Current Pulmonology Reports (2020) 9:151–163
https://doi.org/10.1007/s13665-020-00259-7

PULMONARY RADIOLOGY (M STEPHENS AND S KAPUR, SECTION EDITORS)

Surgical Management of Stage IIIA Non-small Cell Lung Cancer

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Accepted: 5 October 2020 / Published online: 30 October 2020

Abstract

Purpose of Review There remains equipoise regarding the optimal treatment approach for patients with stage IIIA non-small cell lung cancer (NSCLC). The purpose of this review is to examine the role of surgery as a modality in the management of stage IIIA NSCLC.

Recent Findings Over the last two decades, several studies including randomized controlled trials have established the importance of multimodality therapies in the management of locally advanced NSCLC.

Summary Significant disparities exist in the reported advantages of surgery between observational and randomized controlled studies of stage IIIA patients. While some of these differences are likely due to patient selection bias, differences in the study design and treatment-related factors may also contribute to these trends. Preliminary results from studies assessing molecular therapies and immunotherapies in this population indicate a favorable adverse event and clinical response profile. As the therapeutic armamentarium for stage IIIA disease expands, continued evaluation of surgery within multimodality treatment protocols will be increasingly important.

Keywords Non-small cell lung cancer · Lung cancer · Stage IIIA NSCLC · Surgery

Introduction

Lung cancer remains the leading cause of cancer-associated mortality in the United States and accounts for approximately 136,000 deaths per year [1]. Of the 114,000 patients diagnosed with non-small cell lung cancer (NSCLC) annually, nearly 28% are found to have locally advanced (stage III) disease at the time of diagnosis [2, 3]. Using the Tumor, Node, Metastasis (TNM) system, the current American Joint Committee on Cancer (AJCC) criteria for clinical stage III lung cancers define a heterogeneous population, and even within this category of disease, there are subclassifications [4]. Historically, stage III disease was divided into stage IIIA and IIIB, with the former denoting a more favorable burden and extent of disease and providing an opportunity for surgical therapy to be considered [5, 6]. In the most recent staging system, stage III disease has been divided further into IIIA, IIIB, and IIIC [4]. The refinement of these stage III disease subgroups have largely been driven by the differences in outcomes associated with specific primary tumor characteristics [7, 8]. The 8th edition of the staging system, as with other past and future iterations, reflects an effort to better characterize prognosis associated with the phenotypic presentation of the disease and, in the process, has resulted in stage migration. With respect to stage III NSCLC, from the 7th edition to the 8th edition of the staging system, some designated stage IIB disease now has shifted to stage IIIA disease, some designated IIIA disease has shifted to stage IIB disease, and some stage IIIA and IIIB disease has shifted to stage IIIB and IIIC disease, respectively [9]. Despite this stage shifting, surgical therapy continues to remain a viable modality of therapy now for stage IIIA and IIIB disease, whereas in the past, it was reserved for the IIIA subset. This fact largely remains an artifact of the stage shifting as what was once stage IIIA disease and a candidate for surgery as a modality may now be stage IIIB, but still a candidate for surgery as a modality. The implication of

This article is part of the Topical Collection on *Pulmonary Radiology*

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13665-020-00259-7) contains supplementary material, which is available to authorized users.

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this fact is that many studies evaluating surgery as a part of multimodal strategies limited their cohorts to those patients with stage IIIA disease at most.

Classically, the majority of stage IIIA disease has been defined as the presence of positive mediastinal lymph nodes (N2 disease). This definition has largely remained unchanged for most stage IIIA classifications in the revisions to the staging system [10]. In this context and in the current staging system, the phenotypic spectrum of stage IIIA disease includes smaller tumors (≤ 5 cm) with mediastinal lymph node involvement (T1–2N2). However, stage IIIA disease also encompasses more diverse lesion sets that also include larger tumors (> 5 cm) with limited or absent nodal involvement (T3N1, T4N0–1) [4]. It is worth noting that in the prior iterations of the staging system, even larger tumors (> 7 cm) with mediastinal lymph node involvement were considered stage IIIA disease [5, 6]. The variability of tumor characteristics represented by these stage IIIA classifications adds complexity to the evaluation of appropriate treatment options in this cohort. Consequently, the optimal management of stage IIIA patients continues to be rigorously debated.

In the current era, guidelines for therapy reflect the heterogeneous nature of stage IIIA lesions and outline distinct multimodal treatment strategies for various subsets of disease [11, 12]. For patients with operable T3N1 and T4N0–1 tumors, surgical resection followed by adjuvant chemotherapy is generally accepted as the primary therapy. More recently, there has been growing interest in the role of neoadjuvant therapy in these cohorts as well [13–15]. In contrast, the preferred treatment option in patients with positive N2 lymph nodes is less clear. Whereas some guidelines recognize definitive concurrent chemoradiation therapy as the multimodality treatment of choice for all IIIA-N2 patients, other guidelines offer a more nuanced recommendation depending upon the characteristics and extent of N2 node involvement [11]. For patients with discrete N2 nodes, either definitive concurrent chemoradiation therapy or neoadjuvant therapy and surgery are acceptable with the decision for either ultimately being guided by patient preference and input from a multidisciplinary treatment team [12]. These discrepancies in therapeutic options not only reflect the challenges associated with the lack of standardized and objective methods of classifying stage IIIA subgroups but also contribute to the broader uncertainty regarding the exact role of surgery in the management of these patients [16•]. Therefore, it is not surprising that despite evidence demonstrating surgery to be a robust and guideline-concordant method of local control for stage IIIA disease, recent studies in nationally representative samples show that most stage IIIA patients do not receive any form of surgery in clinical practice [17, 18].

