Management of stage I and II nonsmall cell lung cancer

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TITLE PAGE

Multidisciplinary questions in thoracic oncology: The team experience

Management of stages I & II NSCLC

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List of abbreviations

AIS	adenocarcinoma in situ
ATS	American Thoracic Society
BAC	bronchioloalveolar carcinoma
BED	biologically equivalent dose
CRT	chemo-radiotherapy
CT	computed tomography
C/T	consolidation / maximal tumour diameter
DFS	disease-free survival
DLCO	diffusion capacity for CO
EBUS	endobronchial ultrasound
EGFR	epidermal growth factor receptor
ERCC1	excision repair cross-complementation group 1
ERS	European Respiratory Society
ESMO	European Society of Medical Oncology
ESTS	European Society of Thoracic Surgeons
EUS	endoscopic ultrasound
HR	hazard ratio
IASLC	International Association for the Study of Lung Cancer
LVI	lymphovascular invasion
MDT	multidisciplinary team
MIA	minimally invasive adenocarcinoma
MIT	minimally invasive technique
NSCLC	non-small cell lung cancer
OS	overall survival
PET	positron emission tomography
PS	performance status
QOL	quality of life
RCT	randomised controlled trial
RFA	radiofrequency ablation
RT	radiotherapy
SBRT	stereotactic body radiotherapy
SLR	sublobar resection
TKI	tyrosine kinase inhibitor
VATS	video-assisted thoracic surgery
VPI	visceral pleural invasion
WHO	World Health Organisation

ABSTRACT

The incidence of stage I and II non-small cell lung cancer (NSCLC) is likely to increase with the aging population and introduction of screening for high-risk individuals. Optimal management requires multidisciplinary collaboration. Local treatments include surgery and radiotherapy and these are currently combined with (neo)adjuvant chemotherapy in specific cases to improve long-term outcome. Targeted therapies and immunotherapy also may become an important therapeutic modality in this patient group. For resectable disease in patients with low cardiopulmonary risk complete surgical resection with lobectomy remains the gold standard. Minimally invasive techniques (MIT), conservative and sublobar resections are suitable for a subset of patients. Data are emerging that radiotherapy, especially stereotactic body radiation therapy, is a valid alternative in compromised patients who are high-risk candidates for surgery. Whether this is also true for good surgical candidates remains to be evaluated in randomised trials. In specific subgroups adjuvant chemotherapy has been shown to prolong survival; however, patient selection remains important. Neoadjuvant chemotherapy may yield similar results as adjuvant chemotherapy. The role of targeted therapies and immunotherapy in early stage NSCLC has not yet been determined and results of randomised trials are awaited.

INTRODUCTION

Multimodality treatment of stage I and II NSCLC requires a delicate interplay between surgery, radiotherapy (RT) and chemotherapy. More recently, immunotherapy and targeted agents have emerged as potential important treatment modalities. To determine management for each patient, a thorough knowledge is required of the natural history of disease, risk assessment of the individual patient, evaluation of the diagnostic and staging examinations available, multidisciplinary input into individualised treatment plans, and importantly, discussion of the risks and benefits of treatment options with the patient. To this end every patient with presumed or proven lung cancer should be discussed within a dedicated multidisciplinary team (MDT) to ensure the optimal individualized therapeutic plan.

In this article, as part of the "Multidisciplinary questions in thoracic oncology", the different treatment modalities that are currently available for these patients are discussed in depth. The local modalities, surgery and RT, and their integration with systemic treatment are reviewed. Every co-author searched the literature over the past 10 years in his specific discipline. Main databases used were PubMed, Cochrane database and Web of Science. References of the selected papers and abstracts of major meetings were also screened for new, relevant data. As a broad area is covered, this manuscript cannot be considered a systematic review *stricto sensu* but a clear update is provided on management of stage I and II NSCLC. When applicable, levels of evidence are mentioned (table 1). Presently there are a number of grey areas, highlighting the need for further clinical research to provide high-level evidence for future recommendations.

DIAGNOSIS, PATIENT SELECTION AND STAGING

CT screening

The incidence of early stage NSCLC is expected to increase due to wider availability of CT scans and the introduction of screening in high-risk populations (1). This will increase surgical workload. The higher risks of surgical morbidity and mortality in patients with multiple co-morbidities, coupled with an aging population suggests non-surgical management of early stage NSCLC is likely also to rise (2).

Implication of changes in World Health Organisation (WHO) pathological classification

The new WHO classification of lung tumours, published in 2015, integrates immunohistochemistry in the classification of resected lung cancers (3). A complete histological evaluation of the tumor is necessary for diagnosis and is of prognostic value. In this edition the American Thoracic Society (ATS)/ European Respiratory Society (ERS)/ International Association for the Study of Lung Cancer (IASLC) classification of adenocarcinoma published in 2011 was included without changes (4). New subcategories include adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA). Complete histologic review should be performed to look for invasive foci with measurement of invasion. The term bronchioloalveolar carcinoma (BAC) which gave rise to much confusion, is not used anymore. Subtypes of invasive adenocarcinoma should be listed with their relative percentage indicated. This classification also has profound surgical implications which will be discussed further (5).

Implication of changes in 8th edition of TNM classification

In 2017, the 8th TNM classification of lung cancer will be introduced (6, 7). Important changes have been made in the T descriptor on the basis that larger tumours are associated with worse prognosis. Three centimetres (cm) diameter remains the cut-off margin between T1 and T2; T1 is subdivided into T1a (≤1cm), T1b (1.1-2 cm) and T1c (2.1-3 cm). T2 is subdivided into T2a (3.1-4 cm) and T2b (4.1-5 cm). Tumours larger than 5 cm and 7 cm are categorized as T3 and T4, respectively. Using the entire database

available for the 8th TNM classification, 5-year survival has improved [level C evidence]. Overall survival (OS) by clinical and pathological stage for the 7th and 8th TNM classifications are given in tables 2A and 2B, respectively, for comparison (6-8).

