COLLEGE OF ONCOLOGY

National Clinical Practice Guidelines

Non Small Cell Lung Cancer

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Continue

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The following professional associations have participated in the elaboration or reviewing process of the guidelines:

- **College of Oncology**
- **Belgian Society of Medical Oncology (BSMO)**
- **Belgian Thoracic Society: working group oncology**
- **Belgian Society for Radiotherapy-Oncology (BVRO-ABRO)**

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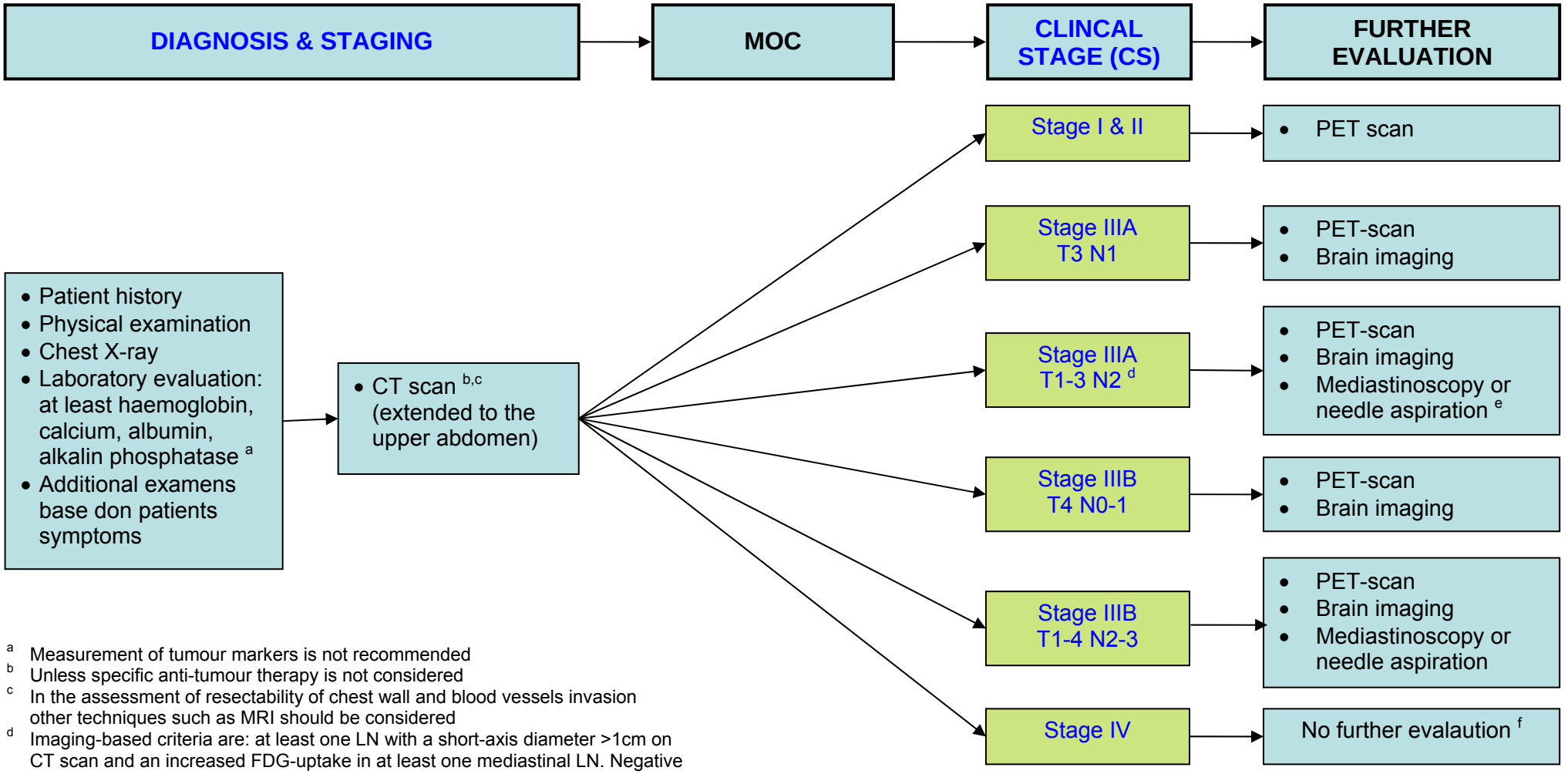

[a] Measurement of tumour markers is not recommended
[b] Unless specific anti-tumour therapy is not considered
[c] In the assessment of resectability of chest wall and blood vessels invasion other techniques such as MRI should be considered
[d] Imaging-based criteria are: at least one LN with a short-axis diameter >1cm on CT scan and an increased FDG-uptake in at least one mediastinal LN. Negative needle aspirations should be confirmed by mediastinoscopy (grade B). Central located tumors should also have a mediastinoscopy or needle aspiration
[e] Biopsies should be taken of at least 4 out of 6 accessible LN stations: 2 ipsilateral, 1 contralateral, 1 subcarinal (grade B)
[f] Unless specific symptoms signs or symptoms (grade C)

Note: All recommendations are grade A unless otherwise indicated

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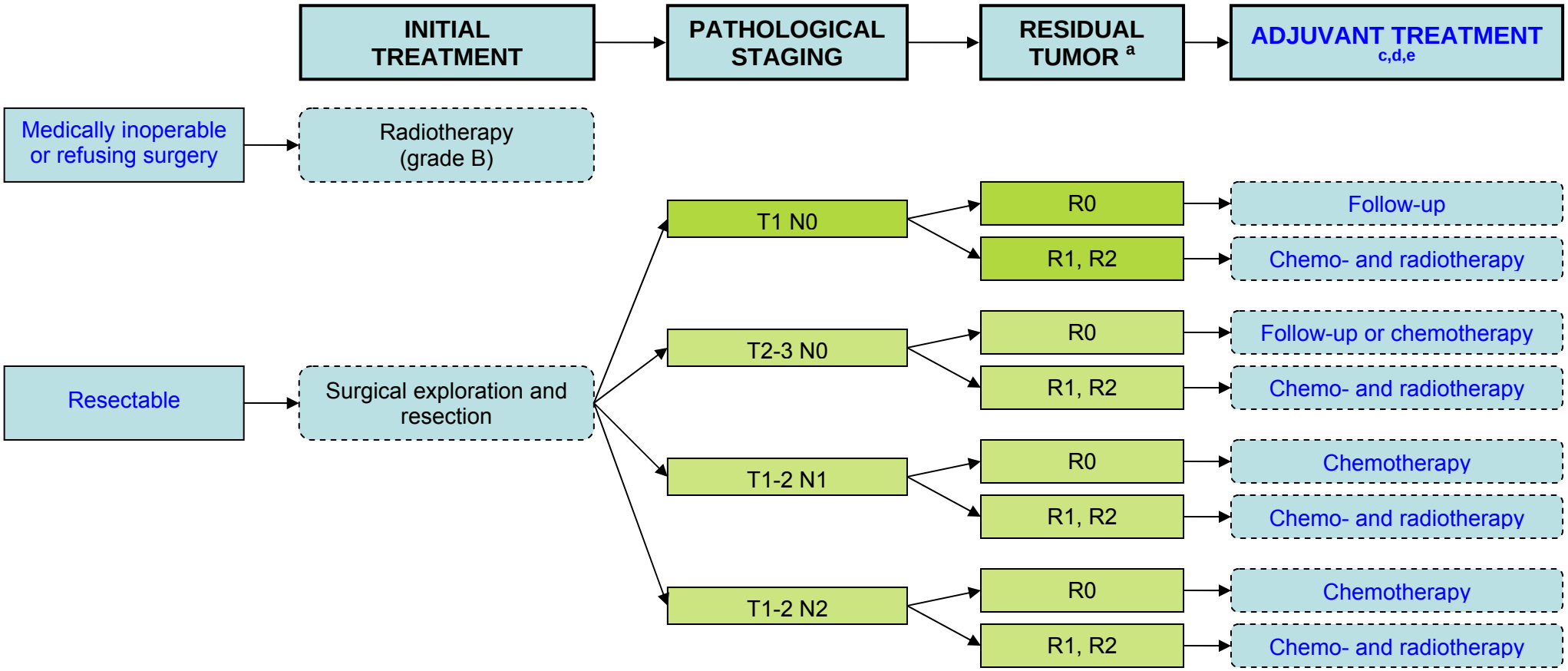