The central objective of the present review is to provide a contemporary analysis of the role of surgery in the management of stage III NSCLC, but particularly in stage IIIA disease. More specifically, this review is aimed at summarizing the published literature describing clinical outcomes of stage IIIA patients managed with surgical and non-surgical methods. Additional perspectives will be provided through a lens focusing on those patients who receive molecular therapies and immunotherapies as part of multimodal treatment algorithms.

Methods

Data Source

The MEDLINE (PubMed) database was queried to identify original articles describing outcomes following the surgical management of stage IIIA NSCLC published between January 1994 and April 2020. The following terms were used to guide this search strategy: “surgery” or “surgical management” combined with “stage IIIA non-small cell lung cancer” or “lung cancer”. Inclusion eligibility was determined by reviewing the abstracts and manuscripts when indicated. Only original articles that focused on outcomes in stage IIIA NSCLC patients were considered. Systemic reviews and meta-analyses published on this topic during the same period were evaluated to contextualize summarized findings and to perform a secondary search of referenced works. Studies that were not published in the English language, performed in preclinical or animal models, or that combined results from stage IIIA patients with a majority of other stage-specific subgroups were excluded. In an effort to draw meaningful conclusions and maintain reliability of interpreted results from published studies, case reports, case series, and studies with < 20 patients were excluded.

It should be acknowledged that the staging system is a clustering of lesion sets that share a similar prognosis independent of treatments rendered and is not a rigid template for therapeutic guidelines, per se. Therefore, for the purposes of this review, the rubric of resectable stage III disease or stage IIIA disease will be used in defining the surgical cohort even in light of the fact that some of the historical stage IIIA disease now has shifted to being stage IIB, IIIB, or IIIC disease.

General Outcomes

Studies were reviewed to compare the general overall survival outcomes following different treatment approaches for stage IIIA NSCLC. For studies that contained a surgical treatment arm, reports were included if they had ≥ 20 patients undergoing lobectomy. To facilitate accurate extraction of survival data, studies were included only if they reported 5-year overall survival (OS) data by Kaplan–Meier analysis segregated by identifiable treatment groups. For data analysis, OS data were extrapolated directly from Kaplan–Meier curves using plot

digitizer software (plotdigitizer.sourceforge.net) at 1-year, 2-year, 3-year, 4-year, and 5-year time points. Median OS and range statistics were calculated and plotted at each time point for the following treatment groups: (I) induction chemotherapy and/or radiation therapy followed by surgery (C/RT + S); (II) surgery followed by chemotherapy and/or radiation therapy (S + C/RT); (III) definitive chemotherapy, radiation therapy, or chemoradiation therapy (C/RT); and (IV) surgery alone. For forest plots, the difference in median OS (Δ_{OS}) was calculated for patients undergoing C/RT + S and definitive C/RT according to the following formula: Δ_{OS} = Median $OS_{C/RTS}$ − Median $OS_{C/RT}$. Hazard ratios for OS were abstracted directly from studies. When not reported, hazard ratios were indirectly calculated from summary statistics.

Molecular Therapies and Immunotherapies

To identify clinical trials investigating the efficacy of molecular therapy and immunotherapies in IIIA NSCLC patients, an additional search strategy in MEDLINE (PubMed) was employed and included the following terms: "EGFR inhibitors" or "ALK inhibitors" or "PD1 inhibitors" or "PDL1 inhibitors" or "molecular therapies" or "immunotherapies" combined with "stage IIIA lung cancer" or "lung cancer". When available, preliminary data were abstracted directly from reports. For unpublished studies, trial characteristics including the name, sponsor, phase, target enrollment, and primary and secondary endpoints were retrieved from clinicaltrials.gov using clinical trial identifiers.

I. History of Surgery for Stage IIIA NSCLC

Prior to the widespread adoption of multimodality treatment protocols for stage IIIA NSCLC, several institutional reports had described poor outcomes with unimodal therapies in this population. For patients undergoing isolated resection, average five-year OS rates were shown to range from 7 to 16% [19–21]. Similarly, poor results were observed for patients with unresectable stage IIIA disease treated solely with radiation therapy [22, 23]. Although surgery was known to offer improved local control over radiation therapy, the long-term success of both therapies was limited by exceedingly high rates of locoregional and distant recurrence. This mechanism of failure suggested that a significant proportion of stage IIIA patients potentially harbor micrometastatic disease at baseline and prompted the study of combination therapies to address both local and systemic disease burdens.

