Optimal individual treatment strategy for every locally advanced non-small cell lung cancer patient

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Aim and Expected impact

Patients with locally advanced (LA) non-small cell lung cancer (NSCLC) experience poor local and distant disease control and lack effective treatment options. Patient variability is large in terms of response to treatment, co-morbidities, tumour location, respiratory tumour motion and the risk of developing anatomical changes. The optimal treatment is therefore highly patient-specific. We aim at developing methods to individualise treatment of lung cancer patients.

Treatment intensification, whether it targets locally (dose escalation) or systemically (immunotherapy), entails a higher risk of severe toxicity. It would be ideal to distinguish patients with a high probability of local or distant failure early. This would allow individualisation of treatment strategies, such that patients with likely distant failure could receive intensified systemic treatment, while local failure prone patients could receive RT dose escalation. The project will culminate in a prospective trial assigning patients to standard treatment, RT dose escalation, or adjuvant immunotherapy based on their risk of distant and local failure.

Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths worldwide. About 30% of NSCLC patients are classified as inoperable locally advanced (LA) NSCLC, stage II-III[1]. The standard treatment consists of concomitant chemotherapy and radiotherapy (RT) at 60-66 Gy/30-33 fractions. Although the treatment intent is curative, both local and distant control are poor. Within five years, ~30% of the patients experience local failure while 40% experience distant failure[2,3]. This results in progression-free survival as low as 20% two years after treatment[4].

Several strategies have been proposed to improve these discouraging outcomes. One approach is to administer up to one year of adjuvant immunotherapy after chemo-RT. The interim analysis of the first phase III trial on immunotherapy (durvalumab) showed an impressive increase in median time to death or distant metastasis of nine months[5]. However, immunotherapy mainly targets distant metastases, addressing the issue of local control only marginally (complete response rate 1.4%). Consequently, immunotherapy cannot stand alone but must be complemented with strategies targeting local control. One approach to improve local control is escalation of RT dose. Unfortunately, large treatment volumes and unrelated comorbidities often result in high toxicity in healthy normal tissue (lungs, heart, oesophagus and bronchi)[6-8]. Dose escalation to the entire tumour resulted in higher mortal toxicity in the experimental high dose arm of the RTOG0617 trial[8]. Targeted dose escalation to the metabolically active region, which is often much smaller than the tumour, could be the solution[9]. This is investigated in a national Danish phase III trial (NARLAL2, NCT02354274, initiated January 2015[10]), see Fig 1.

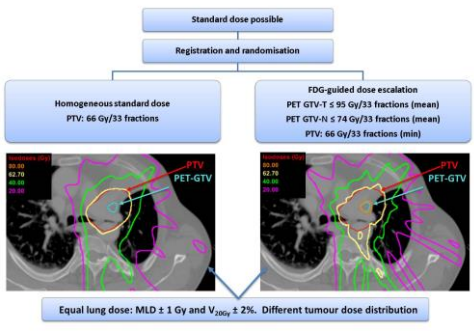

Figure 1: NARAL2: Randomised multicentre phase III trial with loco-regional control as primary endpoint. Due to heterogeneous dose distributions higher dose to the tumour is achieved without increasing dose to the lungs.

Early treatment response

Currently, risk of failure models for LA-NSCLC patients are based on baseline clinical data such as stage, tumour volume, FDG uptake on a pre-treatment PET/CT scan, and histology[11]. The variability within the different risk groups is large - in many cases too large to justify individual treatment adjustment such as local treatment intensification or adjuvant immunotherapy. Early treatment response (during the first weeks) to chemo- and RT could distinguish patients with a high probability of either local or distant failure during treatment. Including early

treatment response into current prognostic and predictive models would allow individualisation of treatment strategies.