[a] RO: Complete resection, R1: Microscopic residual tumor, R2: Macroscopic residual tumor (grade C)
[b] Unresectable peroperatively: in case of massive invasion of mediastinal structures precluding an intrapericardial pneumectomy, pleural or pericardial metastases, multiple (usually lesions (grade C)
[c] In case postoperative radiotherapy is considered, the decision should be individualised (grade D)
[d] Adjuvant chemotherapy: preferably restricted to patients with good PS (WHO 0-1, Karnofsky ≥ 80 %), good recovery from surgery and no significant comorbidity
[e] Adjuvant chemotherapy: preferably a cisplatin/third generation drug doublet in 4 cycles. In case of excessive cisplatin toxicity, carboplatin doublet is an alternative (grade B)

Note: All recommendations are grade A unless otherwise indicated

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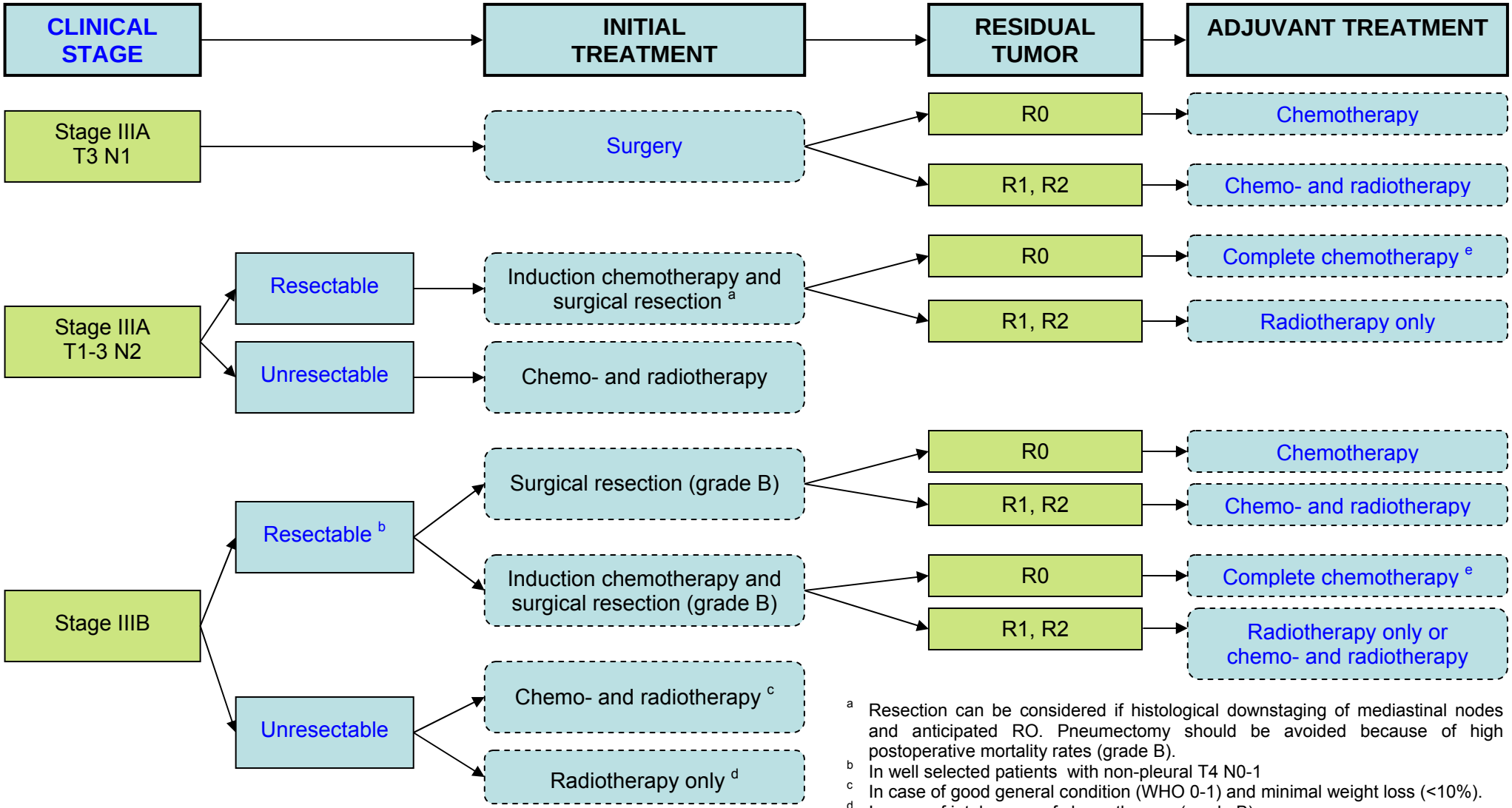

[a] Resection can be considered if histological downstaging of mediastinal nodes and anticipated RO. Pneumectomy should be avoided because of high postoperative mortality rates (grade B).
[b] In well selected patients with non-pleural T4 N0-1
[c] In case of good general condition (WHO 0-1) and minimal weight loss (<10%).
[d] In case of intolerance of chemotherapy (grade B)
[e] In case of pre-operative respons

Note: All recommendations are grade A unless otherwise indicated

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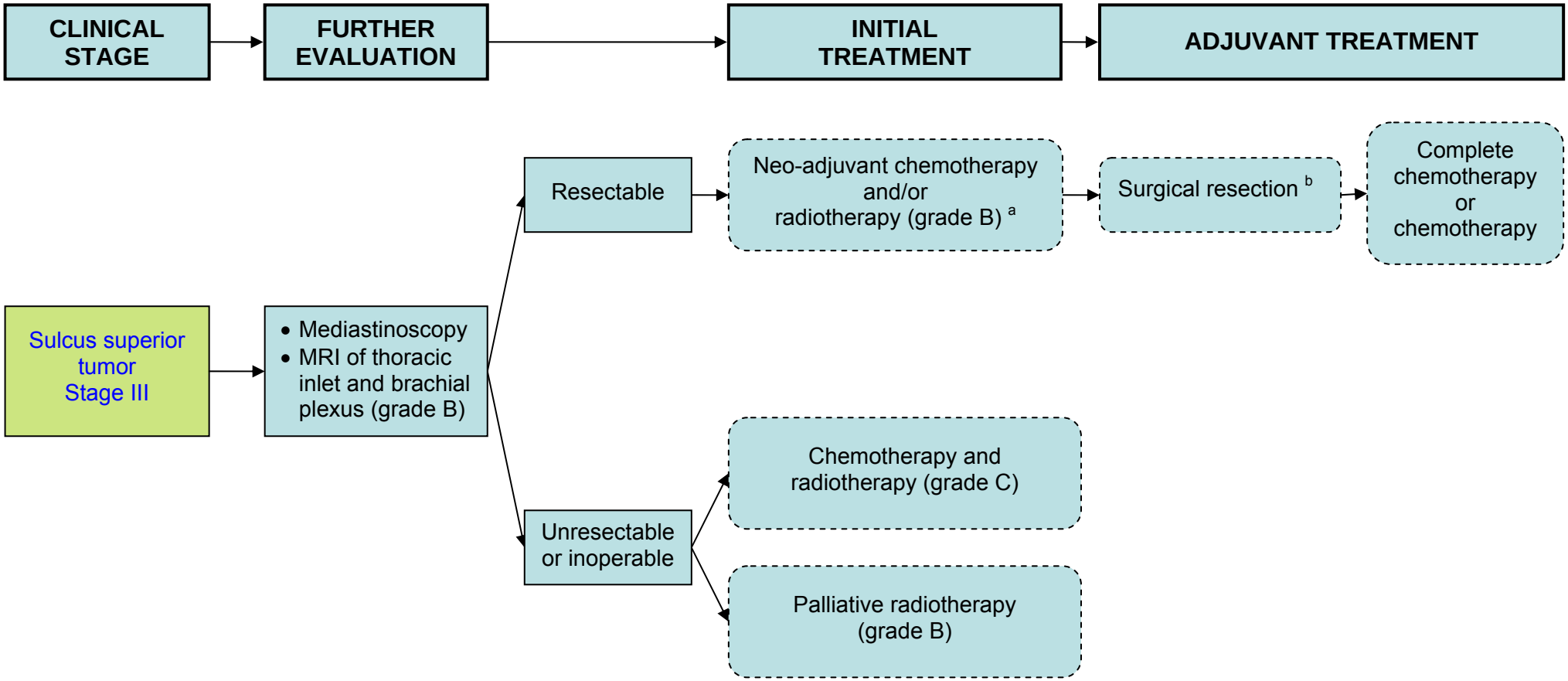

[a] Evaluation by an experienced thoracic surgeon is necessary (grade B)
In case of good performance status

[b] Resection of superior sulcus tumors with involvement of the subclavian vessels or the vertebral column should be done by an experienced surgeon.
Resection of a superior sulcus tumor should consist of a lobectomy instead of a wedge as well as removal of the involved chest wall structures and mediastinal nodes (grade B).