Cardiopulmonary risk assessment

All patients should be discussed in a MDT to decide which treatment option is most suitable on an individual basis. Although there is no clear definition of high-risk patients, it should be kept in mind that empiric selection of patients may deny optimal oncologic management (9). Even with modern computed tomographic (CT) and positron emission tomographic (PET) staging, pathologic upstaging is seen in up to 30% of patients (10, 11). Multiple guidelines exist on selecting patients who are fit for surgery (12-14). The 2nd European Society for Medical Oncology (ESMO) consensus conference on lung cancer recommended detailed assessment of cardiac and pulmonary function in order to estimate surgical morbidity [level C evidence]. Cardiac function is tested using the recalibrated thoracic revised cardiac risk index, made up of history of ischaemic heart disease and cerebrovascular disease, serum creatinine and whether the intended procedure is a pneumonectomy or not. Pulmonary function is determined by the percentage of predicted forced expiratory volume in one second (FEV1) and lung diffusion capacity (DLCO). When percentages are <80% for either one, exercise testing is recommended (maximal oxygen consumption and split lung function) (15). Also for patients undergoing RT and chemotherapy cardiopulmonary function should be assessed. This is especially important in patients with low DLCO and poor performance status (PS) to decide whether they tolerate the anticipated treatment scheme or not.

Lung cancer staging

For a presumable clinical stage I or II NSCLC evaluation of locoregional lymph node spread and screening for distant metastases are required. This is mostly performed by PET-CT scanning which provides anatomic and metabolic information. In case of suspicious lymph nodes or distant lesions every effort should be made to obtain a pathological diagnosis by a MIT or invasive technique. Further lymph node

evaluation is performed by endobronchial ultrasound (EBUS) or endoscopic ultrasound (EUS). In case results are negative, mediastinoscopy or thoracoscopy are the next steps [level D evidence]. Recently, the European Society of Thoracic Surgeons (ESTS) updated guidelines for preoperative staging of NSCLC (16). Also, for patients undergoing SBRT lymph node staging is recommended (17).

TREATMENT MODALITIES

1. Surgery

Introduction

Surgical intervention remains the gold standard for the approximately 30% of NSCLC patients who present with resectable stage I and II disease (18) and who are functionally operable [level C evidence] (15, 19). The extent of resection and precise surgical approach are the subject of discussion. Additionally, with the advances in newer ablative techniques their role in early stage disease is currently debated, especially in medically compromised patients. In this section the indications for sublobar resections (SLR), sleeve resections and MIT approaches by video-assisted and robotic-assisted techniques (VATS/RATS) are discussed.

Conservative interventions: sublobar resection (SLR) and bronchoplastic procedures

Lobectomy has remained the standard of care for resection of early stage NSCLC since the prospective randomised Lung Cancer Study Group trial, comparing lobectomy with SLR (anatomical segmentectomy or wedge resection) for stage I NSCLC, which was published in 1995 (20). The limited resection group had a three-fold increased incidence in local recurrence ($p=0.008$), a 30% increase in overall death rate ($p=0.08$) and a 50% increase in cancer related death ($p=0.09$) compared to patients undergoing lobectomy [level B evidence]. It is important to note that the limited resection arm included anatomical segmentectomies as well as non-anatomical wedge resections and tumours until 3 cm were eligible. Since this study, there has not been another prospective trial on this topic. Several single centre retrospective studies have been published with conflicting conclusions (21, 22). Landreneau et al.

performed a propensity matched comparison between anatomical segmentectomy versus lobectomy for clinical stage I NSCLC. The study reported no significant difference in locoregional recurrence (p=1.00) or in 5-year DFS (p=0.47) (23). Yano et al. published a multi-institutional retrospective study (n=1737) on limited resections (segmentectomy or wedge resection) for cT1 N0 M0 NSCLC (24). CT imaging was used to determine the invasive potential of the tumour on the basis of the ratio of consolidation (C) to the maximal tumour diameter (T) (C/T ratio). Tumours were classified "invasive" if the C/T ratio was more than 0.25 (C/T > 0.25) and "non-invasive" if C/T ≤ 0.25. OS and DFS after limited resection were 94.0% and 91.1% at 5 years, respectively. C/T ≤0.25 predicted for good outcome, especially in cT1a N0 M0 disease. In a meta-analysis by Cao et al., data were reviewed of intentional SLRs versus lobectomy for early stage NSCLC (25). Patients who underwent SLR for small, peripheral NSCLC after intentional selection rather than ineligibility for larger resections, achieved similar long-term survival outcomes as those who underwent lobectomies [level C evidence]. However, patients included in this meta-analysis were a highly selected cohort and these results should be interpreted with caution. Two large prospective trials are currently ongoing (CALGB 140503 and JCOG0802 / WJOG4607L), comparing segmentectomy versus lobectomy in NSCLC and the results are eagerly awaited (table 3) (26, 27).

SLR is a valid alternative to lobectomy in lung cancer patients who meet the following criteria: stage IA disease, tumours up to 2 cm diameter, peripheral tumour location and predominantly ground-glass (non-solid) appearance on CT imaging [level of evidence C] (28). Anatomical segmentectomy is preferred over wedge resection since the latter is associated with higher rates of locoregional recurrence in stage IA NSCLC (29, 30). Although, in case of a predominant ground glass opacity clinical stage IA adenocarcinoma, a wedge resection might be performed with a T1a tumour, and segmentectomy for a T1b tumour due to the low-grade malignancy and favourable prognosis [level C evidence] (31). When dealing with a solid-type, clinical stage IA NSCLC, a lobectomy is recommended (32).

The 2nd ESMO consensus conference on lung cancer concluded that SLR is acceptable for pure ground glass opacities and AIS with minimal invasion (15). Lobectomy is still the preferred treatment for tumours

≤ 2 cm with solid appearance on CT [level C evidence]. Either open thoracotomy or VATS can be utilized as per experience of the thoracic surgeon.

Next to the above mentioned distal lung parenchyma saving procedures, proximal bronchoplastic interventions as sleeve resections may be the treatment of choice in early stage NSCLC with proximal bronchial involvement or positive N1 nodes around a lobar bronchus (33, 34). In this way a pneumonectomy is avoided. Conservative resections are more often performed in carcinoids or in patients with impaired pulmonary reserve (35).

