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Upfront Resection of Locally-Advanced and/or Cavitating NSCLC Followed by Chemoradiotherapy (and adjuvant systemic treatment); Phase 1 multicenter study to assess treatment feasibility and Safety (NVALT32/ UPLAN-I Trial) – Study protocol

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Abstract

Background: Standard treatment of stage III non-small cell lung cancer (NSCLC) with multilevel/bulky N2 or N3 disease is chemoradiotherapy (CRT) followed by immune checkpoint inhibition (ICI, durvalumab). However, no separate recommendations are made for large volume or cavitating tumors, in which infectious complications, bleeding and a high local recurrence rate is frequently seen after treatment with CRT. Upfront resection of a (potentially) resectable large volume and/or cavitating primary lung tumor in patients with extensive stage III NSCLC, followed by CRT could be a strategy to prevent complications of CRT

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Methods/Design: A multicenter feasibility study, enrolling 20 patients with cT3-4N2M0 NSCLC with cavitation or large volume of the primary tumor and/or multilevel or bulky N2 disease, or patients with cT3-4N3M0 disease with a resectable primary tumor. An upfront resection of the primary tumor is followed by CRT (and adjuvant ICI if indicated). The primary study objective is feasibility assessed by the number of patients completing the predefined treatment (upfront resection + CRT). Secondary objectives are safety and complications.

Conclusion: The potential advantages, e.g. reduction of radiotherapy treatment volumes, improved local control and reduction of long-term infectious problems or bleeding complications after upfront resection of the large volume or cavitating lung tumor, may outweigh the complications resulting from surgery and the risk of a delayed start of the standard of care treatment. In this study, we aim to evaluate feasibility and safety of upfront resection of the primary lung tumor, followed by CRT in this NVALT32/UPLAN-I trial.

Keywords: Locally-advanced NSCLC; Chemoradio therapy; Large tumor volume; Cavitation; Upfront surgery; Feasibility; Safety.

Background

Locally-advanced NSCLC

Stage III non-small cell lung cancer (NSCLC) comprises a heterogeneous group of patients resulting in variable prognoses depending on the size and extent of the primary tumor and the degree of lymph node involvement [1]. For resectable stage III NSCLC, induction chemotherapy, radiotherapy or chemoradiotherapy (CRT) followed by a surgical resection has been demonstrated to improve survival in selected patients when compared to treatment with resection alone [2-6]. The recent introduction of immune checkpoint inhibitors (ICIs) as induction therapy shows encouraging activity and preliminary results and shows a favorable safety profile in patients with resectable early-stage or locally advanced NSCLC [7,8]. However, outcomes of overall survival (OS) have yet to be published. Until recently, guideline recommended treatment of irresectable stage III NSCLC (e.g. multilevel or bulky N2 disease or presence of N3 lymph node metastases) was concurrent (c)CRT [1]. Recently, ICI (durvalumab) was successfully added to CRT, showing improved progression free survival (PFS) and OS, now being the standard of care (SoC) treatment for these tumors (9,10). So, in stage III NSCLC, possible resectability influences the treatment strategy, however the definition of resectability is subject of discussion and varies between different surgeons and multidisciplinary teams. Therefore, the role of surgery remains unclear so far.

When compared to small-sized tumors, large volume (>700cc) and/or cavitating lung tumors are less likely to be sterilized by CRT, increasing the local recurrence rate [11-13]. After CRT, the quality of life (QoL) might be impaired due to extensive and prolonged coughing [14-17]. Cardiotoxicity might cause problems and lung function might be seriously impaired after CRT for a large tumor, especially in case of a centrally located tumor. Moreover, necrosis and cavitation of the tumor can cause infectious and/or bleeding complications, including potentially fatal pulmonary hemorrhage [14-17]. It has been suggested that upfront resection of the large tumor in the lung, with postoperative CRT (aiming for the mediastinal lymph node metastases) in patients who have a potentially resectable tumor could be a strategy to prevent complications of tumor cavitation in large volume tumors [17]. Moreover, it has been shown that in highly selected patients diagnosed with stage IIIB NSCLC, surgical resection as part of multimodality therapy might be associated with improved overall survival (OS) [18].