Note: All recommendations are grade A unless otherwise indicated

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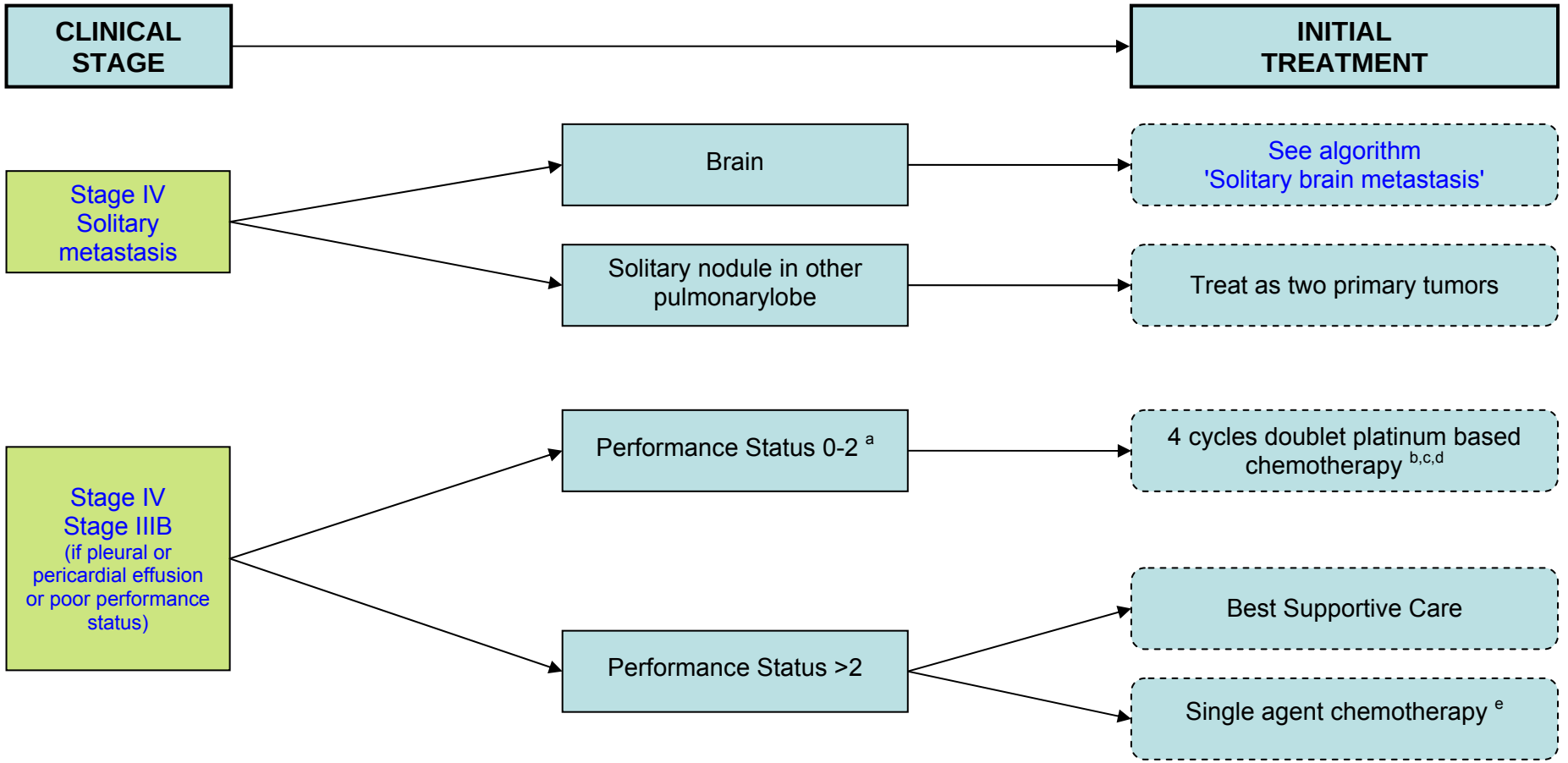

[a] WHO-classification (range 0-4)
[b] The use of platinum and third generation chemotherapy gives better results compared to platinum and second generation chemotherapy (grade B)
[c] In case of cisplatin excessive toxicity, carboplatin serves as an alternative (grade B)
[d] Consist of platinum and just one third generation drug.
[e] The use of a third generation drug is indicated (grade B)

Note: All recommendations are grade A unless otherwise indicated

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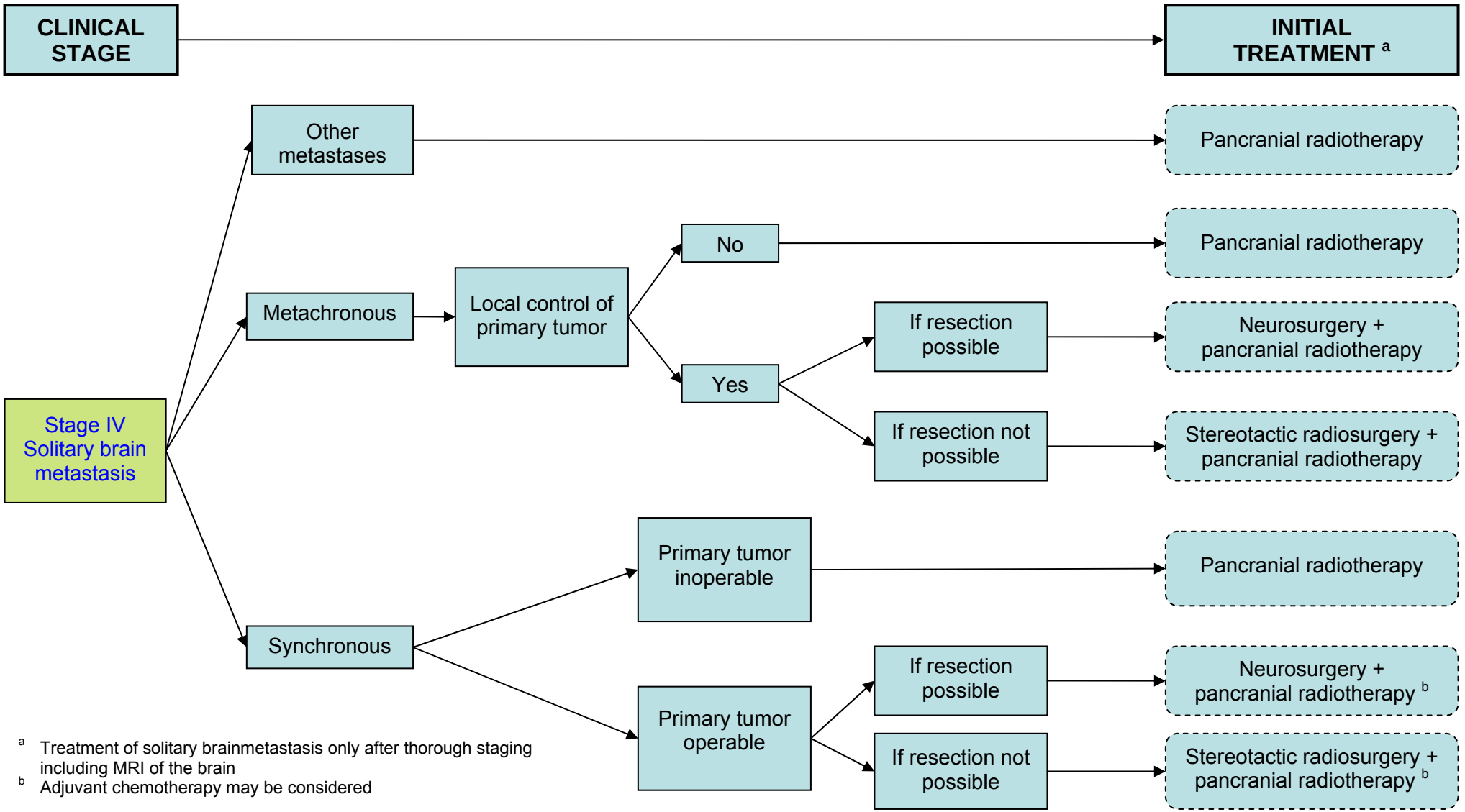

