Clinical staging of NSCLC: current evidence and implications for adjuvant chemotherapy

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Abstract: Survival of all non-small cell lung cancer (NSCLC) patients is disappointing, with a 5-year survival of 18%. Staging NSCLC patients is crucial because it determines the choice of treatment and prognosis. Clinical staging is a complex process that comes with many challenges and with low accuracy between the clinical and pathological stage. Treatment modalities for stage I–III NSCLC consist of surgical resection, radiotherapy and chemotherapy. This review describes the current evidence on staging and the implications on adjuvant chemotherapy. For stage I disease, staging is most accurate. Primary treatment consists of surgery or stereotactic ablative radiotherapy. When a patient has stage II disease, staging is less accurate because more diagnostic modalities are necessary to stage the mediastinal lymph nodes. Surgery remains the primary treatment modality and platinum-based adjuvant chemotherapy gives a 4% 5-year survival benefit. Staging patients with stage III disease is difficult because of the heterogeneity of the patients. It should be decided if a patient has potentially resectable disease with or without risk of incomplete resection. Induction therapy with chemo(radio)therapy followed by surgical resection or definitive chemoradiotherapy are the treatments of choice. The 5-year survival can reach 44% in selected patients. Decisions in staging and treating patients with NSCLC should be made by a multidisciplinary team with sufficient expertise in all aspects of staging and treatment.

Keywords: adjuvant, carcinoma, chemoradiotherapy, chemotherapy, non-small cell lung cancer, radiosurgery, radiotherapy, thoracic surgery

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Introduction

Lung cancer causes most cancer-related deaths worldwide.[1–3] Clinical staging of non-small cell lung cancer (NSCLC) is difficult. Although separate diagnostic modalities have high sensitivity and specificity,[4] comparing the clinical stage (cTNM) and pathological stage (pTNM) has an accuracy that is generally low, between 50–60%.[5–14] Survival of NSCLC remains disappointing with a 5-year survival of 18% for all NSCLC patients, and a 60–80% survival in stage I patients after an anatomical resection.[15,16] It is important to have a correct clinical stage because this determines the choice of initial treatment and thus survival. With a correct clinical stage unnecessary morbidity and mortality of treatment can be minimized. Stage I patients, with tumors up to 5 cm and no lymph node involvement, are usually treated with monotherapy, being either resection or stereotactic ablative radiotherapy (SABR), most often used in patients unfit for surgery. In NSCLC stage II, therapy usually consists of primary treatment, (e.g. resection), followed by adjuvant chemotherapy. In patients with locally advanced NSCLC (stage III) induction chemo- or radiotherapy followed by resection or definitive combined modality treatment (concurrent or sequential chemoradiation) is the standard. In patients with no resection and hence no definitive pathological TNM stage, adjuvant treatment is chosen based on the clinical TNM stage. This opinionated, narrative review will discuss the role of clinical staging of NSCLC and the implications on adjuvant chemotherapy.

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The benefit of adjuvant chemotherapy in patients with resectable NSCLC

The results of the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis have largely determined the current vision on the use of adjuvant chemotherapy in patients with NSCLC. This study, published by Pignon and colleagues in 2008 in *Journal of Clinical Oncology*, showed a survival benefit for patients receiving platinum-based chemotherapy after complete resection of stage II or stage III NSCLC. It showed a 5.4% benefit in 5-year survival when cisplatin-based adjuvant chemotherapy was given, an effect that was even higher in patients with a higher socio-economic status.[17] A Cochrane review published in 2015 on adjuvant chemotherapy after resected NSCLC, comprising 26 trials and more than 11,000 patients, confirmed these findings and demonstrated the clear significant benefit of adjuvant chemotherapy for patients receiving chemotherapy after radical surgery or after surgery combined with radiotherapy. This meta-analysis shows a significant 4% improvement in 5-year overall survival, increasing survival from 60–64% for the whole group of patients. The trials included in this analysis mainly used cisplatin-based chemotherapy, and in some included articles tegafur/uracil was used as the chemotherapeutic agent.[18] Neoadjuvant chemotherapy is reserved for patients with locally advanced NSCLC, since there is no evidence that it plays a beneficiary role in patients with stage I–II NSCLC according to the NATCH trial.[19]

Determining the clinical stage

Staging of NSCLC involves multiple modalities; guidelines recommend use of combined positron emission tomography (PET) and computed tomography (CT) if available, and otherwise a CT scan alone. In case of suspicious mediastinal nodes on the scan, meaning nodes with fluorodeoxyglucose (FDG) uptake or with a small axis diameter >1 cm, minimally invasive techniques are recommended to obtain a tissue diagnosis of these nodes.[4,20] Techniques used include endoscopic ultrasound (EUS) or endobronchial ultrasound (EBUS). If these tests prove to be negative, a (video)mediastinoscopy is recommended. In patients with an intermediate risk of mediastinal lymph node metastasis, meaning a tumor >3 cm (dependent on which guideline is followed),[20,21] a central tumor or a tumor with suspicious N1 lymph nodes, invasive staging of the mediastinum is also recommended, starting with EUS/EBUS. If results are negative but suspicion is high a (video)mediastinoscopy is recommended as well. Magnetic resonance imaging (MRI) of the brain is recommended in patients with stage III disease.[4,21] Accuracy of clinical staging decreases in higher stages of NSCLC.[8] See Figure 1 for the staging algorithm used in most guidelines.

