Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint

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Improvements in outcomes for patients with resectable lung cancers have plateaued. Clinical trials of resectable non-small-cell lung cancers with overall survival as the primary endpoint require a decade or longer to complete, are expensive, and limit innovation. A surrogate for survival, such as pathological response to neoadjuvant chemotherapy, has the potential to improve the efficiency of trials and expedite advances. 10% or less residual viable tumour after neoadjuvant chemotherapy, termed here major pathological response, meets criteria for a surrogate; major pathological response strongly associates with improved survival, is reflective of treatment effect, and captures the magnitude of the treatment benefit on survival. We support the incorporation of major pathological response as a surrogate endpoint for survival in future neoadjuvant trials of resectable lung cancers. Additional prospective studies are needed to confirm the validity and reproducibility of major pathological response within individual histological and molecular subgroups and with new drugs.

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Introduction

Non-small-cell lung cancers (NSCLCs) are the greatest cause of cancer death. Despite recent advances in the treatment of advanced NSCLCs, little improvement in the treatment of resectable NSCLCs has been made in nearly a decade.[1]

Two reasons for the slow progress in resectable (stage I–IIIA) NSCLCs are the operational challenges of multimodality clinical trials and the long wait for results (table 1). For example, the most recent phase 3 trial of adjuvant chemotherapy in NSCLCs, ANITA,[3] was published 12 years after patient enrolment began. 3-year disease-free survival (DFS) after definitive therapy closely associates with 5-year overall survival,[9] but also takes many years to ascertain. In ANITA,[3] the time from study launch until assessment of 3-year DFS for all patients would have taken 9 years. Similarly, trials[10,11] of adjuvant therapy in colon cancer that used 3-year DFS as a primary outcome took 8 years until publication.

Although overall survival is the gold-standard outcome measure for phase 3 trials, the protracted length of these clinical trials in resectable NSCLCs makes this research daunting and expensive—in both human and financial terms. Investigation of promising drugs is often not pursued because the process is too long, too laborious, and might not yield results before expiration of the patent life of the drug; these barriers slow progress and potentially stifle innovation.

One strategy to expedite clinical trials is the use of surrogate measurements. In a seminal paper, Prentice[12] proposed a conservative set of validation rules for surrogates, which stated that the treatment intervention must be associated with the surrogate, the surrogate must be associated with the true outcome, and the surrogate must be able to explain the entirety of the effect on the true outcome. The last requirement is the most difficult to meet because it requires very large sample sizes and meta-analytic methods. For example, Sargent and colleagues[13] pooled 20 898 patients across 18 randomised studies and showed that 3-year DFS after adjuvant therapy for colon cancer was a valid surrogate, in the context of Prentice's criteria, for overall survival.

In its accelerated approval process, the US Food and Drug Administration (FDA) has adopted a less stringent definition of surrogacy, which requires that a surrogate endpoint be "reasonably likely to predict clinical benefit."[14,15] Other groups[16,17] have urged caution in hastily equating a correlate with a surrogate. This caution emphasises that although a correlate might associate with the true outcome, a surrogate should also manifest the treatment effect and equal the magnitude of the treatment effect on the true outcome.

With these considerations in mind, we propose that pathological response after neoadjuvant (preoperative, induction) chemotherapy for resectable NSCLCs can serve as a surrogate for overall survival. This proposal is made on the basis of three findings: (1) the extent of pathological response strongly correlates with improved overall survival; (2) the pathological response is reflective of the effect of neoadjuvant therapy; and (3) the degree of pathological response associates with the degree of benefit in overall survival. Although such descriptions fall short of the Prentice criteria for establishment of surrogacy, they do importantly differentiate pathological response from a simple correlate. Consistent with the definition of surrogacy proposed by the FDA, we believe these findings support the use of pathological response as a surrogate endpoint for overall survival in patients with resectable NSCLCs given neoadjuvant chemotherapy.

