135
30. Sibley GS, Jamieson TA, Marks LB, Anscher MS, Prosnitz LR. Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: the Duke experience. *Int J Radiat Oncol Biol Phys* (1998) 40:149–54. doi:10.1016/S0360-3016(97)00589-0
31. Bezjak A, Paulus R, Gaspar LE, Timmerman RD, Straube WL, Ryan WF, et al. Primary study endpoint analysis for NRG oncology/RTOG 0813 trial of stereotactic body radiation therapy (SBRT) for centrally located non-small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* (2016) 94:5–6. doi:10.1016/j.ijrobp.2015.10.040
32. Videtic GMM, Hu C, Singh AK, Chang JY, Parker W, Olivier KR, et al. A randomized phase 2 study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer: NRG oncology RTOG 0915 (NCCTG N0927). *Int J Radiat Oncol Biol Phys* (2015) 93:757–64. doi:10.1016/j.ijrobp.2015.07.2260
33. Timmerman R, McGarry R, Yiannoutsos C, Papiez L, Tudor K, DeLuca J, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* (2006) 24:4833–9. doi:10.1200/JCO.2006.07.5937
34. Haseltine JM, Rimner A, Gelblum DY, Modh A, Rosenzweig KE, Jackson A, et al. Fatal complications after stereotactic body radiation therapy for central lung tumors abutting the proximal bronchial tree. *Pract Radiat Oncol* (2016) 6:e27–33. doi:10.1016/j.prro.2015.09.012
35. Feddock J, Arnold SM, Shelton BJ, Sinha P, Conrad G, Chen L, et al. Stereotactic body radiation therapy can be used safely to boost residual disease in locally advanced non-small cell lung cancer: a prospective study. *Int J Radiat Oncol Biol Phys* (2013) 85:1325–31. doi:10.1016/j.ijrobp.2012.11.011
36. Feddock J, Cleary R, Arnold SM, McGarry R. Risk for fatal pulmonary hemorrhage does not appear to be increased following dose escalation using stereotactic body radiotherapy (SBRT) in locally advanced non-small cell lung cancer (NSCLC). *J Radiosurg SBRT* (2013) 2:1–7.
37. Kumar S, Feddock J, Li X, Shearer A, Hall L, Shelton B, et al. An update of a prospective study of SBRT for post-chemoradiation residual disease in stage II/III non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* (2017). doi:10.1016/j.ijrobp.2017.07.036
38. Higgins KA, Pillai RN, Chen Z, Tian S, Zhang C, Patel P, et al. Concomitant chemotherapy and radiotherapy with SBRT boost for unresectable, stage III non-small cell lung cancer: a phase I study. *J Thorac Oncol* (2017).
39. Hepel JT, Leonard KL, Safran H, Ng T, Taber A, Khurshid H, et al. Stereotactic body radiation therapy boost after concurrent chemoradiation for locally advanced non-small cell lung cancer: a phase 1 dose escalation study. *Int J Radiat Oncol Biol Phys* (2016) 96:1021–7. doi:10.1016/j.ijrobp.2016.08.032
40. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* (2015) 373:1627–39. doi:10.1056/NEJMoa1507643
41. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* (2015) 373:123–35. doi:10.1056/NEJMoa1504627
42. Socinski M, Creelan B, Horn L, Reck M, Paz-Ares L, Steins M, et al. NSCLC, metastaticCheckMate 026: a phase 3 trial of nivolumab vs investigator's choice (IC) of platinum-based doublet chemotherapy (PT-DC) as first-line therapy for stage iv/recurrent programmed death ligand 1 (PD-L1)-positive NSCLC. *Ann Oncol* (2016) 27(suppl_6):LBA7_PR. doi:10.1093/annonc/mdw435.39
43. Herbst RS, Baas P, Kim D-W, Felip E, Pérez-Gracia JL, Han J-Y, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* (2016) 387:1540–50. doi:10.1016/S0140-6736(15)01281-7
44. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* (2016) 375:1823–33. doi:10.1056/NEJMoa1606774
45. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* (2017) 389:255–65. doi:10.1016/S0140-6736(16)32517-X
46. Butts C, Socinski MA, Mitchell PL, Thatcher N, Havel L, Krzakowski M, et al. Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial. *Lancet Oncol* (2014) 15:59–68. doi:10.1016/S1470-2045(13)70510-2
47. Giaccone G, Bazhenova LA, Nemunaitis J, Tan M, Juhász E, Ramlau R, et al. A phase III study of belagenpumatucel-L, an allogeneic tumour cell vaccine, as maintenance therapy for non-small cell lung cancer. *Eur J Cancer* (2015) 51:2321–9. doi:10.1016/j.ejca.2015.07.035
48. O'Brien MER, Anderson H, Kaukel E, O'Byrne K, Pawlicki M, Von Pawel J, et al. SRL172 (killed *Mycobacterium vaccae*) in addition to standard chemotherapy improves quality of life without affecting survival, in patients with advanced non-small-cell lung cancer: phase III results. *Ann Oncol* (2004) 15:906–14. doi:10.1093/annonc/mdh220
49. Zhou L, Wang XL, Deng QL, Du YQ, Zhao NQ. The efficacy and safety of immunotherapy in patients with advanced NSCLC: a systematic review and meta-analysis. *Sci Rep* (2016) 6:32020–32020. doi:10.1038/srep32020
50. Roszik J, Haydu LE, Hess KR, Oba J, Joon AY, Siroy AE, et al. Novel algorithmic approach predicts tumor mutation load and correlates with immunotherapy clinical outcomes using a defined gene mutation set. *BMC Med* (2016) 14:168. doi:10.1186/s12916-016-0705-4
51. Golden EB, Pellicciotta I, Demaria S, Barcellos-Hoff MH, Formenti SC. The convergence of radiation and immunogenic cell death signaling pathways. *Front Oncol* (2012) 2:88. doi:10.3389/fonc.2012.00088
52. Galluzzi L, Kepp O, Kroemer G. Immunogenic cell death in radiation therapy. *Oncoimmunology* (2013) 2:e26536. doi:10.4161/onci.26536
53. Garnett CT, Palena C, Chakraborty M, Chakarborty M, Tsang K-Y, Schlom J, et al. Sublethal irradiation of human tumor cells modulates phenotype resulting in enhanced killing by cytotoxic T lymphocytes. *Cancer Res* (2004) 64:7985–94. doi:10.1158/0008-5472.CAN-04-1525
54. Lee Y, Auh SL, Wang Y, Burnette B, Wang Y, Meng Y, et al. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. *Blood* (2009) 114:589–95. doi:10.1182/blood-2009-02-206870
55. Habets TH, Oth T, Houben AW, Huijskens MJAJ, Senden-Gijsbers BL, Schnijderberg MCA, et al. Fractionated radiotherapy with 3 x 8 Gy induces systemic anti-tumour responses and abscopal tumour inhibition without modulating the humoral anti-tumour response. *PLoS One* (2016) 11:e0159515. doi:10.1371/journal.pone.0159515
56. Reits EA, Hodge JW, Herberts CA, Groothuis TA, Chakraborty M, Wansley EK, et al. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. *J Exp Med* (2006) 203:1259–71. doi:10.1084/jem.20052494
57. Lugade AA, Moran JP, Gerber SA, Rose RC, Frelinger JG, Lord EM. Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor. *J Immunol* (2005) 174:7516–23.
58. Matsunaga A, Ueda Y, Yamada S, Harada Y, Shimada H, Hasegawa M, et al. Carbon-ion beam treatment induces systemic antitumor immunity against murine squamous cell carcinoma. *Cancer* (2010) 116:3740–8. doi:10.1002/cncr.25134
59. Abuodeh Y, Venkat P, Kim S. Systematic review of case reports on the abscopal effect. *Curr Probl Cancer* (2016) 40:25–37. doi:10.1016/j.currproblcancer.2015.10.001
60. Baird JR, Monjazeb AM, Shah O, McGee H, Murphy WJ, Crittenden MR, et al. Stimulating innate immunity to enhance radiation therapy-induced tumor control. *Int J Radiat Oncol Biol Phys* (2017). doi:10.1016/j.ijrobp.2017.04.014
61. Ohkubo Y, Iwakawa M, Seino K-I, Nakawatari M, Wada H, Kamijuku H, et al. Combining carbon ion radiotherapy and local injection of α-galactosylceramide-pulsed dendritic cells inhibits lung metastases in an in vivo murine model. *Int J Radiat Oncol Biol Phys* (2010) 78:1524–31. doi:10.1016/j.ijrobp.2010.06.048
62. Ando K, Fujita H, Hosoi A, Ma L, Wakatsuki M, Seino K-I, et al. Intravenous dendritic cell administration enhances suppression of lung metastasis

induced by carbon-ion irradiation. *J Radiat Res* (2017):1–10. doi:10.1093/jrr/rrx005
63. Sharabi AB, Nirschl CJ, Kochel CM, Nirschl TR, Francica BJ, Velarde E, et al. Stereotactic radiation therapy augments antigen-specific PD-1-mediated antitumor immune responses via cross-presentation of tumor antigen. *Cancer Immunol Res* (2015) 3:345–55. doi:10.1158/2326-6066.CIR-14-0196
64. Dewan MZ, Galloway AE, Kawashima N, Dewyngaert JK, Babb JS, Formenti SC, et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. *Clin Cancer Res* (2009) 15:5379–88. doi:10.1158/1078-0432.CCR-09-0265
65. Schaue D, Ratikan JA, Iwamoto KS, McBride WH. Maximizing tumor immunity with fractionated radiation. *Int J Radiat Oncol Biol Phys* (2012) 83:1306–10. doi:10.1016/j.ijrobp.2011.09.049
66. Wersäll PJ, Blomgren H, Pisa P, Lax I, Kälkner K-M, Svedman C. Regression of non-irradiated metastases after extracranial stereotactic radiotherapy in metastatic renal cell carcinoma. *Acta Oncol* (2006) 45:493–7. doi:10.1080/02841860600604611
67. Postow MA, Callahan MK, Barker CA, Yamada Y, Yuan J, Kitano S, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. *N Engl J Med* (2012) 366:925–31. doi:10.1056/NEJMoa1112824
68. Seung SK, Curti BD, Crittenden M, Walker E, Coffey T, Siebert JC, et al. Phase 1 study of stereotactic body radiotherapy and interleukin-2 – tumor and immunological responses. *Sci Transl Med* (2012) 4:137ra74. doi:10.1126/scitranslmed.3003649
69. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* (2015) 372:2018–28. doi:10.1056/NEJMoa1501824
70. Shaverdian N, Lisberg AE, Bornazyan K, Veruttipong D, Goldman JW, Formenti SC, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. *Lancet Oncol* (2017) 18:895–903. doi:10.1016/S1470-2045(17)30380-7
71. *Imfinzi Significantly Reduces the Risk of Disease Worsening or Death in the Phase III PACIFIC Trial for Stage III Unresectable Lung Cancer*. Available at: https://www.astrazeneca.com/media-centre/press-releases/2017/imfinzi-significantly-reduces-the-risk-of-disease-worsening-or-death-in-the-phase-iii-pacific-trial-for-stage-iii-unresectable-lung-cancer-12052017.htm (accessed June 19, 2017).

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2017 Kumar, Higgins and McGarry. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

REVIEW
published: 19 September 2017
doi: 10.3389/fonc.2017.00210

Radiotherapy for Oligometastatic Lung Cancer

*Derek P. Bergsma[1], Joseph K. Salama[2], Deepinder P. Singh[1], Steven J. Chmura[3] and Michael T. Milano[1]**

[1] Department of Radiation Oncology, University of Rochester Medical Center, Rochester, NY, United States, [2] Department of Radiation Oncology, Duke University Health System, Raleigh, NC, United States, [3] Department of Radiation and Cellular Oncology, University of Chicago, Chicago, IL, United States

Non-small cell lung cancer (NSCLC) typically presents at an advanced stage, which is often felt to be incurable, and such patients are usually treated with a palliative approach. Accumulating retrospective and prospective clinical evidence, including a recently completed randomized trial, support the existence of an oligometastatic disease state wherein select individuals with advanced NSCLC may experience historically unprecedented prolonged survival with aggressive local treatments, consisting of radiotherapy and/or surgery, to limited sites of metastatic disease. This is reflected in the most recent AJCC staging subcategorizing metastatic disease into intra-thoracic (M1a), a single extra thoracic site (M1b), and more diffuse metastases (M1c). In the field of radiation oncology, recent technological advances have allowed for the delivery of very high, potentially ablative, doses of radiotherapy to both intra- and extra-cranial disease sites, referred to as stereotactic radiosurgery and stereotactic body radiotherapy (or SABR), in much shorter time periods compared to conventional radiation and with minimal associated toxicity. At the same time, significant improvements in systemic therapy, including platinum-based doublet chemotherapy, molecular agents targeting oncogene-addicted NSCLC, and immunotherapy in the form of checkpoint inhibitors, have led to improved control of micro-metastatic disease and extended survival sparking newfound interest in combining these agents with ablative local therapies to provide additive, and in the case of radiation and immunotherapy, potentially synergistic, effects in order to further improve progression-free and overall survival. Currently, despite the tantalizing potential associated with aggressive local therapy in the setting of oligometastatic NSCLC, well-designed prospective randomized controlled trials sufficiently powered to detect and measure the possible added benefit afforded by this approach are desperately needed.

Keywords: lung cancer, non-small cell lung cancer, oligometastases, stereotactic body radiotherapy, oligometastatic disease

OPEN ACCESS

Edited by:
John Varlotto, University of Massachusetts Medical Center, United States

Reviewed by:
Vivek Verma, University of Nebraska Medical Center, United States
John Austin Vargo, West Virginia University Hospitals, United States

****Correspondence:***
Michael T. Milano
michael_milano@urmc.rochester.edu

Specialty section:
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

Received: *28 July 2017*
Accepted: *28 August 2017*
Published: *19 September 2017*

Citation:
Bergsma DP, Salama JK, Singh DP, Chmura SJ and Milano MT (2017) Radiotherapy for Oligometastatic Lung Cancer. Front. Oncol. 7:210. doi: 10.3389/fonc.2017.00210

INTRODUCTION

Although lung cancer incidence and mortality are declining, due in large part to public health smoking cessation efforts, it remains the leading cause of cancer-related mortality both in the United States and worldwide (1). The majority of lung cancer patients have non-small cell lung cancer (NSCLC) and commonly present with metastases involving distant organ sites. Historically, palliative treatment with chemotherapy has been the standard of care for metastatic NSCLC, and outcomes with this approach have been frustratingly dismal, resulting in a median overall survival (OS) of only

8–10 months (2). However, in the past 5 years, clinical trials evaluating the efficacy of targeted therapy with receptor tyrosine kinase inhibitors (TKIs) and immunotherapy with checkpoint inhibitors represent a breakthrough in the care of advanced NSCLC offering improvements in progression-free survival (PFS) and OS (3–5). Despite these advances, long-term PFS remains limited to a relatively small subset of metastatic NSCLC patients.

Radiation therapy, a critical component of curative treatment for non-metastatic NSCLC, has classically been reserved for tumor-related symptom palliation in the metastatic disease setting. The past decade has brought about dramatic improvements in the planning and delivery of radiation treatments due to technical advancements in computing power, diagnostic imaging, and motion management. This has led to the increased use of precisely targeted highly conformal radiation, often in large doses per treatment.

Hypofractionated image-guided radiotherapy (HIGRT), typically referred to as "stereotactic radiosurgery" (SRS) when delivered to an intracranial target in one or more fractions or "stereotactic body radiotherapy" or "stereotactic ablative radiotherapy" (SBRT or SABR) when given to extra-cranial body sites in one or more fractions, has been shown to result in high rates of treated tumor control (6–8) with a favorable toxicity profile and improved convenience (9) when compared to conventionally fractionated external beam radiation (EBRT). Although not yet elucidated entirely, it is postulated that hypofractionated radiotherapy may accomplish tumor killing *via* different biological mechanisms than conventional fractionation, one being the possible infliction of endothelial or vascular damage (10, 11).

The role of radiotherapy, delivered as SBRT or conventionally fractionated EBRT with or without systemic therapy, is rapidly evolving with dramatically increased utilization in the treatment of advanced NSCLC patients with limited sites of metastatic disease termed "oligometastases" (12). Despite these advances, the appropriate selection of oligometastatic patients for curative-intent local treatment, optimal integration of radiotherapy with systemic therapy, and the added long-term benefit such as aggressive treatment approach provides have not been sufficiently clarified.

THE OLIGOMETASTATIC STATE

One of the hallmarks of cancer is the development of pioneer cells that are able to release from the primary tumor site and metastasize to regional lymph nodes and/or distant organs *via* the lymphatics, blood stream, or direct extension (13). The risk of subclinical dissemination in solid tumors, even in the setting of apparently localized disease, is variable and dependent on tumor histology, size, grade, stage, genetics, and a host of other factors, many of which are not yet understood. Hellman and Weichselbaum postulated the existence of an oligometastatic state in which tumors develop sites of distant metastasis in a single or limited number of organs as a function of the underlying biology of tumor cells and the unique receptiveness of distant organ sites ("seed and soil") (14). This concept of oligometastases is derived from the spectrum theory that bridges the gap between the Fisher and Halstedian viewpoints on cancer. Fisher argued many tumors are micro-metastatic from inception even when presenting without clinical/radiographic evidence of distant metastatic disease (15), whereas Halsted postulated orderly spread from the primary tumor into regional lymph nodes and ultimately distant organs (16). In the spectrum theory of cancer, the oligometastatic state may reflect patients with more indolent disease courses that may be cured or rendered disease free for long time intervals with aggressive local treatment of distant metastases. We will further discuss the rationale and review the ever-growing clinical evidence supporting an aggressive treatment approach in select NSCLC patients presenting with oligometastatic disease.

Historically, before the development of systemic therapies with increased efficacy, aggressive metastasis-directed treatments were relied upon to palliate, and occasionally cure, patients with limited metastases (17). In the setting of systemic therapy, which may be able to sterilize micrometastases, control of clinically detectable tumors is perhaps of even more importance. Although prospective clinical trials do not routinely report PFS of individual metastases, observational studies report that the predominant pattern of recurrence in patients with oligometastatic NSCLC treated with first-line systemic therapy appears to be local only (18, 19). This pattern of progression would support the potential PFS benefit of delivering aggressive local therapy to all appreciable metastatic sites, as well as the thoracic primary, if feasible. As unchecked growth of oligometastases may culminate in progressive organ dysfunction eventually leading to death, improved PFS with aggressive local therapy may ultimately result in longer OS. In recent decades, the bulk of published clinical series have included patients with oligometastatic sarcoma, colorectal, or breast cancer (20–22); however, there are an increasing number of single institution studies, the majority retrospective, which report long-term PFS and OS associated with aggressive treatment to all known sites of disease in oligometastatic NSCLC (23).

One of the difficulties in interpreting and applying the available data to predict which patients will benefit from an aggressive treatment approach including local therapies is establishing the appropriate cutoff to define the oligometastatic state. Nearly all published studies of oligometastatic NSCLC have limited inclusion to patients with $\leq$5 metastases; however, the majority enrolled patients with $\leq$3 metastases and over half of all patients included in a recent meta-analysis had only a single metastasis (24). The oligometastatic state is believed to be a relatively common presentation of advanced NSCLC; however, its exact incidence is dependent on the cutoff used for its definition. The relative prevalence of oligometastatic disease in advanced NSCLC has been reported to range from 26 to 50% using cutoffs of $\leq$3–5 metastases (18, 25). The reported rates of oligorecurrence after definitive surgical treatment of NSCLC are even higher, with 33–50% of patients recurring with $\leq$3 lesions (26, 27). It is important to note that the studies reporting rates of oligometastases are likely subjected to selection bias as patients with more metastatic burden may be less likely to be enrolled on protocols and/or treated at tertiary or quaternary referral centers that often report their large institutional experiences.

In general, patients with fewer metastases tend to have better outcomes than those with a more widespread presentation

irrespective of the potential impact of aggressive metastasis-directed local therapy. This has been shown in multiple retrospective studies (25, 27, 28) including a comprehensive analysis of advanced NSCLC patients treated on consecutive Southwest Oncology Group prospective protocols that revealed a significantly longer OS in patients developing a single metastasis (8.7 months) vs multiple metastases in a single organ (6.2 months) or multiple organs (5.1 months) (28). Some argue that oligometastases do not reflect a more indolent biology but rather lead-time bias in which patients are found to have metastatic disease at an earlier point in the natural history of their disease. However, this explanation cannot fully account for the long-term survival of some individuals with oligometastatic disease with up to one-quarter of patients surviving long-term with aggressive treatment to all sites of disease (24, 29). The recent 8th edition of the AJCC staging manual now considers a single extrathoracic metastasis to be M1b vs more widespread extrathoracic M1c disease (30). The M1a substage interestingly includes patients with potentially more metastatic burden than M1b, such as numerous lung metastases and/or malignant pleural effusion(s), as long as it is contained to the thorax.

Another important consideration when defining the oligometastatic state is appropriate patient evaluation/staging. Advancements in modern diagnostic imaging, including more widespread use of brain MRI and FDG-PET/CT, have improved the detection of both intra- and extra-cranial metastatic disease. MRI is superior to CT in staging the brain and may detect the presence of metastases, particularly small lesions, unappreciated by CT (31). The use of PET/CT staging is associated with improved OS, likely due in part to stage migration where patients are bumped into a higher stage category by the detection of otherwise clinically unapparent metastases (32, 33). Based on published studies, approximately 15% of NSCLC patients initially thought to be stage I–III may be upstaged to stage IV with use of PET/CT in addition to contrast CT imaging alone (34, 35). Furthermore, modern imaging may detect widespread metastases in patients thought to have oligometastatic disease, thereby avoiding aggressive metastasis-directed local therapy in those who are unlikely to have a PFS benefit. It is important to consider that the bulk of published studies in oligometastatic NSCLC included patients treated before the routine use of PET/CT for staging (24).

Despite a strong focus on using a strict number of metastases to define oligometastatic disease, other factors including age and performance status, volume of disease, histology, tumor location(s), rate of progression, and genetics may be important in predicting benefit from aggressive local therapy (36). For appropriate clarification of distinct clinical scenarios, oligometastatic disease can be subdivided based on the development of metastases in relation to initial diagnosis and systemic therapy (37). Synchronous or *de novo* oligometastases refers to presentation with a limited number of lesions at initial diagnosis, while oligorecurrence is the metachronous development of new metastases after definitive treatment of initial locoregional thoracic disease. Patients with more widespread presentation experiencing relative disease stability on "mostly effective" systemic therapy aside from a limited number of persistent or recurrent/growing metastases may be referred to as having oligoresistance (or "induced oligometastases") and oligoprogression disease, respectively. The latter two scenarios are fairly common in the setting of oncogene-addicted NSCLC (those patients with ALK rearrangements or EGFR mutations) and are due predominantly to acquired resistance to treatment with TKIs in progressing/resistant tumor clonogens (38).

Timing does appear to be important and an improved prognosis has been observed in patients presenting with oligorecurrence compared to those with *de novo* oligometastases as evidenced by an individual patient data meta-analysis by Ashworth and colleagues including 757 oligometastatic NSCLC patients treated with ablative treatments to all sites of disease which reported the latter to be associated with a HR of 1.96 ($p < 0.001$) on multivariate analysis (24). It is worth mentioning that a more recent publication did not show worse OS outcomes in synchronous patients if treated with aggressive thoracic therapy (ATT) (39). Additional adverse prognostic factors for OS reported in the meta-analysis by Ashworth (24) included higher thoracic stage and/or mediastinal node positivity, presence of brain metastases, non-adenocarcinoma histology, and non-surgical treatment. Nearly 90% of patients included had a single metastatic lesion and the presence of >1 oligometastatic lesion and/or multiple organ involvement was significantly associated with worse PFS. As alluded to previously, there is evidence to support the premise that larger volume, rather than number, of metastases is more predictive of worse outcome. A retrospective study conducted at MD Anderson Cancer Center including 1,284 patients with advanced NSCLC found that the number of extra-cranial metastases correlated with OS; however, among patients with brain- or lung-only metastases, there was an even stronger association with cumulative metastatic tumor volume (40).

DEFINITIVE RADIOTHERAPY-BASED TREATMENT OF OLIGOMETASTASES

Historically, surgical resection has been the preferred metastasis-directed treatment for patients with limited metastases from NSCLC (41). Surgery has the attributes of being both diagnostic, by providing pathologic confirmation of metastatic disease, and therapeutic, by eliminating tumor and/or alleviating tumor-related symptoms (42, 43). The benefit of aggressive metastasis-directed therapy was first shown in patients with limited brain metastases. Patchell and colleagues (44) performed a phase III randomized controlled trial evaluating the impact of surgical resection added to palliative whole brain radiotherapy (WBRT) in a predominantly NSCLC population of patients with a single brain metastasis reporting resected patients lived significantly longer (40 vs 15 weeks, $p < 0.01$). Following this, a number of studies examined the effect of extra-cranial metastasis-directed therapy, typically consisting of surgery and/or radiotherapy, with nearly two-thirds of patients included in a recent meta-analysis of oligometastatic NSCLC patients managed with surgery as the primary treatment. Although surgery was found to be significantly associated with improved OS, there was a strong potential selection bias favoring outcomes in the surgical group (for example, medical co-morbidities) (24).

Unfortunately, many patients with oligometastases present with one or more unresectable deposits and/or may be poor operative candidates due to advanced age and/or medical comorbidities. There is interest in utilizing less invasive, potentially ablative techniques to treat oligometastases including thermal, cryo-, chemical, or irreversible electroporation ablation, but experience with these techniques is limited and restricted to select institutions (45). Furthermore, their role in the treatment of oligometastatic disease, NSCLC, or otherwise is not well defined.

The ability of modern radiotherapy techniques to deliver potentially ablative HIGRT doses, including SRS and SBRT, to numerous organ sites throughout the body has allowed for the aggressive treatment of unresectable metastases. Techniques intrinsic to SRS were initially developed to treat small targets in the brain that were not amenable to conventional surgery (46), however, have since been greatly refined due to improved brain imaging, treatment planning software allowing for MRI-CT image fusion and accurate dose calculation, more widely available LINAC-based delivery, and non-invasive immobilization. SRS alone has replaced WBRT as the recommended upfront treatment for NSCLC patients with oligometastases in the brain (47).

Extra-cranially, SBRT is associated with treated tumor control rates rivaling surgery, often in excess of 90%, among NSCLC patients when escalated to a biologically effective dose (BED) of at least 100 Gy (6, 48). As these treatments deliver very high, potentially ablative, doses of radiation to tumor, often near critical normal organs (i.e., spinal cord, kidney, bowel, and heart), the safe delivery of HIGRT is highly dependent on effective patient immobilization, accurate and reproducible image-guided setup, and respiratory motion analysis and management. As the technical expertise and availability of equipment required to deliver HIGRT rapidly expands, there are a growing number of institutions reporting their experiences, both retrospective and prospective, using these techniques in advanced stage NSCLC patients to target metastases located throughout the body (see **Table 1**).

TREATMENT OF INDIVIDUAL ORGAN SITES

Brain

Brain metastases ultimately develop in 30–50% of NSCLC patients and are typically associated with a very poor prognosis. The increased availability of brain MRI as well as improved systemic therapies that improve survival but often poorly penetrate the blood–brain barrier have led to an increase in the number of NSCLC patients ultimately diagnosed with brain metastases (59). Historically, upfront WBRT constituted the standard of care treatment for brain metastases, despite a lack of proven OS benefit, due to its ability to provide improved central nervous system (CNS) control and decrease the risk of neurologic death, at the risk of potential late neurocognitive toxicity, compared to optimal supportive care (OSC). The utility of WBRT has come under significant scrutiny, particularly based on the results of a recently published phase III, non-inferiority, randomized trial from the United Kingdom (UK) (QUARTZ) which compared WBRT to OSC in NSCLC patients with brain metastases unsuitable for surgical resection or SRS. The study authors concluded that although the OSC alone arm did not meet the predetermined primary endpoint of non-inferiority in regard to quality-adjusted life-years, the absolute benefits of WBRT were clinically insignificant and it should not routinely be used to treat this patient population. Proponents of WBRT argue that the patients enrolled on the QUARTZ trial had extremely poor prognosis, evidenced by the reported median OS of 8–9 weeks, which precluded significant benefit from WBRT. In fact, the prognosis for NSCLC patients with brain metastases varies widely and the anticipated benefit of WBRT may be more substantial in patients with a greater ratio of intra- to extra-cranial disease burden who are at high risk of severe mortality and/or mortality with uncontrolled progression of CNS metastases (60). Furthermore, select patients with adequate performance status, limited brain metastases, and low burden extra-cranial disease may experience improved survival from the improved brain control associated with aggressive CNS-directed local therapies including surgery and/or SRS (61). An aforementioned trial demonstrated that in good performance status patients with a single intracranial metastasis, adding surgical resection to WBRT significantly improved OS (44). Similarly, RTOG 9508 studied the impact of SRS boost after WBRT for patients with 1–3 newly diagnosed brain metastases and revealed an OS benefit with the addition of SRS in patients with a single brain metastasis, mean survival time (MST) of 6.5 vs 4.9 months ($p = 0.039$), as well as in NSCLC patients, MST of 5.9 vs 3.9 months ($p = 0.012$) (62).

The benefit afforded by the addition of upfront WBRT to surgical resection and/or SRS has been intensely studied given the potential for prolonged survival in the most favorable subset of NSCLC patients with brain metastases as well as the appreciable risk of late neurocognitive toxicity with WBRT (61). The Alliance group recently published the results of a trial comparing upfront SRS with or without WBRT in patients (approximately two-third NSCLC) with one to three brain metastases and reported no detriment to OS and less cognitive deterioration in the SRS alone group (63, 64). Furthermore, two additional randomized trials each enrolling surgically resected patients with limited brain metastases, one (in which 20% had NSCLC) comparing SRS vs observation (65) and the other (in which 58% had NSCLC) SRS with or without WBRT (66), show adjuvant SRS may provide an optimal balance between maximizing brain metastasis control in the resection cavity and preservation of neurocognition without compromising survival provided patients are followed closely with salvage therapy (either additional SRS or WBRT) initiated at the time of intracranial progression.