Minimally invasive surgery

MIT like VATS or RATS have been widely implemented as standard treatment for early stage NSCLC. Both procedures are equivalent in outcome [level of evidence C] (36). A retrospective analysis on the National Cancer Database (USA) looked at perioperative outcomes and survival of patients with clinical T1-2, N0 M0 NSCLC undergoing open or MIT: VATS and RATS (37). This is a clinical oncology database jointly sponsored by the American College of Surgeons and the American Cancer Society sourced from hospital registry data that are collected in more than 1 500 Commission on Cancer-accredited facilities. Shorter median length of stay (5 versus 4 days; $p<0.001$), and improved 2-year survival (87% versus 86%; $p=0.04$) were observed when a MIT was used. There was no significant difference in nodal upstaging rates and 30-day mortality rates between the two groups. Comparing the two MIT, there was no significant difference between VATS and RATS in regards to nodal upstaging, 30-day mortality, and 2-year survival rates.

It is important to consider the role of nodal dissection, for which precise criteria have been established, to accurately stage the extent of cancer spread pathologically (38). Medbery et al. conducted a retrospective analysis on the same National Cancer Database and reported nodal upstaging was more frequent in patients treated with lobectomy by thoracotomy than by VATS (12.8% versus 10.3%; $p<0.001$) (39). This difference was non-significant in patient groups treated in academic research facilities (39).

Differences in quality of life (QOL) measures following open compared to VATS anatomic resection were assessed in a prospective study and were found to be similar in both patient groups [level of evidence C]

(40). In addition the patient-reported physical component summary and pain scores after thoracotomy and VATS were also similar in both groups during the first 12 months after surgery (40).

2. Radiotherapy (RT)

Introduction

In addition to the advances in surgery over recent years, there have been dramatic developments in RT for NSCLC patients. RT is established as an alternative curative treatment option for patients with early stage disease, particularly in patients who are considered medically inoperable due to co-morbidities. In this section we compare local ablative therapies for stage I NSCLC and discuss the role of RT in a multidisciplinary setting as adjuvant and definitive treatment for stage I and II NSCLC.

Comparison of local ablative treatments for stage I NSCLC

Whenever there is a contraindication for surgery, RT may offer a valid alternative. Up till now, no valid prospective randomised controlled trial (RCT), comparing surgery and stereotactic body radiotherapy (SBRT) in medically operable patients with early stage NSCLC, has been completed. Therefore the question 'whether SBRT yields similar results as complete surgical resection', remains unanswered [level of evidence C] (41). A recently performed propensity matched comparison between surgery and SBRT in over 117,000 patients with stage I NSCLC, derived from the National Cancer Database (USA) demonstrated that although 95% of patients received surgery, the median OS favoured the surgical group (62.3 versus 33.1 months, $p<0.001$) (41). The main limitation of such analysis is the difficulty in attributing improved outcome to patient selection or better cancer control, particularly since causes of death are unknown. Unfortunately, up till now prospective RCT's, comparing surgery and SBRT in medically operable patients with early stage NSCLC, have all been terminated prematurely due to poor accrual (table 4). A recent combined analysis of patients randomised in both the Dutch ROSEL trial and the U.S. STARS trial comparing SBRT to lobectomy demonstrated a significant 3-year OS advantage in favour of SBRT (95% vs 79%; $p=0.037$) in the 58 included patients (42). DFS was similar in both groups however

severe ≥ grade 3 toxicity was lower in the SBRT group (10% vs 44%). Despite small numbers the data suggest 'at least clinical equipoise between the two treatment modalities' [level of evidence C]. However, as discussed in several Letters to the Editor, it should be noted that mortality in the surgical arm was unacceptably high, that histology was not obtained in every case, and that direct comparison of locoregional control between surgery and RT is not possible (43-49). Further interest lies in comparing SBRT to surgical resection (lobectomy or SLR) in patients considered 'high-risk' for surgery. There are ongoing studies, assessing randomisation in this setting, currently recruiting (Table 5).

The use of radiofrequency ablation (RFA) might rival with SBRT or SLR in early stage NSCLC. One study has compared the selection criteria and short-term outcomes in 3 prospective clinical trials that used SBRT (Radiation Therapy Oncology Group [RTOG] trial 0236), SLR (ACOSOG trial Z4032) and RFA (ACOSOG trial Z4033). The overall 90-day mortality for SBRT, surgery, and RFA was 0%, 2.4%, and 2.0%, respectively (p=0.5) [level of evidence C] (50). The RFA trial included older patients with more impaired lung function. Another study has assessed the outcomes of SLR, RFA and radiation treatment in 116 patients with histologically proven stage I NSCLC from a prospective database (51). The hazard ratio (HR) for primary tumour recurrence adjusted for age and tumour size was 2.73 (95% CI 0.72-10.27) for SLR versus RT, and 7.57 (95% CI 1.94-29.47) for SLR versus RFA. SLR was associated with a higher primary tumour control rate compared to RFA or RT but no differences were observed in OS or DFS [level of evidence C]. Interpretation of data from both these studies is limited as baseline patient characteristics were not comparable and treatment was not randomly assigned. In particular in the second study the RT group included patients treated with both SBRT (57%) and conventionally fractionated RT (43%). The median tumour size was significantly larger in the RT group compared to the other two groups. A large prospective RCT is required to assess the benefits of RFA in comparison to SBRT and surgery.

Adjuvant radiotherapy (RT) in resected early stage NSCLC

A meta-analysis of data from 9 randomised trials of adjuvant RT after resection of stage I-III NSCLC revealed a significant absolute detriment of 7% increased mortality at 2 years with the addition of RT

[level A evidence](52). Subgroup analyses suggested that the adverse effect was greatest for patients with stage I and II disease and therefore adjuvant RT is not recommended for completely resected early stage disease (15, 53).

Definitive radiotherapy (RT) for stage I NSCLC

SBRT makes use of advanced RT planning and delivery techniques to permit high doses of radiation per fraction to be given accurately to small discrete targets with high conformality and rapid dose fall-off within the surrounding normal tissues. The majority of published studies of lung SBRT are single centre retrospective series [level C evidence]. There are technical variations in practice in the literature including whether the reported radiation dose is prescribed to the 100% or to the isodose covering the target, in the type of planning algorithms software and whether a heterogeneity correction was applied. Additionally, there are variations in patient selection, including whether there was pathological confirmation of the treated lesion, staging, including whether the mediastinum was invasively staged and in the CT scanning follow-up intervals for assessment of local disease control. Bearing these limitations in mind, promising outcomes are observed with SBRT, for example, a systematic review of published studies of SBRT for peripherally positioned stage I NSCLC reports 2-year local disease control rates of 91% and 2-year OS rates of 70% (54).