Early tumour response to chemotherapy has previously been investigated on both FDG-PET[12-14] and CT[14]. Unfortunately, these studies are limited by small patient cohorts (21-65 pts) and struggle with conflicting results. Nonetheless, they indicate that local and distant failure as well as survival could be predicted after one series of chemotherapy and thus prior to RT start. Similar to this, early tumour response to RT has been investigated. Studies have shown a correlation between PET response during the first weeks of RT and long term response[15-17]. Unfortunately, these are contradicted by other studies[18]. As for chemotherapy, these contradictory results can be attributed to limited patient numbers (<34 pts) and variability in treatment. PET/CT image analysis can be done using both simple measures (RECIST[19],PERCIST[20]) and more complex image features, radiomics, characterizing the tumour in terms of uptake intensity, shape, and outline irregularities. Currently, radiomics studies based on pre-treatment images have identified a few plausible image features prognostic of treatment outcome for lung cancer [21]. However, the role of radiomics in response assessment is of yet unresolved.

Hypothesis

Early treatment response to chemo-RT will predict the risk of local and distant failure for LA-NSCLC. The predictions will enable a patient-specific treatment strategy, ultimately improving local and distant control while minimising toxicity.

Research Plan

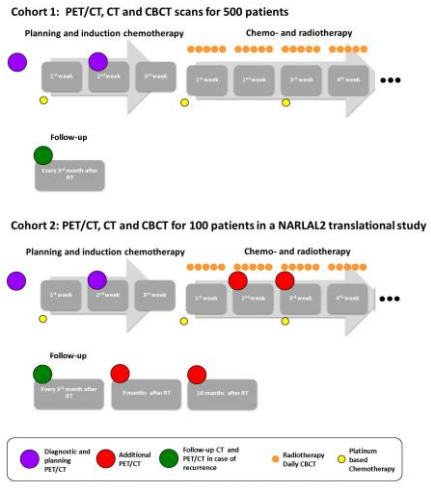

Figure 2: Timing of scans for the two patient cohorts in project 1.
In cohort 1, follow up PET scans are only acquired in case of recurrence.
In cohort 2, follow up PET scans 9 and 18 months after RT is mandotory

Patient cohorts

We will analyse two large patient cohorts (Fig 2). Early tumour response will be assessed based on diagnostic (pre-chemo) and planning (pre-RT) PET/CT in a cohort of 500 patients (Cohort 1), while early tumour response during RT will be assessed on CT/CBCT for Cohort 1 and on PET for 100 patients included in the NARLAL2 trial (Cohort 2).

All PET/CT images will be analysed using both simple measures and radiomics features. For PET, the analysis will be extended by a voxel-to-voxel response by deformable image registration[22]. The difference in dose level in Cohort 2 (standard and escalated) is expected to yield different early and long term response.

All response measures will be correlated to local and distant failure data to find those with the highest prognostic value. They will also be tested for the ability to distinguish patients failing locally and distantly. The early response measures will be combined with pre-clinical data (histology, stage, PS, lung capacity, surgery, chemotherapy) and the competing risks of local and distant failure in a prognostic model. By including data from a randomised patient cohort, features can be assessed for predictive values, identifying patients who might benefit from local treatment intensification. Based on this, a prospective trial will be designed, to be run by the Danish Oncological Lung Cancer Group (DOLG).

The research plan can be summarised in 3 tasks

1. Early response to chemotherapy

The aim of this project is to find the correlation between early tumour response to chemotherapy and the rate of local and distant failure. Early tumour response to chemotherapy on diagnostic and planning PET/CT will be assessed in cohort 1 of 500 patients (Fig 2). PERCIST criterion was observed to be more predictive of treatment outcome than RECIST. However, both criteria were developed to determine overall treatment response, categorized as response, stable disease or progression. These are not ideal to determine local response in detail and the CT response analysis

will hence be extended to include several alternatives to RECIST. The change in the three dimensional tumour volume has been shown to be more predictive of tumour response. Other more complex image features, radiomics, characterize the tumour in terms of i.e. HU inhomogeneity and outline irregularities. The first radiomics publications for lung cancer identify a few plausible image features to be prognostic of treatment outcome on pre-treatment images[21], but the role in response assessment is unresolved. In this project, we will measure the change in these features following treatment. For early response on PET, in-depth image analysis including voxel-to-voxel response by deformable image registration[23], inhomogeneity measures, change in shape and entropy will give detailed knowledge about response. This analysis will be complemented by standard PET measures such as PERCIST, change in metabolic tumour volume, and total lesion glycolysis. All response measures will be correlated to local and distant failure data to gain the highest prognostic value and tested for the ability to distinguish patients failing locally and distantly.