The rationale for assessment of pathological response after neoadjuvant therapy is, foremost, dependent on a similar survival benefit of neoadjuvant versus adjuvant therapy in patients with resectable NSCLCs. Indeed, in

	Treatment	Time from enrolment to publication of data
IALT[1]	Adjuvant therapy	9 years
JRB.10[2]	Adjuvant therapy	11 years
ANITA[3]	Adjuvant therapy	12 years
CALGB 9633[4]	Adjuvant therapy	12 years
LU22[5]	Neoadjuvant therapy	10 years (closed early)
SWOG9900[6]	Neoadjuvant therapy	11 years (closed early)
NATCH[7]	Neoadjuvant versus adjuvant therapy	10 years
GLCCG[8]	Neoadjuvant chemotherapy versus chemoradiation	13 years

Table 1: **Length of time from start of enrolment to publication of studies of perioperative therapy in non-small-cell lung cancers with overall survival as primary endpoint**

meta-analyses, adjuvant[18–20] or neoadjuvant[5,21–23] cytotoxic chemotherapy equally improve survival in patients with stage IB–IIIA NSCLCs. Uniquely, a neoadjuvant approach allows assessment of the in-vivo response to treatment at resection. Of note, several large studies[11,24–26] have failed to show a benefit of neoadjuvant chemoradiotherapy in patients with stage III disease. We do not advocate the use of neoadjuvant chemoradiotherapy outside of superior sulcus tumours or clinical trials; thus our discussion here focuses mainly on neoadjuvant chemotherapy.

We believe that the adoption of a consensus definition of pathological response as a surrogate for overall survival can expedite the development of improved treatments for all patients with NSCLCs. Our goals here are to spur discussion, foster cooperation, and accelerate the research necessary to establish pathological response after neoadjuvant chemotherapy as an accepted and used surrogate for survival in patients with resectable NSCLCs.

Complete pathological response in NSCLCs

Investigators of many trials[5–7,23,24,27–36] of neoadjuvant chemotherapy for resectable NSCLCs have reported the frequency of complete pathological response, however the methods used have varied. Some investigators[5,6,27,33–35] have reported this outcome as a proportion of all patients treated, whereas others[7,23,24] reported only patients whose tumours were surgically explored or completely resected. Because calculations that include all patients treated gives the most conservative sense of response, we report, whenever possible, these data as a proportion of the total number of patients treated. Consideration of the appropriate denominator is important for statistical planning of prospective trials.

Of forerunning trials of neoadjuvant chemotherapy, Pisters and colleagues[27] have reported the proportion of patients who achieved complete pathological response as 12% (nine of 73), Roth and colleagues[28] reported as 0% (none of 28), and Rosell and colleagues[29] reported as 3% (one of 30). Overall, the median rate of complete pathological response reported from 15 trials of neoadjuvant chemotherapy is 4% (range 0–16%).[5–7,23,24,27–36] The rarity of complete pathological response in these studies has restricted statistically significant conclusions with respect to the implications of complete pathological response on survival. However, Pisters and colleagues[27] reported 5-year survival in patients with stage IIIA disease who achieved a complete pathological response of 54%, which is striking compared with the historical standard.

Researchers have investigated the correlation between complete pathological response and overall survival. Betticher and colleagues[31,37] reported that median overall survival was significantly improved in patients with stage IIIA(N2) NSCLCs who had a complete pathological response (p=0·04), defined as greater than 95% pathological response. (Appropriately, most other trials have defined complete pathological response as eradication of all tumour from resected lung and lymph node tissue.) Depierre and colleagues[35] investigated 179 patients with stage IB–IIIA NSCLCs treated with neoadjuvant chemotherapy and reported that 11% of patients achieved a complete pathological response and had a relative risk of death of 0·42 (p<0·001). These results were combined with another trial[36] to total 492 patients with stage IB–II NSCLCs given neoadjuvant chemotherapy.[38] 8% of patients whose tumour was resected had a complete pathological response. An unknown number of patients did not have their tumour resected and were not included in the denominator. Nevertheless, in patients with complete pathological response, the 5-year survival significantly improved (80% *vs* 56% without complete pathological response, p<0·01). In a multivariate analysis,[38] the hazard ratio (HR) for death with complete pathological response was 0·34 (95% CI 0·18–0·64). Of note, in this study and in one other,[39] the rate of complete pathological response was higher in patients with squamous cell histology than in patients without.