Importantly, it is the position of the steep dose fall off within normal tissues that determines the potential toxicity. While toxicity with lung SBRT is generally low with grade 3 or higher rates usually <4% (55-57), the exception is for centrally placed lesions as highlighted in a single centre phase II study. Patients with centrally located tumours were treated with a schedule of 60 to 66 Gy in 3 fractions (54 Gy in 3 fractions equivalent with heterogeneity correction) and after 4 years follow-up had an 11-fold higher risk of developing grade 3–5 toxicities when compared to patients with peripherally located tumours (58). This led to the initial definition of the 'no fly zone' (the volume encompassing 2 cm in all directions around the proximal bronchial tree) used in the RTOG 0236 trial (57) and subsequent SBRT studies [level C evidence].

Various dose fractionation schedules are reported in the literature varying between 1 and 10 fractions with higher number of fractions predominantly being used for more centrally located lesions; however, the optimal dose remains unknown and is complicated by the variation in dose prescription methods used in the literature making comparison of outcomes challenging [level of evidence C]. While schedules with a biologically equivalent dose (BED) of 100 Gy_{10} or more are associated with high local disease control rates (59, 60), a meta-analysis suggests the highest biologically equivalent schedules (>146 Gy_{10}) may be associated with lower survival rates than the medium-high schedules (106 – 146 Gy_{10}) [level C evidence] (61).

To address the dose question for peripheral tumours, the randomised phase II RTOG 0915 trial compared 48 Gy in 4 fractions (BED 105 Gy_{10}) to a single 34 Gy fraction (BED 150 Gy_{10}). One-year OS was 85% in the single fraction arm and 91% in the 4 fraction arm with similar toxicity and local tumour control rates (62). Further follow-up is awaited to decide whether the single fraction schedule will be compared to the RTOG 0236 schedule of 54 Gy in 3 fractions in a phase III setting for peripheral lesions [level B evidence]. For central lesions, the initial results from the RTOG 0813 study investigating maximum tolerated dose for central lesions using 5 fractions, presented in abstract form, suggest that the highest investigated dose level of 60 Gy in 5 fractions is associated with a 7.2% risk of severe dose limiting toxicity (63). Data on efficacy of the various dose levels in the phase II component of the study are awaited prior to decision about the dose to be considered in a phase III setting (63). The EORTC LungTech trial (NCT01795521) investigating the safety of 60 Gy in 8 fractions for centrally lesions is actively recruiting. When comparing studies with treatment of central lesions it is also important to note that there is more than one definition of a 'central' lesion in the literature (64).

For inoperable patients, in comparison with standard fractionation RT, the Scandinavian phase II SPACE RCT compared 3D conformal RT to 70 Gy in 7 weeks with SBRT to 66 Gy in 3 fractions in inoperable patients with stage I peripheral lesions. Initial results, in abstract form, with a median follow up of 37 months reveal no significant difference in DFS or OS [level B evidence]. However, the patients in the SBRT arm experienced significantly less any-grade pneumonitis (19% versus 36%) and oesophagitis (8% versus

30%) with improved dyspnoea, cough and chest pain QOL measures (65). The phase III RTOG 0902 CHISEL trial (NCT01014130) completed recruitment and the results are awaited. There has been no direct comparison between SBRT and RFA in inoperable patients with early stage NSCLC, however due to the greater body of evidence in the literature to support SBRT as definitive treatment for NSCLC, SBRT is considered the most appropriate therapy for inoperable patients with stage I NSCLC [level C evidence]. Despite SBRT being well tolerated, patient selection remains important. The majority of published SBRT trials included lesions up to 5 cm in diameter. Larger lesions are included in multiple retrospective series and can be considered for SBRT if dose constraints to surrounding normal tissues can be met. Alternative more protracted schedules can also be considered, for example 60 Gy in 15 fractions (66) or 70 Gy in 17 fractions (67). As for medically inoperable patients with poor lung function and multiple co-morbidities and advanced age, SBRT needs to be weighed up against the risks of no treatment. The median survival of patients with routinely detected clinical stage I and II disease is approximately 10 months (68) and population-based studies of elderly patients with early stage NSCLC suggest that the observed improvement in OS over time is limited to patients treated with RT, including SBRT, rather than surgery or to those not treated radically [level C evidence] (69). Therefore advanced age alone should not exclude patients from SBRT. With co-morbidities, there are no absolute contraindications to SBRT and in general, patients with ECOG performance status of 0-2 or poor lung function (70, 71) should be considered for treatment. An important relative contraindication to SBRT however is active interstitial lung disease with higher than expected reported cases of severe or fatal pneumonitis in retrospective series (72, 73).

Up to 20% of patients treated with SBRT will relapse with distant metastases after treatment (74, 75). There is no proven role for adjuvant chemotherapy following SBRT particularly in patients with larger lesions (≥4 cm) that would be considered for adjuvant therapy following resection. A study in this patient population would be interesting. However, given the majority of these patients are considered medically inoperable, many may not be suitable candidates for platinum-based systemic therapy.

In summary, SBRT is the standard of care for medically inoperable patients with early stage peripheral NSCLC [15, 16]. As outlined in the section above, in comparison with surgery in operable patients, SBRT remains an alternative and offers at least clinical equipoise with surgery, especially in those considered 'high-risk' for surgery until further evidence is available comparing the two modalities. Prospective trial data are awaited to determine the optimal dose schedules, in particular for central lesions (15, 76).

Definitive (chemo)radiotherapy for stage II NSCLC

For the relatively small proportion of patients with medically inoperable stage II NSCLC not suitable for SBRT, usually because of ipsilateral hilar nodal involvement, the standard of care is treatment with chemo-radiotherapy (CRT) using conventional fractionation and platinum based regimens (77-79). The role of concomitant compared to sequential chemotherapy in this patient group is less clear. In the landmark meta-analysis of over 1200 patients with stage I-III disease concomitant CRT was associated with a 4.5% benefit in OS at 5 years compared to a sequential approach at the expense of a significant increase in acute oesophageal toxicity from 4% to 18% (80). However, less than 3% of the patients included in the analysis had stage I-II with the vast majority having stage III disease [level B evidence]. The added benefit of accelerated RT in the sequential setting is also less clear in stage II disease [level C evidence]. The large meta-analysis assessing accelerated hypo- or hyper-fractionated RT schedules compared to conventionally fractionated treatment in over 2000 patients with NSCLC (81) demonstrated that accelerated schedules were associated with a 2.5 % improvement in OS at 5 years. However, again only a small proportion of included patients, <20%, had stage I-II disease [level C evidence]. Given the paucity of data on definitive CRT specifically in inoperable patients with stage II disease, a population-based outcomes study (>550 patients) was recently performed in this patient group (82). Stage II NSCLC patients treated with concomitant or sequential CRT were included and a median OS of 20.5 months was found. This figure approximates to survival figures in stage III disease from historic phase III trials [level C evidence]. There is likely to be adverse selection bias for these patients with stage II disease given they were considered medically inoperable.

