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2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up

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To complement the existing treatment guidelines for all tumour types, ESMO organises consensus conferences to focus on specific issues in each type of tumour. The 2nd ESMO Consensus Conference on Lung Cancer was held on 11–12 May 2013 in Lugano. A total of 35 experts met to address several questions on non-small-cell lung cancer (NSCLC) in each of four areas: pathology and molecular biomarkers, first-line/second and further lines in advanced disease, early-stage disease and locally advanced disease. For each question, recommendations were made including reference to the grade of recommendation and level of evidence. This consensus paper focuses on early-stage disease.

Key words: ESMO, consensus, lung cancer, non-small-cell lung cancer, early disease

background to the 2nd ESMO Consensus Conference on Lung Cancer, Lugano 2013

In 2009, ESMO decided to complement the ESMO Clinical Practice Guidelines (CPGs) with further recommendations from 'Consensus Conferences'. For lung cancer, the first meeting of this kind was held in Lugano in 2010, which resulted in the publication of two consensus manuscripts [1, 2].

The 2nd meeting, held in Lugano in May 2013, followed the same format as the 1st edition. Four working groups were appointed, each with 8–10 participants from several disciplines and led by a chair. A total of 35 experts were involved in this consensus process (see Panel Members listed in the Appendix). The four specific areas were as follows:

NSCLC pathology and molecular biomarkers,
First line, second line and further lines of treatment in advanced NSCLC,
Early-stage NSCLC (stages I–II),
Locally advanced NSCLC (stage III).

Before the conference, each working group identified a number of clinically relevant questions suitable for consensus discussion and provided the available literature. At the Conference, in parallel sessions, each group discussed and reached agreement on the questions previously chosen. Decisions were made using studies published in peer review journals. The consideration of abstracts was at the discretion of the groups. All relevant scientific literature, as identified by the experts, was considered. A systematic literature search was not carried out.

The recommendations from each group were then presented to the full panel of experts and discussed, and a general consensus was reached. The Infectious Diseases Society of America grading system was used to assign levels of evidence and grades of recommendation [3].

The consensus findings of the group on early-stage NSCLC—approved by the Consensus Conference panel of experts—is reported here. As there was no prior consensus manuscript in this domain available, the section on early-stage NSCLC of the latest CPG [4] was the working basis. Starting from there, 14 questions in nine domain sections were appointed for further discussion.

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†See appendix for Panel Members.

The bulleted recommendations at the end of this paper are based on the 2013 CPGs, complemented and/or refined by the consensus process at the Lugano 2013 meeting.

incidence/epidemiology

Question 1a: should experienced multidisciplinary thoracic cancer centres offer computed tomography (CT) screening outside of a clinical trial?

Question 1b: can CT screening for subclinical lung cancer be offered to individual patients asking for it?

None of the four prospective randomised, controlled trials (RCTs) of lung cancer screening, carried out in the late 1970s using combinations of chest X-ray and sputum cytology [5–8], showed a significant reduction in lung cancer mortality associated with screening.

However, on 4 November 2010, the National Cancer Institute announced the results of the National Lung cancer Screening Trial (NLST) which indicated that lung cancer mortality in specific high-risk groups could be significantly reduced by annual screening with low-dose computed tomography (LDCT). The results of the NLST trial documenting this reduction were published shortly thereafter [9].

Following these findings, LDCT lung cancer screening in selected populations was recommended for the first time by a scientific society [10]. In 2011, the International Association for the Study of Lung Cancer (IASLC) held a CT screening workshop which brought together experts in lung cancer disciplines from across the globe, to consider standards and quality control for CT screening. The workshop report [11] suggested, among other things, that before offering CT screening, quality standards must be developed, endorsed and embraced in organised and individualised settings, and that outcome reporting should be standardised. To reduce the risk of over-diagnosis and over-treatment, standardised protocols for image interpretation and nodule management should be developed, and positive cases should be discussed at multidisciplinary meetings.

To help ensure quality and efficacy control in a screening programme, the programme's clinical, radiological and oncological data should be archived in a database. The IASLC report also proposed surgical standards in the screening context, recommending that screening should only be carried out in centres with access to a full minimally invasive surgical programme; that the number of resections for benign disease should be low (<15%); and that for lung cancers <2 cm with pure ground-glass or part-solid aspect on CT, anatomical segmentectomy with frozen section analysis of N1 and N2 should be practiced.

The 2013 Lung Cancer Screening Guidelines published by the American Cancer Society (ACS) [12] restated the findings of a 2012 systematic review [13], which emphasised that adults requesting lung cancer screening should enter an organised screening programme at an institution with expertise in LDCT screening, and be given access to a multidisciplinary team skilled in the evaluation, diagnosis and treatment of abnormal lung lesions. If these criteria are not met, the risks of cancer screening were considered to be substantial. The review also recommended that physicians should initiate a thorough discussion of the benefits, limitations and risks of LDCT screening with those requesting it, should inform current smokers that they continue to be at risk of developing lung cancer and should encourage them to enter smoking cessation programmes.

Lung cancer risk models are being developed and tested for their ability to identify the best target population for lung cancer screening and also the best screening interval [14]. Until evidence from such models becomes available, the target population and screening interval should be those proposed by the NLST [9].

should experienced multidisciplinary thoracic cancer centres offer CT screening outside of a clinical trial?

- Recommendation: LDCT screening reduces lung cancer mortality [I, A] and can be carried out outside a clinical trial provided it is offered within a dedicated programme with quality control at a high-volume centre of thoracic oncology experienced in LDCT screening, where the multidisciplinary management of suspicious nodules is established. Individuals offered LDCT screening should also be referred to a smoking cessation programme.

can CT screening for subclinical lung cancer be offered to individual patients asking for it?

- Recommendation: LDCT screening should not be offered on an individual basis, but patients requesting screening should be referred to a dedicated programme as recommended above.

diagnosis

Question 2: should the malignancy calculation methods used in LDCT screening be used for the clinical assessment of pulmonary nodules?