For this article the 7th edition of the TNM system is used, since most literature references used in this review refer to this edition.[22] Inaccuracy in staging is caused by a shift from a clinical stage to a different pathological stage. For example, a patient can shift to a pathological higher T-stage if the tumor size is bigger than expected, if there was unexpected infiltration of the visceral pleura or if unexpected, separate tumor nodules are found in the resected specimen. A higher pathological nodal stage can be caused by unforeseen N2 disease. On the other hand, downstaging, especially of T-stage is also possible, for example because of an inflated lung when scanning, inflammation, infiltration or edema.[23] Currently the TNM 8th edition has been introduced in several countries and is due to be implemented in the United States in 2018. Most important changes in the new TNM are: a separate T-stage for every centimeter in growth up to 5 cm, change of tumors from 5–7 cm to T3 stage instead of T2, ingrowth in diaphragm moves to T4 stage instead of T3. An extra category, M1c, was added to stage patients with multiple metastasis in one or more organs outside the thorax.[24] In the future this detailed subdivision, especially in T-stage, may lead to more inaccuracy between cTNM and pTNM.

To present the evidence on clinical staging and the implications on adjuvant chemotherapy we will give an overview of the literature for three different clinical stages:

1: patients with clinical stage I disease
2: patients with clinical stage II disease
3: patients with clinical stage III disease (especially stage IIIA-N2)

Clinical stage I patients

Staging

Patients with clinical stage I disease have a tumor ranging from 0–5 cm and no hilar or mediastinal lymph node involvement. Depending on which guideline is used, staging of the mediastinum is

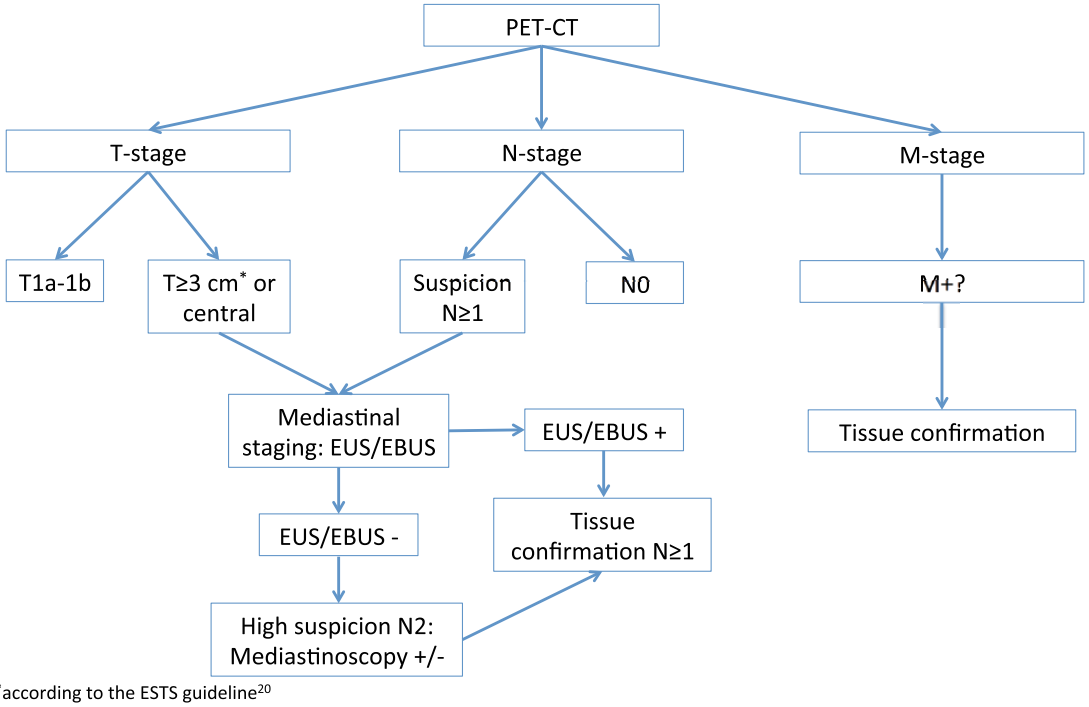


Figure 1. Staging algorithm for NSCLC.
CT, computed tomography; EBUS, endobronchial ultrasound; ESTS, European Society of Thoracic Surgeons; EUS, endoscopic ultrasound; PET, positron emission tomography; US, ultrasound.