In summary, patients with inoperable stage II disease should be treated with definitive RT and consideration of the addition of chemotherapy concomitantly or sequentially should be given based on fitness to tolerate treatment. Further studies are required to assess the benefits of CRT in this population specifically. Additionally the role of treatment dose intensification with isotoxic RT schedules (83), oncogene targeted systemic therapies, DNA damage repair and immune checkpoint inhibitors also need to be explored.

Salvage surgery after stereotactic radiotherapy

For recurrent or persistent NSCLC after SBRT salvage surgery is a valid therapeutic option when a complete resection is feasible and cardiopulmonary functional assessment shows no contra-indication for the anticipated resection. Although surgical salvage is a relatively new concept in thoracic surgery, recent data show that it is feasible in selected patients, not only for NSCLC but also for lung metastases [level E evidence] (19, 49). Technical difficulties in performing the resection are limited on the condition that the hilum and mediastinum are not irradiated before. More long-term data are needed to determine its role more precisely.

3. Systemic therapy

Introduction

In contrast to the previous sections (locoregional treatment), in this section systemic therapy is discussed. Platinum-based chemotherapy, targeted agents, immunotherapy and anti-angiogenic agents as adjuvant therapies for resected early stage NSCLC are discussed.

Adjuvant platinum-based chemotherapy

The RCT's of adjuvant cisplatin-based chemotherapy versus observation in patients with resected stage I-III NSCLC demonstrate statistically significant benefit for the addition of systemic therapy [level A

evidence] (84-88). An overview of these trials is provided in table 6. A meta-analysis of pooled data (n=4584) revealed a 5.3% (OS) and 5.2% (DFS) improvement at 5 years with the addition of cisplatin-based chemotherapy (89). However, a statistically significant interaction between disease stage and chemotherapy effect was observed. In stage IA a potential detrimental effect was found with the addition of chemotherapy. In stage IB a trend was seen favouring the addition of systemic therapy [level B evidence]. A subsequent study of adjuvant carboplatin/paclitaxel in patients with resected stage IB NSCLC demonstrated no OS benefit, however an unplanned retrospective subgroup analysis revealed a benefit for patients with tumours of ≥4 cm (90). Therefore, the ESMO guidelines state that adjuvant chemotherapy can be considered for the latter (15). As mentioned previously, in the forthcoming 8th TNM edition, it is proposed to reclassify tumours ≥ 4 cm as T2b (6) and subsequently these are grouped as stage IIA instead of stage IB (7).

Recently, a Cochrane meta-analysis on adjuvant chemotherapy (without radiotherapy) in resected NSCLC was performed; 35 trials were identified and an analysis based on 8447 participants showed a clear benefit of adjuvant chemotherapy (HR 0.86, 95% CI 0.81-0.92, p<0.0001) with a 5-year absolute survival benefit of 4% (91)[level A evidence]. The most studied adjuvant drug combination is cisplatin/vinorelbine, although the Cochrane meta-analysis showed little variation in effect between different regimens [level A evidence] . Moreover, an exploratory analysis of the E1505 trial (adjuvant chemotherapy +/- bevacizumab in early stage resected NSCLC) presented at the ASCO 2016 annual conference showed no difference in DFS or OS for the four different cisplatin-based chemotherapy regimens (cisplatin with investigator's choice: vinorelbine, docetaxel, gemcitabin or pemetrexed) (92).

No difference in survival has been demonstrated between neoadjuvant and adjuvant treatment [level B evidence] (93, 94). Due to adjuvant trial results most neoadjuvant trials were closed prematurely (95). A potential advantage of neoadjuvant chemotherapy is that compliance may be better. Due to their clinical condition more patients are likely to complete 4 cycles of neoadjuvant chemotherapy, compared to the 50-70% completing 4 treatment cycles demonstrated in most adjuvant studies (94, 96).

Patients enrolled in clinical trials are highly selected and often younger, with good PS and fewer co-morbidities compared to patients in the general population. In a retrospective analysis of the Ontario Cancer Registry it was shown that adjuvant chemotherapy had a detrimental effect in patients with severe co-morbidities (Charlson Score 3+) (97). A subgroup analysis of the JBR.10 study demonstrated that elderly (>65 years) had the same amount of benefit with adjuvant chemotherapy than younger patients, without additional toxicity (98). In the LACE meta-analysis the same was true for patients > 70 years (99). Interestingly, in both studies the elderly received on average fewer chemotherapy cycles and reduced cisplatin dose. OS benefit for elderly (>65 year) with stage I (tumour ≥ 4cm) in a SEER-Medicare analysis (n=3289) although adjuvant chemotherapy was associated with an increased number of serious adverse events (100). However, data on patients > 75 years are lacking as this group was underrepresented in clinical trials [level B evidence]. In clinical trials adjuvant chemotherapy is started within 6-8 weeks of surgery. In daily practice 35% of patients start adjuvant chemotherapy >10 weeks after surgery; however, this did not appear to have a negative impact on survival (97).