[a] Treatment of solitary brainmetastasis only after thorough staging including MRI of the brain

[b] Adjuvant chemotherapy may be considered

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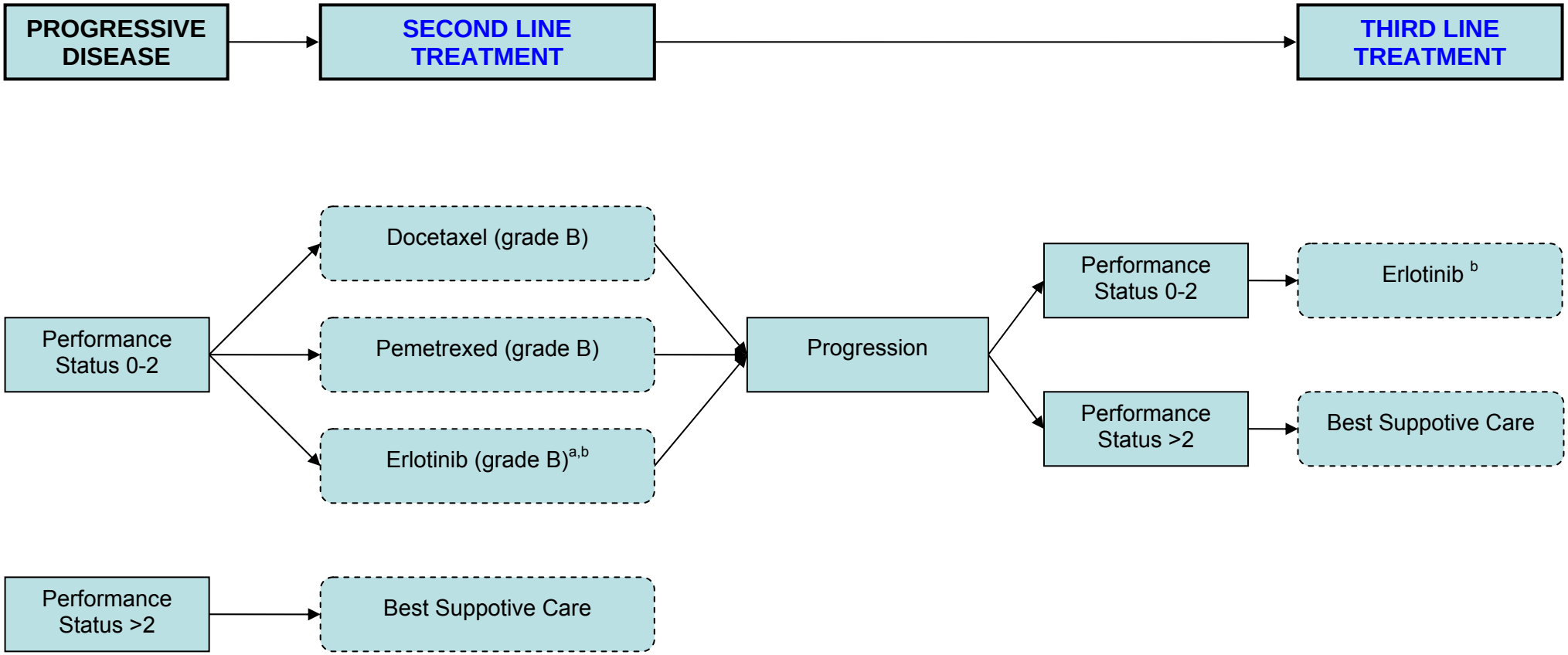

[a] If cases were chemotherapy is not indicated.
[b] Only in EGFR positive tumors

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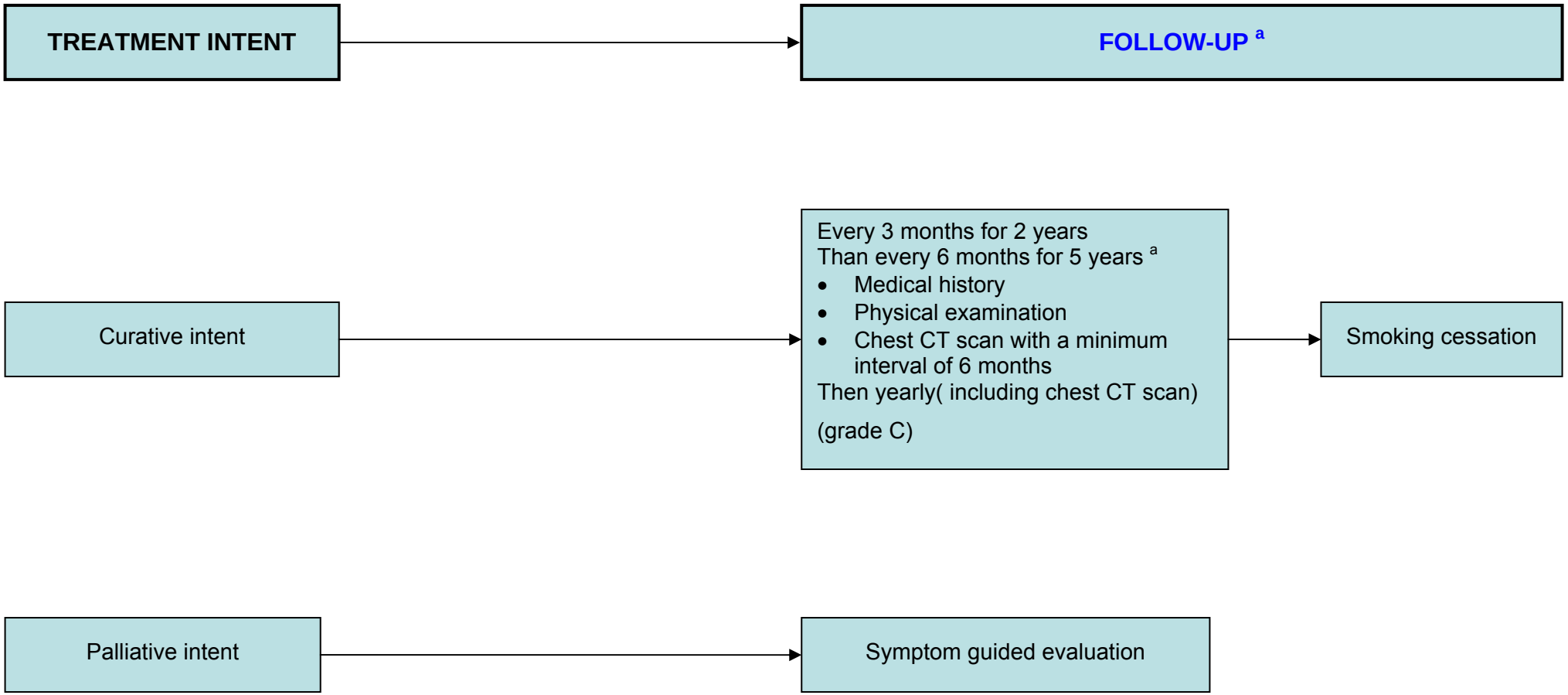

[a] Follow-up should be performed by members of the multidisciplinary team and always in collaboration with the general practitioner (grade C)

Note: All recommendations are grade A unless otherwise indicated

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National Guidelines
Non Small Cell Lung Cancer

INTRODUCTION

The guidelines presented covers diagnosis, treatment and follow up of non small lung cancer (NSCLC). They are adapted from the guidelines of the Belgian Thoracic Society which were revised in 2006 It is based on the existing international guidelines which have been critically appraised (Appendix 1) and on the consensus of national societies.

We will go through the following topics:

- Diagnosis & staging
- Multidisciplinary team meeting (optional)
- Treatment of stage I-III
- Treatment of stage IV
- Follow-up

The sytem of the U.S. Preventive Services Task Force (USPSTF) was used to grade the recommendations (Appendix 1). The USPSTF grades its recommendations according to one of five classifications (GR A, B, C, D, I) reflecting the strength of evidence (E) and magnitude of net benefit (B)(benefits minus harms).

The grade of recommendation is stated in the text as follow:

A.— Strongly recommended. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms*.

B.— Recommended. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms*.

C.— No recommendation. *The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation*.

D.— Recommended against. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits*.