An additional consideration in the treatment of brain oligometastases includes the relatively lower prescribed dose, limited by potential toxicity including the risk of radionecrosis, and resulting high local failure rates associated with single fraction SRS for large lesions (>2 cm). Recently published retrospective data show a multifraction SRS (three to five fractions) approach yields increased local control (LC) and decreased risk of radionecrosis in large brain metastases compared to single fraction SRS (67). There are also emerging data supporting the premise that the cumulative volume of intracranial metastatic burden

TABLE 1 | Summary of select studies of high dose radiation therapy as part of an aggressive local treatment approach targeting oligometastases from non-small cell lung cancer.

Reference	Study design	Year	Patients	Metastases per patient	Multiple organ involvement	RT technique	Included surgical patients	Included intracranial sites	Definitive thoracic therapy	Systemic therapy	Median follow-up (months)	Median progression-free survival (months)	Overall survival (OS)	Toxicity
Gomez et al. (49)	Randomized phase II prospective	2016	49	≤3	Yes	Various	Yes	Yes	Yes	All received induction chemo	12.39	11.9 (LCT) vs 3.9 (no LCT)	Median OS not reached	20 vs 8.3% G3
Iyengar et al. (50)	Phase II prospective	2014	24	≤6	Yes	SBRT	No	No	NA	All progressed through 1st line chemo, all received erlotinib	11.6	14.7	Median 20.4 months	2 G3 RT-related toxicities
Collen et al. (51)	Phase I prospective	2014	26	≤5	Yes	SBRT	No	Yes	Yes (73%)	65% induction chemo	16.4	11.2	Median 23 months	15% G2 + acute, 8% G3 pulmonary
De Ruysscher et al. (52)	Phase I prospective	2012	39	≤5	No[a]	Various	Yes	Yes	Yes	95% chemo	27.7	12.1	Median 13.5 months	15% G3
Griffioen et al. (53)	Retrospective	2013	61	≤3	No[a]	Various	Yes	Yes	Yes	84% chemo	26.1	6.6	2 years 38%	6.6% G3
Weickhardt et al. (54)	Retrospective	2012	25	≤4	Yes	Various	No[b]	Yes	NA	100% tyrosine kinase inhibitor	9.4	6.2	NA	8% G3
Hasselle et al. (55)	Retrospective	2012	25	≤5	Yes	Stereotactic radiosurgery/ SBRT	No	Yes	NA	76% prior to SBRT	14	7.6	1 year 81.1%	8% G3
Jabbour et al. (56)	Retrospective	2011	9	1	No	Conventional RT	No	Yes	Yes	100% chemo	NA	15	Median 28 months	NA
Cheruvu et al. (29)	Retrospective	2011	96	≤8	Yes	SBRT	Yes	Yes	NA	70% chemo	13.5	NA	2 years 25% (oligorecurrence) vs 43% (*de novo* oligometastases)	NA
Yano et al. (57)	Retrospective	2010	44	1	No	Various	Yes	Yes	Yes	16% chemo	NA	NA	Median 74 months	NA
Khan et al. (58)	Retrospective	2006	23	≤2	No	Various	Yes	Yes	Yes	100% upfront chemo	17	12	Median 20 months	17% G3+

Adapted from Bergsma et al. (23).

[a]*A single patient had multiple organ involvement.*

[b]*A single patient underwent surgical ablation.*

LCT, local consolidative therapy; SBRT, stereotactic body radiotherapy.

may matter more than brain metastasis number and OS may not be inferior for patients with 4–10 vs 2–3 brain metastases (68). Overall, although the presence of brain metastases has historically felt to be an adverse prognostic factor (24), the development and widespread implementation of SRS has proven to be a powerful tool in the radiation oncologist's armamentarium for the treatment of oligometastatic NSCLC within the brain.

Lung

For decades, pulmonary metastasectomy has been utilized for lung metastases from several cancer types, predominantly sarcoma and colorectal cancer. Published experiences confirm that resection can lead to prolonged PFS and OS in selected patients. Pulmonary oligometastases in NSCLC patients have been reported to carry a favorable prognosis that is now reflected in the recently published 8th edition of the TNM classification for lung cancer that separates intra-thoracic metastases, including metastatic lung or pleural nodules, as M1a rather than M1b or M1c (69). The safety and efficacy of SBRT delivered to primary NSCLC tumors and lung oligometastases has been well studied in multiple prospective studies (7, 70). Rusthoven and colleagues reported an actuarial 2-year LC of 96% in a prospective phase II study enrolling patients with one to three lung metastases from various solid tumor primaries (13% from primary lung cancer). Treatment was very well tolerated with only 8% grade 3 events and no grades 4 or 5 toxicity reported. A more recent retrospective study of SBRT for lung oligometastases limited to NSCLC reported 88.9% LC and 74.6% OS at 2 years with no grade 4 pulmonary toxicity, chest pain, or rib fractures (71). Of note, the use of PET/CT along with pathological confirmation (if acceptable risk) can be quite helpful as the presence of a contralateral lung nodule in newly diagnosed advanced NSCLC can be difficult to differentiate between a metastasis and a synchronous lung primary (72). Robust motion management is critical when delivering lung SBRT as metastases may be subjected to significant respiratory-induced motion and resulting target uncertainty which can be minimized by abdominal compression, breath hold, respiratory gating, real-time tumor tracking, and/or generation of an internal target volume based on four-dimensional CT at time of simulation (73).

Adrenal Glands

Adrenal gland metastases may be present in 5–10% of NSCLC patients (74) at initial presentation and solitary metastases occur in approximately 2–3% of cases. As solitary adrenal masses found on CT may in fact be benign adenomas, further diagnostic workup with PET/CT or dedicated MRI and possible histological confirmation should be pursued (75). Surgery with adrenalectomy of solitary metastases has been reported to provide favorable outcomes in NSCLC patients per several single and multi-institutional series (76) and conventionally fractionated EBRT can be used for palliation of pain with good response rates as measured by analgesic requirements (77). The use of SBRT in the treatment of adrenal oligometastases is gaining traction as an alternative to adrenalectomy resulting in high rates of palliation and LC rates ($\geq$74%) which appear to correlate well with greater BED (78). Definitive radiation for adrenal metastases is an attractive non-invasive alternative particularly given the not infrequent adverse pathological features of positive margins and incomplete resections seen after adrenalectomy. Treatment appears to be well tolerated with only rare severe toxicity (79, 80); however, care must be taken during treatment planning as adrenal metastases may also exhibit significant motion with respiration and are often near the kidney, spinal cord, and sensitive gastrointestinal organs including the liver, colon, stomach, and small bowel.

Liver

Liver involvement at diagnosis is a relatively uncommon presentation of advanced NSCLC with hepatic metastases reportedly occurring in less than 5% of new diagnoses (81). Histology plays a role in the comparative number of metastases with solitary presentation in 50% of patients with squamous cell carcinoma vs 5% of those with adenocarcinoma. Ultimately, the development of hepatic metastases is not uncommon in the natural history of advanced stage NSCLC. Although there is a wealth of data establishing the benefit of partial hepatectomy for isolated or limited liver metastases from colorectal cancer, the published experience of surgical resection for liver metastases from NSCLC, oligometastatic, or otherwise is lacking. The safety and efficacy of SBRT delivered to hepatic oligometastases from solid tumors has been well established in both retrospective and prospective (82) series with Goodman and colleagues reporting 91% LC at 4 years with only 4.9% grade 3 or greater liver toxicity (83). A major limitation of using these studies in the context of oligometastatic NSCLC is the wide variety of tumor histologies included, with NSCLC comprising a minority of treated cases (21% of patients enrolled on the prospective phase I/II trial by Rusthoven and colleagues); however, a large retrospective study from Moffitt Cancer Center showed that liver metastases of NSCLC origin may exhibit relative radiosensitivity compared to other histologies (84). Contrast (ideally tri-phasic) should be given at simulation to help delineate the target given the similar CT density of metastasis and normal liver. Fiducials may be helpful in aligning to the target for image guidance radiotherapy and motion assessment and management is mandatory due to potential for respiratory-induced tumor motion during treatment (85).

OTHER SITES INCLUDING BONE, KIDNEY, SPLEEN, SKIN, AND LYMPH NODES

There is relatively little data on management of oligometastatic NSCLC involving these sites with the majority being surgical series for solitary bone (86) or skin (87) lesions. Although not limited to patients with oligometastases, Gerszten and colleagues report a single institutional experience detailing outcomes in 500 cases of spine radiosurgery documenting remarkable 100% long-term radiographic control and 93% long-term pain improvement in a subset of 80 lung cases (88). A recent retrospective study from Mayo Clinic analyzed outcomes after SBRT for non-spine bone oligometastases reporting a 91.8% LC at 1 year and acceptable acute and late toxicities; however, a minority of patients included had NSCLC (89). RTOG 0631 is a randomized phase II/III study of image-guided SRS/SBRT for localized spine metastasis,

not limited to NSCLC patients, which has recently closed after adequate accrual with the primary endpoints of feasibility and palliation of pain (NCT00922974). Although the use of SRS or SBRT for bone metastases is promising, more studies are needed evaluating its impact in the context of oligometastatic NSCLC.

ROLE OF ATT

The potential benefit of aggressive therapy directed to the primary tumor (and involved nodes) has been proven in the setting of multiple histologies of advanced stage cancers. For example, in metastatic renal cell carcinoma, randomized controlled trials have shown the significant OS advantage of cytoreductive nephrectomy added to immunotherapy (90). For advanced NSCLC patients with *de novo* oligometastases or oligorecurrence including initial thoracic disease, unchecked growth of locoregional chest disease may lead to significant tumor-related morbidity including cough, pain, shortness of breath, endobronchial obstruction causing airway collapse or post-obstructive pneumonia, superior vena cava syndrome, and/or severe hemoptysis, which may ultimately result in death. Radiotherapy can alleviate symptoms associated with bulky thoracic disease and is often utilized in the palliative treatment of advanced NSCLC patients.

Historical trials conducted by the RTOG in the 1970s showed that dose escalation up to 60 Gy utilizing conventional fractionation, relative to lower doses, led to improved thoracic tumor control in inoperable NSCLC patients treated with definitive radiotherapy (91). The optimal dose of chest radiotherapy in the setting of oligometastatic NSCLC has been debated given the need to balance palliation, including prevention of morbidity related to thoracic disease progression, while also minimizing treatment toxicity and duration as prolonged breaks in systemic therapy could heighten competing risks of systemic disease progression. A large retrospective study using the National Cancer Database evaluated the comparative effectiveness of chest radiotherapy dose escalation and found a positive association between improved survival and higher-dose radiotherapy (BED above 50 Gy) (92). However, a recent meta-analysis of 14 randomized controlled trials with 3,576 patients concluded there was no strong evidence to support extended fractionation schedules of radiotherapy to palliate thoracic symptoms in incurable NSCLC patients as all patients (including those receiving shorter treatment schedules) appeared to benefit in regard to palliation with no apparent difference in OS (93). Of note, patients with good performance status had longer 1-year OS with more fractions (33.3 vs 25.6%); however, the relative effect was not reported due to a high level of heterogeneity. Acute toxicity was an issue with higher radiotherapy doses though most patients were treated before the era of 3D conformal radiotherapy that has the potential to decrease exposure of normal organs to the full prescribed dose.

Although robust prospective randomized evidence is lacking, Li and colleagues recently published a meta-analysis that included 7 retrospective observational cohort studies and 668 synchronous oligometastatic NSCLC patients, of whom 227 (34.0%) received ATT consisting of surgery and/or radiotherapy to a total dose more than 40 Gy (94). Receipt of ATT was associated with significantly improved OS (HR 0.48, $p < 0.00001$) in the entire cohort, as well as in subgroup analyses of patients with single organ metastases (HR 0.42, $p < 0.00001$), solitary (HR 0.49, 95% CI 0.31–0.75) or two to four brain metastases (HR 0.44, 95% CI 0.26–0.73), and patients with thoracic stage I–II (HR 0.38, $p = 0.004$) or stage III (HR 0.32, $p = 0.01$) disease. Pooled cumulative OS at 3 years was significantly higher in the ATT group (23.0 vs 3.7%). A recent prospective phase II study by Li and colleagues evaluating the efficacy and toxicity of definitive thoracic concurrent chemoradiation (BED $\geq$ 60 Gy) followed by consolidation chemotherapy for oligometastatic NSCLC ($\leq$5 metastases) enrolled 64 patients yielding encouraging 14-month median PFS and 26-month median OS at a median follow-up of 28 months (95). These prospectively accrued data are consistent with PFS and OS outcomes reported in other retrospective studies of ATT in oligometastatic NSCLC (25, 96, 97). While most published studies employed conventionally fractionated radiotherapy schedules with sequential or concurrent chemotherapy, HIGRT has also been used as definitive local treatment of smaller primary lung tumors in the oligometastatic setting (51, 53). Whether treatment is surgical or radiotherapy based, the use of ATT for controlling presenting or potential symptoms of thoracic disease is an integral component of an aggressive treatment approach for oligometastatic NSCLC patients with synchronous presentation given the potential for prolonged survival and significant morbidity and/or mortality resulting from uncontrolled locoregional progression.

USE OF RADIOTHERAPY WITH SYSTEMIC THERAPY

Systemic therapy is the standard palliative treatment option for reasonably fit NSCLC patients presenting with either synchronous or metachronous disseminated disease with the agent (chemotherapy, TKIs, or immunotherapy with checkpoint inhibitors) selected based on histological and genotypic information about the primary and/or metastatic tumor. Randomized trials supporting the use of these systemic therapies typically included patients with widespread, rather than limited, metastases. Regardless, the promise of improved systemic control only heightens the importance of effective local treatment modalities to address isolated persistent or progressive metastases. For example, oligoprogression is well documented during treatment of onco-addicted NSCLC (ALK gene rearrangements or EGFR mutations) with TKIs such as crizotinib for ALK+ and erlotinib for EGFR mutated NSCLC. In these patients, local ablative treatment with HIGRT has allowed continuation of targeted therapy with greater than 6 months of additional disease control (50, 54).

The optimal integration of definitive local therapy with systemic therapy in oligometastatic NSCLC is not yet certain. It is common clinical practice to address limited brain metastases with upfront SRS or surgery (if symptomatic or warranted for diagnosis) followed by SRS or WBRT with initiation of systemic therapy or definitive thoracic therapy (if brain only metastases and synchronous presentation); however, medical oncologists typically treat patients with extra-cranial oligometastases with upfront systemic therapy. As alluded to earlier, the use of induction systemic therapy may allow for selection of patients who

are less likely to develop new metastases and may experience improved PFS after consolidation with aggressive local therapy to the chest and limited residual metastases (typically ≤3) (49). The selective use of aggressive metastasis-directed and thoracic therapy in non-progressing patients is a potential source of selection bias in published retrospective studies, namely immortal time bias, which is best controlled for with a randomized controlled study. The recently reported multicenter, phase II randomized controlled trial by Gomez and colleagues utilized local consolidative therapy (LCT) of all active disease and reported a dramatic median PFS benefit (11.9 vs 3.9 months, $p = 0.0054$) compared to maintenance treatment in oligometastatic NSCLC patients (46 of 49 *de novo*) with three or fewer metastatic disease lesions without progression after first-line systemic therapy (49). These randomized prospective data reinforce the sum of available retrospective evidence signaling the significant PFS benefit of adding aggressive local therapy to standard systemic treatment for patients with NSCLC oligometastases.

It should be noted that the administration of systemic therapy may be associated with significant acute toxicities, including chemotherapy-related nausea and myelosuppression and autoimmune phenomena related to immunotherapy, which adversely affect patient quality of life. In the setting of oligometastatic NSCLC, Collen and colleagues reported the results of a small prospective study that showed receipt of induction chemotherapy prior to undergoing SBRT was not prognostic for LC or PFS (51). It is possible that select patients may experience prolonged PFS with aggressive local therapy directed at all metastatic sites in lieu of systemic therapy; however, it is reasonable to consider chemotherapy, or other appropriate systemic agents, as upfront treatment in oligometastatic patients given the OS benefit afforded in both early (adjuvant after resection in node positive and/or larger primary tumors) and advanced stage NSCLC (98). This treatment approach is reflected in the NCCN guidelines version 1.2017. As mentioned earlier, the use of aggressive local therapy in the setting of oncogene-addicted NSCLC is an area of significant interest as studies have reported excellent PFS and OS with the addition of SBRT to erlonitib in patients progressing after first-line platinum-based chemotherapy (50). Salvage of oligoprogression in the setting of advanced NSCLC with a driver mutation may allow continuation of otherwise efficacious and well-tolerated systemic therapy in patient who may not have other effective treatment options (99). Reported toxicities of the above approaches have been quite low with rare reports of severe (grades 4–5) adverse events.

Although the benefit of aggressive primary and metastasis-directed local therapy in the metastatic setting has commonly felt to be due to improved LC of targeted gross tumor(s), Gomez and colleagues reported a significantly prolonged time interval to the appearance of a new lesion among patients randomized to LCT (11.9 vs 5.7 months) (49). This is a provocative finding that suggests an aggressive local treatment approach may alter the natural history of metastatic disease either by limiting the potential for later spread or stimulating systemic immune-surveillance. Furthermore, there are fascinating reports of radiation inducing an "abscopal effect" whereby treating a single lesion results in regression of metastases far away from the treated site, however, these remain mostly anecdotal at present. Preclinical studies show synergistic antitumor effects with radiotherapy *via* pro-immunogenic properties resulting from increased tumor antigen presentation and activation of cytotoxic T cells (100) and emerging clinical data also support this concept with a recent study reporting previous treatment with extra-cranial radiotherapy was associated with significantly improved median OS (11.6 vs 5.3 months, $p = 0.034$) among patients treated with pembrolizumab on the KEYNOTE-001 phase I trial (101). Importantly, predominantly retrospective data to date suggest that the contemporaneous administration of immunotherapy and intracranial SRS or palliative dose extra-cranial radiotherapy is relatively safe without dramatically increased risk of synergistic toxicity; however, efficacy nor the safety of more aggressive extra-cranial dose schedules has not been studied (102, 103). There may even be a detrimental effect of more protracted palliative radiotherapy schedules given the extreme radiosensitivity of circulating lymphocytes and our growing understand of the importance of the immune system in combatting metastatic disease (104).

FUTURE DIRECTIONS AND ONGOING PROSPECTIVE TRIALS

The emerging evidence supports the existence of a subset of advanced NSCLC patients who will benefit from definitive local treatment to limited sites of disease with unparalleled PFS and OS. The challenge has been defining the appropriate patient population and proving the added benefit of aggressive local therapy in a randomized fashion. The phase II study by Gomez and colleagues represents the first randomized controlled trial addressing the question at hand and supports the premise that select advanced NSCLC patients may progress predominantly in known disease sites and aggressive thoracic and metastasis-directed local therapy can result in improved PFS. As follow-up remains short (median of 12.4 months), it is unclear whether the PFS benefit observed will translate into improved OS. It is possible that crossover of patients in the maintenance arm to LCT after progression could minimize the potential OS benefit similar to that seen in randomized trials of targeted agents in NSCLC (105). In addition, as the study was powered to assess the primary outcome, PFS, and was closed early at the recommendation of the data safety monitoring committee due to an overwhelming probability of concluding in favor of the LCT group, it may be insufficiency powered to measure a true difference in OS between arms. Regardless of whether an improvement in OS is ultimately shown, an improvement in PFS is certainly meaningful as a prolonged disease-free interval off of systemic therapy may represent a significant quality of life benefit to the patient.

Further randomized studies are necessary. NRG Oncology has recently opened NRG-LU002 (NCT03137771), a randomized phase II/III trial enrolling NSCLC patients with ≤3 oligometastatic sites that will build upon the experience of Gomez and colleagues and seeks to evaluate the PFS and OS benefit, if it exists, of consolidative SBRT and definitive thoracic therapy after first-line/induction systemic therapy in a national cooperative group setting. SABR-COMET (NCT01446744) is another multi-institutional randomized phase II trial that has completed accrual

of 99 patients (not limited to NSCLC histology) with ≤5 metastases and a controlled primary tumor. Patients were randomized to standard of care with or without SBRT consolidation to all sites of known disease with OS as the primary outcome measure. SARON (NCT02417662) is a UK-based multicenter randomized phase III study enrolling (target of 340) patients with oligometastatic NSCLC and examining the feasibility, safety, and efficacy of consolidation with SBRT or conventional RT to primary and sites of metastases after standard platinum-based doublet chemotherapy. CORE (NCT02759783) is another randomized phase II trial (anticipated accrual of 206 patients) that has opened in the UK enrolling breast, prostate, and NSCLC patients with oligorecurrence and is evaluating the impact of adding SBRT to standard of care with PFS as the primary outcome. These larger randomized studies should increase the power to uncover an OS benefit with the addition of SBRT as comprehensive local therapy in the setting of oligometastatic NSCLC.

Additional questions remain unanswered beyond the measurable added benefit, if any, of an aggressive treatment approach including definitive local therapy. Both SABR-COMET and the randomized phase II study by Gomez and colleagues were evaluating the use of definitive local therapy to sites of limited disease as consolidation after upfront systemic therapy. However, the optimal timing of aggressive local treatment remains undefined. The ongoing Chinese OITROLC trial (NCT02076477) may help answer this question as it randomizes oligometastatic patients (≤5 distant organ metastases) between upfront definitive local therapy to the primary and all sites of metastases vs a consolidative approach after two cycles of induction chemotherapy with 3-month response rate as the primary outcome and 3-year PFS and toxicity as secondary outcomes. As use of SBRT combined with erlotinib showed remarkable outcomes in oligoprogressive metastatic NSCLC (50), a pilot study from Memorial Sloan Kettering Cancer Center (NCT02450591) is now evaluating outcomes when SBRT or surgery is added to erlotinib for newly diagnosed oligometastatic lung adenocarcinoma harboring a sensitizing EGFR mutation with the goal to evaluate feasibility and PFS.

Although crucial before more broadly adopting an aggressive local therapy approach to oligometastatic disease, the safety and optimal dose fractionation when treating multiple oligometastases in various organ sites remains unknown as the bulk of published literature studied the use of SBRT for single metastases within individual organs (8, 106). NRG BR001 (NCT02206334), a phase I study enrolling patients with oligometastatic NSCLC, prostate, or breast cancer, attempts to clarify the tolerability of SBRT when treating patients with multiple metastases at pre-defined doses in seven organ sites including bone and lymph nodes, where little safety data currently exist.

The era of personalized medicine has arrived in the field of oncology, ushered in by advances in imaging and molecular biology. Broad molecular profiling is expected to be a key component of future advancements in the care of patients with NSCLC. Prospective clinical trials are underway to generate clinical and molecular predictors, including comprehensive molecular profiling and/or primary tumor microRNA expression, to guide selection of patients for oligometastases-directed ablative therapy (107, 108). Further investigation, including independent validation, is needed before clinical implementation. Given the transition toward earlier incorporation of immunotherapy, such as the upfront administration of pembrolizumab in some newly diagnosed advanced NSCLC patients, there is considerable interest in combining immunotherapy and radiotherapy to improve outcomes and perhaps even induce the abscopal effect (109). A web search of http://clinicaltrials.gov revealed that there are now at least 14 actively recruiting studies evaluating immunotherapy in NSCLC as of March 31, 2017. These studies will hopefully add knowledge as to the added benefit and optimal incorporation of radiation with immunotherapy, including the most appropriate timing, sequencing, and dosing of each.

Despite the emerging evidence supporting the use of aggressive local treatments in addition to standard of care systemic therapy for oligometastatic NSCLC, as well as the increasing availability of non-invasive potentially ablative radiotherapy techniques, there are practical limitations that must be considered as our society increasingly recognizes the rising costs of health care in the modern era and begins to transition toward a value-based reimbursement model for providers and hospital systems (110). "Payers," including governmental and private health insurers, are increasingly emphasizing an evidence-based approach to justify potentially costly treatments in patients with relatively poor prognosis. This can make obtaining insurance approval for novel and/or investigational uses for expensive treatment modalities, including SRS or SBRT, an onerous challenge for the treating radiation oncology team, as well as increase the financial burden and stress patients and their families experience during cancer treatment (111). This new reality reinforces the need for high level evidence to justify and guide the recommendation for aggressive local treatments in the setting of oligometastatic NSCLC.

CONCLUSION

Tremendous developments in the field of oncology within the past decade, including improvements in imaging and radiotherapy technique allowing for the safe delivery of potentially ablative doses of radiation with minimal toxicity or interruption in quality of life or systemic therapy, have ushered in the next frontier of NSCLC treatment. A steadily increasing number of published retrospective and prospective clinical experiences, including the first successfully completed randomized trial, support the concept that NSCLC patients with limited metastatic disease, termed as oligometastases, will experience improved outcomes with aggressive local treatment with surgery and/or radiation therapy targeting all sites of appreciable disease. The challenge for the oncology community moving forward is to design and accrue to prospective randomized controlled trials that will allow for an accurate assessment of the added benefit of aggressive local therapy as well as the optimal integration with existing and emerging systemic therapies.

