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

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Abstract

Improvements in outcomes for patients with resectable lung cancers have plateaued. Clinical trials in this disease using overall survival as the primary endpoint require a decade or longer to complete, are expensive, and limit innovation. A surrogate for survival, such as pathologic response to neoadjuvant chemotherapy, has the potential to improve the efficiency of trials and

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expedite advances. ≤10% residual viable tumor following neoadjuvant chemotherapy, termed here major pathologic response meets criteria for a surrogate: it strongly associates with improved survival, is reflective of treatment impact, and captures the magnitude of the treatment benefit on survival. We support the incorporation of major pathologic response as a surrogate endpoint for survival in future trials for resectable lung cancers. Additional prospective studies are needed to confirm the validity and reproducibility of major pathologic response within individual histologic and molecular subgroups and with novel therapeutics.

INTRODUCTION

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

The operational challenges of conducting multimodality clinical trials and the long wait for results are two reasons for the sluggish progress in resectable (stage I-IIIA) NSCLCs (Table 1). For example, the most recent phase III trial of adjuvant chemotherapy in NSCLCs, ANITA, was published 12 years after enrollment began.(2) Three-year disease disease-free survival (DFS) following definitive therapy closely associates with 5-year overall survival (3), but this too takes many years to ascertain. In ANITA, it would have taken 9 years from study launch until assessment of 3-year DFS for all patients.(2) Similarly, trials of adjuvant therapy in colon cancer that used 3-year DFS as a primary outcome took 8 years until publication.(4, 5)

Although overall survival remains the gold-standard outcome measure for phase III trials, the protracted length of these clinical trials in resectable NSCLCs makes this research daunting and expensive - in both human and financial terms. Evaluation of promising agents is often not pursued because the process is too long, too laborious, and may not yield results before the drug's patent-life would expire. These barriers slow progress and potentially stifle innovation.

One strategy to expedite clinical trials is the use of surrogate measurements. In a seminal paper by Prentice (12), a conservative set of validation rules for surrogates was proposed:

- The treatment intervention must be associated with the surrogate
- The surrogate must be associated with the true outcome
- The surrogate must be able to explain the entirety of the effect on the true outcome

The last requirement is the most difficult to confirm, requiring the sample sizes of large phase III trials and meta-analysis methods. In an example of a surrogate that passes these criteria, Sargent and colleagues demonstrated in patients with colon cancer that 3-year DFS after adjuvant therapy was a valid surrogate for overall survival.(13) This analysis required pooling of 20,898 patients across 18 randomized studies.

The United States Food and Drug Administration (USFDA), in its accelerated approval process, has adopted a less stringent definition of surrogacy, requiring that a surrogate

endpoint be “reasonably likely to predict clinical benefit.”(14, 15) Other groups have urged caution in hastily equating a *correlate* with a *surrogate*.(16, 17) This caution emphasizes that although a correlate may associate with the true outcome, a surrogate should also manifest the treatment effect and reflect the magnitude of the treatment effect on the true outcome.

With these considerations in mind, we propose that pathologic response following neoadjuvant (pre-operative, induction) chemotherapy for resectable NSCLCs can serve as a surrogate for overall survival. This proposal is based upon the following observations: 1) the extent of pathologic response strongly *correlates* with improved overall survival; 2) the pathologic response is reflective of the effect of neoadjuvant therapy; and 3) the degree of pathologic response associates with the degree of benefit in overall survival. Although such descriptions fall short of the Prentice criteria for establishing surrogacy, they do importantly differentiate pathologic response from a simple correlate. Consistent with the definition of surrogacy proposed by the USFDA, we believe these features support the use of pathologic response as a *surrogate* endpoint for overall survival in patients with resectable NSCLCs treated with neoadjuvant chemotherapy.

