



# Narrative review of the management of stage IIIA non-small cell lung cancer: does different management equal different quality of life?

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**Contributions:** (I) Conception and design: J Trevis, C Pompili; (II) Administrative support: J Trevis; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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**Abstract:** Lung cancer remains the leading cause of cancer related deaths worldwide. A state of equipoise exists due to the expansive evidence base and increasing number of randomised trials testing promising therapeutic drugs and combined treatments. Treatment success should be determined through measuring both efficacy and the maintenance of quality of life (QoL). QoL in lung cancer patients is reported as being lower than in other malignancies, with independence and the ability to perform normal activities ranking as the most important issues. Management of stage IIIA non-small cell lung cancer (NSCLC) remains contentious due to its heterogeneity. For resectable disease, QoL and survival remain higher in those receiving lung parenchyma sparing surgery, such as lobectomy/bilobectomy, compared with pneumonectomy. The addition of neoadjuvant or adjuvant chemotherapy further improves outcomes and has become the standard of care. Whilst some research on QoL in patients receiving chemotherapy has consistently reported a negative correlation between the number of treatment cycles and QoL, other studies have found that chemotherapy may show positive effects on specific QoL domains such as functional activity and pain. Comparatively chemoradiotherapy (CRT) is more effective at reducing tumour/nodal size in resectable disease with no subjective decrease in QoL with the addition of radiotherapy (RT) (despite its increased toxicity) highlighting its potential use as an adjunct. In non-resectable stage IIIA NSCLC, definitive CRT remains the mainstay of treatment. Its efficacy has been well established when compared with RT or supportive care alone. Patients report improved QoL when receiving CRT compared with chemotherapy. Assessing possible effects on health-related QoL remains important when planning multi-modality cancer therapy. This review discusses the differing/compounding impact different treatment strategies for stage IIIA NSCLC have upon patient's QoL and reported outcomes.

**Keywords:** Lung cancer; non-small cell lung cancer (NSCLC); stage IIIA; quality of life (QoL)

Received: 05 June 2020; Accepted: 27 November 2020; Published: 25 May 2022.

doi: 10.21037/ccts-20-114

**View this article at:** <http://dx.doi.org/10.21037/ccts-20-114>

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## Introduction

### *Background—stage IIIA lung cancer*

Lung cancer remains the leading cause of cancer related deaths worldwide (1), with over 1.8 million new cases each year of which 80–85% are non-small cell lung cancer (NSCLC) (1,2). At the time of diagnosis, around 50% of cases are locally advanced, defined as stage III by the 8<sup>th</sup> Edition of the Lung Cancer Stage Classification (3). Further subclassification provides distinction between nodal status with important implications upon the decision-making process for management, prognosis and overall long-term outcomes. Regarding treatment options, stage IIIA NSCLC may be differentiated into resectable or unresectable disease, thus requiring accurate pre-operative staging. Following subclassification, the therapeutic options remain broad, including; neoadjuvant chemotherapy or chemoradiotherapy (CRT) followed by surgery, surgery followed by adjuvant chemotherapy with or without adjuvant radiotherapy (RT), or definitive CRT without surgery (4), and more recently, the addition of targeted therapies (e.g., immunotherapy).

### *Objectives*

Aiming to briefly discuss the management options for stage N2/IIIA NSCLC, whilst primarily addressing their differing/compounding impact upon patient's quality of life (QoL) and reported outcomes. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://ccts.amegroups.com/article/view/10.21037/ccts-20-114/rc>).

## Methods

The following search strategy was employed in order to identify high quality systematic reviews, meta-analyses and relevant studies to fully explore the objectives established for this narrative review; Medline search (1966–June 2020) using the Ovid interface. Key words: Lung cancer, non-small cell lung cancer, NSCLC, stage IIIA, management, treatment, chemotherapy, radiotherapy, surgery, chemoradiotherapy, outcome, QoL, patient reported outcomes (PROs). This was supplemented with hand searches of literature from personal experience in writing numerous studies/reviews in this field of research.