Since ICI, or targeted therapy in case of presence of a driver mutation, has the potential to control systemic disease, local control of the primary tumor in the lung becomes more important [19-21]. Upfront resection of a large volume tumor in the lung might be considered to gain this local control. Moreover, it eliminates the need for CRT on the primary tumor in the lung and thus avoids the potentially serious or life-threatening effects of this treatment.

ICI as part of multimodality treatment

For stage III NSCLC, ICI can be added prior to (neoadjuvant) or following (adjuvant) CRT. In the neoadjuvant setting, several studies have been done or are ongoing, including ICI (single agent or a combination of 2 agents) or ICI in combination with chemotherapy, radiotherapy or CRT, followed by resection as a possible treatment for stage III NSCLC. Recently published results are promising, showing improved outcomes when ICI is added to neoadjuvant therapy (e.g., longer event free survival, more frequently a pathological complete response) when compared to neoadjuvant treatment with chemotherapy alone [7,8,22,23]. However, these studies mainly exclude large volume or cavitating tumors, possibly because these tumors are frequently judged as being irresectable. Therefore, the added toxicity of introducing ICI in a neoadjuvant setting, especially when combined with chemotherapy, radiotherapy, or CRT, still needs to be elucidated for these tumors. In case of a large volume or cavitating tumor, toxicity might be related to infection and necrosis of the large tumor mass and/or the radiation dose to the surrounding organs. Consequently, an alternative treatment strategy may need to be considered when aiming to treat these tumors effectively.

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Surgery

Upfront surgery might benefit patients with large volume stage IIIB/IIIC NSCLC and the potential advantages, e.g. improved local control, reduction of radiotherapy treatment volumes and reduction of long-term infectious problems or bleeding complications because of necrosis of the primary tumor, may possibly outweigh the risk of a delayed start of the SoC treatment. A possible drawback of an upfront resection approach is the risk of (locoregional or systemic) tumor progression when delaying planned CRT and adjuvant ICI. The intervention should not prevent the patient from receiving the SoC treatment, so a safety and feasibility check is necessary in evaluating the role of upfront resection in these patients with large volume or cavitating tumors.

Aim of the study

Aim of the UPLAN-I trial is to evaluate feasibility and safety of upfront resection of the large volume or cavitating tumor in the lung (including a hilar and/or mediastinal lymph node dissection if deemed possible by the treating surgeon), followed by CRT. The role of upfront resection in reducing infectious problems (and bleeding complications) and subsequent impaired QoL, in combination with increasing the disease-free survival (DFS) and improving OS, are evaluated in the future UPLAN- II trial. However, feasibility and safety of this treatment regimen need to be established first (UPLAN-I trial).

Methods/Design

Trial design

This is a multicenter feasibility study which aims to assess the feasibility and safety of upfront resection followed by CRT and adjuvant ICI to treat large volume or cavitated locally-advanced (stage IIIB/IIIC) NSCLC. The study is registered at clinicaltrials.gov (trial number NCT05620199).

After inclusion in the trial and following written informed consent, the patient will have an upfront resection of the primary tumor (preferably with a hilar and/or mediastinal lymph node dissection, if deemed possible according to the treating surgeon), followed by CRT (and adjuvant ICI treatment). Resection will be done within 2-4 weeks after presentation in the multidisciplinary team meeting (MDT) and trial inclusion. The study is feasible (primary endpoint) in case at least 15 of 20 included patients complete the treatment protocol (resection followed by CRT), in which CRT is administered within 4-6 weeks postoperatively (no later than 10 weeks after the MDT). The observation period ends 90 days after finishing CRT. The primary study endpoint is recorded before start of adjuvant systemic therapy. In case no adjuvant systemic treatment is started, the primary endpoint is recorded when the observation period ends, i.e. 90 days after finishing CRT. Treatment with adjuvant ICI is to the discretion of the treating multidisciplinary tumor board.