The rationale for assessing pathologic response following neoadjuvant therapy is built, foremost, on the similar survival benefit of neoadjuvant versus adjuvant therapy in resectable NSCLCs. In meta-analyses, adjuvant (18-20) or neoadjuvant (8, 21-23) cytotoxic chemotherapy equally improve survival in patients with stage IB-IIIA NSCLCs. Uniquely, a neoadjuvant approach permits assessment of the *in vivo* response to treatment at resection. Several large studies have failed to demonstrate a benefit to neoadjuvant chemoradiation in stage III disease.(11, 24-26) We do not advocate the use of neoadjuvant chemoradiation outside of superior sulcus tumors or clinical trials. As such, our discussion here focuses mainly on neoadjuvant chemotherapy.

We believe that the adoption of a consensus definition of pathologic 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 pathologic response after neoadjuvant chemotherapy as an accepted and used surrogate for survival in patients with resectable NSCLCs.

1. COMPLETE PATHOLOGIC RESPONSE IN NSCLCs

The frequency of complete pathologic response (pCR) has been reported in many trials of neoadjuvant chemotherapy for resectable NSCLCs, however the methods vary. Some trials report the frequency of pCR as a fraction of all patients treated, while others consider only those who were surgically explored or completely resected. As the former calculation gives the most conservative sense of the response, we report, whenever possible, the frequency of response as a fraction of the total number of patients treated. The consideration of the appropriate denominator is important for statistical planning of prospective trials.

In forerunning trials of neoadjuvant chemotherapy, Pisters (27), Roth (28), and Rosell (29) reported the frequency of pCR as 12% (9/73), 0% (0/28) and 3% (1/30), respectively. Overall, the median frequency of pCR from 15 trials of neoadjuvant chemotherapy is 4%

(range 0-16%).(8-10, 23, 24, 27-36) The rarity of pCR in these series limits statistically significant conclusions regarding the implications of pCR on survival. However, the report by Pisters of 54% five-year survival in patients with stage IIIA disease who achieved a pCR was provocative.(27)

Prospective trials have evaluated the correlation between pCR and overall survival. Betticher (31, 37) reported that median overall survival was significantly improved in patients with stage IIIA(N2) NSCLCs who had a pCR (p=0·04), defined as ≥95% pathologic response. (Most other trials have defined pCR as eradication of all tumor from resected lung and lymph node tissue.) In 179 patients with IB-IIIA NSCLCs treated with neoadjuvant chemotherapy, Depierre found 11% achieved a pCR and had a 0.42 relative risk of death (p<0·001).(35) These results were combined with another trial (36) to total 492 patients with stage IB-II NSCLCs treated with neoadjuvant chemotherapy.(38) 8% of those resected had a pCR. An unknown number of patients were not resected and were not included in the denominator. Nevertheless, in those with pCR, the five-year survival significantly improved (80% versus 56% without pCR, p<0·01). In a multivariate analysis, the HR for death with pCR was 0·34 (95% CI 0·18-0·64).

Of note, in this study and in one other (39), the rate of pCR was higher in those with squamous cell histology.

In sum, an association between pCR and survival is consistently found following neoadjuvant chemotherapy. Several studies have described the frequency of pCR but fewer describe its impact on survival. This omission is likely due to the infrequency of pCR, which requires large sample sizes in order to demonstrate statistical significance. The need for large trials limits the feasibility and utility of adopting of pCR as a surrogate end-point in future studies.

2. RESIDUAL VIABLE TUMOR AS A SURROGATE FOR SURVIVAL IN NSCLCs

Acknowledging the limited utility of pCR, others have evaluated more liberal definitions of pathologic response following neoadjuvant chemotherapy.

These studies have built upon the retrospective study by Junker (40, 41), who reviewed 40 tumors from patients with stage IIIA/IIIB NSCLCs treated with sequential neoadjuvant chemotherapy, chemoradiation, and surgical resection. The investigators performed a thorough pathologic analysis. The median survival was 36 months in the cohort with <10% residual tumor tissue compared to 14 months in all others (p=0·02).