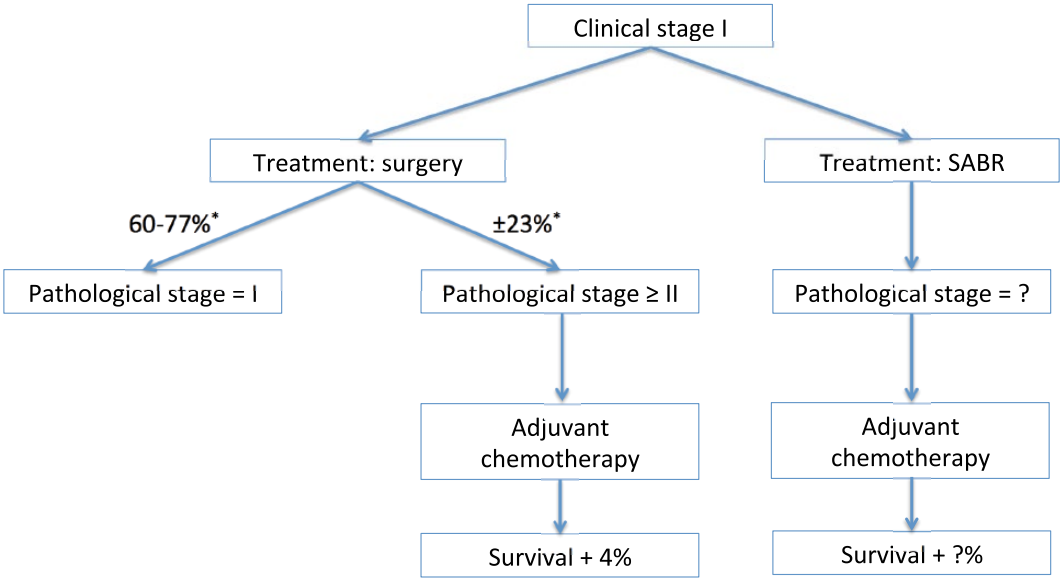
indicated in tumors 3–5 cm.[20,21] Clinical staging is fairly accurate, ranging from 65–75% accuracy between cTNM and pTNM in the era before PET-CT.[6,12–14] Recently the Dutch Lung Surgery Audit (DLSA), a nationwide clinical audit in the Netherlands, was used to examine how accurate clinical staging of stage I tumors was done in 2013 and 2014 in the Netherlands.[9] Accuracy between cTNM and pTNM was 59.9% in a population of 1555 patients, who all had a PET-CT scan in their work up. Combining the subgroups of stage Ia and stage Ib together showed an accuracy of 76.6% for all stage I patients. Of all patients, 22.6% were upstaged to a pathological stage II or higher, which is an indication for adjuvant chemotherapy. Especially patients with larger tumors from 3–5 cm (T2a) had a high risk of having lymph node metastasis (21.2%). The number of unforeseen N2 nodes in cT2a patients was as high as 6.7%. These data support the guideline of the European Society of Thoracic Surgeons (ESTS), which advices mediastinal staging in patients with tumors >3 cm.[20] This is based on a lower negative predictive value (NPV) for PET-CT in patients with a tumor >3 cm, which has been proven in various studies, especially in patients with adenocarcinoma.[25,26]

Primary treatment

For a patient with a clinical stage I tumor who is fit for surgery, two primary treatment options are available:

- Surgical resection, with adjuvant chemotherapy if the pathological stage after resection is stage II or higher
- SABR, with or without adjuvant chemotherapy

It is difficult to state which treatment option is best in patients with stage I NSCLC: three stage III randomized controlled trials were initiated to compare SABR to surgery for resectable stage I NSCLC, but all were closed prematurely due to poor accrual: the STARS trial [ClinicalTrials.gov identifier: NCT00840749], the ROSEL trial [NCT00687986], and the ACOSOG Z4099 trial [NCT01336894]. In 2015, the only randomized evidence, a pooled analysis of the limited included patients in the STARS and ROSEL trial, was published. In this analysis survival and locoregional recurrence were comparable between SABR and surgical resection.[27] Many researchers commented on this study stating it was highly underpowered (2.8% out of a total of 2410 intended patients was included).[28] At present we



*according to Heineman et al.[8]

Figure 2. Flow chart stage I NSCLC.
SABR, stereotactic ablative radiotherapy.

should still consider surgical resection as the gold standard treatment. However, SABR is a good alternative with good outcome and additional randomized trials will analyze SABR in comparison with surgery, to analyze what therapy is best in patients fit for surgery but also suitable for SABR.

Adjuvant therapy

If a patient receives a surgical resection for a clinical stage I tumor, 5-year survival in the pre video-assisted thoracoscopic surgery (VATS)-era was between 60–80%.[15,16] If a patient has a pathological stage II or higher after surgical resection, adjuvant chemotherapy is indicated. This increases survival with 4% in 5 years according to the Cochrane review on adjuvant chemotherapy in curatively resected NSCLC.[18] It is difficult to present data on the survival of a patient receiving SABR and adjuvant chemotherapy, hardly any trials have been published on this subject. Louie and colleagues published a review in 2014 in which this problem is addressed.[29] They describe that models have been developed to predict systemic disease, and it is proposed that patients with larger tumor size, higher pretreatment FDG-PET maximum standard uptake value (SUV-max), as well as contact with mediastinal pleura, might be offered adjuvant chemotherapy after SABR to prevent disease recurrence. Unfortunately there are no data that describe the survival of patients with this treatment strategy. Because of the lack of data on this subject close follow up of patients after SABR is recommended. After radical resection of stage I disease, postoperative radiotherapy (PORT) is not indicated, since this has no added benefit.[30,31] In patients with resected stage I disease and a positive resection margin (R1) postoperative radiation therapy is advised.[16] Figure 2 shows the different treatment options in clinical stage I patients and the respective survival rates.