The meta-analysis showed a clear OS benefit for adjuvant chemotherapy and it is advised in all current guidelines. However, tools to optimally select patients who benefit from chemotherapy are warranted, especially since the updated survival analysis of the International Adjuvant Lung Cancer Trial (IALT) showed that the survival benefit did not persist after 5 years of follow-up, mainly due to increased non-lung cancer mortality in patients treated with adjuvant chemotherapy [level B evidence] (101). The histological NSCLC subtype has not been shown to be a predictive factor of benefit from adjuvant chemotherapy and as yet, there is no fully validated biomarker to identify patient subgroups who may derive particular benefit (91). The IALT biomarker group has studied predictive value of several biomarkers including excision repair cross-complementation group 1 (ERCC1) and P53. ERCC1 expression seemed to be a predictive marker for response to platinum-based chemotherapy, with only ERCC1 negative tumours benefitting from adjuvant chemotherapy (102). Although the randomised adjuvant TASTE trial showed that a biology driven randomised adjuvant trial is feasible, the planned phase III trial

was terminated due to inaccuracy of the ERCC immunohistochemical staining classification (103). Until now, no potential predictive biomarker has been validated in a RCT and none can be used to select patients who benefit from adjuvant chemotherapy. Invasive components of the tumour (vascular, lymphatic or perineural invasion) are also of prognostic significance in early stage NSCLC. Although not evaluated in RCT's it is possible that resected early stage patients with adverse prognostic factors would benefit more from adjuvant treatment than those without. In a meta-analysis (22 studies, total of 25280 patients with resected stage I NSCLC), visceral pleural invasion (VPI) was associated with death (HR 1.427,95% CI 1.221-1.669, p <0.001) and recurrence (HR 1.600, (95% CI 1.284-1.995, p<0.001) (104). This increased risk was found for all subgroups including patients with tumours < 2 cm. Comparable results were found in another analysis including 13 cohort studies (27171 patients) (105) [level C evidence]. Lymphovascular invasion (LVI) was also associated with a worse prognosis in a recent meta-analysis including resected stage I patients (20 studies, 8032 patients) (106). Risk of death was significantly higher in patients with LVI (HR 1.81, 95% CI 1.53-2.14) [level C evidence] . Conflicting studies exist on the prognostic significance of perineural invasion (107, 108). A newer method to evaluate prognosis is the use of an immunoscore. For example, it was shown that stromal CD8+ tumour-infiltrating lymphocytes (TIL) density had a prognostic impact across all stages in multivariate analysis in a study including 797 resected stage I-IIIA NSCLC patients (109). Five-year OS was 61%, 50% and 41% for CD8+ high, intermediate and low score, respectively (p<0.001) [level C evidence].

Adjuvant targeted agents

The effect of adjuvant epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) was tested in the BR19 study [level B evidence] (110). Unselected patients with completely resected stage IB-IIIA NSCLC were randomised between gefitinib or placebo for 2 years. This study was closed prematurely, however it showed no benefit for adjuvant gefitinib (110). In addition, no benefit was shown in the subgroup with an activating EGFR mutation (n=15). With the proven efficacy of EGFR-TKI's in mutation positive advanced disease, the role of adjuvant erlotinib versus placebo has been explored in patients

with completely resected EGFR expressing (immunohistochemistry) or EGFR amplified (fluorescence in situ hybrisation) stage IB to IIIA disease (111). Adjuvant erlotinib for 2 years did not prolong DFS in the EGFR mutation positive NSCLC. Although there was a trend to improved DFS with gefitinib in the EGFR activating mutation positive subgroup (n=161, HR 0.61 95% CI 0.38-0.98, p=0.039), this was not statistically significant due to hierarchical testing [level B evidence]. Discussion points are the dose and duration of treatment. It might be that, in line with results in breast cancer, the treatment period was too short. Currently, there is no role for TKIs in the adjuvant setting, but further research in the EGFR mutant positive patients is warranted and trials are ongoing (table..)

Adjuvant immunotherapy

Another promising adjuvant systemic therapy being investigated is immunotherapy. One of these approaches is targeting MAGE-A3. MAGE-A3 is expressed in 35% of NSCLC patients. A phase II RCT showed that in patients with stage IB-II resected NSCLC expressing MAGE-A3 the HR for DFS was in favour of treatment with recombinant MAGE-A3 protein in combination with an immunostimulant, however this was not statistically significant (HR 0.75, 95% CI 0.46-1.23, p=0.248) (112). In the phase III MAGRIT RCT, presented at ESMO 2014 13,824 patients were screened for MAGE-A3 and 2270 were randomised between adjuvant MAGE-A3 immunotherapy or placebo. Unfortunately, MAGE-A3 immunotherapy did not improve outcome [level B evidence] (113). The full paper has not been published yet.
Other interesting immunotherapy strategies currently being explored in several phase III RCT's are the use of checkpoint inhibitors. As these studies started enrolment in 2015 results are expected within a few years. An overview of these studies is provided in table…

Adjuvant anti-angiogenic agents

As angiogenesis is one of the hallmarks of cancer and important for growth and metastatic potential of tumours, the addition of bevacizumab to platinum-based chemotherapy was tested in a phase III RCT (E1505, n=1501) and presented at World Lung Cancer Conference 2015 (114). Patients with resected IB (>

4 cm) – IIIA NSCLC were treated with 4 cycles of cisplatin with either vinorelbine, pemetrexed, docetaxel or gemcitabine and randomised between addition of bevacizumab for 1 year or chemotherapy alone. At time of interim analysis (all patients randomized), no difference was observed in the primary endpoint OS (HR 0.99 (95% CI: 0.81-1.21, p=0.93) [level B evidence] and in the secondary endpoint DFS (HR 0.98 (95% CI: 0.84-1.14, p=0.75). As low-molecular weight heparin (LMWH) may also improve outcome, it was tested in the NVALT-8 trial (n=202) whether the addition of nadroparin to adjuvant chemotherapy (cisplatin combined with pemetrexed (non-squamous) or gemcitabine (squamous) improved DFS in resected stage I-IIIA NSCLC patients. Results were presented at the ASCO 2016 conference: no significant differences in DFS were found, which is different from the results in the abstract (115).

In summary, international guidelines recommend the use of adjuvant platinum-containing chemotherapy in patients with completely resected stage II disease and consideration of its use in patients with resected stage IB disease with a primary tumour ≥4 cm. According to the proposed 8th TNM edition these are all grouped in stage II (15, 53). Age is not a selection criterion per se, but co-existence of severe comorbidity may lead to detrimental outcome. Currently no predictive biomarkers of clinical benefit are available and new treatment strategies such as EGFR-TKI's, angiogenesis inhibitors and immunomodulation have not yet resulted in improved outcome but additional trials are ongoing.

CONCLUSION: MULTIDISCIPLINARY INTEGRATION

Integration of the different treatment modalities in patients with early stage NSCLC remains quite a challenge for the practicing oncologist. For this reason a thorough discussion within a MDT is required to determine the optimal diagnostic and treatment schedule for each individual patient. Although not always easy to define in daily practice, cardiopulmonary risk assessment is important to decide on the specific treatment or combination of therapeutic modalities that will be administered. PS, age, co-morbidities and patients' preferences need to be taken into account also. Compromised patients will have to be treated less aggressively.