Other groups evaluated the percentage of residual viable tumor in patients following neoadjuvant chemotherapy only. As part of a prospective trial of neoadjuvant chemotherapy for 90 patients with stage IIIA(N2) NSCLCs, Betticher (37) evaluated the degree of pathologic response. The median pathologic response was 60% and 22% had >90% response.(31) In survival analysis, patients with >60% pathologic response had median

overall survival of 61 months compared to 22 months in those with <60% response (p=0·03). No analysis was reported of the group with >90% treatment response.

Recently, Pataer and colleagues (42) performed a comprehensive analysis of 192 patients with resected stage I-IV NSCLCs treated with neoadjuvant chemotherapy. At least one slide per centimeter of greatest tumor diameter was reviewed for each specimen. The average (mean) of the percentages of viable tumor cells in each slide was reported for each patient (Figure 1). Reviewing multiple sections from each tumor takes into account intrinsic intratumoral variability, but interobserver variability among pathologists was not formally assessed.

As a continuous variable in multi-variate analysis, each additional percentage of viable tumor that remained was significantly associated with a 1% increase in the risk of death (HR for death = 1.01, p = 0·005). The degree of pathologic response also correlated with disease-free survival (HR=1.01, p=0·01).

The percent of residual viable tumor was also treated as a categorical variable and analyzed relative to the risk of death is displayed in the panel aside.

Percentage of residual viable tumor following neo-adjuvant chemotherapy	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)

These data demonstrated the robust improved survival in those with 0-10% viable tumor compared to other groups. These correlations remained significant when patients were stratified by stage. In a follow-up report (43), only pathologic stage and pathologic response (≤ 10% viable tumor) associated with overall survival in multivariate analysis (HR=2·39 [p=0·05] if >10% viable tumor).

Pathologic response was also examined per the methods described by Pataer (42) in a prospective trial by Chaft.(44) Here, 50 patients with stage IB-IIIA NSCLCs were treated with neoadjuvant chemotherapy and bevacizumab. 22% patients had ≤10% viable tumor. Of those who had ≤10% viable tumor, 100% were alive at three years, compared to only 49% of those who had resection but >10% residual tumor (p=0·01). This comparison remained significant after adjustment for stage (p=0·02).

In a separate study, Thomas (11) randomized 524 patients with stage IIIA/IIIB NSCLCs to either neoadjuvant chemotherapy alone or chemotherapy followed by concurrent chemoradiation prior to surgical resection. In multivariate analysis limited to the patients with N2 or N3 disease at diagnosis and who were able to receive a complete resection,

<10% residual viable tumor did not correlate with survival. However, this subset analysis may have been impacted by the use of radiation, as discussed below.

In summary, these studies demonstrate the value of analyzing the pathologic response in patients with resectable NSCLCs treated with neoadjuvant chemotherapy. Specifically, the findings that 1) the association between ≤10% residual tumor tissue and survival is strong, 2) the variable degree of pathologic response statistically tracks with the impact on survival, and 3) the significant association between ≤10% viable tumor and survival in multi-variate analysis demonstrating that pathologic response captures a substantial part of the effect of treatment on survival, are all critical to establishing pathologic response as an acceptable surrogate following neoadjuvant chemotherapy.

We propose that ≤10% residual tumor tissue in resected lung and lymph node tissue should be considered a surrogate of overall survival in patients with resectable NSCLCs treated with neoadjuvant chemotherapy. We term this surrogate metric “major pathologic response” or “MPR.” Results from prospective studies by Betticher (31) and Chaft (44) both report that 22% of patients with stage I-IIIA NSCLCs treated with neoadjuvant cisplatin-based chemotherapy achieved a MPR. (The GLCCG study reported by Thomas (11) reported only 7% MPR following chemotherapy, but the majority of these patients were stage IIIB, which is considered and treated differently.) This benchmark may be helpful for statistical planning of future trials integrating MPR as an outcome.

Although the association between MPR and improved survival is consistent across studies, the number of studies evaluating MPR is modest. Validation in larger studies is needed for all NSCLCs across various histologies and genotypes. Additionally, the impact of molecularly targeted or immunologic therapies on pathologic response and the suitability of MPR as a surrogate with these therapies are presently unknown.

