Surrogate markers predicting overall survival for lung cancer: ELCWP recommendations

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ABSTRACT: The present systematic review was performed under the auspices of the European
Lung Cancer Working Party (ELCWP) in order to determine the role of early intermediate criteria
(surrogate markers), instead of survival, in determining treatment efficacy in patients with lung
cancer. Initially, the level of evidence for the use of overall survival to evaluate treatment efficacy
was reviewed. Nine questions were then formulated by the ELCWP. After reviewing the literature
with experts on these questions, it can be concluded that overall survival is still the best criterion for
predicting treatment efficacy in lung cancer. Some intermediate criteria can be early predictors, if
not surrogates, for survival, despite limitations in their potential application: these include time to
progression, progression-free survival, objective response, local control after radiotherapy,
downstaging in locally advanced nonsmall cell lung cancer (NSCLC), complete resection and
pathological TNM in resected NSCLC, and a few circulating markers. Other criteria assessed in
these recommendations are not currently adequate surrogates of survival in lung cancer.

KEYWORDS: Guidelines, lung cancer, surrogate, survival, systematic review

The European Lung Cancer Working Party (ELCWP) is a cooperative research group that has been actively involved in the performance of academic clinical trials in thoracic oncology for more than 30 yrs. Published reports on trials, performed in various stages and with various histological types of lung cancer, can be found at the ELCWP website (www.elcwp.org). The group is also involved in evidence-based medicine and has published a number of meta-analyses and systematic reviews [1], as well as guidelines on the management of small (SCLC) and nonsmall cell lung cancer (NSCLC) [2–6].

Improvement in survival or cure rates is the main therapeutic goal in lung cancer management. Other criteria of efficacy are commonly used as primary end-points in clinical studies and randomised trials, mainly concerning disease control (duration and response) and quality of life (QoL) or symptom control. During the past decade, new

techniques have emerged that have had some impact on the therapeutic approach to lung cancer, such as integration of positron emission tomography into the staging strategy or use of tissue and blood biomarkers for predicting survival prognosis or treatment efficacy. The aforementioned intermediate criteria have been proposed by some researchers for use as primary efficacy criteria in lung cancer. Nevertheless, it is currently not clear whether these criteria can correctly predict overall survival.

Intermediate criteria could provide some advantages by replacing final end-points in clinical trials. They can occur more frequently or sooner than disease-specific mortality or overall survival. The term "surrogate" is generally used in an informal way to indicate that a biomarker or an intermediate end-point can be used instead of the final end-point of interest. A definition of surrogacy was proposed 20 yrs ago by PRENTICE [7],

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who has also defined operational criteria for validating the value of a candidate surrogate: 1) a treatment should impact both on the candidate surrogate and on the true clinical end-point; and 2) the treatment effect on the surrogate should fully capture the treatment effect on the true end-point. As this second condition is difficult to prove and not practically suitable, other definitions have emerged. As mentioned by BUYSE *et al.* [8], a general consensus now exists that the validation of a surrogate end-point can be carried out on the basis of a correlation approach: first, a correlation should be demonstrated at the individual level; that is, the surrogate end-point has to be shown to be predictive of the true outcome; secondly, a correlation should be obtained at the trial level (a correlation that can be assessed through meta-analytical techniques). Nevertheless, showing surrogacy remains a difficult exercise. As we expected to find only scarce demonstrations of surrogacy in the field of lung cancer, we searched for intermediate markers that are ''simply'' predictive/prognostic of the true outcome. Therefore, we avoid in the present report the use of the term surrogate/ surrogacy and instead use the term ''predictive'', ''prognostic'' or ''early'' marker of treatment effect.

The following guidelines have been developed by the ELCWP in order to determine if intermediate criteria can be used as adequate predictive markers of overall survival in patients with lung cancer. The main target of our group is to help clinicians involved in the treatment of patients with lung cancer to integrate study results from the literature into their routine practice.

METHODOLOGY

A preliminary symposium dedicated to this topic was held in Brussels, Belgium, with the participation of a panel of experts (10th Annual Day of Thoracic Oncology; March 21, 2009). This led the ELCWP to make recommendations on the value of intermediate criteria for predicting survival in lung cancer. Initially, the level of evidence for the use of overall survival to evaluate efficacy was reviewed. Furthermore, the guidelines aimed to answer the following nine questions. 1) Can the criteria of progression-free survival (PFS), time to progression (TTP) and disease-free survival (DFS) be used to assess overall survival? 2) Is objective morphological response to chemotherapy a valid efficacy criterion, and which evaluation criteria for response are to be used? 3) Are objective morphological response criteria and local control applicable for the assessment of overall survival in the case of chemoradiotherapy (either sequential or concomitant)? 4) Can quality of life criteria be used to predict overall survival, and which quality of life scoring system should be applied? 5) Can downstaging after induction chemotherapy predict overall survival, and which assessment methodology needs to be used? 6) Do complete resection and pathological TNM have a predictive role for survival? 7) Can metabolic response, assessed by ^{18}F-fluoro-deoxyglucose gathering on positron emission tomography (^{18}F-FDG-PET or PET-CT), predict the efficacy of chemotherapy? 8) What is the role of tissue biological markers for the evaluation of overall survival? 9) What is the role of circulating markers (molecules or cells) for the assessment of overall survival? For each question, a definition of the intermediate criteria is provided.

A review of the literature was performed using the Ovid Medline system. This research was performed by a scientific

librarian, experienced in searching for medical and scientific publications, and by physicians, experts in the treatment of thoracic neoplasms and trained in evidence-based medicine, assisted by a biostatistician.

Ovid Medline was searched using the OvidSP interface. Unless otherwise stated, search terms were MeSH terms (medical subject headings). MeSH terms were also combined with relevant free-text terms that were searched for in all of the fields containing text words, particularly in titles and abstracts. The ''PICO'' (population, intervention, comparator, outcome) model for clinical questions was used to isolate the concepts included in the question [9]. The corresponding search criteria were translated into MeSH terms and free-text keywords (online supplementary material). Completed search strategies included the ''P'' and ''O'' criteria combined with one of the possible intermediate markers listed in the online supplementary material. Results were limited to those published in the period 1986 to March 2010, except when the demonstration of overall survival required retrieval of old surgical series or randomised trials in SCLC. When the number of retrieved citations was too large, additional limits were applied according to publication types and levels of evidence, with randomised controlled trials and meta-analyses having the strongest levels of support. In a few cases, it was also necessary to reduce background noise by excluding studies focused on secondary lung cancers. Citations were exported from Medline into reference manager databases to allow the removal of duplicates and to facilitate the next selection by reviewers. Exported references were scanned for relevance. Articles were rejected on initial screening when titles, abstracts and MeSH terms did not meet the inclusion criteria. The remaining articles were evaluated further for inclusion in the current review. This search was supplemented by screening the references of the selected articles and other literature known by the research team and the ELCWP members.

To be eligible, a study had to fulfil the following criteria: to be dedicated to the study of primary lung cancer, whatever the stage or the histology; to deal with tumour staging, at least for most of the patients included in the study, using the fourth, fifth or sixth edition [10, 11] of the international staging system, except for SCLC; to assess the relationship between one of the intermediate criteria selected for the guidelines and survival, at least in univariate analysis, whether it was the primary objective of the publication or not; to be published in the English, French, German or Dutch language literature, accessible to all co-authors. Abstracts were excluded as they cannot be expected to provide enough detail to allow the assessment of methodology and/or survival information. However, we allowed the consideration of unpublished studies if detailed results and methodology allowing adequate interpretation for the current guidelines were available, for example, an extensive oral presentation on the website of a congress.