I.— Insufficient data to recommend for or against. *Evidence that the [service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined*.

DIAGNOSIS & STAGING

An algorithm for diagnosis and staging is presented here.

Recommendations

- NSCLC is staged according to the TNM-classification and rules, version 1997/2002 (*E: fair; B large;* ***GR B)*** (Appendix 2 and Appendix 3).
- In all patients with (suspected) lung cancer, conventional work-up consists of at least a disease-oriented patient history, a physical examination, a chest xray and a limited laboratory evaluation. The latter should include at least haemoglobin, calcium, albumin, and alkaline phosphatase. The routine measurement of tumour markers as a staging tool is not recommended *(E: very good; B: large;* ***GR A****).*

- Dissemination of NSCLC should be confirmed by appropriate and adequate imaging of bone, liver, adrenals and brain, in case of any of the following otherwise unexplained signs or symptoms such as:
  - weight loss > 10% and/or WHO performance status ≤ 2
  - haematocrit < 0.4 for men, < 0.35 for women
  - bone pain (by patient history or at physical examination)
  - relevant neurological complains and symptoms
  - hepatomegaly
  - increased alkaline phosphatase and/or calcium

  *(E: good, B: large, **GR A**)*
- Once stage IV has been documented in 1 site, further dissemination staging is no longer mandatory because it will not affect management unless specific signs or symptoms apply *(E: poor; B: moderate; **GR C**).*
- Every patient with suspected or confirmed NSCLC should be considered for a contrast-enhanced CT scan of the chest (extended to the upper abdomen), unless specific anti-tumour therapy is not considered *(E: good; B: large; **GR A**).*
- Every patient with NSCLC amenable to radical local treatment -either surgery or radiotherapy- after conventional work-up (recommendation 2 & 5), should be considered for a 'full ring' dedicated FDG-PET scan to rule out occult metastatic disease and to evaluate possible mediastinal lymph node invasion *(E: good; B: large; **GR A**).*
- Appropriate contrast-enhanced brain imaging should be obtained in patients with presumed clinical stage III NSCLC after conventional work-up (recommendation 2 &5) *(E: good, B: large;**GR A**)*
- Invasive mediastinal staging -by either mediastinoscopy or needle aspiration should be performed in all patients without distant metastasis, in whom CT and/or FDG-PET scan suggest N2/3 lymph Node involvement and patients with central located tumors. The imaging-based criteria that suggest this, are:
  - at least one lymph node with a short-axis diameter > 1 cm on the CT scan or
  - an increased FDG-uptake in at least one mediastinal lymph node. Negative needle aspirations should be confirmed by mediastinoscopy *(E: fair; B: large; **GR B**).*
- During cervical mediastinoscopy, biopsies should be taken from at least 4 of the 6 accessible lymph node stations: 2 ipsilateral stations, 1 contralateral station and subcarinal station 7 *(E: fair; B: large; **GR B**)*
- Resectable and operable patients with a negative mediastinal FDG-PET scan can proceed to thoracotomy, provided that all of the following 4 criteria apply:
  - There is clear uptake of FDG in the primary tumour.
  - There is no suggestion of proximal N1 involvement on the PET scan.
  - The tumour is not contiguous to the mediastinum.
  - The short-axis diameters of the nodes visible on the CT scan are less than 1 cm.
  - If any of the above-mentioned criteria apply, then staging tissue-sampling procedures of the mediastinum- should be considered. *(E: limited; B: large; **GR B**)*
- In the assessment of resectability of chest wall and blood vessels invasion:
  - CT alone cannot be relied upon
  - Other techniques such as ultrasound or MRI should be considered

    *(E: good; B: large; **GR A**)*
- In patients with NSCLC and absence of distant metastases, any relevant pleural fluid should be aspirated for cytological examination. If the cytological assessment of the pleural effusion is twice negative, a

thoracoscopic guided biopsy will be performed, provided that the outcome affects further management *(E: good; B: large;* ***GR A****).*

FIRST MULTIDISCIPLINARY TEAM MEETING (MOC)

The objective of this first meeting is to decide on the therapeutic strategy based on the clinical staging ***(GR C)***.

If possible, the general practitioner (GP) of the patient should attend this meeting. Otherwise, the staging has to be fully and clearly communicated to the GP and/or specialist of the patient ***(GR C)***.

Patients should be given clear information about the potential risks and benefits of treatment in order that they can understand adequately the therapeutic decision ***(GR C)***. Information about local support services should be made available to both the patient and their relatives ***(GR C)***. Healthcare professionals should respect patients' wishes to be involved in their own management **(GR B)**.

The need for psychosocial help must be evaluated and offered if required **(GR B)**.

TREATMENT STAGE I-III

Surgery

An algorithm is presented here (CS I & II) and here (CS III).

Criteria of resectability

Definitions (E: fair; B: group consensus; ***GR C****)*

A ***complete resection*** (or R0 resection) requires all of the following:

- Free resection margins proved microscopically
- Systematic nodal dissection
- No extracapsular extension of tumor in nodes removed separately or those at the margin of the main lung specimen
- The highest mediastinal node that has been removed must be negative.

An ***incomplete resection*** includes the requirements established for R1 (microscopic residual tumor) and R2 (macroscopic residual tumor) resections. Thus a resection is considered incomplete if any off the following occur:

- Tumor involvement of resection margins.
- Extracapsular extension of tumor in nodes removed separately, or those at the margin of the main lung specimen.
- Nodes known to be positive but not removed (this would be an R2 resection if recognized by the surgeon).
- Positive cytology of pleural or pericardial effusions.

An ***uncertain resection*** is defined as a resection where the margins are proven to be free of disease microscopically, but one of the following applies:

- The intraoperative lymph node evaluation has been less rigorous than systematic nodal dissection or lobe-specific systematic nodal dissection as described above.
- The highest mediastinal node removed is positive (intracapsular involvement, extracapsular representing R2 resection).
- The bronchial margin shows carcinoma *in situ*.
- Pleural lavage cytology is positive (R1 cy+).

A disease is considered ***irresectable***, if any of the following apply:

- Pre-operatively
  - Extracapsular N2 or N3 disease (in contrast to unexpected N2 discovered at thoracotomy)
  - Malignant pleural effusion
  - T4: invasion of the esophagus, left atrium or aorta
- Per-operatively
  - Massive invasion of mediastinal structures precluding an intrapericardial pneumonectomy
  - Pleural or pericardial metastases
  - Multiple, usually subpleural lesions.

Synchronous lesions are considered separate primaries if 2 or more conditions are fullfilled:

- Anatomically distinct or different histology
- Presence of associated premalignant lesions
- Absence of systemic metastasis
- No mediastinal disease
- Different DNA ploidy.

Recommendations:

- The final aim of surgical resection is to obtain a complete resection (as defined above) with negative margins all around, also after induction therapy *(E: fair; B: group consensus;* ***GR C)***.
- Resection should be considered in limited node-negative multifocal cancer. Anatomic resection by lobectomy is advocated for the larger lesion together with a lesser resection (wedge, segmentectomy) for the smaller lesion. Pneumonectomy may be exceptionally indicated in case of separate primary tumors without lymph node metastases when a complete resection can only be obtained by pneumonectomy. The role of induction or adjuvant treatment has not been determined yet *(E: fair; B: group consensus;* ***GR C****)*

Rules for intra-operative decision considering the extension of the resection

Recommendations

- The standard operation for resection of lung cancer is a lobectomy *(E: good; B: large;* ***GR A****).*
- A pneumonectomy is indicated when this is the only way to obtain complete resection of all tumor *(E: fair; B: moderate;* ***GR B****).*
- When a tumor invades a neighbouring lobe, a wedge resection of that lobe, together with the lobectomy can be performed at the condition that the invasion is only limited. When the invasion is substantial or centrally located, a bilobectomy or pneumonectomy should be performed *(E: poor; B: moderate;* ***GR C****).*
- When adhesions are present to the parietal pleura, at the site of the tumor, the pleura should be removed in continuity with the tumor (extra pleural resection). When these adhesions are firm or the pleura cannot easily be stripped from the underlying muscle, an en-bloc-thoracic wall resection should be performed. This is also the best solution in case of doubt *(E: fair; B: moderate;* ***GR B****).*
- When invasion of pericardium or diaphragm is noticed at the time of operation, a resection of these structures should be performed *(E: fair; B: moderate;* ***GR B****).*
- In case of unforeseen invasion of the vertebrae a partial resection of the vertebrae can be performed in highly selected cases. Adhesions to the aorta are often limited to the adventitia and a subadventitional dissection can often be performed. In case of invasion of the vena cava one should consider whether partial resection and primary or prosthetic reconstruction of the caval vein is warranted, taking into consideration the patients condition, the stage of the tumor and stage of the

operation. In case of invasion of the esophagus the tumor should be considered as irresectable *(E: poor; B: small; **GR C**).*

