Automatization and modelling with deep learning approaches for medical imaging

"In god we trust, all others bring data" - *Edwards Deming*

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Plan

Lung cancer in France

- Lung cancer is the first cause of cancer-related death in France
- Non small cell lung cancer (NSCLC) is the most frequent type (85%) with two major histologic sub-types (adenocarcinoma and squamous cell carcinoma).

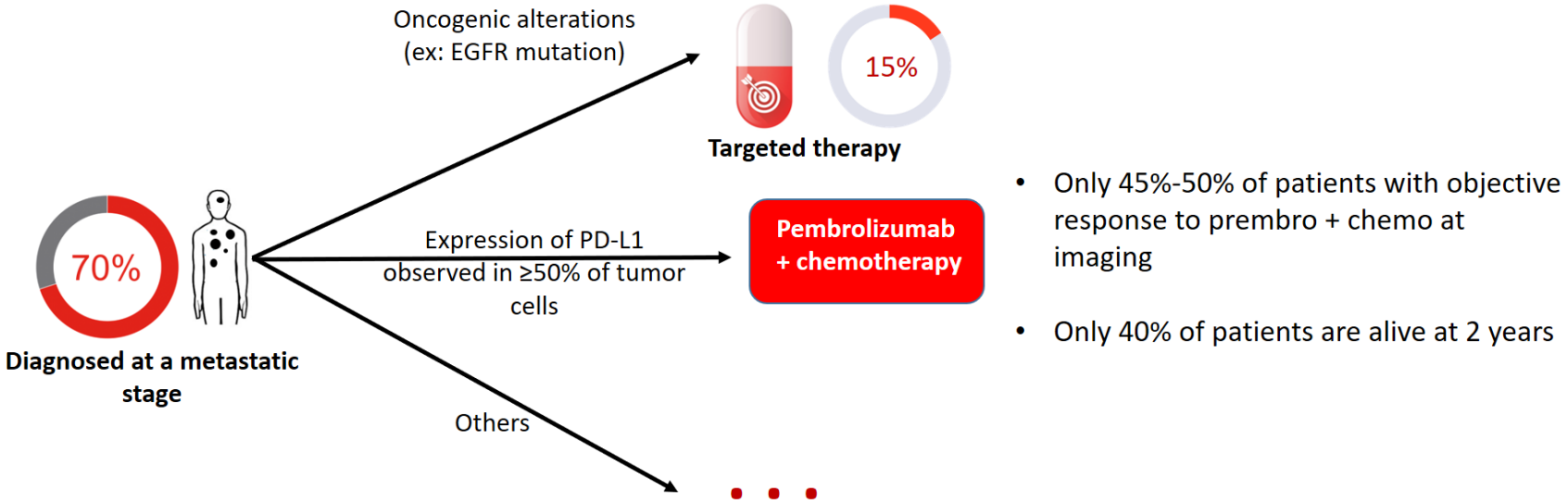
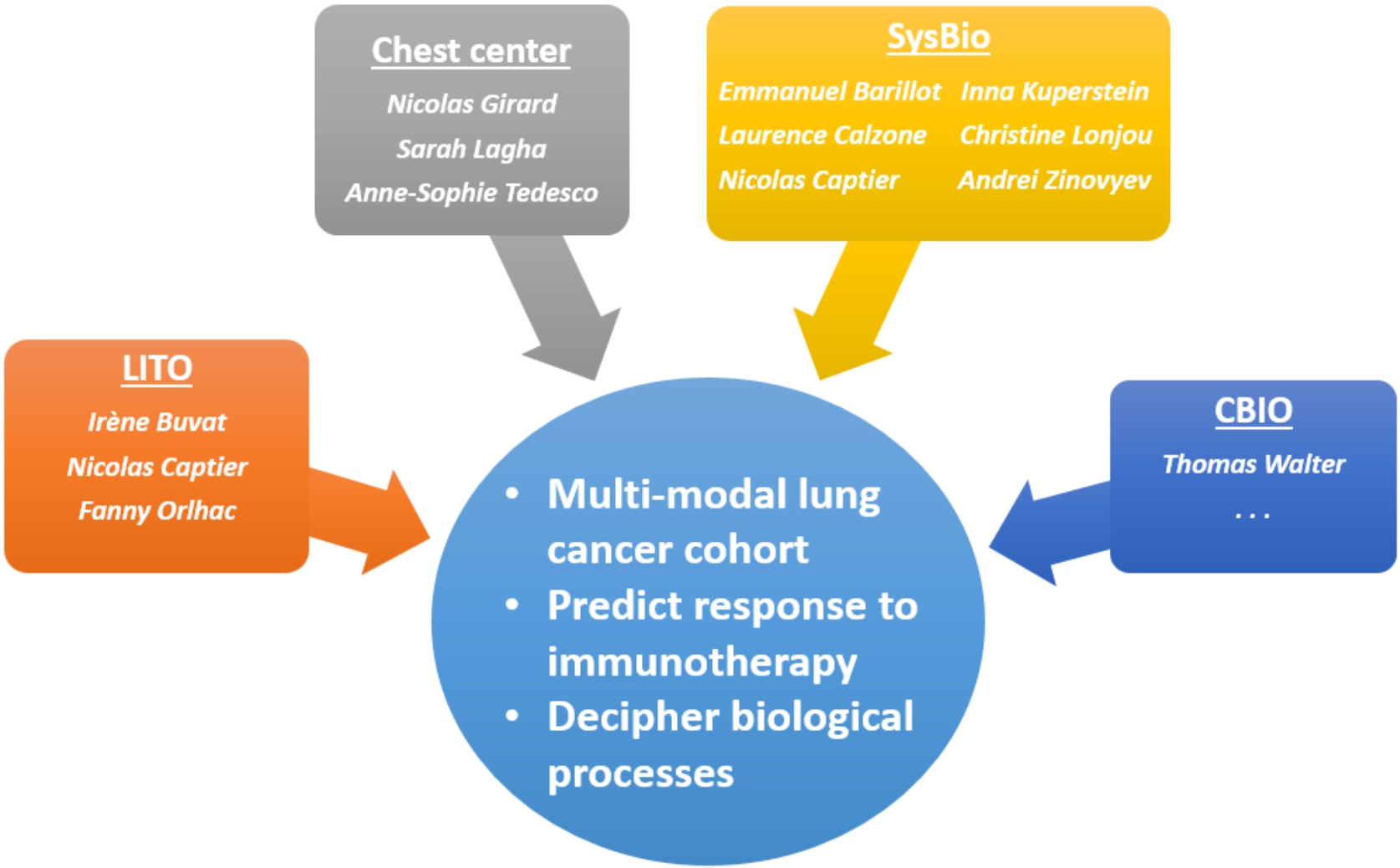