2. Early response to RT

The aim of this project is to find the correlation between early tumour response to RT and the rate of local and distant failure. For early tumour response during RT, assessment based on CT/CBCT can be obtained for all 500 patients (Fig 2, cohort 1), while 100 patients included in the NARLAL2 trial are available for PET analysis (Fig 2,cohort 2). Fig 3 shows two examples, comparing the treatment planning PET/CT to the day14 PET/CT scan, illustrating the heterogeneity in both CT and PET response. The correlation between this response and the long-term local control is expected to differ for standard and escalated doses, enabling a dose dependent prediction of local control. The PET response image analysis will include measures for changes in uptake intensity, shape, position and heterogeneity to reveal the most predictive parameters. The planning PET/CT and day7 PET-CT are both acquired seven days after chemotherapy with the purpose of separating the response to RT from the response to chemotherapy. The day14 PET-CT measures the response to RT before the third series of chemotherapy (Fig 2). Follow up PET scans 9 and 18 months after RT will be used for a detailed pattern of failure analysis and to assess voxel-based response[22]. All PET/CT scans adhere to strict scanning protocols following nuclear medicine guidelines and for each patient, the same scanner is used for all PET/CT scans. The combination of large patient number and strict adherence to the time schedule for PET/CT scans and chemo-RT treatment is expected to yield much more consistent results than previous studies. The response measures will be correlated to local and distant failure data to find those with the highest prognostic value and will be tested for the ability to distinguish patients failing locally and distantly.

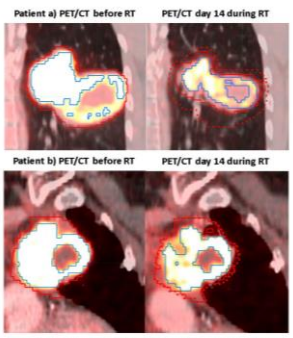

Figure 3: Preliminary NARLAL2 data showing PET/CT response during RT for two patients. Patient a) shows a large response both in maximal PET intensity, volume defined by CT and volume defined by PET, while patient b) shows only small changes. The solid red lines delineates the gross tumour volume on the each CT, while the blue solid line indicates the PET avid volume on each PET scan. The gross tumour volume on the CT before RT is indicated with a dotted red line on the PET/CT during RT.

3. Response models of prospective trial

The aim of this project is to develop a prognostic model providing the risk of distant and local failure, as well as a predictive model including the effect of RT dose escalation. Currently, models for prediction of treatment response for LA-NSCLC patients are based on baseline clinical data such as stage, tumour volume, FDG uptake on a pre-treatment PET/CT scan and histology[11-12]. The variability within the different risk groups is large, and in many cases too large to justify individual adjustments of treatment regimes. Most patients fail after therapy and it is currently not possible to identify the subgroup of patients with benefit from local treatment intensification. To justify individualized treatment adaptations, the competing risks of local and distant failure must be quantified (project 1-2) and the benefit of chemo-RT intensification on local control predicted (project 2). In this final project, results from the previous projects will be incorporated into a single coherent framework to select patients who may benefit from treatment intensification and quantify any such benefit on an individual patient level. Ultimately the model can be used to initiate a prospective protocol assigning patients to local RT intensification and immunotherapy depending on patient specific risk profiles. The prospective trial will be designed in collaboration with the Danish Oncological Lung Cancer Group (DOLG).

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