AUTHOR CONTRIBUTIONS

DB wrote the initial draft of this review, with edits and revisions from each of the other authors: JS, DS, SC, and MM.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* (2016) 66:7–30. doi:10.3322/caac.21332
2. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer. *Cochrane Database Syst Rev* (2010) 5:CD007309. doi:10.1002/14651858.CD007309.pub2
3. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* (2016) 375:1823–33. doi:10.1056/NEJMoa1606774
4. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* (2015) 373:1627–39. doi:10.1056/NEJMoa1507643
5. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* (2011) 12:735–42. doi:10.1016/S1470-2045(11)70184-X
6. Chang JY, Senan S, Paul MA, Mehran RJ, Louie AV, Balter P, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* (2015) 16:630–7. doi:10.1016/S1470-2045(15)70168-3
7. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* (2010) 303:1070–6. doi:10.1001/jama.2010.261
8. Milano MT, Katz AW, Zhang H, Okunieff P. Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. *Int J Radiat Oncol Biol Phys* (2012) 83:878–86. doi:10.1016/j.ijrobp.2011.08.036
9. Nyman J, Hallqvist A, Lund JA, Brustugun OT, Bergman B, Bergstrom P, et al. SPACE – a randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. *Radiother Oncol* (2016) 121:1–8. doi:10.1016/j.radonc.2016.08.015
10. Fuks Z, Kolesnick R. Engaging the vascular component of the tumor response. *Cancer Cell* (2005) 8:89–91. doi:10.1016/j.ccr.2005.07.014
11. Park HJ, Griffin RJ, Hui S, Levitt SH, Song CW. Radiation-induced vascular damage in tumors: implications of vascular damage in ablative hypofractionated radiotherapy (SBRT and SRS). *Radiat Res* (2012) 177:311–27. doi:10.1667/RR2773.1
12. Lewis SL, Porceddu S, Nakamura N, Palma DA, Lo SS, Hoskin P, et al. Definitive stereotactic body radiotherapy (SBRT) for extracranial oligometastases: an international survey of >1000 radiation oncologists. *Am J Clin Oncol* (2015) 40:418–22. doi:10.1097/COC.0000000000000169
13. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* (2000) 100:57–70. doi:10.1016/S0092-8674(00)81683-9
14. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol* (1995) 13:8–10. doi:10.1200/JCO.1995.13.1.8
15. Fisher B. From Halsted to prevention and beyond: advances in the management of breast cancer during the twentieth century. *Eur J Cancer* (1999) 35:1963–73. doi:10.1016/S0959-8049(99)00217-8
16. Halsted WS. I. The results of radical operations for the cure of carcinoma of the breast. *Ann Surg* (1907) 46:1–19. doi:10.1097/00000658-190707000-00001
17. Rubin P. Comment: are metastases curable? *JAMA* (1968) 204:612–3. doi:10.1001/jama.1968.03140200052016
18. Mehta N, Mauer AM, Hellman S, Haraf DJ, Cohen EE, Vokes EE, et al. Analysis of further disease progression in metastatic non-small cell lung cancer: implications for locoregional treatment. *Int J Oncol* (2004) 25:1677–83. doi:10.3892/ijo.25.6.1677
19. Rusthoven KE, Hammerman SF, Kavanagh BD, Birtwhistle MJ, Stares M, Camidge DR. Is there a role for consolidative stereotactic body radiation therapy following first-line systemic therapy for metastatic lung cancer? A patterns-of-failure analysis. *Acta Oncol* (2009) 48:578–83. doi:10.1080/02841860802662722
20. Kanas GP, Taylor A, Primrose JN, Langeberg WJ, Kelsh MA, Mowat FS, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin Epidemiol* (2012) 4:283–301. doi:10.2147/CLEP.S34285
21. Predina JD, Puc MM, Bergey MR, Sonnad SS, Kucharczuk JC, Staddon A, et al. Improved survival after pulmonary metastasectomy for soft tissue sarcoma. *J Thorac Oncol* (2011) 6:913–9. doi:10.1097/JTO.0b013e3182106f5c
22. Salama JK, Chmura SJ. The role of surgery and ablative radiotherapy in oligometastatic breast cancer. *Semin Oncol* (2014) 41:790–7. doi:10.1053/j.seminoncol.2014.09.016
23. Bergsma DP, Salama JK, Singh DP, Chmura SJ, Milano MT. The evolving role of radiotherapy in treatment of oligometastatic NSCLC. *Expert Rev Anticancer Ther* (2015) 15:1459–71. doi:10.1586/14737140.2015.1105745
24. Ashworth AB, Senan S, Palma DA, Riquet M, Ahn YC, Ricardi U, et al. An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. *Clin Lung Cancer* (2014) 15:346–55. doi:10.1016/j.cllc.2014.04.003
25. Parikh RB, Cronin AM, Kozono DE, Oxnard GR, Mak RH, Jackman DM, et al. Definitive primary therapy in patients presenting with oligometastatic non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* (2014) 89:880–7. doi:10.1016/j.ijrobp.2014.04.007
26. Yano T, Okamoto T, Haro A, Fukuyama S, Yoshida T, Kohno M, et al. Local treatment of oligometastatic recurrence in patients with resected non-small cell lung cancer. *Lung Cancer* (2013) 82:431–5. doi:10.1016/j.lungcan.2013.08.006
27. Torok J, Kelsey C, Salama JK. Patterns of distant metastases in surgically managed early stage non-small cell lung cancer. *Paper Presentation, 55th Annual ASTRO Meeting*. Atlanta, GA (2013). 2013 p.
28. Albain KS, Crowley JJ, LeBlanc M, Livingston RB. Survival determinants in extensive-stage non-small-cell lung cancer: the Southwest Oncology Group experience. *J Clin Oncol* (1991) 9:1618–26. doi:10.1200/JCO.1991.9.9.1618
29. Cheruvu P, Metcalfe SK, Metcalfe J, Chen Y, Okunieff P, Milano MT. Comparison of outcomes in patients with stage III versus limited stage IV non-small cell lung cancer. *Radiat Oncol* (2011) 6:80. doi:10.1186/1748-717X-6-80
30. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol* (2016) 11:39–51. doi:10.1016/j.jtho.2015.09.009
31. Zakaria R, Das K, Bhojak M, Radon M, Walker C, Jenkinson MD. The role of magnetic resonance imaging in the management of brain metastases: diagnosis to prognosis. *Cancer Imaging* (2014) 14:8. doi:10.1186/1470-7330-14-8
32. Li J, Xu W, Kong F, Sun X, Zuo X. Meta-analysis: accuracy of 18FDG PET-CT for distant metastasis staging in lung cancer patients. *Surg Oncol* (2013) 22:151–5. doi:10.1016/j.suronc.2013.04.001
33. Tonnies S, Tonnies M, Kollmeier J, Bauer TT, Forster GJ, Kaiser D, et al. Impact of preoperative 18F-FDG PET/CT on survival of resected monometastatic non-small cell lung cancer. *Lung Cancer* (2016) 93:28–34. doi:10.1016/j.lungcan.2015.12.008
34. Dinan MA, Curtis LH, Carpenter WR, Biddle AK, Abernethy AP, Patz EF Jr, et al. Stage migration, selection bias, and survival associated with the adoption of positron emission tomography among medicare beneficiaries with non-small-cell lung cancer, 1998–2003. *J Clin Oncol* (2012) 30:2725–30. doi:10.1200/JCO.2011.40.4392
35. Weber WA, Dietlein M, Hellwig D, Kirsch CM, Schicha H, Schwaiger M. [PET with (18)F-fluorodeoxyglucose for staging of non-small cell lung cancer]. *Nuklearmedizin* (2003) 42:135–44.
36. Palma DA, Salama JK, Lo SS, Senan S, Treasure T, Govindan R, et al. The oligometastatic state – separating truth from wishful thinking. *Nat Rev Clin Oncol* (2014) 11:549–57. doi:10.1038/nrclinonc.2014.96
37. Patel PR, Yoo DS, Niibe Y, Urbanic JJ, Salama JK. A call for the aggressive treatment of oligometastatic and oligo-recurrent non-small cell lung cancer. *Pulm Med* (2012) 2012:480961. doi:10.1155/2012/480961
38. Camidge DR, Pao W, Sequist LV. Acquired resistance to TKIs in solid tumours: learning from lung cancer. *Nat Rev Clin Oncol* (2014) 11:473–81. doi:10.1038/nrclinonc.2014.104
39. Fleckenstein J, Petroff A, Schafers HJ, Wehler T, Schope J, Rube C. Long-term outcomes in radically treated synchronous vs. metachronous oligometastatic non-small-cell lung cancer. *BMC Cancer* (2016) 16:348. doi:10.1186/s12885-016-2379-x

40. Oh Y, Taylor S, Bekele BN, Debnam JM, Allen PK, Suki D, et al. Number of metastatic sites is a strong predictor of survival in patients with nonsmall cell lung cancer with or without brain metastases. *Cancer* (2009) 115:2930–8. doi:10.1002/cncr.24333
41. Pfannschmidt J, Dienemann H. Surgical treatment of oligometastatic non-small cell lung cancer. *Lung Cancer* (2010) 69:251–8. doi:10.1016/j.lungcan.2010.05.003
42. Collaud S, Stahel R, Inci I, Hillinger S, Schneiter D, Kestenholz P, et al. Survival of patients treated surgically for synchronous single-organ metastatic NSCLC and advanced pathologic TN stage. *Lung Cancer* (2012) 78:234–8. doi:10.1016/j.lungcan.2012.09.011
43. Congedo MT, Cesario A, Lococo F, De Waure C, Apolone G, Meacci E, et al. Surgery for oligometastatic non-small cell lung cancer: long-term results from a single center experience. *J Thorac Cardiovasc Surg* (2012) 144:444–52. doi:10.1016/j.jtcvs.2012.05.051
44. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* (1990) 322:494–500. doi:10.1056/NEJM199002223220802
45. Di Lascio S, Pagani O. Oligometastatic breast cancer: a shift from palliative to potentially curative treatment? *Breast Care (Basel)* (2014) 9:7–14. doi:10.1159/000358750
46. Leksell L. The stereotaxic method and radiosurgery of the brain. *Acta Chir Scand* (1951) 102:316–9.
47. Sahgal A, Larson D, Knisely J. Stereotactic radiosurgery alone for brain metastases. *Lancet Oncol* (2015) 16:249–50. doi:10.1016/S1470-2045(14)71106-4
48. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol* (2007) 2:S94–100. doi:10.1097/JTO.0b013e318074de34
49. Gomez DR, Blumenschein GR Jr, Lee JJ, Hernandez M, Ye R, Camidge DR, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol* (2016) 17:1672–82. doi:10.1016/S1470-2045(16)30532-0
50. Iyengar P, Kavanagh BD, Wardak Z, Smith I, Ahn C, Gerber DE, et al. Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. *J Clin Oncol* (2014) 32:3824–30. doi:10.1200/JCO.2014.56.7412
51. Collen C, Christian N, Schallier D, Meysman M, Duchateau M, Storme G, et al. Phase II study of stereotactic body radiotherapy to primary tumor and metastatic locations in oligometastatic nonsmall-cell lung cancer patients. *Ann Oncol* (2014) 25:1954–9. doi:10.1093/annonc/mdu370
52. De Ruysscher D, Wanders R, van Baardwijk A, Dingemans AM, Reymen B, Houben R, et al. Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases: long-term results of a prospective phase II trial (Nct01282450). *J Thorac Oncol* (2012) 7:1547–55. doi:10.1097/JTO.0b013e318262caf6
53. Griffioen GH, Toguri D, Dahele M, Warner A, de Haan PF, Rodrigues GB, et al. Radical treatment of synchronous oligometastatic non-small cell lung carcinoma (NSCLC): patient outcomes and prognostic factors. *Lung Cancer* (2013) 82:95–102. doi:10.1016/j.lungcan.2013.07.023
54. Weickhardt AJ, Scheier B, Burke JM, Gan G, Lu X, Bunn PA Jr, et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. *J Thorac Oncol* (2012) 7:1807–14. doi:10.1097/JTO.0b013e3182745948
55. Hasselle MD, Haraf DJ, Rusthoven KE, Golden DW, Salgia R, Villaflor VM, et al. Hypofractionated image-guided radiation therapy for patients with limited volume metastatic non-small cell lung cancer. *J Thorac Oncol* (2012) 7:376–81. doi:10.1097/JTO.0b013e31824166a5
56. Jabbour SK, Daroui P, Moore D, Licitra E, Gabel M, Aisner J. A novel paradigm in the treatment of oligometastatic non-small cell lung cancer. *J Thorac Dis* (2011) 3:4–9. doi:10.3978/j.issn.2072-1439.2010.12.09
57. Yano T, Haro A, Yoshida T, Morodomi Y, Ito K, Shikada Y, et al. Prognostic impact of local treatment against postoperative oligometastases in non-small cell lung cancer. *J Surg Oncol* (2010) 102:852–5. doi:10.1002/jso.21750
58. Khan AJ, Mehta PS, Zusag TW, Bonomi PD, Penfield Faber L, Shott S, et al. Long term disease-free survival resulting from combined modality management of patients presenting with oligometastatic, non-small cell lung carcinoma (NSCLC). *Radiother Oncol* (2006) 81:163–7. doi:10.1016/j.radonc.2006.09.006
59. Schellinger PD, Meinck HM, Thron A. Diagnostic accuracy of MRI compared to CCT in patients with brain metastases. *J Neurooncol* (1999) 44:275–81. doi:10.1023/A:1006308808769
60. Mehta MP, Aoyama H, Gondi V. The changing role of whole-brain radiotherapy: demise or time for selective usage? *JAMA Oncol* (2017) 3:1021–2. doi:10.1001/jamaoncol.2016.5414
61. Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol* (2012) 30:419–25. doi:10.1200/JCO.2011.38.0527
62. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* (2004) 363:1665–72. doi:10.1016/S0140-6736(04)16250-8
63. Brown PD, Asher AL, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. NCCTG N0574 (Alliance): a phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases. *J Clin Oncol* (2015) 33(15_Suppl):lba4. doi:10.1200/jco.2015.33.15_suppl.lba4
64. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA* (2016) 316:401–9. doi:10.1001/jama.2016.9839
65. Mahajan A, Ahmed S, McAleer MF, Weinberg JS, Li J, Brown P, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol* (2017) 18:1040–8. doi:10.1016/S1470-2045(17)30414-X
66. Brown PD, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Whitton AC, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol* (2017) 18:1049–60. doi:10.1016/S1470-2045(17)30441-2
67. Minniti G, Scaringi C, Paolini S, Lanzetta G, Romano A, Cicone F, et al. Single-fraction versus multifraction (3 x 9 Gy) stereotactic radiosurgery for large (>2 cm) brain metastases: a comparative analysis of local control and risk of radiation-induced brain necrosis. *Int J Radiat Oncol Biol Phys* (2016) 95:1142–8. doi:10.1016/j.ijrobp.2016.03.013
68. Yamamoto M, Serizawa T, Shuto T, Akabane A, Higuchi Y, Kawagishi J, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol* (2014) 15:387–95. doi:10.1016/S1470-2045(14)70061-0
69. Eberhardt WE, Mitchell A, Crowley J, Kondo H, Kim YT, Turrisi A III, et al. The IASLC lung cancer staging project: proposals for the revision of the M descriptors in the forthcoming eighth edition of the TNM classification of lung cancer. *J Thorac Oncol* (2015) 10:1515–22. doi:10.1097/JTO.0000000000000673
70. Rusthoven KE, Kavanagh BD, Burri SH, Chen C, Cardenes H, Chidel MA, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. *J Clin Oncol* (2009) 27:1579–84. doi:10.1200/JCO.2008.19.6386
71. De Rose F, Cozzi L, Navarria P, Ascolese AM, Clerici E, Infante M, et al. Clinical outcome of stereotactic ablative body radiotherapy for lung metastatic lesions in non-small cell lung cancer oligometastatic patients. *Clin Oncol (R Coll Radiol)* (2016) 28:13–20. doi:10.1016/j.clon.2015.08.011
72. Patel PR, Milano MT, Onaitis MW, Salama JK. Treatment considerations for synchronous primary NSCLC and oligometastatic disease. In: Bogart J, Detterbeck FC, editors. *Treatment of High-Risk Early Stage Lung Cancer*. New York, NY: Springer-Verlag (2015).
73. Ehrbar S, Perrin R, Peroni M, Bernatowicz K, Parkel T, Pytko I, et al. Respiratory motion-management in stereotactic body radiation therapy for lung cancer – a dosimetric comparison in an anthropomorphic lung phantom (LuCa). *Radiother Oncol* (2016) 121:328–34. doi:10.1016/j.radonc.2016.10.011

74. Almaghrabi MY, Supiot S, Paris F, Mahe MA, Rio E. Stereotactic body radiation therapy for abdominal oligometastases: a biological and clinical review. *Radiat Oncol* (2012) 7:126. doi:10.1186/1748-717X-7-126
75. Chong S, Lee KS, Kim HY, Kim YK, Kim BT, Chung MJ, et al. Integrated PET-CT for the characterization of adrenal gland lesions in cancer patients: diagnostic efficacy and interpretation pitfalls. *Radiographics* (2006) 26: 1811–24; discussion 1824–6. doi:10.1148/rg.266065057
76. Porte H, Siat J, Guibert B, Lepimpec-Barthes F, Jancovici R, Bernard A, et al. Resection of adrenal metastases from non-small cell lung cancer: a multicenter study. *Ann Thorac Surg* (2001) 71:981–5. doi:10.1016/S0003-4975(00)02509-1
77. Soffen EM, Solin LJ, Rubenstein JH, Hanks GE. Palliative radiotherapy for symptomatic adrenal metastases. *Cancer* (1990) 65:1318–20. doi:10.1002/1097-0142(19900315)65:6<1318::AID-CNCR2820650611>3.0.CO;2-H
78. Chance WW, Nguyen QN, Mehran R, Welsh JW, Gomez DR, Balter P, et al. Stereotactic ablative radiotherapy for adrenal gland metastases: factors influencing outcomes, patterns of failure, and dosimetric thresholds for toxicity. *Pract Radiat Oncol* (2016) 7:e195–203. doi:10.1016/j.prro.2016.09.005
79. Casamassima F, Livi L, Masciullo S, Menichelli C, Masi L, Meattini I, et al. Stereotactic radiotherapy for adrenal gland metastases: University of Florence experience. *Int J Radiat Oncol Biol Phys* (2012) 82:919–23. doi:10.1016/j.ijrobp.2010.11.060
80. Ippolito E, D'Angelillo RM, Fiore M, Molfese E, Trodella L, Ramella S. SBRT: a viable option for treating adrenal gland metastases. *Rep Pract Oncol Radiother* (2015) 20(6):484–90. doi:10.1016/j.rpor.2015.05.009
81. Kagohashi K, Satoh H, Ishikawa H, Ohtsuka M, Sekizawa K. Liver metastasis at the time of initial diagnosis of lung cancer. *Med Oncol* (2003) 20:25–8. doi:10.1385/MO:20:1:25
82. Rusthoven KE, Kavanagh BD, Cardenes H, Stieber VW, Burri SH, Feigenberg SJ, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol* (2009) 27:1572–8. doi:10.1200/JCO.2008.19.6329
83. Goodman BD, Mannina EM, Althouse SK, Maluccio MA, Cardenes HR. Long-term safety and efficacy of stereotactic body radiation therapy for hepatic oligometastases. *Pract Radiat Oncol* (2016) 6:86–95. doi:10.1016/j.prro.2015.10.011
84. Ahmed KA, Caudell JJ, El-Haddad G, Berglund AE, Welsh EA, Yue B, et al. Radiosensitivity differences between liver metastases based on primary histology suggest implications for clinical outcomes after stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* (2016) 95:1399–404. doi:10.1016/j.ijrobp.2016.03.050
85. Wu QJ, Thongphiew D, Wang Z, Chankong V, Yin FF. The impact of respiratory motion and treatment technique on stereotactic body radiation therapy for liver cancer. *Med Phys* (2008) 35:1440–51. doi:10.1118/1.2839095
86. Agarwala AK, Hanna NH. Long-term survival in a patient with stage IV non-small-cell lung carcinoma after bone metastasectomy. *Clin Lung Cancer* (2005) 6:367–8. doi:10.3816/CLC.2005.n.017
87. Ambrogi V, Nofroni I, Tonini G, Mineo TC. Skin metastases in lung cancer: analysis of a 10-year experience. *Oncol Rep* (2001) 8:57–61. doi:10.3892/or.8.1.57
88. Gerszten PC, Burton SA, Ozhasoglu C, Welch WC. Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution. *Spine (Phila Pa 1976)* 32(2007):193–9. doi:10.1097/01.brs.0000251863.76595.a2
89. Owen D, Laack NN, Mayo CS, Garces YI, Park SS, Bauer HJ, et al. Outcomes and toxicities of stereotactic body radiation therapy for non-spine bone oligometastases. *Pract Radiat Oncol* (2014) 4:e143–9. doi:10.1016/j.prro.2013.05.006
90. Flanigan RC, Mickisch G, Sylvester R, Tangen C, Van Poppel H, Crawford ED. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. *J Urol* (2004) 171:1071–6. doi:10.1097/01.ju.0000110610.61545.ae
91. Perez CA, Pajak TF, Rubin P, Simpson JR, Mohiuddin M, Brady LW, et al. Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. *Cancer* (1987) 59:1874–81. doi:10.1002/1097-0142(19870601)59:11<1874::AID-CNCR2820591106>3.0.CO;2-Z
92. Koshy M, Malik R, Mahmood U, Rusthoven CG, Sher DJ. Comparative effectiveness of aggressive thoracic radiation therapy and concurrent chemoradiation therapy in metastatic lung cancer. *Pract Radiat Oncol* (2015) 5:374–82. doi:10.1016/j.prro.2015.07.009
93. Stevens R, Macbeth F, Toy E, Coles B, Lester JF. Palliative radiotherapy regimens for patients with thoracic symptoms from non-small cell lung cancer. *Cochrane Database Syst Rev* (2015) 1:CD002143. doi:10.1002/14651858.CD002143.pub4
94. Li D, Zhu X, Wang H, Qiu M, Li N. Should aggressive thoracic therapy be performed in patients with synchronous oligometastatic non-small cell lung cancer? A meta-analysis. *J Thorac Dis* (2017) 9:310–7. doi:10.21037/jtd.2017.02.21
95. Li T, Lv J, Liu L, Song Y, Li C, Wang J. A phase II prospective study of definitive thoracic concurrent chemoradiation followed by consolidation chemotherapy for oligometastatic non-small cell lung cancer. *J Clin Oncol* (2015) 33(15_suppl):e19008. doi:10.1200/jco.2015.33.15_suppl.e19008
96. Gray PJ, Mak RH, Yeap BY, Cryer SK, Pinnell NE, Christianson LW, et al. Aggressive therapy for patients with non-small cell lung carcinoma and synchronous brain-only oligometastatic disease is associated with long-term survival. *Lung Cancer* (2014) 85:239–44. doi:10.1016/j.lungcan.2014.06.001
97. Xanthopoulos EP, Handorf E, Simone CB II, Grover S, Fernandes AT, Sharma S, et al. Definitive dose thoracic radiation therapy in oligometastatic non-small cell lung cancer: a hypothesis-generating study. *Pract Radiat Oncol* (2015) 5:e355–63. doi:10.1016/j.prro.2014.11.006
98. Hotta K, Matsuo K, Ueoka H, Kiura K, Tabata M, Tanimoto M. Role of adjuvant chemotherapy in patients with resected non-small-cell lung cancer: reappraisal with a meta-analysis of randomized controlled trials. *J Clin Oncol* (2004) 22:3860–7. doi:10.1200/JCO.2004.02.109
99. Cheung P. Stereotactic body radiotherapy for oligoprogressive cancer. *Br J Radiol* (2016) 89:20160251. doi:10.1259/bjr.20160251
100. Golden EB, Chhabra A, Chachoua A, Adams S, Donach M, Fenton-Kerimian M, et al. Local radiotherapy and granulocyte-macrophage colony-stimulatingfactor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial. *Lancet Oncol* (2015) 16:795–803. doi:10.1016/S1470-2045(15)00054-6
101. Shaverdian N, Lisberg AE, Bornazyan K, Veruttipong D, Goldman JW, Formenti SC, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. *Lancet Oncol* (2017) 18(7):895–903. doi:10.1016/S1470-2045(17)30380-7
102. Kroeze SG, Fritz C, Hoyer M, Lo SS, Ricardi U, Sahgal A, et al. Toxicity of concurrent stereotactic radiotherapy and targeted therapy or immunotherapy: a systematic review. *Cancer Treat Rev* (2017) 53:25–37. doi:10.1016/j.ctrv.2016.11.013
103. Bang A, Wilhite TJ, Pike LRG, Cagney DN, Aizer AA, Taylor A, et al. Multicenter evaluation of the tolerability of combined treatment with PD-1 and CTLA-4 immune checkpoint inhibitors and palliative radiation therapy. *Int J Radiat Oncol Biol Phys* (2017) 98:344–51. doi:10.1016/j.ijrobp.2017.02.003
104. Tang C, Liao Z, Gomez D, Levy L, Zhuang Y, Gebremichael RA, et al. Lymphopenia association with gross tumor volume and lung V5 and its effects on non-small cell lung cancer patient outcomes. *Int J Radiat Oncol Biol Phys* (2014) 89:1084–91. doi:10.1016/j.ijrobp.2014.04.025
105. Clarke JM, Wang X, Ready NE. Surrogate clinical endpoints to predict overall survival in non-small cell lung cancer trials – are we in a new era? *Transl Lung Cancer Res* (2015) 4:804–8. doi:10.3978/j.issn.2218-6751.2015.05.03
106. Salama JK, Hasselle MD, Chmura SJ, Malik R, Mehta N, Yenice KM, et al. Stereotactic body radiotherapy for multisite extracranial oligometastases: final report of a dose escalation trial in patients with 1 to 5 sites of metastatic disease. *Cancer* (2012) 118:2962–70. doi:10.1002/cncr.26611
107. Wong AC, Watson SP, Pitroda SP, Son CH, Das LC, Stack ME, et al. Clinical and molecular markers of long-term survival after oligometastasis-directed stereotactic body radiotherapy (SBRT). *Cancer* (2016) 122:2242–50. doi:10.1002/cncr.30058
108. Eke I, Makinde AY, Aryankalayil MJ, Ahmed MM, Coleman CN. Comprehensive molecular tumor profiling in radiation oncology: how it could

be used for precision medicine. *Cancer Lett* (2016) 382:118–26. doi:10.1016/j.canlet.2016.01.041

109. Daly ME, Monjazeb AM, Kelly K. Clinical trials integrating immunotherapy and radiation for non-small-cell lung cancer. *J Thorac Oncol* (2015) 10:1685–93. doi:10.1097/JTO.0000000000000686
110. Aggarwal A, Hughes S. Palliative radiotherapy: evolving role and policy challenges. *J Cancer Policy* (2016) 10:21–9. doi:10.1016/j.jcpo.2016.05.003
111. Kent EE, Forsythe LP, Yabroff KR, Weaver KE, de Moor JS, Rodriguez JL, et al. Are survivors who report cancer-related financial problems more likely to forgo or delay medical care? *Cancer* (2013) 119:3710–7. doi:10.1002/cncr.28262

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2017 Bergsma, Salama, Singh, Chmura and Milano. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

OPINION
published: 05 September 2017
doi: 10.3389/fonc.2017.00201

The Potential of Heavy-Ion Therapy to Improve Outcomes for Locally Advanced Non-Small Cell Lung Cancer

Stephen G. Chun[1], Timothy D. Solberg[2], David R. Grosshans[1], Quynh-Nhu Nguyen[1], Charles B. Simone II[3], Radhe Mohan[1], Zhongxing Liao[1], Stephen M. Hahn[1], Joseph M. Herman[1] and Steven J. Frank[1]*

[1]Department of Radiation Oncology, Division of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, United States, [2]Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, United States, [3]Maryland Proton Therapy Center, University of Maryland Baltimore, Baltimore, MD, United States

Keywords: carbon, heavy ion, locally-advanced lung cancer, hypofractionation, immune therapy

OPEN ACCESS

Edited by:
John Varlotto, UMass Memorial Medical Center, United States

Reviewed by:
John M. Holland, Oregon Health & Science University, United States

****Correspondence:***
Stephen G. Chun
sgchun@mdanderson.org

Specialty section:
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

Received: *31 July 2017*
Accepted: *21 August 2017*
Published: *05 September 2017*

Citation:
Chun SG, Solberg TD, Grosshans DR, Nguyen Q-N, Simone CB II, Mohan R, Liao Z, Hahn SM, Herman JM and Frank SJ (2017) The Potential of Heavy-Ion Therapy to Improve Outcomes for Locally Advanced Non-Small Cell Lung Cancer. Front. Oncol. 7:201. doi: 10.3389/fonc.2017.00201

The treatment of unresectable locally advanced non-small cell lung cancer (LA-NSCLC) remains a daunting challenge. To date, the best median survival achieved in a randomized prospective bi-modality clinical trial for LA-NSCLC is 28.7 months for patients who received standard chemo-radiotherapy on NRG Oncology RTOG 0617 (1). Emerging data from RTOG 0617 and other institutions have also implicated radiation dose to the heart as a driver of cardiovascular events, survival, and patient-reported quality of life (2–5). To improve survival and quality of life for LA-NSCLC, it is critical to explore emerging therapeutic technologies. One such technology is radiation therapy delivered with heavy ions, such as carbon ions. Heavy-ion therapy has both unique biological and physical advantages that may improve local control while also reducing radiation exposure to non-target organs at risk such as the heart. With the technology implemented at several Asian and European centers in conjunction with the planned development of several therapeutic heavy-ion centers in the United States, there will be real opportunity to exploit this technology to gain ground and improve the therapeutic ratio in LA-NSCLC.

LA-NSCLC is highly resistant to conventionally fractionated radiation therapy with cooperative group studies showing locoregional failure rates greater than 60% after definitive chemoradiation (6). From a radiation biology standpoint, there is considerable rationale to support use of heavy-ion therapy to improve local control for these patients. Upon encountering target tissue, interaction of charged heavy ions with matter yields the highest linear energy transfer (LET) of any currently available form of clinical radiation (7). This in turn results in unique clustered DNA lesions, resulting in a lower oxygen enhancement ratio and higher relative biological effectiveness (RBE) that is on the order of threefold greater than photon radiotherapy (7). Early preclinical data have also suggested tumors with EGFR mutation may be more susceptible to heavy-ion therapy than photon irradiation, suggesting that heavy-ion therapy may provide opportunities to further tailor radiation therapy in the heterogeneous genetic landscape of LA-NSCLC (8). Taken together, these properties suggest that heavy ions could improve local control by overcoming DNA repair pathways that confer radiation resistance and provide patient-tailored options for LA-NSCLC.

The physical properties of heavy-ion therapy also provide dosimetric advantages for LA-NSCLC (9). With particle therapy, the energy deposited in tissue increases with depth eventually coming to an abrupt stop, known as the Bragg peak. Using particles, practitioners have the ability to stop the dose deposition at a specified point, reducing or eliminating exposure to tissues distal to the target volumes. These advantages are particularly relevant to recent findings in RTOG 0617 where the importance of radiation conformity to prevent pneumonitis and reduce cardiac doses has been

established (10, 11). Just as proton therapy can reduce cardiac doses in comparison to photon therapy (12), heavy ions also have the potential to further reduce cardiac and pulmonary doses (9, 13). First, the Bragg Peak can reduce radiation doses distal to the target to a far greater degree than photon irradiation. Second, heavy ions exhibit less scattering than protons because of their mass, resulting in a sharper lateral penumbra than proton or photon radiotherapy. Third, pencil beam scanning and arc technologies are expected to provide unprecedented geometric avoidance of non-target organs at risk. The combination of these physical advantages with motion management and Monte Carlo algorithms for plan optimization has potential to produce dramatic improvements in the conformity of the high, intermediate, and low dose regions. While proton therapy exhibits some of these characteristics such as the Bragg Peak, proton therapy has more lateral scattering and lacks the LET of heavy-ion therapy.

In the era of anti-PD-1-/PDL-1-targeted therapies, another important biological advantage of heavy-ion therapy is its potential immunostimulatory effects. While radiation therapy is known to have complex reactions with the immune system and tumor microenvironment, heavy ions have may have unique immune effects that are distinct from photons or proton therapy. Because of their high LET and RBE, preclinical evidence suggests that heavy ions induce non-apoptotic cell death that is independent of the typical p53, bax/bcl, and p21 signal transduction cascades (14, 15). These alternative forms of cell death could provide more diverse tumor epitopes for cytotoxic T-cells to prime immune responses. Another immunological advantage of heavy-ion therapy stems from the unique physical properties discussed earlier. Reducing low and intermediate dose exposure has the potential to reduce integral dose that can cause lymphopenia and hematologic toxicity (16–18). In RTOG 0617, Grade 3+ hematological toxicity was observed in 56% of patients with only one-third of patients completing consolidative chemotherapy (1), highlighting the need to reduce the myelosuppressive effects of definitive chemoradiotherapy. Thus, by reducing lymphopenia from exposure of circulating lymphocytes and also stimulating the local production of immunological epitopes, heavy-ion therapy might be a potent weapon to illicit *in situ* vaccine responses.

Conventionally fractionated radiation therapy as a single modality has dismal cure rates (19), and the primary benefit of concurrent chemotherapy in historic combined modality trials has been to improve local control (20–22), which comes at the cost of myelosuppression, esophagitis, and peripheral neuropathy in LA-NSCLC. However, heavy-ion therapy can deliver doses to tumor targets with greater potency than concurrent chemoradiation without the systemic side effects of chemotherapy. This raises the question of whether heavy-ion therapy can obviate the need for concurrent cytotoxic therapy. Concurrent chemotherapy has significant downsides including high rates of severe esophagitis and immunosuppression. A Phase I–II of carbon ion therapy for patients with LA-NSCLC who were medically unfit to receive concurrent chemotherapy from the Research Institute for Charged Particle Therapy in Chiba, Japan showed promising results (23). In this study, dose was escalated from 68 to 72 cobalt Gy equivalents without dose limiting toxicity. Oncological outcomes were also favorable with a 2-year local control rate of 93.1% and overall survival of 51.9%. There has also been success using carbon ion therapy without cytotoxic chemotherapy for medically inoperable early-stage NSCLC (13, 24–26). Exploration of heavy-ion technology as a strategy to avoid concurrent cytotoxic chemotherapy should be encouraged as a way to reduce toxicities and health-care costs for patients without compromising oncological efficacy.