Figure 1: Current standard-of-care for NSCLC in France

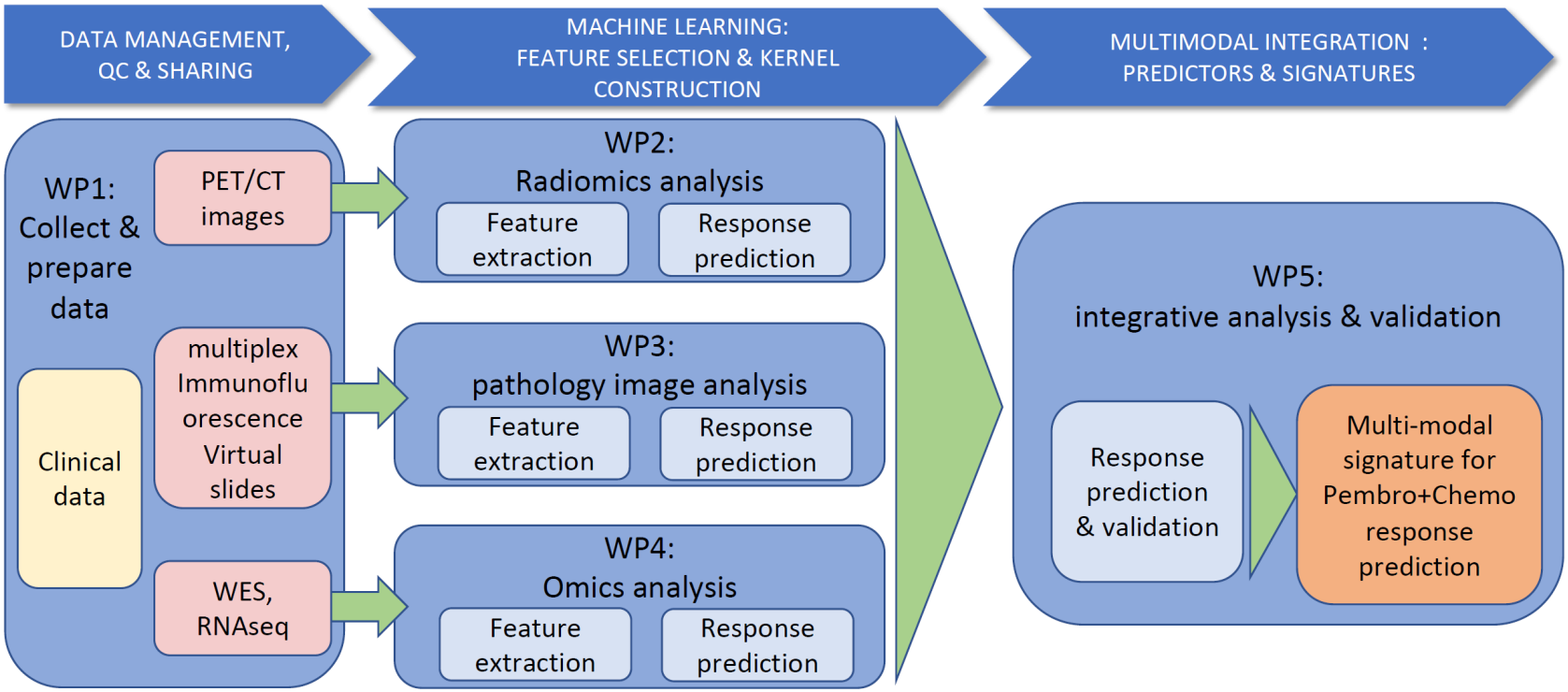
Can we optimize this current standard-of-care through the integration of multimodal factors predicting the efficacy of immunotherapy combined with chemotherapy ?

TIPIT project : immunotherapy in lung cancer - I



*200 NSCLC patients with sufficient available tumor material and first-line treatment with immunotherapy and chemotherapy.

TIPIT project : immunotherapy in lung cancer - II



- How can we overcome the limitations set by the modest cohort size ($\sim$ 200 patients) ?
- Which tools can we use to provide biological interpretations to our signatures ?
- How can we integrate the different modalities to improve robustness, predictive power and interpretability ?

Plan

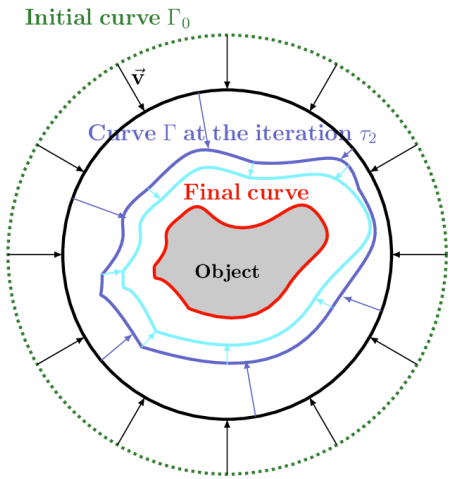
1. A few words about the TIPIT project
2. Segmenting lung lesions on CT scans with a U-Net architecture
3. A multiple instance learning model to exploit the full potential of PET scans

A challenging segmentation of lung lesions in CT scans

We need to address the challenging task of segmenting the biopsied lung lesions on CT scans.