In 1994, there were two seminal randomized controlled trials that independently evaluated the therapeutic efficacy of induction chemotherapy and surgery compared to surgery alone for stage IIIA patients [24, 25]. Despite minor differences in their inclusion criteria and experimental design, both studies demonstrated that the addition of preoperative chemotherapy significantly improved 5-yr OS compared to surgery-only therapy. During the same period, other trials reported OS benefits when combining chemotherapy and radiation therapy versus radiation therapy alone [26, 27]. Collectively, these efforts added validity to the multimodal treatment paradigm for managing stage IIIA disease and provided the rationale for the continued assessment of combinational therapies in these patients.

II. Current Treatment Approaches and Outcomes for Stage IIIA Disease

Over the past two decades, there have been multiple primary studies comparing various combinations and sequences of local and systemic therapies for stage IIIA disease. The search criteria for the present review identified 9 randomized trials (n = 1424 patients) and 10 observational studies (n = 137,813 patients) that report long-term OS outcomes following different treatment approaches in stage IIIA patients (Table 1). To facilitate the pooling of survival data across various studies, treatments first were defined according to four major categories: (I) induction chemotherapy and/or radiation therapy followed by surgery (C/RT + S or "induction"); (II) surgery followed by chemotherapy and/or radiation therapy (S + C/RT or "adjuvant"); (III) definitive chemotherapy, radiation therapy, or chemoradiation therapy (C/RT or "no surgery"); and (IV) surgery alone (S). Figure 1 shows the aggregate median OS estimates for each treatment group extrapolated from all studies. The calculated 5-year OS rate was greatest for patients undergoing C/RT + S (36%), followed by S + C/RT (30%), C/RT (22%), and S (20%).

As expected, there was a significant variation in the treatment arms compared within randomized and observational reports. The most common treatment groups compared in observational studies were induction (C/RT + S) vs. no surgery (C/RT) (n = 8) [17, 28–34]. This was followed by induction (C/RT + S) vs. adjuvant (S + C/RT) (n = 3) [29, 32, 35], adjuvant (S + C/RT) vs. no surgery (C/RT) (n = 2) [29, 32], and no surgery (C/RT) vs. surgery alone (S) (n = 1) [18]. In the randomized trial setting, there were three studies that each directly compared induction (C/RT + S) vs. no surgery (C/RT) [36–38], induction (C/RT + S) vs. surgery alone (S) [24, 25, 39], and adjuvant (S + C/RT) vs. surgery alone (S) [40–42].

Surgery as a Single or Bimodality Therapy

There were 6 studies (all randomized trials) that compared surgery utilized as a single modality versus as part of a bimodality approach. Bimodality regimens in these studies were equally split between adjuvant therapy (n = 3) [40–42] and induction therapy (n = 3) [24, 25, 39]. Two of the three adjuvant therapy studies reported no statistically significant difference in OS when comparing patients undergoing

Table 1 Overall and progression-free survival outcomes reported in published studies of stage IIIA NSCLC patients

Author	Year	Intervention		Sample size		Median OS (months)		5-yr OS (%)		Median PFS (months)		5-yr PFS (%)	
		Control	Test	Control	Test	Control	Test	Control	Test	Control	Test	Control	Test
Roth[a]	1994	S	C + S	32	28	14	21	15	36	–	–	–	–
Rosell[a]	1994	S	C + S	30	30	10	22	0	17	5	12	0	16
Debevec[a]	1996	S	S + RT	35	39	20.4	28.8	23	28	–	–	–	–
Nagai[a]	2003	S	C + S	31	31	16	17	22	10	9	10	21	10
Tada[a]	2004	S	S + C	60	69	36	36	36.1	28.2	16.1	18.3	–	–
Kang	2006	C/RT	C/RT + S	15	38	12	27	10	44.3	–	–	–	–
van Meerbeeck[a]	2007	C/RT	C + S	165	167	17.5	16.4	14	15.7	11.3	9	13	12
Albain[a]	2009	C/RT	C/RT + S	194	202	22.2	23.6	20	27	10.5	12.8	11	22
Ou[a]	2010	S	S + C	71	79	24	33	19.1	31.1	20	32	14.7	17.9
Koshy	2013	C/RT	C/RT + S	9857	564 (L) 188 (P)	14	29 (L) 19 (P)	10.9	33.5 (L) 20.8 (P)	–	–	–	–
			S + C		510 (L) 123 (P)		25 (L) 23 (P)		20.3 (L) 13.4 (P)		–		–
Aggarwal	2014	C/RT	C/RT + S	103	146	20.2	30.9	27	36	–	–	–	–
Patel	2014	C/RT	C/RT + S	51,979	9360	19.2	37.4	20	38	–	–	–	–
Hancock	2014	C/RT	S	57,899	2517	14	31	11.4	30	–	–	–	–
Darling	2015	C/RT	C/RT + S	111	104	20.4	50.4	18	45	13.2	48	24	47
Eberhardt[a]	2015	C/RT	C/RT + S	80	81	34.8	49.3	40	44	18	21	35	32
Dickhoff	2016	C/RT	C/RT + S	2180	209	20.4	NR	27	51	–	–	–	–
			S + C		535		33		36		–		–
Counago	2018	C/RT	C/RT + S	129	118	29	56	28	38	15	46	20	49
Tao	2019	S + C	C + S	535	68	37.5	NR	38	61	14	24	13	41.5
Rajaram	2020	C/RT	C + S	366	159	27.5	61.2	29.2	50.8	14.6	22.8	20.5	33.1