Obtaining a definitive tissue diagnosis before treatment is desirable for patients presenting with early-stage NSCLC. However, this can be challenging for lesions that are inaccessible by bronchoscopy, as complications following a transthoracic needle biopsy are reported in up to 15% in population studies, especially in the elderly, smokers and those with chronic obstructive pulmonary disease (COPD) [15]. The pre-test risk of malignancy can be determined using algorithms which take into account the relevant medical history, smoking habits and radiologic characteristics of the lung nodule in question, in order to decide if additional diagnostic or therapeutic procedures are indicated [16]. All such algorithms have limitations, which are partly related to the underlying populations from which they were derived. More recently, studies evaluating LDCT screening for lung cancer detection have shown that incorporating the nodule volume doubling time (VDT) [17] and/or fluorodeoxyglucose–positron emission tomography (FDG–PET) uptake [18, 19] can also reduce the number of benign lesions excised.

However, VDT measurements are not routinely carried out outside clinical trials. Differences may exist between the CT-screened populations and others presenting with lung cancer, hence the sole use of existing algorithms, VDT or FDG–PET in isolation, for the purpose establishing a diagnosis of

early-stage NSCLC cannot be supported at the present time. Instead, it is recommended that indeterminate solitary pulmonary nodules (SPNs) should be assessed by expert multidisciplinary tumour boards, who will consider all relevant patient, epidemiological and procedure-related factors, and apply the existing guidelines for the assessment of lung nodules, such as the ones of the Fleischner Society [20], recently expanded to subsolid nodules [21]. Expert multidisciplinary tumour boards may be best placed to assess the likelihood of benign disease in their own populations including, where available, algorithms that have been validated for the population in question [22].

should the malignancy calculation methods used in LDCT screening be used for the clinical assessment of pulmonary nodules?

- Recommendation: No, standard existing guidelines for assessment of SPN must be applied [V, C].

Question 3a: is tissue-based diagnosis needed before surgical intervention?

In principle, tissue-based diagnosis is crucial to any radical treatment of lung cancer, and any reasonable attempt at pre-surgical (i.e. pre-resectional) tissue diagnosis is to be pursued [16, 23].

In the event of a nodule with increased likelihood of malignancy as per current diagnostic algorithms and/or unsuccessful or too hazardous preoperative diagnostic procedures [15], experienced multidisciplinary groups can advise to proceed to surgery according to the principles of minimal invasiveness. The location, size and solid component of the nodule will have to be considered when estimating the likelihood of malignancy and the most favourable approach for the surgical procedure.

is tissue-based diagnosis needed before surgical intervention?

- Recommendation: A pre-surgical pathological diagnosis is recommended. In some patients with clinical stage I/II lesions this is not feasible, and a high likelihood of malignancy based on assessment of clinical and imaging findings in an experienced multidisciplinary group may be sufficient [III, B].

Question 3b: is tissue-based diagnosis needed before stereotactic ablative radiotherapy?

A significant proportion of patients with early-stage NSCLC do not receive a surgical therapy, mainly due to reasons of co-morbidity and age [24]. Population studies show that patients with early-stage NSCLC are less likely to have a pathologically confirmed diagnosis compared with those with more advanced stage disease, and that both the elderly and those with co-morbidities were less likely to have a pathological diagnosis of lung cancer [25]. Obtaining a tissue diagnosis in unfit or borderline operable patients can be more challenging than doing so in those who are fit to undergo surgery. For fit patients, the American College of Chest Physicians (ACCP) guidelines have recommended surgery without a preoperative diagnosis, when the likelihood of malignancy exceeds 65% [26].

A number of arguments have been used to support the use of stereotactic ablative radiotherapy (SABR) in inoperable patients without tissue confirmation of their tumour, but following assessment by an expert multidisciplinary team. Population data also support the view that failure to establish a pathological diagnosis reflects extensive comorbidity, as such patients have poorer survival outcomes following SABR [24]. Reassuringly, in populations where a final diagnosis of benign disease is made in only 6% or less of resected tumours [27], the patterns of local control and disease recurrence were similar in SABR patients cohorts either with or without a preoperative diagnosis [28]. Although the ACCP guidelines have recommended a 65% pre-test likelihood of malignancy before proceeding to 'non-surgical biopsy and/or surgical resection unless specifically contraindicated', an 85% likelihood of malignancy has been suggested before proceeding with SABR without pathological diagnosis [29]. The latter is consistent with the recommendations of the IASLC that in centres performing CT screening, a final pathological diagnosis of benign disease should not exceed 15% [11].

is tissue-based diagnosis needed before stereotactic ablative radiotherapy?

- Recommendation: An attempt should generally be made to obtain a pathological diagnosis before SABR. In the event that tissue sampling is considered excessively hazardous, there should be at least an 85% chance of malignancy, based upon accepted criteria [III, A].

staging and risk assessment

Question 4a: what is high risk for surgery? what is the role of validated risk models?

Risk is a continuous outcome usually expressed as a probability from 0% to 100%; therefore, what constitutes 'high' is arbitrary. In a clinical setting, patients are the most appropriate persons to define what is 'high' as relative value depends on personal (usually unexplained or unquantifiable) beliefs. With regard to a clinical trial or guidelines the value used to define 'high' should simply be stated.

Risk needs to relate to meaningful specific outcomes. While a simple principle, respiratory literature (especially on exercise testing) is littered with studies that use combined outcomes with several end points (e.g. death, pneumonia and arrhythmia), which complicates interpretation [30]. The CALGB 9238 trial was a prospective multicentre study to validate the use of primary exercise VO_2 measurement for the prediction of surgical risk [31]. Patients with a peak exercise VO_2 <65% of predicted or <16 ml/kg/min were indeed more likely to suffer complications ($P = 0.0001$), and poor outcome (respiratory failure or death, $P = 0.0356$). The author's conclusion was that their data provided a multicentre validation for the use of exercise VO_2 for preoperative assessment of lung cancer patients, but that an aggressive approach may be warranted in some patients, as 58 patients who did not meet the algorithm for operability were resected. They had a 2% mortality rate and a survival twice as long compared with non-surgical patients.

So, while cardiopulmonary exercise testing is used to screen for patients 'at risk', additional discussion in a multidisciplinary tumour board and with the patient is needed.

The risk of in-hospital death can, for example, be estimated using a validated scoring method such as the Thoracoscore [32]. Each risk model should indeed be validated, an example is the Goldman cardiac risk index recommended by the American College of Cardiology/American Heart Association (ACC/AHA), that was recalibrated for lung resection cohorts [33], and validated in the latter setting [34].