## Discussion

### *What the guidelines recommend*

The heterogeneity of stage IIIA N2 disease is reflected in the treatment combinations available. A lack of a universally agreed definition on resectability and descriptors of lymph node (LN) characteristics, coupled with unclear randomised evidence, means contention remains on what the optimal treatment is (5). Treatment approaches from the National Institute for Health and Care Excellence (NICE), American College of Chest Physicians (ACCP), and European Society for Medical Oncology (ESMO) highlight this heterogeneity with consensus maintained on a multimodal approach (*Table 1*).

There remains an emphasis on the utilisation of the multidisciplinary team, patient preference, high volume centres, and for individual patient risks to be taken into account (6–8). Generally, there is acceptance for the use of surgery in low volume (non-bulky) mediastinal node involvement (6–8). NICE however specifically recommends the use of trimodality treatment for all resectable N2 disease. Therapies based on definitive CRT remain reserved for more extensive, higher volume (bulky) and unresectable disease (6–8). With regards to immunotherapy, due to its relative infancy, guidance is yet to reflect its routine use stating that there is currently no place for targeted therapy in the treatment of stage IIIA N2 NSCLC; other than within clinical trials (7,8).

### *QoL and lung cancer*

QoL in lung cancer patients is reported to be lower than in those suffering from other malignancies (9). Research has shown that routine collection of QoL data effectively supplements clinical evaluation and laboratory results, whilst helping to predict survival (9) particularly in lung cancer patients. Assessment through patient reporting allows for the potential to uncover needs that would not otherwise be found by the physician, as demonstrated by significant incongruity between clinicians' ratings and patients self-reporting (10,11). QoL data can also help to guide therapeutic decision making (9); of particular importance when a pathology confers little outcome for return to full health or is deemed incurable. The aim therefore becomes to improve health related QoL, defined by Ebrahim as being 'determined by QoL and modified by physical impairment, limitation of functional state,

**Table 1** Overview of treatment strategies recommended by the UK, European and American guidelines [modified from Putora *et al.* (5)]

Guideline	Resectable	Non resectable
NICE	LN extent: single station (LN non-bulky and bulky = definitive surgery + neo/adjuvant chemotherapy/CRT) LN extent: multi-station single zone (LN non-bulky and bulky = definitive surgery + neo/adjuvant chemotherapy/CRT) LN extent: multizone (LN non-bulky and bulky = definitive surgery + neo/adjuvant chemotherapy/CRT)	Definitive CRT
ESMO	LN extent: single station (LN bulky and non-bulky = NP) LN extent: multi-station single zone (Bulky and non-bulky = definitive CRT) LN extent: multizone (Bulky and non-bulky = definitive CRT)	Definitive CRT
ACCP	LN extent: single station (Bulky = definitive CRT; non-bulky = NP) LN extent: multi-station single zone (Bulky = definitive CRT; non-bulky = NP) LN extent: multizone (Bulky = definitive CRT; non-bulky = NP)	Definitive CRT

LN, lymph node; CRT, chemoradiotherapy; NP, no preference on any modality; NICE, National Institute for Health and Care Excellence; ACCP, American College of Chest Physicians; ESMO, European Society for Medical Oncology.

perceptions, and opportunities of social activity' (12).

Together, disease severity and progression impact negatively upon QoL in lung cancer patients. QoL is further compounded by symptom severity and number, treatment side effects, type of cancer, tumour localisation, and prognosis for cure and survival (9). The mental and social resources of a patient before the onset of disease are also crucial (9). Research suggests that patients assess their functioning in five dimensions: physical, psychological, cognitive, social, and life roles. Both generalised and disease-specific symptoms have been shown to exacerbate psychological symptoms (13). Functional impairment is said to be the most important risk factor for depression (13), together with independent contribution from fatigue, symptom burden, and performance status (14). Therapeutic success should not only be determined by efficacy and prolongation of survival, but also the achievement of a satisfactory level of self-assessed QoL, where independence and the ability to perform normal activities rank as the most important issues among lung cancer patients (15).

### Resectable stage IIIA NSCLC

Surgery continues to be a mainstay management option for patients in early stage disease (I and II), where the mean five-year survival rate is 90% for pathological stage I, declining to 41% in confirmed stage IIIA disease (3). There continues to be controversy around the efficacy of surgery for this group of patients, especially so for N2 disease (16).

