CLINICAL INVESTIGATION

Looking backwards to move forward: a review of randomized lung cancer treatment trials to inform future research

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Lung cancer is the commonest cancer worldwide, with more than 1.6 million new cases annually, and the incidence continues to increase. However, progress in improving survival rates has been slow. To investigate whether the number and type of clinical trials might have had a role in this slow progress, a review of all randomized treatment trials was undertaken. A total of 1748 trials that quoted the sample size in the title or abstract was identified in the Cochrane Library Central Register. In summary, the review indicated that the number of trials published per year is increasing (although the median size of trials has remained at approximately 100 patients), the number of randomized Phase II trials has increased, and the majority of trials investigate non-small-cell lung cancer and chemotherapy. Global collaboration is required to run larger trials addressing some of the key unanswered questions

Keywords: chemotherapy • global collaboration • lung cancer • Phase II • randomized trials • sample size

Background

Progress in clinical medicine largely depends on the results of randomized clinical trials (RCT), but the trials themselves need to address key unanswered questions in a logical fashion and be large enough to produce reliable answers. If this does not happen, there is a risk that inconclusive or contradictory results may point clinical practice and subsequent research in the wrong direction. This longitudinal review of all published randomized trials in lung cancer explores changes in the patterns of the trials undertaken, and argues that to improve the rate of progress in treatment, a global strategy is necessary in order to conduct large relevant collaborative trials (a preliminary version of this review was presented at the 15th World Conference on Lung Cancer (WCLC), in Sydney, Australia, in October 2013 [1]).

Lung cancer incidence

Lung cancer is the most common cancer worldwide, with, in 2008, an estimated 1,610,000 new cases diagnosed (12.7% of all cancers) [2], 1,377,000 deaths [2] and 24,483,000 healthy life years lost [3]. Despite the fact that lung cancer is perhaps the only cancer where the cause of the vast majority of cases is known, over the next decades the number of new cases is still predicted to increase across the globe, not only in developing countries but also, despite the decline in smoking, in developed countries; for example doubling in the USA (from 186,605 in 2000 to 407,710 in 2050 [4]) and nearly trebling in the Asian–Pacific Rim region (from 484,000 in 2000 to 1,392,700 in 2050 [5]).

Improvements in treatment

Unfortunately, the continued increase in new cases of lung cancer has not been matched by an increase in survival rates. In the USA, the National Cancer Institute Cancer Trends Progress Report 2011–2012 update [6] compared the 5-year survival rate of patients diagnosed in 1975 with those diagnosed in 2003, and showed that, in contrast to the other major cancers (prostate improving from 66 to 99%, breast from 75

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to 90%, and colorectal from 49 to 66%) the 5-year survival rates for patients with lung cancer remain low, and have shown little improvement, (from 12% for those diagnosed in 1975 to 16% for those diagnosed in 2003). Similar absolute improvements over time have also been reported by Cancer Research UK [7] comparing patients diagnosed in 1971 with those diagnosed in 2005. The estimated 5-year survival rates of patients with prostate cancer has improved between these two dates from 31 to 81%, with breast cancer from 52 to 85%, and with colon and rectal cancers from around 24 to approximately 55%. In contrast the 5-year survival for patients with lung cancer only improved from approximately 4 to 8%.

Despite major technical advances in imaging and surgery [8], the disappointingly small improvements in lung cancer survival may be mainly due to the low levels of early detection, failure to discover effective new drugs and the characteristics of this population, but this also raises the questions of whether lung cancer treatment is adequately researched, whether the trials have been too small and too disparate and whether a global research strategy might help.

Lung cancer research

In terms of the number of publications relating to lung cancer, there does not appear to be a lack of research. Figure 1 plots the worldwide incidence in 2008 of the seven most common cancers [2] against the total number of publications identified for each on the Cochrane Library Central Register of Controlled Trials [9] as searched in October 2013. This somewhat crude comparison nevertheless suggests that the correlation for lung cancer research echoes that of other cancers apart from breast cancer – which appears relatively over-researched – and stomach cancer – which appears relatively under-researched – although the latter, given the higher incidence in Asia, may also reflect a bias against papers not written in English.

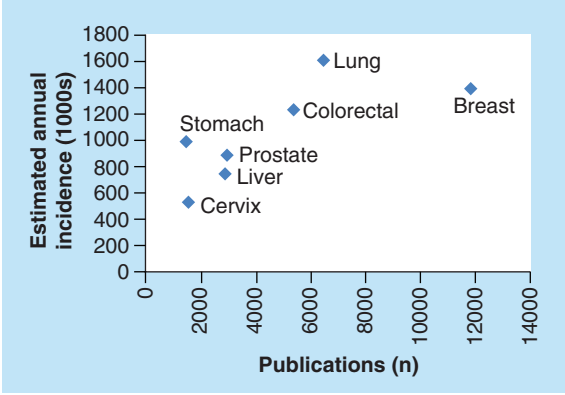

Figure 1. Worldwide incidence of most common cancers plotted against the number of publications.