Table 1. Recalibrated thoracic revised cardiac risk index (adapted from [33] with permission from Elsevier)

Weighted factors	
Ischaemic heart disease	1.5 points
History of cerebrovascular disease	1.5 points
Serum creatinine >2 mg/dl	1 point
Pneumonectomy planned	1.5 points
Class groupings	
A	0 points
B	1–1.5 points
C	2–2.5 points
D	>2.5 points

Definitions: Ischaemic heart disease: history of myocardial infarction, history of positive exercise test, current complaint of chest pain (myocardial ischaemia), nitrate therapy, ECG with pathologic Q waves; Cerebrovascular disease: transient ischaemic attack, stroke.

what is high risk for surgery? what is the role of validated risk models?

- Recommendation: Validated risk-specific models can be used to estimate postoperative mortality and morbidity [III, B].

Question 4b: what is optimal functional cardiopulmonary evaluation before resection?

When discussing surgical resection for lung cancer, not only technical resectability should be considered, but also the functional operability, in particular cardiac and pulmonary.

To evaluate cardiac risk, use of the revised cardiac risk index (RCRI) is recommended—this has recently been modified into the so-called recalibrated thoracic RCRI (Table 1, Figure 1) [33]. To calculate this index, four weighted factors are used, and patients are grouped into four classes with increasing risk. This index has recently been externally validated [34].

A collaborative task force of the European Respiratory Society (ERS) and European Society of Thoracic Surgeons (ESTS) established clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemoradiotherapy) [35]. In case FEV1 or DLCO are <80%, exercise testing and split lung function

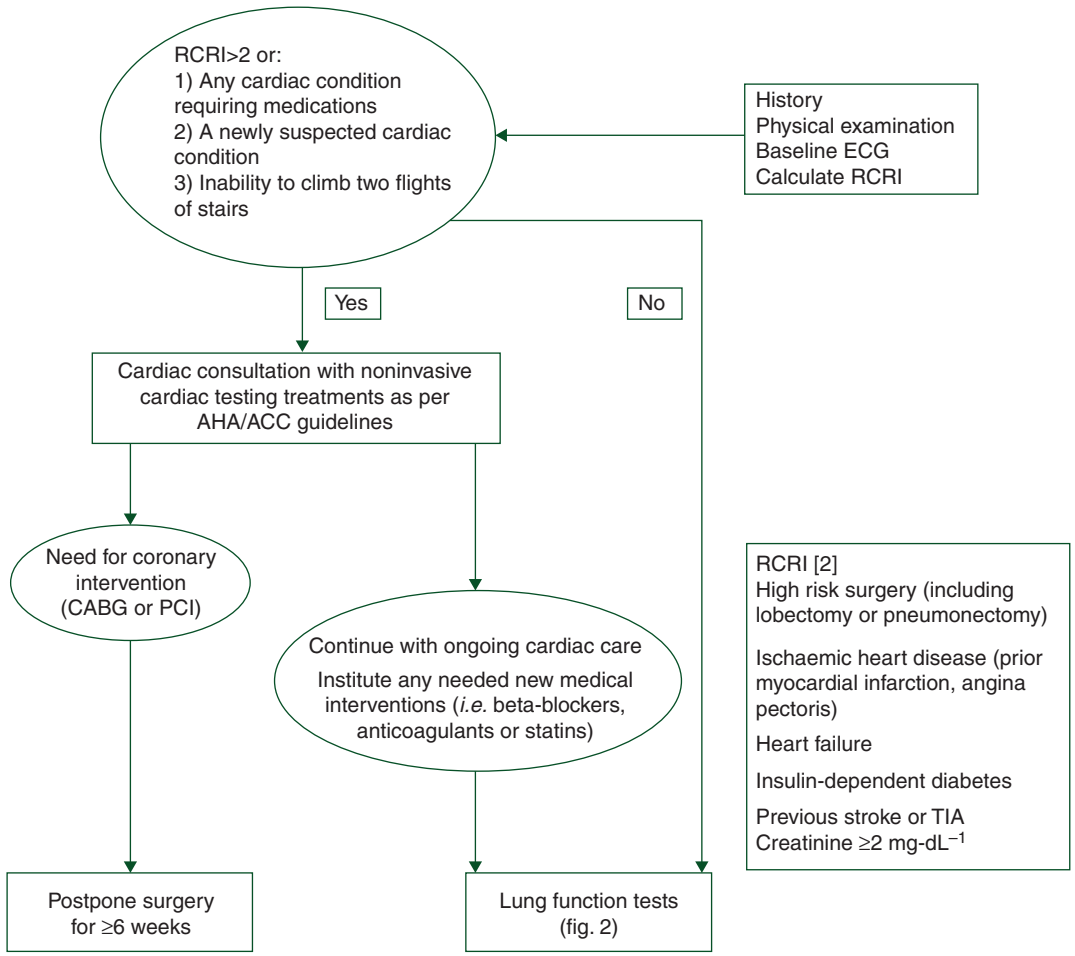

Figure 1. Preoperative cardiac evaluation (reprint from [35], with permission from the European Respiratory Society).

are recommended to determine the maximum extent of resection (Figure 2). For sub-lobar resection (wide wedge resection or anatomical segmentectomy), no precise functional criteria are available. A volume reduction effect may also be taken into account, especially in patients with heterogeneous emphysema [36, 37].

what is optimal functional cardiopulmonary evaluation before resection?

- Recommendations: Before considering surgical resection precise assessment of cardiac and pulmonary function is necessary to estimate risk of operative morbidity [III, A]. For cardiac assessment, use of the recalibrated thoracic RCRI is recommended [III, A]. For functional respiratory assessment FEV1 and DLCO are required; in case either one is <80%, use of exercise testing and split lung function are recommended. In these patients, VO_{2max} can be used to measure exercise capacity and predict postoperative complications [III, A].

treatment of early stages I and II

Question 5a: For which patients is limited (sub-lobar) resection an acceptable choice?

