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A MATHEMATICAL MODEL FOR TUMOR VOLUME EVALUATION USING TWO-DIMENSIONS[1]

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Abstract: *Many recent papers present different ways to show the volume of a tumor from a few two-dimensional images. The three-dimensional fundamental shape of tumors is assumed to be a hemi-ellipsoid as presented in different studies. The three measurements were essential for tumor volume calculations: length, width, and height. Tumor volume measurements task is a very intensive routine is cancer research. Recent papers present how to reconstruct the 3-D tumor from a set of 2-D images, this in order to find the tumor volume. In this paper we report on a new approach to calculating the volumes based on measurements of two dimensions, length and width, after having identified a statistical constant that replaced the need of measuring the tumor height. Results: Our new method was examined on a subcutaneously implanted tumor placed on a mouse's thigh. The width, length, and height of tumors were measured, in four groups of BALB/c mice, using a digital caliper. The tumor dimensions were periodically measured for several weeks. It was shown that this new model can assist in tumor volume measurements using digital images, and in CT scan tumor size assessments.*

Key words: *tumor volume; tumor reconstruction; tumor imaging; hemi-ellipsoid; mice model*

1. Introduction

When using medical imaging that involve radiation such as computed tomography, it is important to minimize the patient exposure. The high exposure is delivered due to the need of a number of images to reconstruct the tumor shape, and dimensions (Junzhou, 2006).

The three-dimensional fundamental shape of tumors is assumed to be a hemi-ellipsoid in different studies. Researches that use the assumption of a hemi-ellipsoid tumor shape were published regarding breast cancer (Wapnir, 2001), prostate cancer (Sosna, 2003) (Egorov, 2006) cervical cancer (Mayr, 2002), glioma cancer (Schmidt, 2004), and others (James, 1999).

A typical ellipsoid volume is giving by:

$$V = \frac{\pi}{6}(length)\cdot(width)\cdot(height) \qquad (1)$$

This study aims to assist in tumor volume measurements by developing a new model that reduces the essential number of dimensions for the volume, and therefore reduces the number of images needed.

The new mathematical model for tumor volume measurement was investigated using a mice model, which is described in the methods section.

2. Methods and Materials

The mice model

In order to examine a new method of tumor volume measurements a subcutaneously implanted tumor was placed on a mouse's thigh. The width, length, and height of tumors were measured, in four groups of BALB/c mice, using a digital caliper. In cancer treatments, determination of the growth rate of tumor volume as a function of time is a standard method of determining the efficiency of a particular treatment.

Since changes in the growth rate reflect the efficiency or inefficiency of a treatment, extreme precision in the measurements is critical. The KHJJ tumor line was derived from a primary mammary tumor arising in a BALB/c mouse, after implantation of a hyperplastic alveolar nodule (Rockwell, 1972). Four groups of mice—26 individuals altogether—were tested in the experiments. All the mice were of the same BALB/c type and of similar size (28 ± 1.4 SD gram average weight). There were two separate groups for each gender (see Table 1). The mice received a tumor transplant on the thigh. The mice were kept and treated according to the Ben-Gurion University of the Negev guidelines for treating animals in scientific experiments.

Table 1: Members of each group of mice and the period of the measurements

Group	Research period	Number of mice in group	Gender
1	63 days	8	male
2	39 days	2	male
3	36 days	5	female
4	43 days	11	female

Preparation of the tumor segments

The KHJJ tumor segments were prepared from a KHJJ tumor about 200 mm^3 in size. This tumor was taken from a mouse that had been sacrificed moments before dissection. The tumor had to be without signs of necrosis and with smooth margins. The tumor was separated properly from any remaining healthy tissue and washed three times with PBS. Then the tumor was cut through the middle to ensure that there was no necrotic tissue inside. The segments were prepared by cutting the tumor into 1 mm^3 sections for transplantation. These segments were kept moist by dripping PBS on them until implantation. This procedure was carried out in sterile conditions under a sterile hood.