Currently used fractionation schedules for carbon therapy differ greatly from standard photon techniques. Given differential biological effects on tumors normal tissues as a function of dose per fraction, hypofractionated approaches are commonplace in the practice of heavy-ion therapy. The use of hypofractionated treatment schedules may allow for a greater number of patients to be treated at select centers at a reduced cost. Coupled with the potential for reduced toxicity and improved outcomes, this could make heavy-ion therapy a cost effective treatment, despite the high upfront costs of building such facilities likely on the order of $200–300 million (USD).

As the number of heavy-ion therapy centers is expected to increase in the United States in the coming years, there will be opportunity to explore its role for LA-NSCLC. We have outlined rationale for robust exploration of heavy-ion therapy in LA-NSCLC for the purpose of improving what are presently suboptimal outcomes in this population.

AUTHOR CONTRIBUTIONS

All authors have contributed to conceptualization and writing of this manuscript.

REFERENCES

1. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* (2015) 16(2):187–99. doi:10.1016/S1470-2045(14)71207-0
2. Movsas B, Hu C, Sloan J, Bradley J, Komaki R, Masters G, et al. Quality of life analysis of a radiation dose-escalation study of patients with non-small-cell lung cancer: a secondary analysis of the radiation therapy oncology group 0617 randomized clinical trial. *JAMA Oncol* (2016) 2(3):359–67. doi:10.1001/jamaoncol.2015.3969
3. Guberina M, Eberhardt W, Stuschke M, Gauler T, Heinzelmann F, Cheufou D, et al. Heart dose exposure as prognostic marker after radiotherapy for resectable stage IIIA/B non-small-cell lung cancer: secondary analysis of a randomized trial. *Ann Oncol* (2017) 28(5):1084–9. doi:10.1093/annonc/mdx069
4. Wang K, Eblan MJ, Deal AM, Lipner M, Zagar TM, Wang Y, et al. Cardiac toxicity after radiotherapy for stage III non-small-cell lung cancer: pooled analysis of dose-escalation trials delivering 70 to 90 Gy. *J Clin Oncol* (2017) 35(13):1387–94. doi:10.1200/JCO.2016.70.0229
5. Dess RT, Sun Y, Matuszak MM, Sun G, Soni PD, Bazzi L, et al. Cardiac events after radiation therapy: combined analysis of prospective multicenter trials for locally advanced non-small-cell lung cancer. *J Clin Oncol* (2017) 35(13):1395–402. doi:10.1200/JCO.2016.71.6142

6. Machtay M, Paulus R, Moughan J, Komaki R, Bradley JE, Choy H, et al. Defining local-regional control and its importance in locally advanced non-small cell lung carcinoma. *J Thorac Oncol* (2012) 7(4):716–22. doi:10.1097/JTO.0b013e3182429682
7. Durante M, Loeffler JS. Charged particles in radiation oncology. *Nat Rev Clin Oncol* (2010) 7(1):37–43. doi:10.1038/nrclinonc.2009.183
8. Amornwichet N, Oike T, Shibata A, Nirodi CS, Ogiwara H, Makino H, et al. The EGFR mutation status affects the relative biological effectiveness of carbon-ion beams in non-small cell lung carcinoma cells. *Sci Rep* (2015) 5: 11305. doi:10.1038/srep11305
9. Kubo N, Saitoh JI, Shimada H, Shirai K, Kawamura H, Ohno T, et al. Dosimetric comparison of carbon ion and X-ray radiotherapy for stage IIIA non-small cell lung cancer. *J Radiat Res* (2016) 57(5):548–54. doi:10.1093/jrr/rrw041
10. Chun SG, Hu C, Choy H, Komaki RU, Timmerman RD, Schild SE, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: a secondary analysis of the NRG oncology RTOG 0617 randomized clinical trial. *J Clin Oncol* (2017) 35(1):56–62. doi:10.1200/JCO.2016.69.1378
11. Chun SG, Hu C, Bradley JD. Reply to D. Ball et al. *J Clin Oncol* (2017) 35(13):1493–4. doi:10.1200/JCO.2016.71.5755
12. Tucker SL, Liu A, Gomez D, Tang LL, Allen P, Yang J, et al. Impact of heart and lung dose on early survival in patients with non-small cell lung cancer treated with chemoradiation. *Radiother Oncol* (2016) 119(3):495–500. doi:10.1016/j.radonc.2016.04.025
13. Shirai K, Kawashima M, Saitoh JI, Abe T, Fukata K, Shigeta Y, et al. Clinical outcomes using carbon-ion radiotherapy and dose-volume histogram comparison between carbon-ion radiotherapy and photon therapy for T2b-4N0M0 non-small cell lung cancer-A pilot study. *PLoS One* (2017) 12(4):e0175589. doi:10.1371/journal.pone.0175589
14. Durante M, Brenner DJ, Formenti SC. Does heavy ion therapy work through the immune system? *Int J Radiat Onco Biol Phys* (2016) 96(5):934–6. doi:10.1016/j.ijrobp.2016.08.037
15. Loeffler JS, Durante M. Charged particle therapy – optimization, challenges and future directions. *Nat Rev Clin Oncol* (2013) 10(7):411–24. doi:10.1038/nrclinonc.2013.79
16. Yovino S, Kleinberg L, Grossman SA, Narayanan M, Ford E. The etiology of treatment-related lymphopenia in patients with malignant gliomas: modeling radiation dose to circulating lymphocytes explains clinical observations and suggests methods of modifying the impact of radiation on immune cells. *Cancer Invest* (2013) 31(2):140–4. doi:10.3109/07357907.2012.762780
17. Pignalosa D, Lee R, Hartel C, Sommer S, Nikoghosyan A, Debus J, et al. Chromosome inversions in lymphocytes of prostate cancer patients treated with X-rays and carbon ions. *Radiother Oncol* (2013) 109(2):256–61. doi:10.1016/j.radonc.2013.09.021
18. Tang C, Liao Z, Gomez D, Levy L, Zhuang Y, Gebremichael RA, et al. Lymphopenia association with gross tumor volume and lung V5 and its effects on non-small cell lung cancer patient outcomes. *Int J Radiat Oncol Biol Phys* (2014) 89(5):1084–91. doi:10.1016/j.ijrobp.2014.04.025
19. Perez CA, Pajak TF, Rubin P, Simpson JR, Mohiuddin M, Brady LW, et al. Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. *Cancer* (1987) 59(11):1874–81. doi:10.1002/1097-0142(19870601)59:11<1874::AID-CNCR2820591106>3.0.CO;2-Z
20. Curran WJ Jr, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst* (2011) 103(19):1452–60. doi:10.1093/jnci/djr325
21. Belani CP, Choy H, Bonomi P, Scott C, Travis P, Haluschak J, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol* (2005) 23(25):5883–91. doi:10.1200/JCO.2005.55.405
22. Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* (1999) 17(9):2692–9. doi:10.1200/JCO.1999.17.9.2692
23. Takahashi W, Nakajima M, Yamamoto N, Yamashita H, Nakagawa K, Miyamoto T, et al. A prospective nonrandomized phase I/II study of carbon ion radiotherapy in a favorable subset of locally advanced non-small cell lung cancer (NSCLC). *Cancer* (2015) 121(8):1321–7. doi:10.1002/cncr.29195
24. Miyamoto T, Yamamoto N, Nishimura H, Koto M, Tsujii H, Mizoe JE, et al. Carbon ion radiotherapy for stage I non-small cell lung cancer. *Radiother Oncol* (2003) 66(2):127–40. doi:10.1016/S0167-8140(02)00367-5
25. Miyamoto T, Baba M, Sugane T, Nakajima M, Yashiro T, Kagei K, et al. Carbon ion radiotherapy for stage I non-small cell lung cancer using a regimen of four fractions during 1 week. *J Thorac Oncol* (2007) 2(10):916–26. doi:10.1097/JTO.0b013e3181560a68
26. Iwata H, Demizu Y, Fujii O, Terashima K, Mima M, Niwa Y, et al. Long-term outcome of proton therapy and carbon-ion therapy for large (T2a-T2bN0M0) non-small-cell lung cancer. *J Thorac Oncol* (2013) 8(6):726–35. doi:10.1097/JTO.0b013e318288ab02

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2017 Chun, Solberg, Grosshans, Nguyen, Simone, Mohan, Liao, Hahn, Herman and Frank. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

REVIEW
published: 11 August 2017
doi: 10.3389/fonc.2017.00169

Radiation Therapy in Extensive Stage Small Cell Lung Cancer

Branislav Jeremic[1], Antonio Gomez-Caamano[2], Pavol Dubinsky[3], Nikola Cihoric[4], Franesc Casas[5] and Nenad Filipovic[1]*

[1] BioIRC Centre for Biomedical Research, BioIRC, Kragujevac, Serbia, [2] Hospital Clínico Universitario, Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain, [3] East Slovakia Institute of Oncology, Louis Pasteur University Hospital, Kosice, Slovakia, [4] Department of Radiation Oncology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland, [5] Hospital Clínic de Barcelona, Barcelona, Spain

Lung cancer is the major cancer killer in the Western world, with the small cell lung cancer (SCLC) representing around 15–20% of all lung cancers. Extensive disease small cell lung cancer (ED SCLC) is found in approximately two-thirds of all cases, composed of both metastatic (M1) and non-metastatic (but presumably with tumor burden too large for locoregional-only approach) variant. Standard treatment options involve chemotherapy (CHT) over the past several decades. Radiation therapy (RT) had mostly been used in palliation of locoregional and/or metastatic disease. In contrast to its established role in treating metastatic disease, thoracic RT (TRT) had never been established as important part of the treatment aspects in this setting. In the past two decades, thoracic oncologists have witnessed wide introduction of modern RT and CHT aspects in ED SCLC, which led to more frequent use of RT and rise in the number of clinical studies. Since the pivotal study of Jeremic et al., who were the first to show importance of TRT in ED SCLC, a number of single-institutional studies have reconfirmed this observation, while recent prospective randomized trials (CREST and RTOG 0937) brought more substance to this issue. Similarly, the issue of prophylactic cranial irradiation was investigated in EORTC and the Japanese study, respectively, bringing somewhat conflicting results and calling for additional research in this setting. Future studies in ED SCLC could incorporate questions of RT dose and fractionation as well as the number of CHT cycles and type of combined Rt-CHT (sequential vs concurrent).

Keywords: extensive disease, small cell lung cancer, thoracic radiotherapy, chemotherapy, prophylactic cranial irradiation

OPEN ACCESS

Edited by:
John Varlotto, University of Massachusetts Medical School, United States

Reviewed by:
John Austin Vargo, West Virginia University Hospitals, United States
Nitin Ohri, Albert Einstein College of Medicine, United States

****Correspondence:***
Branislav Jeremic
nebareje@gmail.com

Specialty section:
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

Received: *05 July 2017*
Accepted: *26 July 2017*
Published: *11 August 2017*

Citation:
Jeremic B, Gomez-Caamano A, Dubinsky P, Cihoric N, Casas F and Filipovic N (2017) Radiation Therapy in Extensive Stage Small Cell Lung Cancer. Front. Oncol. 7:169. doi: 10.3389/fonc.2017.00169

INTRODUCTION

Lung cancer is the major cancer killer in the Western world (1), with the small cell lung cancer (SCLC) representing around 15–20% of all lung cancers (2). While its incidence is declining in men, it continues to rise in women (3). In spite of significant efforts and refinements in staging system (4), division by "extensiveness" of the disease is still widely used. Extensive disease small cell lung cancer (ED SCLC) is found in approximately two-thirds of all cases, composed of both metastatic (M1) and non-metastatic (but presumably with tumor burden too large for locoregional-only approach) variant. Standard treatment options involve chemotherapy (CHT) over the past several decades (5). Various efforts to optimize treatment outcome with CHT, such as maintenance CHT or higher CHT doses unequivocally failed (6–10). With CHT, the median survival times (MST) are 9–12 months, while 5-year survivals of only 1–2% (9, 11–13).

Radiation therapy (RT) had mostly been used in palliation of locoregional and/or metastatic disease. In contrast to its established role in treating metastatic disease, thoracic RT (TRT) had never been established as important part of the treatment aspects in this setting. This was largely due to conflicting reports in the past several decades about its usefulness in controlling intrathoracic tumor burden (14–17), and predominantly metastatic nature of the disease. It is likely that inferior diagnostic and staging tool as well as outdated RT and CHT aspects such as 2D RT planning, modest RT doses, and non-platinum-based CHT significantly contributed to poor RT performance in this setting.

THORACIC RT

In the past two decades, thoracic oncologists have witnessed wide introduction of modern RT (3D planning, altered RT fractionation) and CHT (platinum-based) aspects in ED SCLC. This has resulted in more frequent use of RT and, importantly, rise in the number of clinical studies addressing the issue of optimization of treatment approaches by focusing on important aspects of RT.

The turning point in the history of modern treatment of ED SCLC occurred with the publication of seminal paper of Jeremic et al. (13) in 1999. It was the very first study which tested, in a prospective randomized Phase III fashion, standard treatment option (CHT) vs CHT and TRT, with a prophylactic cranial irradiation (PCI) given in both arms. This trial was based on observations from the past studies that, in ED SCLC, there were frequent intrathoracic failures, which also frequently occur even in patients who achieved initial complete response (CR) after CHT. Hence, study of Jeremic et al. (13) had its premises in the following: (1) significant proportion of patients with ED SCLC experience intrathoracic (locoregional) treatment failure, which cannot be successfully treated with second line CHT, (2) these failures may also become the source of subsequent metastatic disease (in patients with previous non-metastatic ED SCLC) and lead to death, (3) TRT could control intrathoracic tumor burden, (4) if successful, this may lead to improved and prolonged intrathoracic tumor control, and, if significant, may lead to an improvement in overall survival. Ultimate question, overshadowing all these considerations was: which subgroup of patients may have been suitable for testing the place and role of TRT in ED SCLC.

In the Jeremic trial (13), subjects were adult treatment-naive patients with good PS and biopsy-proven ED SCLC. All patients initially received three cycles of standard-dose cisplatin/etoposide (PE) regimen, after which complete patient reevaluation and restaging was performed both at local (intrathoracic) and the distant level. Randomization included only patients who achieved either a CR at both local and distant level, labeled as CR/CR or those who achieved a partial response (PR) within the thorax accompanied with the CR elsewhere (labeled as PR/CR). They received either accelerated hyperfractionated RT (Acc Hfx RT) and concurrent low-dose daily CHT, given on each RT day, followed by PCI, and then by additional two cycles of PE (group I) or four additional cycles of PE and PCI (Group II). Patients achieving worse response were not randomized. Total tumor dose was 54 Gy in 36 fractions, 1.5 Gy BID, while PCI dose was 25 Gy in 10 daily fractions. When deemed appropriate, palliative RT was given to patients with metastatic lesions with 30 Gy in 10 daily fractions.

A total of 210 patients entered this study. TRT added to CHT offered superior outcome over CHT alone in terms of both the MST and 5-year survival rates [17 vs 11 months ($p = 0.041$), and 9.1 and 3.7%, respectively]. Similar was observed for the local recurrence-free survival (the median time to local recurrence, 30 vs 22 months, and 5-year local recurrence-free survival, 20 vs 8.1%, respectively; $p = 0.062$), but RT added to CHT did not offer better distant metastasis-free survival ($p = 0.35$).

To enlighten the effects of TRT on local (intrathoracic) level, local CR rates were evaluated after three cycles of induction CHT at week 9 (i.e., just before the randomization), week 15 (i.e., when either Acc Hfx RT/CE in group I or 2 additional cycles of PE in group II were administered), and at week 21 (2 more cycles of CHT in each group). Local CR rate was similar after 9 weeks (47 vs 44%, $p = 0.77$), but after week 15, the local CR rate became significantly higher in group I than in group II (96 vs 61%, $p = 0.000007$). This was maintained at week 21 (96 and 66% for the two groups, respectively; $p = 0.00005$). Therefore, fourth and the fifth cycles of CHT barely improved response in group I once Acc Hfx RT/CE had been given. Similarly, the sixth and seventh cycles of PE in group II brought only a few percent increase in response rates. What these results imply is that perhaps one may not need more than 3–4 CHT cycles in this patient population, possible food for thoughts for future trials.

Jeremic et al. (13) were the first to show that TRT plays indispensible role in the treatment of patients with ED SCLC after initial CHT. Beside primary study endpoints, an analysis of various pretreatment prognostic factors showed that higher KPS score and no significant weight loss were strong prognosticators of improved treatment outcome. As a potential guide for future studies, the number of metastases independently influenced survival. It was shown that metastatic tumor burden should be taken into account since patients with ≥2 metastases had significantly worse outcome than those with only one metastasis. Since approximately 90% of all patients in the study of Jeremic et al. (13) had 1–2 metastases, subsequent discussions in this field frequently labeled this disease extent as *limited extensive disease*.

Overall impact of the study of Jeremic et al. (13) was not easy to comprehend in the years following its publication. However, 10 years after its publication, the study of Ou et al. (18) retrospectively analyzed the data from several counties in southern California with estimated population of 6.2 million. Of a total of 3,428 ED SCLC patients, RT was given to 1,204 (35.1%) patients. For this group, the 2-year, and MST were 9.3%, and 8 months, respectively, being significantly better than in those who did not receive RT (3.8%, and 4 months, respectively; $p < 0.0001$). Analysis of prognostic factors showed that delivered RT exerted independent and positive influence of on treatment outcome ($p < 0.001$).

A recent survey of 473 practicing US radiation oncologist attempted to identify the current pattern of practice of TRT in ED SCLC (19). In spite of great variation in the patient selection and doses of RT used, TRT was recommended after systemic CHT by 96% of the respondents. The type of the institution influenced

the decision with patients treated in private clinics being more likely to receive TRT than patients treated at academic centers ($p = 0.0101$). Interestingly, lower TRT recommended doses were associated with respondents claiming higher self-rated knowledge of individual clinical trials.

Past several years also brought studies that investigated the same issue. In a prospective study from Canada (20), the median time to disease progression was 8.4 months and the MST was 13.7 months. Additionally, two single-institutional, retrospective studies showed the same. In the Chinese study (21), for TRT-treated group MST was 17.2 months, and 5-year survival was 10.1%, respectively ($p = 0.0001$), while another Canadian study (22) reported on MST of 14 months and 2-year survival of 14% for TRT/CHT treatment.

Recently, in an EORTC (23) prospective phase III study patients with World Health Organization PS of 0 to 2 and confirmed ED SCLC without clinical evidence of brain, leptomeningeal, or pleural metastases, who achieved any response to 4–6 cycles of PE were treated with either TRT (30 Gy in 10 fractions) or no TRT, while all patients receiving PCI. Overall survival was longer in the TRT arm ($p = 0.066$), whereas 12-, 18-, and 24-month survival rates in the 2 arms were 33, 16, and 13% vs 28, 16, and 3%, respectively. Although the trial was negative for the primary endpoint of 1-year overall survival, significance was achieved at 18 months ($p = 0.03$) and was maintained at 24 months ($p = 0.004$). MST from the time of randomization was 8 months, but when calculated from diagnosis, it was 12 months. Progression-free survival was longer in the TRT arm ($p = 0.001$). Intrathoracic progression (isolated or accompanied by progression elsewhere or as the first site of disease progression) was seen less frequently in the TRT arm. Almost a 50% reduction in intrathoracic recurrences (80 vs 44%, respectively; $p = 0.001$) was observed.

Although EORTC study (23) characteristics (study design, patient eligibility, treatments offered) differed from those of Jeremic et al. (13) (**Table 1**), it is tempting to discuss and compare the two studies (**Table 2**) in order to obtain better perspective for future studies planning and execution. EORTC study (23) reconfirmed the importance of local control as initially suggested by Jeremic et al. (13). However, more intensive TRT given with concurrent CHT in a shorter OTT in the study of Jeremic et al. (13) may have led to faster improvement in local control which, in turn, may have led to faster improvement in the overall survival. More intensive tumor cell kill was accompanied with somewhat higher incidence of acute toxicity, which in both studies was acceptable and, in the study of Jeremic et al. (13), only high-grade acute esophageal toxicity was significantly more frequent in the TRT group. What this attempted comparison hints at is the large gap in both the patients' and the treatment aspects when considering the two studies' characteristics (13, 23) perhaps being at the two extremes, hence the necessity to fill in the existing gap with more clinical research.

One such attempt have been materialized in the Radiation Therapy Oncology Group study 0937 (24) during which patients with 1–4 extracranial metastases were deemed eligible after achieving either CR or PR to initial CHT. Patients received either PCI alone or PCI + TRT to the thorax and metastases. PCI was given with 25 Gy in 10 daily fractions in 2 weeks, while TRT was given with 45 Gy in 15 daily fractions in 3 weeks. Between March 2010 and February 2015, a total of 86 patients were randomized. The study crossed the futility boundary for OS and was closed at planned interim analysis prior to meeting accrual target. With the median follow-up of 9 months, 1-year overall survival was similar between the groups: 60.1% (95% CI: 41.2–74.7%) for PCI and 50.8% (95% CI: 34.0–65.3%) for PCI + + TRT ($p = 0.21$). Three and 12-month rates of progression were 53.3 and 79.6% for PCI, and 14.5 and 75% for PCI + TRT. Time to progression favored PCI + TRT ($p = 0.01$). Not to be forgotten, there were some imbalances in the two groups, which might better explain the negative results for overall survival despite improvements in thoracic control, including the higher number of patients with PR vs CR to CHT and 2–4 vs 1 metastases in the group receiving RT. Treatment-related toxicity was also similar between the two arms. The authors concluded that overall survival exceeded predictions for both arms with the consolidative RT delaying progression but not improving the 1-year overall survival.

Although this trial will definitely be seen as a negative trial, it brought several important findings. The first site of failure after CHT is likely to be in sites of presenting disease; RT to these sites

TABLE 1 | Patient and treatment characteristics.

Issue	Jeremic et al.	CREST
Less favorable patients (PS2)	0%	10%
Initial (pre-randomization) CHT	3 cycles	6 cycles
TRT (dose/fx)	54 Gy/36fx BID—Hyperfx	30 Gy/10fx QD—Hypofx
CHT-TRT	CHT followed by concurrent TRT-CHT	CHT followed by TRT (no concurrent part)
PCI—TRT	PCI followed TRT-CHT	Concurrent in almost 90% pts

CHT, chemotherapy; TRT, thoracic radiotherapy; fx, fraction; BID, hyperfractionation (2 fx a day); QD, conventional fractionation (1 fx a day); PCI, prophylactic cranial irradiation.

TABLE 2 | Outcomes.

Issue	Jeremic et al.	CREST	Comments
Importance of improved LC	Yes	Yes	Leads to improved OS
Tempo of achieving improvement of LC	Faster	Slower	Leads to a faster improvement of OS in Jeremic et al.
OTT	Shorter	Longer	Possible due to better patient characteristics in Jeremic et al.
Incidence of high-grade toxicity	5% (lung) 20% (esophagus)	1.2% (lung) 1.6% (esophagus)	Higher TRT doses and concurrent CHT in Jeremic et al.
Duration of CHT	Shorter	Longer	Shorter appropriate in favorable patients?

LC, local control; OS, overall survival; OTT, overall treatment time; TRT, thoracic radiotherapy; CHT, chemotherapy.

alters failure patterns; late RT without concurrent CHT is not durable; and, oligometastatic ED SCLC survival seems to again approach that of LD SCLC, confirming the postulates and results of Jeremic et al. (13). Ineffective RT dose and schedule, advanced age, and an imbalance in disease burden in the two groups all likely contributed to lack of survival advantage with consolidative RT in this trial. In addition, considering all trial aspects, authors suggested that perhaps a more appropriate treatment for this patient population with low volume systemic disease could have been early RT concurrent with cycle three or four of CHT in patients with a favorable response to cycles one and two of CHT followed by PCI, similar to the Jeremic trial (13).

PROPHYLACTIC CRANIAL IRRADIATION

Contrary to the place and role of PCI in limited disease SCLC, where several PRCTs and MAs exist, in ED SCLC data concerning it is much more limited. A large PRCT of EORTC included responders to 4–6 cycles of CHT (25). In this trial, patients were randomized to receive either PCI (20 Gy in 5 daily fractions or 30 Gy in 12 daily fractions) or observation. PCI offered significantly lower cumulative risk of brain metastasis at 1-year (14.8 vs 40.4%, $p < 0.001$), which led to an improvement in the progression-free survival (14.7 vs 12 weeks, respectively, $p = 0.02$). Finally, PCI led to an improvement in 1-year overall survival (27 vs 13%, respectively, $p = 0.003$) as a consequence of improved CNS control.

The same EORTC trial (25, 26) collected self-reported patient data using both Quality of Life Questionnaire C30 and Quality of Life Questionnaire Brain Cancer Module while investigating the effect of PCI on quality of life (QoL). In the first report, side-effects of PCI, including fatigue and hair loss, were significantly more severe in the group of patients receiving PCI (25). However, no significant differences were seen in the remaining endpoints. Importantly, in a subsequent report, there was a limited effect of PCI on these factors, none reaching the level of clinical significance as (26). Severe worsening in global health status (35 vs 22%) from base line up to 3 months was observed in the PCI group; however, one must not forget that there was a 94% participation rate at baseline, followed by poor compliance during the follow-up (60 and 55% at 6 weeks and 3 months, respectively). However, the control arm was significantly superior when an exploratory analysis of other symptom scale factors was performed.

These results have profoundly influenced the practice of RT in ED SCLC as PCI was overwhelmingly accepted as standard of treatment in this setting (5, 27). However, fresh data from a Japanese trial (28) seem to question that, in that trial, patients with any response to platinum-based doublet CHT and no brain metastases on MRI received PCI (25 Gy in 10 fractions) or observation. All patients were required to have brain MRI at 3-month intervals up to 12 months and at 18 and 24 months after enrollment. The primary endpoint was overall survival. 224 patients were randomly assigned. In the planned interim analysis, of the first 163 enrolled patients, Bayesian predictive probability of PCI being superior to observation was 0.011%, resulted in early termination of the study because of futility. In the final analysis, the MST was 11.6 months in the PCI group and 13.7 months in the observation group ($p = 0.094$). The most frequent grade ≥3 adverse events at 3 months were anorexia, malaise, and muscle weakness in lower limbs, which were all similar between the two groups. No treatment-related deaths occurred in either group.

While the Japanese study (28) reconfirmed the importance of CNS metastasis control, it failed to observe its influence on overall survival. Except, perhaps, fewer patients in that study, other possible reasons may exist as explanations for the existing discrepancy between Japanese (28) and EORTC (25) study. Japanese patients with ED SCLC were enrolled after they had been confirmed not to have brain metastases by MRI before randomization. By contrast, in the EORTC study (25), brain imaging at diagnosis was available in only 29% of randomized patients, while the proportion of patients who had brain imaging just before randomization was not stated. It is also very likely that in the EORTC study (25), some randomized patients actually had asymptomatic brain metastases before randomization since mandatory staging and follow-up procedures did not include brain imaging unless suggestive clinical symptoms were present. The longer overall survival reported by the EORTC study (25) in the PCI group might have reflected responses of asymptomatic brain metastases that had already been present before randomization. Although observation group encountered higher incidence of brain metastases than the PCI group in the Japanese trial (28), this did not result in shorter survival in the observation group, which contrasts EORTC study (25) findings. Possible explanation for this difference may be in difference in the proportion of patients who received subsequent treatment. Eighty-eight percent of patients in the PCI group and 89% of patients in the observation group received second-line CHT, however, more patients in the observation group received third-line or fourth-line CHT than did those in the PCI group. Additionally, in the Japanese study (28), anorexia, nausea, and malaise, which could be caused by CHT, were frequent and severe in patients in the PCI group beyond 3 months after randomization. The persistence of these adverse events, and the resultant impairment in QoL during subsequent CHT, might have decreased the feasibility and tolerability of such treatment in the PCI group in that study. The PCI group and the observation group had similar overall survival probably because of this decreased feasibility and tolerability. Also, the higher frequency of brain metastases seen in Japanese study (28) is mainly attributable to the detection of asymptomatic brain metastases by MRI. Not to be forgotten, the difference in the proportions of patients who had subsequent therapy between the two studies is presumably because some patients with symptomatic brain metastases in the control group of the EORTC study (25) would not have had subsequent CNS RT or CHT because of deterioration in their general condition, whereas patients with asymptomatic brain metastases detected by MRI in the CREST study did receive both CNS RT and subsequent CHT. Finally, the patients in the PCI group had more liver metastases, likely negatively to influence overall survival. Considering the impact of two studies on daily clinical practice, one may perhaps conclude that the Japanese study (28) may now slightly erode the firm position PCI had had in the past several years since the publication of the EORTC study (25) as "non-believers" would now how have somewhat stronger rationale

against the use of PCI. It is reasonable to expect that these results would call for additional studies with more uniform diagnostic and follow-up criteria, including precise documentation of QoL aspects, which must take into account therapy administered at the time of CNS progression.