This review summarises the key evidence behind the multidisciplinary decision making for individual patients with early stage NSCLC (table 6). It also highlights some of the grey areas where further research is needed and discusses ongoing clinical trials. Undoubtedly, further development of MIT and SBRT, newly introduced chemotherapeutic and targeted agents in combination with further advances in immunotherapy, will provide a broad spectrum of therapeutic modalities. It is important to maintain clinical equipoise in presenting options to patients and to enrol patients in clinical trials where possible in order to better define the optimal treatment and improve outcomes for future patients with this disease.

Table 1. *Levels of evidence*

Level	Description
A	Randomised controlled trials with a consistent pattern and rich body of data
B	Randomised controlled trials with a limited number of patients or inconsistent results
C	Non-randomised trials, observational studies
D	Panel consensus judgment
E	Expert opinion

Table 2A. *Overall survival by stage according to the 7th TNM classification(8).*

Stage 7th ed.	5 year survival for clinical stage	5 year survival for pathologic stage
IA	82%	83%
IB	66%	71%
IIA	52%	57%
IIB	47%	49%

Table 2B*. Overall survival by stage according to the 8th TNM classification(6, 7).*

Stage 8th ed.	5 year survival for clinical stage	5 year survival for pathologic stage
IA1	92%	90%
IA2	83%	85%
IA3	77%	80%
IB	68%	73%
IIA	60%	65%
IIB	53%	56%

Table 3. *Current randomised controlled trials comparing lobectomy versus sublobar resection (SLR) .*

	US CALGB 140503 Trial (26) (NCT00499330)	**Japanese Trial (27) (JCOG0802/WJOG4607L)**
Surgical study arm 1	Lobectomy	Lobectomy
Surgical study arm 2	Limited resection (anatomical segmentecomy or non-anatomical wedge)	Anatomical segmentectomy
Eligibility	Peripheral lung nodule ≤ 2 cm on perioperative CT scan and located in outer 1/3 of lung and presumed to be NSCLC	Peripheral NSCLC (suspicion) ≤ 2 cm (proportion max. diameter of tumor to consolidation >0.5)
Primary end-point	DFS	OS
Secondary end-points	OS; LR; systemic recurrence rates; PFT; correlation preoperative PETCT with outcome; false –ve rate for PET if nodal metastase; utility of annual follow-up CT	PFT; relapse-free survival; LR; proportion of completion of segmentectomy; LOS; duration chest tube; operation time; blood loss; number of auto-sutures
Target Recruitment	1297 patients	1100 patients

LR: local recurrence; PFT: pulmonary function test; DFS: disease free survival; OS: overall survival; LOS: length of stay in hospital; SLR: sublobar resection

Table 4. *Completed randomised controlled trials comparing SBRT vs Surgery*

	Dutch ROSEL Trial (42) (NCT00687986)	**U.S. STARS Trial (42) (NCT00840749)**	**U.S. ACOSOG z4099 Trial (116) (NCT01336894)**
Surgical study arm	Anatomical resection with lymph node dissection	Anatomical resection	SLR +/- brachytherapy
SBRT study arm	60 Gy in 3 # or 60 Gy in 5#	60 Gy in 3# or 60 Gy in 4 #	Variable dose in 3#
Eligibility	Operable patients, Stage IA disease	Operable patients, Stage IA & IB disease ≤4 cm	'High operable risk' patients, stage IA disease
Primary end-point	5 year local control	3 year OS	5 year OS
Secondary end-points	Toxicity, OS, quality adjusted life years	Toxicity, progression-free, disease-specific survival	Toxicity, DFS
Recruitment	22 patients	36 patients	13 patients

DFS: disease-free survival; OS: overall survival; SBRT: stereotactic body radiotherapy; SLR: sublobar resection

Table 5. *Planned/ongoing randomised controlled trials comparing SBRT vs Surgery*

	U.S. POSTLIV Trial (NCT01753414)	**U.S. STABLE-MATES Trial (NCT02468024)**	**U.S. Trial Mayo Clinic (NCT01622621)**	**U.K. SABRTooth Trial (NCT02629458)**
Surgical study arm	Complete resection and lymph node dissection	SLR	SLR	Complete resection
SBRT study arm	55 Gy in 5#	54 Gy 3#	54 Gy 3#	Various dose/# schedules
Eligibility	Lobectomy or pneumonectomy, tumour ≤3 cm	'High operative risk' tumour ≤4 cm	'High operative risk' peripheral tumour ≤5 cm	'High operative risk' peripheral tumour ≤5 cm
Primary end-point	2 year loco-regional control	3 year OS	2 year OS	Average recruitment 3 patients per month
Secondary end-points	Time to local/distant failure, DFS, OS	Toxicity, progression-free survival	Toxicity, progression-free survival	
Target recruitment	76 patients	258 patients	96 patients	54 patients

DFS: disease-free survival; OS: overall survival; SBRT: stereotactic body radiotherapy; SLR: sublobar resection

Table 6. *completed randomized, placebo controlled trials on (neo)-adjuvant chemotherapy*

	ALPI trial (86)	**Big Lung Trial (87)**	**IALT trial (84)**	**JBR.10 (88)**	**ANITA (85)**
Chemotherapy	Adjuvant MVP, 3 cycles q3w	(neo)adjuvant MIC, MVP, CV or NP, all 3 cycles q3w	Adjuvant CV, NP, CE or C + vinblastin, 3-4 cycles q3 or4w	Adjuvant NP 4 cycles q4w	Adjuvant NP 4 cycles q4w
Cisplatin dose	100 mg/ m^2 d1	MIC/NVP: 50 mg/ m^2 d1 CV/NP 80 mg/ m^2 d1	80-120 mg/ m^2	50 mg/ m^2 d1,8	100 mg/ m^2 d1
Eligibility (stage)	I, II, IIIA	I, II, IIIA	I, II, III	IB, II	IB, II, IIIA
Primary end-point	OS	OS	OS	OS	OS
Secondary end-points	DFS, toxicity	DFS	DFS, 2nd primary cancer, AE	DFS, toxicity, safety	DFS, safety
N	1209	381	1867	482	840
Subgroups					
Elderly	No age limit	No age limit	Upper age limit 75	No age limit	No age limit
Co-morbidity	Not specified	Not specified "fit to receive chemo"	Not specified	"Only fit patients"	Not specified
WHO PS	Not specified	Not specified	Not specified	Only PS 0-1	PS 0-2