In comparison to earlier stage disease, stage IIIA NSCLC patients have more postoperative complications, such as longer median hospital stay and higher proportions of arrhythmias (17). Surgery in stage IIIA NSCLC has seen an upward trend in the use of tissue sparing lobectomy in place of the more extensive pneumonectomy (18), which conveys worse survival rates as reported by Schulte *et al.* of 45 months *vs.* 31 months respectively (19,20). Albain *et al.* has reported a similar trend, where higher mortality rates (26%) with pneumonectomy were observed, reflecting an increased rate of surgical related deaths (8% compared to 2% with chemotherapy alone) (21,22). Shao *et al.* has shown in their albeit small sample size of 51 stage IIIA patients, that those whom underwent video-assisted thoracic surgery (VATS) did not encounter any increase in intraoperative complications, with a mean survival time of  $44.0 \pm 2.6$  months) and a five-year overall survival (OS) of 51.1%, concluding that VATS in stage IIIA patients is a safe and feasible treatment (23). However, survival rates and QoL for stage IIIA patients continue to show a lack of improvement (24,25).

In the first instance, stage IIIA NSCLC patients generally report lower pre-operative QoL baselines compared to early stage disease patients, highlighted by Yilmaz *et al.* where a mean preoperative walking distance of 346 m was described compared to 457 m in the early stage disease group (26). With lower baseline physiological reserves and thus potential hindrance on daily QoL, preservation of QoL through type of resection should

be central in decision making. Several studies (27–29) have shown patients receiving lobectomy to have higher levels of QoL when compared to pneumonectomy; mean QoL was >10 points higher for the lobectomy group with less pain, coughing and dyspnoea at 24 months (19). Patients receiving lobectomy have also been shown to return to their physical baselines between 1–6 months postoperatively (19,28,29).

However, Schulte *et al.* has shown that both pneumonectomy and lobectomy patients have worse QoL outcomes when compared to other major visceral operations, such as oesophageal resection, at 24 months post-operatively. Increases in pain, dyspnoea and coughing were reported in both groups, with higher coughing reported in the lobectomy group at discharge (19). Subsequently, both groups demonstrate an expected reduction in QoL at discharge which was slow to recover and ultimately failed to return to preoperative levels at 24 months, particularly in the pneumonectomy group (19). Supported by Ferguson *et al.*'s meta-analysis, concluding that pneumonectomy was associated with a postoperative increase in breathlessness and pain at 12 months, with continued fatigue, anxiety and physical functioning (dyspnoea) being reported five years on in 34% of patients (28,30,31). Overall surgery remains a key aspect of treatment for those with resectable stage IIIA NSCLC, however when performed alone it demonstrates poor outcomes, with 30–70% of patients experiencing recurrence or death (1,32,33).

### Chemotherapy

The standard of care for resectable locally advanced NSCLC requires a multimodal approach whereby the addition of chemotherapy has added benefit. The literature suggests two approaches to chemotherapy for this patient group, namely, induction or adjuvant regimens (1). The NSCLC Meta-analysis Collaborative Group reports a 5% absolute increase in five-year survival with the use of adjuvant chemotherapy in patients with locally advanced NSCLC (34), representing an increased OS from 30% to 35%, improving median survival from 45 to 54 months (35,36). This report also highlighted that there was no significant positive or negative effect of chemotherapy on complete resection rate; nor benefit upon locoregional recurrence, with no excess of early mortality in the preoperative chemotherapy arm as a result of deferred surgery (33).

Despite becoming standard of care for stage IIIA lung cancer management, the routine collection of QoL outcomes for this treatment modality and specific subclassification remain minimal. In advanced stage lung cancer, chemotherapy aims to decrease tumour mass, reduce cancer associated symptoms and therefore improve QoL following cessation of treatment related side effects (37). The desire for symptom relief may even exceed the wish for survival (38). However, the literature addressing the impact of chemotherapy upon QoL in lung cancer patients in general reports a negative correlation between the number of chemotherapy cycles and QoL (9,37,39), particularly in the over 65 age group. Similar trends have been reported by Wintner and colleagues (40), whereby they state that QoL worsens as patients progress through treatment lines, i.e., those receiving third line therapy showed significantly worse QoL compared to those receiving first line therapy. This deterioration was particularly seen in the physical functioning dimension of QoL assessment, thought to be due to the high levels of symptom burden shown by the QLQ-C30 subscales (41). Chemotherapy is also reported to impact upon performance of occupational and family roles in this age group as well as daily duties, including physical and social functioning (9,37). Whilst in the under 65 age group, its impact predominantly limits psychological functioning whereby it is common for levels of anxiety to rise, often related to a reduction in QoL (37,42).