3. PATHOLOGIC NODAL RESPONSE: DOWNSTAGING AND CLEARANCE

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

Several studies demonstrated a positive association between nodal downstaging and improvement in overall survival in patients with pathologically confirmed IIIA(N2) NSCLCs following neoadjuvant chemotherapy (24, 31, 32, 37, 45) and in IIIA/IIIB NSCLCs following chemoradiation.(11, 46)

A robust association between full nodal clearance and improved overall survival following neoadjuvant therapy (37, 47, 48) and chemoradiation (25) has also been described in trials of IIIA(N2) NSCLCs. Only one prospective study failed to show a correlation between nodal clearance and survival following neoadjuvant chemotherapy.(24)

Collectively, these trials demonstrate a strong association between nodal response and improved survival following neoadjuvant therapy (both chemotherapy and chemoradiation)

for patients with NSCLCs with N2 disease. However, the utility of nodal response as a surrogate for survival is limited because it is dependent on the accuracy of nodal assessment and is only applicable to those pathologically confirmed nodal disease at diagnosis.

4. PATHOLOGIC RESPONSE FOLLOWING NEOADJUVANT CHEMORADIATION: IS IT THE SAME?

Although we do not advocate the routine use of neoadjuvant chemoradiation, a brief review of the studies evaluating pathologic response following neoadjuvant chemoradiation is instructive in the context of considering pathologic response as a surrogate measurement.

One setting in which neoadjuvant chemoradiation is standard is in patients with superior sulcus tumors. In patients with these tumors, the association between pCR and improved survival was evaluated in the INT0160 (49) and JCOG9806 (50) trials. pCR occurred in 29% and 16% of patients enrolled, respectively. Those who achieved a pCR had an improved survival compared to those with any residual disease at the time of resection, although only INT0160 was large enough to reach statistical significance (p=0·02).(49)

In non-superior sulcus tumors treated with neoadjuvant chemoradiation, the median frequency of pCR is 10% (range 5-15%) in stage IIIA/IIIB disease.(11, 46, 51-53) Two trials evaluated in patients with stage IIIA(N2) only; the frequencies of pCR were 10% (48) and 14%.(25)

It may be noted that pCR is numerically more frequent in neoadjuvant chemoradiation trials (median 10%) than in chemotherapy trials (median 4%). As neoadjuvant chemoradiation is not superior to chemotherapy alone and as chemoradiation trials include a preponderance of stage IIIA/IIIB disease, this finding may be puzzling, especially when considering the possibility that pCR may be a surrogate for survival. We conjecture that, although pCR in the primary tumor of patients treated with chemoradiation is indicative of the effect of radiation on local disease control, it does not reflect the impact of treatment on occult, distant, non-irradiated sites of disease. In contrast, the effect of systemic chemotherapy in the resected tumor is likely proportional to its effect in micrometastatic disease. In the context of Prentice's criteria discussed above (12), pathologic response following neoadjuvant chemotherapy more fully captures the impact of treatment on survival in comparison to neoadjuvant chemoradiation.

Consistent with this hypothesis, two studies noted that the addition of pre-operative radiation to neoadjuvant chemotherapy increased the frequency of pCR (17% versus 2%) or <10% residual tumor (22% versus 7%), respectively, but pre-operative radiation did not improve survival.(11, 34) Similarly, a historical trial of pre-operative radiation alone demonstrated high rates of pCR, but pCR had no association with survival.(54)

5. PERSPECTIVES ON THE USE OF PATHOLOGIC RESPONSE SURROGATES IN THE NEOADJUVANT TREATMENT OF OTHER CANCERS

Perhaps the earliest evaluation of the correlation between pathologic response and survival was in sarcomas in the 1980s.(55) However, the experience in breast cancer is the largest and most persuasive demonstration of the benefits of using pathologic response as a surrogate.

