Assuming tumors have a spherical shape: Impact on modeled clinical outcome

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BACKGROUND

Assumptions in modeling

- Knowledge gaps and assumptions are important aspects of mechanistic modeling. Assessing their strength of evidence and impact on the model **enhance the model's credibility** and the confidence in model outputs.

The spherical shape assumption in lung cancer

- The ISELA model (*In Silico* Epidermal growth factor receptor (EGFR)-mutant Lung Adenocarcinoma) is a mechanistic model which **predicts tumor progression** in patients with advanced EGFR-mutated lung adenocarcinoma [1].
- Here, we investigate a simplifying assumption made in the ISELA model and in other models [2][3], namely the assumption that tumors have a spherical shape.

METHODS

Analysis of two lung cancer datasets

- To evaluate the impact of tumor shape assumptions on the estimated tumor volume with respect to real-world data, two lung cancer datasets [4][5] - here called LUAD and NSCLC datasets respectively - were analyzed to assess the sphericity of lung tumors.
- As individual longest tumor radii were available for each tumor (LUAD: n=40, NSCLC: n=59), the estimated spherical volume was computed under the **spherical assumption (SA)** and compared to available **clinically reconstructed tumor volume (CRV)**.
- The **ellipsoid assumption (EA)** was also explored as an alternative -less simplifying- shape assumption.
- The shortest radius was only available in the LUAD dataset and was used to compute the **eccentricity parameter e** (Fig. 1).
- As the three tumor axes are rarely reported and were unavailable in these datasets, the three tumor axes under EA were defined **with proportionality relationships to the longest available radius** (two assumptions on the c axis were explored, Fig. 2). The estimated elliptical volume was then compared to the CRV (Fig. 2 and Fig. 3).

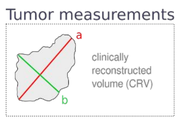
nova DISCOVERY

AACR American Association for Cancer Research

Exploring the **impact of assuming spherical tumors** on the **modeled clinical outcome** through the analysis of **tumor measurements** and ***in silico* simulations**

1 Define shape assumptions, and relationships between axes, based on the available data and compute the **estimated tumor volume** for each shape assumption

Tumor measurements



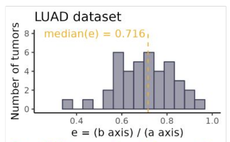
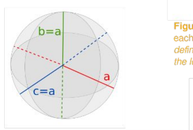
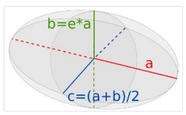


Figure 1: Histogramm of eccentricity computed for each tumor in the LUAD dataset. *Eccentricity is defined as the ratio between the shortest axis b and the longest axis a.*



$$V = \frac{4}{3} * \pi * a * b * c$$



2 Compare the estimated tumor volume under different shape assumptions to **clinically reconstructed volume (CRV)**

The assumption of c=(a+b)/2 better approximates the CRV compared to c=a with 44.4% and 61.6% of tumors being overestimated respectively (both datasets aggregated).

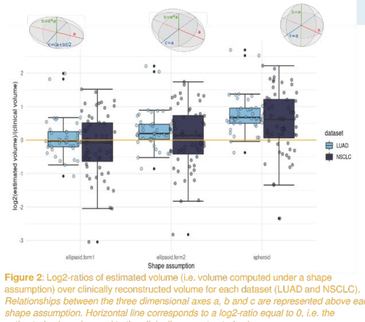


Figure 2: Log2-ratios of estimated volume (i.e. volume computed under a shape assumption) over clinically reconstructed volume for each dataset (LUAD and NSCLC). *Relationships between the three dimensional axes a, b and c are represented above each shape assumption. Horizontal line corresponds to a log2-ratio equal to 0, i.e. the estimated volume is equal to the clinically reconstructed volume.*