Clinical stage II disease

Staging

Clinical stage IIA disease is comprised of T2bN0 or T1a-2aN1 disease. Clinical stage IIB disease consists of T2bN1 or T3N0 disease.[22] Clinical staging in these patients is moderately accurate. This is mostly due to the necessity of staging the mediastinum. Guidelines by the ESTS and American College of Chest Physicians (ACCP) recommend staging the mediastinum in patients with an intermediate risk of mediastinal lymph node metastasis: hence this is advised when a patient has suspicious N1 lymph nodes on PET-CT, a central tumor or a tumor >3 cm (see Figure 1).[4,20] The rationale for this advice is a

Table 1. Median sensitivity and specificity of invasive diagnostic modalities to stage the mediastinum according to the ACCP clinical practice guidelines.[4]

Modality	Sensitivity	Specificity
Mediastinoscopy	78%	100%
Videomediastinoscopy	89%	100%
EBUS	89%	100%
EUS	89%	100%
Combination EUS/EBUS	91%	100%

ACCP, American College of Chest Physicians; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound.

study that showed that patients with N1 disease on a CT scan have N2 or N3 nodes in 30%.[32] The evidence for mediastinal staging in central tumors comes from a study that showed the number of patients with unforeseen N2 disease in central tumors was almost 10 times higher than in peripheral tumors (2.9% *versus* 21.6%).[11] Advice on how to stage the mediastinum is largely based on the ASTER trial. This trial showed a sensitivity of 79% for surgical staging of the mediastinum alone, 85% sensitivity for endosonography alone and 94% sensitivity for endosonography followed by surgical staging.[33] It is therefore that the staging algorithm starts with EUS combined with EBUS, and when these prove negative it should be followed by mediastinoscopy. This approach results in fewer unnecessary thoracotomies. EBUS can be used to visualize and biopsy mediastinal stations 2R/2L, 4R/4L, 7 and hilar stations 10, 11 and 12. EUS is particularly useful for mediastinal stations 4L, 7, 8, 9 and the left adrenal. Mediastinoscopy can be used to biopsy stations 2R/L, 4R/L and 7. Where the ASTER trial started with staging the mediastinum endosonographically with EUS, in a study by Kang and colleagues it was proven that adding EBUS to EUS increases the accuracy and sensitivity of mediastinal staging significantly. It is therefore concluded that EBUS is the primary procedure and an EBUS centered approach should be chosen to stage the mediastinum, followed by EUS.[34]

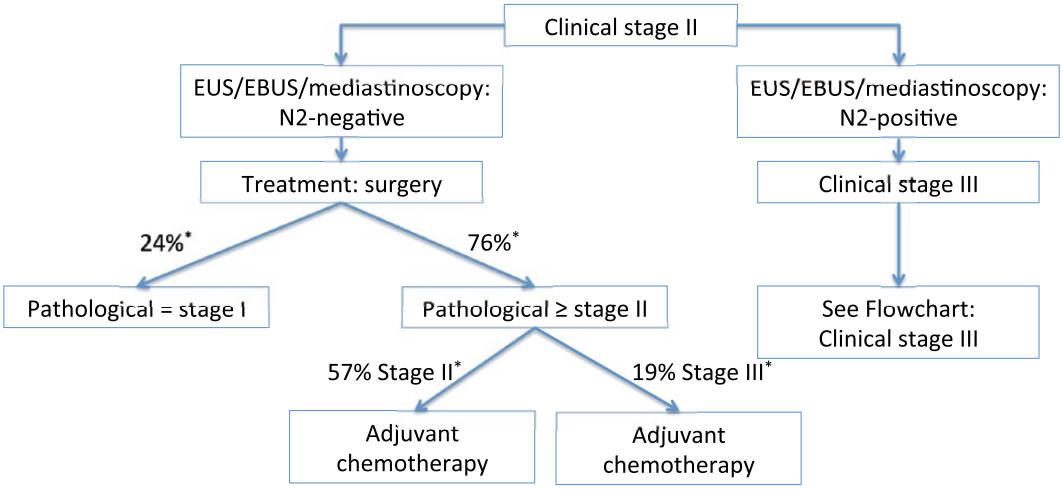
If needed, more radical lymph node dissections are possible by video-assisted mediastinoscopic lymphadenectomy (VAMLA) or transcervical extended mediastinal lymphadenectomy (TEMLA). Although the published series come from dedicated centers the NPV can reach 100% and sensitivity 100%.[35,36] However data on these techniques and diffusion into clinical practice are very limited and the increase in staging accuracy comes with the cost of a higher morbidity than in (video)mediastinoscopy.

Table 1 shows the median sensitivity and specificity of the different mediastinal staging techniques according to the ACCP clinical practice guidelines.[4] Although median sensitivity and specificity of these separate diagnostic tests are high, an analysis on stage I–IIIB tumors showed an accuracy of 54.6% between cTNM and pTNM in the Netherlands, in a population of 2336 patients in 2013 and 2014 who all had a PET-CT.[8] As can be seen in Figure 3 57% of clinical stage II patients had pathological stage II disease in this dataset, 24% is downgraded to pathological stage I disease and 19% is upgraded to pathological stage III disease. In this series with 6.3% unforeseen N2 nodes especially clinical staging of nodes proved to be difficult. Table 2 shows all studies comparing cTNM and pTNM and their respective accuracies, which range from 47–91%. The study from Jakobsen and colleagues is a positive outlier; they used a different definition for discrepancy, since it had to have therapeutic consequences for the patient and SABR and induction therapy were not used as primary treatment options.[10]

Primary treatment and adjuvant treatment

In patients with clinical stage II disease the current opinion is that when a patient is fit for surgery a radical resection is advised. Dependent on the pathological outcome adjuvant therapy is given. If a patient has pathological stage I disease there is no indication for adjuvant therapy. If a patient has pathological stage II disease, adjuvant chemotherapy is advised, as described earlier. As mentioned before this gives a 4% benefit in 5-year survival according to the Cochrane review on patients who get a resection with curative intent.[18] In a randomized controlled trial (NATCH trial) that allocated patients to adjuvant chemotherapy before their surgery it was shown that not all patients (33.8%) actually started the planned treatment after resection, due to patient refusal, surgical complications or physicians recommendation.[19] Even if the start of adjuvant chemotherapy is delayed due to slow recovery after surgery it remains effective if started up to 4 months after surgery.[37,38]