C/RT: chemotherapy and/or radiation therapy; C: chemotherapy; RT: radiation therapy; S: surgery; L: lobectomy; P: pneumonectomy; OS: overall survival; PFS: progression-free survival

[a] Randomized controlled trial

postoperative radiotherapy [40] or chemotherapy [41] to observation. In contrast, a more recent analysis by Ou et al. found that patients receiving adjuvant vinorelbine and carboplatin or paclitaxel and carboplatin after resection

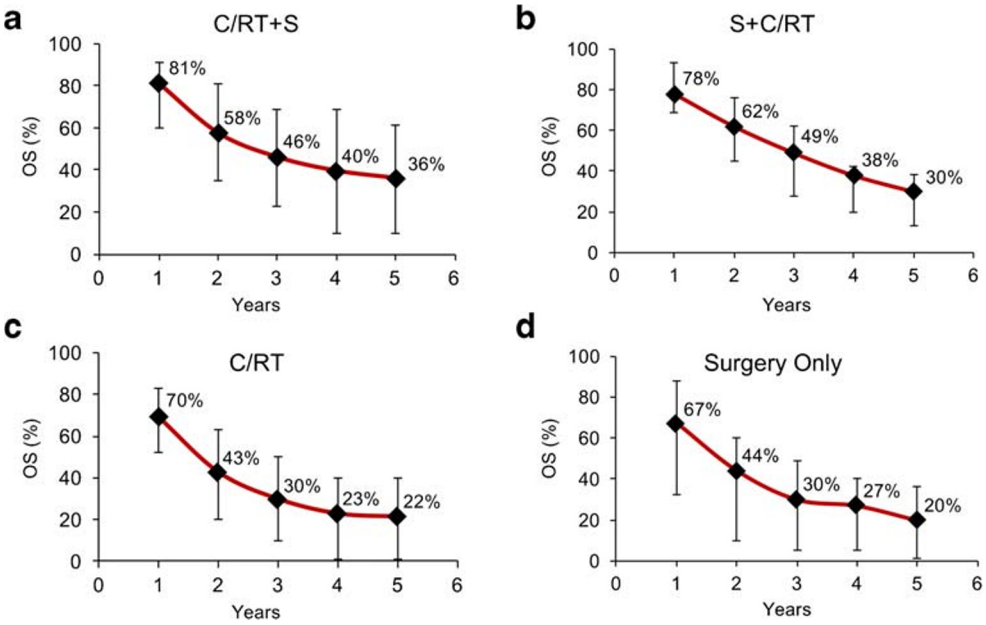

Fig. 1 Median estimates of overall survival (OS) for stage IIIA patients treated with **a** C/RT + S, **b** S + C/RT, **c** C/RT, and **d** surgery only in published studies. Error bars represent the range of values at each specified time point. Trend lines are shown in red

demonstrated improved 5-year OS and progression-free survival (PFS) compared to those followed by observation [42]. Although only a few randomized trials specifically have evaluated adjuvant chemotherapy following resection for stage IIIA disease, a recent meta-analyses performed by the Lung Adjuvant Chemotherapy (LACE) collaborative group assessed stage-specific subgroup results for patients enrolled in the five largest adjuvant chemotherapy trials conducted to date [43]. In support of the findings by Ou et al., the LACE group reported significantly improved 5-year OS and PFS in the subgroup of patients with stage III cancer [43]. In a follow-up study, this group also showed that the strongest survival benefit was observed in patients receiving adjuvant vinorelbine and cisplatin [44].

Of the three studies evaluating neoadjuvant chemotherapy preceding surgery compared to surgery-only therapy, two were conducted at the start of this analysis period [24, 25]. These studies, led by Roth et al. and Rosell et al., demonstrated an average 5-year OS advantage of 19% for patients randomized to preoperative chemotherapy compared to surgery alone [24, 25]. As previously described, these trials helped to form the evidence base supporting the utilization of multimodality therapies in the management of stage IIIA patients.

In 2003, Nagai et al. conducted a similar study randomizing patients with IIIA disease to induction chemotherapy with cisplatin and vindesine followed by surgery or surgery alone [39]. Unlike prior reports, Nagai and colleagues did not observe an OS or PFS advantage with neoadjuvant chemotherapy. One potential explanation for these disparate results is the relatively low response to neoadjuvant chemotherapy observed in the study by Nagai et al. (0% complete, 28% partial) compared to that of Roth et al. (4% complete, 31% partial) and Rosell et al. (7% complete, 53% partial) [24, 25, 39]. In addition, when compared to the surgery-only arm, neoadjuvant patients in the Nagai et al. trial experienced a relatively lower complete resection rate (65% neoadjuvant vs. 77% surgery only) and higher rate of exploratory thoracotomy (19% neoadjuvant vs. 6% surgery only) [39]. While the authors suggest that these discrepant results may be due to the greater proportion of non-N2 patients included in previous trials compared to their own, it is not clear that this fully explains the differences in outcomes.