The recommendations were graded according to the Grades of Recommendation Assessment, Development and Evaluation (GRADE) system [12]; the methodology is summarised in table 1. Selection of the publications was made according to this system. The best level of evidence was systematically looked for. The search was first limited to meta-analyses and randomised controlled trials; if none was available, we looked for case–control, cohort or prospective studies; finally, case reports, case

TABLE 1   Grades of Recommendation Assessment, Development and Evaluation system

First step: quality of evidence and definitions

4. High quality

Further research is very unlikely to change our confidence in the estimate of effect

3. Moderate quality

Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

2. Low quality

Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

1. Very low quality

Any estimate of effect is very uncertain

Second step: criteria for assigning grade of evidence

Type of evidence

Randomised trial: high

Observational study: low

Any other evidence: very low

Decrease grade if:

Serious (-1) or very serious (-2) limitation to study quality

Important inconsistency (-1)

Some (-1) or major (-2) uncertainty about directness

Imprecise or sparse data (-1)

High probability of reporting bias (-1)

Increase grade if:

Strong evidence of association: significant relative risk of >2 (<0.5) based on consistent evidence from two or more observational studies, with no plausible
confounders (+1)

Very strong evidence of association: significant relative risk of >5 (<0.2) based on direct evidence with no major threats to validity (+2)

Evidence of a dose–response gradient (+1)

All plausible confounders would have reduced the effect (+1)

Third step: strength of recommendation

Fs: strong recommendation for using an intervention

Fw: weak recommendation for using an intervention

Aw: weak recommendation against using an intervention

As: strong recommendation against using an intervention

Determinants of strength: balance between desirable and undesirable effects; quality of evidence; values and preferences; costs (resource allocation)

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series and expert opinion were considered. We graded the recommendations as strongly or weakly, for or against using an intervention. When no data were available to answer a question, we decided that the recommendation was against the use of the intervention.

A draft was written and discussed during three workshops of the ELCWP (March 28 and October 16, 2009, and April 16, 2010) by all the co-authors who reviewed the evidence found in the literature. Thereafter, the guidelines were reviewed by the ELCWP at a meeting held in Brussels in November 2010 and approved by the panel of experts. The authors included medical oncologists, thoracic surgeons, pneumologists, radiation oncologists and methodologists involved with the management of thoracic malignancies (target audience) as recommended by the AGREE collaboration group for the evaluation of guideline quality (www.agreecollaboration.org). Remarks and suggestions were then integrated into the final version of the guidelines. The level of evidence, quality of evidence and grade of recommendation are listed in table 2.

PRELIMINARY QUESTION: THE USE OF OVERALL SURVIVAL TO EVALUATE TREATMENT EFFICACY

According to the US Food and Drug Administration [13], survival is defined as the duration between registration or randomisation in a study and death from any cause (measured in intent-to-treat). Cure is more difficult to define. The World Health Organization (WHO) proposed a definition based on survival duration in the group of patients with the disease, in comparison to that observed in a general population with comparable demographic criteria but without the disease [14]. Another option is to consider that the patient is cured when he survives in good health for a sufficient length of time comparable to that of a group of patients with known low probability of recurrence.

The assessment of survival as a marker of treatment efficacy in lung cancer patients can be evaluated in five instances: resectable NSCLC, unresectable non-metastatic NSCLC, advanced and metastatic NSCLC, and limited and extensive disease SCLC. This evaluation is based on the review of the literature performed by the ELCWP (www.elcwp.org) [2–6].

TABLE 2	Summary of the recommendations based on level of evidence, quality of evidence and grade of recommendation (Grades of Recommendation Assessment, Development and Evaluation system)			
Recommendation		Level of evidence	Quality of evidence	Grade of recommendation
1.1) Time-to-progression is an intermediate marker for overall survival in advanced NSCLC treated with first-line chemotherapy		MA	3	Fs
1.2) Progression-free survival is a potential intermediate marker for survival in the setting of docetaxel or vinca-alcaloids first-line based regimens		MA	2	Fw
2.1) Objective response is an intermediate criterion for overall survival in advanced NSCLC treated with first-line or salvage chemotherapy		MA/RT	4	Fs
2.2) Objective response is an intermediate criterion for overall survival in extensive disease SCLC treated with first-line chemotherapy		MA/ReS	2	Fw
2.3) Objective response is a potential intermediate criterion for overall survival in operable NSCLC treated with induction chemotherapy and in locoregionally advanced NSCLC treated by chemotherapy and radiotherapy		ReS	2	Fw
3.1) Although commonly used, conventional criteria for response assessment of primary lung tumour treated by (chemo)radiotherapy cannot be used as intermediate criteria for survival		ReS	1	Aw
3.2) Local control, for which the definition has to be clarified, may be a possible intermediate criterion for overall survival		ReS	1	Fw
4) Response at the QoL level cannot be recommended as an intermediate criterion for overall survival due to a lack of robust data		ReS	1	Aw
5) Although not strictly demonstrated, there are numerous arguments from subgroup analyses of randomised trials and retrospective studies that mediastinal downstaging and, to a lesser extent, TN downstaging are associated with better survival in locally advanced NSCLC treated by induction chemotherapy or chemoradiotherapy before surgery		ReS	2	Fw
6.1) Complete resection is a prognostic factor for survival in resected NSCLC and can be used as an intermediate criterion for overall survival		Cohort/ReS	3	Fs
6.2) Pathological TNM is a prognostic factor for survival in resected NSCLC and can be used as an intermediate criterion for overall survival		Cohort	3	Fs
7) Metabolic response assessed by PET scan should not be used for the routine assessment of response to treatment in lung cancer patients in place of morphological criteria		ReS/CS	1	Aw
8) Tissue biological markers have not to be used for evaluation of treatment efficacy and are not adequate intermediate criteria for overall survival in lung cancer patients		CS	1	Aw
9.1) It is suggested that some circulating markers (CEA, Cyfra 21-1 and pro-GRP, and to a lesser extent NSE, CA-125 and CA19-9), used as single criterion to assess overall survival, could be adequate intermediate criteria for survival in lung cancer patients		ReS	2	Fw
9.2) The persistence of circulating tumour cells in NSCLC may have a prognostic impact on further survival		Cohort	1	Fw

NSCLC: nonsmall cell lung cancer; SCLC: small cell lung cancer; QoL: quality of life; PET: positron emission tomography; CEA: carcinoembryonic antigen; pro-GRP: pro-gastrin releasing peptide; NSE: neurone-specific enolase; MA: meta-analysis; RT: randomised trial; ReS: retrospective studies; CS: case series; Fs: strong recommendation for using an intervention; Fw: weak recommendation for using an intervention; Aw: weak recommendation against using an intervention.

1) For obvious ethical reasons, no randomised trials have been performed comparing surgery alone to another medical treatment or no therapy in operable patients with resectable NSCLC. The level of evidence that surgery improves overall survival and curability is based on historical data from retrospective and prospective surgical series [15]. In accordance with other guidelines, surgery is the treatment of choice for stage I and II diseases and remains an option for stage III NSCLC. Randomised trials and meta-analyses have demonstrated that adjuvant and, to a lesser extent, induction cisplatin-based chemotherapy, as well as UFT (Uracil-Tegafur) in Japanese patients, prolonged survival in comparison with surgery alone, at least in stage II and III NSCLC [16, 17].

2) The evidence of the curative role of radiotherapy alone for unresectable non-metastatic NSCLC comes from control arms of randomised trials of treatment with irradiation alone or by extrapolation from series of inoperable patients with resectable NSCLC (stages I and II). A 5-yr survival of 4–10% was documented [18, 19]. The addition of chemotherapy to curative radiotherapy, administered either sequentially or concomitantly, yielded improved survival and cure rates in comparison with those for radiotherapy alone. This evidence came from randomised trials and meta-analyses [20–25].

3) At least 15 randomised trials and five meta-analyses confirmed that survival improvement is obtained with first-line

chemotherapy in comparison with best palliative care alone in advanced and metastatic NSCLC [20, 26–29]. Two randomised trials demonstrated that salvage chemotherapy with docetaxel or erlotinib also improved survival in comparison with palliative care [30, 31].

4) The effect on survival of chemotherapy for first-line treatment of SCLC was first observed in old randomised trials comparing alkylating agents with inert compounds, which showed improved survival with cyclophosphamide monotherapy [32]. Currently, multiple drug administration has become the standard chemotherapy. In this instance, two meta-analyses demonstrated that cisplatin- and/or etoposide-based chemotherapy is more effective and yielded better survival than other regimens [33, 34]. In limited disease SCLC, 15 randomised trials and three meta-analyses demonstrated that the addition of radiotherapy to chemotherapy increased survival in comparison with chemotherapy alone [35–37]. There has been only one randomised trial comparing topotecan with palliative care for salvage treatment, with improved survival with chemotherapy [38].

Overall survival has the advantage of being unambiguous (the patient is dead or alive). Assessing the distribution of survival duration in a group of patients makes use of probability theory and not simple mortality rate. The main disadvantages of this are the impact of subsequent treatment on overall survival and, in the case of long-term survival, the follow-up duration and the risk of loss to follow-up.