If a patient is resected and unforeseen N2 nodes are found (pathological stage IIIA-N2) in the



*according to Heineman et al.[8]

Figure 3. Flow chart stage II NSCLC.
EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound.

resected specimen it is advised to give adjuvant chemotherapy. The goal of this treatment is to reduce risk of relapse based on micrometastasis.[39] Adjuvant radiotherapy is not the standard treatment in these patients; the value of this treatment is under research in the LungART trial.[40] In a large retrospective cohort from the Netherlands the 4-year survival for upfront surgery is 39% for patients with unforeseen N2 disease.[41]

After radical resection of stage II disease, there is no place for PORT, since this has no added benefit on survival.[30,31] However, in patients with resected stage II disease and a positive resection margin (R1) postoperative radiation therapy is advised.[16]

Clinical stage III disease

Staging

Clinical stage III disease is comprised of a varied group of patients for whom different treatment options are available. Clinical stage IIIA consists

Table 2. Studies on accuracy of clinical staging comparing clinical or imaging TNM with pTNM.

Author	Year	Version TNM	Comparison	Clinical stage	Patients	Accuracy	Unforeseen N2
Gdeedo[7]	1997	1992	iTNM *versus* pTNM	I–IV	74	35%	
Cetinkaya[5]	2002	1997	cTNM *versus* pTNM	I–IV	180	48%	
D'Cunha[6]	2005	1997	cTNM *versus* pTNM	I	422	72%	13,5%
Lopez-Encuentra[12]	2005	1997	cTNM *versus* pTNM	I–IV	2377	47%	
Lee[11]	2007	1997	cTNM *versus* pTNM	I	224	75%	7.1%
Macia[13]	2009	1997	cTNM *versus* pTNM	I–IV	176	58%	11.9%
Stiles[14]	2009	1997	cTNM *versus* pTNM	IA	266	65%	11.7%
Jakobsen[10]	2013		cTNM *versus* pTNM	I–IV	810	91%	
Heineman[8]	2016	2007	cTNM *versus* pTNM	I–IIIB	2336	54.6%	6.3%
Heineman[9]	2016	2007	cTNM *versus* pTNM	I	1555	59.9%	5.5%

cTNM, clinical TNM; iTNM, imaging TNM; pTNM, pathological TNM.

of patients with T1a-2bN2, T3N1-2 or T4N0-1 disease. Clinical stage IIIB disease is T4N2 or any N3 disease.[22] Correct clinical staging in these groups is difficult, and it is known that accuracy of clinical staging decreases in higher stages. The staging algorithm is the same as for other NSCLC patients described earlier in this article, and a MRI of the brain is advised in clinical stage III disease to rule out metastasis. In all patients with clinical stage III invasive mediastinal staging is indicated, either because of a tumor >3 cm, a central tumor with extension in mediastinal structures, N1 nodes or suspicious N2 nodes on the PET-CT.[4,20,39] Especially patients with suspicious N2 nodes deserve extra attention: false positive PET findings can cause incorrect upstaging, tissue confirmation is therefore always mandatory to prevent denying a curative resection.[42,43] Accuracy of clinical staging in stage III patients is around 51% in a study comparing staging and treatment in stage III patients with an upfront resection in the Netherlands.[41] If a patient is treated with induction therapy, restaging the mediastinum is difficult: CT and PET are unreliable and a repeat mediastinoscopy can be technically difficult. EBUS can reach a sensitivity of 64-76%.[36,44] There is no preferential restaging technique; it depends mainly on the invasive method used initially to stage the mediastinum.[45] It is very important to identify the subcategories correctly in stage III disease, because treatment differs substantially between them.[39] Before any treatment is started a multidisciplinary team (MDT) should classify a patient in one of three groups:

- Potentially resectable
- Potentially resectable with an increased risk of incomplete resection
- Definitely unresectable

Primary treatment and adjuvant treatment

Patients with potentially resectable disease who have histologically or cytologically-proven clinical stage IIIA-N2 disease are advised to be treated by induction therapy with chemo(radio)therapy followed by resection or definitive chemoradiotherapy. The North American Intergroup trial is the only randomized trial that investigated treatment with full-dose definitive concurrent chemoradiotherapy *versus* induction-concurrent chemotherapy and radiotherapy followed by surgery; both groups were equal in survival although progression-free survival was better in the group that also had a resection. It is advised though that a patient should be able to have a lobectomy after induction therapy, since mortality after pneumonectomy is unacceptably high (26% 30-day mortality rate in right sided pneumonectomies). Cisplatin and etoposide were used as chemotherapeutic agents in this trial.[46] A manuscript describing an analysis, systematic review and meta-analysis showed a much more acceptable rate of 7% 30-day mortality in patients with a pneumonectomy after neoadjuvant therapy though, with a significant higher mortality in right sided pneumonectomies compared with left sided pneumonectomies (11% *versus* 5% respectively).[47] In a retrospective analysis of the Dutch Cancer Registry by Dickhoff and colleagues, overall survival in 4 years was 51% with induction therapy and resection. This analysis consisted of a heterogeneous group of stage IIIA patients combining results of stage IIIA-N2 patients and patients with T4 disease.[41]