In breast cancer, pCR is a routinely used measurement of pathologic response and robustly correlates with survival in many multi-institutional, randomized trials.(56-62) Based on its correlation with survival, the ability to reflect the effect of treatment on survival, and the capacity to capture the magnitude of the benefit of treatment on survival pCR is increasingly adopted as a surrogate measurement. Work is ongoing to develop a universal definition of pCR and to address the validity of pCR as a surrogate across molecular subtypes.(63-66)

As a result, pCR is preliminarily supported by regulatory agencies, including the USFDA, as a potential mechanism for accelerated approval of new therapies. The USFDA released a draft “Guidance for Industry,” which outlines proposals of the use of pCR as an acceptable endpoint in clinical trials.(67) Additionally, the USFDA Breast Oncology Group recently presented a meta-analysis of 12,993 patients in 12 randomized trials of neoadjuvant chemotherapy in patients with breast cancer.(68) The association between pCR and DFS and OS was robust. And, although the rate of pCR varied between individual breast cancer subgroups, the HR for death within each subgroup was improved in those who had pCR.

No drug has yet been approved on the basis of neoadjuvant pathologic response but trials incorporating pCR as a primary outcome have already begun (Table 2). Demonstrating the ability to accelerate the duration of clinical trials, the B-40 (69) and GBG44 (70) trials have used pCR as a primary endpoint in the pursuit of expeditious approval of neoadjuvant bevacizumab in resectable breast cancers. Both trials were reported five years after beginning enrollment. Moving forward, the I-SPY trials (64) also use pCR as the primary endpoint with the explicit purposes of more efficient trial design and drug development.

The collective experience in breast cancers demonstrates that pathologic response to neoadjuvant therapy 1) can serve as a surrogate for survival, 2) is most useful when a definition of pathologic response is broadly accepted, 3) should be validated in individual histologic and molecularly defined subgroups and for specific pharmacologic agents, 4) can hasten the pace of clinical trials and, ultimately, and 5) expedite delivering advances in care to all patients.

6. COMMENTARY

Various measurements of pathologic response following neoadjuvant chemotherapy *correlate* with overall survival in patients with NSCLCs. pCR after neoadjuvant chemotherapy correlates with improved survival, but its usefulness as a surrogate is limited by its infrequency. Nodal response also correlates with improved survival but is dependent

on the accuracy of nodal staging and is applicable only to patients with documented nodal disease.

In contrast, an assessment of the residual viable tumor, specifically “major pathologic response” (MPR, ≤10% residual viable tumor in resected lung and lymph node tissue) is well suited to be adopted as a *surrogate* of survival in NSCLCs treated with neoadjuvant chemotherapy (Tables 3 and 4). MPR reliably and significantly associates with survival in retrospective and prospective studies, reflects treatment-specific anti-tumor activity, manifests the magnitude of the impact of treatment on survival, is applicable to all stages of NSCLCs, is independent of pre-treatment staging accuracy, and can be determined using relatively simple and inexpensive methods.

Unresolved Issues, Limitations, and Pitfalls

Potential pathologic surrogates for survival in NSCLCs following neoadjuvant therapy have been considered for decades but still none are widely used or accepted. Although we advocate that MPR should be considered a surrogate for survival, we also acknowledge that others may object to the definition of MPR as a “surrogate.” MPR falls short of Prentice’s criteria for surrogacy and studies formally assessing MPR and its association with survival have been relatively modestly sized, especially in contrast to breast cancer or to 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 remain to be refined in breast cancer, there has been substantial benefit and increasing acceptance (including at the regulatory level) of using pCR as a surrogate for survival in trials. Therefore, assured by the features of MPR discussed in this review (summarized in Table 3), we believe that MPR is a reasonable surrogate for survival and should be systematically evaluated as an endpoint in neoadjuvant clinical trials.

By highlighting the potential impact of the MPR, we hope to spur the lung cancer community to perform the larger studies needed to confirm MPR as a surrogate. It is appropriate to wait for these larger, confirmatory studies before using MPR as the primary endpoint for regulatory approval. In the meantime, we encourage the routine assessment (per methods reported in (42)) of the percent of residual tumor in patients with NSCLCs treated with neoadjuvant chemotherapy.