Tumor transplantation

Each mouse, before the transplant, was anesthetized with a low dose of 80 ml/kg Ketamine and 8 ml/kg Xylazine anesthetics for about 40 minutes. The tumor segments were prepared for dissection a few moments before the process.

The mouse's right leg was shaved, the thigh skin was pulled up with forceps, and then a subcutaneous slit was made along the skin. A 1 mm^3 tumor segment was inserted using a trocar into the small pocket under the skin on the thigh. A small, flat stick covered with antibiotic ointment was pressed on the skin slit while the trocar was removed.

Tumor volume measurements

Once the tumor became palpable 5–10 days after transplant, its size was measured using a digital caliper. Only one person measured all the tumors in the experiments to prevent observation differences, since it was found that measurements by more than one person can lead to different results. The tumor was measured every other day, within four hours before or after the previous measurement. The tumor was measured between the skin surface layers. The length and width were measured with an accuracy of 0.01 mm using a digital caliber. The length was measured along the imaginary longitude of the leg; the width was measured in the direction of the latitude. The height was measured between the leg surface layer and the upper skin of the tumor. The caliper was placed perpendicular to the tumor so that the height could be measured properly. The tumor was measured from a volume of about 50 mm^3 until it had grown up to 1500 mm^3. Each volume measurement was repeated three times for verification.

Measuring tumor volume is problematic mainly because of inaccuracy in the measurement of tumor height, which contributes the largest error to volume results. The difficult part in achieving precise measurements is determining where to position the caliper in order to measure height. It is clear that a new approach eliminating the need to measure the height, while still providing a precise assessment of the tumor volume, could be very helpful. Tumor length and width can be measured very accurately because they can be observed directly. The 0.01 mm instrumental error associated with the caliper can lead to a 0.5%–1.0% error in a volume of 50 mm^3. The intensive repetitions in this study indicate that the total error for length and width is about 0.1 mm each, leading to a 3% error in the resulting volume. The tumor height error is very large when measuring with a caliper, around 0.5 mm, and can add a 7% error to the volume value. The total estimated volume error is around 10% (Dethlefsen 1968).

In order to minimize the volume error, we suggest an approach that relies only on length and width measurements to calculate volume. Such a calculation may a priori reduce

the uncertainty regarding the volume if a geometrical dependence of volume on length and width can be established:

$$Volume = f(width, length) \tag{2}$$

3. Results and Discussion

The dimensions of the tumor in the mouse model were measured only from the time it reached a volume of 50 mm^3 until it had grown to 1500 mm^3.

Different tumor growth rates were observed for different mice. Figure 1 shows examples from two mice groups—a male group and a female group. The graphs demonstrate a change in tumor dimensions over time.