In conclusion, an improvement in overall survival or rate of cure is widely accepted as an important goal of lung cancer therapy and is generally considered as the leading criterion of efficacy of a treatment in lung cancer patients.

The subsequent questions are not listed in any particular hierarchical order.

QUESTION 1: CAN THE CRITERIA OF PFS, TTP AND DFS BE USED TO ASSESS OVERALL SURVIVAL?

PFS is defined as the duration between registration or randomisation in a study and the first objective aggravation of the disease or death. TTP is the time from study enrolment to the first date of disease progression. DFS is the period between registration or randomisation in a study and tumour recurrence or death. This criterion is mainly used in the adjuvant and surgical settings when no more target lesions are available [39].

To date, two meta-analyses have been published assessing the predictive value of TTP on overall survival in lung cancer patients [40, 41]. A pooled analysis of selected randomised controlled trials was orally presented during the 2008 American Society of Clinical Oncology (ASCO) meeting [42]. Although not published in full, it was selected for the present guidelines because detailed results and methodology were available on the ASCO website. The results of these three studies are reported in table 3. The three studies dealt with advanced NSCLC treated with first-line chemotherapy in randomised controlled trials. In the two published studies [40, 41], a statistically significant correlation between TTP and overall survival was detected, although it was of limited amplitude. In the study reported by HOTTA et al. [41], the median TTP ratio accounted for less than half the variability (41%) of the median survival ratio. To predict a statistically significant improvement in the survival time at the p-value of 0.05, an increase in the median TTP of 1.8 months must be observed for trials with 750 patients, and 2.2 months and 3.3 months for those with 500 and 250 patients, respectively [40]. Some evidence for a relationship between PFS and overall survival is provided in the latter study [42]: a 30% reduction in the risk of progression assessed by PFS predicts a statistically significant effect on overall survival in patients with advanced NSCLC treated with first-line docetaxel- or vincalcaloid-containing regimens. It must be pointed out that this positive association between improved PFS and further increase in survival was recently not confirmed in randomised trials comparing chemotherapy to epidermal growth factor receptor tyrosine kinase inhibitors (TKIs), despite a high hazard ratio for PFS favouring the TKI treatment [43–45].

We did not find meta-analyses or specific studies with, as their primary objective, the assessment of PFS, TTP or DFS as an intermediate marker for overall survival in resectable NSCLC treated by surgery with or without chemotherapy, in unresectable NSCLC treated by chemoradiotherapy, in NSCLC receiving salvage chemotherapy, and in SCLC.

TABLE 3	Meta-analyses or pooled analysis assessing the role of time-to-progression and progression-free survival as intermediate end-point for overall survival in lung cancer patients						
Reference	End-point	Population	Considered studies	Period	Studies n	Patients n	Relationship between the intermediate criteria and overall survival
JOHNSON et al. [40]	TTP	Advanced NSCLC	RCT of first line CT	1966–2005	191	44125	r^2=0.19 p=0.0003 Multivariate analysis
HOTTA et al. [41]	Median TTP ratio	Advanced NSCLC	Phase III RCT of first line CT	1987–2002	54	23457	r^2=0.33 p<0.01 Multivariate analysis
BUYSE et al. [42]	PFS	Advanced NSCLC	RCT of first line CT#	2003–2006	7	2838	r^2=0.61

TTP: time-to-progression; NSCLC: nonsmall cell lung cancer; RCT: randomised controlled trial; CT: chemotherapy; PFS: progression-free survival. #: RCT comparing docetaxel to vincalcaloids regimens.

PFS, TTP and DFS have potential advantages in prospective studies, by reducing the number of patients to be accrued, and the follow-up and study durations, as well as in alleviating the effect of subsequent treatment on the study end-point. There are numerous disadvantages related to the parameters used, as follows. Which is the best criterion determining objective progression? How do you consider disagreements on evaluation criteria among investigators? How do you manage the absence of blinding in interpretation of results? Most importantly, all these parameters are highly dependent on the duration between two disease assessments and the type of assessment, which must be independent of the treatment arm.

Recommendations

1) TTP is an intermediate marker for overall survival in advanced NSCLC treated with first-line chemotherapy. Level of evidence: meta-analyses; quality of evidence: 3; grade of recommendation: Fs.

2) PFS is a potential intermediate marker for survival in the setting of docetaxel or vinca-alcaloid first-line regimens. Level of evidence: meta-analyses; quality of evidence: 2; grade of recommendation: Fw.

Statements

More evidence is needed to confirm that TTP or PFS and DFS are intermediate criteria predicting overall survival in the following settings: in patients with resectable NSCLC treated by surgery with or without chemotherapy, with unresectable NSCLC treated by chemoradiotherapy, with NSCLC treated by salvage chemotherapy and with SCLC. DFS cannot be recommended as an intermediate marker for overall survival, owing to the lack of data.

QUESTION 2: IS OBJECTIVE MORPHOLOGICAL RESPONSE TO CHEMOTHERAPY A VALID EFFICACY CRITERION, AND WHICH EVALUATION CRITERIA FOR RESPONSE ARE TO BE USED?

The first definition of objective response was proposed by C.G. Zubrod in 1960. Currently, three systems are available (table 4).

All are based on expert opinions without adequate statistical methodology applied for choosing the cut-off determining the different categories of response. The WHO system was published in 1979 [14]. The South West Oncology Group (SWOG) used its own definition, close to that of the WHO, in its studies [46]. RECIST (Response Evaluation Criteria In Solid Tumours) was developed in 2000, to be used in clinical studies [47]. The main differences between RECIST and WHO/SWOG criteria were the following: use of unidimensional instead of bidimensional measurement, limitation in the number of target lesions (maximum five per organ with an overall maximum of 10 lesions), and different cut-offs for response and progression. A new version of RECIST has recently been published [48]. The main modifications of version 1.1 are that a maximum of two lesions per organ are considered and that a complete response on lymph nodes is defined as a node no more than 10 mm in short axis.

Seven meta-analyses have been published to date that assess, as the primary objective of the study, the relationship between objective response to chemotherapy and survival [40, 49–54]. Objective response and/or disease control (objective response plus stable disease) predict improvement in overall survival in the following situations: advanced NSCLC receiving first-line or salvage chemotherapy and extensive disease SCLC treated by first-line chemotherapy (table 5). In three meta-analyses, the impact of response on overall survival was quantified. A statistically significant ($p<0.05$) increase in overall survival could be observed for an increase in response rate of 18% requiring 750 patients to be included in randomised trials. This value increases to 21% and 30% if the number of patients is 500 or 250, respectively [40]. In two other studies, each 1% increase in response rate resulted in an improvement in median survival time of 0.26 months in patients receiving TKI [54] or 0.07 months with salvage chemotherapy [51]. When specified, the evaluation criteria for response were most often those of the WHO and RECIST. However, no formal comparison between the two systems has been performed for lung cancer patients. We also looked at large retrospective studies pooling

TABLE 4	World Health Organization (WHO), South West Oncology Group (SWOG) and RECIST (Response Evaluation Criteria In Solid Tumours) criteria for response assessment		
	WHO	**SWOG**	**RECIST[#]**
Complete response	Complete disappearance of all measurable and assessable tumoural lesions not less than 4 weeks apart	Complete disappearance of all measurable and assessable tumoural lesions, including normalisation of markers and other abnormal laboratory values for at least 3–6 weeks	Complete disappearance of all tumoural lesions for at least 4 weeks
Partial response	Decrease ⩾50% of the product of the two greatest perpendicular diameters for at least 4 weeks	Decrease ⩾50% of the product of the two greatest perpendicular diameters for at least 3–6 weeks	Decrease ⩾30% of the sum of the greatest diameters
Stable disease	No response or progression	Decrease <50% or increase <50% (<10 cm^2) of the product of the two greatest diameters for at least 3–6 weeks	No response or progression
Progression	Increase >25% of the product of the two greatest perpendicular diameters or appearance of a new lesion	Increase >50% or >10 cm^2 of the product of the two greatest diameters or appearance of a new lesion or clear aggravation of any assessable lesion	Increase >20% of the sum of the greatest diameters or appearance of a new lesion

Data taken from [14, 46, 47]. [#]: the final evaluation according to RECIST criteria takes into account the response on target and non-target lesions.

