Combined modality therapy in Stage IIIA non–small cell lung cancer: clarity or confusion despite the highest level of evidence?

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ABSTRACT

Recent years have witnessed a number of clinical trials in Stage IIIA non–small cell lung cancer (NSCLC) comparing (A) induction chemotherapy (CHT) with induction CHT and radiotherapy (RT), each followed by surgery; (B) either induction CHT or induction RT-CHT, each followed by surgery, with definitive RT-CHT (no surgery). Due to the heterogeneity of patient, tumor and treatment characteristics across these trials, various meta-analyses (MAs) have been performed to define the optimal treatment approach in this setting for this clinical presentation. Six such MAs exist. In spite of the differences between MAs, it appears that RT does not add extra benefit to induction CHT administered before surgery, and that a trimodality (i.e. including surgery) regimen is not superior to definitive concurrent RT-CHT. While one can consider both induction CHT followed by surgery and exclusive concurrent RT-CHT as feasible in this setting, lack of pre-treatment predictive factors identifying patients who might preferentially benefit from a surgical approach limits its use to well-planned clinical trials.

KEYWORDS: Stage IIIA, NSCLC, radiotherapy, chemotherapy, surgery, meta-analysis

INTRODUCTION

Over the past three decades thoracic oncologists have intensively debated the most appropriate treatment for patients with Stage IIIA (typically as pN2) non–small cell lung cancer (NSCLC). A range of combined modality approaches have been tested and tried for cure. Surgery has been employed [preceded by induction chemotherapy (CHT), with or without concurrent radiation therapy (RT)] in a number of studies and it has shown promising results in this patient population [1–8]. In patients treated without surgery, definitive concurrent RT-CHT became the standard treatment approach for inoperable Stage III NSCLC patients [9–11]. Recently, a number of prospective randomized clinical trials (RCTs) compared various induction regimens followed by surgery with definitive non-surgical treatment. Notwithstanding the various study designs and eligibility criteria in these RCTs, their findings were consistent: either concurrent RT-CHT or sequential CHT-RT without surgery is as effective as either induction approach followed by surgery [12–18].

In spite of this strong evidence for the lack of benefit from the addition of surgery, many thoracic surgeons and oncologists as well as professional bodies [19, 20] continue to suggest that surgery is indicated for some 'appropriate' patients with Stage IIIA disease, although the definition of 'appropriateness' is variable. For example, in one study [16] an unplanned *post-hoc* subgroup analysis suggested a survival benefit for surgery in lobectomy-suitable patients. Given this controversy, a number of meta-analyses (MAs) have been carried out to help in resolving the issue, looking at the differences between the patient and/or tumor and/or treatment characteristics of these randomized studies. These MAs have addressed two separate questions (Table 1):

(A) Which is the more effective induction treatment before surgery: induction CHT alone or with RT?
(B) Which is the most effective overall curative approach: induction CHT (with or without RT) followed by surgery, or RT-CHT alone (no surgery)?

Our aim was to review the quality of the MAs with respect to their content and their conclusions regarding the role of surgery in Stage IIIA NSCLC.

MATERIAL AND METHODS

References were identified through a search of PubMed using the terms 'meta-analysis', 'systematic review', 'non–small cell lung cancer', 'surgery', 'radiotherapy', 'chemotherapy' and 'Stage IIIA' for the interval from 1990 until September 2016; through searches of the references of the identified articles; and through searches of the authors' own files. The year 1990 was selected as the starting point for the survey as it marks the contemporary era of RT delivery. Findings were restricted to fully published English language articles.

Since our study was neither a MA nor a systematic review, but rather an 'ordinary' review, we did not attempt any qualitative or quantitative data synthesis. This was due to the extreme heterogeneity in the subjects and therapies across both of the original studies included in these analyses/reviews and, consequently, in their findings.