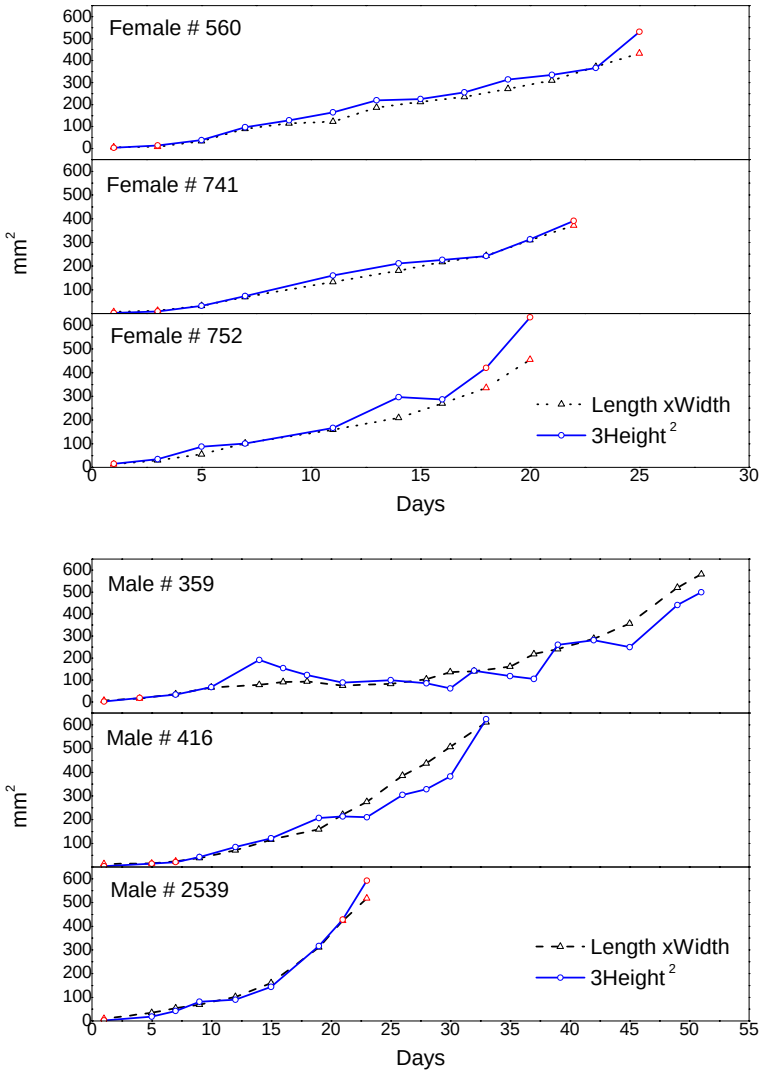

Figure 1. (Length × width) and (3 × height^2) over time. The red points represent data pertaining to volumes that were found to be irrelevant: (a) three female mice; (b) three male mice

We compared the average product of length and width with the square of height. A rough fit was discovered between the two values, with the square of the height multiplied by a factor of 3 being approximately equal to the length multiplied by the width:

$$3H^2 \cong LW \tag{3}$$

The examples in Figure 2 agree with Equation 3 for most of the points that represent different volumes. In addition, it should be noted that the different tumor growth rates did not affect the fit. A linear fit of all the results, shown in Figure 2, resulted in the following equation:

$$H = 1.63\sqrt{LW} \tag{4}$$

The correlation represented by Equation 4 was found to be high, with a linear correlation coefficient of R = 0.919. For a normal distributed data set, the likelihood estimator can be obtained by a least squares analysis (Alfassi, 2005). Therefore this correlation coefficient shows best the validity of Equation 4.

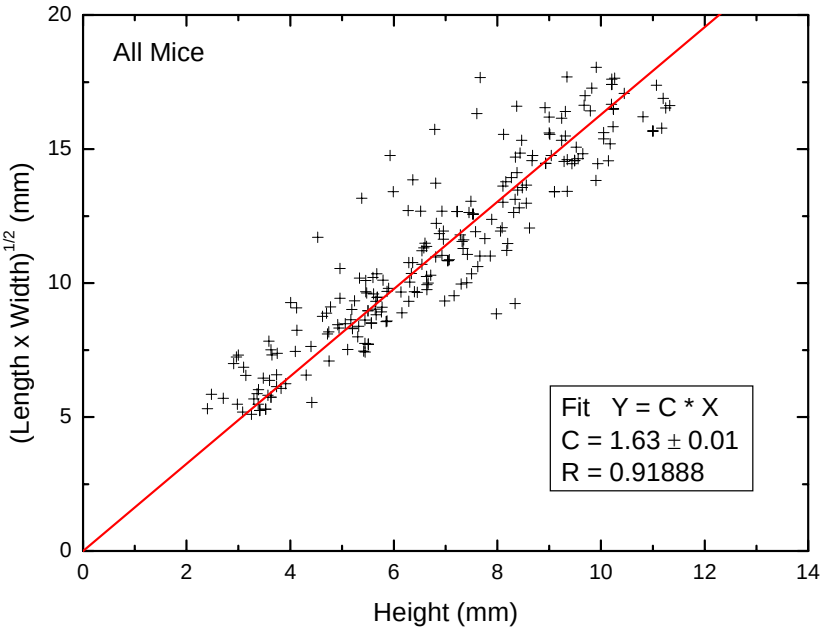

Figure 2. The linear fit of the square root of length × width corresponded to the height in all the measurements of mice.