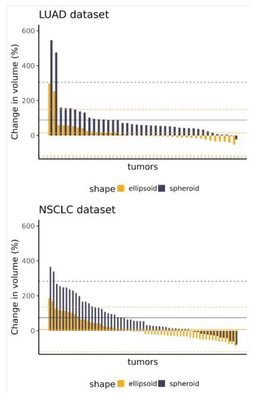


Figure 3: Change in volume (in %) under the spherical formula and the ellipsoid formula (b=e*a, c=(a+b)/2) computed for each tumor in the LUAD and in the NSCLC datasets. *Change in volume is defined as (estimated volume - clinical volume)/clinical volume *100. Solid line corresponds to the mean and dashed line corresponds to mean +/- two times the standard deviation.*

In both datasets, **tumor volumes under the EA are closer to the CRV**. In the LUAD dataset, tumor volumes have a median relative change equal to -1.81% under the EA and 59.8% under the SA.

Comparison of predictions between simulations showed that **only 4% of the virtual patients changed their treatment response status** (non-responder/responder). In patients classified as responding to the treatment in both simulations, the median TTP difference was 11 days.

3 Implement an **alternative shape assumption, the EA**, in the ISELA model and generate virtual populations of patients by defining the **eccentricity e for each patient**

one arm with spherical tumors (e=1), one arm with ellipsoidal tumors (e=0.716)

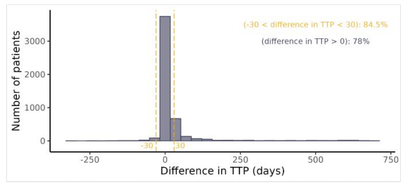


Figure 4: Histogram of the difference of time to progression (TTP). Difference of TTP is defined as the TTP obtained for each patient in the spheroid arm (e=1) minus TTP obtained for its equivalent patient in the ellipsoid arm (e=0.716).

arms with each a different eccentricity (e=0.4, 0.7 or 1)

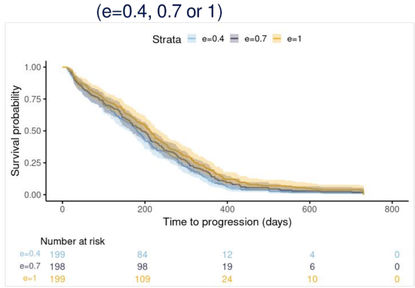


Figure 5: Impact of the eccentricity parameter e - defining the relationships between the axes a, b and c in an ellipsoidal tumor - on model outcome, time to progression (TTP). *200 patients are simulated with only their e parameter differing between the three arms. e=1 corresponds to a perfectly spherical tumor.*

Patients having in real-life an eccentricity of 0.7 have a median simulated **TTP underestimated of 18 days** under the SA.

The median TTP is equal to 181, 195 and 213 days in the e=0.4, e=0.7 and e=1.0 arms respectively.

Exploration of the SA and the EA through *in silico* simulations

- To quantify the impact of the SA on the model's primary output -time to progression (TTP)-, **an alternative ISELA model assuming ellipsoid tumors was implemented**.
- **Two clinical arms** -one under the SA and the other under the EA- were **simulated on the same virtual patients** (n=5000) with only the sphericity parameter differing, thus allowing a patient per patient comparison (Fig. 4).
- The impact of the eccentricity (e) was assessed by simulating 3 arms with each a different e value (n=200) (Fig. 5).

CONCLUSION

- The initial knowledge gap related to the form of the tumor, which led us to the **SA**, is assessed as having a **low impact on TTP**, thus increasing the general credibility of the model.

  In fact, real-data analyses confirmed that the tumor volume is overestimated under the SA but *in silico* comparisons of the SA and the EA demonstrated that the primary model output (TTP) is slightly impacted.
- Datasets are of crucial importance for modeling, especially for hypothesis testing. The LUAD and NSCLC datasets allowed us to study the SA and to define a promising alternative, the **EA** which **better predicts tumor volume** (a secondary model output).

  Additional studies are needed to further explore the EA and validate its use as support to clinical decision making.

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