Surgery Following Neoadjuvant Therapy or Preceding Adjuvant Therapy

In total, there were 3 studies (all observational) that directly compared surgery following neoadjuvant therapy versus preceding adjuvant therapy [29, 32, 35]. In a retrospective single-institution analysis, Tao et al. compared outcomes between patients receiving neoadjuvant chemotherapy and surgery versus those receiving upfront surgery followed by adjuvant chemotherapy [35]. The authors performed a propensity-matched analysis to control for potentially confounding demographic and clinical factors between these two treatment groups. In 58 propensity-matched pairs, they found that there was no statistically significant differences in OS or PFS between these treatment groups at 5 years [35].

Dickhoff et al. evaluated population-based outcomes of stage IIIA patients undergoing neoadjuvant and adjuvant therapies within the Netherlands Cancer Registry [32]. Unlike Tao et al., Dickhoff and colleagues included both chemotherapy and radiation therapy in their analysis. Their work demonstrated favorable 5-year OS rates in general and superior outcomes for patients receiving neoadjuvant therapy and surgery compared to those receiving upfront resection followed by adjuvant therapy (51% induction vs. 36% adjuvant). However, there are a few important caveat to these findings. First, the median age of patients undergoing neoadjuvant therapy and surgery was younger than that of the upfront surgery group (60 years induction vs. 66 years adjuvant). Second, 49% of patients undergoing upfront surgery for clinical IIIA tumors in their analysis were found to have incorrectly staged disease at pathologic evaluation [32]. Of those upfront surgical patients who had concordant clinical and pathologic IIIA staging, only 34% received adjuvant chemotherapy and 8% received adjuvant C/RT [32]. As a result, the 5-yr OS rates reported for stage IIIA patients undergoing upfront resection in this registry cohort should be interpreted in the context of these staging inaccuracies.

Koshy et al. performed a nationally representative analysis of long-term outcomes associated with the receipt of neoadjuvant chemoradiation therapy compared to surgery followed by adjuvant therapy (chemotherapy, radiation therapy, or chemoradiation therapy) among clinical IIIA patients in the United States [29]. One of the major strengths of this study is that the authors' segregated neoadjuvant and adjuvant cohorts according to the type of surgical resection received (lobectomy vs. pneumonectomy). They reported statistically significant differences in the 5-year OS trends across these surgical groups, with neoadjuvant patients generally faring better than those treated with resection and adjuvant therapy [29]. The authors suggest that these survival differences may, at least in part, be due to the treatments rendered. However, differences in the types and burden of comorbidities may have also influenced these results, as 25.5% of neoadjuvant patients and 38.9% of adjuvant therapy patients had ≥ 1 comorbidity. Unfortunately, due to limitations in the variables contained within the National Cancer Database (NCDB), the authors were unable to provide more granular data regarding the nature of these comorbidities and their potential impact on treatment decisions.

Multimodality Therapies with or without Surgery

Consistent with the therapeutic principles outlined in current treatment guidelines, the most frequently compared treatment

groups in studies of stage IIIA patients are multimodal therapies with and without surgery. Overall, the search methodology employed in this review identified 8 observational analyses [17, 28–34] and 3 randomized trials [36–38] comparing these therapeutic approaches. When measuring the difference in median OS between treatment arms, there was a striking difference in the reported survival advantage conferred by induction therapy (C/RT + S) between observational and randomized analyses (Fig. 2a). In the observational series, the median OS advantage conferred by C/RT + S treatment over definitive C/RT was found to be 16.6 months [17, 28–34]. This value is nearly 12-fold greater than that observed in the trial setting [36–38]. Moreover, while every observational report with such data describes a significantly lower risk of mortality in patients treated with C/RT + S compared to definitive C/RT, these findings have not been replicated in any randomized trial to date (Fig. 2B).

There are several potential explanations for these outcome disparities. The first and most likely explanation is the selection bias inherent to non-randomized study designs. All observational reports listed here retrospectively compared outcomes between similarly staged (IIIA) patients that, for reasons unknown, were managed differently. Therefore, it is plausible that the same patient and provider factors that influenced individual treatment decisions may also confound long-term survival endpoints. Evidence of this bias can be appreciated when comparing the relative 5-year OS rates observed across study designs. For example, the average 5-year OS rate was significantly lower in C/RT + S patient enrolled in randomized trials compared to those who were included in retrospective studies (29% randomized C/RT + S vs. 40% observational C/RT + S). However, the opposite trend was observed for definitive C/RT patients (25% randomized C/RT vs. 21% observational C/RT). These data suggest that patient selection factors may potentially bias retrospective C/RT + S cohorts toward improved surgical candidacy and possibly long-term survival.

Another explanation for the disagreement between randomized and observational reports may be related to relative differences in the surgical therapies utilized across studies. It is well established that patients undergoing pneumonectomy following induction therapy tend to experience worse outcomes compared to those undergoing lobectomy. When evaluating the ratio of pneumonectomies to lobectomies performed in C/RT + S patient cohorts, it was found that randomized trial participants had a 3.3-fold greater pneumonectomy-to-lobectomy ratio compared to those included in observational analyses (Supplementary Table 1). Although this is not a validated metric, it does reveal a significant disparity in the utilization of pneumonectomy procedures in these studies. Whether due to differences in underlying disease burden or complexities in postoperative management, it is possible that such treatment-related factors may also contribute to disparate survival outcomes across studies.