- Invasion of the pulmonary artery beyond the trunk is no contra-indication for resection. In an upper lobe resection and with limited invasion of the pulmonary artery, a sleeve resection of the pulmonary artery can be performed in order to preserve the lower lobe *(E: poor; B: small; **GR C**).*
- When a tumor extends up to the carina a sleeve-pneumonectomy can be performed in very selected patients and experienced centers *(E: poor; B: moderate; **GR C**).*
- When during the operation an unforeseen positive N2 node is found, the resection should proceed with thorough lymph node dissection when a complete resection is possible. Involvement of mediastinal lymph node is not an indication to extent the pulmonary resection *(E: poor; B: moderate; **GR C**).*
- A frozen section of the bronchial margin should be obtained in case of proximal extension or doubt:
  - when the margin is invaded by tumor, a further resection should be considered.
  - when only carcinoma in situ or dysplasia is present, further resection is not strictly necessary but careful follow-up is mandatory *(E: poor; B: moderate; **GR C**).*
- A frozen section of a lymph node should be obtained if invasion of this node could influence the kind of resection *(E: poor; B: group consensus; **GR C**).*
- In case of unknown histology of a suspect pulmonary nodule, a wedge resection should, when anatomically possible, be performed to confirm the diagnosis of malignancy on frozen section. In case of centrally lobar located tumors and suspect iconography a lobectomy can directly be performed *(E: poor; B: moderate; **GR C**).*
- Pneumonectomy should not be done for unproven histology *(E: poor; B: negative; **GR D**).*

Requirements for the reports of surgery and pathology

Recommandations

- Surgical and pathological reports:
  - Should classify the tumour type according to the 1999 WHO classification of lung tumours.
  - Should stage the tumour according to the 1997 TNM-classification and guideline.
  - Should include the minimum dataset for lung cancer surgical report (Appendix 4) and histopathology report (Appendix 5) *(E: fair; B: high; **GR C**).*

Neo-adjuvant treatment for operable stage I & II

Recommendations

- For patients with clinical stage I (IA - IB) NSCLC and no medical contraindication to operative intervention, the use of neoadjuvant chemotherapy has been shown to be feasible, but is not recommended outside the setting of a clinical trial *(E: poor; B: small to moderate; **GR I**).*
- For patients with clinical stage I (IA - IB) NSCLC and no medical contraindication to operative intervention, the routine use of neoadjuvant radiotherapy should not be performed *(Evidence: good; B: none/negative; **GR D**).*

Adjuvant treatment for resected NSCLC [1-37]

An algorithm is presented here (CS I & II) and here (CS III).

Complete surgical resection is recognized today as the standard therapy in patients with early stage NSCLC (stages I, II, and some IIIA). But even after complete resection, patients are still at risk to develop recurrence of the disease. The overall 5-year survival rate after complete resection is only 40 to 45%, and differs according to the pathological stage: 67% for stage IA, 57% for stage IB, 55% for stage IIA, and 38% for stage IIB [1]. Many operated patients still die of lung cancer, either due to local relapse, distant relapse, or both. Therefore, adjuvant therapy has been studied extensively.

Recommendations

- Target group of this "early stage" guideline:
  - Patients with resected stages pI and pII NSCLC.
  - Patients with resected stage pIIIA, based on either pT3N1 or pT1-3 with unforeseen pN2.
- Indication of adjuvant chemotherapy:
  - In general, adjuvant chemotherapy is indicated because it reduces the hazard of relapse and it improves 5-year survival rate in a clinically meaningful degree. Adjuvant chemotherapy should preferably be restricted to patients with good Performance Status (Karnofsky =80%), good recovery from surgery so that adjuvant treatment can be started within 6 to 8 weeks post surgery, and absence of significant comorbidity *(E: very good; B: large,* ***GR A****)*.
- Indication of adjuvant radiotherapy:
  - In general, adjuvant radiotherapy is not indicated because there is no proven benefit in 5-year survival rate. Adjuvant radiotherapy should be avoided in resected stages I and II *(E: very good; B: none;* ***GR D****)*.
  - In situations with positive section margins, residual local disease, patients with unforeseen N2, postoperative radiotherapy has been shown to reduce local recurrence. It should be used on an individualised basis *(E: fair; B moderate;* ***GR C****).*
  - If adjuvant radiotherapy is considered, it is unclear what is the optimal sequence of adjuvant chemotherapy and radiotherapy, but in the available studies on adjuvant chemotherapy, radiotherapy was usually administered after adjuvant chemotherapy
  - Adjuvant concurrent chemoradiotherapy should be avoided (*E: good; B: none;* ***GR D****)*.
- Which chemotherapy improves survival in these patients?
  - Adjuvant chemotherapy should preferably be cisplatin-based, but carboplatin can be an alternative in case of excessive toxicity concerns with cisplatin. A modern doublet with Cisplatin (dose intensity of at least 25 mg/m² per week) and a 3rd generation drug is to be preferred. It should be the aim to administer four cycles (*E: good; B: moderate;* ***GR B****)*.
- Stages that are more likely to benefit from adjuvant chemotherapy.
  - In general there are no stages that are more likely to benefit from adjuvant chemotherapy because different stages were included in the existing trials and most trials did not find significant interaction with stage in multivariate analysis. Based on relapse patterns and the low number of stage IA in the randomized studies, we do not recommend adjuvant chemotherapy for stage pIA. Based on the overall evidence, most benefit is to be expected in stages pII and pIIIA. Patients with stage pIIIB or pIV, solely due to a satellite lesion or another nodule in the same or an other ipsilateral lobe, who had complete resection, have in general not been included in

the randomised trials, but it seems reasonable to offer adjuvant chemotherapy to these patients as well *(E: good; B: moderate; **GR B**)*.

- Indication of adjuvant molecular-biological treatment.
  - Adjuvant molecular-biological treatment is not indicated as there are no data at present that suggest a benefit with this strategy (*E: poor; B: unknown; **GR D***).

Treatment for medically inoperable stage I & II

Recommendations

- Patients with early lung cancer deemed medically inoperable or refusing surgery, and without contraindication to radiation therapy should be offered this modality as definitive treatment. This radiation therapy should deliver a dose in excess of 66 Gy or a biological equivalent dose and should use the new tools of radiotherapy (3D conformal radiotherapy) *(E: fair; B: large; **GR B**).*
- Patients with early lung cancer who are unfit for and/or refuse surgery and radiotherapy, should not be offered specific anti-tumour therapy *(E: poor; B: none/negative; **GR D**).*
- Endoluminal treatments may be considered for very early lung cancer such as carcinoma *in situ* or micro-invasive cancer. These patients should preferably be discussed with highly experienced teams *(Evidence: poor; B: moderate; **GR C**).*
- A combined chemo-radiotherapy approach should not be considered outside a study protocol *(E: poor; B: small; **GR I**).*

Treatment stage III

In case of resectable disease [38-44]

An algorithm is presented here.

Potentially resectable disease means that, based on optimal preoperative staging, a complete resection is anticipated. A complete resection (R0) is obtained when the macroscopic and microscopic margins are free of tumor, a systematic nodal dissection is performed with the most proximal lymph node station free of tumor and without extracapsular extension of tumour in these nodes. It is essential that the treatment decisions for stage III patients are taken in a multidisciplinary team with high-level experience in staging and assessment of resectability of the tumor.

Recommendations for potentially resectable IIIA-N2 disease

- The results of upfront surgery or RT for clinical N2 disease are disappointing (<10% 5 year survival); as results are disappointing we do not recommend upfront surgery or radiotherapy *(E: good; B: none; **GR D**).*
- The combination of systemic treatment followed by locoregional treatment (surgery or radiotherapy) improves the outcome as compared to locoregional treatment alone. At present, there is no evidence which locoregional radical treatment should be preferred *(E: very good; B: large; **GR A**).*
- If the N2 disease is felt to be resectable at presentation, the combination of induction treatment followed by surgery can be considered in case of histological downstaging of mediastinal nodes, and anticipated complete resection. Pneumonectomy should be avoided since the high postoperative mortality in this group after induction treatment *(E: good; B: moderate; **GR B**).*

- In case of unresectable N2-disease at presentation, non-surgical combined modality treatment is to be preferred.