2003 review

A review undertaken in 2003 to assess the quantity and quality of all published randomized lung cancer treatment trials and presented at the 10th WCLC [10] indicated that only four of nearly 1000 trials accrued more than 1000 patients, and that clinicians (and patients) could only rely on a few meta-analyses to guide treatment decision making. This presentation built on a number of letters [11–13] suggesting that greater global collaboration was needed to design and run large trials to improve the survival rates and quality of life of lung cancer patients. This was subsequently supported by an open letter signed by many of the leaders in the field [14] suggesting that the International Association for the Study of Lung Cancer might take the lead in encouraging such collaboration.

2013 review methods

Ten years on, an update and extension of the 2003 review of trials has been undertaken, to see what changes have occurred, what patterns have emerged, and whether this information might help the design of future research. In order to identify such trials, the Cochrane Library was chosen [9], as, in contrast to e-libraries such as PubMed, this includes published abstracts from major cancer meetings including the American Society of Clinical Oncology, the European Cancer Organisation and the European Society for Medical Oncology, as Song *et al.* [15] estimate that up to 50% of all trials are not fully published. In addition, and in contrast to the 2003 review [10], which only collected data on the number of patients randomized, the current review also collected information regarding the lung cancer subgroup studied, the treatment modality investigated, the trial design, the outcome and the country of affiliation of the first author

Publications identified

A search of the Central Register of Controlled Trials on the Cochrane Library in August 2013, using the terms '(lung OR bronchus) AND (cancer OR carcinoma)' in all text, so as to be as inclusive as possible, produced a total of 7324 reports.

First trials

The earliest report of a study on the Cochrane Library that included lung cancer patients appears to have been run by Krantz *et al.* (who published the results of a clinical study of nitrogen mustard and DON [6-diazo-5-oxo-L-norleucine] in patients with a range of cancers) in 1959 [16], and the first publication of a study specifically for lung cancer may be that reported by Lees *et al.* (comparing the palliative effect of tret-

amine and nitrogen mustard) in 1961 [17]. The first identified publication of a lung cancer trial that specifically mentions randomization was by Morrison *et al.* in 1963, randomizing 58 patients to surgery or radiotherapy [18].

Inclusions & exclusions

Randomization is a key component of evidence-based medicine that, given a reasonable sample size, ensures that the groups being compared are balanced, not only in terms of all the known characteristics (e.g., age, sex, height, weight and so forth) but, most importantly, in every other possible known and unknown characteristic. This means that any differences observed must be due to the treatments being compared. Therefore in order to assess the quality and quantity of lung cancer trials it was decided to list and analyze all the RCT irrespective of how they were designated (Phase III, Phase II, superiority, equivalence and so forth).

Decisions were also taken to restrict the review to information available in the title and abstract, rather than try to access every full publication, and to exclude trials of screening and diagnosis (as the focus of this review was on the treatment and supportive care of patients with lung cancer), those trials that included a mix of cancer types (but where the lung cancer patients had not been analyzed separately), and trials where the patient was not the randomized factor (e.g., when, to compare anti-emetics, patients receive different anti-emetics with different cycles of chemotherapy).

In addition, as it was found that the Cochrane Library was only up to date to 2011, it was decided to exclude 164 reports from 2012 and 2013.

Meeting abstracts

Unfortunately, the inclusion of meeting abstracts on the Cochrane Library was found to be very inconsistent (e.g., the 2007 American Society of Clinical Oncology abstracts were missing, as were several years of European Cancer Organisation/European Society for Medical Oncology meeting abstracts, and only 1 year [2000] of abstracts from the WCLC were included), and therefore all 1915 meeting abstracts identified in this review were excluded from the analysis.

Full publications

Of the 5245 full publications up to and including the year 2011, a total of 1868 different RCT of lung cancer were identified. The reason for the exclusion of the other reports is shown in Table 1. These include 1765 reports that did not relate to a trial of lung cancer (an unfortunate consequence of a wide search criteria), and 175 that were duplicate entries on the database. In addition, as the size of the trial was of primary interest, a further 120 trials were also excluded from the analysis, either because the sample size was not quoted in the title or abstract (50 trials), or because, although the title indicated it was a randomized trial, the abstract could not be accessed (70 trials). This therefore left a total of 1748 trials, and it is worth noting that these 1748 trials appeared in 315 different journals.

Number of trials & number of patients

Figure 2 plots the number of lung cancer treatment trials published per year from 1963 to 2011, and shows a consistent increase over time, with currently approximately 100 trials being published per year. Figure 3 shows the number of patients included in each published trial, and indicates an increase in larger trials in the last decade, although the largest reported trial still included fewer than 2000 patients. Table 2 summarises these data, with only 21 (1%) trials including

Table 1. Lung cancer publications identified.

Publication type	Lung cancer research papers	Proportion of total (%)
Randomized trials identified	1868	35.6
Non-randomized studies	536	10.2
Spin-off publications (prognostic factors, quality of life, and so forth)	295	5.6
Reviews, letters, editorials, comments, and so forth	269	5.1
Abstract not found	145	2.8
Multiple reports of same trial	159	3.0
Not lung cancer or lung cancer treatment	1765	33.7
Duplicate entries	175	3.3
Other	33	0.6
Total	5245	–

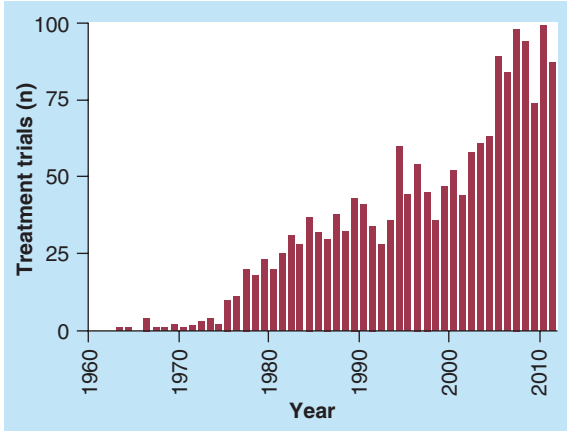

Figure 2. Number of lung cancer treatment trials published per year.