Finally, when assessing the differences in median OS between C/RT + S and definitive C/RT cohorts, it appears that there is a trend toward a greater survival advantage with C/RT + S over time (Fig. 2a, Supplementary Fig. 1). This signal may reflect general improvements in medical and/or surgical therapies or greater collective experience in the appropriate selection and management of stage IIIA patients over the past two decades. Future studies comparing the trends and efficacy of specific chemotherapy and radiation regimens during this period are warranted.

III. Molecular Therapies and Immunotherapies

In the last decade, advances in next-generation sequencing technologies have expanded our understanding of the

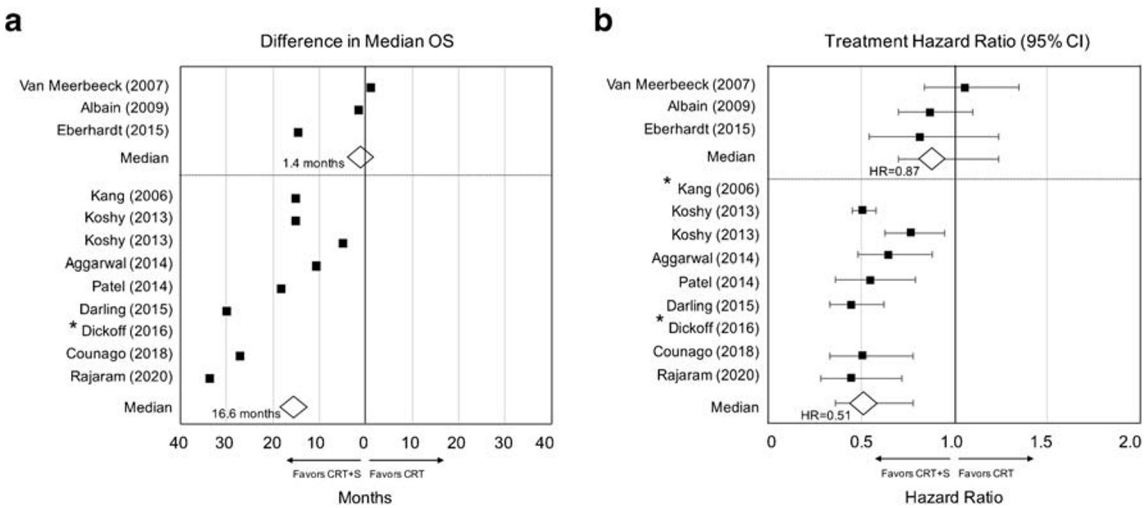

Fig. 2 **A**Absolute differences in median overall survival (OS) between stage IIIA patients treated with C/RT + S and C/RT. **b** Reported hazard ratios (95% CI) associated with treatment approach. Randomized controlled trials are listed above and observational studies below the black dotted line. Data were not available in studies labeled with an asterisk*

Table 2 (A, B) Preliminary results and (C, D) ongoing clinical trials utilizing molecular therapies for the treatment of resectable NSCLC

Author	Trial identifier	Trial name	Phase	Year	Molecular therapy	Treatment sequence	Total sample size	Stage IIIA (%)	MPR (%)	TRAE (%)	OS-5 yr (%)	PFS-5 yr (%)
A												
Zhong	NCT 00600587	Induction Erlotinib Therapy in Stage III A (N2) NSCLC	II	2015	Erlotinib	Neoadjuvant	12	100	–	–	–	–
Zhong	NCT 01407822	EMERGING-CTONG 1103	II	2019	Erlotinib	Neoadjuvant + Adjuvant	72	100	9.7	75.7	40	10
Xiong	NCT 01217619	ESTERN	II	2019	Erlotinib	Neoadjuvant	19	100	42	36.8	42	21
Chen	NCT 01297101	Evaluating Efficacy and Safety of Erlotinib Versus Gemcitabine Plus Cisplatin as Neoadjuvant Chemotherapy	II	2019	Erlotinib	Neoadjuvant	39	100	–	69.2	17 (4 yr)	25 (4 yr)
Zhang	NCT 01833572	Preoperative Gefitinib for EGFR Mutant II–IIIa NSCLC	II	2020	Gefitinib	Neoadjuvant	35	77.1	24.2	85.7	63	41
Author	Trial identifier	Trial name	Phase	Year	Molecular therapy	Treatment sequence	Total sample size	Stage IIIA (%)	OS-5 yr (%)	PFS-5 yr (%)		
B												
Yue	NCT 01683175	EVAN	II	2018	Erlotinib	Adjuvant	51	100	97 (2 yr)	81.4 (2 yr)		
Zhong	NCT 01405079	ADJUVANT/CTONG 1104	III	2018	Gefitinib	Adjuvant	111	65	–	34 (3 yr)		
Cascone	NCT 00254384	Docetaxel, Cisplatin, and Erlotinib Hydrochloride in Treating Patients With Stage I–III NSCLC Following Surgery	II	2018	Erlotinib	Adjuvant	47	38	–	–		
Pennell	NCT 00567359	SELECT	II	2019	Erlotinib	Adjuvant	100	28	86	56		
Wislez	NCT 00775385	IFCT 0801 TASTE	II	2014	Erlotinib	Adjuvant	76	24	–	–		
Kelly	NCT 00373425	RADIANT	III	2015	Erlotinib	Adjuvant	623	14.9	64	48		
Goss	NCT 00049543	NCIC CTG BR19	III	2013	Gefitinib	Adjuvant	251	12	53	49		
Trial identifier	Trial name	Sponsor	Phase	Molecular therapy	Treatment sequence	Target accrual	Target stages	Primary endpoint	Other relevant secondary endpoints			
C												
NCT 03433469	Osimertinib in Treating Participants With Stage I–IIIA EGFR-mutant NSCLC Before-Surgery	University of California San Francisco	II	Osimertinib	Neoadjuvant	27	I-IIIA	MPR	OS; PFS; ORR; AE			
NCT 03088930	Evaluating Crizotinib in the Neoadjuvant Setting in Patients With NSCLC	University of Colorado, Denver	II	Crizotinib	Neoadjuvant	18	I-IIIA	ORR	OS, PFS, MPR			
NCT 04197076	Neoadjuvant Therapy in Resectable NSCLC Stages IIIA	Shanghai Chest Hospital	II	Gefitinib	Neoadjuvant	200	IIIA	PFS; PCR	OS, ORR, TRAE, QoL			
D												
NCT 02193282	ALCHEMIST	National Cancer Institute	III	Erlotinib	Adjuvant	450	IB-IIIA	OS	PFS; AE			
NCT 02511106	ADAURA	AstraZeneca	III	Osimertinib	Adjuvant	682	IB-IIIA	PFS	OS; AE; QoL			