RESULTS
Meta-analyses addressing Question A

Addressing Question A (Table 2), Shah *et al.* [21] compared induction RT-CHT with induction CHT alone in patients with Stage IIIA (N2) NSCLC who were to undergo surgery. They identified seven studies, reporting on a total of 526 patients. Their study included only one fully published RCT, two RCTs only in abstract form, one Phase II randomized trial, and three retrospective reviews. None of the studies showed a survival benefit for induction RT-CHT compared with induction CHT alone. The MAs performed on two RCTs (one Phase III and one Phase II) ($n = 156$ patients) demonstrated no benefit in overall survival (OS) from adding RT (HR 0.93; 95% CI 0.54–1.62; $P = 0.81$), nor did the MAs performed on two out of three available retrospective studies ($n = 183$ patients, HR 0.77, 95% CI 0.50–1.19; $P = 0.24$). The inclusion of retrospective papers, and data presented in abstract form only, clearly limited the quality of this MA.

In the second of the MAs addressing Question A, Xu Y-P *et al.* [22] analyzed seven RCTs involving 1049 patients. Their analysis consisted of two parts (Table 2): the first focused on Question A (three RCTs, $n = 229$ patients), while the second focused on Question B (four RCTs, $n = 820$ patients). Concerning Question A, they found that although induction RT-CHT before surgical resection led to a significant increase in the rate of pathological complete remission in resected mediastinal lymph nodes in Stage IIIA (N2) NSCLC patients compared with those who received induction CHT (HR 3.61; 95% CI 1.07–12.15; $P = 0.04$), there was no significant difference in tumor downstaging, OS (three trials), (HR 0.79; 95% CI 0.57–1.09; $P = 0.15$) or progression-free survival (PFS) (two trials) (HR 0.67; 95% CI 0.39–1.15; $P = 0.15$). This

Table 1. Questions in meta-analyses

Author (year)	Question
Shah *et al.* [21]	**A.** Which is the more effective induction treatment before surgery: CHT alone or RT-CHT?
Xu Y-P *et al.* [22]	**A.** Which is the more effective induction treatment before surgery: CHT alone or RT-CHT?
	B. Which is the most effective curative approach: induction CHT, with or without RT, followed by surgery, or RT-CHT alone?
Ren *et al.* [25]	**B.** Which is the most effective curative approach: induction CHT, with or without RT, followed by surgery, or RT-CHT alone?
McElnay *et al.* [26]	**B.** Which is the most effective curative approach: induction CHT, with or without RT, followed by surgery, or RT-CHT alone?
Xu X-L *et al.* [27]	**B.** Which is the most effective curative approach: induction CHT, with or without RT, followed by surgery, or RT-CHT alone?
Guo SX *et al.* [24]	**A.** Which is the more effective induction treatment before surgery: CHT alone or RT-CHT?

RT = radiotherapy; CHT = chemotherapy.