In patients with potentially resectable disease with an increased risk of incomplete resection it is advised to give concurrent chemoradiotherapy as induction therapy followed by surgery. This is a strategy that can be used for sulcus superior tumors as well as for central T3/4 tumors. Cisplatin and etoposide are used for this purpose again.[48] Eberhardt and colleagues confirmed these findings in the ESPATUE trial, in which patients with pathologically-proven stage IIIA-N2 disease or selected stage IIIB patients received induction chemotherapy, as well as concurrent chemoradiotherapy (with cisplatin, paclitaxel and vinorelbine). After this, patients were restaged and when the tumor was resectable they were randomized between either a chemoradiotherapy boost or surgery. For both arms overall survival was good (40% *versus* 44%), just as progression-free survival (35% *versus* 32%).[49]

Patients with pathologically-proven and unresectable N2 disease were randomized in the EORTC trial; induction therapy with three cycles of chemotherapy was given and patients who showed any response were randomized to two arms. The first arm was given surgical resection; the second arm was given radiotherapy. No difference in overall survival or progression-free survival was noted (16.4 *versus* 17.5 months).[50] Hence in unresectable disease, it is not advised to do a resection after induction therapy. Definitive radiotherapy and chemotherapy combinations remain the treatment of choice for these patients. Concurrent chemoradiotherapy gives better overall survival

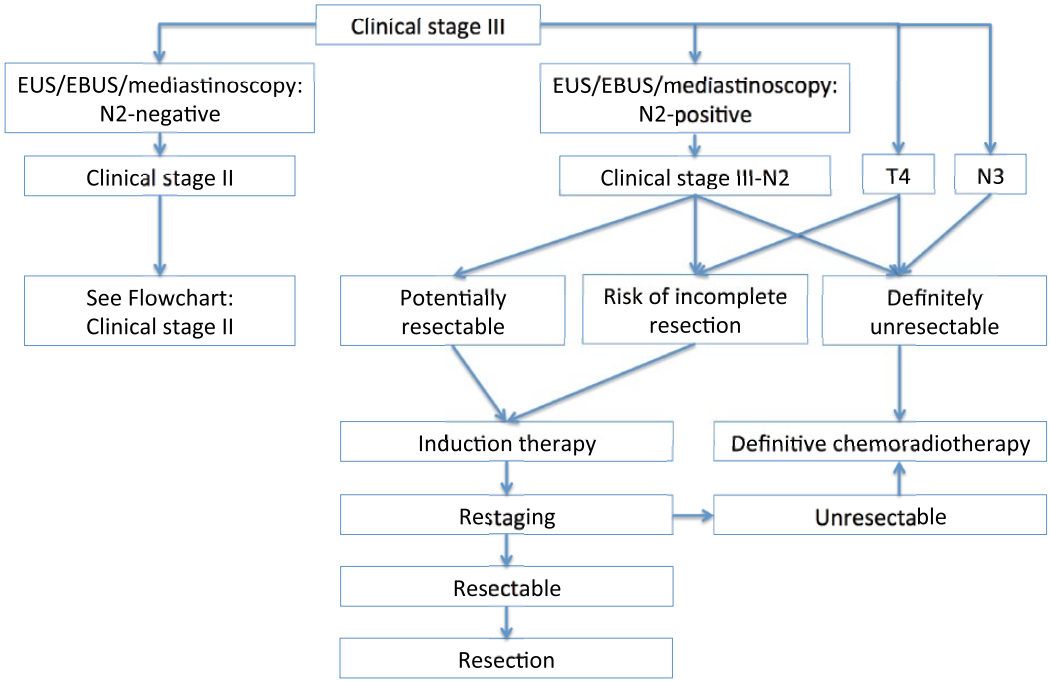


Figure 4. Flow chart stage III NSCLC.
EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound.

rates than sequential chemoradiotherapy.[51] Figure 4 shows the different treatment options in clinical stage III patients and the respective survival rates. It is suggested PORT might give a survival benefit in patients with unforeseen N2 disease, this is still under research in the LungART trial.[40] In patients with positive bronchial margin (R1) after resection who were not treated with radiotherapy preoperatively this should be considered.[16]

Conclusion

This article describes how accurate clinical staging is for different clinical stages and what consequences this has for treatment and especially adjuvant chemotherapy. Although separate diagnostic modalities in staging lung cancer have fair sensitivities and specificities, all modalities combined have moderate accuracy in diagnosing the correct stage NSCLC of a patient. As we tried to show in this article, staging algorithms differ per stage, just as treatment options. Surgical resection often changes the clinical stage to a different pathological stage. Because of this change the choice of adjuvant treatment should always depend on the pathological stage if available. Since accuracy of staging is low, it is important to obtain tissue confirmation before denying a potentially curative resection. Because of this complexity we advise that every patient with NSCLC is discussed in an MDT after every new investigation or surgery. After assessment of the actual disease stage it should be determined whether additional investigations are warranted, and whether current evidence indicates adjuvant treatment at that moment. Future research on clinical staging of NSCLC should focus on ways to improve the accuracy of the staging process and the reproducibility of the outcomes and functioning of the MDT.