In contrast, others such as Ranson *et al.* and Brown have shown that chemotherapy may show positive effects on specific domains e.g. functional activity and pain (43,44). Milosevic and colleagues (39), in a sample of 120 patients (25% stage III), found that chemotherapy was superior to alternative treatment modalities, when compared to symptomatic management only. Reporting an improvement in physical, business, social and emotional functioning, along with a reduction in numerous symptoms, e.g., dyspnoea, insomnia, loss of appetite, dysphagia and haemoptysis. Conversely, they acknowledge the deterioration of other symptoms, i.e., nausea and vomiting, fatigue and hair loss.

Overall, management of disease and treatment related symptoms may improve QoL; with the literature recommending controlling levels of fatigue, pulmonary rehabilitation, social and spiritual support with early instigation of palliative treatment allowing for an improved QoL (9).

### Post-operative radiotherapy

Up to 40% of resectable N2 tumours have local recurrence (1) and therefore medical reduction strategies such as RT are required. Nonetheless, the detriment of post-operative radiotherapy (PORT) on OS has been well reported by the PORT Meta-analysis Trialists Group, demonstrating a two-year OS decrease of 7% in PORT compared to surgery alone (45). Despite this, the detriment of PORT was found to be inversely related to nodal status, with a beneficial trend found for N2 disease (45). The more recent 2016 meta-analysis by Cochrane included this data, expressing an 18% increase in relative risk of death in the PORT group, reducing OS from 58% to 53% (46), stating that the number of patients needed to harm is greater than the number of patients needed to treat (47). However, this meta-analysis reviewed trials from 1966–1998 and as such does not account for current advances in RT technology and techniques.

One trial included in this meta-analysis (48) showed five-year OS in those receiving surgery and PORT to be lower (30%) compared to surgery alone (43%) ( $P=0.002$ ) (1,48), accountable to a 23% increase in intercurrent death rate in the PORT group. However, this study showed that this detriment of PORT was in those with stage II disease, with no difference demonstrated in patients with stage I or III (49). This finding is supported by Corso *et al.* whereby an absolute five-year OS benefit of 6.3% in the N2 PORT group was found comparable to a detriment of 9.3% and 4.3% in the N0 and N1 groups respectively (50). When compared with resection as a definitive treatment following induction chemotherapy, research has suggested that PORT has equal efficacy to surgery (51) when measuring median (16.4 *vs.* 17.5 months) and five-year OS (15.7% *vs.* 14%) (hazard ratio = 1.06, 95% CI, 0.84 to 1.35).

Milosevic *et al.* reported the impact of RT upon QoL showing that patients experienced reduced pain and coughing, with beneficial effects on dyspnoea seen weeks to months post treatment (39). However, this study also highlighted that appetite is decreasing, and nausea and vomiting were worsened by RT (39). When comparing QoL outcomes in patients who underwent either surgery or RT (only) in early stage NSCLC, Schwartz *et al.* found that there was no significant difference between the two groups scores, with a substantial decline in both physical and mental health QoL seen in both surgical patients and those undergoing RT, concluding that the two modalities are comparable in their effect on QoL (52).

### Combined chemoradiotherapy

The benefit of CRT in decreasing tumour size has been expressed by several studies (21,53,54). Pless *et al.* demonstrated a pathological complete response/nodal downsizing of 61% with the addition of neoadjuvant CRT compared with 44% with neoadjuvant chemotherapy alone (53). When comparing bimodality treatments to trimodality, Sorensen *et al.* and the meta-analysis by McElnay *et al.* showed that trimodality treatment (sequential CRT with surgery) improved survival rates when compared to CRT alone (5,55,56). A finding supported by The Intergroup study (INT 0139), where progression free survival (PFS) was 29% in the neoadjuvant trimodality group *vs.* 19% in the bimodal group ( $P=0.02$ ) but conversely, OS was not significantly different at 3-years (38% *vs.* 33%, respectively) (5). Furthermore, in regard to sequential CRT, Pless *et al.*'s study (neoadjuvant concurrent CRT with surgery *vs.* neoadjuvant chemotherapy and surgery) showed that there was no significant difference in event-free survival between trimodality and bimodality treatment [12.8 *vs.* 11.6 months ( $P=0.67$ )] or OS (37 *vs.* 26 month) (53). Albain *et al.* has reported similar findings when comparing neoadjuvant CRT plus surgery *vs.* definitive CRT, finding no overall significant difference in median survival between treatment modalities (23.6 *vs.* 22.2 months) but did find a 5-year PFS improvement within the trimodality group (median 12.8 months PFS *vs.* 10.5 months) (21). In turn, this opens the question of whether an increase in aggressive treatment combinations equates to improvements in QoL at the cost of higher toxicity.