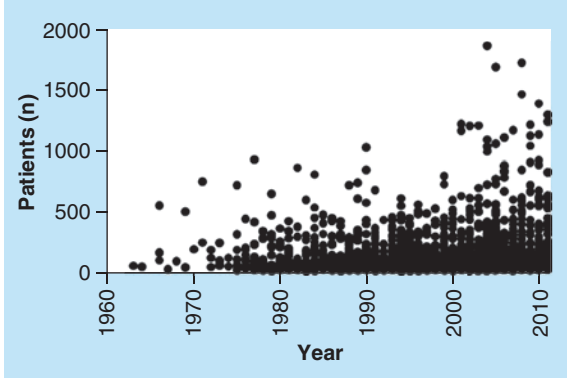

Figure 3. Number of patients included in lung cancer trials by year.

more than 1000 patients. However, six of these were three- or four-arm trials, which reduces the power to detect differences between individual experimental arms and the control arm, and therefore only 15 trials were found that accrued >500 patients per arm (Table 3 lists, for information, the 15 two-arm trials [19–33] and Table 4 shows the three- or four-arm trials [34–39]). Although there was an increasing number of larger trials, nearly half (853; 48.8%) included fewer than 100 patients, and the overall median size has hardly changed over the last three decades (Figure 4) (data plotted from 1975 when at least ten trials per year were published).

Table 2. Number of patients included in lung cancer trials.

Trial size (n)	Trials (n)	Proportion of total (%)
1000+	21	1
500–999	79	5
250–499	225	13
100–249	570	33
50–99	529	30
<50	324	19
Total	1748	–

Phase of trials

Although the vast majority of trials were simply called 'randomized' in the title and/or abstract, a total of 276 were reported as Phase II, compared with 247 that were reported as Phase III. Nevertheless, plots of the Phase II and III trials (Figures 5 & 6, with median trial size data, Figures 7 & 8, shown from 2001 when >10 trials designated as randomized Phase III were published per year) suggest that, over the last 10 years, the number of Phase II trials has increased significantly although the median number of patients included has remained unchanged, whereas the number of Phase III trials has increased at a much slower rate, but the number of patients in each trial has roughly doubled, from approximately 200 to approximately 400 patients.

Histology

Of the 1748 trials identified, 1034 (59%) specifically investigated the treatment of non-small-cell lung cancer (NSCLC) patients, and 366 (21%) small-cell lung cancer (SCLC) patients. The remaining 20% simply indicated in the title and/or abstract that the trial involved 'lung' cancer patients. Using data from 1975 (only one trial previous to 1975 reported looking at a subgroup of lung cancer patients – the MRC trial of radiotherapy vs surgery in SCLC, reported in 1966 [40]), Figures 9 & 10 show that the annual number of SCLC trials published has been relatively consistent over time, whereas the interest in NSCLC has increased dramatically over the last 10 years.

Modality investigated

Table 5 lists the treatment modality investigated and highlights the overwhelming interest in chemotherapy, and the lack of surgical trials, although the 269 supportive care trials can be subdivided (based on the primary treatment) and 80 of these were related to the supportive care of patients undergoing surgery (for example trials to reduce air leaks, or improving post-operative care). Of the remaining supportive care trials, 111 related to chemotherapy, and 26 to radiotherapy.

Trial design

The majority of randomized lung cancer trials identified here (1528; 87%) have simply compared two arms, with only 157 (9%) having three arms, 32 (2%) four arms, five trials having five arms and a single seven armed trial [41]. Only 17 trials incorpo-

Table 3. Published two-arm lung cancer trials with >1000 patients.