In order to determine accurately the relationship between H^2 and LW, these values were analyzed separately for each gender, with the following results:

$$\text{Females: } f = \frac{H}{\sqrt{LW}} = 1.58 \pm 0.01 \tag{5}$$

$$\text{Males: } f = \frac{H}{\sqrt{LW}} = 1.69 \pm 0.03$$

A new formula for calculating tumor volume without the use of tumor height was obtained from the analysis of the measurements:

$$V = \frac{\pi}{6} f \left(length \cdot width\right)^{\frac{3}{2}} \tag{6}$$

The new formula is based on some symmetry assumptions that inherent in the classical volume formula, as the classical volume formula is a simple expression of an ellipsoid volume. A comparison of the new volume calculation with the classical calculation based on three dimensions, seen in Figure 3, shows no apparent difference in volume values. The total mouse mass growth-rate usually differs between males and females. The difference in the tumor growth-rate can be explained by the distinction in tumor growth-rate between genders.

The total volume error can be reduced using this new method in tumors placed subcutaneously to around 4%, compared to the 10% error that was obtained in the old-fashioned volume measurements. The error bars in Figure 3 are larger for the classical volume values and smaller for the new volume results.

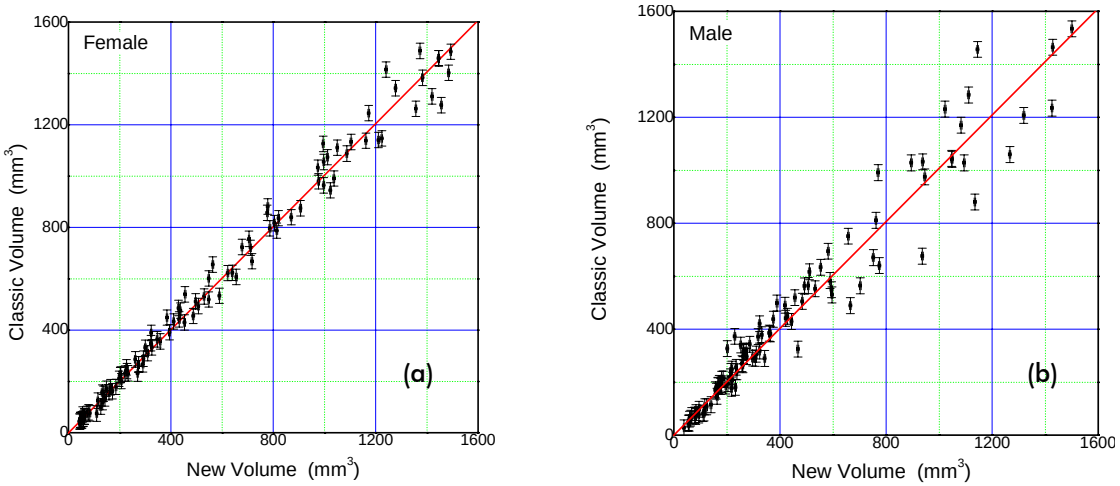

Figure 3. A comparison of the volume calculated according to the classical three-dimensional formula with the volume calculated according to the new method. The fit shows a good match between the results of the two methods: (a) in female mice; (b) in male mice.

4. Conclusions

The new method for tumor volume calculations was studied using the mice model described above. This model showed improved error estimation for the tumor volume. The old method results were plotted against the new method results, shown in Figure 3. The linear fit line for this graph obtained a slope of 1.00, proving the consistency of the new method. The new method of calculating volume should reduce the error in the volume measurements because it depends on visual measurements that can be accurately obtained. Since the nominal errors for length and width are similar, using the new method, presented in Equation 4, should limit the height error to about 1.5 times the error in length. This new method, not only reduces the error of the tumor volume, but also reduces the number of parameters needed to be measured down to two (length and width) from three (including the height). The new method can be helpful in several cases where a digital photo of a tumor can be taken, and may shorten the time needed for handling mice in the lab (see Appendix).