Although lobectomy is still considered standard therapy for early-stage T1N0 lung cancer, anatomical segmentectomy or wide wedge resection are currently reconsidered for small, non-invasive or minimally invasive lesions, especially those with ground-glass opacity (GGO) characteristics [38–40]. Two recent reviews [41, 42] and one meta-analysis [43] concluded that well selected use of sub-lobar resection, especially for pure adenocarcinoma *in situ* ≤2 cm, yielded similar survival and recurrence rates as lobectomy. Definitive recommendations can only be made when the results of large randomised trials become available.

In some specific subsets of early-stage adenocarcinoma, systematic lymph node dissection may not always be required [44]. Recent analysis of the Italian COSMOS screening study showed that systematic nodal dissection can be avoided in early-stage, clinically N0 lung cancer when the maximum standardised uptake value on PET scanning is <2.0 and the pathological nodule size is ≤10 mm [45].

A lung volume reduction effect may be observed in patients with heterogeneous emphysema operated for a concurrent lung cancer located in a diseased part of the lung. A 'COPD index' has been described for better patient selection in this situation [46]. Several therapeutic surgical options are available and a specific algorithm has been developed (Figure 3) [36, 37].

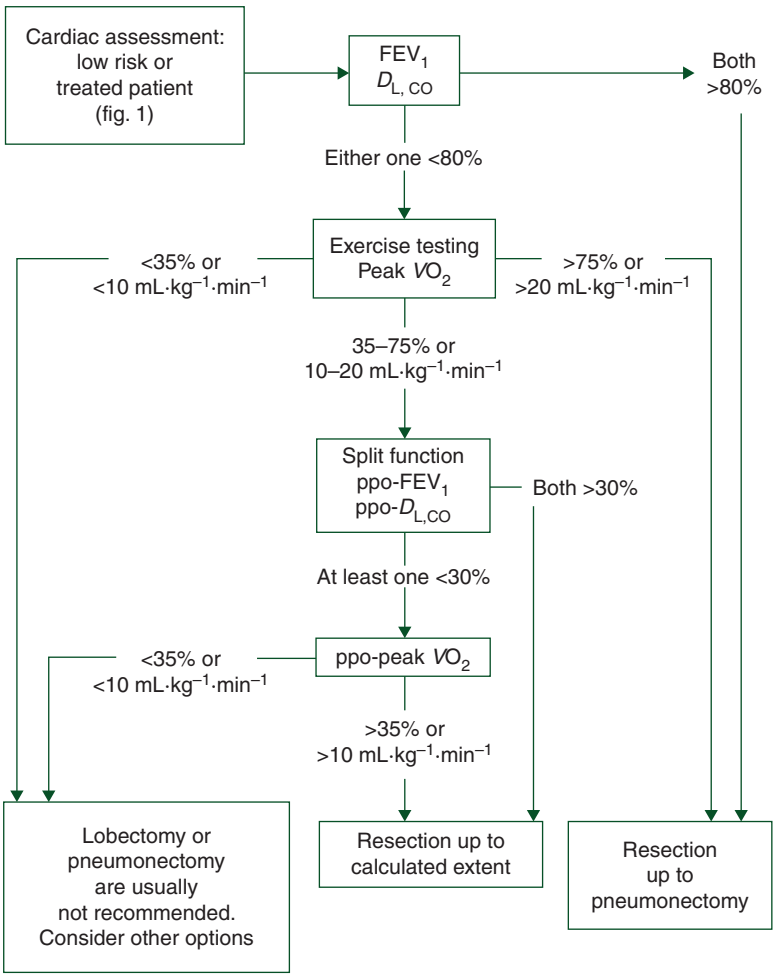

Figure 2. Preoperative respiratory evaluation (reprint from [35], with permission from the European Respiratory Society).

for which patients is limited (sub-lobar) resection an acceptable choice?

- Recommendations: Sub-lobar resection is generally considered acceptable for pure GGO lesions or adenocarcinoma *in situ* or with minimal invasion [III, B]. Lobectomy is still considered the standard surgical treatment of tumours ≤2 cm in size that have a solid appearance on CT [II, B]. In patients with emphysema and limited pulmonary function, a lung volume reduction effect may be observed by resecting the lung cancer and emphysematous lung parts [III, B].

Question 5b: When is open versus video-assisted thoracic surgery (VATS) versus robotic surgery is preferred for early-stage NSCLC?

A summary of the literature up to 2012 has been reported in a meta-analysis of 21 comparative studies, two randomized and 19 non-randomized [47]. The results suggest that either form of access yielded similar results with no differences in in-hospital pulmonary outcomes or mortality. The authors highlighted reduced systemic recurrence (i.e. improved disease-free survival, DFS) in patients who underwent minimal access (video-(VATS)) lobectomy. However, since the majority of studies were non-randomised, improved DFS may be due to case selection bias. An update published in 2012 reported lower in-hospital morbidity and shorter length of hospital stay in patients who underwent VATS lobectomy [48].

There are no randomised trials comparing robotic surgery with either open or VATS surgery. A number of case series have been reporting good outcomes with robotic surgery [49–51]. One study reported similar case–controlled outcomes with robotic and VATS lobectomy [52].