Residual viable tumour as a surrogate for survival in NSCLCs

In acknowledgment that the rarity of complete pathological response restricted its use as a surrogate, other researchers have done studies to investigate more liberal definitions of pathological response after neoadjuvant chemotherapy. These studies have built on the retrospective study by Junker and colleagues[40,41] who did a thorough pathological analysis of 40 tumours from patients with stage IIIA/IIIB NSCLCs given sequential neoadjuvant chemotherapy, chemoradiotherapy, and surgical resection. The median survival was 36 months in the cohort with less than 10% residual tumour tissue compared with 14 months in all other cohorts with more than 10% residual tumour (p=0·02).

Other groups have investigated the percentage of residual viable tumour in patients after only neoadjuvant chemotherapy. As part of a prospective trial of neoadjuvant chemotherapy for 90 patients with

stage IIIA(N2) NSCLC, Betticher and colleagues[37] investigated the degree of pathological response, and reported that the median pathological response was 60%, and 22% of patients had a greater than 90% response.[31] In survival analysis, patients with greater than 60% pathological response had a median overall survival of 61 months compared with 22 months in those with less than 60% pathological response (p=0·03). No analysis was reported of the group with greater than 90% treatment response.

Pataer and colleagues[42] did a comprehensive analysis of 192 patients with resected stage I–IV NSCLCs given neoadjuvant chemotherapy. At least one slide per centimetre of greatest tumour diameter was reviewed for each specimen. The mean percentage of viable tumour cells, averaged across all reviewed slides, was reported for each patient (figure). Review of several sections from each tumour takes into account intrinsic intratumoural variability, but interobserver variability between pathologists was not formally assessed.

As a continuous variable in multivariate analysis, each additional percentage of viable tumour that remained was significantly associated with a 1% increase in the risk of death (HR 1·01, p=0·005). The degree of pathological response also correlated with DFS (HR 1·01, p=0·01). The percentage of residual viable tumour was also treated as a categorical variable and was analysed relative to the risk of death (table 2). Table 2 shows the robust improvement in survival in patients with 0–10% viable tumour compared with patients with viable tumour greater than 10%. These correlations remained statistically significant even after controlling for stage of disease. In a follow-up report,[43] on multivariate analysis, only pathological stage and pathological response (≤10% viable tumour) associated with overall survival (HR 2·39, p=0·05 if >10% viable tumour).

Chaft and colleagues[44] did a prospective trial that investigated pathological response with the methods described by Pataer and colleagues.[42] Of 50 patients with stage IB–IIIA NSCLCs given neoadjuvant chemotherapy and bevacizumab, 22% patients had 10% or less viable tumour. Of these patients, 100% were alive at 3 years compared with only 49% of those who had undergone tumour resection but had more than 10% residual tumour (p=0·01); this remained significant after adjustment for stage (p=0·02).

In another study, Thomas and colleagues[8] randomly assigned 524 patients with stage IIIA/IIIB NSCLCs to either neoadjuvant chemotherapy alone or chemotherapy followed by concurrent chemoradiotherapy before surgical resection. In a multivariate analysis of patients with N2 or N3 disease at diagnosis who received a complete resection, less than 10% residual viable tumour did not correlate with survival. However, this subset analysis might have been affected by the use of radiotherapy.

We propose that 10% or less residual tumour tissue in resected lung and lymph node tissue should be regarded as a surrogate of overall survival in patients with resectable NSCLCs given neoadjuvant chemotherapy. We term this surrogate measurement major pathological response. Results from prospective studies by Betticher and colleagues[31] and Chaft and colleagues[44] report that 22% of patients with stage I–IIIA NSCLCs given neoadjuvant cisplatin-based chemotherapy achieved a major pathological response. (The GLCCG[8] study reported by Thomas and colleagues reported only 7% major