Q: per; w: weeks; d: day; mg: milligram; MVP: mitomycin, vindesine, cisplatin; MIC: cisplatin, mitomycin, ifosfamide; CE; cisplatin, etoposide; CV: cisplatin, vindesine; NP: cisplatin, vinorelbin; C: cisplatin; DFS: disease-free survival; OS: overall survival; AE: adverse events; WHO PS: world health organisation performance status

Table 7: Planned/ongoing phase III randomised controlled trials comparing adjuvant EGFR-TKI to placebo after complete resection in EGFR-mutant (exon 19 deletion/exon 21 L858R) NSCLC patients

	ADJUVANT (NCT 01405079)	**International ADAURA trial (NCT 02511106)**	**Korean trial (NCT 02795884)**	**Japanese WJOG6410L trial**
Experimental arm	Gefitinib 250 mg once daily, 24 months	Osimertinib 80/40 mg once daily	Intercalated: erlotinib 150 mg once daily d 8-21, pemetrexed/ cisplatin d1 4 cycles q3w Maintenance: erlotinib 150 mg once daily 1 year	Gefitinib 250 mg once daily, 24 months
Comparator arm	NP 4 cycles q3w	Placebo once daily	NP 4 cycles q3w	NP 4 cycles q3w
Eligibility	Stage IIA-IIIA	Stage IB-IIIA, predominantly non-sqcc, with/without adjuvant chemo	Stage IB-IIIA non-sqcc	Stage II-III
Primary end-point	DFS	DFS	DFS	DFS
Secondary end-points	OS, 3 year DFS, 5 year DFS and OS, AE, QoL	2, 3 and 5 year DFS, OS, HRQoL, pharmacokinetics	OS, AE	OS, AE type of recurrence
Target recruitment	220 patients	700 patients	227 patients	230 patients

EGFR: epidermal growth factor receptor; TKI: tyrosine kinase inhibitor; d: day; q:per; w: weeks; mg: milligram; PD: progressive disease; NP; cisplatin, vinorelbine; sqcc: squamous cell carcinoma; OS: overall survival; DFS: disease free survival; AE: adverse events; HRQoL: health related quality of life

Table 7 continued

	Chinese EVIDENCE trial (NCT02448797)	**Chinese ICTAN trial (NCT 01996098)**	**ICWIP (NCT 02125240)**
Experimental arm	Icotinib 125 mg three times daily until PD	Arm A Icotinib 125 mg three times daily 6 months Arm B Icotinib 125 mg three times daily 12 months	Icotinib 125 mg three times daily until PD
Comparator arm	NP 4 cycles q3w	Platinum-based chemotherapy 4 cycles	Placebo three times daily until PD
Eligibility	Stage II-IIIA adenocarcinoma, no right pneumonectomy	Stage IIA-IIIA	Stage II-IIIA adenocarcinoma, adjuvant 4 cycles cisplatin based chemo
Primary end-point	DFS	DFS	DFS
Secondary end-points	OS	OS, AE, QoL	OS, AE, HRQoL
Target recruitment	320 patients	477 patients	300 patients

Table 8: Planned/ongoing phase III randomised controlled trials comparing adjuvant immunotherapy to placebo after complete resection in NSCLC patients

	IMpower010 (NCT02486718)	**ANVIL (NCT02595944)**	**EORTC-ETOP PEARLS trial (NCT02504372)**	**Canadian Cancer Trials Group (NCT02273375)**
Experimental arm	Atezolizumab 1200 mg IV 16 cycles q3w	nivolumab IV q2w, up to 1 year	pembrolizumab 200 mg IV q3w up to 1 year	MEDI4736 IV up to 1 year
Comparator arm	observation	observation	placebo	placebo
Eligibility	Stage IB (>/=4cm)-IIIA, adjuvant cisplatin based chemotherapy	Stage IB (>/=4cm)-IIIA, adjuvant cisplatin based chemotherapy tested for PD-L1, EGFR/ALK-	Stage IB (>/=4cm)-IIIA, adjuvant cisplatin based chemotherapy tested for PD-L1	Stage IB (>/=4cm)-IIIA, +/- adjuvant chemotherapy
Primary end-point	DFS	DFS, OS	DFS	DFS in PD-L1+ patients
Secondary end-points	OS, AE, pharmacokinetics, immunogenicity	1, 2, 5 year DFS and OS, AE, outcomes according to PD-L1 patterns and mutational load	OS, LCSS	DFS in all patients, OS (PD-L1+/all), LCSS (PD-L1+/all), AE, QoL, cost utility ratio, pharmacokinetics
Target recruitment	845 patients	714 patients	1380 patients	1100 patients

IV: intravenous; q: per; w: weeks; mg: milligram; cm: centimeter; PD-L1: programmed death-ligand1; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; DFS: disease free survival; OS: overall survival; AE: adverse events; LCSS: lung cancer specific survival

Table 6. *Summary: treatment options for stage I- II NSCLC according to proposed 8th TNM classification.*

cTN	c stage	Medically operable	Medically inoperable	References
T1a(mi) N0	IA1	SLR	sublobar/SBRT/RFA	(9, 11-15, 19, 42, 51)
T1a N0	IA1	SLR/lobectomy	sublobar/SBRT/RFA	
T1b N0	IA2	SLR/lobectomy	sublobar/SBRT/RFA	
T1c N0	IA3	lobectomy	SBRT/RFA	
T2a N0	IB	lobectomy/sleeve	SBRT/external RT	
T2b N0	IIA	lobectomy/sleeve/ pneumonectomy consider adjuvant chemotherapy	SBRT/external RT	(14, 15, 19, 89-91)
T1a-c N1	IIB	lobectomy – adjuvant chemotherapy	(chemo)radiation	
T2a-b N1	IIB	lobectomy – adjuvant chemotherapy	(chemo)radiation	
T3 N0	IIB	lobectomy/sleeve/ pneumonectomy/ extended resection consider adjuvant chemotherapy	(chemo)radiation	

c: clinical; mi: minimally invasive; RT: radiotherapy; SBRT: stereotactic body radiotherapy; SLR: sublobar resection

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