Objectives of the study

The primary aim of the UPLAN-I trial is to evaluate feasibility and safety of upfront resection of large volume or cavitating tumors in the lung (including a hilar and/or mediastinal lymph node dissection if deemed possible by the treating surgeon), followed by CRT. The treatment protocol is regarded feasible when at least 15 out 20 patients (75%) are able to undergo CRT without delay (of more than 10 weeks after de MDT). Secondary aims are establishing safety and recording the incidence of complications.

Feasibility and safety of this treatment regimen need to be established in this trial. When feasibility and safety are confirmed in this UPLAN-I trial, the role of upfront resection in reducing infectious problems and subsequently improved QoL, in combination with decreasing the risk of a local recurrence and improving OS, are evaluated in the future UPLAN-II trial.

Endpoints of the UPLAN-I trial

Primary endpoint: feasibility as assessed by the number of patients completing the predefined treatment protocol (upfront resection + CRT).

Secondary endpoints: (1) safety (according to CTCAE version 5.0) will be assessed throughout the study and (2) complications (according to the standardized Clavien-Dindo classification of surgical complications) will be registered [24,25].

Sample size calculation

Upfront resection is considered feasible if at least 15 of 20 included patients complete the treatment protocol. In this case we will have 97.5% confidence that the treatment will be feasible in at least 50% of future patients. If in reality the probability of an individual patient completing the protocol is 80% (as we believe it is), then we have 80% power of finding at least 15 out of 20 patients in our study doing so and declaring the treatment feasible.

Patient selection

Patients with clinically staged (c)T3-4N2 (multilevel or bulky N2 or presence of cavitation of the primary tumor with single level N2, stage IIIB) NSCLC or cT3-4N3 (stage IIIC) NSCLC with pathologically proven N2 or N3 lymph node metastasis will be screened for study eligibility. All patients will be discussed in the MDT meeting, where tumor resectability (defined as deemed possible to do an R0 or R1 resection) will be assessed by at least two thoracic surgeons. Inclusion and exclusion criteria are listed in table 1.

Participation

In order to be eligible to participate in this study a patient must meet provision of signed, written and dated informed consent prior to any study specific procedures

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Table 1: Inclusion and exclusion criteria UPLAN-I trial.

Inclusion criteria	Exclusion criteria
1. Pathologically proven NSCLC, staged according to the 8th edition of the AJCC staging, with a clinical indication for CRT (according to current guidelines).	1. Irresectable primary lung tumor before start of CRT (as deemed by the MDT).
2. cT3-4N2 tumors with cavitation of the primary tumor and/or multilevel or bulky N2.	2. Pneumonectomy deemed necessary (by the treating surgeon) to achieve a complete resection (R0).
3. cT3-4N3 tumors.	3. Sulcus superior tumor with invasion of the thoracic wall.
4. Male or female aged at least 18 years.	4. cT3-4 based on satellite nodule/lesion in the ipsilateral lung.
5. The patient must have an Eastern Cooperative Oncology Group (ECOG)/WHO performance status of 0 or 1.	5. Patients with a locoregional recurrence or a second primary cancer.
6. A pretreatment PET/CT scan (of the thorax) and an MRI (or CT scan) of the brain <6 weeks before the surgery is considered SoC and must be done prior to start of treatment.	6. Patients who underwent prior high-dose radiotherapy, significantly overlapping with the current PTV
7. Pathologically proven N2 or N3 lymph node metastasis, or a high suspicion of presence of N2 or N3 lymph node metastasis, based on diagnostic tests and the expert opinion formulated in a multidisciplinary team meeting. Patients should be eligible for concurrent or sequential CRT.	7. Small cell lung cancer or a pulmonary carcinoid tumor
8. Patients should be operable to the discretion of the treating pulmonary physician, surgeon and anesthesiologist, based on lung function testing, co-morbidities and performance scoring.	8. Patients who are pregnant or breastfeeding
9. EGFR/ALK mutations and never-smokers may be included in the study (since endpoints are settled after finishing CRT and before starting adjuvant systemic treatment).	