Table 2. Meta-analyses—characteristics and findings

Author (year)	Comparison	N	Type of studies	Summary of findings	Comment
Shah et al. [21]	Induction CHT + surgery vs induction RT-CHT + surgery	7	RCT (one full) RCT (two abstracts) Phase II (one full) Retrospective (three full)	HR 0.93; 95% CI 0.54–1.62; $P = 0.81$ (for two RCTs; $n = 165$) HR 0.77, 95% CI 0.50–1.19; $P = 0.24$ (for two retrospective studies; $n = 183$)	• No benefit of adding RT to induction CHT • Included retrospective studies and abstracts
Xu Y-P et al. [22]	Induction CHT + surgery vs induction RT-CHT + surgery	3	RCT ($N = 229$)	OS (3 trials); HR 0.79; 95% CI 0.57–1.09; $P = 0.15$ PFS (2 trials), HR 0.67; 95% CI 0.39–1.15; $P = 0.15$	• No benefit of adding RT to induction CHT • No superiority of trimodality Tx over concurrent RT-CHT in both OS and PFS
	Induction CHT +/- RT + surgery vs concurrent or sequential RT-CHT	4	RCT ($N = 820$)	OS (4 trials), HR 0.95; 95% CI 0.81–1.10; $P = 0.49$ PFS (2 trials), HR 0.90; 95% CI 0.77–1.05; $P = 0.19$	
Ren et al. [25]	Induction CHT ± RT + surgery vs concurrent RT-CHT	3	RCT ($N = 1,048$)	2-year OS: HR 1.00; 95% CI 0.85–1.17; $P = 0.98$ 4-year OS: HR 1.13; 95% CI 0.85–1.51; $P = 0.39$ 3-year PFS: HR 1.05; 95% CI 0.61–1.81; $P = 0.86$	• No superiority of trimodality Tx over concurrent RT-CHT in both OS and PFS
McElnay et al. [26]	Bimodality approach (CHT+surgery) vs concurrent RT-CHT	4	RCT ($N = 229$) (bimodality trials)	HR 1.01; 95% CI 0.82–1.23; $P = 0.954$	• No superiority of either bimodality or trimodality Tx over concurrent RT-CHT
	Trimodality approach (RT-CHT +surgery) vs concurrent RT-CHT	2	RCT ($N = 820$) (trimodality trials)	HR 0.87; 95% CI 0.75–1.01; $P = 0.068$	
		6	RCT ($N = 1049$) (all trials combined)	HR 0.92; 95% CI 0.81–1.03; $P = 0.157$	
Xu X-L et al. [27]	Induction CHT ± RT + surgery vs concurrent RT-CHT	5	RCT only ($n = 851$)	HR 0.94; 95% CI 0.81–1.09; $P = 0.686$	• No difference in OS in RCTs • OS superior with surgical approach in retrospective studies • Pooled studies suggest superiority in OS of surgical approach • No difference in PFS • Retrospective studies disproportionate weighting
		4	Retrospective only ($n = 11\,154$)	HR 0.58; 95% CI 0.46–0.71; $P = 0.008$	
		9	Pooled studies ($n = 12\,005$)	HR 0.70; 95% CI 0.56–0.87; $P = 0.000$	
Guo SX et al. [24]	Induction CHT + surgery vs induction RT-CHT + surgery	12	Phase III RCT (three) Phase II (one) Retrospective (six) Abstracts (two) (total $n = 2724$)	HR 0.75; 95% CI 0.63–0.89; $P = 0.001$ (tumor downstaging) ($n = 6$) HR 0.72; 95% CI 0.60–0.88; $P = 0.001$ (pCR) ($n = 6$) HR 0.64; 95% CI 0.48–0.85; $P = 0.002$ (local control) ($n = 5$) HR 0.89; 95% CI 0.68–1.19; $P = 0.44$ (5-year OS) ($n = 4$) HR 0.74; 95% CI 0.43–1.26; $P = 0.26$ (5-year PFS) ($n = 4$) HR 0.77; 95% CI 0.50–1.18; $P = 0.24$ (5-year OS) ($n = 2$) HR 0.73; 95% CI 0.51–1.07; $P = 0.20$ (5-year PFS) ($n = 2$)	• Difference favoring induction RT-CHT in tumor downstaging, pCR and local control, but not OS or PFS • Different N studies used for different endpoints

RCT = randomized controlled trial; HR = hazard ratio; CI = confidence interval; RT = radiation therapy; CHT = chemotherapy; OS = curative survival; PFS = progression-free survival; Tx = treatment; MA = meta-analysis; pCR = pathological complete response in mediastinal lymph nodes.

higher quality MA because of its use of RCTs only produced a result identical to that of Shah et al. [21]. A recent prospective RCT [23] not included in either MA showed that the addition of induction RT to CHT did not improve outcomes; thus, it confirmed these MAs.