Summary	Points	Outcome	Ref.
IALT – adjuvant cisplatin-based CT for completely resected NSCLC	1867	Improved OS with CT (HR: 0.86; 4% benefit at 5 years)	[19]
Non-inferiority trial of cisp/gem vs cisp/pem for advanced NSCLC	1725	Pem better for adeno/large cell, gem better for squamous	[20]
Second- or third-line gefitinib vs placebo for advanced/metastatic NSCLC	1692	No OS benefit with gefitinib	[21]
INTEREST – second-line gefitinib vs doc in advanced NSCLC	1466	No survival difference observed	[22]
ZODIAC – second-line doc/vandetanib vs doc/placebo for advanced NSCLC	1391	Improved PFS with vandetanib (HR: 0.79; $p < 0.0001$)	[23]
Carbo/pac with vadimezan or placebo for advanced NSCLC	1299	No survival difference observed	[24]
Second-line vandetinib vs erlotinib for advanced NSCLC	1240	No difference in PFS observed	[25]
Carbo/pac vs gefitinib for advanced non-smokers with adeno	1217	Improved PFS with gefitinib (HR: 0.74; $p < 0.001$)	[26]
CT (with MVP) for completely resected stage I–IIIa NSCLC	1209	No survival difference observed	[27]
Cisp/gem with erlotinib vs placebo for advanced NSCLC	1172	No survival difference observed	[28]
Isotretinoin for chemo-prevention of second primaries in stage I NSCLC	1166	No differences observed	[29]
FLEX – cisp/vinorelbine ± cetuximab for EGFR$^+$ advanced NSCLC	1125	Improved OS with cetuximab (HR: 0.87; $p = 0.044$)	[30]
ACOSOG Z0030 – node sampling vs mediastinal dissection	1111	Lymphadenectomy adds little morbidity to resection	[31]
TRIBUTE – carbo/pac with erlotinib vs placebo for advanced NSCLC	1059	No survival difference observed	[32]
Adjuvant bestatin for stage I/II NSCLC	1030	Trend in favour of bestatin in terms of DFS	[33]

adeno; Adenocarcinoma; carbo: Carboplatin; cisp: Cisplatinum; CT: Chemotheraphy; DFS: Disease-free survival; doc: Docetaxel; gem: Gemcitabine; HR: Hazard ratio; MVP: Mitomycin, vinblastine and cisplatin; NSCLC: Non-small-cell lung cancer; OS: Overall survival; pac: Paclitaxel; PFS: Progression-free survival; pem: Pemetrexed.

Table 4. Published three- or four-arm lung cancer trials with >1000 patients.

Summary	Points	Outcome	Ref.
TAX 326 – doc/cisp vs doc/carbo vs vinorelbine/cisp for advanced NSCLC	1218	Improved OS for doc/cisp vs vinorelbine/cisp (HR: 0.85; $p = 0.044$)	[34]
Cisp/pac vs cisp/gem vs cisp/doc vs carbo/pac for advanced NSCLC	1207	No survival differences observed	[35]
Gem/carbo vs gem/pac vs carbo/pac for advanced NSCLC	1135	No survival differences observed	[36]
INTACT-1 – gem/cisp with gefitinib 500 mg/d, gefitinib 250 mg/d or placebo for advanced NSCLC	1093	No survival differences observed	[37]
AVAIL – Cisp/gem with bevacizumab 7.5 g, bevacizumab 15 g or placebo for non-squamous NSCLC	1043	PFS increased for both doses of bevacizumab (HR: 0.82 and 0.75, respectively)	[38]
INTACT-2 – pac/carbo with gefitinib 500 mg/d, gefitinib 250 mg/d or placebo for advanced NSCLC	1037	No survival differences observed	[39]

carbo: Carboplatin; cisp: Cisplatinum; doc: Docetaxel; gem: Gemcitabine; HR: Hazard ratio; NSCLC: Non-small-cell lung cancer; OS: Overall survival; pac: Paclitaxel; PFS: Progression-free survival.

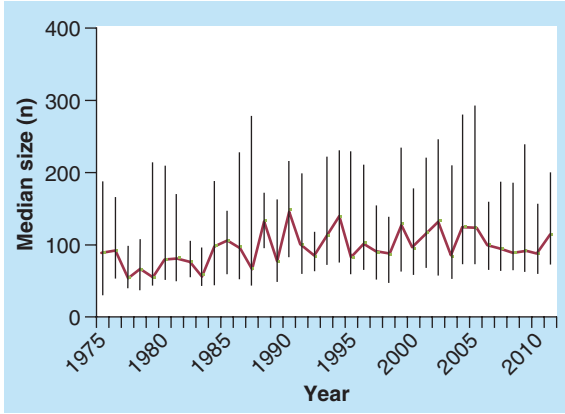

Figure 4. Median size (and interquartile range) of randomized lung cancer trials per year.

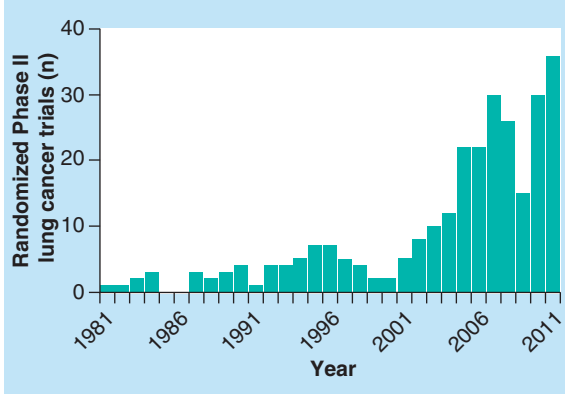

Figure 5. Number of randomized Phase II lung cancer trials per year.

rated two randomizations, and only eight were 2 × 2 designs.

Country of affiliation

Table 6 shows the country of the affiliation of the first author, with those from the USA having published the most trials, but with authors from China, who have only been publishing extensively in the last 10 years, already the second largest contributor, an observation also commented on by Subramanian *et al.* [42].