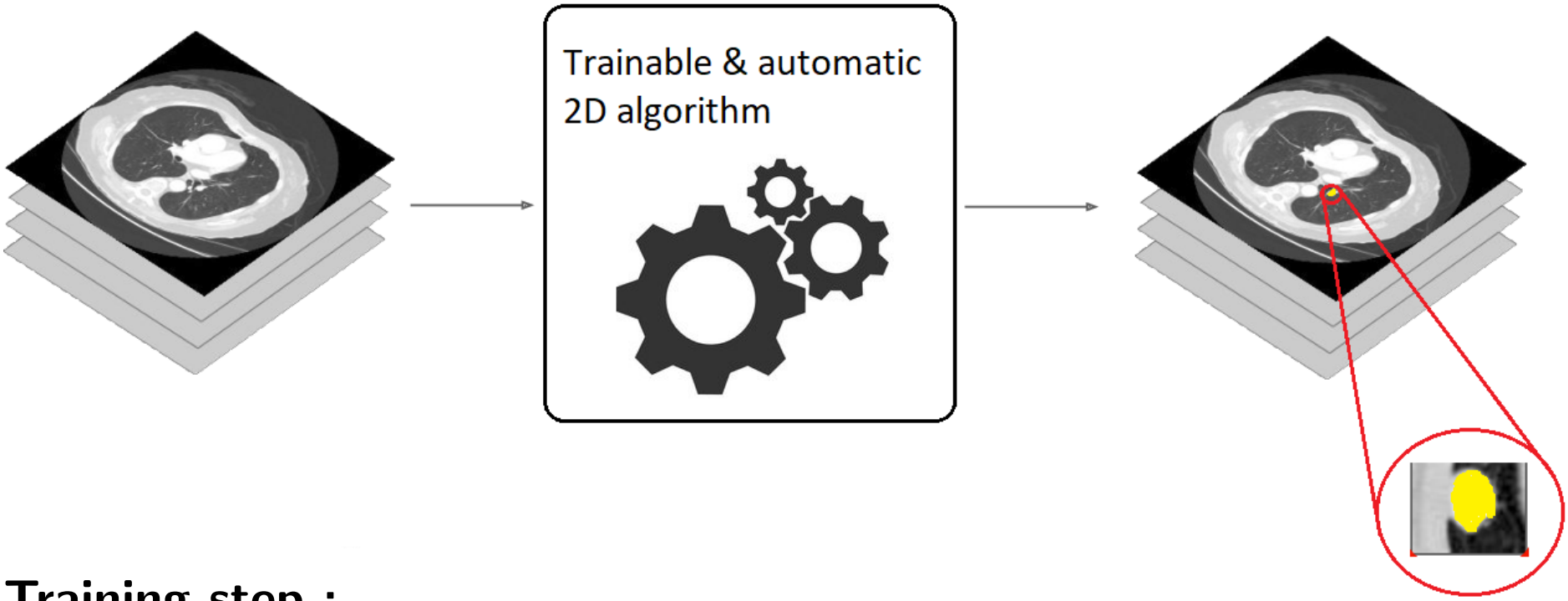
Manual segmentation

Semi-automatic segmentation



- These methods are time consuming and semi-automatic segmentation is maybe too general.
- We need to develop and train an automatic pipeline specific to our segmentation task.

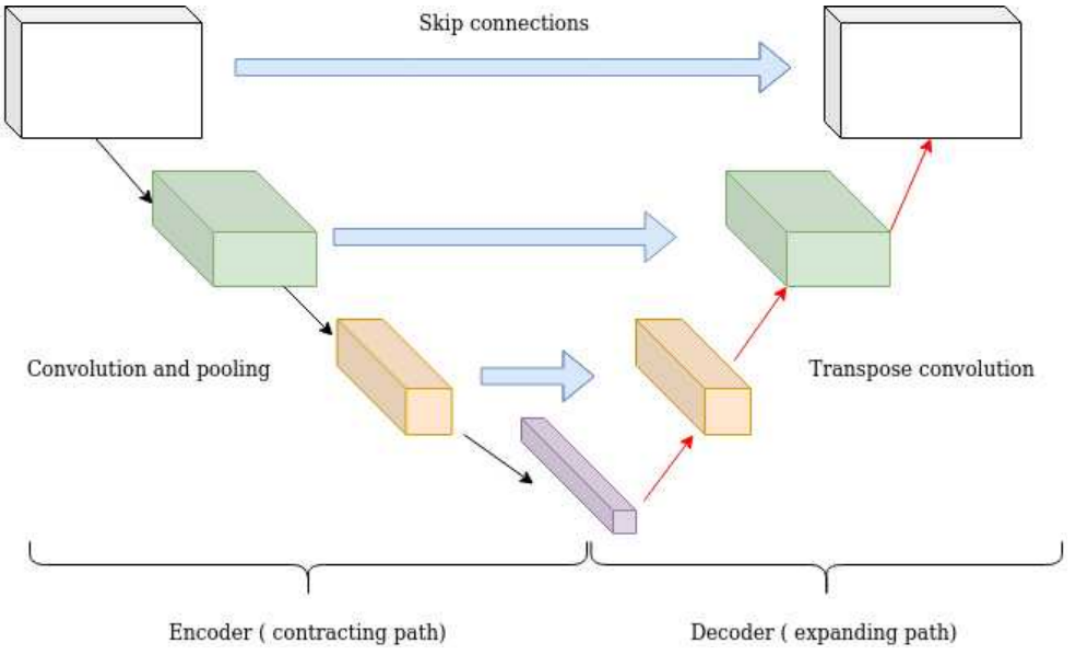
Building an automatic segmentation algorithm

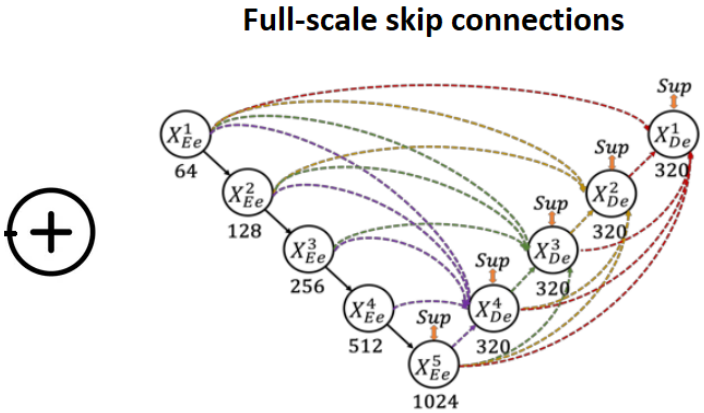


Training step :

- 198 patients for the training cohort (23725 256*256 2D slices) with a 80% – 20% validation split **at the patient level**
- Data augmentation to make the learning task more robust (rotation, zoom, brightness...).
- Training with binary focal loss (i.e extension of binary cross-entropy loss) and early stopping.

A brief digression : U-Net3+ architecture





- Each decoder layer incorporates same and smaller scale feature maps from the encoder and larger scale feature maps from the decoder.
- We want to capture and combine fine-grained and coarse grained details.

Some results

Testing step :

- 20 independent patients, manually segmented by a Curie radiologist
- Dice index and Jaccard index **in 3D**.