TABLE 5	Meta-analyses assessing response as an intermediate marker for overall survival in lung cancer			
	Patients n	Effect on survival	U/M	Response criteria
NSCLC treated by chemotherapy[#]				
SEKINE et al. [52]	6768	OR: r^2=0.36 (p=0.00003)	M	
TSUJINO et al. [54]	6171	OR: p<0.0001 (↑MST 0.26 month/ ↑1% OR)	U	WHO, RECIST
		DCR: p=0.003 (↑MST 0.17 month/ ↑1% DCR)		
Advanced NSCLC receiving first line chemotherapy				
JOHNSON et al. [40]	44125	OR: r^2=0.16 (p<0.0001)	M	WHO
HOTTA et al. [50]	43551	OR: r=0.08 (p<0.0001)	M	
		DCR: r=0.08 (p<0.0001)		
SHANAFELT et al. [53]	2794	OR: r^2=0.22 (↑MST 1 week/ ↑3.3% OR)	U	
NSCLC receiving salvage chemotherapy				
HOTTA et al. [50]	4318	OR: p=0.69	M	
		DCR: p=0.013		
KURATA et al. [51]	4292	OR: p<0.001 (↑MST 0.07 month/ ↑1% OR)	M	
		SD: p=0.04 (↑MST 0.038 month/ ↑1% SD)		
Extensive disease SCLC receiving first line chemotherapy				
HOTTA et al. [49]	8779	OR: r^2=0.33	U	WHO, RECIST, other

U: results obtained in univariate analysis; M: results obtained in multivariate analysis; NSCLC: nonsmall cell lung cancer; OR: overall response; MST: median survival time; WHO: World Health Organization; RECIST: Response Evaluation Criteria In Solid Tumours; DCR: disease control rate; SD: stable disease; SCLC: small cell lung cancer. [#]: first line and salvage chemotherapy combined.

prospective trials performed for lung cancer (table 6) [55–58]. Objective response was also found to be a significant predictor for better survival in advanced and metastatic NSCLC [55–57] and in SCLC [58], whatever the stage of the disease, treated by chemotherapy.

No meta-analyses or randomised trials having the evaluation of response as an intermediate criterion for survival were available in the following clinical settings: induction chemotherapy for operable NSCLC, sequential or concomitant chemoradiotherapy for locoregionally advanced NSCLC, and limited disease and recurrent SCLC. Better survival was found in patients with NSCLC presenting with an objective response to induction chemotherapy before surgery or to treatment for locoregionally advanced NSCLC, induction chemotherapy before radiotherapy, chemoradiotherapy, or radiotherapy alone [59–64]. The level of evidence was from analyses of secondary objectives of randomised trials published on each topic (table 6) and phase II studies [66–74]. We found only one study in SCLC showing that patients with complete response had longer survival than those with partial response or no change, those progressing under firstline treatment with chemotherapy or chemoradiotherapy having the worst prognosis [65].

There are few formal comparisons allowing determination of which evaluation criteria are to be used. In the RECIST publication [47], a comparison between RECIST 1.0 and WHO criteria did not find any significant difference for assessing objective response or progression, whether considering the whole population or only lung cancer patients. Further studies have been performed in patients with lung cancer, which are summarised in table 7. Overall, there was no significant difference between the two systems of evaluation for response determination [47, 75–79].

Recommendations

1) Objective response is an intermediate criterion for overall survival in advanced NSCLC treated with first-line or salvage chemotherapy. Level of evidence: meta-analyses and randomised trials; quality of evidence: 4; grade of recommendation: Fs.

2) Objective response is an intermediate criterion for overall survival in extensive disease SCLC treated with first-line chemotherapy. Level of evidence: meta-analyses and retrospective studies; quality of evidence: 2; grade of recommendation: Fw.

3) Objective response is a potential intermediate criterion for overall survival in operable NSCLC treated with induction chemotherapy and in locoregionally advanced NSCLC treated by chemotherapy and radiotherapy. Level of evidence: retrospective studies; quality of evidence: 2; grade of recommendation: Fw.

Statements

More evidence is needed to confirm that objective response is an intermediate criterion predicting overall survival in the following settings: operable NSCLC treated with induction chemotherapy, locoregionally advanced NSCLC and limited disease SCLC treated by chemotherapy and radiotherapy.

WHO and RECIST 1.0 criteria appear to have the same efficacy in predicting objective response in locoregionally advanced and metastatic NSCLC. On the basis of the available data, it is not possible to determine the best response criterion to be used in other settings related to lung cancer management, the equivalence of WHO and RECIST criteria having to be confirmed in larger studies.

The cut-off point to define response/progression, as proposed by the WHO and the RECIST systems, needs validation assessment.

TABLE 6 Retrospective analyses of prospective studies assessing response as an intermediate marker for overall survival in lung cancer

	Patients n	Population	Therapy	Effect on survival	p-value	U/M	Response criteria
Pooled analyses assessing the predictive value of response on survival as primary objective							
Lara Jr et al. [55]	984	NSCLC IV	CT	OR: HR 0.61 / DCR: HR 0.45	<0.001 / <0.001	U	RECIST SWOG
Yamamoto et al. [56]	806	NSCLC III/IV	CT	DCR / Phase II 14.5 versus 10.4 months / Phase III 12.1 versus 8.8 months	0.04 / 0.002	U	RECIST
Paesmans et al. [57]	1052	Advanced NSCLC	CT	OR: RR 2.20	<0.001	M	WHO
Lebeau et al. [58]	1280	SCLC LD/ED	CT	CR: MST 16 months / PR: 12 months / No response 10 months	<0.001	M	WHO
Retrospective analyses of individual prospective randomised trials having as secondary objective the assessment of response as intermediate criteria for survival							
Depierre et al. [59]	179	NSCLC IB-IIIA	CT → surgery	OR: RR 0.37 / CR: RR 0.42	0.0001 / 0.0007	U	WHO
Nagai et al. [60]	31	NSCLC IIIAN2	CT → surgery	PR: MST 30 months / SD: MST 18 months / PD: MST 12 months	0.05	U	
Sculier et al. [61]	462	NSCLC III	CT-RT	PR: MST 57 weeks / SD: MST 32 weeks / PD: MST 16 weeks	<0.001	M	WHO
Groen et al. [62]	160	NSCLC III	RT or CT-RT	OR: MST 16 months / No response: MST 10 months	<0.001	U	WHO
Crino et al. [63]	66	NSCLC III	RT or CT-RT	OR: RR 3.86	<0.001	M	WHO
Huber et al. [64]	303	NSCLC III	CT → RT or CT-RT	OR to induction CT correlated with survival	0.01	M	WHO
Joss et al. [65]	266	SCLC LD/ED	CT or CT-RT	CR > PR/no change > progression	<0.001	U	WHO

U: results obtained in univariate analysis; M: results obtained in multivariate analysis; NSCLC: nonsmall cell lung cancer; CT: chemotherapy; OR: overall response; HR: hazard ratio; RECIST: Response Evaluation Criteria In Solid Tumours; DCR: disease control rate; SWOG: Southwest Oncology Group; RR: relative risk; WHO: World Health Organization; SCLC: small cell lung cancer; LD: limited disease; ED: extensive disease; CR: complete response; MST: median survival time; PR: partial response; SD: stable disease; PD: progressive disease; CT-RT: chemoradiotherapy; RT: radiotherapy.

TABLE 7	Comparison between World Health Organization (WHO) and RECIST (Response Evaluation Criteria In Solid Tumours) 1.0 for response assessment in lung cancer						
Study	P/R	Patients n	Population	RR-RECIST%	RR-WHO%	PD-RECIST%	PD-WHO%
THERASSE et al. [47]	R	1197	ND	32	32		
WERNER-WASIK et al. [75]	P	22	Locally advanced NSCLC	87	87		
CORTES et al. [76]	R	164	Metastatic NSCLC	52	52	26	26
WATANABE et al. [77]	R	120	Metastatic NSCLC	19	20	13	17.5
PARK et al. [78]	R	28	NSCLC	39	43	25	29
KONISHI et al. [79]	R	32		38	47	6	6

P: prospective study; R: retrospective study; RR: response rate; PD: progressive disease; ND: no data; NCSLC: nonsmall cell lung cancer.