FUTURE TASKS

Research interests in the field of ED SCLC seem to have been revived in the past decade, after a dry decade post-Jeremic trial (13). Both PRCTs and single-institutional studies clearly show that thoracic oncologists understood the implication of the Jeremic trial (13). Indeed, in spite of CREST (23) and RTOG0937 (24) controversies, more emphasis is and will be made on the place and role of RT in this setting, including employment of modern RT technologies (29). Future studies should address important RT-related (optimal TRT and extrathoracic RT dose/fractionation and its timing) and CHT-related questions (number of cycles and its concurrent vs sequential administration). They may include, but are not limited to the following: palliative vs curative TRT dose; sequential vs concurrent RT-CHT; concurrent RT-CHT at cycle 3 vs concurrent RT-CHT at cycle 5; total of 4 vs total of 6 cycles of CHT.

AUTHOR CONTRIBUTIONS

Study design: BJ. Drafting of manuscript: BJ, AG-C, PD, NC, FC, and NF. Major revision of the manuscript, and final critique of the manuscript: BJ, AG-C, PD, NC, FC, and NF. Finalization of manuscript: BJ.

FUNDING

This study was funded by the grants from the Serbian Ministry of Education, Science and Technological Development III41007, ON174028.

REFERENCES

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. *Lancet* (2012) 380:2095–128. doi:10.1016/S0140-6736(12)61728-0
2. Houston KA, Henley SJ, Li J, White MC, Richards TB. Patterns in lung cancer incidence rates and trends by histologic type in the United States, 2004–2009. *Lung Cancer* (2014) 86:22–8. doi:10.1016/j.lungcan.2014.08.001
3. Howlader N, Noone AM, Krapcho M. *SEER Cancer Statistics Review, 1975–2010*. Bethesda, MD: National Cancer Institute (2013).
4. Nicholson AG, Chansky K, Crowley J, Beyruti R, Kubota K, Turrisi A, et al. The international association for the study of lung cancer lung cancer staging project: proposals for the revision of the clinical and pathologic staging of small cell lung cancer in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol* (2015) 11:300–11. doi:10.1016/j.jtho.2015.10.008
5. Früh M, De Ruysscher D, Popat S, Crinò L, Peters S, Felip E, et al. Small-cell lung cancer (SCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* (2013) 24(Suppl 6):vi99–105. doi:10.1093/annonc/mdt178
6. Splinter TAW. Chemotherapy of small cell lung cancer (SCLC): duration of treatment. *Lung Cancer* (1989) 5:186–96. doi:10.1016/0169-5002(89)90167-0
7. Bunn PA Jr. Clinical experience with carbolatin (paraplatin) in lung cancer. *Semin Oncol* (1992) 19(Suppl 2):1–11.
8. Schiller JH, Adak S, Cella D, DeVore RF III, Johnson DH. Topotecan versus observation after cisplatin plus etoposide in extensive-stage small-cell lung cancer: E7593 – a phase III trial of the eastern cooperative oncology group. *J Clin Oncol* (2001) 19:2114–22. doi:10.1200/JCO.2001.19.8.2114
9. Ihde DC, Mulshine JL, Kramer BS, Steinberg SM, Linnoila RI, Gazdar AF, et al. Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small cell lung cancer. *J Clin Oncol* (1994) 12:2022–34. doi:10.1200/JCO.1994.12.10.2022
10. Leyvraz S, Pampallona S, Martinelli G, Ploner F, Perey L, Aversa S, et al. A threefold dose intensity treatment with ifosfamide, carboplatin, and etoposide for patients with small cell lung cancer: a randomized trial. *J Natl Cancer Inst* (2008) 100:533–41. doi:10.1093/jnci/djn088
11. Bunn PA Jr, Cohen MH, Ihde DC, Fossieck BE Jr, Matthews MJ, Minna JD. Advances in small cell bronchogenic carcinoma: a commentary. *Cancer Treat Rep* (1977) 61:333–42.
12. Beck LK, Kane MA, Bunn PA Jr. Innovative and future approaches to small cell lung cancer treatment. *Semin Oncol* (1988) 15:300–14.
13. Jeremic B, Shibamoto Y, Nikolic N, Milicic B, Milisavljevic S, Dagovic A, et al. The role of radiation therapy in the combined modality treatment of patients with extensive disease small-cell lung cancer (ED SCLC): a randomized study. *J Clin Oncol* (1999) 17:2092–9. doi:10.1200/JCO.1999.17.7.2092
14. Livingston RB, Moore TN, Heilbrun L, Bottomley R, Lehane D, Rivkin SE, et al. Small-cell carcinoma of the lung: combined chemotherapy and radiation: a Southwest Oncology Group study. *Ann Intern Med* (1978) 88:194–9. doi:10.7326/0003-4819-88-2-194
15. Dillman RO, Taetle R, Seagren S, Royston I, Koziol J, Mendelsohn J. Extensive disease small cell carcinoma of the lung: trial of non-cross resistant chemotherapy and consolidation radiotherapy. *Cancer* (1982) 49:2003–8.doi:10.1002/1097-0142(19820515)49:10<2003::AID-CNCR2820491010>3.0.CO;2-G
16. Nou E, Brodin O, Bergh J. A randomized study of radiation treatment in small cell bronchial carcinoma treated with two types of four-drug chemotherapy regimens. *Cancer* (1988) 62:1079–90. doi:10.1002/1097-0142(19880915)62:6<1079::AID-CNCR2820620610>3.0.CO;2-S
17. Beith JM, Clarke SJ, Woods RL, Bell DR, Levi JA. Long-term follow-up of a randomized trial of combined chemoradiotherapy induction treatment, with and without maintenance chemotherapy in patients with small cell carcinoma of the lung. *Eur J Cancer* (1996) 32A:438–43. doi:10.1016/0959-8049(95)00608-7
18. Ou S-HI, Ziogas A, Zell JA. Prognostic factors for survival in extensive stage small cell lung cancer (ED-SCLC): the importance of smoking history, socioeconomic and marital statuses, and ethnicity. *J Thorac Oncol* (2009) 4:37–43. doi:10.1097/JTO.0b013e31819140fb
19. Mitin T, Jain A, Degnin C, Chen Y, Henderson M, Thomas CR Jr. Current patterns of care for patients with extensive stage small cell lung cancer: survey of US radiation oncologists on their recommendations regarding thoracic consolidation radiotherapy. *Lung Cancer* (2016) 100:85–9. doi:10.1016/j.lungcan.2016.08.005
20. Yee D, Butts C, Reiman A, Smylie M, Fenton D, Chu Q, et al. Clinical trial of post-chemotherapy consolidation thoracic radiotherapy for extensive-stage small cell lung cancer. *Radiother Oncol* (2012) 102:234–8. doi:10.1016/j.radonc.2011.08.042
21. Zhu H, Zhou Z, Wang Y, Bi N, Feng Q, Li J, et al. Thoracic radiation therapy improves the overall survival of patients with extensive-stage small cell lung cancer with distant metastasis. *Cancer* (2011) 117:5423–31. doi:10.1002/cncr.26206
22. Giuliani ME, Atallah S, Sun A, Bezjak A, Le LW, Brade A, et al. Clinical outcomes of extensive stage small cell lung carcinoma patients treated with consolidative thoracic radiotherapy. *Clin Lung Cancer* (2011) 12:375–9. doi:10.1016/j.cllc.2011.03.028

23. Slotman BJ, van Tinteren H, Praag JO, Knegjens JL, El Sharouni SY, Hatton M, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. *Lancet* (2015) 385:36–42. doi:10.1016/S0140-6736(14)61085-0
24. Gore EM, Hu C, Sun AY, Grimm DF, Ramalingam SS, Dunlap NE, et al. Randomized phase II study comparing prophylactic cranial irradiation alone to prophylactic cranial irradiation and consolidative extra-cranial irradiation for extensive disease small cell lung cancer (ED-SCLC): NRG oncology RTOG 0937. *J Thorac Oncol* (2017). doi:10.1016/j.jtho.2017.06.015
25. Slotman B, Faivre-Finn C, Kramer G, Rankin E, Snee M, Hatton M, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* (2007) 357:664–72. doi:10.1056/NEJMoa071780
26. Slotman BJ, Mauer ME, Bottomley A, Faivre-Finn C, Kramer GW, Rankin EM, et al. Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international phase III randomized controlled trial by the EORTC radiation oncology and lung cancer groups. *J Clin Oncol* (2009) 27:78–84. doi:10.1200/JCO.2008.17.0746
27. Jain A, Luo J, Chen Y, Henderson MA, Thomas CR Jr, Mitin T. Current patterns of care for patients with extensive-stage SCLC: survey of U.S. radiation oncologists on their recommendations regarding prophylactic cranial irradiation. *J Thorac Oncol* (2016) 11:1305–10. doi:10.1016/j.jtho.2016.04.031
28. Takahashi T, Yamanaka T, Seto T, Harada H, Nokihara H, Saka H. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* (2017) 18:663–71. doi:10.1016/S1470-2045(17)30230-9
29. Lu D, Xanthopoulos E, Dixit N, James P, Mitra N, Levin W, et al. Comparison of intensity-modulated radiation therapy, adaptive radiation therapy, proton radiation therapy, and adaptive proton radiation therapy for small cell lung cancer. *Appl Radiat Oncol* (2016) 5:20–7.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2017 Jeremic, Gomez-Caamano, Dubinsky, Cihoric, Casas and Filipovic. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

MINI REVIEW
published: 29 September 2017
doi: 10.3389/fonc.2017.00228

Prophylactic Cranial Irradiation Following Surgical Resection of Early-Stage Small-Cell Lung Cancer: A Review of the Literature

Brooke C. Bloom[1†], Alexander Augustyn[2†], Boris Sepesi[3], Sunil Patel[4], Shalin J. Shah[2], Ritsuko U. Komaki[2], Steven E. Schild[5†] and Stephen G. Chun[2†]*

[1] Trinity University, San Antonio, TX, United States, [2] Division of Radiation Oncology, Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, United States, [3] Department of Thoracic and Cardiovascular Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, United States, [4] Department of General Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, United States, [5] Department of Radiation Oncology, Mayo Clinic Scottsdale, Scottsdale, AZ, United States

OPEN ACCESS

Edited by:
John Varlotto,
University of Massachusetts Medical Center, United States

Reviewed by:
John Austin Vargo,
West Virginia University Hospitals, United States
Valdir Carlos Colussi,
UH Seidman Case Medical Center, United States

***Correspondence:**
Stephen G. Chun
sgchun@mdanderson.org

[†]These authors have contributed equally to this work.

Specialty section:
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

Received: 31 July 2017
Accepted: 07 September 2017
Published: 29 September 2017

Citation:
Bloom BC, Augustyn A, Sepesi B, Patel S, Shah SJ, Komaki RU, Schild SE and Chun SG (2017) Prophylactic Cranial Irradiation Following Surgical Resection of Early-Stage Small-Cell Lung Cancer: A Review of the Literature. Front. Oncol. 7:228. doi: 10.3389/fonc.2017.00228

With increasing use of low-dose screening CT scans, the diagnosis of early-stage small-cell lung cancer (SCLC) without evidence of mediastinal nodal or distant metastasis is likely to become more common, but the role of adjuvant therapies such as prophylactic cranial irradiation (PCI) are not well understood in this population. We performed a review of the literature pertaining to the impact of PCI in patients who underwent surgical resection of early-stage SCLC. Four studies were identified that were pertinent including three single-institution retrospective analyses and a National Cancer Database analysis. Based upon these studies, we estimate the rate of brain metastases to be 10–15% for Stage I and 15–25% for Stage II disease without PCI. However, the impact of PCI on the development of brain metastases and its ultimate impact on overall survival were not consistent across these studies. In summary, there is sparse evidence to guide recommendations for PCI following resection of early-stage SCLC. While it may be reasonable to offer PCI to maximize likelihood of cure, alternative strategies such as observation with close imaging follow-up can also be considered for the appropriate patient given the known neurocognitive side effects of PCI.

Keywords: small-cell lung cancer, early stage, surgical resection, prophylactic cranial irradiation, brain metastasis

BACKGROUND

Small-cell lung cancer (SCLC) is a common smoking-related malignancy that accounts for approximately 15% of all lung cancers (1, 2). For limited-stage SCLC (3), combined modality therapy with concurrent chemotherapy and early thoracic radiation (TRT), followed by prophylactic cranial irradiation (PCI) is considered to be the standard of care (4–7). Although not commonly performed, surgical resection for selected patients with early-stage tumors without evidence of mediastinal nodal metastases may be reasonable. However, the role of adjuvant therapies such as PCI for surgically resected early-stage SCLC has not been formally studied in a prospective clinical trial.

For limited-stage SCLC treated with curative-intent definitive chemoradiation, multiple studies have demonstrated that PCI reduces brain metastases and improves overall survival dating back to

the 1970s (2, 4, 8). The brain has long been established to be a sanctuary site for SCLC where there is poor chemotherapy penetration and roughly 50% of patients develop brain metastases (2, 9). However, in these studies, most patients had bulky and unresectable disease treated with chemoradiotherapy, and the applicability of this data to surgical resected early-stage SCLC is questionable. Moreover, the absolute survival benefit (5.4%) seen in the meta-analysis by Auperin et al. was small (4), suggesting that the benefit of PCI for surgically resected early-stage SCLC might be even smaller.

Historically, there have been few opportunities to study PCI for surgically resected SCLC. From a clinical standpoint, most limited-stage cases are not amenable for oncologic resection due to locally-advanced presentation. Furthermore, two historic trials did not demonstrate a clear role for surgery for SCLC (10, 11). For these reasons, there is little information available on surgical resection for SCLC and even less information available on the role of adjuvant therapy. For patients with early-stage SCLC (AJCC Stages I and II) who have undergone oncologic resection, the impact of adjuvant therapy such as PCI is debatable (12, 13). However, with increasing use of low-dose screening CT scans (LDCT), it is conceivable that patients with resected early-stage SCLC will become more common, particularly in regions that have high rates of tobacco use.

In this mini-review, we present the studies in the literature comparing outcomes of patients with and without PCI after surgical resection for early-stage (Stages I and II) SCLC. This included single-institution retrospective and a National Cancer Database (NCDB) analyses. The purpose of this review is to provide a concise resource to personalize recommendations for patients who have undergone surgical resection for early-stage SCLC.

METHODS

We performed a PubMed search using terms, "surgical resection," "small-cell lung cancer," "early-stage," and "prophylactic cranial irradiation" to identify studies addressing the role of PCI for surgically resected SCLC. For the purpose of this mini-review, we excluded studies that did not include PCI. Using these criteria, three single institutional retrospective analyses (2, 14, 15), and a population-based analysis of the United States NCDB (16) were identified that compared outcomes of patients treated with and without PCI for surgically resected early-stage SCLC.

RESULTS

In reviewing the literature, three small single institution retrospective analyses were identified from the Tumor Hospital, Shan Dong Province, China (14), the Shanghai Chest Hospital, China (2), and the University of Heidelberg (15). In these studies, patients who underwent surgical resection for Stages I and III disease were compared with respect to whether they received PCI. A retrospective analysis of the United States NCDB that addressed PCI in this population with respect to overall survival was also identified (16). Rates of brain metastases reported in these studies are summarized in **Table 1**.

TABLE 1 | Brain metastasis rates reported in the literature for surgically resected early-stage small-cell lung cancer.

Citation	Brain metastasis rate
Xu et al. (2), Shanghai Chest Hospital	Stage I—13.6% (no PCI) vs. 10.5% (PCI) Stage II—22.4% (no PCI) vs. 12.8% (PCI)
Zhu et al. (14), Shandong Cancer Hospital	Stage I (no PCI)—9.4% Stage II (no PCI)—18.2%
Bischof et al. (15), University of Heidelberg	Stages I and II combined—22% (no PCI) vs. 0% (PCI)

PCI, prophylactic cranial irradiation.

In the largest study by Xu et al. (2) from the Shanghai Chest Hospital, 349 patients were analyzed, of whom 115 received PCI and 234 did not receive PCI. Approximately half ($N = 189$) of the patients had Stages I and II disease for whom the association of PCI on oncologic outcomes is summarized in **Table 1**. For Stage I SCLC, patients who received PCI had no survival advantage (HR 1.61, 95% CI 0.68–3.83) or associated reduction in development of brain metastases (13.6 vs. 10.5%). For Stage II SCLC, PCI was associated with an overall survival benefit on multivariable analysis (HR 0.54, $p = 0.047$), as well as a statistical trend toward reduction in brain metastases (22.4 vs. 12.8%, $p = 0.094$).

In another single institution analysis from the Tumor Hospital, Shan Dong, China, 193 patients were analyzed with respect to delivery of PCI after surgical resection for Stages I–III SCLC (14). While PCI was associated with a survival and brain metastasis free survival benefit in all patients, subgroup analysis of Stage I patients showed no survival benefit associated with PCI. PCI was associated with a twofold reduction in brain metastases with 9% of developing them in the PCI group and 22% in the non-PCI group. The non-PCI brain metastasis rates were listed as 9.4% for Stage I and 18.2% for Stage II. Further subgroup analysis comparing brain metastases rates by stage groups was not reported.

The smallest study evaluating the impact of PCI on rates of brain metastases from the University of Heidelberg reported 39 patients who underwent resection for Stages I and II SCLC from 1995 to 2006 (15). This study contains the additional confounding factor in that it sought to evaluate both the role of adjuvant thoracic radiation therapy (TRT) as well as the role of PCI on a very small number of patients. PCI was administered to a total dose of 28–30 Gy in standard fractions of 2 Gy daily. In this study, 44% of patients received no form of radiation, while 15% received PCI alone, 3% received TRT alone, and 38% received both PCI and TRT. Rates brain metastases were grouped for all Stages I and II patients with a 22% brain metastasis rate for patients without PCI and no brain failures reported in the PCI group. The authors reported that PCI had a significant ($p = 0.01$) survival benefit although the magnitude of this benefit is not reported.

From the United States, an NCDB analysis was performed on patients treated with surgical resection for T1-T2N0 SCLC from 2003 to 2011 (16). In this study, 99 patients (52.1%) of patients received radiation therapy to the brain, which was interpreted as PCI delivery. On multivariable analysis, radiation was not associated with a significant survival benefit when used either alone

or in conjunction with chemotherapy. Information on rates of brain metastases was not reported because such information is not captured in the NCDB.

DISCUSSION

Currently, the best available information on PCI for early-stage SCLC is based upon underpowered retrospective analyses that do not set a clear precedent for standard of care. These retrospective studies help us estimate the brain metastasis rate for early-stage SCLC to be roughly 10–15% for Stage I disease and for 15–25% for Stage II disease. PCI is known to cause neurocognitive side effects (17), and the overall survival benefit is likely to be less than 5% based upon extrapolation from unresectable SCLC (4). Without a clear standard of care regarding PCI in these patients, we advocate multidisciplinary evaluation and patient-tailored recommendations. While offering PCI may be reasonable to maximize likelihood of cure, close interval follow-up using serial brain MRIs may also be a reasonable strategy in the compliant patient.

Exploration of PCI for resected early-stage SCLC may represent an opportunity for investigation with the implementation of LDCT. Multiple prospective trials lead the conclusion from the United States Preventative Task Force that LDCT reduce lung cancer mortality (18). With increasing use of screening, thoracic surgeons using video-assisted thorascopic surgery for diagnostic wedge resection may also increase diagnoses of early-stage SCLC. Analyses of the Surveillance, Epidemiology, and End Results Program database have also supported a role for surgical resection for this population (19, 20). As such, especially in geographic regions where tobacco use remains prevalent, early-stage resected SCLC may become more common with increased screening and early detection. While a formal randomized trial for this situation may not be feasible, it may be possible to develop a prospective registry to better understand oncologic outcomes in these patients. Data from such a registry might also provide useful information in conjunction with molecular profiling to shed light on the need for adjuvant treatments such as PCI, immune therapy, or cytotoxic chemotherapy.

Although PCI has been established to cause neurocognitive side effects in a substantial number of patients, emerging strategies may mitigate the risk of this toxicity. The *N*-methyl-D-aspartate inhibitor memantine has previously shown to improve neurocognitive side effects from whole-brain radiation therapy for patients with overt metastases (21). Intensity-modulated radiation therapy has also been employed with hippocampal avoidance specifically for the purpose of improving neurocognition (22, 23). These strategies have been combined in NRG Oncology CC-001 with the intent of improving quality of life and cognition for patients receiving prophylactic whole-brain radiation. Results of NRG Oncology CC-001 will be helpful in determining whether PCI with hippocampal avoidance is a reasonable strategy to prevent brain failures while minimizing neurocognitive consequences.

In summary, there is little information currently available on PCI for resected early-stage SCLC. With increased screening, these patients may represent a new frontier for investigation. It may be reasonable to offer PCI for the purpose of minimizing intracranial recurrence rate while counseling patients that the reduction in brain metastases and improvement in survival is likely to be small. While the side effects of whole-brain PCI may be unpalatable to some patients, strategies such as memantine and hippocampal avoidance have potential to mitigate the toxicities of PCI and should be explored enthusiastically.

AUTHOR CONTRIBUTIONS

BB and AA: contributed to data collection and writing of manuscript. SJS, BS, and RK: contributed to data interpretation and writing of manuscript. SES and SC: contributed to data interpretation, data collection, and writing of manuscript.

REFERENCES

1. Govindan R, Page N, Morgensztern D, Read W, Tierney R, Vlahiotis A, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. *J Clin Oncol* (2006) 24(28):4539–44. doi:10.1200/JCO.2005.04.4859
2. Xu J, Yang H, Fu X, Jin B, Lou Y, Zhang Y, et al. Prophylactic cranial irradiation for patients with surgically resected small cell lung cancer. *J Thorac Oncol* (2017) 12(2):347–53. doi:10.1016/j.jtho.2016.09.133
3. Micke P, Faldum A, Metz T, Beeh KM, Bittinger F, Hengstler JG, et al. Staging small cell lung cancer: veterans administration lung study group versus international association for the study of lung cancer – what limits limited disease? *Lung Cancer* (2002) 37(3):271–6. doi:10.1016/S0169-5002(02)00072-7
4. Auperin A, Arriagada R, Pignon JP, Le Pechoux C, Gregor A, Stephens RJ, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med* (1999) 341(7):476–84. doi:10.1056/NEJM199908123410703
5. Pignon JP, Arriagada R. Role of thoracic radiotherapy in limited-stage small-cell lung cancer: quantitative review based on the literature versus meta-analysis based on individual data. *J Clin Oncol* (1992) 10(11):1819–20. doi:10.1200/JCO.1992.10.11.1819
6. Jett JR, Schild SE, Kesler KA, Kalemkerian GP. Treatment of small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* (2013) 143(5 Suppl):e400S–e19S. doi:10.1378/chest.12-2363
7. Amini A, Byers LA, Welsh JW, Komaki RU. Progress in the management of limited-stage small cell lung cancer. *Cancer* (2014) 120(6):790–8. doi:10.1002/cncr.28505
8. Aroney RS, Aisner J, Wesley MN, Whitacre MY, Van Echo DA, Slawson RG, et al. Value of prophylactic cranial irradiation given at complete remission in small cell lung carcinoma. *Cancer Treat Rep* (1983) 67(7–8):675–82.
9. Arriagada R, Le Chevalier T, Riviere A, Chomy P, Monnet I, Bardet E, et al. Patterns of failure after prophylactic cranial irradiation in small-cell lung cancer: analysis of 505 randomized patients. *Ann Oncol* (2002) 13(5):748–54. doi:10.1093/annonc/mdf123
10. Lad T, Piantadosi S, Thomas P, Payne D, Ruckdeschel J, Giaccone G. A prospective randomized trial to determine the benefit of surgical resection of residual disease following response of small cell lung cancer to combination chemotherapy. *Chest* (1994) 106(6 Suppl):320S–3S. doi:10.1378/chest.106.6.320S
11. Fox W, Scadding JG. Medical research council comparative trial of surgery and radiotherapy for primary treatment of small-celled or oat-celled carcinoma of bronchus. Ten-year follow-up. *Lancet* (1973) 2(7820):63–5. doi:10.1016/S0140-6736(73)93260-1
12. Fruh M, De Ruysscher D, Popat S, Crino L, Peters S, Felip E, et al. Small-cell lung cancer (SCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* (2013) 24(Suppl 6):vi99–105. doi:10.1093/annonc/mdt178

13. Le Pechoux C. Prophylactic cranial irradiation or no prophylactic cranial irradiation after adjuvant chemotherapy in resected small cell lung cancer? *J Thorac Oncol* (2017) 12(2):173–5. doi:10.1016/j.jtho.2016.12.002
14. Zhu H, Guo H, Shi F, Zhu K, Luo J, Liu X, et al. Prophylactic cranial irradiation improved the overall survival of patients with surgically resected small cell lung cancer, but not for stage I disease. *Lung Cancer* (2014) 86(3):334–8. doi:10.1016/j.lungcan.2014.09.019
15. Bischof M, Debus J, Herfarth K, Muley T, Kappes J, Storz K, et al. Surgery and chemotherapy for small cell lung cancer in stages I-II with or without radiotherapy. *Strahlenther Onkol* (2007) 183(12):679–84. doi:10.1007/s00066-007-1740-z
16. Yang CF, Chan DY, Speicher PJ, Gulack BC, Wang X, Hartwig MG, et al. Role of adjuvant therapy in a population-based cohort of patients with early-stage small-cell lung cancer. *J Clin Oncol* (2016) 34(10):1057–64. doi:10.1200/JCO.2015.63.8171
17. Wolfson AH, Bae K, Komaki R, Meyers C, Movsas B, Le Pechoux C, et al. Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. *Int J Radiat Oncol Biol Phys* (2011) 81(1):77–84. doi:10.1016/j.ijrobp.2010.05.013
18. Moyer VA; U.S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* (2014) 160(5):330–8. doi:10.7326/M13-2771
19. Varlotto JM, Recht A, Flickinger JC, Medford-Davis LN, Dyer A-M, DeCamp MM. Lobectomy leads to optimal survival in early-stage small cell lung cancer: a retrospective analysis. *J Thorac Cardiovasc Surg* (2011) 142(3):538–46. doi:10.1016/j.jtcvs.2010.11.062
20. Schreiber D, Rineer J, Weedon J, Vongtama D, Wortham A, Kim A, et al. Survival outcomes with the use of surgery in limited-stage small cell lung cancer: should its role be re-evaluated? *Cancer* (2010) 116(5):1350–7. doi:10.1002/cncr.24853
21. Brown PD, Pugh S, Laack NN, Wefel JS, Khuntia D, Meyers C, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol* (2013) 15(10):1429–37. doi:10.1093/neuonc/not114
22. Gondi V, Tolakanahalli R, Mehta MP, Tewatia D, Rowley H, Kuo JS, et al. Hippocampal-sparing whole-brain radiotherapy: a "how-to" technique using helical tomotherapy and linear accelerator-based intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* (2010) 78(4):1244–52. doi:10.1016/j.ijrobp.2010.01.039
23. Lin SY, Yang CC, Wu YM, Tseng CK, Wei KC, Chu YC, et al. Evaluating the impact of hippocampal sparing during whole brain radiotherapy on neurocognitive functions: a preliminary report of a prospective phase II study. *Biomed J* (2015) 38(5):439–49. doi:10.4103/2319-4170.157440

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2017 Bloom, Augustyn, Sepesi, Patel, Shah, Komaki, Schild and Chun. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

ORIGINAL RESEARCH
published: 14 May 2018
doi: 10.3389/fonc.2018.00146

The Role of Race and Economic Characteristics in the Presentation and Survival of Patients With Surgically Resected Non-Small Cell Lung Cancer

John M. Varlotto[1,2], Kerri McKie[2], Rickie P. Voland[3], John C. Flickinger[4], Malcolm M. DeCamp[5], Debra Maddox[6], Paul Stephen Rava[1,2], Thomas J. Fitzgerald[1,2], William Walsh[2,6], Paulo Oliveira[2,7], Negar Rassaei[8], Jennifer Baima[2,9] and Karl Uy[2,10]*

[1] Department of Radiation Oncology, University of Massachusetts Medical Center, Worcester, MA, United States, [2] University of Massachusetts Medical School, Worcester, MA, United States, [3] School of Nursing, University of Wisconsin, Madison, WI, United States, [4] Department of Radiation Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA, United States, [5] Division of Thoracic Surgery, Northwestern Memorial Medical Center, Chicago, IL, United States, [6] Department of Medical Oncology, University of Massachusetts Medical Center, Worcester, MA, United States, [7] Division of Pulmonary, Allergy and Critical Care Medicine, Worcester, MA, United States, [8] Department of Pathology, Penn State Hershey Medical Center, Hershey, PA, United States, [9] Division of Physical Medicine and Rehabilitation, Worcester, MA, United States, [10] Division of Thoracic Surgery, University of Massachusetts Medical Center, Worcester, MA, United States

OPEN ACCESS

Edited by:
Charles A. Kunos,
National Cancer Institute (NIH),
United States

Reviewed by:
Michael Chan,
Wake Forest University,
United States
Sunyoung Jang,
Princeton Radiation Oncology,
United States

***Correspondence:**
John M. Varlotto
john.varlotto@umassmemorial.org

Specialty section:
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

Received: 25 December 2017
Accepted: 20 April 2018
Published: 14 May 2018

Citation:
Varlotto JM, McKie K, Voland RP, Flickinger JC, DeCamp MM, Maddox D, Rava PS, Fitzgerald TJ, Walsh W, Oliveira P, Rassaei N, Baima J and Uy K (2018) The Role of Race and Economic Characteristics in the Presentation and Survival of Patients With Surgically Resected Non-Small Cell Lung Cancer. Front. Oncol. 8:146. doi: 10.3389/fonc.2018.00146

Background: Little is understood regarding the inter-relation between economic, marital, and racial/ethnic differences in presentation and survival of surgically resected lung cancer patients. Our investigation will assess these differences in addition to known therapeutic, patient, and histopathologic factors.

Methods: A retrospective review of the Surveillance Epidemiology and End Reporting database was conducted through the years 2007–2012. The population was split into nine different ethnic groups. Population differences were assessed *via* chi-square testing. Multivariable analysis (MVA) were used to detect overall survival (OS) differences in the total surgical population (TS, $N = 35,689$) in an ear (T1–T2 < 4 cm N0) surgical population [early-stage resectable (ESR), $N = 17,931$]. Lung cancer-specific survival (LCSS) was assessed in the ESR.