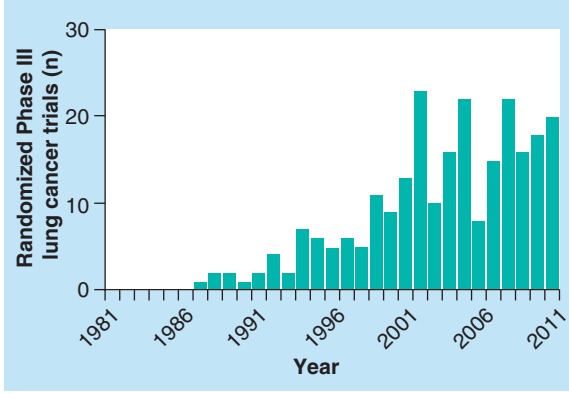

Figure 6. Number of randomized Phase III lung cancer trials per year.

Discussion

The aim of this project was to review all the published randomized trials of lung cancer treatment, to try and identify changing patterns over time and under-researched areas. Such information could be very useful in informing future research. Inevitably there were limitations:

- The Cochrane Library was the only database searched, and unfortunately proved to have serious deficiencies (approximately 2 years out of date, with an inconsistent coverage of meeting abstracts and numerous duplicate entries);
- The review was limited to the title and abstract of each publication, for logistical reasons;
- Multiple reporting of trials (with different first authors and including different numbers of patients) complicated the search, and highlights the need for the trial name or reference to be quoted routinely;
- Many journals have not put publications prior to the year 2000 online, and this, together with the general lack of open access to papers, and the fact that many institutions have disposed of their paper libraries, makes accessing papers difficult (especially for independent researchers);
- There was some subjective interpretation and decisions about categorizsation.

Thus the current experience highlights the major difficulties relating to the compilation of a comprehensive research database, which include:

- The incompleteness of e-libraries (e.g., as of November 2013, only 5652 journals were indexed for Medline [43], despite Medical Journals Links [44] compiling information on more than 11,000 peer-reviewed medical journals, and new journals are being set up daily [45]);
- The fact that few journals are open access; and
- The lack of a good e-library of meeting abstracts.

In addition a comprehensive database should also include:

- Ongoing trials (but currently not all trials are registered);

- Unpublished trials (although an unknown but probably large proportion of trials are unpublished or even unpresented at meetings [46–48]); and
- Be kept up to date (but the number of new trial publications is over-whelming [49]).

However, despite such limitations, the strength of this review is the fact that it is a longitudinal overview covering all lung cancer types and treatment modalities. This therefore substantially extends the results reported by Subramanian *et al.* [42] who only compared trials of medical treatment for NSCLC that were ongoing in 2012 (using the Clinical Trials Register [50]) with a similar survey of trials active in 2009.

The key findings from the current review are that:

- The median size of the randomized trials identified has hardly changed over time (due to a increasing proportion of small trials and still too few large trials);
- There has been a marked increase in the number of randomized Phase II trials;
- The majority of trials focus on chemotherapy; and
- Most are two-arm trials.

Trial Size

The sample size calculations for trials should be based on realistic estimates of the performance of the treatments being investigated. It is sobering to look at the outcomes of some of the key meta-analyses in lung cancer (Tables 7 & 8 [51–74]), which show that, even when adding a treatment modality (e.g., chemotherapy or radiotherapy) the hazard ratio for the overall survival is usually approximately 0.85, which is equivalent to approximately a 5% survival benefit at 3 or 5 years. The number of events (deaths) required to reliably detect a hazard ratio of 0.85 ranges from approximately 1200 (with 80% power) to almost 1600 (with 90% power). Thus, small or even medium-sized trials that are designed to detect large benefits as a result of changing the dose or schedule of a drug, or substituting one drug for another, are very unlikely to provide an accurate assessment of the experimental treatment. Such small trials are therefore likely to produce false-positive or false-negative results, which may result in patients being given suboptimal treatment, may point future research in entirely the wrong direction and usually require further trials to discover the true result. Equally, 'false-equivalent' results, where small or medium-sized survival differences, or differing toxicity profiles, are not reliably detected, may lead to the assumption that the new treatment is as good as the current standard treatment, leading to a proliferation of treatments being adopted as equally effective alternatives and confusion over the control arm to use in subsequent trials.

The reason for the large proportion of small trials noted in the current review may be multifactorial, and

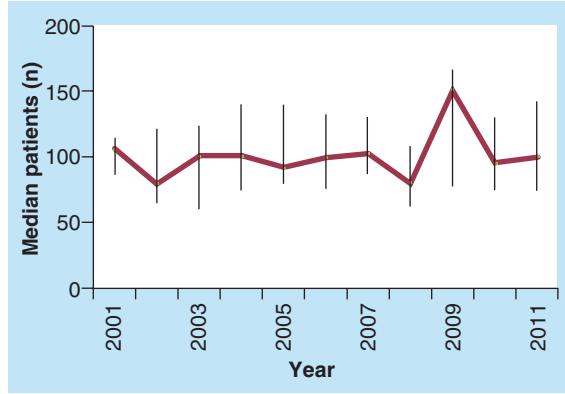

Figure 7. Median number (and inter-quartile range) of patients included in randomized Phase II lung cancer trials per year.