In clinical stage I patients, surgical resection or SABR are the modalities of choice. As we showed there is no evidence for adjuvant chemotherapy in patients treated with SABR, especially because the pathological stage remains unknown in these patients and it is assumed they have pathological stage I disease. In patients with clinical stage II disease surgery is the treatment of choice: after resection the pathological stage is known and adjuvant treatment can be chosen. In patients who had a radical resection adjuvant chemotherapy gives a 4% survival benefit when the pathological stage is stage II or higher. In patients with pathological stage III disease the overall survival is improved with adjuvant chemotherapy, but this will only lead to an overall survival of 39% in 4

years. When a patient is suspected of clinical stage III disease it is mandatory to confirm N2 disease by tissue biopsies of the mediastinal lymph nodes. This alters the primary choice of treatment and it should be decided if a radical resection would be possible. If this might be an option, advice is to give induction therapy and do a resection after restaging. With this strategy 5-year survival can reach 44%. If a patient is definitely unresectable chemoradiotherapy is the treatment of choice. In all chemotherapy regimens cisplatin plays a role. Postoperative radiotherapy is mainly reserved for patients with R1-resections.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

References

1. Allemani C, Weir HK, Carreira H, *et al.* Global surveillance of cancer survival 1995–2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet* 2015; 385: 977–1010.
2. Jemal A, Siegel R, Ward E, *et al.* Cancer statistics, 2009. *CA Cancer J Clin* 2009; 59: 225–249.
3. Parkin D, Bray F, Ferlay J, *et al.* Global cancer statistics, 2002. *CA Cancer J Clin* 2005; 55: 74–108.
4. Silvestri GA, Gonzalez AV, Jantz MA, *et al.* Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; 143: e211S–e250S.
5. Cetinkaya E, Turna A, Yildiz P, *et al.* Comparison of clinical and surgical-pathological staging of the patients with non-small cell lung cancer. *Eur J Cardiothorac Surg* 2002; 22: 1000–1005.
6. D'Cunha J, Herndon JE II, Herzan DL, *et al.* Poor correspondence between clinical and pathological staging in stage I non-small cell lung cancer: results from CALGB 9761, a prospective trial. *Lung Cancer* 2005; 48: 241–246.
7. Gdeedo A, Van Schil P, Corthouts B, *et al.* Comparison of imaging TNM [(i)TNM] and pathological TNM [pTNM] in staging of bronchogenic carcinoma. *Eur J Cardiothorac Surg* 1997; 12: 224–227.
8. Heineman DJ, Ten Berge MG, Daniels JM, *et al.* The quality of staging non-small cell lung cancer in the Netherlands: data from the Dutch Lung Surgery Audit. *Ann Thorac Surg* 2016; 102: 1622–1629.
9. Heineman DJ, Ten Berge MG, Daniels JM, *et al.* Clinical staging of stage I non-small cell lung cancer in the Netherlands – need for improvement in an era with expanding nonsurgical treatment options: data from the Dutch Lung Surgery Audit. *Ann Thorac Surg* 2016; 102: 1615–1621.
10. Jakobsen E, Green A, Oesterlind K, *et al.* Nationwide quality improvement in lung cancer care: the role of the Danish Lung Cancer Group and Registry. *J Thorac Oncol* 2013; 8: 1238–1247.
11. Lee PC, Port JL, Korst RJ, *et al.* Risk factors for occult mediastinal metastases in clinical stage I non-small cell lung cancer. *Ann Thorac Surg* 2007; 84: 177–181.
12. López-Encuentra A, García-Luján R, Rivas JJ, *et al.* Comparison between clinical and pathological staging in 2994 cases of lung cancer. *Ann Thorac Surg* 2005; 79: 974–979.
13. Macia I, Moya J, Escobar I, *et al.* Quality study of a lung cancer committee: study of agreement between preoperative and pathological staging. *Eur J Cardiothorac Surg* 2010; 37: 540–545.
14. Stiles BM, Servais EL, Lee PC, *et al.* Point: clinical stage IA non-small cell lung cancer determined by computed tomography and positron emission tomography is frequently not pathologic IA non-small cell lung cancer: the problem of understaging. *J Thorac Cardiovasc Surg* 2009; 137: 13–19.
15. Cerfolio RJ and Bryant AS. Survival of patients with true pathological stage I non-small cell lung cancer. *Ann Thorac Surg* 2009; 88: 917–922.
16. Howington JA, Blum MG, Chang AC, *et al.* Treatment of stage I and II non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; 143: e278S–e313S.
17. Pignon JP, Tribodet H, Scagliotti GV, *et al.* Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol* 2008; 26: 3552–3559.

18. Burdett S, Pignon JP, Tierney J, *et al.* Adjuvant chemotherapy for resected early-stage non-small cell lung cancer. *Cochrane Database Syst Rev* 2015; 2: CD011430.

19. Felip E, Rosell R, Maestre JA, *et al.* Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. *J Clin Oncol* 2010; 28: 3138–3145.

20. De Leyn P, Dooms C, Kuzdzal J, *et al.* Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small cell lung cancer. *Eur J Cardiothorac Surg* 2014; 45: 787–798.

21. Oncoline: Cancer Clinical Practice Guidelines, 18 December 2015. Available at: http://oncoline.nl/niet-kleincellig-longcarcinoom (accessed 16 February 2017).

22. Sobin LH, Gospodarowicz MK and Wittekind C. *TNM classification of malignant tumours*. 7th ed. England: Wiley-Blackwell, Oxford, 2009.

23. Lampen-Sacher K, Zhao B, Zheng J, *et al.* Correlation between tumor measurement on computed tomography and resected specimen size in lung adenocarcinomas. *Lung Cancer* 2012; 75: 332–335.

24. Goldstraw P, Chansky K, Crowley J, *et al.* The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2016; 11: 39–51.

25. Gómez-Caro A, Boada M, Cabañas M, *et al.* False-negative rate after positron emission tomography/computer tomography scan for mediastinal staging in cI stage non-small cell lung cancer. *Eur J Cardiothorac Surg* 2012; 42: 93–100.