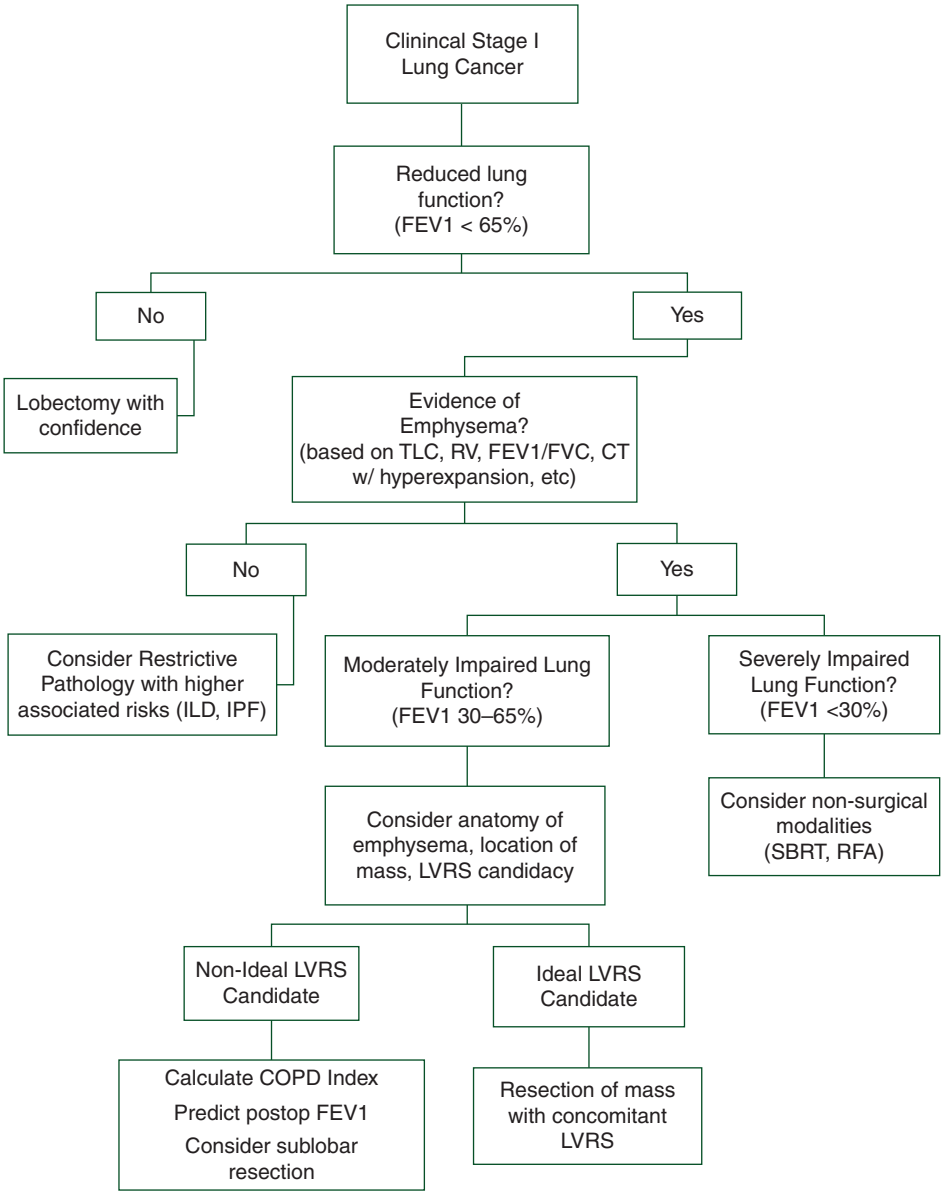

Figure 3. Algorithm for patients with clinical stage I lung cancer and limited pulmonary function due to emphysema (reprinted from [37], with permission from Elsevier).

In summary, high-level randomised evidence comparing VATS to open surgery is sparse. There is no high-quality evidence reporting comparative outcomes between robotic versus either VATS or open surgery. The majority of case–control studies conducted to date have been small with limited external validity (the vast majority were single institution).

when is open versus VATS versus robotic surgery preferred for early-stage NSCLC?

- Recommendation: Either open or VATS access can be utilised as appropriate to the expertise of the surgeon [II, A].

Question 6: what is the optimal management of multifocal lung cancer?

Surgical data regarding the management of multifocal lung cancer mainly come from retrospective analyses. Bearing this in mind, current evidence supports surgery as up-front approach for patients with synchronous nodules in multiple lobes, either ipsilateral or contralateral. Recent studies of patients undergoing resection of multiple nodules—two synchronous tumours in most cases—and without evidence of lymph node involvement have demonstrated 5-year survival rates >50% [53–55]. However, 5-year survival decreases with the extent of lymph-nodal involvement [55, 56], and patients with multifocal lung cancer and documented N2 disease are generally excluded from complete resection because of poor prognosis following surgery [55–57]. Besides nodal involvement, in a recent pooled analysis based on individual patient data of 467 individuals undergoing resection of multifocal lung cancer in multiple lobes, the following poor prognostic factors for survival have been identified: advanced age, male gender and unilateral tumour location [55]. The fact that bilateral cancers seem to have a more favourable prognosis may simply reflect the fact that these patients are more likely to be those with true multiple cancers, and benefitting most from surgery because of non-metastatic disease. When judging on surgical resectability the aforementioned prognostic factors should be taken into account.

No consensus exists on the optimal type of surgery for patients with multifocal lung cancer, although lobectomy for the main tumour plus sub-lobar resection of the smaller nodule(s) seems a reasonable approach.

If surgery is not feasible, other approaches such as local ablative (SABR) and/or systemic therapy should be considered, though scientific data on this are lacking. Therefore, especially in the latter case scenario, all treatment decisions should be taken within the context of a multidisciplinary tumour board.

what is the optimal management of multifocal lung cancer?

- Recommendation: Complete resection is recommended whenever possible. If not, additional alternative approaches such as local ablative (e.g. SABR) and/or systemic treatment should be discussed within the context of a multidisciplinary tumour board [III, B].

Question 7: should factors, other than stage, guide the choice of adjuvant therapy?

Adjuvant chemotherapy is recommended in stage II and III and should be cisplatin based [58]. The most frequently studied regimen is cisplatin–vinorelbine [59, 60].

The indication should be further discussed in a multidisciplinary tumour board and should consider host factors such as age, comorbidities, performance status (PS), as well as time since surgery and pathology report [V, A].

According to data reported from clinical trials, age *per se* is not a factor of selection [II, A] [61, 62].

Patients with severe comorbidity were excluded from clinical trials. In the Ontario Cancer Registry, a detrimental effect from adjuvant chemotherapy was seen in patients with greater co-morbidity (Charlson score 3+) but still fit for chemotherapy [III, C] [63].

Evidence of benefit from adjuvant chemotherapy has been established in patients PS 0, 1 rarely PS 2 [I, A].

The precise interval limits to start adjuvant chemotherapy have not been properly addressed in clinical trials. Some trials (IALT) restricted inclusion to patients resected within 60 days before randomisation. The Ontario Registry of Canada looked more carefully at timing and concluded that no difference was observed between 2 cohorts (0–10 versus 11–16 weeks) [III, C] [63].

In case of R1 resection (positive resection margin, chest wall), postoperative radiotherapy should be considered [III, B]. Even if such patients were not included in the RCTs, adjuvant chemotherapy is advised for R1 resection regardless of nodal status [V, A]. In case chemotherapy and radiotherapy are both administered, radiotherapy should be administered after chemotherapy [V, C].