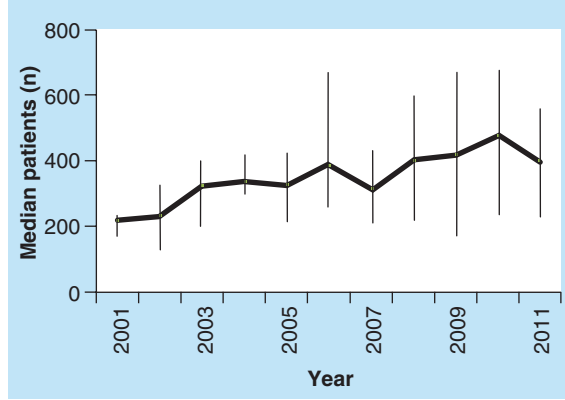

Figure 8. Median number (and inter-quartile range) of patients included in randomized Phase III lung cancer trials per year.

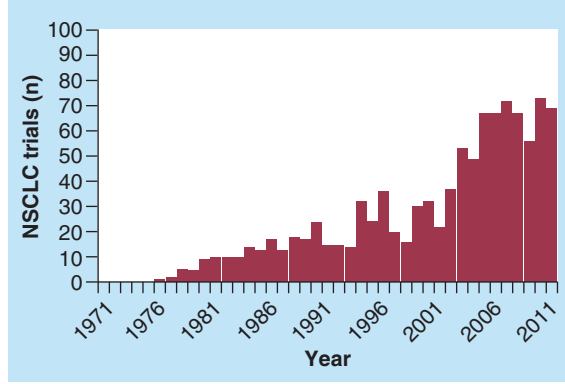

Figure 9. Number of non-small-cell lung cancer trials per year.
NSCLC: Non-small-cell lung cancer.

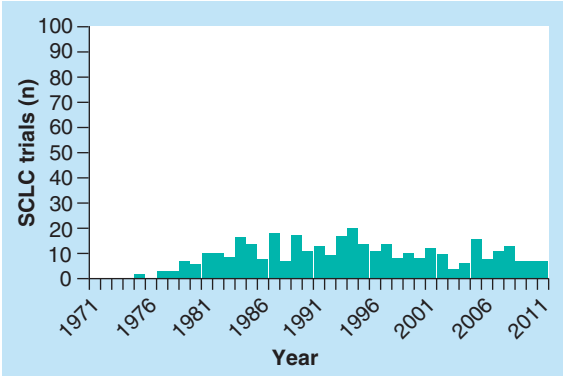

Figure 10. Number of small-cell lung cancer trials per year.
SCLC: Small-cell lung cancer.

certainly setting up and running large clinical trials still represents a major challenge, as they are expensive, time-consuming and involve coping with the regulatory complexity and inconsistencies across countries. In addition, many academic institutions and individuals are expected to fulfill their research requirements and publish a number of articles each year, which may in fact be a disincentive to join large multicenter trials because listing all participants as authors is rarely possible. Therefore, ways need to be found to run local studies and national trials alongside international global trials and either to make better use of the limited supply of trial patients or find ways to significantly increase those offered participation. A total of 293,915 patients were randomized into the 1748 trials identified in this review, including 16,492 in the 87 trials published in 2011 (which only represents ~1% of all the lung cancer patients diagnosed worldwide [2]). One radical proposal has been for a simple pragmatic web-based 1-week global trial [10] that, if it successful in accruing 10% of all the patients diagnosed in a week, would result in a trial of 3000 patients and thus be by far the largest lung cancer trial ever.

An alternative to conducting one large trial is to run a meta-analysis (MA) to clarify the benefits or detriments of new treatments by combining all the trials asking a similar question. There has been a rapid increase in the number of meta-analyses being published (Figure 11), with 40% of all publications with 'lung cancer' and 'meta-analysis' in their title as searched on Pubmed in November 2013, being published in the last 2 years. However, the proliferation of MA publications is self-limiting due both to running out of questions to address, and of not having the appropriate trials to answer important generic questions. Thus when Macbeth *et al.* [13] identified relevant trials for a MA of palliative radiotherapy, they "encountered heterogeneity both of patient selection and of treatment regimens that ruled out meta-analyses and left questions unanswered." Therefore, when it is only possible to run single-centrer trials, it is vital that they are designed to fit in with parallel research so that prospective or retrospective meta-analyses can be performed, as inefficient and ineffective clinical research is wasteful and perhaps unethical.

Table 5. Modality being assessed.

Trialed modality	Trials	Proportion of total (%)
Chemotherapy	832	48
Supportive care	269	15
Radiotherapy	136	8
Immunotherapy	125	7
New Agents	95	5
Traditional Chinese medicine	49	3
Surgery	23	1
Other	142	8
Modality versus modailty	77	4
Total	1748	–

Phase II trials

Phase II studies are an important step in the evolution of a new treatment. Traditionally they are small studies set up to investigate the efficacy of the treatment by examining the response rate in a relatively small number of patients (often <100). However, just because they are small, does not mean there are not major issues regarding aspects such as ethics [75], the dangers of over-analysing and over-hyping the results [76], and the lack of attention to trial design detail [77]. As highlighted in the current review, in the last few years randomized Phase II studies have gained popularity as the control arm will provide a comparator for the response rate in the new treatment, and often, given 'encouraging' results in the Phase II study, the trial can be rolled over into a Phase III. However, it is important to remember that Phase II studies are not designed to be conclusive, rather they are hypothesis generating. So trials, such as that reported by Jahnke *et al.* [78] that randomized 61 patients to four different chemotherapy regimens, and concluded that "the efficacy and toxicity profile of platinum-free combinations is comparable to that of platinum-based doublets" raise many of the concerns mentioned above. The reasons behind the recent proliferation of Phase II trials (see Figure 5) is unclear, and whilst it may be due to a greater use of randomized design, academic pressures may conflict with the need to address wider research questions, and it may therefore be seen as an opportune

way to conduct an institutionally based trial and gain publication.