26. Wang J, Welch K, Wang L, *et al.* Negative predictive value of positron emission tomography and computed tomography for stage T1–2N0 non-small cell lung cancer: a meta-analysis. *Clin Lung Cancer* 2012; 13: 81–89.

27. Chang JY, Senan S, Paul MA, *et al.* Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 2015; 16: 630–637.

28. Meyers BF, Puri V, Broderick SR, *et al.* Lobectomy versus stereotactic body radiotherapy for stage I non-small cell lung cancer: post-hoc analysis dressed up as level-1 evidence? *J Thorac Cardiovasc Surg* 2015; 150: 468–471.

29. Louie AV, Palma DA, Dahele M, *et al.* Management of early-stage non-small cell lung cancer using stereotactic ablative radiotherapy: controversies, insights and changing horizons. *Radiother Oncol* 2014; 114: 138–147.

30. Burdett S and Stewart L; PORT Meta-analysis Group. Postoperative radiotherapy in non-small cell lung cancer: update of an individual patient data meta-analysis. *Lung Cancer* 2005; 47: 81–83.

31. PORT Meta-analysis Trialist Group. Postoperative radiotherapy in non-small cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. *Lancet* 1998; 352: 257–263.

32. Hishida T, Yoshida J, Nishimura M, *et al.* Problems in the current diagnostic standards of clinical N1 non-small cell lung cancer. *Thorax* 2008; 63: 526–531.

33. Annema JT, van Meerbeeck JP, Rintoul RC, *et al.* Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial. *JAMA* 2010; 304: 2245–2252.

34. Kang HJ, Hwangbo B, Lee GK, *et al.* EBUS-centred versus EUS-centred mediastinal staging in lung cancer: a randomised controlled trial. *Thorax* 2014; 69: 261–268.

35. Witte B, Wolf M, Huertgen M, *et al.* Video-assisted mediastinoscopic surgery: clinical feasibility and accuracy of mediastinal lymph node staging. *Ann Thorac Surg* 2006; 82: 1821–1827.

36. Zielinski M, Szlubowski A, Kolodziej M, *et al.* Comparison of endobronchial ultrasound and/or endoesophageal ultrasound with transcervical extended mediastinal lymphadenectomy for staging and restaging of non-small cell lung cancer. *J Thorac Oncol* 2013; 8: 630–636.

37. Salazar MC, Rosen JE, Wang Z, *et al.* Association of delayed adjuvant chemotherapy with survival after lung cancer surgery. *JAMA Oncol* 2017; 3: 610–619.

38. West HJ. Bringing adjuvant chemotherapy for resected non-small-cell lung cancer into real-world practice: better late than never? *JAMA Oncol* 2017; 3: 619.

39. Eberhardt WE, De Ruysscher D, Weder W, *et al.* 2nd ESMO consensus conference in lung cancer: locally advanced stage III non-small cell lung cancer. *Ann Oncol* 2015; 26: 1573–1588.

40. Le Péchoux C. Role of postoperative radiotherapy in resected non-small cell lung cancer: a reassessment based on new data. *Oncologist* 2011; 16: 672–681.

41. Dickhoff C, Dahele M, de Langen AJ, *et al.* Population-based patterns of surgical care for

stage IIIA NSCLC in the Netherlands between 2010 and 2013. *J Thorac Oncol* 2016; 11: 566–572.

42. Fischer B, Lassen U, Mortensen J, *et al.* Preoperative staging of lung cancer with combined PET-CT. *N Engl J Med* 2009; 361: 32–39.
43. Van Tinteren H, Hoekstra OS, Smit EF, *et al.* Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small cell lung cancer: the PLUS multicentre randomised trial. *Lancet* 2002; 359: 1388–1393.
44. Herth FJ, Annema JT, Eberhardt R, *et al.* Endobronchial ultrasound with transbronchial needle aspiration for restaging the mediastinum in lung cancer. *J Clin Oncol* 2008; 26: 3346–3350.
45. Murgu SD. Diagnosis and staging lung cancer involving the mediastinum. *Chest* 2015; 147: 1401–1412.
46. Albain KS, Swann RS, Rusch VW, *et al.* Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small cell lung cancer: a phase III randomised controlled trial. *Lancet* 2009; 374: 379–386.
47. Kim AW, Boffa DJ, Wang Z, *et al.* An analysis, systematic review, and meta-analysis of the perioperative mortality after neoadjuvant therapy and pneumonectomy for non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2012; 143: 55–63.
48. Rusch VW, Giroux DJ, Kraut MJ, *et al.* Induction chemoradiation and surgical resection for superior sulcus non-small cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160) *J Clin Oncol* 2007; 25: 313–318.
49. Eberhardt WE, Pöttgen C, Gauler TC, *et al.* Phase III study of surgery versus definitive concurrent chemoradiotherapy boost in patients with resectable stage IIIA(N2) and selected IIIB non-small cell lung cancer after induction chemotherapy and concurrent chemoradiotherapy (ESPATUE). *J Clin Oncol* 2015; 33: 4194–4201.
50. Van Meerbeeck JP, Kramer GW, Van Schil PE, *et al.* Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small cell lung cancer. *J Natl Cancer Inst* 2007; 99: 442–450.
51. Aupérin A, Le Péchoux C, Rolland E, *et al.* Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small cell lung cancer. *J Clin Oncol* 2010; 28: 2181–2190.