OS: overall survival; PFS: progression-free survival; MPR: major pathological response; TRAE: treatment-related adverse events; PCR: pathologic complete response; AE: adverse events; ORR: objective response rate; QoL: quality of life

Table 3 (A) Preliminary results and (B, C) ongoing clinical trials utilizing immunotherapies for the treatment of resectable NSCLC

Author	Trial identifier	Trial name	Phase	Year	Immunotherapy	Treatment sequence	Total sample size	Stage IIIA (%)	MPR (%)	TRAE (%)	OS (%)	PFS (%)
A												
Provencio	NCT 03081689	NADIM	II	2019	Nivolumab	Neoadjuvant	46	100	83	–	–	95.7 (1 yr)
Shu	NCT 02716038	MAC	II	2020	Atezolizumab	Neoadjuvant	30	77	57	–	84 (2 yr)	49 (2 yr)
Kwiatkowski	NCT 02927301	LCMC3	II	2019	Atezolizumab	Neoadjuvant	101	38.6	18	54.5	–	–
Forde	NCT 02259621	Neoadjuvant Nivolumab, or Nivolumab in Combination With Ipilimumab, in Resectable NSCLC	II	2018	Nivolumab	Neoadjuvant	21	33	42.9	22	–	–
Cascone	NCT 03158129	NEOSTAR	II	2019	Nivolumab; Nivolumab + Ipilimumab	Neoadjuvant	44	20	24	11.4	–	–
Li	ChiCTR-OIC-17013726	IBI308 Monotherapy for Neoadjuvant Treatment of Resectable NSCLC	IB	2019	Sintilimab	Neoadjuvant	40	–	40.5	45	–	–
Trial name	Trial identifier	Sponsor	Phase	Immunotherapy	Treatment sequence	Target accrual	Target stages	Primary endpoint	Other relevant secondary endpoints			
B												
TOP 1501	NCT 02818920	Duke University	II	Pembrolizumab	Neoadjuvant + Adjuvant	35	IB-IIIA	Surgical feasibility rate	PFR, ORR, MPR, AE			
PRINCEPS	NCT 02994576	Gustave Roussy Cancer Campus	II	Atezolizumab	Neoadjuvant	60	IB-IIIA	Rate of toxicity and morbidity	–			
SAKK 16/14	NCT 02572843	Swiss Group for Clinical Cancer Research	II	Durvalumab	Neoadjuvant + Adjuvant	68	IIIA	EVS	OS, ORR, MPR, AE			
KEYNOTE 671	NCT 03425643	Merck Sharp & Dohme Corp.	III	Pembrolizumab	Neoadjuvant + Adjuvant	786	II-IIIB	OS, EVS	MPR, PCR, AE, QoL			
CheckMate 816	NCT 02998528	Bristol-Myers Squibb	III	Nivolumab + Ipilimumab; Nivolumab	Neoadjuvant	350	IB-IIIA	EVS, PCR	OS, MPR, time to death or distant metastases			
IMpower030	NCT 03456063	Hoffmann-La Roche	III	Atezolizumab	Neoadjuvant + Adjuvant	374	II-IIIB	MPR, EVS	OS, PFS, ORR, PCR, AE, QoL			
AEGEAN	NCT 03800134	AstraZeneca	III	Durvalumab	Neoadjuvant + Adjuvant	800	II-IIIB	MPR, EVS	OS, PFS, PCR, QoL			
NEOMUN	NCT 03197467	AIO-Studien-gGmbH	II	Pembrolizumab	Neoadjuvant	30	II-IIIA	AE, ORR, MPR	OS, PFS			
C												
ANVIL	NCT 02595944	National Cancer Institute	III	Nivolumab	Adjuvant	903	IB-IIIA	OS, PFS	AE			
IMpower010	NCT 02486718	Hoffmann-La Roche	III	Atezolizumab	Adjuvant	1280	IB-IIIA	PFS	OS; AE			
PEARLS	NCT 02504372	Merck Sharpe & Dohme Corp.	III	Pembrolizumab	Adjuvant	1080	IB-IIIA	PFS	OS			
BR31 (IFCT1401)	NCT 02273375	Canadian Cancer Trials Group	III	Durvalumab	Adjuvant	1360	IB-IIIA	PFS	OS, AE, QoL			