Results: In the TS population, as compared to Whites, Blacks, and Hispanics presented with younger age, more adenocarcinomas, lower rates of marriage, lower rates of insurance, less stage I tumors, and had less nodes examined, but their type of surgical procedures and OS/LCSS were the same. MVA demonstrated that lower OS and LCSS were associated with males, single/divorced/widowed partnership, lower income (TS only), and Medicaid insurance. MVA also found that Blacks and Hispanics had a similar OS/LCSS to Whites and that all ethnic groups were associated with a similar or better outcomes. The 90-day mortality and positive nodes were correlated with not having insurance and not being married, but they were not associated with ethnicity.

Conclusion: In TS and ESR groups, OS was not different in the two largest ethnic groups (Black and Hispanic) as compared to Whites, but was related to single/widowed/divorced status, Medicaid insurance, and income (TS group only). Nodal positivity was associated with patients who did not have a married partner or insurance suggesting that these factors may impact disease biology. Economic and psychosocial variables may play a role in survival of ear lung cancer in addition to standard histopathologic and treatment variables.

Keywords: lung cancer, surgical resection, socioeconomic status, marital status, racial differences

INTRODUCTION

Surgery is the standard treatment option for patients with early-stage, medically operable patients because of its known long-term efficacy (1).

The relationship between patients chosen for surgical therapy and their outcome in relation to economic, insurance, partnership, and racial issues has been infrequently studied. A recent retrospective study using the VA Central Cancer Registry in stage I/II non-small cell lung cancer (NSCLC) from 2001 to 2010 demonstrated that the disparity between Blacks and Whites receiving an operation decreased to similar rates during this time period. Furthermore, there was no survival difference between Black and Whites undergoing an operation, and no lung cancer-specific survival (LCSS) differences between races (2). Using data compiled from 38 state and the District of Columbia population-based cancer registries compiled by the North American Association of Central Cancer Registries, Sineshaw et al. demonstrated that the receipt of curative-intent surgery varied by state and was lower in blacks than whites in every state (statistically significant in Texas and Florida) (3). Similarly, using the Surveillance Epidemiology and End Reporting (SEER) database from 2007 to 2012, Taioli and Flores noted that even after adjusting by age and insurance status, blacks were less likely to receive surgery, but more likely to receive radiation than white patients (4). However, none of these studies evaluate race in relation to economic, marital, and insurance variables. Nor have these reports analyzed differences in outcome in the many different ethnic groups who are found in the United States.

Because lung cancer screening was shown to be of benefit in 2011 (5) and was approved by CMS in 2015, early-stage resectable (ESR) NSCLC is expected to increase and result in more lung cancer survivors (6). Therefore, assessing the presentation and outcomes of patients undergoing surgery for NSCLC and inter-relationship of ethnicity in regards to marital, economic, histologic, treatment, and insurance variables will be increasingly important.

The purpose of our study is to investigate the presenting characteristics of patients undergoing a definitive surgical procedure in nine different ethnic groups [White non-Hispanic (White), Black, White Hispanic (Hispanic), American Indian/Alaskan native (AI/AN), Chinese, Japanese, Other Asian, South Asian, and Other Race] and to assess prognosis and 90-day mortality for all surgical patients and for those presenting with early-stage, resectable tumors (ESR, <4 cm without involved nodes). The prognostic importance of race will be determined in a multivariate model that adjusts for known histopathologic and patient-related factors as well as income, marital status, and insurance.

MATERIALS AND METHODS

Data Source

Data for this study were taken from the SEER program of the National Cancer Institute, which started to collect and publish cancer incidence and survival data from population-based cancer registries in 1973. The "SEER-18" database used in this study includes registries in Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, Greater California, Kentucky, Louisiana, New Jersey, Greater Georgia, and the Alaska Native Tumor Registry (7). Data are available from all cases diagnosed from 2000 and later for these registries. The SEER 18 sites cover approximately 28% of the American population (7).

Cohort Selection

We included adults, ages who were at least 18 years old and who were diagnosed with histologically proven NSCLC in the SEER-18 database during 2007–2012.

Outcome and presenting characteristics were examined for all surgical patients (TS) ($N = 35,689$) and patients with presenting with ESR disease ($N = 17,931$) for whom sufficient information was collected to assess the outcome of treatment in relation to patient, economic, histopathologic, and insurance variables. Patients included in this investigation had NSCLC as their first primary cancer. Only microscopically confirmed tumors using NSCLC codes (8012-8014,8022,8031-8033,8046,8052,8070-8073, 8082,8084,8123,8140,8200,8230,8250-8255,8260, 8310,8333,8430,8470,8480-8481,8490,8550,8560,8972,8980) were included in this study.

Only patients undergoing a definitive surgical procedure without pre-operative radiation were included in this analysis. The surgical procedures defined as definitive were as follows: sublobar resection (sublobar resection; segmental resection, including lingulectomy; or wedge resection); and lobectomy or greater (lobectomy or bi-lobectomy, with or without extension to include the chest wall; lobectomy with mediastinal node dissection; extended lobectomy or bi-lobectomy, not otherwise

specified; pneumonectomy with mediastinal node dissection; or pneumonectomy, not otherwise specified).

Outcome Variables and Other Covariates

The outcome variables were overall survival (OS) and LCSS. Deaths from other causes were treated as censoring events. The main purpose of our investigation was to examine whether there are differences in presenting characteristics and outcomes in nine different ethnic groups by examining marital status, household income (<$50,000; $50–$74,999; >$75,000), type of insurance (insured, Medicaid, uninsured, unknown) in addition to established histopathologic and patient factors. Household income was listed in the SEER registry by median household income per county. The population was split into nine different ethnic groups as follows: White non-Hispanic (White), Black, White Hispanic (Hispanic), AI/AN, Chinese, Japanese, South Asian (Asian Indian and Pakistani), Other Asian (Filipino, Thai, Vietnamese, Korean, Kampuchean, Laotian, and Hmong), and Other Race (OR, Chamorran, Fiji Islander, Guamanian, Hawaiian, Melanesian, Micronesian, New Guinean, Pacific Islander, Polynesian, Samoan, Tahitian, Tongan, unknown, and other) in both the entire lung cancer surgical population as well as those presenting with ESR disease. We originally wanted to include black Hispanic patients as a separate patient category in this manuscript and its companion study assessing ethnic differences in all lung cancer patients and those with Stage IV disease, but since we wanted similar populations in both studies and because the number of Black Hispanic patients was scant in both the TS population and the ESR groups, we decided to include Black Hispanic patients in the Black category, similar to a past study (8). Black Hispanic patients represented approximately 0.6% of patient group undergoing surgical resection (19/3,276). Throughout this manuscript, the term population(s) will refer to total population of surgical patients (TS) and those with ESR disease, while group(s) will refer to the nine different ethnicities.

Variables examined for their potential effect on outcome were gender; age; year of diagnosis; marital status; race; ethnicity; tumor stage; *t*-stage, *n*-stage; nodes examined; nodes positive; node density (number of nodes positive/number of nodes examined); tumor size; histology; grade; SEER registry location; median family income; resection type; post-operative radiation; and tumor location. Median follow-up time was calculated by the methods of Schemper and Smith in which death becomes a censored follow-up time and was noted to be 36 and 35 months in the TS and ESR groups, respectively (9).

Statistical Analysis

Chi-square and *t*-test were used to compare difference between the ethnic groups with respect to treatment, patient characteristics, and tumor characteristics. Cox proportional hazards models estimates (10) were used to calculate adjusted hazard ratios with their 95% confidence intervals, and to show how treatment and other covariates were related to OS and LCSS. Medicare eligibility was controlled through use of two strata for age at diagnosis (≥65 vs <65 years old) because individual cases will change when they enroll in Medicare. The cox proportional hazards assumption was checked by visual examination of survival plots.

RESULTS

Presenting Characteristics

Complete demographic and histologic details of the TS and ESR patients can be seen in **Table 1**. Median age of the patients in the TS and ESR populations were both 68.0 years. There was a female

TABLE 1 | Demographic characteristics of both the TS and early-stage resectable patients.

	All surgical (*N* = 35,689)	Favorable (*N* = 17,931)
Age—years		
Median	68.0	68.0
Sex—no. (%)		
Female	(50.4%) 17,989	(55.1%) 9,882
Male	(49.6%) 17,700	(44.9%) 8,693
Race—no. (%)		
White Hispanic	(4.98%) 1,779	(4.60%) 823
White non-Hispanic	(78.60%) 28,052	(79.60%) 14,273
Black	(9.18%) 3,276	(8.42%) 1,509
Chinese	(1.59%) 568	(1.61%) 288
Japanese	(0.85%) 302	(0.78%) 139
South Asian	(0.31%) 112	(0.31%) 56
Other Asian	(2.83%) 1,011	(2.96%) 531
Other Race	(1.28%) 457	(1.41%) 252
American Indian/Alaskan Native	(0.37%) 132	(0.33%) 60
Surveillance Epidemiology and End Reporting Registry—no. (%)		
Alaska Natives	(0.10%) 35	(0.07%) 13
Atlanta	(3.05%) 1,090	(2.79%) 501
California excl SF/SJM/LA	(19.24%) 6,865	(19.63%) 3,521
Connecticut	(5.99%) 2,138	(6.44%) 1,155
Detroit	(6.23%) 2,223	(6.40%) 1,148
Greater Georgia	(9.45%) 3,374	(9.46%) 1,696
Hawaii	(1.54%) 549	(1.56%) 279
Iowa	(4.32%) 1,544	(4.10%) 736
Kentucky	(9.90%) 3,534	(9.56%) 1,715
Los Angeles	(7.64%) 2,728	(7.38%) 1,324
Louisiana	(5.54%) 1,977	(5.15%) 924
New Jersey	(13.34%) 4,760	(13.92%) 2,496
New Mexico	(1.41%) 503	(1.42%) 254
Rural Georgia	(0.23%) 83	(0.23%) 42
San Francisco-Oakland	(4.47%) 1,594	(4.51%) 809
San Jose-Monterey	(2.14%) 762	(1.94%) 347
Seattle	(4.08%) 1,457	(4.34%) 779
Utah	(1.33%) 473	(1.07%) 192
Income—no. (%)		
<50k	(29.84%) 10,649	(28.67%) 5,140
50k–74k	(52.88%) 18,871	(53.40%) 9,575
≥75k	(17.29%) 6,169	(17.94%) 3,216
Marital status—no. (%)		
Divorced	(12.13%) 4,330	(12.06%) 2,162
Married	(57.33%) 20,460	(56.19%) 10,076
Separated	(0.98%) 350	(0.91%) 163
Single	(11.23%) 4,009	(10.75%) 1,927
Unknown	(3.52%) 1,258	(3.89%) 698
Domestic partner	(0.09%) 33	(0.06%) 11
Widowed	(14.71%) 5,249	(16.14%) 2,894
AJCC T 6th edition—no. (%)		
T0	(0.03%) 9	0
T1	(41.75%) 14,900	(69.25%) 12,417
T2	(42.36%) 15,119	(30.75%) 5,514

(*Continued*)

TABLE 1 | Continued

	All surgical (*N* = 35,689)	Favorable (*N* = 17,931)
T3	(5.63%) 2,010	0
T4	(9.91%) 3,537	0
TX	(0.32%) 114	0
Insurance—no. (%)		
Insured	(87.45%) 31,210	(88.26%) 15,826
Medicaid	(9.85%) 3,516	(9.48%) 1,700
Uninsured	(2.07%) 740	(1.63%) 292
Unknown	(0.62%) 223	(0.63%) 113
Lateral location—no. (%)		
Bronchus, left	(0.38%) 136	(0.09%) 16
Bronchus, right	(0.32%) 116	(0.06%) 11
Bronchus, unknown	(0.03%) 9	(0.02%) 3
Left lower	(13.95%) 4,980	(13.76%) 2,467
Left upper	(26.30%) 9,388	(26.14%) 4,687
Left NOS	(0.69%) 248	(0.31%) 56
Left overlapping	(0.36%) 127	(0.12%) 22
Lung, NOS	(0.22%) 80	0
Right lower	(17.45%) 6,228	(17.30%) 3,102
Right middle	(5.00%) 1,786	(5.50%) 986
Right upper	(32.99%) 11,774	(35.71%) 6,404
Right NOS	(1.14%) 407	(0.45%) 81
Right overlapping	(1.15%) 410	(0.54%) 96
Histology—no. (%)		
Adenocarcinoma	(61.74%) 22,037	(67.12%) 12,036
Adenosquamous	(2.86%) 1,021	(2.44%) 438
Large cell	(3.01%) 1,075	(2.53%) 454
Non-small cell	(3.72%) 1,327	(2.76%) 495
Other	(0.99%) 355	(0.73%) 131
Squamous	(27.67%) 9,874	(24.41%) 4,377
Grade—no. (%)		
Moderately, II	(41.20%) 14,703	(45.29%) 8,121
Poorly, III	(36.31%) 12,960	(28.56%) 5,121
Undifferentiated, IV	(1.96%) 701	(1.39%) 250
Unknown	(6.94%) 2,476	(5.64%) 1,012
Well, I	(13.59%) 4,849	(19.11%) 3,427
Surgical Procedure—no. (%)		
(Bi)Lobectomy	(76.16%) 27,182	(76.79%) 13,769
Penumonectomy	(5.52%) 1,971	(0.94%) 169
Segmentectomy	(3.04%) 1,084	(4.06%) 728
Sub-lobar resection, NOS	(0.62%) 222	(0.41%) 74
Wedge	(14.65%) 5,230	(17.80%) 3,191
Radiation—no. (%)		
No	(85.23%) 30,419	(96.77%) 17,352
Yes	(14.77%) 5,270	(3.23%) 579
Year of diagnosis—no. (%)		
2007	(17.03%) 6,077	(16.81%) 3,015
2008	(17.10%) 6,103	(16.90%) 3,030
2009	(16.99%) 6,062	(17.22%) 3,087
2010	(16.67%) 5,949	(16.83%) 3,018
2011	(16.44%) 5,868	(16.63%) 2,982
2012	(15.78%) 5,630	(15.61%) 2,799

predominance to both populations (50.4%—TS and 55.1%—ESR). The three largest ethnic groups in the TS were White, Black, and Hispanic, and they represented 78.6, 9.2, and 5.0% of the population, respectively. Likewise, the ESR population's three largest ethnic groups were White (79.6%), Black (8.4%), and Hispanic (4.6%). A similar proportion of patients presented with a low median family income (<$50,000) and was noted to be 29.8 and 28.7% in the TS and ESR populations, respectively. The majority of patients were married, 57.3% (TS) and 56.2% (ESR). 87.4% (TS) and 88.3% (ESR) patients were insured. Adenocarcinoma was the predominant histology (61.7%—TS and 67.1%—ESR).

Univariate Analysis of All Patients Undergoing Surgical Resection of Lung Cancer

Table 2 contains the demographic, histologic, and treatment details for the TS population for the nine different ethnic groups and used the White population as the reference group. Blacks presented with a younger age, less stage I tumors, less grade I tumors, lower income, higher percentage of adenocarcinomas, less nodes examined, and were less likely to be insured, but their number of nodes positive, nodal density, OS, and LCSS was the same. Their 30 and 90-day mortality did not differ as compared to Whites. Hispanic patients presented with younger age, higher median household income, lower rates of insurance, higher percentage of females, lower percentage of Stage I, more grade 1 tumors, higher percentage of adenocarcinomas, and had less nodes examined, but they had a similar number of nodes positive, nodal density, OS and LCSS. Hispanics had a similar 90-day mortality, but their 30-day mortality was higher than Whites (mean 1.8 vs 1.1%). Of all the ethnic groups, the Japanese presented with a highest mean age (70.9), the highest female predominance (62.3%), and the highest rates of insurance (98.0%), but there was a similar OS and LCSS to Whites. Blacks (58.3%) and Hispanics (59.2%) presented with a lower proportion of patients with Stage I NSCLC as compared to Whites (63.2%), but similar rates were noted in all other ethnic groups. The Other Asian group presented with the highest percentage of adenocarcinomas (78.5%), while American/Alaskan Natives presented with the highest percentage of squamous cell carcinomas (35.6%). The Chinese had the highest proportion of patients receiving a (bi)lobectomy at 86.1%, but the least receiving a pneumonectomy (2.5%) as well as a wedge resection (8.8%). Likewise, the Chinese were least likely to undergo a sub-lobar resection for tumors greater than 2 cm with only 5.0% receiving such treatment. Blacks (8.2), Hispanics (8.5), and Other Asians (8.3) were found to have less mean nodes examined than Whites (9.0), and a higher proportion of patients with positive nodes was noted in the Other Asian group (26 vs 21.8%), but none of the other ethnic groups differed from Whites in terms of the median number of nodes explored or number of nodes positive. The only ethnic group that differed from Whites in regards to nodal density was the Other Asian group, 0.10-Other Asians vs 0.07-Whites. The 30-day mortality was higher in the Hispanic patients, but lower in the Other Race and Japanese ethnic groups. The 90-day survival was significantly higher in the Other Race and Other Asian groups. As compared to Whites, OS and LCSS was significantly greater in the Chinese, South Asian, Other Asian, and the Other Race groups. Unadjusted OS by ethnic group can be found in the Kaplan–Meier survival in **Figure 1A**.

TABLE 2 | Demographic, histologic, and treatment details in the TS population for the nine different ethnic groups.

N = 35,689	White non-Hispanic	White Hispanic	Black	Chinese	Japanese	South Asian	Other Asian	Other Race	American Indian/ Alaskan
Patient numbers	28,052	1,779	3,276	568	302	112	1,011	457	132
Age at diagnosis, years									
Mean (95% CI)	67.4 (67.3–67.5)	**66.1 (65.5–66.6)**	**63.2 (62.8–63.5)**	66.9 (66.0–67.8)	**70.9 (69.7–72.0)**	**64.3 (62.1–66.6)**	**65.8 (65.2–66.5)**	**64.4 (63.4–65.4)**	**63.7 (62.1–65.4)**
Median (range)	68 (6–85)	68 (4–85)	63 (12–85)	68 (23–85)	73 (33–85)	65 (8–85)	67 (29–85)	66 (20–85)	64 (40–85)
Insurance, % (95% CI)									
Insured	90.1 (89.8–90.5)	**76.5 (74.5–78.5)**	**76.6 (75.1–78.0)**	**76.6 (73.1–80.1)**	**98.0 (96.4–99.6)**	**71.4 (62.9–79.9)**	**75.9 (73.2–78.5)**	**83.6 (80.2–87.0)**	**70.5 (62.6–78.3)**
Medicaid	7.5 (7.2–7.8)	**20.1 (18.3–22.0)**	**18.3 (17.0–19.6)**	**21.7 (18.3–25.1)**	**1.3 (0.0–2.6)**	**21.4 (13.7–29.1)**	**21.4 (18.8–23.9)**	**13.1 (10.0–16.2)**	**25.8 (18.2–33.3)**
Uninsured	1.8 (1.7–2.0)	**2.4 (1.7–3.1)**	**4.0 (3.3–4.6)**	1.2 (0.3–2.1)	**0.3 (0.0–1.0)**	6.2 (1.7–10.8)	2.7 (1.7–3.7)	2.4 (1.0–3.8)	0.8 (0.0–2.3)
Unknown	0.5 (0.5–0.6)	1.0 (0.5–1.4)	**1.2 (0.8–1.5)**	0.5 (0.0–1.0)	0.3 (0.0–1.0)	0.9 (0.0–2.7)	**0.1 (0.0–0.3)**	0.9 (0.0–1.7)	3.0 (0.1–6.0)
Income, % (95% CI)									
<50K	31.6 (31.1–32.2)	**18.3 (16.5–20.1)**	**40.5 (38.8–42.1)**	**1.8 (0.7–2.8)**	**2.6 (0.8–4.5)**	**6.5 (2.3–12.0)**	**4.3 (3.0–5.5)**	**5.3 (3.2–7.3)**	**24.2 (16.8–31.6)**
50K–74K	51.3 (50.8–51.9)	**61.8 (59.6–64.1)**	50.7 (49.0–52.4)	54.8 (50.6–58.9)	**87.4 (83.7–91.2)**	46.4 (37.0–55.8)	**66.0 (63.0–68.9)**	**70.0 (65.8–74.2)**	**70.5 (62.6–78.3)**
>75K	17.0 (16.6–17.5)	**19.8 (18.0–21.7)**	**8.8 (7.8–9.7)**	**43.5 (39.4–47.6)**	**9.9 (6.5–13.3)**	**46.4 (37.0–55.8)**	**29.8 (26.9–32.6)**	**24.7 (20.8–28.7)**	**5.3 (1.4–9.2)**
Sex, % (95% CI)									
Female	50.0 (49.4–50.6)	**54.5 (52.2–56.8)**	51.4 (49.7–52.6)	47.7 (43.6–51.8)	**62.3 (56.8–67.7)**	42.0 (32.7–51.2)	49 (45.9–52.0)	54.3 (49.7–58.9)	47.7 (39.1–56.3)
Male	50.0 (49.4–50.6)	**45.5 (43.2–47.8)**	48.6 (46.9–50.3)	52.3 (48.2–56.4)	**37.7 (32.2–43.2)**	58.0 (48.8–67.3)	51.0 (48.0–54.1)	45.7 (41.1–50.3)	52.3 (43.6–60.9)
Marital Status									
Married (including common law)	58.9 (58.3–59.5)	**54.2 (51.9–56.6)**	**37.2 (35.5–38.8)**	**74.6 (71.1–78.2)**	63.6 (58.1–69.0)	**73.2 (66.9–81.5)**	**71.1 (68.3–73.9)**	60.0 (56.4–64.5)	50.0 (41.4–58.6)
Single (never married)	9.5 (9.1–9.8)	**15.3 (13.7–17.0)**	**26.8 (25.3–28.3)**	**6.7 (4.6–8.8)**	**6.0 (3.3–8.6)**	8.9 (3.6–14.3)	7.6 (6.0–9.3)	10.1 (7.3–12.8)	12.1 (7.2–17.9)
Widowed	15.1 (14.7–15.6)	14.6 (12.9–16.2)	**12.9 (11.8–14.1)**	**9.2 (6.8–11.5)**	19.9 (15.3–24.4)	**5.4 (1.1–9.6)**	**12.1 (10.1–14.1)**	14.2 (11.0–17.4)	12.1 (7.2–17.9)
Other	16.5 (16.1–17.0)	15.9 (14.2–17.6)	**23.0 (21.6–24.5)**	**9.5 (7.1–11.9)**	**10.6 (7.1–14.1)**	12.5 (6.3–18.7)	**9.2 (7.4–11.0)**	15.8 (12.4–19.1)	**25.8 (18.2–33.3)**
Stage, % (95% CI)									
1	63.2 (62.6–63.7)	**59.2 (56.9–61.5)**	**58.3 (56.6–60.0)**	61.3 (57.2–65.3)	59.3 (53.7–64.8)	65.2 (56.2–74.1)	61.7 (58.7–64.7)	66.3 (62.0–70.7)	56.1 (47.5–64.6)
2	12.9 (12.5–13.3)	12.5 (10.9–14.0)	**14.5 (13.3–15.7)**	11.8 (9.1–14.5)	11.9 (8.2–15.6)	**7.1 (2.3–12.0)**	11.3 (9.3–13.2)	12.9 (9.8–16.0)	17.4 (10.9–24.0)
3	17.0 (16.6–17.5)	18.5 (16.7–20.4)	**19.0 (17.7–20.4)**	17.4 (14.3–20.6)	20.5 (15.9–25.1)	22.3 (14.5–30.2)	**20.2 (17.7–22.7)**	15.8 (12.4–19.1)	22.0 (14.8–29.1)
4	6.9 (6.6–7.2)	**9.8 (8.4–11.2)**	8.1 (7.1–9.1)	9.5 (7.1–11.9)	8.3 (5.2–11.4)	5.4 (1.1–9.6)	6.8 (5.3–8.4)	5.0 (3.0–7.0)	4.5 (0.9–8.1)
Histology, % (95% CI)									
Adenocarcinoma	60.2 (59.6–60.7)	**66.9 (64.8–69.1)**	**62.6 (61.0–64.3)**	**78.3 (74.9–81.7)**	**66.9 (61.5–72.2)**	**77.7 (69.8–85.5)**	**78.5 (76.0–81.1)**	**71.8 (67.6–75.9)**	**47.0 (38.3–55.6)**
Adenosquamous	2.9 (2.7–3.1)	3.4 (2.6–4.3)	2.9 (2.3–3.5)	2.8 (1.5–4.2)	3.0 (1.1–4.9)	**0.9 (0.0–2.7)**	2.2 (1.3–3.1)	1.8 (0.5–3.0)	3.8 (0.5–7.1)
Large cell	3.1 (2.9–3.3)	2.4 (1.7–3.1)	3.6 (3.0–4.3)	2.5 (1.2–3.7)	3.3 (1.3–5.3)	5.4 (1.1–9.6)	**1.2 (0.5–1.9)**	2.0 (0.7–3.2)	4.5 (0.9–8.1)
Non-small cell	3.7 (3.5–3.9)	(2.3–3.7)	**5.4 (4.6–6.1)**	2.6 (1.3–4.0)	2.3 (0.6–4.0)	2.7 (0.0–5.7)	**2.0 (1.1–2.8)**	**1.8 (0.5–3.0)**	8.3 (3.6–13.1)
Others	0.9 (0.8–1.1)	**1.7 (1.1–2.4)**	1.1 (0.7–1.4)	1.1 (0.2–1.9)	0.7 (0.0–1.6)	0.9 (0.0–2.7)	0.7 (0.2–1.2)	2.0 (0.7–3.2)	0.8 (0.0–2.3)
Squamous	29.3 (28.7–29.8)	**22.7 (20.8–24.7)**	**24.4 (22.9–25.9)**	**12.7 (9.9–15.4)**	**23.8 (19.0–28.7)**	**12.5 (6.3–18.7)**	**15.4 (13.2–17.7)**	**20.8 (17.1–24.5)**	35.6 (27.3–43.9)
Surgical category, % (95% CI)									
(Bi)Lobectomy	75.7 (75.2–76.2)	76.5 (74.5–78.5)	75.8 (74.3–77.2)	**86.1 (83.2–88.9)**	80.4 (76.0–85.0)	80.4 (72.9–87.8)	**81.4 (79.0–83.8)**	77.9 (74.1–81.7)	77.3 (70.0–84.5)

(*Continued*)

TABLE 2 | Continued

N = 35,689	White non-Hispanic	White Hispanic	Black	Chinese	Japanese	South Asian	Other Asian	Other Race	American Indian/ Alaskan
Pneumonectomy	5.7 (5.4–6.0)	5.5 (4.4–6.5)	5.4 (4.6–6.2)	**2.5 (1.2–3.7)**	3.6 (1.5–5.8)	3.6 (0.1–7.1)	**3.9 (2.7–5.0)**	4.6 (2.7–6.5)	9.1 (4.1–14.1)
Segmentectomy	3.1 (2.9–3.3)	3.2 (2.4–4.0)	2.9 (2.3–3.4)	2.3 (1.1–3.5)	3.6 (1.5–5.8)	**0.9 (0.0–2.7)**	2.7 (1.7–3.7)	**1.8 (0.5–3.0)**	2.3 (0.0–4.8)
Sub-lobar resection, NOS	0.6 (0.5–0.7)	0.9 (0.5–1.3)	1.0 (0.6–1.3)	0.4 (0.0–0.8)	0.7 (0.0–1.6)	0.9 (0.0–2.7)	0.5 (0.1–0.9)	1.1 (0.1–2.1)	NA
Wedge Resection	14.9 (14.5–15.4)	13.9 (12.3–15.6)	15.0 (13.8–16.2)	**8.8 (6.5–11.1)**	11.6 (8.0–15.2)	14.3 (7.7–20.9)	**11.6 (9.6–13.5)**	14.7 (11.4–17.9)	11.4 (5.9–16.8)
Sub-lober > 2 cm, % (95% CI)									
No	92.6 (92.3–92.9)	(91.5–93.8)	(91.3–93.1)	**95.0 (93.3–96.7)**	(89.4–95.2)	(87.0–96.8)	(91.3–94.4)	(92.7–96.7)	(91.1–98.3)
Yes	7.4 (7.1–7.7)	7.4 (6.2–8.5)	7.8 (6.9–8.7)	**5.0 (3.3–6.7)**	7.7 (4.8–10.6)	8.1 (3.2–13.0)	7.1 (5.6–8.7)	5.3 (3.3–7.3)	5.3 (1.7–8.9)
Number of nodes examined									
Mean (95% CI)	9.0 (8.9–9.1)	**8.5 (8.2–8.9)**	**8.2 (8.0–8.5)**	9.0 (8.3–9.7)	9.0 (8.1–9.8)	9.9 (8.0–11.8)	**8.3 (7.8–8.7)**	8.6 (7.9–9.3)	8.3 (6.7–9.9)
Median (range)	7 (0–90)	7 (0–87)	6 (0–90)	7 (0–90)	7 (0–44)	6.5 (0–68)	6 (0–60)	7 (0–67)	6 (0–54)
Number of nodes positive									
Mean (95% CI)	0.6 (0.6–0.7)	0.7 (0.6–0.7)	0.6 (0.6–0.7)	0.7 (0.5–0.9)	0.8 (0.6–1.1)	0.8 (0.4–1.2)	0.7 (0.6–0.9)	0.8 (0.6–0.9)	0.8 (0.5–1.2)
Median (range)	0 (0–61.0)	0 (0–26.0)	0 (0–29.0)	0 (0–28.0)	0 (0–21.0)	0 (0–13.0)	0 (0–16.0)	0 (0–24.0)	0 (0–17.0)
Node positivity, % (95% CI)									
No	78.2 (77.7–78.6)	77.5 (75.6–79.5)	76.7 (75.3–78.1)	74.5 (70.9–78.1)	73.8 (68.9–78.8)	75.9 (67.8–83.9)	**(71.3–76.7)**	76.8 (72.9–80.7)	74.2 (66.7–81.8)
Yes	21.8 (21.4–22.3)	22.5 (20.5–24.4)	23.3 (21.9–24.7)	25.5 (21.9–29.1)	26.2 (21.2–31.1)	24.1 (16.1–32.2)	**26.0 (23.3–28.7)**	23.2 (19.3–27.1)	25.8 (18.2–33.3)
Node density									
Mean (95% CI) (0.06–0.07)	0.07 (0.06–0.07)	0.08 (0.07–0.09)	0.08 (0.07–0.08)	0.09 (0.07–0.11)	0.08 (0.06–0.10)	0.08 (0.04–0.11)	**0.10 (0.08–0.11)**	0.08 (0.07–0.10)	0.08 (0.05–0.10)
Median (range)	0 (0–1.0)	0 (0–1.0)	0 (0–1.0)	0 (0–1.0)	0 (0–1.0)	0 (0–1.0)	0 (0–1.0)	0 (0–1.0)	0 (0–0.9)
30-day survival, % (95% CI)									
No	1.1 (1.0–1.2)	**1.8 (1.2–2.4)**	1.1 (0.7–1.4)	1.1 (0.2–1.9)	**0.3 (0.0–1.0)**	3.3 (0.1–6.4)	1.3 (0.6–2.0)	**0.2 (0.0–0.7)**	3.1 (0.1–6.0)
Yes	98.9 (98.8–99.0)	**98.2 (97.6–98.8)**	98.9 (98.6–99.3)	98.9 (98.1–99.8)	**99.7 (99.0–100.0)**	100.0 (93.6–99.9)	98.7 (98.0–99.4)	**99.8 (99.3–100.0)**	96.9 (94.0–100.0)
90-day survival, % (95% CI)									
No	4.1 (3.9–4.4)	5.2 (4.1–6.3)	4.0 (3.3–4.7)	2.8 (1.4–4.2)	2.4 (0.6–4.2)	1.9 (0.0–4.5)	**2.7 (1.7–3.7)**	**1.9 (0.6–3.2)**	6.9 (2.5–11.3)
Cancer death, % (95% CI)									
No	76.6 (76.1–77.1)	77.7 (75.7–79.6)	76.1 (74.7– 77.6)	**82.7 (79.6–85.9)**	75.8 (71.0–80.7)	**85.7 (79.1–92.3)**	**81.1 (78.7–83.5)**	**84.9 (81.6–88.2)**	81.1 (74.3–87.8)
Yes	23.4 (22.9–23.9)	22.3 (20.4–24.3)	23.8 (22.4–25.3)	**17.3 (14.1–20.4)**	24.2 (19.3–29.0)	14.3 (7.7–20.3)	**18.9 (16.5–21.3)**	**15.1 (11.8–18.4)**	18.9 (12.2–25.7)
Other cause death, % (95% CI)									
No	91.9 (91.6–92.2)	**93.5 (92.4–94.7)**	92.4 (91.5–93.3)	**94.9 (93.1–96.7)**	91.4 (88.2–94.6)	94.6 (90.4–98.9)	**94.0 (92.5–95.4)**	**95.0 (93.0–97.0)**	90.9 (85.9–95.9)
Yes	8.1 (7.8–8.4)	**6.5 (5.3–7.6)**	7.6 (6.7–8.5)	**5.1 (3.3–6.9)**	8.6 (5.4–11.8)	5.4 (1.1–9.6)	**6.0 (4.6–7.5)**	**5.0 (3.0–7.0)**	9.1 (4.1–14.1)

95% confident intervals are given in parentheses. W is used as reference population. All characteristics differing from the W are in bold-print and have brown colored backgrounds. Otherwise, green and blue depict individual rows are different colors for ease of visualization.