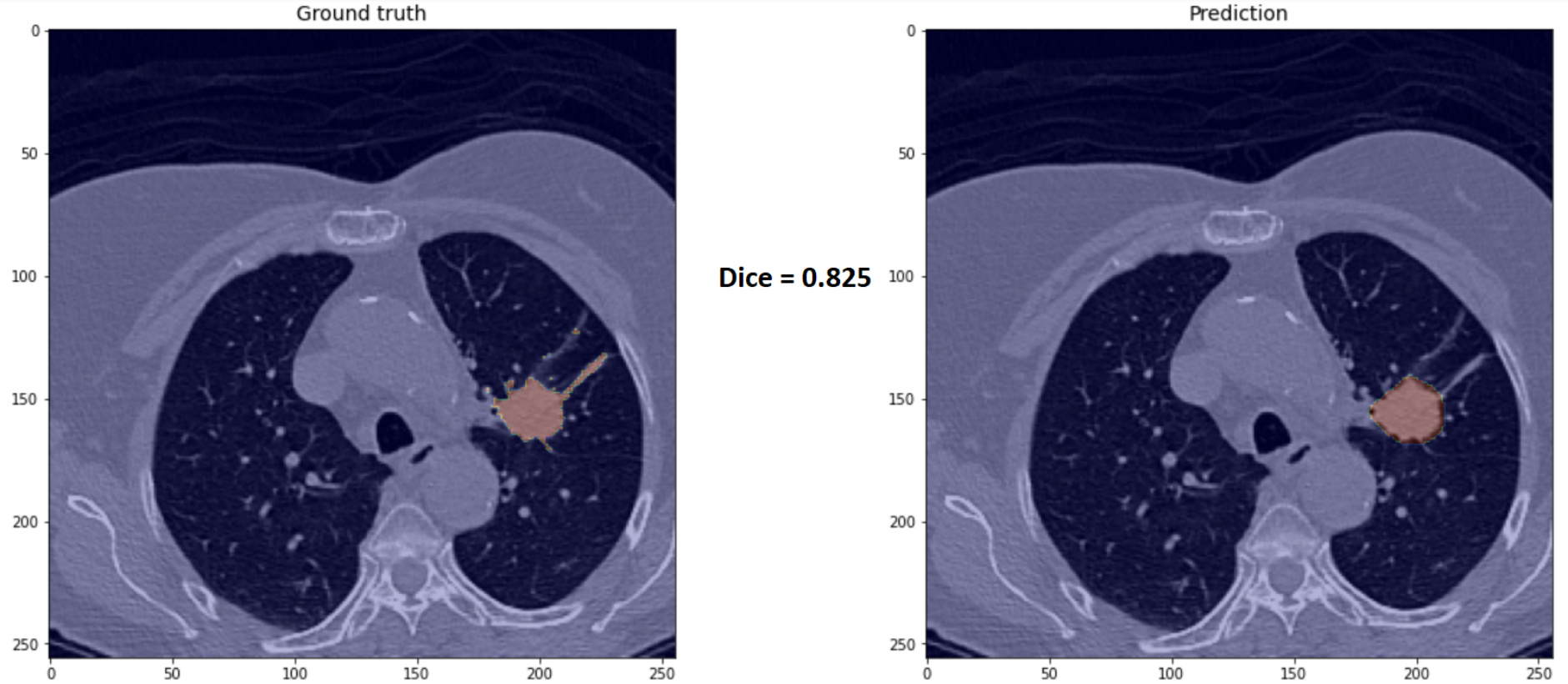
Mean 3D Dice index across the 20 CT scans : 0.657

Some possible explanations

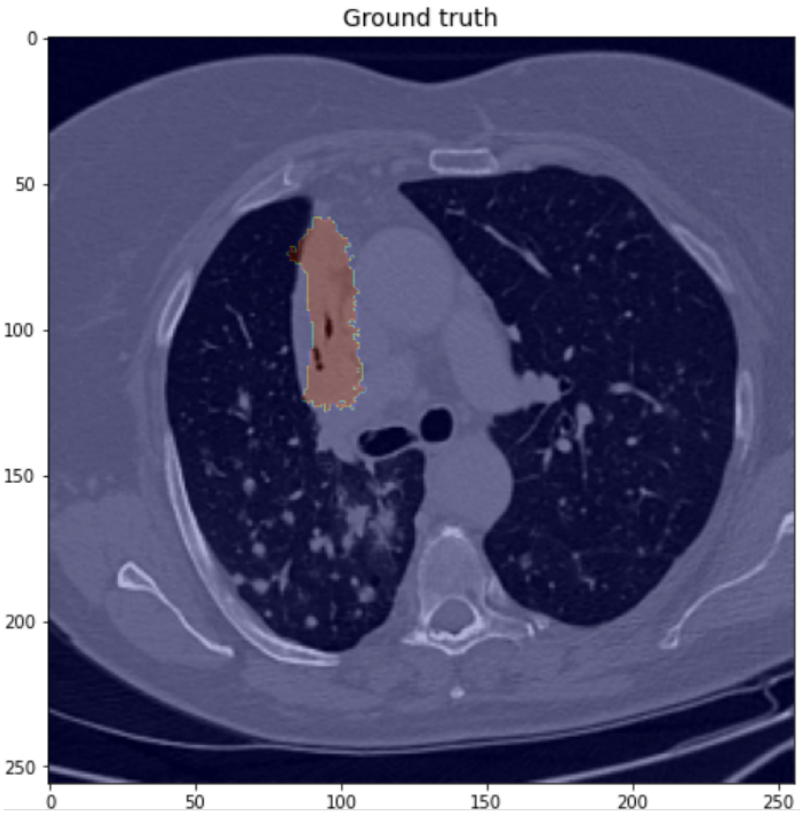
1. The U-Net is lacking some important information since it has been trained with 8-bit images (0 - 255) and not Hounsfield unit images.
2. Some test images are quite difficult to segment (even for a radiologist)

* The 2D Dice index was not used since the wide range of slices with no tumor lead to an optimistic bias (i.e by convention Dice = 1).

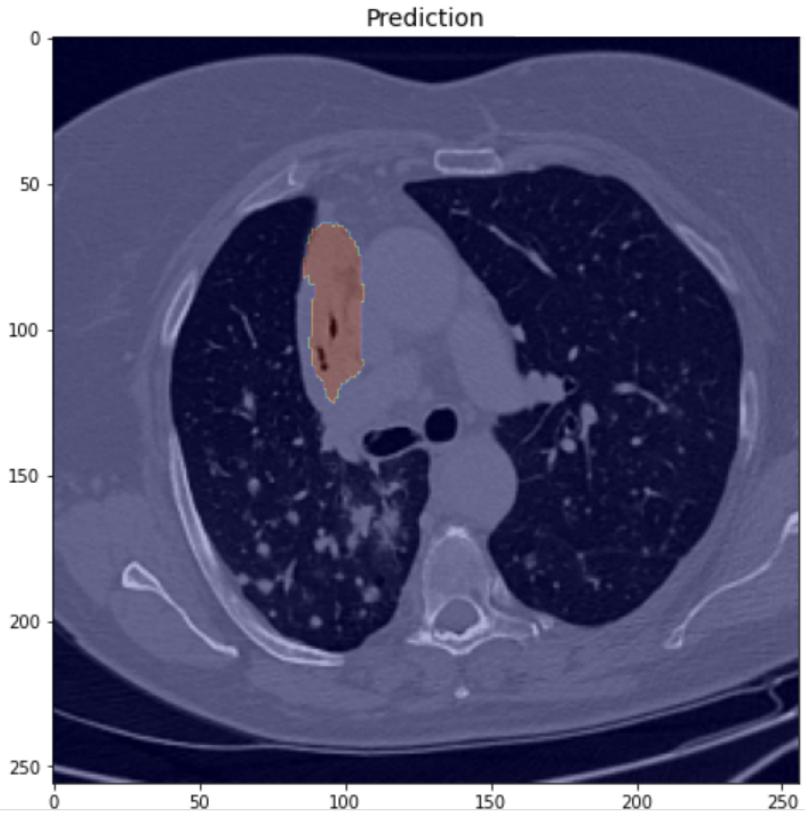
Results : example 1



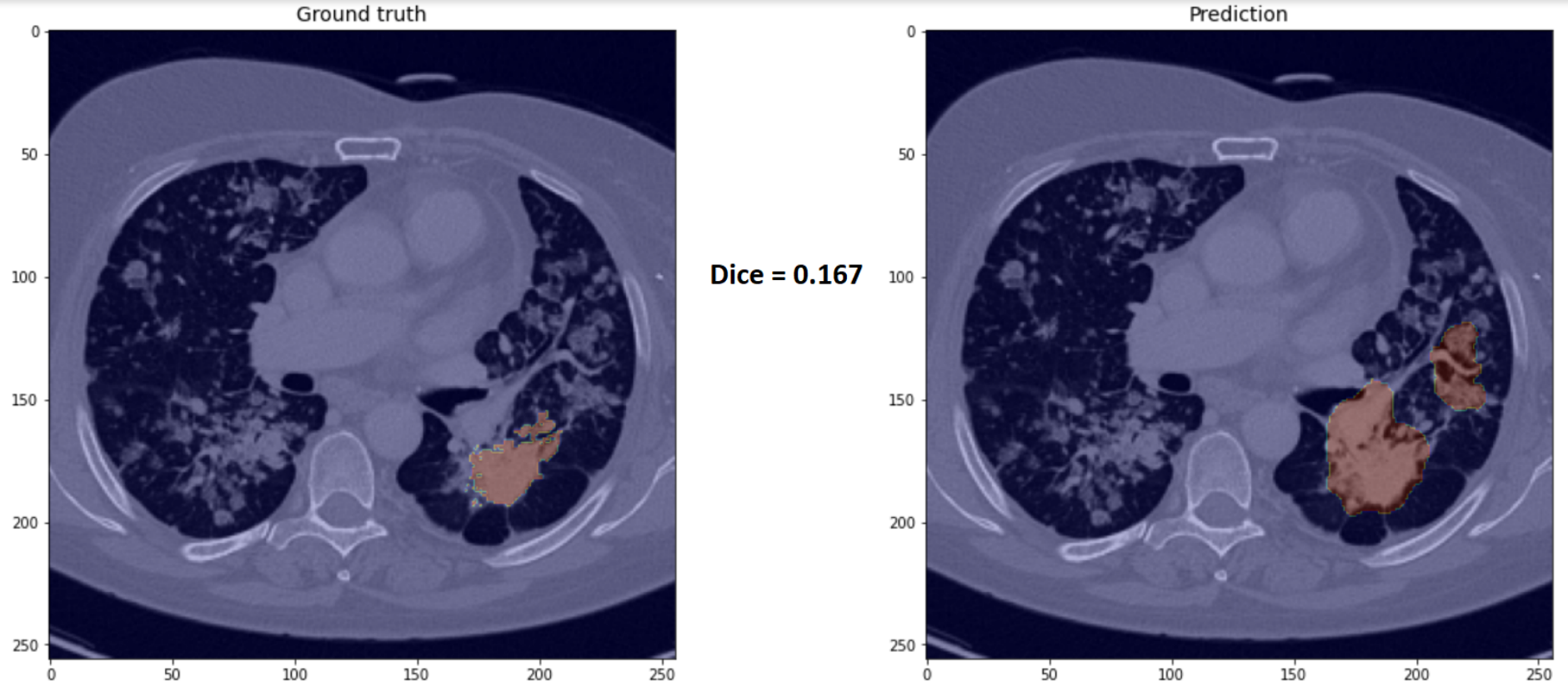
Results : example 2



Dice = 0.908

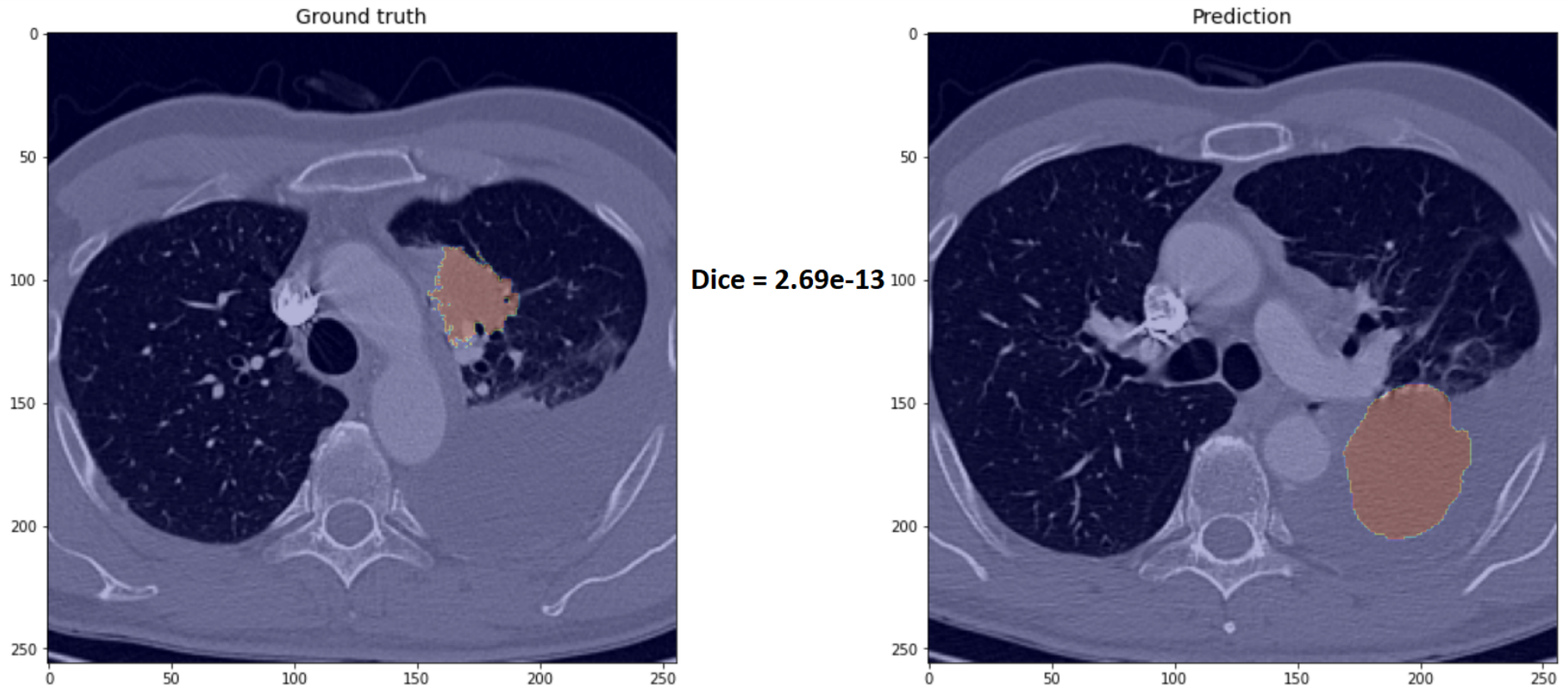


Results : example 3



Results : example 4

Warning : these are not the same slices (left and right) !



Plan

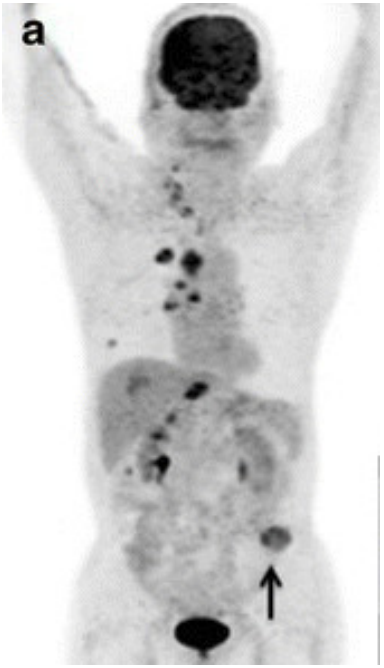
1. A few words about the TIPIT project
2. Segmenting lung lesions on CT scans with a U-Net architecture
3. A multiple instance learning model to exploit the full potential of PET scans
   - Introduction
   - Imaging assessment of the response to therapy
   - A multiple instance learning model

Predict the response to therapy from baseline PET scans

TIPIT : prediction of the response to therapy at patient-level

- 200 metastatic NSCLC patients treated with chemo + immuno
- Multi-modal data collected at baseline (transcriptomics, medical imaging, pathological, clinical)

Imaging data capture the whole baseline tumor burden. How can we integrate this information and build a predictive model ?



Notable challenges :

- Complex inputs with a lot of information to deal with.
- Moderate number of patients.
- Strong need for interpretable predictions.

RECIST 1.1 : procedure at baseline

The radiologist selections up to **5 target lesions** among measurable lesions (2 per organ max).

baseline

Selection criteria :

- Sufficient size (measurable lesions)
- Suitability

Uni-dimensional measurement of macroscopic tumour burden :

$$\begin{cases} TB = \sum_{i=1}^{N} L_D^i \\ L_D^i : \text{longest diameter of target i} \end{cases}$$

RECIST 1.1 : evaluation of response after therapy ignition

- **Progressive disease (PD):**
  - $\geq 20\%$ **increase** of TB (relative to NADIR)
  - Appearance of new lesions
  - Unequivocal progression of non-target lesions
- **Partial response (PR)** : $\geq 30\%$ **decrease** of TB (relative to baseline)
- **Stable disease (SD)** : when neither partial response nor progressive disease can be established
- **Complete response (CR)** : disappearance of all target lesions

With these 4 different classes we can easily derive a binary outcome :

$y = 0$ i.e partial response + complete response

$y = 1$ i.e progressive disease + stable disease

Pseudo-progression and immunotherapy

With immunotherapy, RECIST procedure must be adapted to account for unconventional response patterns :

- Response after an increase in tumour burden
- Response during or after appearance of new lesions

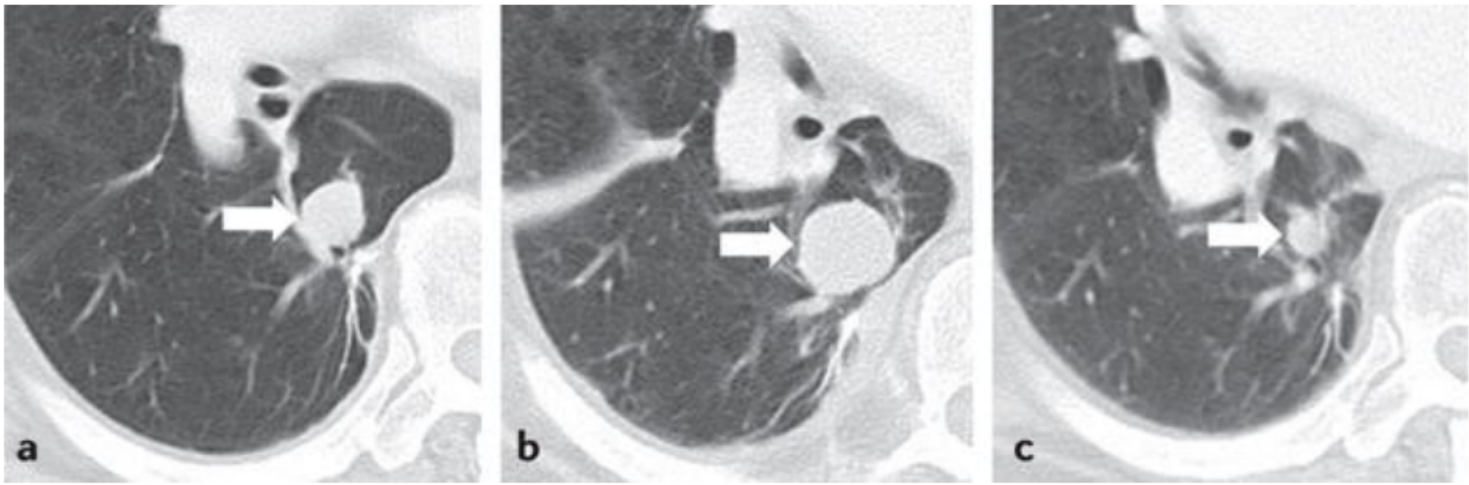
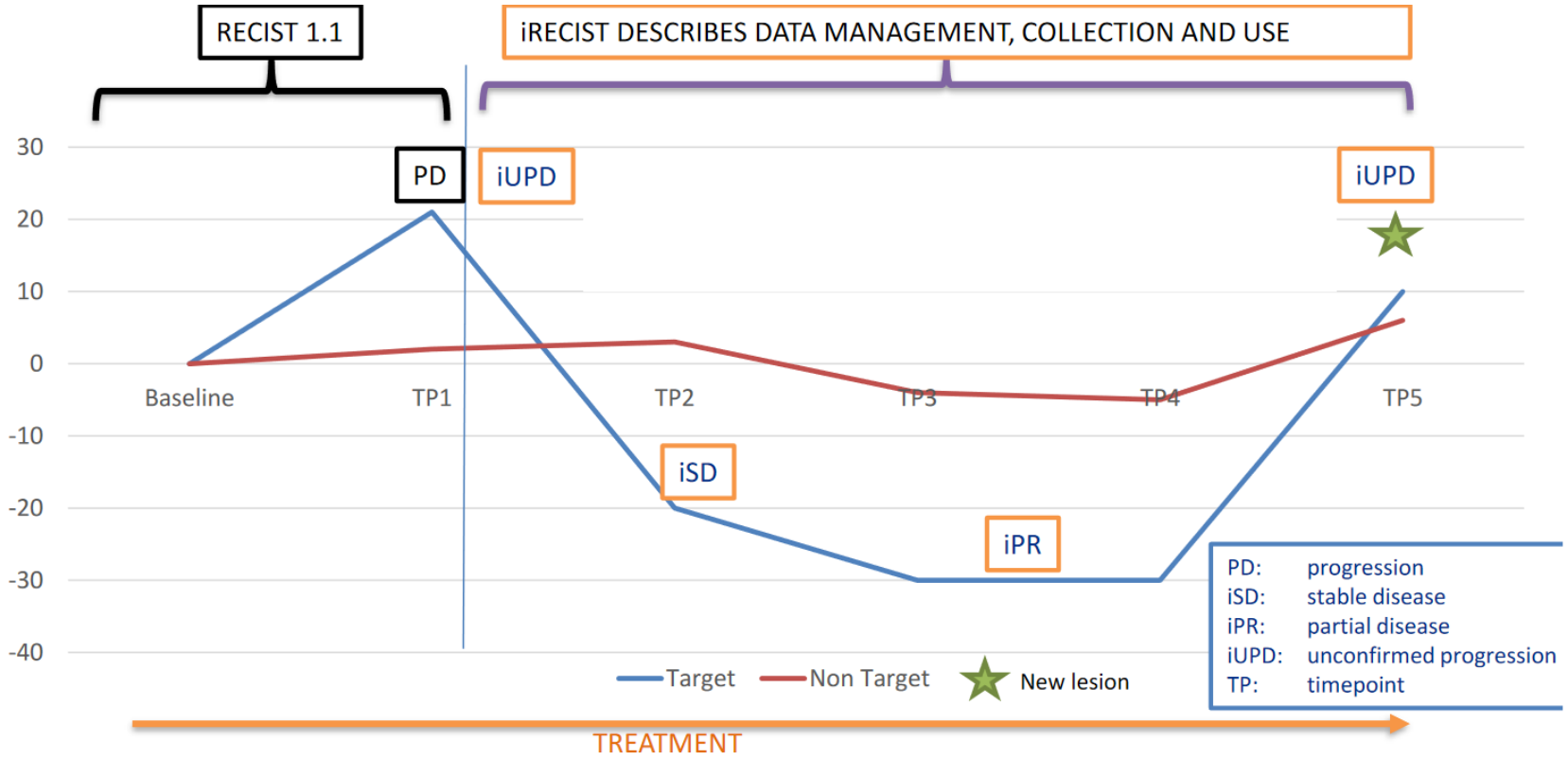


Figure 2: 77-year-old male with advanced-stage melanoma treated with ipilimumab[1].

[1] "Monitoring immune-checkpoint blockade: response evaluation and biomarker development" - Nishino *et al.* 2017

iRECIST : dynamic assessment of response

Progression requires confirmation on a consecutive scan at least 4 weeks apart (worsening).



For our TIPIT patients we can use the different images that have been acquired during a fixed period of time (ex: 6 months) to update the response to therapy.

Some of my thoughts about these measures...

RECIST and iRECIST procedures are **efficient and standardised surrogates** for therapy efficacy.

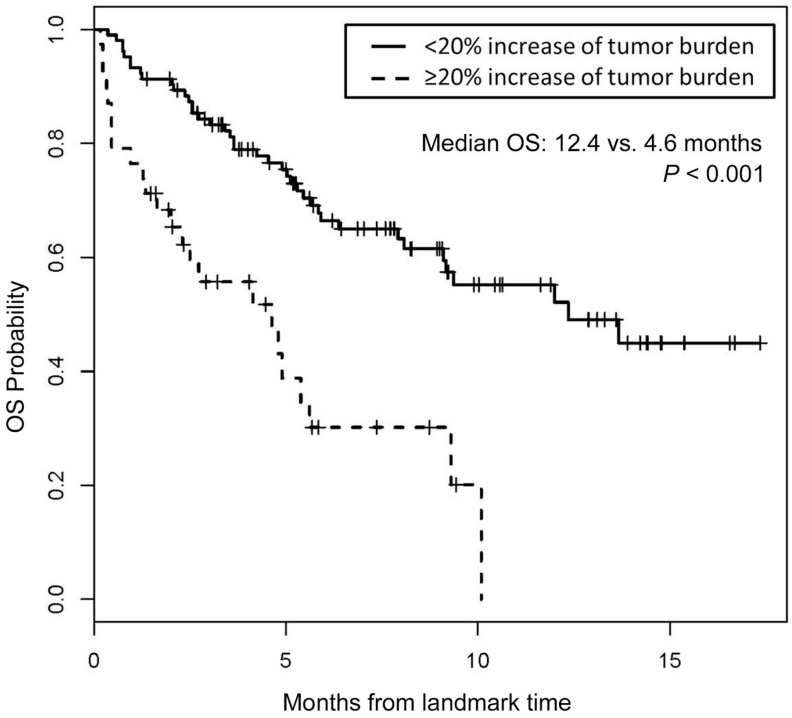


Figure 3: 160 patients with advanced NSCLC treated with commercial nivolumab or pembrolizumab monotherapy - tumour burden evolution at 8 weeks[2].

They are also **very complex**, **radiologist - dependent** and **deriving a precise and usable model for these processes seems a bit utopian**.

[2] "Tumor Response Dynamics of Advanced Non–small Cell Lung Cancer Patients Treated with PD-1 Inhibitors: Imaging Markers for Treatment Outcome" - Nishino *et al.* 2017

Simplification : combination of two latent phenomena

- **A significant and confirmed change in the total macroscopic tumour load observed at baseline**

$$z = \begin{cases} 1 \text{ if } \sum_{i=1}^{N_{\text{total}}} \delta_i \geq \tau \\ 0 \text{ otherwise} \end{cases} \qquad \delta_i\text{: relative size change for tumour i}$$

- **A confirmed appearance of new macroscopic lesions after the beginning of therapy**

$$w = \begin{cases} 1 \text{ if new lesions have appeared} \\ 0 \text{ otherwise} \end{cases}$$