Schumacher *et al.* in their study have shown that there is no subjective decrease in QoL with the addition of concurrent neoadjuvant CRT when compared to sequential in locally advanced NSCLC (57). QoL was assessed before and after each intervention in both groups using the EORTC QLQ-C30 and the QLQ-LC (41,58) where no statistically significant differences between both groups were found (57). Both groups reported lower levels of physical functioning and increases in symptoms of pain, fatigue and dyspnoea at the end of their treatment compared to at the end, finding lower rates of haemoptysis in the CRT group (57). Interestingly, although these reductions in QoL scales were found, there were no significant decreases in "Global health" or "Overall QoL" in either group as one could assume with higher toxicity and decreases in physical function, highlighting the potential use of additional CRT as an adjunct to treatment for stage IIIA NSCLC patients (58).



## Non-resectable stage IIIA NSCLC

### Definitive CRT

Definitive CRT remains the mainstay of treatment for unresectable stage IIIA NSCLC; due to the local impact of RT, and systemic effect of chemotherapy in the effort to reduce/prevent micrometastases, whilst acting as a radiosensitiser, increasing the therapeutic index of the RT (1,59).

The literature is well established, as reported in the review by Yoon *et al.*, for the survival benefits conferred by CRT when compared to RT or supportive care alone (1). A meta-analysis conducted by Aupérin and colleagues concluded that concurrent CRT granted a 5-year absolute OS benefit of 4.5% and a decreased locoregional progression by an absolute rate of 6.1% at 5 years (HR =0.77) when compared to a sequential regimen (60), further solidified by the results from the RTOG 9410 randomised trial (61). Conversely, concurrent CRT has demonstrated significantly increased rates of acute grade 3–4 non-haematologic toxicity, particularly acute oesophagitis, along with a lack of reduction of distant disease progression compared to sequential (1,60). As a result, there remains a place for sequential CRT, namely in those unable to tolerate concurrent therapy as it has been shown to provide a 5-year OS advantage over RT alone (1).

When considering QoL outcomes within this group, a randomised trial by Strøm *et al.* [2013] compared the impact of chemotherapy *vs.* CRT in the palliation of unresectable stage III NSCLC (62). Both survival and QoL were measured and compared between the two arms. QoL was measured using the EORTC QLQ-C30 questionnaire V3 plus the supplementary questionnaire LC13 (58). Scores ultimately remained static in the CRT arm (though patients reported a significant worsening of their symptoms during treatment). The chemotherapy arm however reported a significant and clinically relevant deterioration in the months following therapy in QoL which unlike the CRT cohort did not return to baseline and progressively worsened. Researchers therefore concluded that CRT (despite the increased toxicity levels) was superior to chemotherapy alone given the higher survival rates and increased reported QoL (62). These results reinforce the findings from an earlier study by Pijls-Johannesma *et al.* in which QoL was assessed following the use of high-dose RT or concurrent CRT whilst treating lung cancer patients (63). Concluding that QoL decreased after patients received

either treatment, thought to be due to treatment-related side effects, but returned to baseline within 3 months (63). Further describing predictors for QoL to be; oesophagitis, gender, tumour stage (whereby stage III disease was associated with increased QoL compared to stage I-II), and fatigue. This study indicates that concurrent CRT or high dose RT is well-tolerated treatment options regarding the preservation of QoL.