Most recently, Guo et al. [24] reported on the third MA addressing Question A. They initially included twelve studies, with a total of 2724 patients. Of these, there were three RCTs, one Phase II study, six retrospective studies and two studies not fully published (abstracts only). However, the lack of a complete set of data concerning all end points used led to four studies being discarded. Of a potential eight studies, six were used for investigating tumor downstaging and pathological mediastinal lymph node complete response (pCR), while five were used for assessing local control. In these three separate analyses, induction RT-CHT was found to be superior to induction CHT, both followed by surgery (HRs 0.75, 0.72 and 0.64, respectively). Four studies identified as PRCTs were actually three—the fourth one was a retrospective analysis of a National Cancer Database in the USA; hence, it was a retrospective one. Nevertheless, no difference in either OS (four studies: HR 0.89) or PFS (three studies: HR 0.74) was found. The same was observed when two additional retrospective studies were examined separately (OS: HR 0.77; PFS: HR 0.73).

Meta-analyses addressing Question B

Three recent MAs have investigated whether induction with either CHT or RT-CHT, followed by surgery, is more effective than RT-CHT alone (no surgery) (Table 2). In the second component of the aforementioned MA of Xu Y-P et al. [22], the authors found that there was no significant difference in OS or PFS in patients who received induction CHT or RT-CHT prior to surgery compared with those who received either sequential or concurrent RT-CHT without surgery (HR 0.95; 95% CI 0.81–1.10; $P = 0.49$).

In a recent MA, Ren et al. [25] selected three RCT studies with 1048 patients and showed no difference in 2-year OS (HR 1.00; 95% CI 0.85–1.17; $P = 0.98$), 4-year OS (HR 1.13; 95% CI 0.85–1.51; $P = 0.39$) or 3-year PFS (HR 1.05; 95% CI 0.61–1.81; $P = 0.86$) between the two approaches. These findings, though clear, did not prevent these authors from speculating that adding RT to induction CHT might improve PFS results in a multimodality setting (based on the findings of a single study, which was actually an unplanned, post-hoc subgroup analysis [16]).

In another recent MA, McElnay et al. [26] identified six relevant trials [12–16, 18] and separated them into bimodality (CHT followed by surgery) and trimodality (RT-CHT followed by surgery) groups. The results of both bimodality and trimodality trials were the same: there was no statistically significant difference in OS when either of the two were compared with RT-CHT alone; this was also confirmed when the data of all studies were pooled. Although the authors acknowledged the lack of statistical significance, they could not refrain from suggesting a potential benefit from surgery (HR 0.87; 95% CI 0.75–1.01; $P = 0.068$) in the trials of trimodality (RT-CHT followed by surgery), saying that there was 'a distinct possibility of 13% relative improvement in OS'. It is not clear what a 13% difference in HR actually means in terms of 'relative' or 'absolute' survival; their further speculation that patients who receive surgery as part of trimodality treatment are likely to have an OS better than from definitive RT-CHT was tendentious since this has not been supported prospective RCTs.

Finally, the MA of Xu X-L et al. [27] included five RCTs ($n = 851$) and four retrospective studies ($n = 11\,154$). When the analysis was confined to the prospective RCTs, no difference was found in OS (HR 0.94; 95% CI 0.81–1.09; $P = 0.686$) between various induction (CHT alone or RT-CHT) regimens followed by surgery and combined RT-CHT without surgery (mostly concurrent RT-CHT). In contrast, when this analysis was applied to the retrospective group of studies, a surgical approach showed superiority with respect to OS (HR 0.58; 95% CI 0.46–0.71; $P = 0.008$). Also, when the datasets were pooled, the significant difference favoring the surgical approach remained (HR 0.70; 95% CI 0.56–0.87; $P = 0.000$). Interestingly, and in contrast to the findings of INT0139 [16], when PFS was used as an end point, this MA showed no difference between surgical and non-surgical approaches for this end point (HR 0.91; 95% CI 0.78–1.06). A major critique of this MA is the inclusion of retrospective studies (with a range of HRs, from 0.45 to 0.77), in particular that of Koshy et al. [28], which had a disproportionate impact because of the thousands of patients included in its analysis. The Koshy study [28] is concerning due to the nature of its patient source (i.e. the National Cancer Database in the USA—a hospital-based registry), since it cannot control for multiple confounders such as the types of chemotherapy administered, whether there was pre-treatment pathologic proof of clinical N2 disease, the extent of mediastinal nodal involvement (bulky versus non-bulky), the number of mediastinal nodal stations involved, the use of positron emission tomography scans for staging, patient performance status, total radiotherapy dosage employed, overall treatment time, fractionation size, or radiotherapy treatment technique. In addition, the majority of the population in this study consisted of patients who underwent concurrent RT-CHT and had inoperable disease, which is associated with a worse prognosis.