In the context of maintenance therapy, disease control rate (response plus stable disease) needs validation assessment.

QUESTION 3: ARE OBJECTIVE MORPHOLOGICAL AND METABOLIC RESPONSE CRITERIA AND LOCAL CONTROL APPLICABLE TO ASSESS OVERALL SURVIVAL IN THE CASE OF CHEMORADIOTHERAPY (EITHER SEQUENTIAL OR CONCOMITANT)?

There are many problems when defining response by conventional criteria (WHO and/or RECIST) due to pneumonitis and fibrosis modifications induced by thoracic irradiation, which must be differentiated from residual neoplastic tissue. As these changes are time-related and increase by the use of radio-sensitising chemotherapeutic agents, timing of evaluation after treatment could influence response assessment.

The role of new evaluation techniques like PET(-CT) was assessed in a few small retrospective studies. In 73 NSCLC patients treated by radical radiotherapy or chemoradiotherapy, there was poor agreement between PET and CT response assessment (kappa 0.35) using respectively European Organization for Research and Treatment of Cancer (EORTC) and WHO criteria. In multivariate analysis, only PET response was associated with survival (p< 0.0001) [80]. In a second study including 50 patients treated with induction chemoradiotherapy, followed by surgery in 37 cases, change in standardised uptake value (SUV) on PET-CT after induction treatment was not related to survival (p=0.75) [81]. Lastly, SUV_{max} after induction chemoradiotherapy predicted survival in operated patients with NSCLC. The median survival was longer for the patients with SUV_{max} <4 than in those with SUV more than 4, namely, 56 months versus 19 months (p<0.001) [82].

Local control is another commonly used approach to undertake intrathoracic response assessment. In a consensus expert conference held in Bruges, Belgium in 1993, the proposals for defining lung cancer local control after thoracic irradiation were complete disappearance of all radiographic abnormalities by chest film CT and residual radiographic abnormality assessed by chest CT at 3 and 6 months, which then remains stable for an additional 6 months or more. This definition has never been the topic of a validation study.

Literature on this question is relatively disappointing. We found only a few retrospective studies or secondary analyses of randomised trials assessing the association between local control and survival in lung cancer. BIRCH et al. [83] observed for limited disease SCLC that survival was longer for patients achieving local control after chemoradiotherapy than for those who did not. In a small retrospective study including limited and extensive disease SCLC, COX et al. [84] had the same observation. DOSORETZ et al. [85] showed that local control resulted in improved survival in irradiated medically inoperable NSCLC. In a retrospective study of Radiation Therapy Oncology Group randomised trials, local control was associated with significantly better survival [86]. However, the ELCWP could not confirm these results in a phase III trial comparing chemotherapy to chemotherapy followed by radiotherapy in stage III unresectable NSCLC [87]. A significant increase in local control duration was obtained in the combination arm: median of 158 weeks versus 31 weeks, with respective 2-yr rates of 57% and 24% (p=0.0007). This better local control duration did not result in a statistically significant increase in survival duration: median of 54 weeks (95% CI 43–73 weeks) versus 42 weeks (95% CI 35–51 weeks), with 2-yr survival rates of 22% (95% CI 11–33%) and 18% (95% CI 8–28%).

Recommendations
1) Although commonly used, conventional criteria for response assessment of primary lung tumours treated by (chemo) radiotherapy cannot be used as intermediate criteria for survival. Level of evidence: retrospective studies; quality of evidence: 1; grade of recommendation: Aw.

2) Local control, for which the definition has to be clarified, is a possible intermediate criterion for overall survival. Level of evidence: retrospective studies; quality of evidence: 1; grade of recommendation: Fw.

Statement
The roles of conventional WHO or RECIST criteria, of metabolic response criteria (PET imaging) and of local control as intermediate criteria in the context of lung cancer treated by (chemo)radiotherapy have to be assessed in prospective studies.

QUESTION 4: CAN QUALITY OF LIFE CRITERIA BE USED TO PREDICT OVERALL SURVIVAL? WHICH QUALITY OF LIFE SCORING SYSTEM HAS TO BE APPLIED?

We identified some data in the literature related to this topic, although there are many papers suggesting a prognostic role for baseline QoL data [88–90]. Several scoring systems exist and have been validated with the availability of modules dedicated to lung cancer symptoms and treatment side-effects. Those which have been studied in association with the

predictive value of QoL on other outcomes (response to chemotherapy, PFS and survival) are the EORTC QoL core questionnaire (30 items) complemented by the lung cancer module LC13 [91, 92] and the Functional Assessment of Cancer Therapy – Lung (FACT-L) with a module specific for the symptoms of the disease (LCSS) [93]. Before looking at this predictive value, it is relevant to define what is meant by a response at the QoL level. OSOBA et al. [94] defined an increase in the overall EORTC QoL score of >10 points as a response, a decrease of >10 points as a progression, and intermediate results as stabilisation, on the basis of concordance between QoL score evolution and a subjective question. CELLA et al. [95] proposed a definition of response for two outcomes for the LCSS score (from 0 to 28, with increasing values for increasing QoL) and the TOI (Trial Outcome Index, which is the sum of LCSS and functional and physical wellbeing scales, from 0 to 84). For the first outcome, an increase of 2–3 points is needed and, for the TOI, an increase of 5–7 points is required. Definitions of stabilisation and progression are derived from these thresholds. This proposal resulted from the analysis of a clinical trial and used the association between QoL evolution and response to chemotherapy or PFS.

One report on a meta-analysis suggests that an association between QoL and radiological response exists (positive correlation), but this meta-analysis was not dedicated to lung cancer and suffered from a serious selection bias: out of more than 350 studies identified by the literature search, only 21 could be included in the quantitative review [96].

ETON et al. [97] have shown, for patients with advanced lung cancer, using the database of a clinical trial and the FACT-L scoring system, that classification into four groups (I: high baseline FACT-L score with improvement; II: high baseline with deterioration; III: low baseline with improvement; IV: low baseline with deterioration) has prognostic value for TTP and overall survival. Group I had the best results, followed by group II, group III and group IV (p<0.001).

CELLA et al. [98] studied the QoL evolution among patients treated in the IRESSA Dose Evaluation in Advanced Lung Cancer (IDEAL)-2 trial testing gefitinib as second-line treatment for NSCLC. The patients with a QoL response (>2 point improvement on the LCSS scale) had a significantly prolonged survival compared with the other patients (median of 13 months compared with 5 months after a landmark of 8 weeks; p<0.001). Data from IDEAL-1 point in the same direction [99]. In the Iressa NSCLC Trial Assessing Combination Treatment (INTACT) trials looking at the addition of gefitinib to a chemotherapy regimen in the first-line setting, the association between QoL and anti-tumoural response has been studied using the EORTC QoL questionnaire. The associations with different scales (overall scale, physical scale, pain, cough and dyspnoea) and response were all significant. However, we do not have any available data about the value of QoL response for PFS or overall survival [100, 101].

Recommendation
Response at the QoL level cannot be recommended as an intermediate criterion for overall survival owing to a lack of robust data. Level of evidence: retrospective studies; quality of evidence: 1; grade of recommendation: Aw.

Statement
The association between response at the QoL level and long-term outcomes, as suggested in some instances (recurrent NSCLC treated with gefitinib), needs further investigation, including adequate determination of cut-off points defining a response, and of the most appropriate questionnaire.

QUESTION 5: CAN DOWNSTAGING AFTER INDUCTION CHEMO(RADIO)THERAPY PREDICT OVERALL SURVIVAL, AND WHICH ASSESSMENT METHODOLOGY NEEDS TO BE USED?
Downstaging can be defined as a shift to a lower disease stage after a treatment. In NSCLC, studies assessing the prognostic role of downstaging on survival after induction chemotherapy have been performed at the mediastinal (N stage) or the TN level. The literature is generally heterogeneous. Inclusion criteria are quite different from one study to another according to stage, mediastinal evaluation (clinical or pathological definition), type of treatment (induction chemotherapy or chemoradiotherapy before surgery; nonsurgical treatment only) and type of downstaging (N or TN). Most of the publications are case series or retrospective analyses of phase II studies of small sample size. We found only two phase III trials in which these questions were retrospectively analysed. The first trial compared the role of surgery to radiotherapy in stage IIIA pathological N2 NSCLC treated by induction chemotherapy [102]. In the surgery arm including 154 randomised patients, mediastinal downstaging was an independent prognostic factor for survival in multivariate analysis (p=0.04). In the second trial, comparing chemoradiotherapy alone to chemoradiotherapy followed by surgery in stage III pathological N2 NSCLC, mediastinal downstaging in the surgical group (164 patients) was associated with better survival in univariate analysis with median survival times for pathological N0 and N1–3 of 34.4 months and 26.4 months, respectively (p<0.0001) [103].