Recommendations for stage IIIB disease

- A well selected subgroup of patients with non-pleural T4 N0-1 may benefit from surgery whether or not following induction treatment *(E: moderate; B: moderate;* ***GR B****).*
  Those patients should be discussed at the multidisciplinary meeting of highly experienced teams.

In case of unresectable disease [45-96]

An algorithm is presented here.

Stages considered as locally advanced Non Small Cell Lung Cancer are stage IIIA and stage IIIB except in case of malignant pleural or pericardial effusion (generally managed as stage IV).
The patients with locally advanced non metastatic Non Small Cell Lung Cancer considered in these guidelines are those with unresectable stage IIIA (see previous chapter) and those with unresectable stage IIIB disease (see previous chapter).

Recommendations

- In case of good general condition (PS 0-1) and minimal weight loss (<10%), the treatment of choice would be a combination of a cisplatin-based chemotherapy and radiotherapy. Sequential or concurrent chemoradiotherapy are both better than radiotherapy alone *(E: very good; B: large;* ***GR A****).*
- For those patients who cannot tolerate chemotherapy, good local control can be obtained by radiotherapy *(E: moderate; B: moderate;* ***GR B****).*
- Concurrent chemoradiotherapy is associated with an increased rate of acute toxicities, but in some data appears to be associated with a slightly improved survival in comparison with sequential treatment; thus systemic dose of platinum based concurrent chemoradiotherapy should be discussed with highly experienced teams *(E: moderate; B: small;* ***GR C****).*
- Consolidation chemotherapy after chemoradiotherapy is of no proven benefit *(E: poor; B: none/negative;* ***GR D****).*

In case of sulcus superior tumors

An algorithm is presented here.

Recommendations

- For patients with a superior sulcus tumor, a tissue diagnosis should be obtained prior to the initiation of therapy *(E: poor; B: large;* ***GR C****).*
- Patients with a superior sulcus tumor without evidence of mediastinal node involvement or distant metastases should be evaluated by an experienced thoracic surgeon for potential resection. Long-term outcome is associated with completeness of resection *(E: fair; B: large;* ***GR B****).*
- Patients with a superior sulcus tumor being considered for resection should undergo evaluation with an MRI of the thoracic inlet and brachial plexus, in addition to a CT of the chest *(E: fair; B: large;* ***GR B****).*
- Resection of superior sulcus tumors with involvement of the subclavian vessels or the vertebral column should not be undertaken outside of specialized centers *(E: poor; B: none/negative;* ***GR D****).*
- Patients with a superior sulcus tumor being considered for curative resection should undergo a cervical mediastinoscopy. Involvement of

mediastinal nodes (before combined CT/RT?) represents a contraindication to resection *(E: good; B: large; **GR A**).*

- Patients with a potentially resectable, nonmetastatic superior sulcus tumor (and good performance status) should undergo preoperative chemoradiotherapy prior to resection. A reasonable alternative for such patients is preoperative radiotherapy (*E: fair; B: moderate; **GR B**).*
- At the time of resection of a superior sulcus tumor, every effort should be made to achieve a complete resection *(E: good; B: large; **GR A**).*
- Resection of a superior sulcus tumor should consist of a lobectomy (instead of a wedge), as well as removal of the involved chest wall structures *(E: fair; B: moderate; **GR B**).*
- For patients with a superior sulcus tumor, post-operative radiotherapy is not recommended, in either completely or incompletely resected patients, because of lack of a demonstrated survival benefit *(E: poor; B: none; **GR D**).*
- Patients with a good performance status and an unresectable but nonmetastatic Superior sulcus tumor should be considered for combination chemotherapy and radiotherapy with intent to cure *(E: poor; B: moderate; **GR C**).*
- Palliative radiotherapy should be considered in patients who are not candidates for treatment with curative intent (ie, surgery, chemoradiotherapy etc.)*(E: fair; B: moderate; **GR B**).*

TREATMENT STAGE IV [97-195]

An algorithm is presented here.

Recommendations

- Target group
  - Stage IV NSCLC, with the exception of selected patients with solitary brain metastasis or more than one lesion of the lung (e.g: a tumor with a tumor nodule in a different lobe).
  - Stade IIIB NSCLC when multimodality treatment (chemo- en radiotherapy) is not indicated.
- Patients who are considered for systemic chemotherapy
  - Chemotherapy is indicated in patients with extended NSCLC and WHO performance status 0 or 1, irrespective of age *(E: very good; B: large; **GR A**).*
  - Chemotherapy might be indicated in selected patients with extended NSCLC and co-morbidity and/or WHO performance status 2 *(E: good; B: small; **GR C**).*
- Chemotherapy with an effect on survival
  - Platinum-based combination chemotherapy in association with best supportive care significantly improves the survival of patients with extended NSCLC *(E: very good; B: large; **GR A**).*
- Cisplatin- versus carboplatin-based chemotherapy
  - Cisplatin remains the standard care for extended NSCLC, but carboplatin can be an alternative in case of excessive toxicity *(E: good, B: small, **GR C**).*
- Do 3rd generation platinum regimens give better survival compared to 2nd generation platinum regimens ?

  - The use of 3rd generation platinum regimens in patients with extended NSCLC gives better survival compared to 2nd generation platinum regimens *(E: very good; B: moderate;* ***GR B***).
- Survival differences with different 3rd generation platinum doublets
  - The differences in survival between different doublets of platinum and 3rd generation drugs are small *(E: good; B: small;* ***GR C***).
- Are combinations of platinum with 2 or more 3rd generation drugs superior to combinations of platinum with one 3rd generation drug?
  - Combination chemotherapy in patients with extended NSCLC should be platinum-based with not more than one 3rd generation drug *(E: good; B: moderate;* ***GR B****)*.
- Optimal duration of the chemotherapy
  - In the absence of early progression or excessive toxicity, platinum-based combination chemotherapy in patients with extended NSCLC should excist of 3 to 4 cycles (*E: very good, B: moderate,* ***GR B****).*
- Monochemotherapy with 3rd generation drugs
  - Best supportive care in association with monochemotherapy with a 3rd generation drug improves the survival of patients with extended NSCLC *(E: very good; B: moderate;* ***GR B***).
  - The use of monotherapy with a 3rd generation drug in older patients with extended NSCLC is equally effective as the use of a combination of these drugs *(E: good; B: moderate;* ***GR B****)*.
  - If possible a combination of a platinum derivative with a 3rd generation drug should be used in patients with extended NSCLC *(E: good; B: moderate;* ***GR B****).*
- Combinations without a platinum derivativet
  - The use of platinum-based chemotherapy in patients with extended NSCLC seems more effective than treatments without platinum *(E: very good; B: small;* ***GR C****)*.
- Role of 2nd line (3rd lijn) chemotherapy (an algorithm is presented here)
  - Patients with progressive NSCLC after first line treatment should be treated with docetaxel 75mg/m^2 in 2nd line until progression or severe toxicity *(E: very good; B: moderate;* ***GR B****).*
  - *2*nd line pemetrexed 500 mg/m^2 is equally effective as docetaxel, and causes less neutropenia and neutropenia-associated complications *(E: very good; B: moderate,* ***GR B****)*.
  - Erlotinib in 2nd line for patients who are not able to receive chemotherapy, gives better survival compared to best supportive care only *(E: zeer goed; B: matig;* ***GR B****)*.
  - Erlotinib in 3rd line gives better survival compared to best supportive care only *(E: very good; B: moderate;* ***GR B****)*.
  - A survival benefit after treatment with erlotinib in patients with EGFR negative tumors cannot be expected.
  - There is insufficient data about other 2nd or 3rd line chemotherapy *(E: poor, B: none, GR I*).
- Does chemotherapy improves quality of life and does it lead to symptom control?
  - First and 2nd line chemotherapy in case of extended NSCLC leads to improved quality of life and less disease related symptoms irrespective of the side-effects *(E: very good, B: moderate,* ***GR B****)*.
- Role of clinical trials
  - Inclusion in clinical trials of patients with extended NSCLC is strongly recommended *(E: very good, B: large,* ***GR A***).

Solitary brain metastasis

An algorithm is presented here.