Adding chemotherapy after radiotherapy for patients with stage II-N1 disease may be considered [V, C]. Although this was not properly assessed in clinical studies, there may be a similar benefit as for resected patients with stage II-N1 disease.

should factors, other than stage, guide the choice of adjuvant therapy?

- Recommendation: Pre-existing comorbidity, performance status and time since surgery should be taken into account in this decision taken in a multidisciplinary tumour board [V, A].
- In the current state of knowledge, the choice of adjuvant therapy should not be guided by molecular analyses such as, e.g. ERCC1 or mutation testing [IV, B].

Question 8: what are the indications for salvage surgery after SABR?

The outcome of SABR has been extensively documented in the literature [64]. Conversely, salvage surgery after SABR has been reported sporadically [65, 66]. In a recent Japanese series, post-SABR occurrence local failure or new primary lung was common (~40% after 3 years), and about half of these patients had salvage therapy [67]. The current—very limited—experience seems to support the feasibility of surgery after SABR [68]. In one series, however, up to 25% of the patients subjected to SABR initially refused surgery [69].

In some cases, surgery after SABR is carried out for complications related to SABR [70]. Acute complications of SABR, such as skin irritation, fatigue or cough occur in in 5%–40% of the patients and usually are transient [71]. Less common are late

complications such as radiation pneumonitis, chest wall pain or rib fracture, haemoptysis or bronchial stenosis or necrosis. Therefore, along with pre-existing comorbidities, chest wall morbidity and pulmonary toxicity after SABR need to be carefully factored into the decision-making process for secondary surgery [69, 70]. Irrespective of whether post-SABR surgery is done in an elective or in an emergency setting, histological diagnosis of lung cancer will be crucial for subsequent treatment.

what are the indications for salvage surgery after SABR?

- Recommendation: Salvage surgery, if feasible, may be offered to patients having complications after SABR [V, B]. Salvage surgery may be offered, if feasible, using the same indications as for primary surgery in progressive disease after SABR, albeit surgery in these patients may be more difficult due to higher operative risk [V, B].

follow-up

Question 9a: what is the optimal follow-up after surgery for early-stage NSCLC?

The incidence of lung cancer at primary screening of high-risk patients with LDCT is as low as 1% per patient per year, but this approach has been proven to reduce lung cancer deaths [9]. A significant proportion (20%–40%) of patients who underwent a complete resection for pathological stage IA–IIB NSCLC develop a locoregional or distant recurrence [59, 72]. These patients have a constant hazard rate for disease recurrence of 6%–7% per patient per year during the first 4 years, diminishing to 2% per patient per year thereafter [72]. In addition, they have a smooth increase of the hazard rate for second primary cancer from 1% to 3% per patient per year during the first 3 years, which does not diminish over time [73, 74].

Event dynamics studied in 1506 resected NSCLC patients demonstrated distinct recurrence peaks occurring at around 9 months, and at the end of the second and fourth year [74]. Based on these results, a surveillance strategy can be recommended for patients who underwent a curative resection for stage I–II NSCLC, despite the absence of a well-designed randomised, controlled trial addressing the effect on survival outcomes with this strategy.

The ESMO 2013 CPGs recommended follow-up visits every 3–6 months during 2–3 years, less often (e.g. annually) thereafter, with history and physical examination, chest X-ray and annual CT as appropriate tools [III, B]. Based on the above-mentioned data, surveillance every 6 months for 2–3 years with a contrast-enhanced spiral CT at 12 and 24 months, and thereafter an annual visit including chest CT in order to detect second primary tumours can be advised.

Despite several reports on a better sensitivity of PET-CT to detect disease recurrence in asymptomatic patients, compared with spiral chest CT scan alone, this is not recommended because no survival benefit has been demonstrated [II, D]. PET-CT can be helpful for the work-up of a suspected lung cancer lesion detected at CT surveillance [75].

what is the optimal follow-up after surgery for early-stage NSCLC?

- Recommendation: Surveillance every 6 months for 2–3 years with a visit including history, physical examination and—preferably contrast enhanced—spiral chest CT at 12 and 24 months is recommended, and thereafter an annual visit including history, physical examination and chest CT in order to detect second primary tumours [III, B]. Follow-up PET-CT is not recommended [II, D].

Question 9b: what is the optimal follow-up after SABR for early-stage NSCLC?

Considering that SABR is still a relatively new technique in Europe, close follow-up after treatment is important. The frequency of the follow-up visits and imaging should be tailored to the individual centre according to experience and also to the individual patient, taking into account suitability for salvage treatment.

The incidence of early and late radiation-induced lung changes on chest CT ranges from 54%–79% to 80%–100%, respectively [76]. The late changes can mimic the appearance of recurrent disease, but only a small proportion of patients will have local recurrence confirmed by biopsy or further imaging [77, 78].

The clinical utility of surveillance with FDG–PET-CT after SABR at pre-defined time points has not been clearly defined [76, 77]. PET-CT is generally carried out when recurrence after SABR is suspected based on serial spiral chest CT. However, PET should be interpreted with caution as moderate hypermetabolic activity may persist for up to 2 years following treatment without definite evidence of recurrence [79]. Optimal SUV max thresholds that correlate with a high risk of recurrence are still to be defined, as evidence is very limited, due to the low incidence of local recurrences in the available literature. A growing body of evidence, mainly from retrospective studies, suggests that SUV max above 5 at 6 months or more from SABR is associated with a high risk of local recurrence [76, 80–82]. However, due to false-positive findings on PET, patients suitable for salvage treatment should undergo a biopsy.

what is the optimal follow-up after SABR for early-stage NSCLC?

- Recommendations: In centres where SABR was recently implemented, we recommend follow-up of patients as per ESMO CPG 2013 plus 6 monthly CT scans for 3 years to benchmark treatment-related acute/late side-effects and local control against the available literature [III, B]. For individual patients, follow-up as per ESMO CPG 2013 and 6 monthly CT for 3 years are recommended for patients who are suitable for salvage treatment (e.g. surgery, local ablative therapy) [III, B]. The frequency of the follow-up visits can be tailored to the individual patient for those not suitable for salvage treatment [V, B]. The clinical utility of surveillance with FDG–PET during follow-up after SABR at pre-defined time points has not been clearly defined and is not recommended [III, D]. The selective use of FDG–PET is recommended when recurrence after SABR is suspected based on serial spiral chest CT [III, B]. Due to a high number of false-positive findings on FDG–PET, patients suitable for salvage therapy should undergo a biopsy, whenever possible [III, B].