### Targeted therapy

Within the population of patients who have received CRT alone, for inoperable advanced NSCLC, there still remains poor outcomes, with most having disease progression and only 15–30% remaining alive at 5-years (64,65). As a result, progress has been primarily sought through optimization of CRT regimens. Whilst these regimens demonstrate greater response rates and survival (1,61,66,67), it is burdened with increased toxicity when compared to sequential therapy, generating the need for an efficacious treatment for stage IIIA NSCLC with reduced/minimal related toxicity. The heterogeneity of lung cancer biology has steered investigation into numerous targeted therapies, utilising mutations such as EGFR, ELM4-ALK (1).

### Immunotherapy

It has been suggested that RT may promote tumour immunogenicity (68) through both a synergistic and abscopal effect due to systemic immune activation (67). Promising results have been reported from the PACIFIC trial, targeting immune checkpoints through the use of durvalumab in patients with unresectable stage IIIA NSCLC, who have not demonstrated disease progression following concurrent CRT. The trials primary endpoints, OS and PFS have shown significant improvement when compared to placebo, *i.e.*, 66.3% *vs.* 55.6% 24-month OS, 16.8 *vs.* 5.6 months PFS (64,65). Furthermore, a secondary endpoint analysis published by Hui *et al.*, looked to explore the impact upon PROs. This was of particular importance as the previous standard of care involved observation and can therefore be presumed to have no detriment upon PROs (64,65). It should however be mentioned that a limitation of this study was the possible non-capture of immunotherapy related symptoms from utilising the EORTC questionnaire—originally designed for analysing the impact of chemotherapy (69), thus creating scope

for further development of such QoL questionnaires for this emerging treatment method. Considering the aforementioned, it was concluded that the addition of up to 12 months of durvalumab did not compromise patients' symptoms, functioning or QoL when compared with placebo (70) supported by a paper by Garassino and colleagues, complementing the clinical safety profile also observed (64,65,71). This is supported by further literature investigating immunotherapies such as nivolumab, pembrolizumab and atezolizumab, which have gained approval for second line treatment of advanced NSCLC, based on a multitude of studies demonstrating increased response rates, OS and PSF over docetaxel (71-79). Whilst also collectively reporting favourable safety outcomes when compared to chemotherapy (platinum based and/or docetaxel) (71-79). PROs and QoL analysis reported an improved QoL measures at 15 weeks compared to chemotherapy in those receiving pembrolizumab. Overall, these findings suggest that immunotherapies may be an encouraging treatment able to preserve QoL in patients with NSCLC demonstrating improved clinical and QoL measures when compared to the previous optimal treatment of platinum-based chemotherapy (13).

## Summary

Due to the heterogeneity of the lung cancer patients, in presentation, histopathology and response to treatment, treatment success should be viewed from two key standpoints; survival and maintenance of a good QoL (31). The assessment of health-related QoL remains important in the planning of cancer therapy, with success of medical treatment and pulmonary rehabilitation shown to diminish with increasing symptoms, and therefore reducing QoL (26). The basis for improving QoL in lung cancer patients is limited by the number and severity of symptoms, especially fatigue, pain and dyspnoea.

This continues to be a challenging cohort of patients to manage, expressed by the variation in international consensus. Multi-disciplinary management continues to play a crucial role for these patients and QoL considerations need to be discussed with patients during the decision-making process. Therefore, management of these patients should heavily rely on patient centeredness, with treatments offered at an individualised level and implementation of new strategies to predict the evolution of QoL.

## Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the Guest Editors (Fabrizio Minervini and Marco Scarci) for the series "Controversies in the Management of Stage IIIA Non-Small-Cell Lung Cancer" published in *Current Challenges in Thoracic Surgery*. The article has undergone external peer review.

*Reporting Checklist:* The authors have completed the Narrative Review reporting checklist. Available at <https://ccts.amegroups.com/article/view/10.21037/ccts-20-114/rc>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://ccts.amegroups.com/article/view/10.21037/ccts-20-114/coif>). The series "Controversies in the Management of Stage IIIA Non-Small-Cell Lung Cancer" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

*Ethical Statement:* The authors are 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.

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doi: 10.21037/ccts-20-114

**Cite this article as:** Trevis J, Barclay P, Marshall N, Pompili C.  
Narrative review of the management of stage IIIA non-small  
cell lung cancer: does different management equal different  
quality of life? *Curr Chall Thorac Surg* 2022;4:15.