It should be noted the effect size measured by surrogate metrics is often larger than the effect size when survival is ultimately determined.(74) Therefore, trials incorporating MPR should be designed to evaluate a significant increase in MPR (e.g. doubling from the expected 20% with standard therapy, to 40% with experimental therapy) to order to ensure a clinical meaningful impact on survival. For example, in a phase III trial of 235 patients with resectable *HER2* amplified breast cancer, the addition of neoadjuvant (and adjuvant) trastuzumab doubled the pCR rate and increased the primary endpoint, 3-year event-free survival, from 56% to 71% (p= 0·013).(75) The B-40 study evaluating neoadjuvant

bevacizumab in resectable breast cancers is designed to evaluate only a 30% increase in pCR (29% → 38%), but it is unknown if this difference will be clinically meaningful.(69)

An important limitation of the use of MPR is the inability to capture the impact of treatment related adverse events. Therefore, we advocate that any trials using surrogate endpoints such as MPR be based on a careful evaluation of toxicity in preceding trials and designed to monitor the long-term outcomes, including survival, in order to fully evaluate the risk/benefit ratio of treatment.

Future studies are needed to formally assess the interobserver variability of MPR using the methods described above, especially prior to use in multi-institution studies. Additionally, the validity of MPR as a surrogate following novel therapies such as tyrosine kinase inhibitors or immunotherapies is unknown and should be evaluated separately. We advocate that MPR first be examined as a secondary endpoint and *potential* surrogate marker in studies using therapies with unique mechanisms of action. Studies of therapies that cause minimal cell death should not evaluate MPR as a possible surrogate; the biologic impact of the therapy is unlikely to be reflected by MPR and therefore MPR would be a dubious surrogate in this context.

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

Our goal here is to crystallize an organized and cooperative effort to clarify these remaining uncertainties by integrating MPR in ongoing and future studies of neoadjuvant therapy in NSCLCs.

7. SUMMARY STATEMENTS AND PROPOSALS

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

Major pathologic response (MPR) following neoadjuvant chemotherapy associates with overall survival in patients with resectable NSCLCs. MPR directly reflects the impact of chemotherapy and the magnitude of MPR reflects the magnitude of improvement in overall survival. MPR also associates with disease-free survival.(42) MPR is a surrogate of overall survival in this setting and should be an integrated as an endpoint in clinical trials.

We propose “major pathologic response” (MPR), defined as ≤10% residual viable tumor in the resected lung and lymph node tissue, as an assessable and reliable surrogate measurement of survival (Table 4). Methods of evaluation are described in (42) and are detailed in figure 1.

We feel that MPR may serve as an acceptable endpoint for accelerated approval of an agent or regimen used in the perioperative setting for patients with resectable NSCLCs. Overall survival should be examined prior to full regulatory approval to comprehensively validate the surrogate and to assessed the long term benefits and toxicities.

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Search Strategy and Selection Criteria

Data for this review were identified via searches of PubMed using the search terms “pathologic response,” “nodal response,” “neoadjuvant,” “induction,” “preoperative,” “chemotherapy,” “lung cancer,” and “non-small cell lung cancer.” References from relevant articles were identified and incorporated. Abstracts and reports from meetings were included only when they related directly to previously published work or important unpublished work. Articles published in English up to March 1, 2013 were included. Studies of exclusively stage IIIB or IV NSCLCs were excluded.