Phase III trials

Whilst it is encouraging that over the last decade the median sample size of randomized Phase III trials has doubled (from ~200 to 400 patients), this still falls far short of that needed to reliably detect small or even medium sized treatment differences. Trial size needs to reflect both the expected treatment difference and outcomes that are clinically (rather than statistically) significant, and thus it makes little sense to run a trial of many thousands of patients to detect a tiny clinically unimportant difference. Nevertheless, the majority of Phase III trials are still underpowered, usually as a result of over-estimating the expected differences. Of course, examples can always be quoted of small trials that have shown significant differences, but the true result is usually tempered by confirmatory trials and meta-analyses. The number of Phase III trials also continues to rise, but it will be interesting to see if this trend continues over the next decades, as more and more targeted drugs are developed for specific populations, and the emphasis moves towards individualized treatment rather than the utilitarian concept of group benefit.

Chemotherapy

The opportunity for trials of chemotherapy may reflect a research agenda that is largely driven by pharmaceutical companies, whereas this is lacking in trials of radiotherapy, surgery and palliative care. These other treatment domains may benefit from more input from patients to define the key questions, the key outcomes, and to inform sample size by defining worth-whileness. For example, the James Lind Alliance [79] brings together patients, carers, and clinicians to identify and prioritise the important areas where research is needed, and input from such organisations could inform future research in lung cancer treatment. The James Lind Alliance also works closely with an online resource called the UK Database of Uncertainties about the Effects of Treatments (UK DUETs), which has been established to publish uncertainties about the effects of treatment. UK DUETS, as of December 2013, contained 28 research recommendations relating to lung cancer [80], including: chemotherapy versus best

Table 6. First author's country of affiliation.

Countries	Trials
USA	409
China	274
Japan	188
Italy	132
UK	124
Germany	79
France	75
Canada	49
Netherlands	46
Greece	45
Total	1748

Table 7. Lung cancer meta-analyses showing significant survival benefits (1994–2009).

Population	Control arm	Test arm	Trials	N	HR/RR/OR	P value	OS (%)	Ref
SCLC limited	CT	+ RT	13	2140	RR 0.86	0.001	5.4 at 3 years	[51]
NSCLC locally advanced, unresectable	RT	+ CT	14	2589	RR 0.88	–	–	[52]
NSCLC resected	CT	+ Immuno	11	1520	OR 0.70	0.001	7.5 at 5 years	[53]
NSCLC advanced	Platinum + new agent	New agent	8	2374	HR 0.87	<0.001	–	[54]
NSCLC advanced	Platinum CT	+ Gem	13	4556	HR 0.90	–	3.9 at 1 year	[55]
NSCLC	Surgery	+ UFT	6	2003	HR 0.74	0.001	4.3 at 5 years	[56]
NSCLC advanced	Non-platinum CT	Platinum CT	11	4602	OR 0.88	0.044	–	[57]
NSCLC locally advanced	RT	Concurrent CTRT	9	1764	HR 0.89	–	4 at 2 years	[58]
NSCLC advanced	Supportive care	+ CT	16	2714	HR 0.77	<0.0001	9 at 1 year	[59]
NSCLC	Surgery	+ Platinum CT	12	7334		–	–	[60]
NSCLC advanced	Standard duration CT	Extended duration CT	13	3027	HR 0.92	0.03	–	[61]

CT: Chemotherapy; Gem: Gemcitabine; HR: Hazard ratio; Immuno: Immunochemotherapy; NSCLC: Non-small-cell lung cancer; OR: Odds ratio; OS: Overall survival; RR: Relative risk; RT: Radiotherapy; SCLC: Small-cell lung cancer; UFT: Tegafur + uracil.

Table 8. Lung cancer meta-analyses showing significant survival benefits (2010–2013).

Population	Control arm	Test arm	Trials	N	HR/RR/OR	P value	OS (%)	Ref.
NSCLC	Surgery	+ neoadjuvant CT	13	3224	HR 0.84	0.0001	–	[62]
NSCLC locally advanced	Sequential CTRT	Concurrent CTRT	6	1205	HR 0.84	0.004	5.7 at 3 years	[63]
SCLC extensive	Platinum etop	Platinum irinotecan	6	1476	HR 0.81	0.044	–	[64]
NSCLC advanced metastatic	Platinum CT	+ cetuximab	4	2018	HR 0.87	0.005	–	[65]
NSCLC stage III-IV	Standard rx	+ immuno	12	3134	–	0.0007	–	[66]
NSCLC advanced	Platinum regimens	Platinum + pem	4	2518	HR 0.91	0.04	–	[67]
NSCLC advanced elderly	One drug	two drugs	12	2306	OR 1.80	0.0001	–	[68]
NSCLC	Standard fraction RT	Hyper or accelerated RT	10	2000	HR 0.88	0.009	2.5 at 5 years	[69]
SCLC	Standard rx	+ PCI	16	1983	OR 0.73	0.01	–	[70]
NSCLC advanced	No main CT	+ Single agent main	11	3686	HR 0.84	–	–	[71]
NSCLC advanced	Platinum CT	+ Bevacizumab	4	2194	HR 0.90	0.03	4 at 1 year	[72]
NSCLC advanced	CT	+ Chinese herbal medicine	24	2109	RR 1.36	0.0003	–	[73]
NSCLC stage I	Open lobectomy	VATS lobectomy	20	3457	OR 1.82	–	–	[74]