NSCLC = non-small cell lung cancer; 'c' = clinically staged; WHO = world health organization; PET = positron emission tomography; CT = computed tomography; MRI = magnetic resonance imaging; SoC = standard of care; AJCC = American Joint Committee on Cancer; CRT = chemoradiotherapy; EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase; MDT = multidisciplinary team; 'R0' = complete resection.

(Figure 1). Patients will be discussed in an MDT consisting of thoracic surgeons, pulmonary physicians, radiologists, nuclear medicine radiologists, pathologists, and radiation-oncologists. Patients should be able to undergo an anatomical resection of the tumor in the lung and should be eligible for CRT.

Staging procedures

An initial contrast-enhanced computed tomography (CT) scan of the thorax and upper abdomen, a fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT) and a magnetic resonance imaging (MRI) of the brain are required for adequate staging. Mediastinal and hilar lymph nodes >1 cm on CT scan or FDG avid on PET/CT, will be evaluated by EUS/EBUS or mediastinoscopy according to current guidelines on mediastinal staging of NSCLC (26). A CT-guided transthoracic biopsy or trans-bronchial cytology/ biopsy will be performed for cytological or histological confirmation of NSCLC, unless pathology proven N2 or N3 lymph node metastasis is present. Patients will be staged according to the 8th edition of the TNM Classification of Malignant Tumors from the Union for International Cancer Control (UICC) (27).

Surgery

Within 2-4 weeks after presentation in the MDT, patients will undergo a resection of the tumor in the lung. Patients will be operated in 1 of the participating thoracic surgery centers.

Surgery with curative intent will be performed under general anaesthesia, by an experienced thoracic surgery team and with a perioperative pain management to the discretion of the treating medical team. Before start of surgery, intravenous antibiotics will be administered and will be continued postoperatively according to local protocol and to the discretion of the treating surgeon. Resection of the primary tumor (preferably lobectomy) will be performed. A hilar and/ or mediastinal lymph node dissection will preferably be done, however only if deemed possible and to the discretion of the treating surgeon.

Postoperatively, vital signs and blood sampling for SoC treatment will be measured. Adverse events and complications after the operation will be registered according to CTCAE version 5.0 and to the standardized Clavien-Dindo classification of surgical complications, respectively [24,25].

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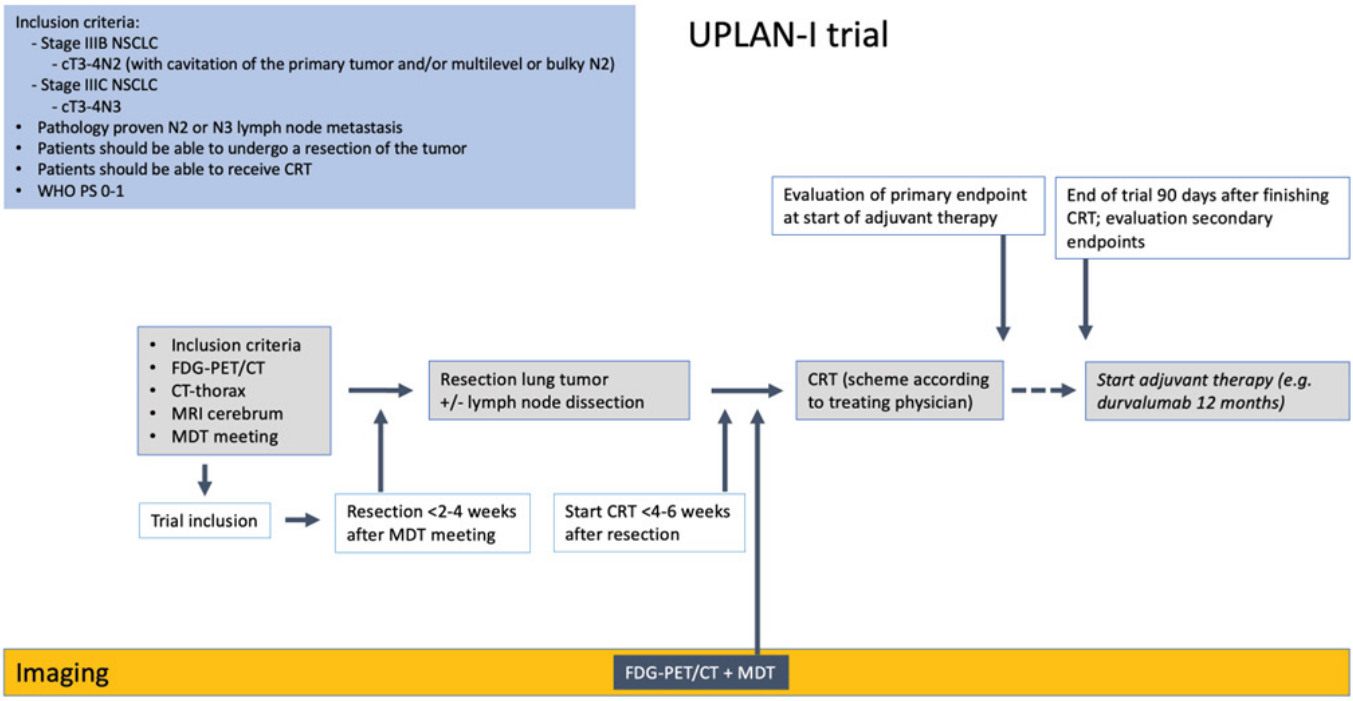