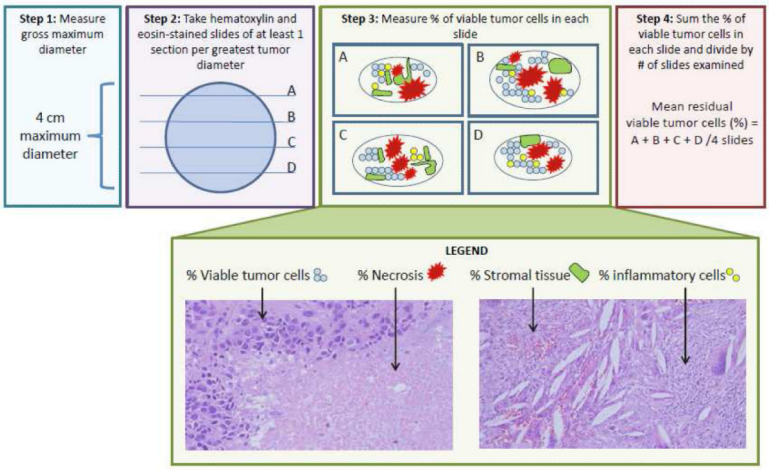

Figure 1.
Methods for assessment of % viable residual tumor

Table 1

Length of time from commencement of enrollment until publication for clinical trials of perioperative treatments for NSCLCs

Trial	Disease	Setting	Outcome measured	Time from enrollment to publication of data
IALT(1)	NSCLCs	Adjuvant therapy	Overall Survival	9 years
JRB.10(6)	NSCLCs	Adjuvant therapy	Overall Survival	11 years
ANITA(2)	NSCLCs	Adjuvant therapy	Overall Survival	12 years
CALGB 9633(7)	NSCLCs	Adjuvant therapy	Overall Survival	12 years
LU22(8)	NSCLCs	Neoadjuvant therapy	Overall Survival	10 years (closed early)
SWOG9900(9)	NSCLCs	Neoadjuvant therapy	Overall Survival	11 years (closed early)
NATCH(10)	NSCLCs	Neoadjuvant versus adjuvant therapy	Overall Survival	10 years
GLCCG(11)	NSCLCs	Neoadjuvant chemotherapy versus CRT	Overall Survival	13 years

Table 2

Impact of the use of neoadjuvant therapy paired with pathologic surrogates on the expedience of clinical trials in breast cancer

Trial	Disease	Setting	Outcome measured	Time from enrollment to publication of data
NSABP B18(56)	Breast cancers	Neoadjuvant versus adjuvant therapy	Overall Survival	10 years
NSABP B-27 (59, 71)	Breast cancers	Neoadjuvant therapy	Overall Survival	11 years
			Pathologic complete response	8 years
Buzdar et al (72, 73)	HER2+ breast cancers	Neoadjuvant trastuzumab	Overall Survival	6 years
			Pathologic complete response	4 years
NSABP B-40 (69)	Breast cancers	Neoadjuvant bevacizumab	Pathologic complete response	5 years
GBG44 (70)	Breast cancers	Neoadjuvant bevacizumab	Pathologic complete response	5 years

Table 3

Optimal qualities of pathologic surrogates for survival following neoadjuvant therapy

Optimal qualities of pathologic surrogates for survival following neoadjuvant therapy	
1)	**Valid:** Improvement in the surrogate outcome should correlate with improvement in overall survival, including in specific histiologic and molecular subgroups.
2)	**Reflective:** Surrogate outcome should reflect the biologic impact of treatment as well as the magnitude of the effect of the treatment on survival.
3)	**Moderate frequency:** Surrogate outcome should be sufficiently frequent to permit statistically relevant assessments using reasonable sample sizes, but sufficiently infrequent enough that improvement is attainable.
4)	**Defined:** Surrogate outcome should have an unequivocal definition.
5)	**Feasible:** Surrogate outcome should be easily and feasibly assessable with universally acceptable methods.
6)	**Reproducible:** Surrogate outcome should be reproducible with minimal inter-observer variability.

Table 4

Proposals

Proposals	
1)	"Major pathologic response" (MPR), defined as =10% residual tumor following neoadjuvant therapy, should be adopted as an outcome measurement in NSCLCs.
2)	Methods for assessing the degree of pathologic response should adhere to those described by Pataer et al..
3)	Future neoadjuvant clinical trials integrating prospective assessment of pathologic response should be prioritized for resectable NSCLCs.
4)	MPR may ultimately be an acceptable endpoint for accelerated regulatory approval, but trials should still be designed to evaluate overall survival in order to validate the initial findings and comprehensively assess the impact of toxicity.