Mediastinal downstaging in NSCLC has been assessed by noninvasive (CT and PET scan), minimally invasive (oesophageal (EUS) or endobronchial (EBUS) endoscopic procedures), and invasive procedures (re-mediastinoscopy and video-assisted thoracoscopic surgery (VATS)). In its 2007 guidelines, the European Society of Thoracic Surgeons did not recommend a particular procedure for restaging but recommended that cyto-histological proof be obtained by a minimally invasive or invasive procedure, depending on the availability and specific expertise of staff at the centre [104]. The literature on mediastinal restaging was recently reviewed [105]. Sensitivity, specificity, false-negative and false-positive rates for mediastinal CT restaging were on average 63%, 70%, 31% and 34%, respectively. Respective values for PET scan were 63%, 70%, 26% and 34%. Combined PET-CT seems more adequate, with sensitivity of 62–77%, specificity of 88–92%, false-negative rate of 20–25%, false-positive rate of 7–25%, and an accuracy of 79–83% [106, 107]. Few studies have assessed the role of minimally invasive procedures for mediastinal re-staging. EUS was evaluated in three very small studies, EBUS in one, and transbronchial needle aspiration in another. Average sensitivity and false-negative rates were 84% and 14%, respectively. Re-mediastinoscopy is technically challenging due to adherence and fibrosis. In a few studies, the sensitivity of this technique was 63%, with 100% specificity and accuracy of 84–93%. The false-negative rate was 22%. VATS was assessed in a small

series of 70 patients [108]. The procedure was unsuccessful in 17 patients owing to fibrosis. Reported sensitivity, specificity and negative predictive value were 75%, 100% and 76%, respectively.

Recommendation

Although not strictly demonstrated, there are numerous assertions from subgroup analyses of randomised trials and retrospective studies that mediastinal downstaging and, to a lesser extent, TN downstaging are associated with better survival in locally advanced NSCLC treated by induction chemotherapy or chemoradiotherapy before surgery. Level of evidence: retrospective studies; quality of evidence: 2; grade of recommendation: Fw.

Statements

The association between downstaging after induction chemotherapy (or chemoradiotherapy) and long-term outcomes should be confirmed and needs further investigation in adequately powered prospective studies.

PET-CT is the recommended noninvasive technique for mediastinal restaging, being more precise than CT scan, which appears insufficiently accurate in this setting. When pre-operative pathological persistent mediastinal neoplastic infiltration has to be confirmed, minimally invasive or invasive techniques are feasible, each one appearing with similar efficacy. The choice of the technique will depend on the local expertise and the initial technique used for demonstrating mediastinal invasion.

QUESTION 6: DO COMPLETE RESECTION AND PATHOLOGICAL TNM HAVE A PREDICTIVE ROLE FOR SURVIVAL?

The basis of the definition of complete resection is the *Union Internationale Contre le Cancer* (UICC) residual tumour classification (R classification) [109]. R0 category consists of the absence of residual tumour in the primary site, lymph nodes and distant sites, which appears insufficient in lung cancer, and is mainly for the mediastinal definition of complete resection. The Complete Resection subcommittee of the International Association for the Study of Lung Cancer (IASLC) Staging Committee, after an extensive review of the literature, proposed the definition of complete resection based on an international consensus [110]: ''Complete resection requires all of the following: free resection margins proved microscopically; systematic nodal dissection or lobe-specific systematic nodal dissection; no extracapsular nodal extension of the tumour; and the highest mediastinal node removed must be negative. Whenever there is involvement of resection margins, extracapsular nodal extension, unremoved positive lymph nodes, or positive pleural or pericardial effusions, the resection is defined as incomplete. When the resection margins are free and no residual tumour is left, but the resection does not fulfil the criteria for complete resection, there is carcinoma *in situ* at the bronchial margin, or positive pleural lavage cytology, the term uncertain resection is proposed.'' R1 is defined as a persistence of microscopic tumour tissue and R2 as macroscopic incomplete resection.

The level of evidence of the prognostic role of R0 in NSCLC is relatively low. There have been many studies derived from retrospective analyses of phase II and surgical series, mainly including stage IIIA-N2 NSCLC. In most of them, R0 was a predictive factor for survival in either univariate or multivariate

analysis. We found only one phase III trial in which R0 was evaluated in multivariate analysis as a secondary end-point [102]. In 154 stage IIIAN2 NSCLC patients receiving induction chemotherapy followed by surgery, R0 was an independent prognostic factor for survival with median survival times of 24 (R0) *versus* 12 months (R1/R2). For a few large series, including pathological stage I–IV NSCLC patients, incomplete resection was reported as a poor prognostic factor for survival in multivariate analysis. Involved resection margins were associated with an increased risk of death (hazard ratio 1.49; p<0.001) among 3,211 patients from a Norwegian registry [111]. In another surgical series of 836 patients, a hazard ratio of 8.2 (p<0.001) was observed in R1/R2 in comparison with R0 cases [112]. Doubling or tripling of the risk of death was observed in a series of 446 patients (p<0.01) [113].

The IASLC reported the largest recent studies, assessing the prognostic role of pathologic TNM in 9137 resected NSCLC. In multivariate analysis, pathological stage using the seventh version proposed by the IASLC was a significant prognostic factor for survival (p<0.0001) [114]. In large series or registry studies of more than 500 patients, pTNM [111, 115–117] and, when analysed separately, pT or pN [112, 118, 119], were found to be independently associated with survival. Lastly, pTNM, pT, or pN was found to be a significant predictor for survival in six randomised trials assessing the role of adjuvant chemotherapy after surgery and considering pathological stage in analyses of prognostic factors [120–125]. In these studies, the fifth version of the UICC and American Joint Committee on Cancer Staging system was most often used, although the fourth version was applied in three studies.

Recommendations

1) Complete resection is a prognostic factor for survival in resected NSCLC and can be used as an intermediate criterion for overall survival. Level of evidence: cohort and retrospective studies; quality of evidence: 3; grade of recommendation: Fs.

2) Pathological TNM is a prognostic factor for survival in resected NSCLC and can be used as an intermediate criterion for overall survival. Level of evidence: cohort studies; quality of evidence: 3; grade of recommendation: Fs.

Statement

The definition of complete resection proposed by the Complete Resection subcommittee of the IASLC is recommended.

QUESTION 7: CAN METABOLIC RESPONSE, ASSESSED BY ^{18}F-FLUORODEOXYGLUCOSE GATHERING ON POSITRON EMISSION TOMOGRAPHY (^{18}F-FDG-PET OR PET-CT), PREDICT THE EFFICACY OF CHEMOTHERAPY?

In a systematic review of the literature with a meta-analysis [126, 127], primary tumour SUV_{max} measured on ^{18}F-FDG-PET has been shown to have prognostic value in NSCLC. This observation needs to be confirmed by a multivariate analysis taking into account the known prognostic factors; nevertheless, it strongly suggests than PET may be more useful than only providing imaging.

PET has been proposed for the assessment of response to chemotherapy. Criteria were defined in 1999 by the EORTC PET

Study Group [128]. A complete metabolic response is complete resolution of ^{18}F-FDG uptake within the tumour volume so that it is indistinguishable from surrounding normal tissue. A partial metabolic response consists of the reduction of a minimum of 15% in tumour SUV after one cycle of chemotherapy, and greater than 25% after more than one treatment cycle. A reduction in the extent of the tumour uptake is not a requirement for partial metabolic response. A stable metabolic disease is an increase in tumour SUV <25% or a decrease <15% and no visible increase in the extent of tumour uptake (20% in the longest dimension). A progressive metabolic disease consists of an increase in tumour SUV >25% within the tumour region defined on the baseline scan, visible increase in the extent of tumour uptake (20% in the longest dimension), or appearance of new FDG uptake in metastatic lesions. For the experts, 25% was found to be a useful cut-off point, but there was a need for reproducibility analysis to determine the appropriate cut-off for statistical significance. 10 yrs later, that analysis has yet to be performed.