Figure 1: Flowchart UPLAN-I trial

Restaging

After resection, restaging will take place preceding start of CRT. A FDG-PET/CT scan will be performed in order to exclude metastases that may have developed in the time between first presentation and recovery from surgery.

Adjuvant chemoradiotherapy

Within 4-6 weeks after surgery, patients will be treated with CRT. A delay of 4 weeks due to complications or toxicity management is deemed acceptable. The CRT treatment regime is initiated according to the preference of the treating multidisciplinary team. In case of a R1 or R2 resection of the primary tumor in the lung, the resection margin (preferably marked during the resection) will be included in the radiation field. The radiation field will include all hilar, mediastinal, supraclavicular and contralateral lymph nodes when deemed suspicious, regardless of whether or not a lymph node dissection has been done.

Follow-up

Patients are discussed in the MDT within 2 weeks after surgery. A routine control visit at the outpatient clinic is planned 2-3 weeks after surgery. During the treatment with CRT, patients visit the outpatient clinic weekly for physical control, blood sampling, and examination for (serious) adverse events. Information regarding all (serious) adverse events will be recorded in the patient's medical records. This information will include start and stop date of the event, CTC grading (Appendix 1) and the relation to study medication. At a later moment, this information will be transferred from the medical records to the electronic Case Report Forms (eCRFs). All adverse events occurring after signing informed consent and inclusion in the study, and until start of the adjuvant therapy (after CRT), should be recorded. Adverse events and serious adverse events will be recorded throughout the treatment period (surgery and c CRT), including the follow-up period (ending at the start of adjuvant therapy, or 90 days after finishing CRT when no adjuvant systemic treatment is started). The clinical course of each event must be followed until resolution or stabilization. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general practitioner or a medical specialist.

Any serious adverse event which occurs within 30 days after surgery is considered to be possibly related to study participation and should be recorded as well.

Nature and extent of the burden and risks associated with participation, benefits and group relatedness

Today, SoC treatment of NSCLC stage IIIB/IIIC is considered to be CRT, followed by durvalumab. In current practice, upfront resection followed by CRT in the treatment of large volume (or cavitated) locally-advanced NSCLC may be part of the treatment in selected patients and is done in daily clinical practice in several hospitals. Since guideline recommendations mention both treatment options, all described procedures in this study protocol can be considered standard care [1]. Because of the fact that this treatment strategy (upfront resection followed by CRT), which we evaluate in this feasibility study, is already common practice,

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all diagnostic examinations, investigations (CT-scan, PET/CT scan, blood sampling, ECG, lung function testing, etc.) and either type of treatment, are considered SoC treatment.