- In patients with an isolated brain metastasis from NSCLC being considered for curative resection of a stage I or II lung primary tumor, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represent a contraindication to resection **(GR C)**.
- In patients with no other sites of metastases and a synchronous resectable N0,1 primary NSCLC, resection or radiosurgical ablation of an isolated brain metastasis are recommended (as well as resection of the primary tumor) **(GR C)**.
- In patients with no other sites of metastases and a previously completely resected primary NSCLC (metachronous presentation), resection or radiosurgical ablation of an isolated brain metastasis is recommended **(GR C)**.
- In patients who have undergone a curative resection of an isolated brain metastasis, adjuvant whole-brain radiotherapy is suggested, although there is conflicting and insufficient data regarding a benefit with respect to survival or the rate of recurrent brain metastases **(GR C)**.
- In patients who have undergone curative resections of both the isolated brain metastasis and the primary tumor, adjuvant chemotherapy may be considered **(GR C)**.

FOLLOW-UP [196-223]

An algorithm is presented here.

Recommendations

- Target groups
  - Patients who are treated with curative intent. They include patients with NSCLC stages I to III treated with curative intent by surgical resection, or combined modalities including chemotherapy and surgery or chemotherapy and radiotherapy as well as patients with limited SCLC treated with combined chemotherapy and radiotherapy.
  - Patients treated with palliative intent
- Objectives
  - In patients treated with curative treatment, the main purpose is the diagnosis of recurrence and second cancers early enough to allow curative retreatment. Other potential benefits are the diagnosis and management of toxicities and complications related to treatment as well as general support.
  - In patients treated with palliative intent, the main purposes are the diagnosis and management of toxicities and complications related to treatment as well as control of the symptoms.
- Follow-up of toxicities and complications related to the curative treatment
  - The surveillance depends on toxicity that is present at that time or to be anticipated and should be performed for a three to six months period. After this period, the patient should be entered into the surveillance program for detection of recurrence and second cancers *(E: poor; B: moderate,* ***GR C****)*.
- Diagnosis of recurrence and second cancers after curative treatment

- The surveillance includes medical history, physical examination and chest X-ray every 3 months for the first two years, every 6 months up to 5 years. Chest Ct scans may replace chest X-ray not more frequently than at 6 months interval. Patients should always have rapid access to the multidisciplinary team *(E: poor; B: moderate;* ***GR C****)*.

- Follow-up of the patients treated with palliative intent
  - The surveillance depends on toxicity that is present at that time or to be anticipated. Thereafter, the frequency of visits will depend on the control of symptoms, often every 1-2 months during the first 6 months. Medical history and physical examination should be performed at each visit and additional tests, including chest X-ray, in case of clinical indication. Patients should always have rapid access to the multidisciplinary team *(E: poor; B: moderate;* ***GR C****)*.
- Who should perform surveillance?
  - After the initial curative or palliative treatment, surveillance for diagnosis and management of toxicities and complications should be performed by the appropriate specialists . Long term surveillance after curative treatment should be done by members of the multidisciplinary lung cancer team. The follow-up should always be performed in collaboration with the general practitioner *(E: poor, B: moderate,* ***GR C****)*.
- Smoking cessation
  - Patients should not smoke during follow-up in particular after curative treatment *(E: fair; B: moderate;* ***GR B****)*.

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Grades of evidence, benefit and recommendations

Grades of evidence (adapted to the method of the US Preventive Services Task Force) (ref…)		
Very good	Meta-analysis - several prospective randomized controlled trials	
Good	At least one prospective randomized controlled trials	
Limited	Well designed, prospective, non-radomized data - historical comparison	
Small	Small retrospective series - case reports	
Grades of benefit of the intervention (according to the method of the US Preventive Services Task Force)		
Substantial	Benefits substantially outweigh harms	
Moderate	Benefits outweigh harms	
Small	Benefits are not clinically relevant compared to the possible harm	
Zero/Negative	Harms are equal to the benefits or harms outweigh benefits	
Grades of recommendation (according to the method of the US Preventive Services Task Force)		
Strongly recommended	(Very) good evidence	Substantial benefit
Recommended	(Very) good evidence Moderate evidence	Moderate benefit Substantial/moderate benefit
Slightly recommended - no recommendation	(Very) good evidence Limited evidence Limited evidence	Small benefit Substantial/moderate benefit Consensus within the group
Recommendsed against	Moedrate to (very) good evidence	Zero/Negative benefit
Evidence is insufficient	Limited evidence	Small, zero or negative benefit

pT	Primary Tumour
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour ≤ 3 cm
T2	Tumour > 3 cm or involves main brochus ≥ 2 cm from carina or invades visceral pleura or partial atelectasis
T3	Tumour invades chest wall or diaphragm or pericardium or mediastinal pleura or tumour in the main bronchus < 2 cm from carina or total atelectasis
T4	Tumour invades mediastinum, heart, great vessels, trachea, oesophagus, vertebral body, carina; chest wall, diaphragm, pericardium, mediastinal pleura or tumour in the main bronchus < 2 cm from carina or total atelectasis

pN	Regional Lymph Nodes *
Nx	Regional lymph nodes cannot be assessed.
N0	No regional lymph nodes metastasis.
N1	Metastasis in ipsilateral mediastinal and/or ipsilateral hilar lymph nodes
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph nodes
N3	Metastasis in contralateral mediastinal or hilar, scalene or supraclavicular lymph nodes

M	Distant Metastasis
Mx	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases, includes separate tumour nodule(s) in different lobe

G	Histologic grade
Gx	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Notes 1) The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1.
2) Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor. In these cases, fluid is non-bloody and is not an exudate. Where these elements and clinical judgement dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be staged as T1, T2, or T3.

TNM Stage grouping

Occult carcinoma	Tx	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2 T3	N1 N0	M0 M0
Stage IIIA	T1,T2 T3	N2 N1,N2	M0 M0
Stage IIIB	Any T T4	N3 Any N	M0 M0
Stage IV	Any T	Any N	M1

Last Name…….. First Name…….. Date of Birth…….. Sexe……
Surgeon……...
Date of surgery……

Clinical data
Previous history:

cTNM: T N M
Histology (if known):
Preoperative treatment: Radiotherapy Chemotherapy Other:……..
Professionnel exposure:

Specimen type
Main tumor
- Surgical approach: - open thoracotomy
  - Sternotomy
  - VATS
- Lateralisation: left right
- Sleeve resection: yes no
- Pneumectomy: yes no
- Lobectomy: upper middle lower
- Segmentectomy (I → X):
- Wedge excision: upper middle lower
- Complementory resections: parietal pleura pericardium left atrium chest wall
  vertebra diaphragm Other (precise)
- Distance from main carina: <20 mm >20 mm

Other tumors (precise location):
Lymph node stations:
Frozen sections: yes no
- Bronchial section yes no
- Lymph nodes + station:
- Other: precise

Macroscopical resection: R0 R1 R2
If R1, clip for radiotherapy: yes no
Complications:

Conclusion
Surg TNM: T N M

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Last Name…….. First Name……..…… Date of Birth……..…… Sexe……
Surgeon……... Pathologist…….…..... Report N° ……
Date of surgery…… Date of receipt…… Date of reporting…….

Frozen specimen: yes no
Mineralogy: yes no
Photos: yes no

Macroscopy:

Main tumor

- Localisation: central peripheral
  Segments:
- Size (3 dimensions):
- Distance from bronchial margin:…….mm

Other tumors

- Localisation: central peripheral
  Segments:
- Size (3 dimensions):
- Distance from bronchial margin:…….mm

Pulmonary parenchyma: other lesions (precise):

Microscopy

Results of frozen sections:

Histological type: SCC BAC Adenocarcinoom
SCLC Large cell Carcinoma Mixte: specify…… Other……...
Differentiation: well moderately poorly
Tumour embolism: vascular lymphatic perinervous
Local invasion:
Involved Margins: bronchi mediastinal vascular visceral pleura chest wall
Specify: parietal pleura, intercostal muscle, rib, vertebra, diaphragm

- Distance from normal lung (wedge):…….. mm

Lymph nodes:

- total number:
- ipsilateral hilar/intrapulmonar (station 10-14) (N1): present number:…..… number with metastases…… Capsular rupture: yes no
- ipsilateral mediastinal (station 1-9) (N2): present number:…..… number with metastases…… Capsular rupture: yes no
- contralateral mediastinal/hilar (N3) : present number:…..… number with metastases…… Capsular rupture: yes no
- cervical or supraclavicular both sides: present number:…..… number with metastases…… Capsular rupture: yes no

Non-neoplastic pathology:

Conclusion

pTNM: T N M
Resection: R0 R1 R2