Data on lung cancer in this context are limited and heterogeneous. A few small studies have assessed the predictive effect of metabolic response for further survival. In a series of 57 patients with advanced NSCLC treated by chemotherapy, changes in SUV have been shown to have relatively similar adequacy to changes in tumour/muscle ratio and to be better than changes in net-influx constants [129]. In another series of 51 NSCLC patients (15 treated by induction chemotherapy and 31 by palliative chemotherapy), metabolic response assessed by the EORTC criteria was not associated with a significant difference in survival, while it became significant when patients were divided into two groups according to the median change in SUV [130]. In a group of 30 patients with stage IIIAN2 NSCLC treated by induction chemotherapy, the best cut-off in decrease of SUV_{max} to predict 5-yr survival was 60%; a decrease of 25% was not discriminatory [131]. In a systematic review of the literature about the prediction of histopathological response and further survival in stage III disease treated by induction treatment, DE GEUS-OEI et al. [132] showed the great heterogeneity of studies in terms of cut-off of SUV used and definition of pathologic response. In the series reported above, DOOMS et al. [131] defined a group with good prognosis by combining pathological (pN0 or pN2 with <10% cancer cells in mediastinal lymph nodes) and metabolic (>60% decrease of SUV max in the primary tumour) criteria. Finally, complete (but not partial) metabolic response has been associated with better survival in a series of 31 stage III NSCLC patients [133].

The predictive effect of initial SUV_{max} of the primary tumour for morphological response to chemotherapy has been the topic of one paper on advanced NSCLC (87 patients) [134]. SUV_{max} (dichotomised by the median) was the single significant predictor in univariate and multivariate analyses, but the patients with high SUV_{max} had shorter duration of response and there was no overall difference in survival between patients with high and low SUV_{max}.

The early assessment of the metabolic response after the first course of chemotherapy has been investigated in two small studies, suggesting some potential utility for predicting further survival [135, 136].

Studies of the prediction of morphological response by the metabolic response have been described in two reports. In the first one, the metabolic response was shown to have high predictive value (96%), meaning that, if PET scan does not show a response, it is very unlikely for one to be documented by morphological tests [129]. The positive predictive value is, however, not very good (71%). In the second study, performed on 89 patients, the correlation between metabolic response (either visual or based on SUV_{max}) and morphological response was poor and the SUV_{max} measured after chemotherapy did not predict further survival [73]. We also have to take into account potential methodological problems due to the lack of standardisation.

Recommendation

Metabolic response assessed by PET scan should not be used for the routine assessment of response to treatment in lung cancer patients in place of morphological criteria. Level of evidence: retrospective studies and case series; quality of evidence: 1; grade of recommendation: Aw.

Statements

The cut-off point of 25% to define response/progression, as proposed by the EORTC for metabolic response, needs validation assessment.

Metabolic response requires further investigation with strict methodology in terms of PET scan examination standardisation, morphological response assessment, and outcome definition.

QUESTION 8: WHAT IS THE ROLE OF TISSUE BIOLOGICAL MARKERS FOR THE EVALUATION OF OVERALL SURVIVAL?

Numerous biomarkers have been tested in lung cancer for prognostic purposes or for predicting response to chemotherapy or radiotherapy. Determination of the presence or absence of a tissue biomarker can be performed by various techniques (immunohistochemistry, PCR, fluorescence in situ hybridisation and high-throughput techniques, etc.) that assess cancer biology at different levels: protein expression, RNA or DNA abnormalities. The question is whether differential expression of tissue biomarkers during treatment, before and after chemotherapy for example, could reliably predict treatment efficacy and overall survival.

Many studies on tissue biomarkers in lung cancer have been published. They have looked at the prognostic role for survival of these biological markers, usually obtained at initial diagnosis, mainly in NSCLC surgical series. To a lesser extent, their predictive role for treatment sensitivity was studied. However, we found only one published study assessing the relationship between the modifications of tissue biomarkers during therapy and overall survival [137]. 54 patients with stage III NSCLC were treated by induction chemotherapy followed by concomitant chemoradiotherapy, and surgery if the tumour became resectable. There was no difference in the apoptotic indices before and after neoadjuvant treatment and no statistically significant impact on survival was observed.

One potential explanation of the lack of studies is related to the difficulties in easily obtaining adequate tissue samples in lung cancer patients. This problem is yet more pronounced when a good response is observed and no surgery is planned.

Recommendation

Tissue biological markers should not be used for evaluation of treatment efficacy and are not adequate intermediate criteria for overall survival in lung cancer patients. Level of evidence: case series; quality of evidence: 1; grade of recommendation: Aw.

Statements

The role of tissue biological markers in assessing overall survival in lung cancer needs further investigation with adequate methodology; that is, in terms of positivity definition, and standardisation in the evaluation methods and statistical methodology (multivariate analysis taking into account known prognostic factors).

QUESTION 9: WHAT IS THE ROLE OF CIRCULATING MARKERS (MOLECULES OR CELLS) FOR THE ASSESSMENT OF OVERALL SURVIVAL?

We aimed to determine if modification in the levels of circulating markers before and after therapeutic procedures in lung cancer patients can reliably predict overall survival. We selected the markers as described in the methodology section. We also specifically searched for biological markers known as potential prognostic factors in either NSCLC or SCLC: lactate dehydrogenase, alkaline phosphatases, white cell and neutrophil counts,

platelet count, haemoglobinaemia, natraemia, calcaemia, bilirubinaemia, cyfra 21-1, carcinoembryonic antigen (CEA), neurone-specific enolase (NSE), pro-gastrin releasing peptide (pro-GRP), and other cancer markers such as CA19-9 and CA-125. Publications were eligible if the correlation between the marker and overall survival was assessed.

Although the prognostic role for survival of the selected variables taken at initial diagnosis has been extensively studied, few studies, summarised in table 8, have been published that assess the prognostic role on survival of their expression before and after treatment [138–141, 143, 144, 146–153]. Criteria used by the authors to define response based on the levels of circulating markers were variable, allowing only indirect comparisons between studies. It must be pointed out that, of these studies, the majority was retrospective.

Post-therapy CEA normalisation or significant decrease seems to be related to better survival in early stage NSCLC treated by surgery [138, 140–142], in advanced NSCLC with chemotherapy [139, 143], and after salvage gefitinib in relapsing NSCLC [144]. Cyfra 21-1 decrease has been reported to be significantly associated with improved survival in two studies [139, 143] while no association was observed in a third [146]. For other factors, it could be suggested from small studies that decreases

TABLE 8 Studies assessing the relationship between modification of circulating markers levels after treatment and survival in lung cancer