A possible risk is a delayed start of treatment with CRT, since the resection precedes the start of CRT and because possible complications of surgery might postpone the start of CRT. The aim is to start the CRT within 4-6 weeks after resection. The risk of delayed treatment with CRT is potentially acceptable, considering that upfront surgery might benefit patients with large volume stage IIIB/IIIC NSCLC, and the potential advantages, e.g. improved local control, reduction of radiotherapy treatment volumes and reduction of long-term infectious problems or bleeding complications, may possibly outweigh this risk of a delayed start of the SoC treatment.

Study discontinuation/withdrawal

Subjects can leave the study at any time for any reason. If they wish to do so, it is without any consequences and SoC treatment will follow. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

In case >5 patients included do not complete the treatment protocol (resection followed by CRT), because of medical reasons, not due to patients wish only, within the established time frames or have grade 3 (or higher) complications according to the Common Terminology Criteria for Adverse Events (CTCAE) related to the treatment protocol, the study team will meet to decide upon possible termination of the study.

Data analysis

The primary endpoint is the number of patients that completed the treatment protocol (upfront resection + CRT). The percentage of such patients will be given with a two-sided 95% Pearson-Clopper confidence interval (28). For patients that did not complete the treatment protocol, the reasons for this will be recorded. All data will be centrally recorded in eCRFs (Castor). No formal interim analysis is planned. However, the total number of patients to be included is small (N=20) and the patients will be monitored continuously during and after treatment. If 6 or more patients do not complete treatment as planned, the study will be stopped since then the primary endpoint of at least 15 out of 20 patients successfully completing the treatment protocol will not be met.

Discussion

For patients with irresectable stage III (T3 or T4) NSCLC) (e.g. multilevel or bulky N2 disease or presence of N3 lymph node metastases), current guidelines recommend treatment with CRT followed by ICI. This treatment approach in unresectable stage III NSCLC results, according to the PACIFIC-trial, in a median OS of 47.5 month and 5-year OS rates of 42.9% [9,10,29,30]. However, in large volume NSCLC and in cavitating tumors, chances of sterilization of the tumor by CRT alone are reduced, with an increased local recurrence rate when compared to small-sized tumors [11,12]. Tumor cavitation is associated with worse RFS and OS [12]. Necrosis and cavitation of the tumor can cause infectious complications with subsequent impaired QoL and may also lead to interruption of, or the need for postponing, systemic treatment [15,16]. Moreover, cavitation is associated with bleeding complications and even fatal pulmonary hemorrhage after CRT [17-20]. Consequently, it has been suggested that upfront resection with postoperative CRT in patients who have a potentially resectable tumor could be a strategy to prevent complications of tumor cavitation (e.g. infectious complications, bleeding) in large volume tumors [17]. Besides describing the possible risks of treatment of large tumor volumes and tumors with cavitation, the role of upfront surgery in these patients has been investigated to a limited extent, although it is already part of treatment in a selected group of patients. Upfront surgery might benefit patients with large volume stage IIIB/C NSCLC and the potential advantages, e.g. improved local control, reduction of radiotherapy treatment volumes and reduction of long-term infectious problems or bleeding complications, may possibly outweigh the risk of a delayed start of the SoC treatment, e.g. CRT and adjuvant systemic treatment (durvalumab). Therefore, we aim to evaluate the feasibility and safety of upfront resection of the large volume or cavitating tumor in the lung (including a hilar and/or mediastinal lymph node dissection if deemed possible by the treating surgeon), followed by CRT in the UPLAN-I trial.

After completion of the UPLAN-I trial and determining that upfront resection is feasible and can be performed safely, the role of upfront resection in reducing infectious problems (and bleeding complications) and subsequent impaired QoL, in combination with decreasing the risk of a local recurrence (RFS) and improving OS, will be evaluate in a future phase III trial (UPLAN-II trial).

Disclosure statement

No potential conflict of interest was reported by the author(s)

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