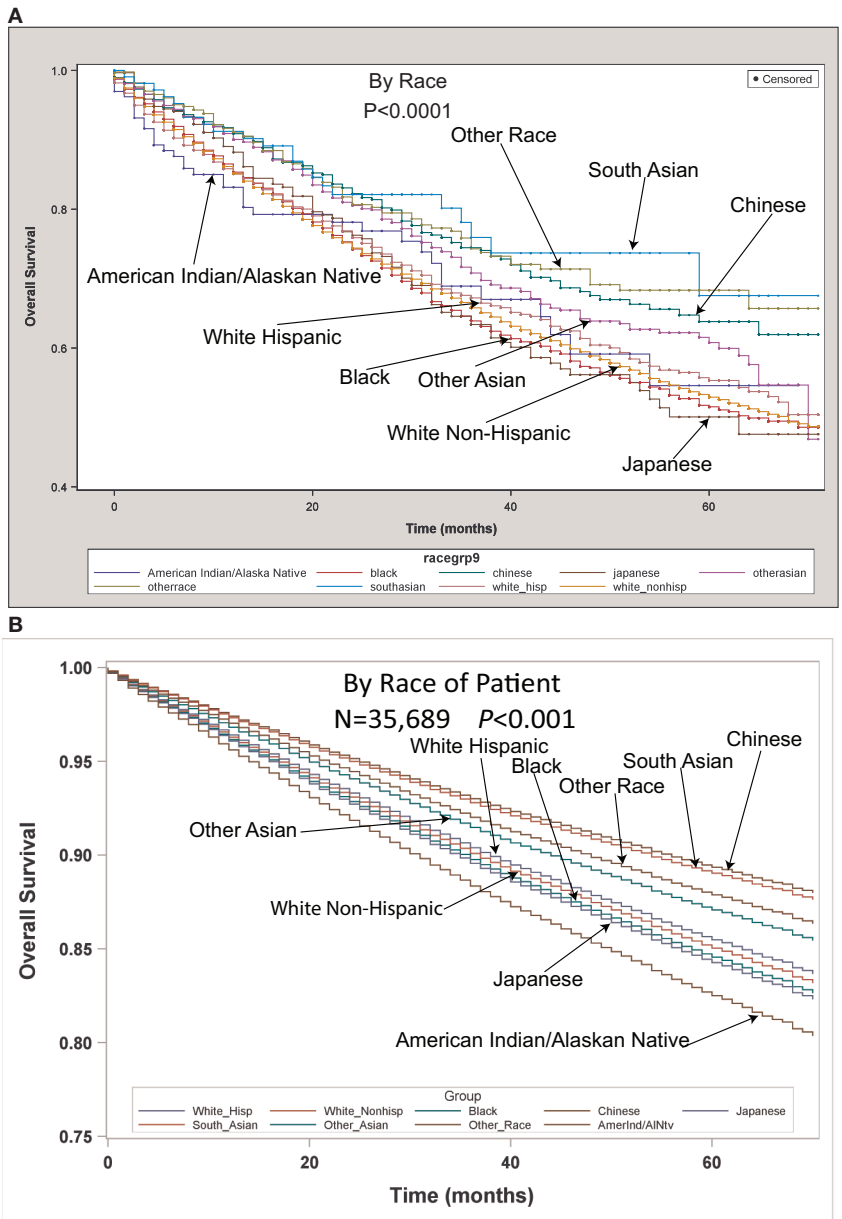

FIGURE 1 | **(A)** Unadjusted overall survival (OS) by ethnic group in the TS population. **(B)** Multivariable adjusted OS by ethnic group in the TS population.

OS in the Total Surgical Population

Multivariable analysis (MVA) for OS for TS population can be seen in **Table 3**. Age ($p < 0.0001$, HR = 1.029) and male sex ($p < 0.0001$, HR = 1.453) were significantly associated with OS. OS was significantly better than Whites (HR = 0.693–0.843) in all groups except for AI/ANs, Japanese, Blacks, and Hispanics who had a similar OS. MVA-adjusted OS by ethic group can be seen in **Figure 1B**. As compared to Connecticut, worse survival was noted in California, Greater Georgia, Iowa, Kentucky, Louisiana, and Utah. OS was not income dependent. Insured patients had a better OS than those on Medicaid ($p < 0.0001$, HR = 1.286). Married patients had a better OS than divorced ($p < 0.0001$, HR = 1.191), widowed ($p < 0.0001$, HR = 1.229), and single patients ($p < 0.0001$, HR = 1.1215). As compared to Stage I, Stages II–IV were associated with a worse OS with a progressively increasing HR (all $p < 0.0001$, HR = 1.702–3.273). As compared to patients with adenocarcinoma, all histologies were associated with a worse OS ($p < 0.0001$ to <0.0008, HR = 1.119–1.564). Using well-differentiated tumors as a reference, all other tumor grades were associated with a worse OS (all $p < 0.0001$, HR = 1.665–3.273). Segmentectomies and (bi)lobectomies were associated with a better OS than pneumonectomies, $p = 0.0011$, HR = 0.80; $p < 0.0001$, HR = 0.72, respectively. Patients who received radiation ($p < 0.0001$, HR = 1.162) experienced worse

TABLE 3 | Multivariate analysis of overall survival in the TS population.

All surgical (N = 35,689)	p-Value	Hazard ratio
Age—years	**<0.0001**	**1.029**
Sex		
Female	–	1
Male	**<0.0001**	**1.453**
Race		
White Hispanic	0.49	0.968
White non-Hispanic	–	1
Black	0.46	1.026
Chinese	<0.0001	0.693
Japanese	0.06	1.027
South Asian	0.01	0.843
Other Asian	0.01	0.843
Other Race	0.02	0.772
American Indian/Alaskan Native	0.74	1.065
Surveillance Epidemiology and End Reporting Registry		
Alaska Natives	0.72	0.873
Atlanta	0.40	1.062
California excl SF/SJM/LA	0.001	1.167
Connecticut	–	1
Detroit	0.95	0.996
Greater Georgia	0.0005	1.217
Hawaii	0.33	1.102
Iowa	0.01	1.176
Kentucky	0.0001	1.249
Los Angeles	0.06	1.111
Louisiana	0.004	1.198
New Jersey	0.12	1.081
New Mexico	0.22	1.127
Rural Georgia	0.82	1.049
San Francisco-Oakland	0.12	1.107
San Jose-Monterey	0.49	1.059
Seattle	0.07	1.126
Utah	0.008	1.269
Income		
<$50,000	0.05	1.06
$50,000–75,000	–	1
>75,000	0.24	0.963
Marital status		
Divorced	<0.0001	1.191
Married	–	1
Separated	0.18	1.144
Single	<0.0001	1.215
Unknown	0.05	1.118
Domestic partner	0.67	0.783
Widowed	<0.0001	1.229
Stage		
I	–	1
II	<0.0001	1.702
III	<0.0001	1.867
IV	<0.0001	3.273
Insurance		
Insured	–	1
Medicaid	<0.0001	1.286
Uninsured	0.08	1.135
Unknown	0.33	1.286
Lateral location		
Bronchus, Left	0.92	1.014
Bronchus, right	0.01	1.42
Bronchus, unknown	0.33	0.613
Left lower	0.08	1.056
Left upper	0.10	1
Left NOS	0.04	1.211
Left overlapping	0.15	0.801
Lung, NOS	<0.0001	2.061
Right lower	<0.0001	1.23
Right middle	0.75	1.015
Right upper	–	1
Right NOS	0.45	1.062
Right overlapping	<0.0001	1.371
Histology—no. (%)		
Adenocarcinoma	–	1
Adenosquamous	0.0008	1.196
Large cell	<0.0001	1.348
Non-small cell	0.0003	1.174
Other	<0.0001	1.564
Squamous	<0.0001	1.159
Grade		
Moderately, II	<0.0001	1.702
Poorly, III	<0.0001	1.867
Undifferentiated, IV	<0.0001	3.273
Unknown	<0.0001	1.665
Well, I	–	1
Surgical procedure		
(Bi)Lobectomy	<0.0001	0.721
No surgery		
Pneumonectomy	–	1
Segmentectomy	0.0011	0.800
Sub-lobar resection, NOS	0.13	1.172
Wedge	0.63	0.978
Radiation post-operative	<0.0001	1.162
Number of nodes examined	<0.0001	0.988
Number of nodes positive	<0.0001	1.04
Node density	<0.0001	1.429
Year of diagnosis—no. (%)		
2007	–	1
2008	0.95	1.002
2009	0.28	0.969
2010	0.02	0.927
2011	0.0018	0.888
2012	<0.0001	0.787

OS. Number of nodes examined was associated with better OS ($p < 0.0001$, HR = 0.988), but number of nodes positive ($p < 0.0001$, HR = 1.04) and lymph node density ($p < 0.0001$, HR = 1.429) were associated with worse OS. Compared to year 2007, those patients diagnosed in 2010–2012 had significantly better OS with progressively decreasing hazard ratios. OS by insurance status can be seen in **Figure 2**.

OS in the ESR Population

Multivariable analysis for OS for ESR population can be seen in **Table 4**. Age ($p < 0.0001$, HR = 1.034), and male sex ($p < 0.0001$, HR = 1.506) were significantly associated with OS. OS was significantly better than Whites in the Other Race ($p = 0.0051$, HR = 0.555) and Other Asian groups ($p = 0.012$, HR = 0.736), but it was similar in all other ethnic groups. As compared to Connecticut, worse survival was noted in California, Greater Georgia, Kentucky, Louisiana, and Utah. OS was not income dependent. Insured patients had a better OS than those on Medicaid ($p < 0.0001$, HR = 1.385). Married patients had a

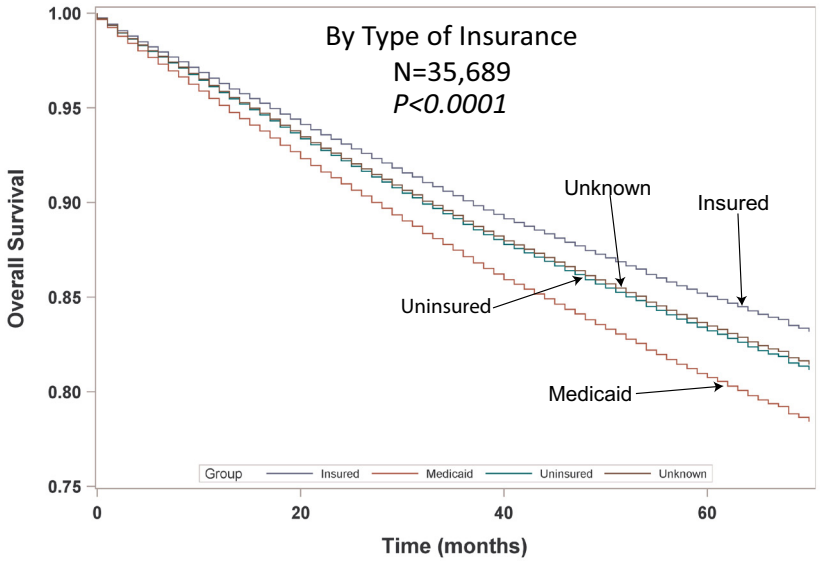

FIGURE 2 | Multivariable adjusted overall survival by insurance type in TS population.

better OS than divorced ($p < 0.0001$, HR = 1.301), widowed ($p < 0.0001$, HR = 1.292), and single patients ($p = 0.0015$, HR = 1.121). Increasing tumor size ($p < 0.0001$, HR = 1.016) and T2 vs T1 ($p < 0.0129$, HR = 1.107) had a worse OS. Only the right lower lobe location was associated with survival ($p < 0.0089$, HR = 1.132). In comparison to patients with adenocarcinoma, large cell carcinoma, NSCLC-NOS, and squamous cell carcinoma were associated with a worse OS ($p < 0.0011$ to <0.0001, HR = 1.15–1.381). Using well-differentiated tumors as a reference, all other tumor grades were associated with a worse OS (HR = 1.572–1.846). Segmentectomies ($p < 0.0090$, HR = 1.235), pneumonectomies ($p < 0.0001$, HR = 1.782), and wedge resections ($p < 0.0001$, HR = 1.301) were associated with a worse OS than (bi)lobectomies. Patients who received radiation ($p < 0.0001$, HR = 1.36) experienced worse OS. Number of nodes examined was associated with better OS ($p < 0.0001$, HR = 0.984). Compared to year 2007, those patients diagnosed in 2010 and 2012 had significantly better OS.

LCSS in the ESR Population

Multivariate analysis for LCSS for ESR population can be seen in **Table 5**. Age ($p < 0.0001$, HR = 1.023) and male sex ($p < 0.0001$, HR = 1.393) were significantly associated with LCSS. LCSS was not significantly associated with race or income. As compared to Connecticut, worse LCSS was noted in Greater Georgia, Kentucky, and Louisiana. Insured patients had a better LCSS than those on Medicaid ($p < 0.0001$, HR = 1.445). Married patients had a better LCSS than divorced ($p < 0.0004$, HR = 1.301) and widowed ($p < 0.0036$, HR = 1.200). Increasing tumor size ($p < 0.0001$, HR = 1.020) and T2 vs T1 ($p = 0.0003$, HR = 1.213) were associated with a worse LCCS. Only the right middle lobe location was associated with LCSS ($p < 0.0469$, HR = 0.803). As compared to patients with adenocarcinoma, NSCLC-NOS ($p < 0.002$, HR = 1.382) and large cell carcinoma ($p = 0.0003$, HR = 1.543) were correlated with a worse LCSS. Using well-differentiated tumors as a reference, all other tumor grades were associated with a worse LCSS (HR = 1.693–2.171). Segmentectomies ($p < 0.0065$, HR = 1.329), pneumonectomies ($p = 0.0027$, HR = 1.781), and wedge resections ($p < 0.0001$, HR = 1.353) were associated with a worse LCSS than (bi) lobectomies. Patients who received radiation ($p < 0.0001$, HR = 1.556) experienced worse LCSS. Number of nodes examined was associated with better LCSS ($p < 0.0001$, HR = 0.978). Compared to year 2007, those patients diagnosed in all other years, except for 2011 had a significantly better LCSS. OS and LCSS by marital status can be seen in **Figures 3A,B**.

90-Day Mortality Analysis

Multivariate analysis for 90-day OS for TS population can be seen in **Table 6**. Age ($p < 0.0001$, HR = 1.045) and male sex ($p < 0.0001$, HR = 1.547) were significantly associated with 90-day OS. 90-day mortality was the same in all ethnic groups. Higher median income (>$75,000) was associated with a better survival. As compared to Connecticut, worse survival was noted in Louisiana and Utah. Insured patients had a better 90-day OS than those on Medicaid ($p = 0.0005$, HR = 1.359) and those with unknown insurance ($p = 0.0003$, HR = 2.774). Married patients had a better OS than single ($p = 0.0188$, HR = 1.239) and unmarried/domestic partner patients ($p = 0.0310$, HR = 3.523). Right bronchus ($p = 0.0001$, HR = 2.652), bronchus unknown ($p = 0.0012$, HR = 6.926), and right lower lobe ($p < 0.0001$, HR = 1.386) were associated with worse 90-day mortality than the right upper lobe location. As compared to Stage I, Stages II–IV were associated with a worse OS with a progressively increasing HRs (all $p < 0.0001$, HR = 1.607–4.381). As compared to patients with adenocarcinoma, NSCLC-NOS ($p < 0.0034$, HR = 1.460), other ($p < 0.0001$, HR = 2.334), and squamous cell carcinoma ($p < 0.0001$, HR = 1.436) had a higher risk of 90-day mortality.

TABLE 4 | Multivariate analysis for overall survival in early-stage resectable population.

Early-stage resectable (*N* = 17,931)	*p*-Value	Hazard ratio
Age—years	<0.0001	1.034
Sex		
Female	–	1
Male	<0.0001	1.506
Race		
White Hispanic	0.08	0.856
White non-Hispanic	–	1
Black	0.80	0.984
Chinese	0.15	0.787
Japanese	0.19	0.757
South Asian	0.35	0.702
Other Asian	0.012	0.736
Other Race	0.0051	0.555
American Indian/Alaskan Native	0.69	0.873
Surveillance Epidemiology and End Reporting Registry		
Alaska Natives	0.63	0.598
Atlanta	0.47	1.098
California excl SF/SJM/LA	0.05	1.173
Connecticut	–	1
Detroit	0.57	1.06
Greater Georgia	0.004	1.312
Hawaii	0.11	1.32
Iowa	0.70	1.043
Kentucky	0.0099	1.286
Los Angeles	0.77	1.028
Louisiana	0.03	1.258
New Jersey	0.22	1.108
New Mexico	0.38	1.158
Rural Georgia	0.13	0.503
San Francisco-Oakland	0.61	1.06
San Jose-Monterey	0.95	0.99
Seattle	0.18	1.154
Utah	0.05	1.397
Income		
<$50,000	0.71	1.019
$50,000–74,000	–	1
≥75,000	0.19	0.93
Marital status		
Divorced	<0.0001	1.301
Married	–	1
Separated	0.23	1.239
Single	0.0015	1.211
Unknown	0.54	1.062
Domestic partner	0.84	1.221
Widowed	<0.0001	1.292
Tumor size	<0.0001	1.016
Tumor stage		
T1	–	1
T2	0.01	1.107
Insurance		
Insured	–	1
Medicaid	<0.0001	1.385
Uninsured	0.69	1.065
Unknown	0.67	0.887
Lateral location		
Bronchus, left	0.29	0.468
Bronchus, right	0.87	0.891
Bronchus, unknown	0.89	0.872
Left lower	0.36	0.952
Left upper	0.92	1.004
Left NOS	0.14	1.454
Left overlapping	0.90	1.055
Right lower	0.0089	1.132
Right middle	0.09	0.869
Right upper	–	1
Right NOS	0.84	0.946
Right overlapping	0.75	0.926
Histology—no. (%)		
Adenocarcinoma	–	1
Adenosquamous	0.16	1.15
Large cell	0.0011	1.381
Non-small cell	0.001	1.317
Other	0.78	0.942
Squamous	<0.0001	1.236
Grade		
Moderately, II	<0.0001	1.621
Poorly, III	<0.0001	1.846
Undifferentiated, IV	0.0019	1.572
Unknown	<0.0001	1.707
Well, I	–	1
Surgical procedure		
(Bi)Lobectomy	–	1
Pneumonectomy	<0.0001	1.782
Segmentectomy	0.009	1.235
Sub-lobar resection, NOS	0.10	1.442
Wedge	<0.0001	1.301
Radiation post-operative	<0.0001	1.36
Number of nodes examined	<0.0001	0.984
Year of diagnosis		
2007	–	1
2008	0.03	0.904
2009	0.13	0.929
2010	0.0016	0.832
2011	0.44	0.949
2012	0.0004	0.661

Using well-differentiated tumors as a reference, 90-day mortality was higher in patients having poorly differentiated, undifferentiated, and unknown differentiated tumors. Pneumonectomies were associated with a significantly higher 90-day mortality than all other resection types ($p = 0.0281$ to <0.0001, HR = 0.418–0.775), except for sub-lobar, NOS which had a higher mortality ($p = 0.0012$, HR = 1.885). Patients who received radiation experienced a significantly lower 90-day mortality ($p < 0.0001$, HR = 0.217). Number of nodes examined was associated with better OS ($p = 0.0001$, HR = 0.984), but number of nodes positive and lymph node density were associated with worse OS. Similar 90-day mortality was noted to 2007 for years 2008–2012.

Characteristics Associated With Nodal Positivity

In **Table 7**, a multivariate analysis was performed for the risk of having nodal positivity in patients undergoing a definitive surgical procedure with a T1–T2 tumor <2 cm and at least one lymph node examined. The results were adjusted for type of surgical resection. Age ($p < 0.0001$, HR = 1.036) and male sex ($p < 0.0001$, HR = 1.386) were significantly associated with positive nodes.

TABLE 5 | Multivariate analysis for lung cancer-specific survival in early-stage resectable population.

Early-stage resectable (*N* = 17,931)	*p*-Value	Hazard ratio
Age—years	<0.0001	1.023
Sex		
Female		1
Male	<0.0001	1.393
Race		
White Hispanic	0.26	0.877
White non-Hispanic	–	1
Black	0.54	0.949
Chinese	0.41	0.839
Japanese	0.07	0.534
South Asian	0.76	0.872
Other Asian	0.06	0.745
Other Race	0.10	0.655
American Indian/Alaskan Native	0.14	0.348
Surveillance Epidemiology and End Reporting Registry		
Alaska Natives	0.44	2.575
Atlanta	0.82	0.96
California excl SF/SJM/LA	0.17	1.183
Connecticut	–	1
Detroit	0.36	1.13
Greater Georgia	0.02	1.344
Hawaii	0.60	1.134
Iowa	0.16	1.218
Kentucky	0.0025	1.473
Los Angeles	0.41	1.112
Louisiana	0.0065	1.457
New Jersey	0.55	1.07
New Mexico	0.05	1.497
Rural Georgia	0.36	0.585
San Francisco-Oakland	0.92	0.985
San Jose-Monterey	0.65	0.909
Seattle	0.76	1.046
Utah	0.31	1.278
Income		
<$50,000	0.17	0.912
$50,000–74,000	–	1
≥75,000	0.62	0.965
Marital status		
Divorced	0.0004	1.272
Married	–	1
Separated	0.96	0.988
Single	0.06	1.16
Unknown	0.61	0.935
Domestic partner	0.97	0
Widowed	0.0036	1.2
Tumor size	<0.0001	1.02
Tumor stage		
T1	–	1
T2	0.0003	1.213
Insurance		
Insured		1
Medicaid	<0.0001	1.445
Uninsured	0.89	1.029
Unknown	0.84	0.932
Lateral location		
Bronchus, left	0.92	0
Bronchus, right	0.63	1.41
Bronchus, unknown	0.97	0
Left lower	0.68	0.971
Left upper	0.91	0.994
Left NOS	0.42	1.334
Left overlapping	0.77	1.16
Right lower	0.09	1.111
Right middle	0.05	0.803
Right upper	–	1
Right NOS	0.86	0.941
Right overlapping	0.91	0.966
Histology—no. (%)		
Adenocarcinoma	–	1
Adenosquamous	0.43	1.106
Large cell	0.0003	1.543
Non-small cell	0.002	1.382
Other	0.87	0.957
Squamous	0.06	1.104
Grade		
Moderately, II	<0.0001	1.81
Poorly, III	<0.0001	2.171
Undifferentiated, IV	0.005	1.693
Unknown	<0.0001	2.013
Well, I	–	1
Surgical procedure		
(Bi)Lobectomy	–	1
Pneumonectomy	0.003	1.781
Segmentectomy	0.007	1.329
Sub-lobar resection, NOS	0.08	1.61
Wedge	<0.0001	1.353
Radiation post-operative	<0.0001	1.556
Number of nodes examined	<0.0001	0.978
Year of diagnosis—no. (%)		
2007	–	1
2008	0.02	0.875
2009	0.02	0.857
2010	0.001	0.779
2011	0.06	0.842
2012	0.003	0.612

Positive nodes were not associated with any ethnic or income group. As compared to Connecticut, a greater risk of positive nodes was found in Greater Georgia, Hawaii, and Utah. T2 tumor had a higher risk of positive nodes than T1 tumors ($p = 0.0004$, HR = 1.289). Patients without a married partner ($p < 0.0033$, HR = 1.376) or without insurance ($p < 0.0003$, HR = 1.376) were more likely to have positive nodes. Right lower lobe location ($p < 0.0353$, HR = 1.185) was associated with a higher likelihood of positive nodes than the right upper lobe location. As compared to patients with adenocarcinoma, adenosquamous cell ($p < 0.0316$, HR = 1.416), large cell ($p < 0.0252$, HR = 1.426), and squamous cell carcinomas ($p = 0.0437$, HR = 1.149) had a higher risk of having positive nodes. Using well-differentiated tumors as a reference, nodal positivity was higher in patients having poorly differentiated ($p < 0.0001$, HR = 2.157), moderately differentiated ($p < 0.0001$, HR = 1.784), and unknown differentiated tumors ($p < 0.0001$, HR = 1.802). Number of nodes examined was not associated with nodal positivity. Nodal positivity was less likely in years 2010–2012 ($p = 0.0427$–0.0027), with a progressively decreased HR (0.821–0.0027).