Study	P/R	Marker	Patients n	Population	Therapy	Effect on survival	p-value	U/M
OKADA *et al.* [138]	R	CEA	1000	NSCLC cI	Surgery	↓ for high post-surgical level	<0.0001	M
NISMAN *et al.* [139]	P	CEA	45	Advanced NSCLC	CT	↑ if ↓ ≥35%	0.04	U
SAWABATA *et al.* [140]	R	CEA	19	ADC I	Surgery	↓ for high post-surgical level	0.006	U
SAWABATA *et al.* [141]	R	CEA	242	NSCLC IA	Surgery	↓ for high post-surgical level	<0.0001	M
SAWABATA *et al.* [142]	R	CEA	297	NSCLC cI	Surgery	↓ for high post-surgical level	0.002	M
BRÉCHOT *et al.* [143]	P	CEA	116	NSCLC I–IV	Various	↑ if ↓ ≥50%	0.006	U
CHIU *et al.* [144]	R	CEA	89	Relapsing NSCLC	Gefitinib	↑ if ↓ ≥50% at 4 weeks	0.03	U
SPIRIDONIDIS *et al.* [145]	R	CEA, CA19-9, CA-125	36	NSCLC I–IIIB	CT or CT-RT	↑ if ↓ if decrease	0.0002	U
NISMAN *et al.* [139]	P	Cyfra 21-1	45	Advanced NSCLC	CT	↑ if ↓ ≥35%	0.01	M
HAMZAOUI *et al.* [146]	?	Cyfra 21-1	63	NSCLC/SCLC III–IV	CT	↑ if ↓ ≥70%	0.44	U
BRÉCHOT *et al.* [143]	P	Cyfra 21-1	116	NSCLC I–IV	Various	↑ if ↓ ≥50%	0.0001	M
SUNAGA *et al.* [147]	R	Pro-GRP	29	SCLC I–IV	CT	↑ if ↓ ≥50%	0.001	M
OKUSAKA *et al.* [148]	R	Pro-GRP	18	SCLC in PR	CT	↑ if return to normal	<0.05	U
BRÉCHOT *et al.* [143]	P	NSE	116	NSCLC I–IV	Various	↑ if ↓ ≥50%	0.018	U
FIZAZI *et al.* [149]	R	NSE	135	SCLC LD/ED	CT-RT, CT	↑ if return to normal	0.02	M
BRÉCHOT *et al.* [143]	P	CA-125	116	NSCLC I–IV	Various	↑ if ↓ ≥50%	0.0006	U
CHIU *et al.* [144]	R	CA-125	89	Relapsing NSCLC	Gefitinib	No effect	0.12	U
CHIU *et al.* [144]	R	CA19-9	89	Relapsing NSCLC	Gefitinib	↑ if ↓ ≥25% at 8 weeks	<0.0001	U
GAUTHIER *et al.* [150]	R	Anaemia	242	NSCLC IB–II	Surgery + CT	No effect	0.06	U
LAURIE *et al.* [151]	R	Anaemia	652	SCLC LD	CT-RT	No effect	0.33	U
ISHIKAWA *et al.* [152]	P	CTC	74	Relapsing NSCLC	Gefitinib	↑ if ratio T0/T2w or T0/T4w <1.2	0.002 / 0.004	U
CHEN *et al.* [153]	P	CTC	67	NSCLC I–IIIB	CT-RT	Persistence of CTC	<0.001	M
YAMASHITA *et al.* [154]	P	CTC	103	NSCLC I–IIIA	Surgery	Persistence of CTC	NS	M

P: prospective study; R: retrospective study; U: results obtained in univariate analysis; M: results obtained in multivariate analysis; CEA: carcinoembryonic antigen; NSCLC: nonsmall cell lung cancer; CT: chemotherapy; ADC: adenocarcinoma; CT-RT: chemoradiotherapy; SCLC: small cell lung cancer; pro-GRP: pro-gastrin releasing peptide; PR: partial remission; NSE: neurone-specific enolase; LD: limited disease; ED: extensive disease; CTC: circulating tumour cells; NS: statistically nonsignificant.

in the following in terms of blood levels were predictive of better survival: pro-GRP in SCLC, CA19-9 in relapsing NSCLC, CA-125 in NSCLC, and NSE in NSCLC and SCLC [143, 144, 147–149]. Anaemia occurring during chemotherapy or chemoradiotherapy has not been demonstrated to have prognostic significance in two larger studies on NSCLC and SCLC [150, 151]. Lastly, the persistence of circulating tumour cells in blood was of prognostic significance in locoregional NSCLC treated by chemoradiotherapy and in relapsing NSCLC treated with gefitinib [152–154].

Recommendations

1) Some circulating markers (CEA, Cyfra 21-1, pro-GRP and, to a lesser extent, NSE, CA-125, and CA19-9), used as single criterion to assess overall survival, could be adequate intermediate criteria for survival in lung cancer patients. Level of evidence: retrospective studies; quality of evidence: 2; grade of recommendation: Fw.

2) The persistence of circulating tumour cells in NSCLC may have a prognostic impact on further survival. Level of evidence: cohort studies; quality of evidence: 1; grade of recommendation: Fw.

Statement

The suggested role of circulating markers in assessing overall survival in lung cancer needs further prospective investigation with adequate methodology (including the cut-off determination), that is, in terms of statistical methodology (multivariate analysis taking into account known prognostic factors).

CONCLUSIONS

Overall survival, or healing for curable disease, is the leading criterion of efficacy of a treatment in lung cancer patients. Intermediate criteria are potential or adequate surrogates for survival, despite some limitations: TTP, PFS, objective response, local chest control after radiotherapy, mediastinal and TNM downstaging in locally advanced NSCLC after induction therapy before surgery, complete resection and pathological TNM in resected NSCLC, and a few circulating markers (CEA, Cyfra 21-1, pro-GRP and, to a lesser extent, NSE, CA-125, and CA19-9). At the present time, some criteria cannot be used for predicting overall survival in lung cancer (and therefore certainly not as surrogates for overall survival): conventional criteria for radiotherapy response assessment of primary lung tumour, quality of life evolution under treatment, metabolic response assessment by FDG-PET scan, and tissue biological markers. The recommendations in this study highlight the need for well-designed prospective studies in many instances where intermediate criteria are of possible interest.

POTENTIAL LIMITATIONS AND PROBLEMS
Literature biases

First, we searched for prospective studies and meta-analyses looking, as the primary objective, at the association between intermediate criteria and overall survival. This approach was recently discussed by BUYSE [155] to demonstrate a possible association between a surrogate and a clinical end-point, requiring data from multiple randomised trials or meta-analyses. In most instances considered in these guidelines, this literature was lacking. Secondly, we searched for secondary end-points of prospective studies and retrospective series. Although we used multiple keywords for each topic and an extensive literature search system (Ovid), it is possible that some studies and series in which some of the selected criteria were actually reported as secondary end-points were not retrieved. However, the impact of this literature bias on the conclusions of these guidelines seems limited as the level of evidence of this type of study is relatively weak (low or very low grade of evidence according to the GRADE system). Furthermore, the inclusion of nonrandomised studies should induce biases in the interpretation of the literature results for assessing association between criteria like determination of objective response and survival. Another potential source of bias is related to the considered languages. We only took into account reports written in English, French, German and Dutch languages that were comprehensible by all of the authors. It must be underlined that most of the results came from clinical trials in which patients were strictly selected and do not fully represent the population treated in routine practice.

Validation studies

Although we found some statistical associations between intermediate criteria and survival in meta-analyses and small-sized randomised studies, validation studies are required before definite conclusions can be drawn in most instances. These studies need to be prospectively designed with the primary objective being the determination of the relationship between the considered surrogate and the true end-point. They have to consider the clinical value of the association when the effect of the intermediate criterion in predicting survival accounts for only a limited part of the variability of the survival ratio, as we observed with TTP [40, 41]. The potential surrogate may have a substantial noise component due to issues in defining the intermediate criterion or other factors that may affect the clinical outcome. Therefore, there are some issues concerning the application of a surrogate in situations other than those in which the surrogacy was asserted. These require knowledge about the relevant biological variables whereby the treatment or the considered populations may affect the outcome of primary interest.

Grades of recommendations

In order to grade the guidelines, the ELCWP has chosen the GRADE system. This internationally accepted grading system for recommendations has previously been used for lung cancer by the American College of Chest Physicians [156]. GRADE has certain advantages. It allows grading of recommendations based on the level of scientific evidence, which is further modulated by the quality of the literature (table 1). It also allows integration into the grade of the recommendations of some subjective variables, such as the balance between desirable and undesirable effects, and the values and preferences or the costs (resource allocation), by guideline writers, which may be of importance in routine practice but cannot always be derived from the literature.

Impact of supplementary treatment on overall survival

We selected studies assessing a possible relationship between a surrogate and overall survival. Preceding or subsequent therapeutics after the investigated treatment can impact on overall survival and, potentially, on the relationship with the intermediate criteria. Unfortunately, in light of the currently available data, it was not possible to avoid this potential bias in our literature interpretation.

PERSPECTIVES

We found that validation of intermediate criteria as surrogate end-points in lung cancer has not really been achieved; furthermore, such a validation may be dependent on the treatment category considered and the population of patients included in the trial. The development of new therapies leads us to consider the use of intermediate criteria to assess their effectiveness in order to achieve possible reductions in sample size, study duration or cost. A further set of intermediate outcomes based on data from gene expression or proteomic platforms will be proposed in the near future. In this context, the identification of a set of intermediate outcomes may be important, taking into account the fact that biological pathways could influence the beneficial or harmful effects of the treatment, influencing the final outcome.

To convincingly validate these early markers as surrogates, a strict methodology has to be developed. Some recommendations have already been proposed by BUYSE and co-workers [8, 155] on the use of meta-analyses for validation of clinical surrogates and biomarkers.

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