Table 2. Summary of recommendations

Incidence/Epidemiology

- Screening with low-dose CT reduces lung cancer-related mortality [I, A]. It is not yet ready for large-scale implementation, because of unanswered questions regarding definition of at-risk population, timing, interval and method of CT (especially 2D versus 3D evaluation), how to handle (false-) positive findings and especially cost-effectiveness in relation to smoking cessation.
- LDCT screening can be carried out outside a clinical trial provided it is offered within a dedicated programme with quality control, in a centre with experience in CT screening, a large volume of thoracic oncology activity and multidisciplinary management of suspicious findings [I, B]. Candidates are current or former heavy smokers (≥30 pack-years or ≤15 years since smoking cessation) aged 55–74 years, who are well informed about potential benefit and risks. Individuals offered LDCT screening should be referred to a smoking cessation programme.
- LDCT screening should not be offered on an individual basis, but patients requesting screening should be referred to a dedicated programme as recommended above [V, B].
- Other screening methods, such as chest X-ray, sputum analysis or biomarkers are not recommended for clinical use [I, C].

Diagnosis

- Bronchoscopy is the recommended test to obtain a pathological diagnosis of centrally located tumours [III, A].
- The diagnostic approach to non-calcified pulmonary nodules should be based on existing standard guidelines [III, A]. Likelihood of malignancy calculation methods used in CT screening studies should not yet be used for the clinical assessment of pulmonary nodules [V, C].
- A pre-treatment pathological diagnosis is recommended. In some patients with clinical stage I/II lesions, this is not feasible, and a high likelihood of malignancy based on assessment of clinical and imaging findings in an experienced multidisciplinary group may be sufficient [III, B].
- A pre-treatment pathological diagnosis is strongly recommended for all patients before SABR, unless a multidisciplinary tumour board is of the opinion that the risk-benefit ratio of the procedure is unacceptable [III, B].
- An attempt should generally be made to obtain a pathological diagnosis before SABR. In the event that tissue sampling is considered excessively hazardous, there should be at least an 85% chance of malignancy, based upon accepted criteria [IIIA].

Staging and risk assessment

- In non-metastatic NSCLC, detailed locoregional staging according to the 7th TNM staging system [83] and cardiopulmonary fitness of the patient determine the choice of treatment [III, A].
- For patients with a non-centrally located resectable tumour and absence of nodal metastasis on both CT and PET images, surgical resection is recommended [I, A].
- For patients with suspect mediastinal lymph node metastasis on CT or PET images (unless bulky) pathological confirmation of nodal disease is recommended [I, A].
- The preferred first technique for pathological confirmation of suspect nodes is needle aspiration under endobronchial ultrasound and/or endoscopic ultrasound guidance. Mediastinoscopy is the test with the highest negative predictive value to rule out mediastinal lymph node disease [I, A].
- The risk of postoperative morbidity and mortality can be estimated using validated risk-specific models [III, B].
- Before considering surgical resection, precise assessment of cardiac and pulmonary function is necessary to estimate risk of operative morbidity [III, A].
- For cardiac assessment, use of the recalibrated thoracic revised cardiac risk index (RCRI) is recommended [III, A].
- Formal lung function testing should be undertaken to estimate postoperative lung function. For patients with FEV1 and DLCO >80% in their pulmonary function tests and no other major comorbidities, surgical resection is recommended [III, A]. For others, exercise testing and split lung function are recommended. In these patients, VO_{2max} can be used to measure exercise capacity and predict postoperative complications [III, A].
- Comorbidities should be evaluated and optimised before surgery [III, A].

Treatment of early stages I and II

- Surgery should be offered to patients with stage I and II NSCLC who are willing to accept procedure-related risks [III, A].
- Anatomical resection (lobectomy) is preferred over lesser resections such as wedge or segment resection [I, A].
- Sub-lobar resection is generally considered acceptable for pure GGO lesions or adenocarcinomas *in situ* or with minimal invasion [III, B]. Lobectomy is still considered the standard surgical treatment of tumours ≤2 cm in size that have a solid appearance on CT [II, B].
- In patients with emphysema and limited pulmonary function, a lung volume reduction effect may be observed by resecting the lung cancer and emphysematous lung parts [III, B].
- Lymph node dissection should conform to IASLC specifications for staging [III, A].
- Either open thoracotomy or VATS access can be utilised as appropriate to the expertise of the surgeon [III, A].
- For patients with multifocal lung cancer, complete resection is recommended whenever possible. If not, additional alternative approaches such as local ablative (e.g. SABR) and/or systemic treatment should be discussed within the context of a multidisciplinary tumour board [III, B].
- Adjuvant chemotherapy should be offered to patients with resected stage II and III NSCLC [I, A] and can be considered in patients with resected stage IB disease and a primary tumour >4 cm [II, B]. Pre-existing comorbidity, time from surgery and postoperative recovery need to be taken into account in this decision taken in a multidisciplinary tumour board [V, A].
- For adjuvant chemotherapy, a two-drug combination with cisplatin is preferable [I, A]. In randomised studies, the attempted cumulative cisplatin dose was up to 300 mg/m^2, delivered in three to four cycles. The most frequently studied regimen is cisplatin–vinorelbine.
- In the current state of knowledge, the choice of adjuvant therapy should not be guided by molecular analyses such as, e.g. ERCC1 or mutation testing [IV, B].