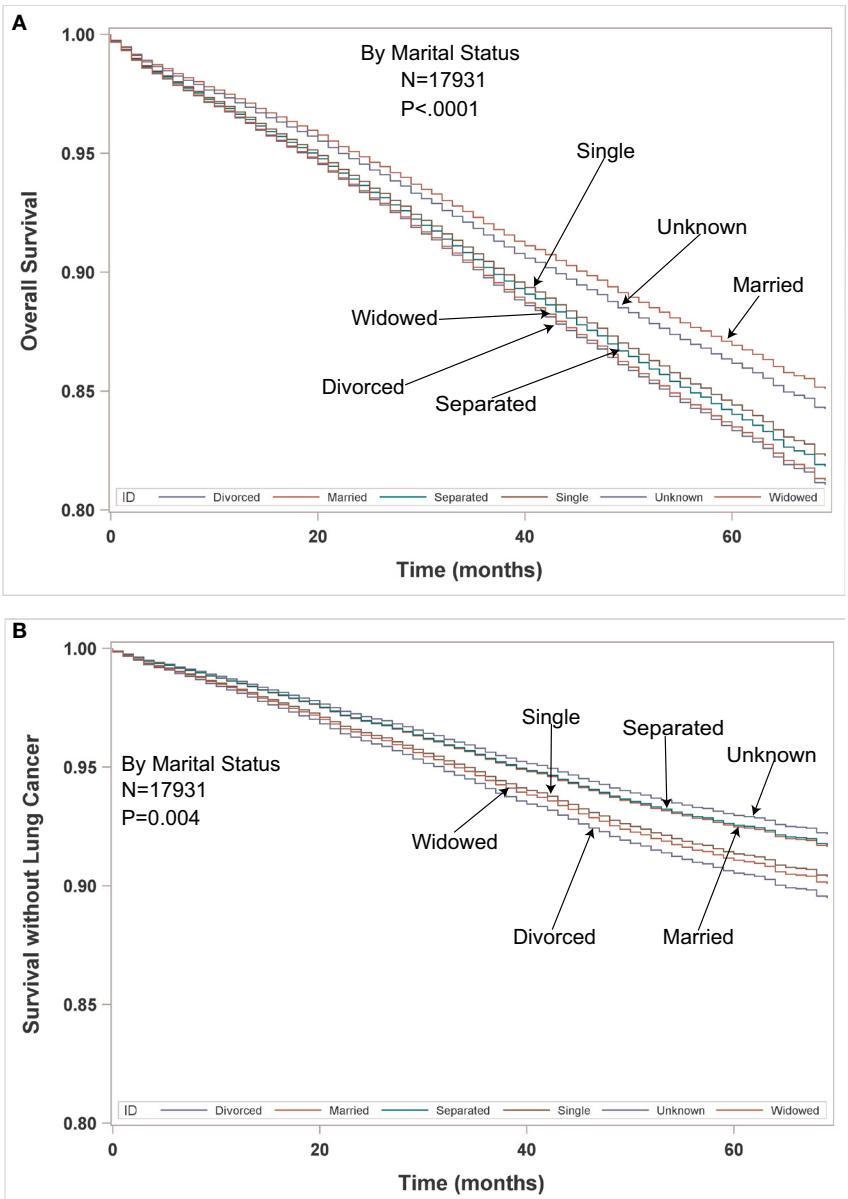

FIGURE 3 | **(A,B)** Multivariable adjusted overall survival and lung cancer-specific survival in the early-stage resectable population by marital status.

DISCUSSION

The purpose of our investigation was to assess difference in outcomes (OS and 30/90 day mortality), presentation, and treatment in nine different ethnic groups who underwent surgical resection of NSCLC. As compared to Whites, the unadjusted OS and LCSS was significantly greater in the Chinese, South Asian, Other Asian, and the Other Race groups. After multivariable adjustment, OS was significantly better than Whites in all groups except for AI/ANs, Japanese, Blacks, and Hispanics who had a similar OS. Despite presenting with higher stage tumors, lower median incomes, lower rates of insurance, less nodes examined, less grade 1 tumors, and lower marriage rates, the OS and LCSS of the Black group were not significantly different than that of the Whites. In comparison to the White group, Hispanics had a similar LCSS, but had an improved OS despite having a higher unadjusted 30-day mortality. Although Hispanics presented with a lower percentage of Stage I patients, lower marriage rates, less nodes examined, and lower rates of insurance, they presented with many better prognostic features compared to the Whites including higher income, lower tumor grades, younger age, higher percentage of female patients, and a higher percentage of adenocarcinomas. The Chinese and Other Asian groups were more likely to receive a (bi) lobectomy than the Whites, but the other ethnic groups largely did not differ in the type of surgical procedure. The reason for the higher 30-day mortality (unadjusted) in the Hispanic population

TABLE 6 | Multivariate analysis for 90-day overall survival in TP.

All surgical (*N* = 35,689)	*p*-Value	Hazard ratio
Age—years	<0.0001	1.045
Sex		
Female	–	1
Male	<0.0001	1.547
Race		
White Hispanic	0.09	1.219
White non-Hispanic	–	1
Black	0.96	1.005
Chinese	0.58	0.861
Japanese	0.11	0.532
South Asian	0.58	0.672
Other Asian	0.21	0.772
Other Race	0.11	0.563
American Indian/Alaskan Native	0.11	1.861
Surveillance Epidemiology and End Reporting Registry		
Alaska Natives	0.80	0.813
Atlanta	0.34	1.212
California excl SF/SJM/LA	0.51	1.098
Connecticut	–	1
Detroit	0.41	0.858
Greater Georgia	0.10	1.301
Hawaii	0.91	1.036
Iowa	0.91	1.022
Kentucky	0.09	1.317
Los Angeles	0.13	1.271
Louisiana	0.04	1.428
New Jersey	0.39	1.134
New Mexico	0.25	1.332
Rural Georgia	0.16	1.854
San Francisco-Oakland	0.96	0.99
San Jose-Monterey	0.79	1.068
Seattle	0.10	1.347
Utah	0.01	1.735
Income		
<$50,000	0.07	1.16
$50,000–75,000	–	1
>75,000	0.01	0.782
Tumor stage		
I	–	1
II	<0.0001	1.607
III	<0.0001	2.238
IV	<0.0001	4.381
Marital status		
Divorced	0.78	0.974
Married	–	1
Separated	0.88	0.954
Single (never married)	0.02	1.239
Unknown	0.52	1.1
Unmarried or domestic partner	0.03	3.523
Widowed	0.13	1.127
Insurance		
Insured	–	1
Medicaid	0.0005	1.359
Uninsured	0.24	1.279
Unknown	0.0003	2.774
Lateral location		
Bronchus, left	0.51	0.786
Bronchus, right	0.0001	2.652
Bronchus, unknown	0.0012	6.926
Left lower	0.37	0.917
Left upper	0.43	1.063
Left NOS	0.01	1.628
Left overlapping	0.34	1.369
Lung, NOS	0.0004	2.37
Right lower	<0.0001	1.386
Right middle	0.80	0.965
Right upper	–	1
Right NOS	0.004	1.587
Right overlapping	<0.0001	2.725
Histology—no. (%)		
Adenocarcinoma	–	1
Adenosquamous	0.79	1.044
Large cell	0.42	1.139
Non-small cell	0.003	1.46
Other	<0.0001	2.334
Squamous	<0.0001	1.436
Grade		
Moderately, II	0.23	1.134
Poorly, III	0.003	1.378
Undifferentiated, IV	0.005	1.745
Unknown	0.0004	1.584
Well, I	–	1
Surgical procedure		
Sub-lobar resection, NOS	0.001	1.885
(Bi)lobectomy	<0.0001	0.475
Pneumonectomy	–	1
Segmentectomy	<0.0001	0.418
Wedge	0.03	0.775
Radiation post-operative	<0.0001	0.217
Number of nodes examined	0.0001	0.984
Number of nodes positive	0.51	0.986
Node density	0.08	1.352
Year of diagnosis—no. (%)		
2007	–	1
2008	0.35	1.087
2009	0.41	1.077
2010	0.82	1.021
2011	0.96	0.996
2012	0.53	1.065

is currently unknown, but the all other populations had a similar or better (Japanese or Other Race) 30-day survival to the White population. Although the unadjusted 90-day mortality was lower in the Other Asian and Other Race populations, there was no difference between the other ethnic groups and the Whites. However, the MVA demonstrated that there was no significant difference between the ethnic groups as compared to Whites. It should be noted that we included stage IV patients in this analysis of patients undergoing a definitive surgical procedure because a satellite nodule in a different lobe of the ipsilateral lung was classified by the AJCC staging as metastatic until 2010 when the new AJCC seventh edition classified this situation as T4 (11). The percentage of each ethnic group undergoing a definitive surgical procedure for Stage IV disease varied from 4.5 to 9.8%. Only the Hispanic group had significantly different percentage of Stage IV patients than the White patients (9.8% of Hispanics vs 6.9% of Whites). Two thousand five hundred sixty three patients with Stage IV tumors underwent a definitive surgical procedure.

TABLE 7 | Multivariate analysis for node positivity by various factors for T1–T2 tumors <2 cm with at least one node removed, adjusted for type of surgical resection.

All surgical patients with T1 or T2 tumors <2 cm (*N* = 7,580)	*p*-Value	Hazard ratio
Age—years	<0.0001	1.036
Sex		
Female	–	1
Male	<0.0001	1.386
Race		
White Hispanic	0.99	0.998
White non-Hispanic	–	1
Black	0.89	0.986
Chinese	0.06	0.488
Japanese	0.32	0.699
South Asian	0.70	0.675
Other Asian	0.31	0.808
Other Race	0.38	0.754
American Indian/Alaskan Native	0.09	1.219
Surveillance Epidemiology and End Reporting Registry		
Alaska Natives	0.97	1
Atlanta	0.38	1.19
California excl SF/SJM/LA	0.36	1.13
Connecticut	–	1
Detroit	0.59	0.912
Greater Georgia	0.02	1.415
Hawaii	0.05	1.83
Iowa	0.95	0.988
Kentucky	0.41	1.144
Los Angeles	0.77	0.953
Louisiana	0.49	1.136
New Jersey	0.93	1.012
New Mexico	0.43	1.256
Rural Georgia	0.90	1.099
San Francisco-Oakland	0.97	1.008
San Jose-Monterey	0.54	0.837
Seattle	0.11	1.323
Utah	0.04	1.705
Income		
<$50,000	0.10	1.151
$50,000–75,000	–	1
>75,000	0.39	0.922
Tumor size		1.008
Tumor stage		
T2 vs T1	0.0004	1.289
Marital status		
Other	0.003	1.191
Married	–	1
Insurance		
Insured	–	1
Other	0.0003	1.376
Lateral location		
Bronchus, left	0.95	1.047
Bronchus, right	0.95	1
Left lower	0.90	0.989
Left upper	0.62	0.965
Left NOS	0.83	1.088
Left overlapping	0.95	1.047
Lung, NOS	0.99	1
Right lower	0.04	1.185
Right middle	0.08	0.782
Right upper	–	1
Right NOS	0.30	0.653
Right overlapping	0.87	1.087
Histology—no. (%)		
Adenocarcinoma	–	1
Adenosquamous	0.03	1.419
Large cell	0.03	1.426
Non-small cell	0.46	1.113
Other	0.11	0.199
Squamous	0.04	1.149
Grade		
Moderately, II	<0.0001	1.784
Poorly, III	<0.0001	2.157
Undifferentiated, IV	0.89	1.047
Unknown	<0.0001	1.802
Well, I	–	1
Number of nodes examined	0.28	0.995
Year of diagnosis—no. (%)		
2007	–	1
2008	0.70	0.971
2009	0.71	0.969
2010	0.04	0.821
2011	0.003	0.679
2012	0.003	0.519

One thousand six hundred twenty-seven patients were classified as having tumors nodules in different ipsilateral lobes during the years 2007–2009. One thousand one hundred twenty-nine underwent a sub-lobar resection (966 wedge, 92 segmentectomy, and 71 sub-lobar, NOS). Although some patients may have undergone a diagnostic wedge procedure, we assume that most of the remaining patients who did not have tumor nodules in different ipsilateral lobes ($N = 936$) may have been found to have metastatic disease shortly after their surgical procedure. However, the performance of staging investigations and their timing in relation to surgical procedures is not available in SEER. Nevertheless, after removing the patients who would now be re-classified as having Stage III NSCLC, the numbers were too small for further characterization of these patients by ethnicity.

It is interesting to note that the multivariable analyses for OS in the TS and ESR, and LCSS in the ESR populations yielded similar results to the multivariable analyses for OS in our companion manuscript containing two different lung cancer populations (all patients presenting with NSCLC and those presenting with Stage IV disease). In all four lung cancer populations in both manuscripts, well-established risk factors (12, 13) for OS and LCSS were noted in all multivariable analyses including tumor size, stage, differentiation, gender, age, and *t*-stage. After adjustment for histolopathologic, gender, age, treatment, and marital variables, all ethnicities in all analyses had similar or significantly better OS and LCSS (ESR group only) compared to the White group. Adenocarcinoma was uniformly associated with a better OS. A consistently lower OS and LCSS were noted for all four lung cancer populations in Greater Georgia, Louisiana, and Kentucky. Similarly, patients in California and Iowa had poorer outcomes except for OS in the Stage IV population in California and OS

in the ESR group in Iowa. The reason for the consistently poor outcomes across all stages and presentations in these registries is currently not known, but we believe that the number physician per 100,000 may be a factor because all five states rank in the bottom half of states in terms of the density of total active physicians as well as primary care physicians (14). Of interest, the highly significantly survival decrement ($p < 0.0001$) for tumor location in the mainstem bronchi in the companion manuscript was less significant in the surgical patients where only the right mainstem ($p = 0.01$) remained significant for OS in the TS group. There was no OS or LCSS decrement noted in the ESR population for the mainstem bronchi location. However, there was only a small number of tumors associated with the mainstem bronchi ($N = 30$) in the ESR group. We hypothesize that surgery neutralizes the effects of mainstem bronchi locations because this modality effectively eradicates a location that can cause obstructive pneumonias in a compromised patient group. Interestingly, although the companion paper noted that both lower lobe locations were noted to be associated with decreased OS, only the right lower lobe location was noted to be associated with worse OS in the surgical patients. The association of the lower lobes with worse outcomes has been noted in other investigations (15, 16). Our analysis demonstrates that the worse OS survival in patients having tumor located in the right lower lobe may be due to an increased risk of nodal involvement. Prognosis in all lung cancer populations was improved by being married, not having Medicaid, and being insured, but unlike the previous analysis, income was not correlated with LCSS and OS in the surgical patients in this investigation with the exception of borderline worse of OS in the TS population for those individuals with a median household income of <$50,000 ($p = 0.0457$). In addition, all lung cancer populations were noted to have a general improvement in OS during the years of this study. The improvement in the surgical populations may have been due to variables that are not contained within SEER such as improved staging, increased use of chemotherapy, and better post-operative care. However, the improved OS in the ESR group would argue against the increased use of adjuvant therapy because chemotherapy would be less likely to be used in this group (17, 18). Likewise, it may be argued that better post-operative care did not contribute to the better OS of the TS population because the 90-day mortality did not improve during the years of this study.

This manuscript was able to assess some treatment-related factors because SEER-18 does contain some variables related to radiation and surgery. Patients receiving pre-operative radiation were excluded because it was felt that this treatment could obscure/improve histolopathologic variables. Because SEER-18 does not contain information pertaining to chemotherapeutic treatment, we deliberately decided to separately assess a surgical sub-group of patients with tumors 4 cm or less without nodal involvement because these patients would be unlikely to receive chemotherapy (17, 18). Furthermore, we decided to investigate LCSS as well in this group of early-stage patients because of their relatively high likelihood of surviving lung cancer and possibly succumbing to other smoking-related causes. Worse OS and LCSS were consistently noted after a pneumonectomy despite multivariable analyses that accounted for histopathologic, patient, and tumor location variables. The adverse survival of patients undergoing a pneumonectomy was identified in recent retrospective study that demonstrated that that the lower survival may be due to an increased risk of distal metastases (19). Although the immune effects of a larger lung cancer procedures such as pneumonectomy as compared to (bi)lobectomy and sub-lobar resections is not known, it has been shown that transthoracic surgery for esophageal cancer as compared to smaller and less invasive surgical procedures (gastrectomy for cancer and cholecystomy for benign gallstones) has been associated with a transient immunosuppression (increased T-cell apoptosis and decreased T-cell cytokine production) during post-operative days 1–3 (20). Interestingly, a different research group noted that both transhiatal and transthoracic esophagectomies were associated with reduced TH1-type cytokine production on post-operative day 1, but depression of Th2-type cytokine was more profound with the latter procedure (21). In both surgical populations, the number of nodes examined was strongly correlated with OS and LCSS and was similarly noted in a past SEER analysis (22). The better outcomes associated with an increasing number of nodes examined may be due to the removal of microscopic disease that may or may not be recognized (especially in the ESR group) by routine pathologic methods (23), but because there is no OS with mediastinal lympadenectomy as compared to nodal sampling (24), one might infer that the beneficial effects of lymph node examination may be due to upstaging cancers that would otherwise be classified as node negative. Post-operative radiation was associated with poorer OS and LCSS. Although past retrospective analyses have demonstrated a possible survival benefit for radiation therapy in patients with N2 disease (25, 26), others have not (27). However, there has been general agreement that post-operative radiation results in a survival decrement in patients with N0 and N1 disease (25, 26). A recent retrospective investigation demonstrated that there was an OS benefit for post-operative radiation therapy for patients who experience a positive resection margin for all nodal stages (28). We would assume that the patients who receive post-operative radiation therapy for nodal stages N0–N1 during the years of our study had a positive margin, but SEER does not have information concerning margin status, and our results show a strongly negative effect of radiation on OS and LCSS in the surgical patients. Although there may be negative selection factors (i.e., positive margin, lymphatic, and/or vascular invasion) in the patients receiving radiation, it may be that radiation therapy has no efficacy and could possibly only have deleterious effects in the post-operative setting, especially in those with N0–N1 disease.

The MVA for 90-day OS revealed that mortality was not related to ethnicity, but was significantly correlated with single/unmarried partner status, Medicaid or unknown insurance, and income. Nevertheless, several known histopathologic and patient prognostic factors associated with aggressive disease/poor outcomes predicted 90-day mortality included increasing patient age, male sex, tumor differentiation, stage, and non-adenocarcinoma histology and suggest that aggressive tumor spread and/or understaging at the time of resection may be the reasons for poor early survival. However, because financial and partnership variables did affect 90-day mortality, one may conclude that patients may be able to improve their short-term

survival by better economic and emotional support. Of interest, even after accounting for histopathologic characteristics, tumor locations in the right mainstem bronchus and right lower lobe were associated with a decrement in OS. We hypothesize that operative complications associated with these locations may be a reason why these sites adversely affect OS in the TS and ESR populations. Treatment-related factors related to an increased mortality included the performance of a pneumonectomy and less nodes examined. We decided to include radiation in this analysis because we felt that radiation could possible result in an increased early mortality. Interestingly, radiation was strongly associated with an improved 90-day survival which may be due to patient selection factors which are not acknowledged by SEER including a better ECOG performance status, less co-morbidities, and lower risk of immediate post-operative infections. Early mortality did not improve during the years of our investigation suggesting that post-operative care was not associated with the improved outcomes in surgical patients.

The decision to assess tumors generally considered eligible for a sub-lobar resection (T1–T2 tumors <2 cm in size) was made in order to assess which patients would benefit from a lymphadenectomy. Not surprisingly, nodal positivity was associated with known prognostic factors including advanced age, male sex, *t*-stage, aggressive histologies (adenosquamous, large cell, and squamous carcinomas), and tumor differentiation. Importantly, it should be noted that ethnicity was not associated with an increased risk of having positive nodes. Although income was not associated with nodal positivity, not being insured and not being married were both strongly associated with having node involvement. Because this analysis revealed that the right lower lobe location was associated with positive nodes, we believe that this may be a reason why this location is associated with a lower OS in both the TS and ESR populations.

We originally performed this analysis to assess the effects of the presentation and outcome differences by ethnicity as compared to Whites in patients undergoing surgical resection for lung cancer. In comparison to White patients, OS, LCSS, and 90-day mortality were similar or better in all ethnic groups for all three analyses. Median household income was largely not associated with OS or LCSS in the TS and ESR patients, but was strongly associated with 90-day mortality. Because this variable was assigned to patients based upon the median county income, we assume this variable may have adversely affected 90-day survival due to the hospital care received in more wealthy and less affluent areas. Of importance, Medicaid insurance and not being married were associated with lower OS and LCSS as well as an increased risk of 90-day mortality. We feel that not Medicaid insurance is more likely to represent an individual's economic status and demonstrates the importance of having insurance. However, of great interest, is that having Medicaid and not being married are factors that were also associated with an increased risk of nodal involvement. This suggests that economic and psychological factors can possibly be associated with lung cancer biology. Lower socioeconomic status may affect tumor biology through poor nutrition (29). Recently, it was noted that unmarried lung cancer patients had a greater incidence of depression, less social support, and a survival decrement (30), and that the survival decrement noted in patients with new-onset or persistent depression may be more so in early-stage (Stages I–II) than in patients with more advanced stages (31). We feel that our results suggest that the economic effects of not having insurance and not being married are associated with real changes in tumor biology and aggressiveness.

It should be noted that the SEER database lacks may variables that would have been useful for our analysis including smoking history, body mass index, ECOG performance status, lymphatic and/or vascular invasion, patient co-morbidities, chemotherapy administration, type of surgical procedure (i.e., VATS, robotic surgery, and traditional thoracotomy), radiation dose, and radiation field arrangement. However, we have no reasons to think that any of these variables would have influenced our outcomes because we could account for median household income, type of insurance, and most major histopathologic variables.

In summary, the main purpose of our investigation was to assess difference in outcomes (OS and 30/90 day mortality), presentation, and treatment in nine different ethnic groups who underwent surgical resection of NSCLC. As a secondary aim, we also wanted to assess whether tumor biology (nodal involvement) varied by ethnicity. Even in the analyses that were not adjusted for treatment, histopathologic, patient, and marital factors; Blacks and Hispanics had the same OS and LCSS as the White group. We did not find disparities due to ethnicity in patients undergoing surgical resection for NSCLC, but noted that the disparities may be due to having Medicaid insurance and not being married. Because having Medicaid insurance and not being married were associated with lower OS, LCSS and 90-day OS as well as nodal positivity, we feel that economic and psychosocial variables may play a role in the biological aggressiveness of early-stage lung cancer patients undergoing resection in addition to standard histopathologic and treatment variables. Although marriage was equally as important as socioeconomic factors in our assessment, a study from an earlier time period (1989–2003) suggested that lower socioeconomic status was an independent prognostic factor, but marriage was note (32). However, this past investigation by Ou et al. also noted that race was not a prognostic factor in multivariate modeling.

CONCLUSION

In TS and ESR populations, OS was not different in the two largest ethnic groups (Black, Hispanic) as compared to Whites, but was related to single/divorced status, medicaid insurance, and income (TS population only). Nodal positivity was associated with patients who did not have a married partner or insurance suggesting that these factors may impact disease biology. Economic and psychosocial variables may play a role in survival of early-stage lung cancer in addition to standard histopathologic and treatment variables.

AUTHOR CONTRIBUTIONS

Writing, editing, and manuscript approval—JV, KM, RV, MD, JF, NR, TF, PR, WW, DM, KU, JB, and PO. Data acquisition—JV, KM, and RV. Data analysis—JV, KM, RV, MD, and JF.

REFERENCES

1. National Comprehensive Cancer Network guidelines. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp (Accessed: November 22, 2016).
2. Williams CD, Salama JK, Moghanaki D, Karas TZ, Kelley MJ. Impact of race on treatment and survival among U.S. Veterans with early-stage lung cancer. *J Thorac Oncol* (2016) 11(10):1672–81. doi:10.1016/j.jtho.2016.05.030
3. Sineshaw HM, Wu XC, Flanders WD, Osarogiagbon RU, Jemal A. Variations in receipt of curative-intent surgery for early-stage non-small cell lung cancer (NSCLC) by state. *J Thorac Oncol* (2016) 11(6):880–9. doi:10.1016/j.jtho.2016.03.003
4. Taioli E, Flores R. Appropriateness of surgical approach in black patients with lung cancer-15 years later, little has changed. *J Thorac Oncol* (2017) 12:573–7. doi:10.1016/j.jtho.2016.08.119
5. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* (2011) 365:395–409. doi:10.1056/NEJMoa1102873
6. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, et al. Cancer treatment and survivorship statistics, 2012. *CA Cancer J Clin* (2012) 62:220–41. doi:10.3322/caac.21149
7. Surveillance, Epidemiology, and End Results (SEER) Program. *SEER Public-Use Data (1973–2012)*. Bethesda, MD: National Cancer Institute, DCCPS, Surveillance Research Statistics Branch (2012). Available from: http://seer.cancer.gov/registries/list.html (Accessed: March 16, 2016).
8. Iqbal J, Ginsburg O, Rochon PA, Sun P, Narod SA. Differences in breast cancer stage at diagnosis and cancer-specific survival by race and ethnicity in the United States. *JAMA* (2015) 313:165–73. doi:10.1001/jama.2014.17322
9. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials* (1996) 17:343–6. doi:10.1016/0197-2456(96)00075-X
10. Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. New York: Springer (2000). 350 p.
11. Diederich S. Lung cancer staging update: the revised TNM classification. *Cancer Imaging* (2010) 10:s134–5. doi:10.1102/1470-7330.2010.9022
12. Hsu CP, Hsia JY, Chang GC, Chuang CY, Shai SE, Yang SS, et al. Surgical-pathologic factors affect long-term outcomes in stage IB (pT2 N0 M0) non-small cell lung cancer: a heterogeneous disease. *J Thorac Cardiovasc Surg* (2009) 138:426–33. doi:10.1016/j.jtcvs.2008.12.035
13. Chansky K, Sculier JP, Crowley JJ, Giroux D, Van Meerbeeck J, Goldstraw P, et al. The International Association for the Study of Lung Cancer Staging Project: prognostic factors and pathologic TNM stage in surgically managed non-small cell lung cancer. *J Thorac Oncol* (2009) 4:792–801. doi:10.1097/JTO.0b013e3181a7716e
14. American Association of Medical Colleges. *State Physician Workforce Databook*. Washington, DC: Association of American Medical Colleges (2015).
15. Ou SH, Zell JA, Ziogas A, Anton-Culver H. Prognostic factors for survival of stage I nonsmall cell lung cancer patients: a population-based analysis of 19,702 stage I patients in the California cancer registry from 1989 to 2003. *Cancer* (2007) 110:1532–41. doi:10.1002/cncr.22938
16. Qiang G, Liang C, Yu Q, Xiao F, Song Z, Tian Y, et al. Risk factors for recurrence after complete resection of pathological stage N2 non-small cell lung cancer. *Thorac Cancer* (2015) 6:166–71. doi:10.1111/1759-7714.12159
17. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol* (2008) 26:3552–9. doi:10.1200/JCO.2007.13.9030
18. Strauss GM, Herndon JE II, Maddaus MA, Johnstone DW, Johnson EA, Harpole DH, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol* (2008) 26:5043–51. doi:10.1200/JCO.2008.16.4855
19. Varlotto JM, Recht A, Flickinger JC, Medford-Davis LN, Dyer AM, Decamp MM. Factors associated with local and distal recurrence and survival in patients with resected nonsmall cell lung cancer. *Cancer* (2009) 115:1059–69. doi:10.1002/cncr.24133
20. Kono K, Takahashi A, Iizuka H, Fujii H, Sekikawa T, Matsumoto Y. Effect of oesophagectomy on monocyte-induced apoptosis of peripheral blood T lymphocytes. *Br J Surg* (2001) 88:1110–6. doi:10.1046/j.0007-1323.2001.01833.x
21. van Sandick JW, Gisbertz SS, ten Berge IJ, Boermeester MA, van der Pouw Kraan TC, Out TA, et al. Immune responses and prediction of major infection in patients undergoing transhiatal or transthoracic esophagectomy for cancer. *Ann Surg* (2003) 237:35–43. doi:10.1097/00000658-200301000-00006
22. Varlotto JM, Recht A, Nikolov M, Flickinger JC, Decamp MM. Extent of lymphadenectomy and outcome for patients with stage I nonsmall cell lung cancer. *Cancer* (2009) 115(4):851–8. doi:10.1002/cncr.23985
23. Ramirez RA, Wang CG, Miller LE, Adair CA, Berry A, Yu X, et al. Incomplete intrapulmonary lymph node retrieval after routine pathologic examination of resected lung cancer. *J Clin Oncol* (2012) 30(23):2823–8. doi:10.1200/JCO.2011.39.2589
24. Darling GE, Allen MS, Decker PA, Ballman K, Malthaner RA, Inculet RI, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. *J Thorac Cardiovasc Surg* (2011) 14:662–70. doi:10.1016/j.jtcvs.2010.11.008
25. PORT Meta-analysis TrialistsGroup. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. *Lancet* (1998) 352(9124):257–63. doi:10.1016/S0140-6736(98)06341-7
26. Lally BE, Zelterman D, Colasanto JM, Haffty BG, Detterbeck FC, Wilson LD. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. *J Clin Oncol* (2006) 24:2998–3006. doi:10.1200/JCO.2005.04.6110
27. Wisnivesky JP, Halm EA, Bonomi M, Smith C, Mhango G, Bagiella E. Postoperative radiotherapy for elderly patients with stage III lung cancer. *Cancer* (2012) 118(18):4478–85. doi:10.1002/cncr.26585
28. Wang EH, Corso CD, Rutter CE, Park HS, Chen AB, Kim AW, et al. Postoperative radiation therapy is associated with improved overall survival in incompletely resected stage II and III non-small-cell lung cancer. *J Clin Oncol* (2015) 33:2727–34. doi:10.1200/JCO.2015.61.1517
29. Conklin AI, Forouhi NG, Brunner EJ, Monsivais P. Persistent financial hardship, 11-year weight gain, and health behaviors in the Whitehall II study. *Obesity (Silver Spring)* (2014) 22:2606–12. doi:10.1002/oby.20875
30. Sullivan DR, Forsberg CW, Ganzini L, Au DH, Gould MK, Provenzale D, et al. Depression symptoms and health domains among lung cancer patients in CanCORS study. *Lung Cancer* (2016) 100:102–9. doi:10.1016/j.lungcan.2016.08.008
31. Sullivan DR, Forsberg CW, Ganzini L, Au DH, Gould MK, Provenzale D, et al. Longitudinal changes in depression symptoms and survival among patients with lung cancer: a national cohort assessment. *J Clin Oncol* (2016) 34(33):3984–91. doi:10.1200/JCO.2016.66.8459
32. Ou SH, Zell JA, Ziogas A, Anton-Culver H. Low socioeconomic status is a poor prognostic factor for survival in stage I nonsmall cell lung cancer and is independent of surgical treatment, race, and marital status. *Cancer* (2008) 112:2011–20. doi:10.1002/cncr.23397

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2018 Varlotto, McKie, Voland, Flickinger, DeCamp, Maddox, Rava, Fitzgerald, Walsh, Oliveira, Rassaei, Baima and Uy. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: info@frontiersin.org | +41 21 510 17 00

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership