Prediction Of The Evolution Of Thyroidal Lung Nodules Using A Mathematical Model

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Refractory thyroid carcinomas are a therapeutic challenge owing to some being fast-evolving - and consequently being good candidates for trials with molecular targeted therapies - whilst others evolve slowly. This variation makes it difficult to decide when to treat. We have developed a diagnostic tool to help physicians predict the evolution of thyroidal lung nodules.

Objectives

The evolution of lung metastases from thyroid origin may be difficult to evaluate. Furthermore, when unwell patients are concerned, physicians try to minimize the use of invasive techniques, restricting treatment (by radiofrequency ablation for example) to nodules that become progressive. Thus, an accurate prognosis of each nodule is critical. *We propose a numerical method of predicting the actual tumour growth for a specific patient.*

Classically, accurate mathematical models describing tumoral growth involve a large number of parameters that cannot always be recovered from experimental data. The model proposed here is **tuned for each patient** thanks to two medical images following the evolution of a nodule. From this analysis, it is possible to obtain **an estimate of the evolution of a targeted nodule using only non-invasive techniques.**

Our model describes, not only the volume of the tumour, but also **its localization and shape**. It takes into account nutrient concentration, cell-cycle regulation and evolution of populations of cells, as well as mechanical effects. Our prediction relies on parameters estimation using temporal series of MRI or scans. The approach uses optimization techniques and Proper Orthogonal Decomposition (POD) to estimate the parameters of the chosen mathematical model (adapted to the type of cancer studied) that best fit with the real evolution of the tumour shown on the images.

Method

Macroscopic description of cellular densities

We use a macroscopic model describing cellular densities (P=proliferating cancer cells, Q=quiescent cancer cells, N=dead cells, S=healthy tissue). The cellular division is controlled by the oxygen concentration denoted by C.

The cellular densities evolve through :

$$\begin{aligned}
\partial_t P + \nabla\cdot(P\mathbf{v}) &= \gamma P - (1-\gamma)P + \gamma Q,\\
\partial_t Q + \nabla\cdot(Q\mathbf{v}) &= (1-\gamma)P - \gamma Q - \gamma_2 Q,\\
\partial_t N + \nabla\cdot(N\mathbf{v}) &= \gamma_2 Q,\\
\partial_t S + \nabla\cdot(S\mathbf{v}) &= 0.
\end{aligned}$$

Where the growth function is a smoothed Heaviside function centered around the hypoxia threshold τ_h.

$$\gamma(C) = \frac{1+\tanh(C-\tau_h)}{2}.$$

The velocity v is related to the movement created by the growth of volume du to the cellular division. This velocity is also to be determined.

First, we make the assumption that cells are incompressible which gives a condition on this velocity, namely:

$$\nabla\cdot\mathbf{v} = \gamma P.$$

However, this condition is not sufficient to close the system and determine the velocity.

Description of the movement

In order to close the system and compute the velocity, we have to make an additional assumption: the movement is considered as fluid or visco-elastic.

For the simulations presented here, we have used a Darcy-type law:

$$\mathbf{v} = -k\nabla\Pi,$$

where the potential ∏ can be computed thanks to the expression of the divergence of the velocity.

Results

We recover the parameters of the mathematical model adapted for a particular patient. Here is the case of a male patient, 79 years old; a poorly differentiated thyroid carcinoma was discovered in 2005 with iodine refractory synchronous lung metastases. From 2005 a continuous follow up with thoracic CT and serum thyroglobulin was done. Because of a synchronous prostatic cancer the patient could not be included in the Vandetanib or Sorafenib phase III trials.

From the two initial images, we obtain the parameters that fit the best the two images. The parametrized model can then be used for prognosis.

First test case

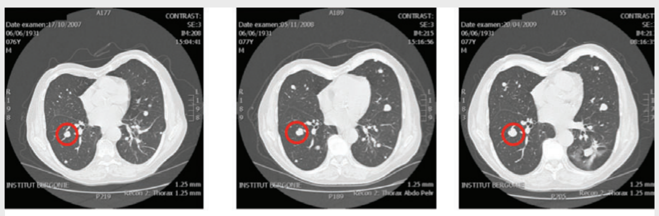

Fig 1. Evolution of an untreated lung metastatic nodule from thyroid carcinoma.

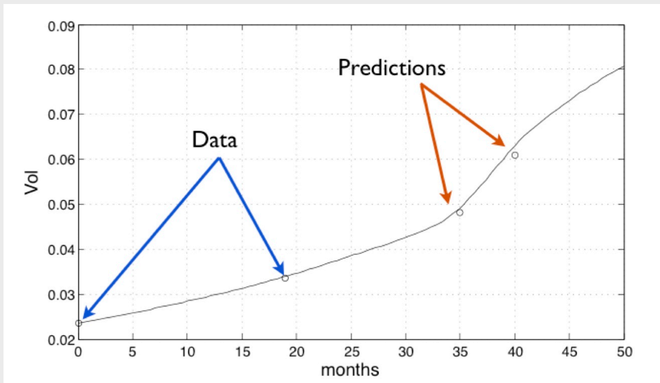

Fig 2. Results of a prediction of the evolution of the nodule based on the mathematical model.

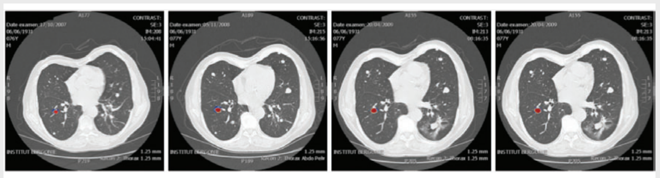

Fig 3. In addition to computing the volume of the tumour, the model can be used to predict the localization of the tumour (plotted in red).

Hence, given two images of the patient, we are able to recover the volume, shape and localization of the tumor at later times with a reasonnable accuracy.

In the next test case, two different lung nodules belonging to a 68 years old male patient with a kidney metastatic cancer are identified using the same procedure. While not concerning lung metastases from thyroid cancer, it allows us to validate the procedure on a quicker evolution.

Second test case

FIRST NODULE

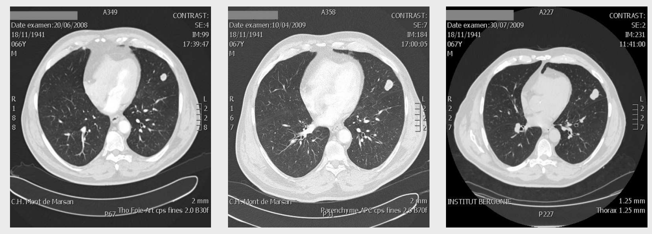

Fig 4. Evolution of an untreated lung metastatic nodule.

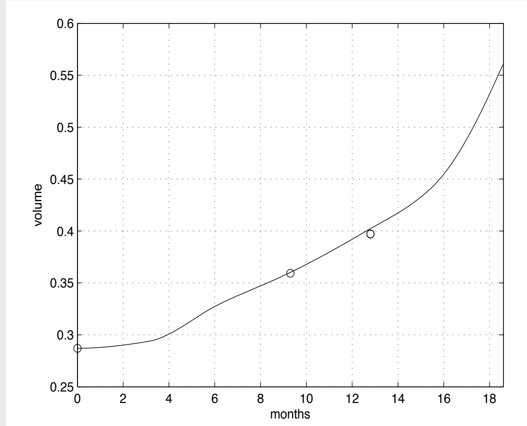

Fig 5. Results of a prediction of the evolution of the nodule based on the mathematical model.

SECOND NODULE

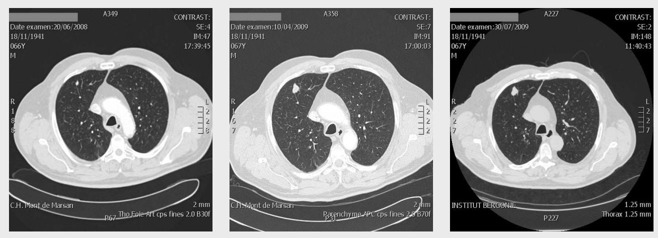

Fig 6. Evolution of an untreated thyroidal nodule in the lung.

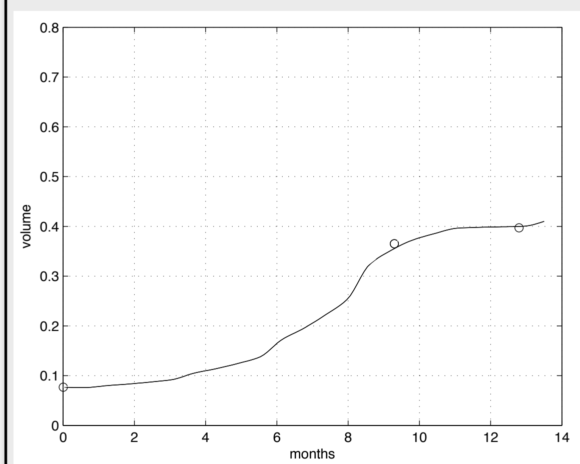

Fig 7. Results of a prediction of the evolution of the nodule based on the mathematical model

Conclusions

For oncologists the development of such tools is of interest in therapy planning (and in the evaluation of an antitumoral treatment). For example a slowly evolving tumour prediction could reinforce the decision to wait without specific treatment. In the opposite case the simulation can support the decision to start a radiofrequency thermal ablation (for example) or a molecular targeted therapy.

We plan to extend our numerical tool to other cancer types (brain, liver,...) and to take advantage of functional imaging (TEPscan, MRI) in order to increase the reliability of the procedure.

References

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http://www.math.u-bordeaux1.fr/MAB/mc2/

Institut Bergonié
http://www.bergonie.org