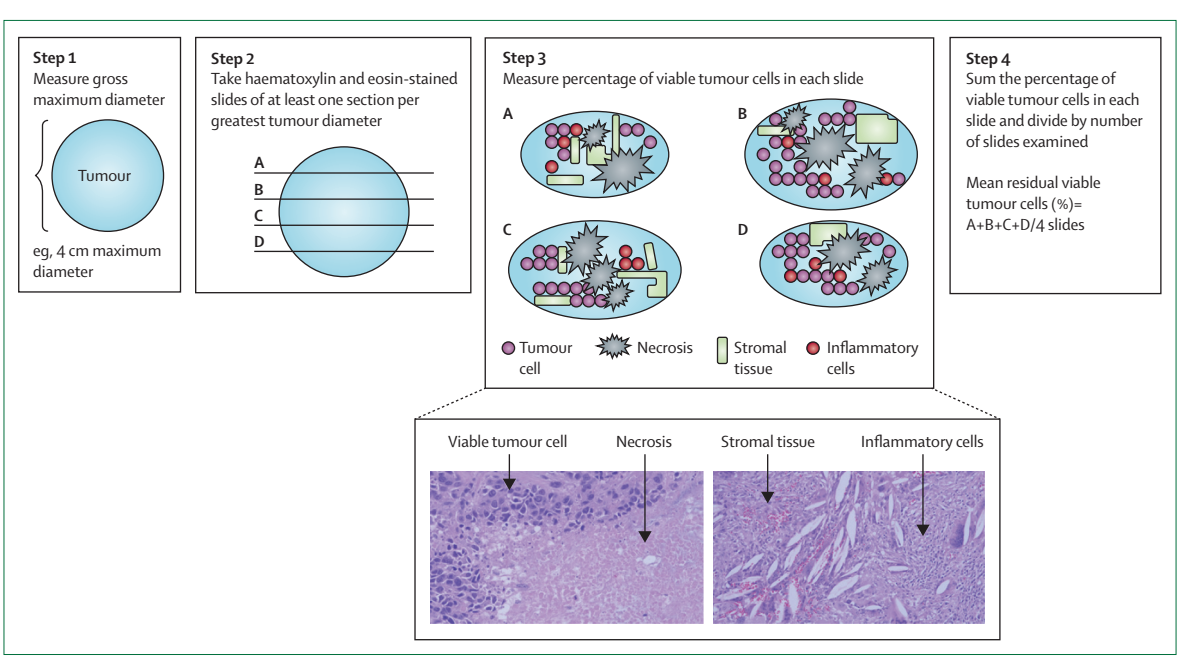

Figure: **Method for assessment of percentage viable residual tumour**

pathological response after chemotherapy, but most of these patients were stage IIIB, which is treated differently.) This benchmark might be helpful for statistical planning of future trials that integrate major pathological response as an outcome.

Although only few studies have investigated major pathological response, the association between major pathological response and improved survival is consistent across these studies (with the exception of the GLCCG[8] study, which included radiotherapy and is considered differently). Validation by larger studies is needed for all NSCLCs across various histologies and genotypes. Additionally, the effect of molecularly targeted or immunological therapies on pathological response and the suitability of major pathological response as a surrogate with these therapies are presently unknown.

Pathological nodal response: downstaging and clearance

The association between nodal response to neoadjuvant therapy and overall survival has also been investigated. Nodal downstaging (N2→N1 or N0) and nodal clearance (N2→N0) have been assessed, although such analyses are confined to patients with pathologically confirmed nodal disease at diagnosis.

Several studies have shown a positive association between nodal downstaging and improvement in overall survival in patients with pathologically confirmed stage IIIA(N2) NSCLCs after neoadjuvant chemotherapy[24,31,32,37,45] and in stage IIIA or IIIB NSCLCs after chemoradiotherapy.[8,46] A robust association between full nodal clearance and improved overall survival after neoadjuvant therapy[37,47,48] and chemoradiotherapy[25] has also been described in trials of stage IIIA(N2) NSCLCs. Only one prospective study[24] did not show a correlation between nodal clearance and survival after neoadjuvant chemotherapy. Collectively, these trials show a strong association between nodal response and improved survival after neoadjuvant therapy (both chemotherapy and chemoradiotherapy) for patients with NSCLCs with N2 disease. However, the use of nodal response as a surrogate for survival is restricted because it is dependent on the accuracy of nodal assessment and is only applicable to patients with pathologically confirmed nodal disease at diagnosis.

	Hazard ratio for death
1–10%	1·00
11–30%	2·51 (95% CI 0·91–6·96)
31–50%	3·39 (95% CI 1–40–8·22)
51–70%	4·57 (95% CI 1·98–10·52)
71–100%	4·78 (95% CI 2·06–11·11)

Table 2: **Percentage of residual viable tumour after neoadjuvant chemotherapy relative to the risk of death**

Pathological response after neoadjuvant chemoradiotherapy: is it the same?

Although we do not advocate the routine use of neoadjuvant chemoradiotherapy, a brief review of the studies investigating pathological response after neoadjuvant chemoradiation is instructive in the consideration of pathological response as a surrogate measurement.

In patients with superior sulcus tumours, neoadjuvant chemoradiation is standard. INT0160[49] and JCOG9806[50] trials have investigated the association between complete pathological response and improved survival in patients with superior sulcus tumours. Of patients enrolled, complete pathological response occurred in 29% of patients in INT0160[49] and in 16% of patients in JCOG9806.[50] Patients who achieved a complete pathological response had an improved survival compared with those with any residual disease at the time of resection, although only INT0160[49] was statistically significant (p=0·02).

Of non-superior sulcus tumours treated with neoadjuvant chemoradiotherapy, the median proportion of patients who achieved a complete pathological response was 10% (range 5–15%) in stage IIIA or IIIB disease.[8,46,51–53] Two trials have investigated complete pathological response in patients with stage IIIA(N2); the frequencies of complete pathological response were 10%[48] and 14%.[25]

Notably, complete pathological response is numerically more frequent in neoadjuvant chemoradiotherapy trials (median 10%) than in chemotherapy trials (median 4%). Because neoadjuvant chemoradiotherapy is not better than chemotherapy alone and because chemoradiotherapy trials include a preponderance of stage IIIA/IIIB disease, this finding could be puzzling, especially with respect to the possibility that complete pathological response could be a surrogate for survival. We postulate that, although complete pathological response in the primary tumour is indicative of effect of radiotherapy on local disease, it is not reflective of the effect of treatment on occult, distant sites of disease that have not been irradiated. By contrast, the effect of systemic chemotherapy in the resected tumour is probably proportional to its effect in micrometastatic disease. With respect to Prentice's criteria,[12] pathological response after neoadjuvant chemotherapy more fully reflects the effect of treatment on survival than neoadjuvant chemoradiotherapy.

Consistent with this hypothesis, two studies noted that the addition of preoperative radiotherapy to neoadjuvant chemotherapy increased the proportion of patients with a complete pathological response (17% *vs* 2%) or less than 10% residual tumour (22% *vs* 7%), respectively, but preoperative radiotherapy did not improve survival.[8,34] Similarly, a historical trial of preoperative radiotherapy alone showed high rates of complete pathological response, but no association with survival.[54]

Use of pathological response surrogates in the neoadjuvant treatment of other cancers

In the 1980s, Rosen and colleagues[55] reported the earliest investigation of correlation between pathological response and survival in sarcomas. However, the greatest and most persuasive experience showing the benefit of pathological response as a surrogate is in breast cancer.

In breast cancer, complete pathological response is routinely used as a measurement of pathological response and complete pathological response has strongly associated with survival is many multi-institutional, randomised trials.[56–62] Thus, on the basis of the association between complete pathological response and survival, the ability of complete pathological response to equal the effect of treatment on survival, and the capacity to capture the magnitude of the benefit of treatment on survival, complete pathological response is increasingly adopted as a surrogate measurement. Continued work is underway to develop a universal definition of complete pathological response and to address the validity of complete pathological response as a surrogate across molecular subtypes.[63–66]

As a result, complete pathological response has received preliminary support from regulatory agencies such as the FDA as an acceptable endpoint for accelerated approval of new therapies. The FDA released a Draft Guidance for Industry,"[67] which outlines proposals of the use of complete pathological response as an acceptable endpoint in clinical trials. Additionally, the FDA Breast Oncology Group[68] presented a meta-analysis of 12 randomised trials of 12 993 patients with breast cancer given neoadjuvant chemotherapy. The association between complete pathological response and DFS and overall survival was robust. Although, the rate of complete pathological response varied between individual breast cancer subgroups, the HR for death within each subgroup was improved in those who had complete pathological response.

Several recent trials (table 3) have incorperated complete pathological response as a primary endpoint, including the B-40,[72] GBG44,[73] and NeoSphere.[74] Each trial has shown the ability of complete pathological response as a primary endpoint to accelerate the duration of clinical trials for resectable breast cancers; all of these trials were reported 4–5 years after enrolment began. Importantly, on the basis of an improvement in complete pathological response noted in the NeoSphere trial,[74] the FDA recently granted accelerated approval to pertuzumab for use in combination with trastuzumab and docetaxel for neoadjuvant treatment of patients with HER2-positive resectable breast cancers. Pertuzumab is the first therapy to be granted accelerated approval by the FDA on the basis of a pathological response correlate, and provides proof that pathological response correlates can increase the pace of drug development.

Findings from breast cancer show that pathological response to neoadjuvant therapy can serve as a surrogate for survival, is most useful when a definition of pathological response is broadly accepted, should be validated in individual histological and molecularly defined subgroups and for specific drugs, decrease the latency between clinical trial initiation and availability of results, and, ultimately, expedite delivery of advances in care to all patients.

	Treatment	Outcome measured	Time from enrolment to publication of data
NSABP B18[56]	Neoadjuvant versus adjuvant therapy	Overall survival	10 years
NSABP B-27[59]	Neoadjuvant therapy	Overall survival	11 years
NSABP B-27[69]		Pathological complete response	8 years
Buzdar et al[70]	Neoadjuvant trastuzumab*	Overall survival	6 years
Buzdar et al[71]		Pathological complete response	4 years
NSABP B-40[72]	Neoadjuvant bevacizumab	Pathological complete response	5 years
GBG44[73]	Neoadjuvant bevacizumab	Pathological complete response	5 years
NeoSphere[74]	Neoadjuvant trastuzumab plus pertuzumab	Pathological complete response	4 years

*For HER2+ breast cancer.

Table 3: **Effect of the use of neoadjuvant therapy paired with pathological surrogates on the expedience of clinical trials in breast cancer**

Conclusions

Various measurements of pathological response after neoadjuvant chemotherapy associates with overall survival in patients with NSCLCs. Complete pathological response after neoadjuvant chemotherapy associates with improved survival, but its usefulness as a surrogate is restricted by its infrequency. Nodal response also associates with improved survival, but is dependent on the accuracy of nodal staging and is applicable only to patients with documented nodal disease.

By contrast, an assessment of the residual viable tumour, specifically major pathological response, is well suited to be adopted as a surrogate of survival in patients with NSCLCs given neoadjuvant chemotherapy (panels 1, 2). Major pathological response reliably and statistically significantly associates with survival in retrospective and prospective studies, reflects treatment specific anti-tumour activity, manifests the magnitude of the effect of treatment on survival, is applicable to all stages of NSCLC, is independent of pretreatment staging accuracy, and can be determined with fairly simple and inexpensive methods.

Potential pathological surrogates for survival in NSCLCs after neoadjuvant therapy have been considered for decades, but still none are widely used or accepted. Although we advocate that major pathological response should be considered a surrogate for survival, we also acknowledge that others might object because major pathological response falls short of Prentice's criteria for surrogacy and studies formally assessing major pathological response and its association with survival have been small in size,

Panel 1: **Optimum qualities of a pathological surrogate for survival after neoadjuvant therapy**

- Valid: Improvement in the surrogate outcome should correlate with improvement in overall survival, including in specific histiological and molecular subgroups
- Reflective: Surrogate outcome should reflect the biological effect of treatment and the magnitude of the effect of the treatment on survival
- Moderately frequent: Surrogate outcome should be sufficiently frequent to allow statistically relevant assessments with reasonable sample sizes, but sufficiently infrequent enough that improvement is attainable
- Defined: Surrogate outcome should have an unequivocal definition
- Feasible: Surrogate outcome should be easily and feasibly assessable with universally acceespecially compared with studies in breast cancer or the global burden of NSCLCs.

However, the continued disappointing outcomes and stagnant progress for patients with resectable NSCLCs and the need for improved efficiency for clinical trials in this disease prompt a call to action. Despite various nuances that are still to be refined in breast cancer, substantial benefit and increasing acceptance (including at the regulatory level) of use of complete pathological response as a surrogate for survival in trials has been seen. Therefore, assured by the features of major pathological response discussed in this Personal View (panel 1), we believe that major pathological response is a reasonable surrogate for survival and should be systematically investigated as an endpoint in neoadjuvant clinical trials.

Having emphasised the potential effect of major pathological response, we hope to spur the lung cancer community to undertake the large studies needed to support major pathological response as a surrogate, before major pathological response as a primary endpoint is put forward for regulatory approval. In the meantime, we encourage the routine assessment (with methods described in the figure, reported by Pataer and colleagues[42]) of the percentage of residual tumour in patients with NSCLCs given neoadjuvant chemotherapy.

Notably, the size of effect identified for surrogate measurements is often larger than the size of effect when survival is ultimately determined.[75] Therefore, trials incorporating major pathological response should be designed to investigate a significant increase in major pathological response (eg, doubling from the expected 20% with standard therapy to 40% with experimental therapy) to ensure a clinical meaningful effect on survival. For example, in a phase 3 trial of 235 patients with resectable *HER2* amplified breast cancer, the addition of neoadjuvant (and adjuvant) trastuzumab doubled the complete pathological response rate and increased the primary endpoint, 3-year event-free survival, from 56% to 71% (p=0·013).[76] The B-40[72] study evaluating neoadjuvant bevacizumab in resectable breast cancers is designed to assess only a 30% increase in complete pathological response (from 29% to 38%), but whether this difference will be clinically meaningful is unknown.

An important limitation of the use of major pathological response is the inability to establish the effect of treatment-related adverse events. Therefore, we advocate that any trials using surrogate endpoints, such as major pathological response, be based on a careful investigation of toxic effects in preceding trials and be designed to monitor the long-term outcomes, including survival, to fully evaluate the risk-to-benefit ratio of treatment.

Future studies are needed to formally assess the interobserver variability of major pathological response, especially before use in multi-institution studies. Additionally, the validity of major pathological response as a surrogate after novel therapies such as tyrosine-kinase inhibitors or immunotherapies is unknown and should be investigated separately. We advocate that major pathological response first be examined as a secondary endpoint and potential surrogate marker in studies of therapies with unique mechanisms of action. We do not advocate use of major pathological response as a possible surrogate in trials investigating therapies that cause minimal cell death; the biological effect of such a therapy is unlikely to seen by examining major pathological response, and therefore would be a dubious surrogate in this context.

Panel 2: **Proposals**

- Major pathological response, defined as less than 10% residual tumour after neoadjuvant therapy, should be adopted as an outcome measurement in non-small-cell lung cancers
- Methods for assessment of the degree of pathological response should adhere to those described by Pataer and colleagues[42]
- Future neoadjuvant clinical trials integrating prospective assessment of pathological response should be prioritised for resectable NSCLCs
- Major pathological response could ultimately be an acceptable endpoint for accelerated regulatory approval, but trials should still be designed to investigate overall survival to validate the initial findings and comprehensively assess the toxic effects

Search strategy and selection criteria

We identified data for this Personal View by searches of PubMed with the terms "pathologic response", "nodal response", "neoadjuvant", "induction", "preoperative", "chemotherapy", "lung cancer", and "non-small cell lung cancer" published in English from Jan, 1, 1980, to March 1, 2013. We also identified and used references from relevant articles. We included abstracts and reports from meetings when they related only directly to previously published work or important unpublished work. We excluded studies that investigated stage IIIB or IV NSCLCs.

Additionally, further work is needed to determine the applicability of major pathological response across the many histological and ever-increasing different genetic subgroups of NSCLCs. Lastly, the ability of major pathological response to distinguish the relative benefits of two different regimens in comparative studies (A+B *vs* A or A *vs* B) is untested.

Chemotherapy given in neoadjuvant or adjuvant settings are similar in terms of the effect on overall survival for patients with resectable NSCLCs. However, the neoadjuvant approach uniquely allows assessment of efficacy during treatment and degree of pathological response after treatment.

Major pathological response is a surrogate of overall survival in this setting and should be an integrated as an endpoint in clinical trials (panel 2). Methods of evaluation are described by Pataer are colleagues[42] and are detailed in the figure. We believe that major pathological response can serve as an acceptable endpoint for accelerated approval of a drug or regimen used in the perioperative setting for patients with resectable NSCLCs. Overall survival should be examined before full regulatory approval to comprehensively validate the surrogate and assess the long-term benefits and toxic effects.

Contributors

MDH and JEC did the literature search and tables and collected the data. All authors contributed to the conception of the Personal View, data interpretation, writing, and approval of the final version of this Personal View.

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Conflicts of interest

We declare that we have no conflicts of interest.

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