CT: Chemotherapy; etop: Etoposide; HR: Hazard ratio; Immuno: Immunochemotherapy; Main : Maintenance, NSCLC: Non-small-cell lung cancer; OR: Odds ratio; OS: Overall survival; PCI: Prophylactic cranial irradiation; Pem: Pemetrexed; RR: Relative risk; RT: Radiotherapy; rx: Treatment; SCLC: Small-cell lung cancer; VATS: Video-assisted thoracoscopic surgery.

supportive care for extensive SCLC, exercise training in the first 12 months postresection, effectiveness of surgery for N2 disease, routine versus symptom-led follow-up, and so forth.

Trial design

Many of the elements of trial design (such as sample size, randomization, choice of treatment arms, exclusions and so forth) that were developed in the 1950s (and summarized by, for example, Fox [81]) hold true today, but recently much effort has gone into improving the methodology of trial design; for example multiarm trials are more efficient as they use the same control group to compare with different experimental arms, multistage multiarm trials use interim analyses of surrogate end points to drop unsuccessful arms [82] and even add new ones [83] and Bayesian adaptive trials change the randomization balance as the trial progresses so that more patients receive what is predicted to be the best treatment [84]. The overwhelming use of two-arm trials noted in the current review suggests that little of this new methodology seems to have filtered through to the lung cancer community, and greater effort needs to be given to the use of more innovative designs.

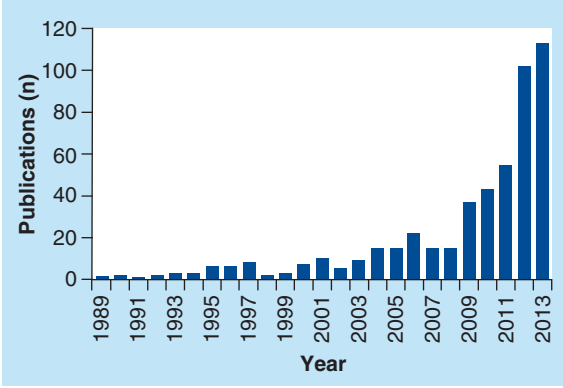

Figure 11. Number of lung cancer meta-analyses publications per year.

Conclusion

The message emerging from the previous (2003) review of randomized lung cancer trials was that greater collaboration was required to develop a global strategy and conduct larger trials and hopefully as a result improve the survival rate of lung cancer patients. The current (2013) review suggests that over the past decade little has changed for the better, and that while there has been a handful of larger trials published, this has been outweighed by the increase in small randomized Phase II trials. This practice of running multiple small trials to test slightly different drug regimens, or different doses, or different schedules makes little sense, know-

ing as we do that even the addition of a modality (i.e., the addition of chemotherapy to surgery) only adds minimally to survival. What is needed is the ability to look at the bigger picture, to highlight the areas that have been over-researched and those that have been under-researched, to indicate where there is agreement and where there is conflict, to spot the important gaps, and to encourage and support research in the areas where the greatest progress aRaTpA in benefitting the greatest number of patients might be made. This need to improve the quantity and quality of trials in lung cancer has been highlighted for more than 20 years [85–87] with, for example Brundage and Mackillop stating in 1996 that "we need strategies that identify the most important controversies and improve consensus amongst clinicians". The results of the current review suggest that such global collaboration is still required to run large trials that will produce reliable results and influence practice worldwide, a view echoed by a recent editorial in the Lancet [88].

Future perspective

Over the next 5–10 years the concept of personalized medicine will continue to grow, and whilst this may shift research away from randomized trials, and towards predictive analyses of large databases [89], the need for global collaboration and strategy will be just as important, as trying to reliably identify subgroups of patients that benefit (or do not benefit) from specific treatments using small databases is fraught with problems. Thus, without better global cooperation (which ought to be feasible given the existence of the International Association for the Study of Lung Cancer and the levels of net-working and goodwill seen at the WCLC conferences) improving the outcomes for lung cancer patients will continue to be disappointing.

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Executive summary

Background

- Lung cancer is the most common cancer, and the incidence continues to increase.
- Progress in improving the survival rates for lung cancer patients is slow.
- A review of all published randomized treatment trials in lung cancer was undertaken.

Results

- A total of 1748 trials was identified.
- The number of trials published per year is increasing, although the size of trials has remained the same, at a median of approximately 100 patients.
- The number of randomized Phase II trials has increased.
- The majority of trials investigate non-small-cell lung cancer and chemotherapy, and are two-arm trials.

Conclusion

- Global collaboration is required to run larger trials addressing some of the key unanswered questions.

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