DISCUSSION

A MA is considered the highest level of evidence in 'evidence-based' oncology. It has frequently been used as the tool for either supporting existing standards or establishing new ones. Rigorous criteria are used in all aspects of its design and execution. Its outcome should then lead to unambiguous interpretation. It goes without saying that the 'quality' of its findings depend on the quality of the source data itself.

It is obvious from this review that these six MAs show different levels of compliance with the standard set above. Most concerning are those who include retrospective studies, abstract data from unpublished series, or data from cancer databases that cannot provide important patient and/or tumor and/or treatment characteristics. Importantly, none of these MAs used individual patient data. It is, therefore, not surprising that results may vary between some of the MAs.

One of the major concerns with all the MAs is that they did not provide pooled data on treatment-related toxicities, in particular

Grade 5 toxicities (treatment-related deaths), although Xu Y-P *et al.* [22] listed this outcome for each trial. Previous RCTs had suggested that mortality is usually four to five times higher in the surgical arms [14–16], and may be as high as 26% if a right pneumonectomy follows induction RT-CHT [16]. It can also be higher when a 90-day, not just a 30-day, measure of post-operative mortality is taken into account [29]. This is important since more recent studies show reduced Grade 5 and lower toxicity being associated with induction regimens followed by surgery, which is to be compared with the lower toxicity achieved in modern definitive concurrent RT-CHT regimens.

CONCLUSIONS

Whatever the limitations of these MAs, it is feasible to draw some conclusions about treatment approaches for Stage III lung cancer. Regarding Question A on the preferred form of induction treatment (CHT or RT-CHT), the consensus appears to be that there is no significant difference between CHT alone or RT-CHT when both are followed by surgery. Regarding Question B, the general conclusion would be that there is no additional benefit from the addition of surgery in the management of Stage III NSCLC. Perhaps most striking is the difficulty the authors have of accepting the validity of their own conclusions when it comes to the role for surgery in Stage IIIA NSCLC. Witness the fact that some authors used 'specific interpretation' of their findings to speculate as to potential benefits from surgery, when none appear to exist. One should perhaps then turn to the simple question thoracic oncologists seem to be posing when first seeing a Stage III NSCLC patient: what makes this particular patient suitable for induction CHT or induction RT-CHT, followed by surgery? Which patient characteristics and/or tumor characteristic(s) can one use to claim that in this particular situation, with one or more of these characteristics, a surgical approach would be preferred over a non-surgical one? Which factor(s) (in which combinations) could *predict* that a surgical approach is preferable over a non-surgical one?

Unfortunately, our recent investigation of potential predictors of surgical superiority over non-surgical ones has not disclosed a single predictive pre-treatment patient- and/or tumor-related factor [30]. Furthermore, no single prospective RCT has evaluated this. Hence, in the absence of predictive factors *before* treatment, we are unable to identify patients who could preferentially benefit from surgery. Until the time we can identify, test and prove one or more possible predictive factors, surgery should not be used as a standard treatment approach outside a well-planned clinical trial.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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