This work presents a test-case study of the new mathematical method offered for a tumor placed subcutaneously. These findings should encourage future studies towards reducing the amount of medical imaging scans needed for internal tumor volume reconstruction.

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Appendix

We developed a Windows-utility-program to insert a digital photograph of a tumor (shown in Figure 4). This program could be used to measure tumor length and width, and the tumor volume could be calculated using the new method presented in this paper. It would also be possible to use the classical method of calculating volume, if desired, once the tumor height has been determined. The caliper is not necessary to measure the tumor volume if one uses this program with digital photographs of the tumor. The program can be downloaded from http://www.bgu.ac.il/~iorion/.

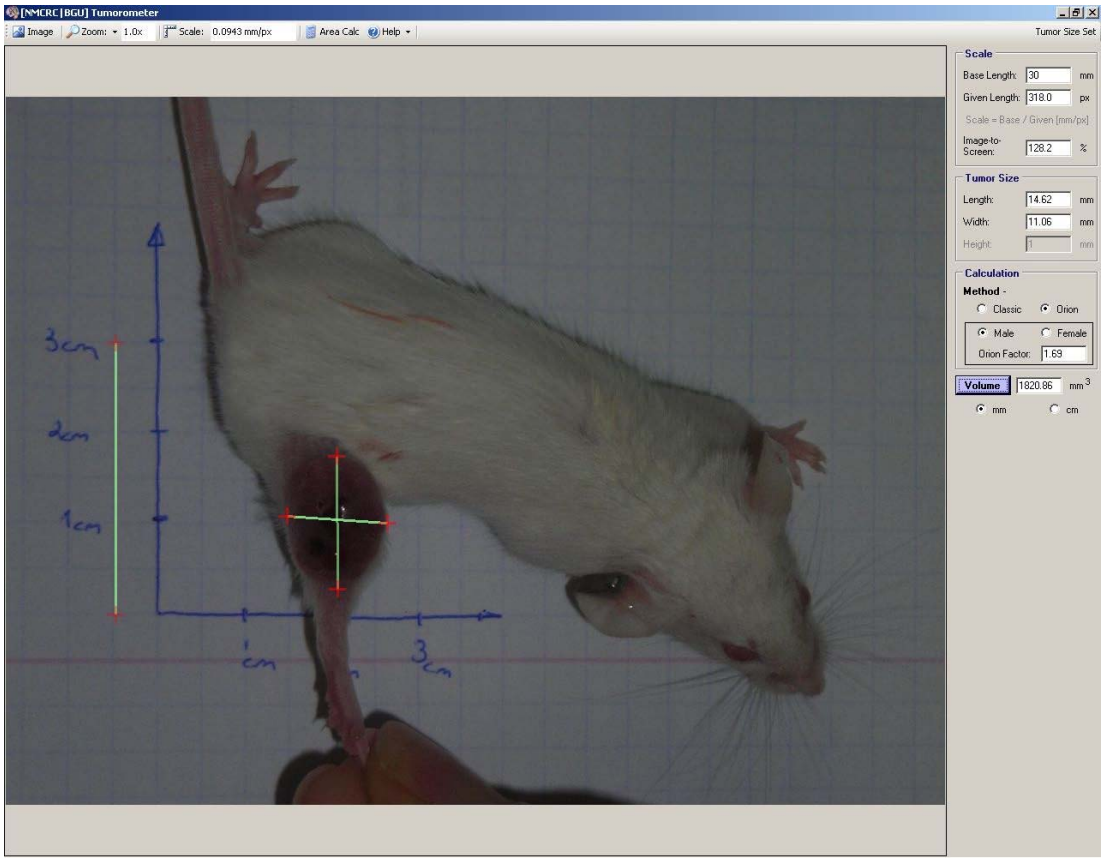

Figure 4. An example of tumor volume measurements using the Windows utility program

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