Continued

Table 2. *Continued*

- In the current state of knowledge, targeted agents should not be used in the adjuvant setting [II, A].
- In view of the equivalence of neo-adjuvant and adjuvant chemotherapy for overall survival, the consistent results and broad evidence base support adjuvant chemotherapy as the timing of choice [I, A].
- The non-surgical treatment of choice for stage I NSCLC is stereotactic ablative radiotherapy (SABR). The dose should be to a biologically equivalent tumour dose of ≥100 Gy, prescribed to the encompassing isodose [III, A].
- SABR for early-stage peripheral lung tumours is associated with low toxicity in patients with COPD and the elderly [III, A].
- Salvage surgery, if feasible, may be offered to patients having complications post-SABR [V, B].
- Salvage surgery, if feasible, may be offered, using the same indications as for primary surgery in progressive disease after SABR, but surgery may be more difficult with higher operative risk [V, B].
- For medically inoperable patients with tumours with a size >5 cm and/or central location, radical radiotherapy using more conventional or accelerated schedules is recommended [III, A].
- Postoperative radiotherapy in completely resected early-stage NSCLC is not recommended [I, A].
- In case of R1 resection (positive resection margin, chest wall), postoperative radiotherapy should be considered [IV, B].
- Even if such patients were not included in RCTs, adjuvant chemotherapy should be given to R1 resection regardless of nodal status [V, A].
- In case chemotherapy and radiotherapy are administered, radiotherapy should be administered after chemotherapy [V, C].

Follow-up

- NSCLC patients treated with radical intent should be followed for treatment-related complications, detection of treatable relapse or occurrence of second primary lung cancer [III, A].
- Surveillance every 6 months for 2–3 years with a visit including history, physical examination and—preferably contrast enhanced—spiral chest CT at 12 and 24 months is recommended, and thereafter an annual visit including history, physical examination and chest CT in order to detect second primary tumours [III, B].
- Follow-up PET-CT is not recommended [II, D].
- In centres where SABR was recently implemented, we recommend follow-up of patients as per ESMO CPG 2013 plus 6 monthly CT scans for 3 years to benchmark treatment-related acute/late side-effects and local control against the available literature [III, B].
- For individual patients, follow-up as per ESMO CPG 2013 and 6 monthly CT for 3 years are recommended for patients who are suitable for salvage treatment (e.g. surgery, local ablative therapy) [III, B]. The frequency of the follow-up visits can be tailored to the individual patient for those not suitable for salvage treatment [V, B].
- The clinical utility of surveillance with FDG–PET during FU after SABR at pre-defined time points has not been clearly defined and is not recommended [III, D].
- The selective use of FDG–PET is recommended when recurrence after SABR is suspected based on serial spiral chest CT [III, B].
- Due to a high number of false-positive findings on PET, patients suitable for salvage therapy should undergo a biopsy, whenever possible [III, B].
- NSCLC patients should be offered smoking cessation, as this leads to superior treatment outcomes. Combining behaviour techniques with pharmacotherapy is the preferred approach [I, A].

Table 3. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,…), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]From [3] with permission from the Infectious Diseases Society of America.

note

A summary of recommendations is provided in Table 2. Levels of evidence and grades of recommendation have been applied using the system shown in Table 3. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

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conflict of interest

RS has reported consultancy/honoraria: Abbott, Amgen, Astellas, Boehringer Ingelheim, Daiichi-Sankyo, GlaxoSmithKline, Genentech, Eli Lilly, Roche. EF has reported Consultancy/honoraria: Lilly, GlaxoSmithKline, Pfizer, Roche, Boehringer Ingelheim. SP has reported Consultancy/honoraria: Roche, Eli Lilly, AstraZeneca, Pfizer, Boehringer Ingelheim, Bristol-Myers Squibb, Merck Serono, Daiichi-Sankyo, Tesaro. KK has reported Speakers' bureau: Abbott Diagnostics, Roche, AstraZeneca, Eli Lilly, Pfizer. BB has reported Research grants: Pfizer, Roche, Boehringer Ingelheim, AstraZeneca. JV has reported that he is the Eli Lilly Chair in Respiratory Oncology at the Leuven University (research funding) and is the AstraZeneca Chair in Personalised Lung Cancer Care at the Leuven University (research funding). WE has reported Advisory board: GlaxoSmithKline, Amgen, Novartis, Merck, Teva, Roche, AstraZeneca, Lilly, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb; Speakers' bureau: Roche, AstraZeneca, Lilly, Boehringer Ingelheim, Pfizer, GlaxoSmithKline, Amgen, Novartis, Hexal, Merck; research grants: Eli Lilly. ME has reported Advisory board and/or research funding: Genentech, Boehringer Ingelheim, Lilly, Endocyte. PB has reported Research grants: Pfizer. MR has reported Advisory board: Hoffmann-La Roche, Lilly, Pfizer, AstraZeneca, Bristol-Myers Squibb, Daiichi-Sankyo; Speakers' honoraria: Hoffmann-La Roche, Lilly, Pfizer, Bristol-Myers Squibb, AstraZeneca, Daiichi-Sankyo. LP-A has reported Scientific advisor/Speakers' bureau: Lilly, Roche, Pfizer, Merck, Boehringer Ingeheim, Desi pharma, Celgene. PM has reported Speakers' bureau: Roche. MN has reported Speakers' bureau: Roche, Lilly, Boehringer Ingelheim, Pfizer, Otsuka; Research grants: Roche, Lilly, Boehringer Ingelheim, Pfizer, Novartis. SS has reported Research grants and honoraria: Varian Medical Systems; member of phase III trial management group conducted by Lilly Oncology. CF-F has reported Research grants AstraZeneca, Eli Lilly. GR has reported Speakers' bureau/grants: Covidien. EL has reported Research support: ScreenCell and PointHope; previously Speakers' bureau for Roche and Imedex and Advisory board for Strategen, Abbott Molecular and GlaxoSmithKline; patent pending with Clearbridge BioMedics; stock in Pfizer. VW has reported Consultancy/honoraria: Lilly, Roche, Boehringer Ingelheim and AstraZeneca (for lectures); Advisory role: Lilly, Roche, AstraZeneca; currently conducting research sponsored by Merck Serono. TM has reported Speakers' bureau and Honoraria from: AstraZeneca, Roche, Eli Lilly, Merck Serono, Eisai, Bristol-Myers Squibb BeiGene, AVEO, Pfizer, Taiho, Boehringer Ingelheim, GlaxoSmithKline Biologicals, Clovis Oncology; research funding from AstraZeneca. LB has reported Speakers' honoraria: Pfizer, Roche, Abbott Molecular Inc.; research supported by and stock held in Roche. SN, AM, KS, ES, AA, PVS, J-YD, WW, DDR, CLP, PDL, GV and CD have declared no potential conflicts of interest. LC and KO'B have not reported any potential conflicts of interest.

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appendix

members of the panel

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