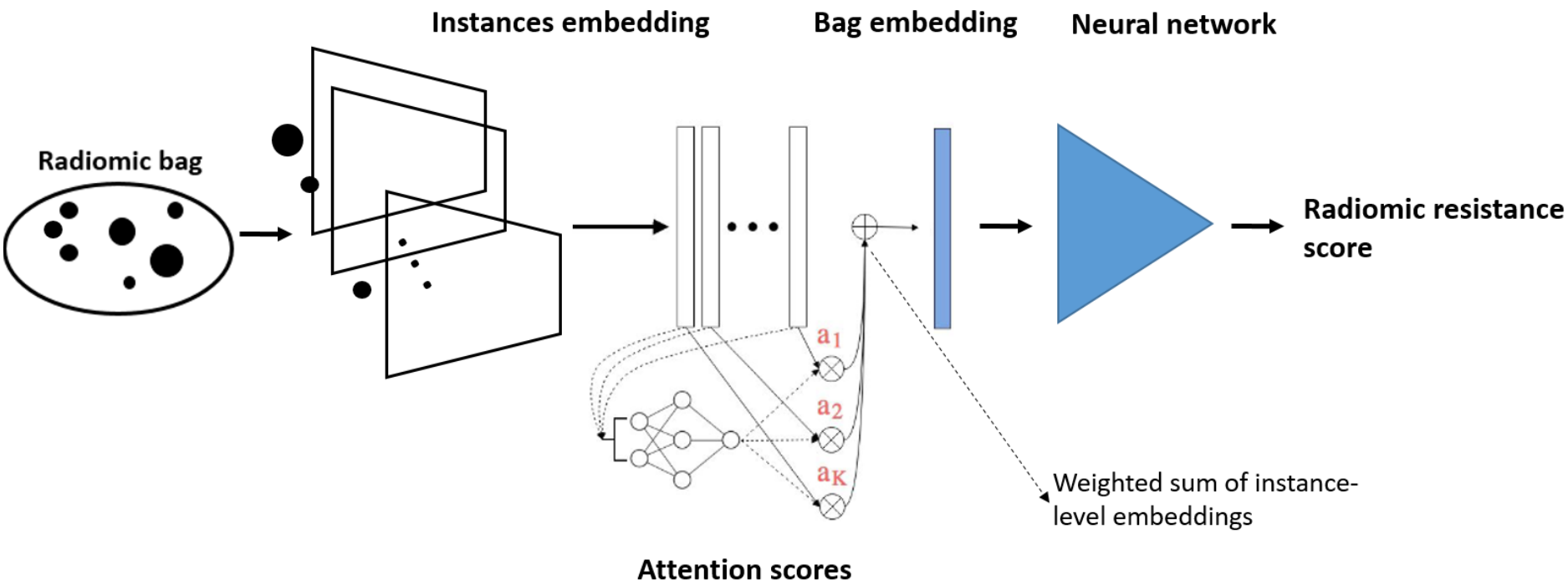
Model with latent secondary outcomes

$$y = \begin{cases} 1 \ (\text{PD} + \text{SD}) \\ 0 \ (\text{PR} + \text{CR}) \end{cases} = 1_{\{(z+w)\geq 1\}}$$

Prediction of the outcome z : Multiple Instance Learning

We could try to predict a patient-level **"resistance score"** (in $[0, 1]$) that would mimic $\sum_{i=1}^{N_{\text{total}}} \delta_i$

- Each tumour contributes separately to this patient-level score.
- The resistance is encoded in the radiomic signature of the tumour at baseline.

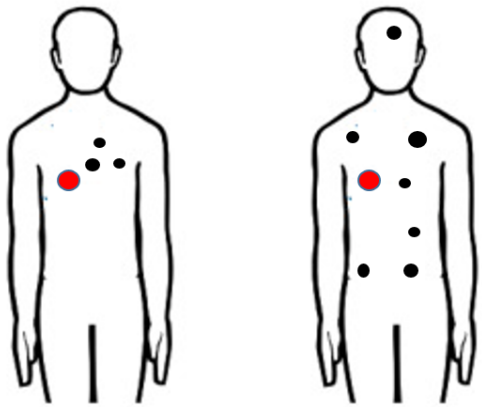


[2] "Attention-based Deep Multiple Instance Learning" - Ilse *et al.* 2018

Prediction of the outcome w

To predict the appearance of new macroscopic lesions despite the therapy using only baseline information, we need patient - level features.

1. **Characterisation of the metastatic distribution at baseline**

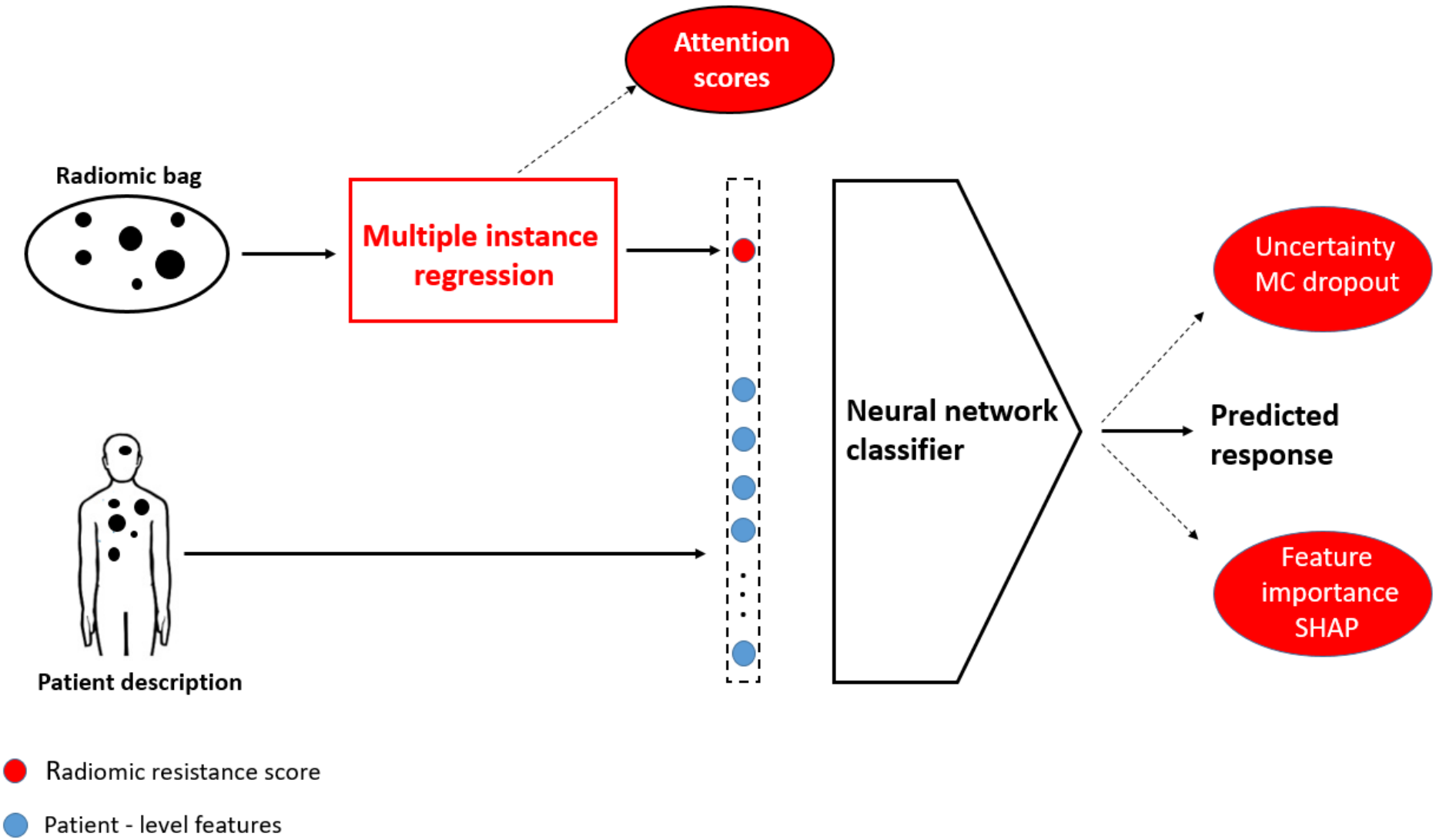


- Number of lesions
- Impacted organs
- Maximum distance between two lesions
- ...

2. **Radiomic resistance score :** resistance of already visible macroscopic lesions provides information on the resistance of new comers and microscopic lesions.

3. **Potential covariates (i.e clinical features)**

Presentation of the final model



Interpretable and **flexible** approach **trainable in an end-to-end manner**