OS: overall survival; PFS: progression-free survival; EVS: event-free survival; MPR: major pathological response; PCR: pathologic complete response; TRAE: treatment-related adverse events; AE: adverse events; ORR: objective response rate; QoL: quality of life

molecular pathogenesis of lung cancer. Tumor expression profiling and genetic variant analyses have shown that mutational events in receptor tyrosine kinases (TKR), such as anaplastic lymphoma kinase (ALK) and epidermal growth factor receptor (EGFR), are among the most frequently encountered in the NSCLC population [45••]. Mechanistic studies have demonstrated that activating mutations in these oncogenes can promote tumor initiation, proliferation, survival, or therapeutic escape [46, 47]. Clinically, the use of targeted TKR inhibitors in patients with metastatic NSCLC harboring these molecular derangements has been shown to be well tolerated and associated with improved outcomes [48–53]. Given the known toxicity and therapeutic limitations of existing cytotoxic chemotherapeutics, such work has motivated efforts to test molecular therapies as neoadjuvant and adjuvant agents for locoregional disease.

There were 12 prospective trials with published results that evaluated molecular therapies in conjunction with surgery in participants that include stage IIIA patients [54–65]. Most studies were phase II in design ($n = 9$, 75%) and tested the TKR inhibitor erlotinib ($n = 9$, 75%) (Table 2A, B). Long-term outcomes following the use of TKR inhibitors as adjuvant therapies in these preliminary analyses were encouraging, with 5-year OS and PFS rates ranging from 53 to 86% and 48 to 56%, respectively. However, one should caution against the direct extrapolation of these results to the stage IIIA population, as stage IIIA patients currently represent fewer than one-third of all trial patients with available long-term survival data. In contrast, stage IIIA patients are more robustly represented in published neoadjuvant trials. In this setting, treatment with erlotinib or gefitinib has been associated with mixed major pathologic response rates, but favorable long-term OS [54–58]. Additional ongoing studies of osimertinib, crizotinib, gefitinib, and erlotinib in stage IIIA patients are summarized in Table 2C, D [66–70].

In concert with the study of molecular-based therapies, there has been increasing interest in understanding the immune system response to cancer tumorigenesis. Investigations into the programmed cell death protein-1/programmed death ligand-1 (PD-1/PDL-1) pathway have established inhibition of PD-1 or PDL-1 as a viable therapeutic mechanism for anti-tumor activity. Since 2014, multiple immunotherapies have received FDA approval for the treatment of a spectrum of malignancies, including metastatic lung cancer [71].

To date, 6 prospective trials have published preliminary data on the use of neoadjuvant immunotherapy in resectable NSCLC (Table 3A) [72–77]. Major pathologic response rates have varied across these studies, ranging from 18% to 83%. In trials with study cohorts primarily represented by stage IIIA patients, major pathologic response rates have been much greater (NADIM trial: 100% stage IIIA, 83% MPR; MAC trial: 77% stage IIIA, 57% MPR). Moreover, these studies demonstrate relatively low rates of treatment-related adverse events, suggesting that immunotherapies are well tolerated in the neoadjuvant setting. To date, there have been no reported 5-year OS or PFS data. Table 3 B and C highlight the ongoing trials of immunotherapy in both neoadjuvant and adjuvant protocols [78–89]. Of the 12 trials currently underway, 8 (66.7%) are phase III, 4 (33.3%) are investigating immunotherapy as an adjuvant therapy, and only 1 (8.3%) is targeting only stage IIIA patients. Building upon the latest advances in tumor molecular genetics, thoracic oncology, and surgery, these trials hold the promise of providing truly personalized therapies for the management of this challenging and heterogeneous patient population.

Conclusions

In conclusion, the role of surgery in the management of stage IIIA NSCLC remains controversial. While observational reports have consistently shown a survival advantage with multimodality therapies that include surgery, due to differences in study design, patient selection, and treatment-related factors, these findings have not yet been reproduced in randomized controlled trials. The development of molecular therapy and immunotherapies has changed the landscape of treatment options for stage IIIA disease. Looking to the future, the basis of multimodality treatment for stage IIIA NSCLC patients will likely continue to evolve to include medical and surgery therapies tailored to the specific genetic and clinical characteristics of the patient.

Compliance with Ethical Standards

Conflict of Interest Omar Toubat and Anthony W. Kim declare no conflict of interest. Anthony W. Kim reports personal fees, non-financial support, and other from Roche-Genentech outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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