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TUMOUR GROWTH PARAMETER ESTIMATION FROM DOUBLING TIMES

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Abstract

Awarness of tumour growth characteristics is important in treatment of deadly disease Cancer. Experiments take lengthy time to explore the characteristics and availability of required sample size is another drawback in making conclusions about tumour growth characteristics. Mathematical modeling and statistical theory facilitates in predicting results without conducting experiments practically and making inferences about tumour growth parameters from sample characteristics. In this paper, the proliferation rates and interval estimates of proliferation rates with different confidence levels of various human cancer tumours were estimated with the help of tumour growth equation and sampling theory using doubling times from experimental data.

Keywords:

Proliferation rate;
Tumour doubling time;
Tumour growth parameter;
Cell proliferation;
Tumour spheroid growth.

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1. Introduction

Cancer is a deadly disease with a symptom of abnormal and uncontrolled growth of tissue at any part of the human body. The characteristics of tumours such as location, stage of the tumour, size and nature of the tumour cells plays very important role in treatment of Cancer. If the growth of the tumour is very rapid, it could be dangerous to the patient. If tumour cells reach another place through blood vessels, it will initiate a new growth at different place of the body in addition to the already grown tumour at previous site. In the fast growing tumours, delay in treatment may lead to further tumour growth and complications in the patients. The early treatment may reduce the chances of metastasis and increase the chances of cure and survival of the patient. The tumour doubling time is one such character which indicates time taken by the tumour to double its size or volume will be helpful in treating cancer. Doubling times varies from tissue to tissue depending upon the nature of the tissue cells. In Mathematical terminology, another parameter, the rate at which tumor cells grow or multiply themselves is known as proliferation rates can be estimated from tumour doubling times by considering the tumour in a spherical shape. With the information of a specific character like proliferation rate of tumor cells belonging to a particular type of tumour, the task will be very easy in dealing with cancer related research work and also in treatment of cancer by any method of treatment. The proliferation rates of the different tumour cells, the range values of the tumour proliferation rates and confidence intervals for population

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proliferation rates with 0.90, 0.95 and 0.99 confidence levels were estimated from the tumor doubling times with the help of tumour growth equation and statistical theory from the experimental data.

2. Literature Review

Cancer research related to tumour spheroids and mathematical modeling of tumor growth dates back to late 1960's. Growth of multi cell tumours were examined by Burton A.C. (1966), Judah Folkman and Mark Hochberg (1973), H.P. Greenspan (1973), R.M. Sutherland (1974), etc. Mathematical models have been developed by considering the behaviour of multi cell tumour spheroids *in vitro* experiments using diffusion theory. Burton A.C (1966) developed a model using diffusion theory and showed that the growth of solid tumours is not exponential but it follows Gompertzian relation. The doubling times of various histological types of human tumours were studied by Malaise et al, (1973) [7], experimental potential doubling times of human tumours were obtained by E.H. Cooper, A.J. Bedford and T.E. Kenny [4], the experimental doubling times of primary and metastatic human tumours were calculated by Renato Baserga [8], range of doubling times of were studied by Esmael Mehrara et. al [3] and doubling times of cell lines from various panels based on clinical research were taken from the website of National cancer institute of United States of America[9] .

3. Methodology

By assuming only proliferating cells contribute to the growth of the tumour spheroid and considering a total N number of cells with volume v of each cell in the tumor spheroid containing only N_p proliferating cells with proliferation rate s, the increase in total number of cells N in time Δt is taken as ΔN . The ΔN can be calculated as the product of number of proliferating cells, proliferation rate and time.

$$\Delta \mathrm{N} = \mathrm{N_p} \times \mathrm{s} \times \Delta \mathrm{t}\ ,\ \Delta \mathrm{N} = (\mathrm{s}.\Delta \mathrm{t})\mathrm{N_p}.$$

If we take $\Delta t \to 0$, $\frac{\Delta N}{\Delta t} = s.N_p$ (i.e) $\frac{dN}{dt} = s.N_p$ (s is the proliferation rate which can be taken as rate constant of cell production). In place of individual cells, if we consider volume as whole, it will become $\frac{dV}{dt} = s.V_p$ (where $V_p = v.N_p$). If all the cells are proliferating or when the tumour is small, we consider $N = N_p$ and $V = V_p$. By considering the initial radius of tumour spheroid as R_0 , $\frac{dV}{dt} = s\ \frac{4\pi}{3}\ R_0$. This will lead to the differential equation $\frac{dR_0}{dt} = \frac{s}{3}R_0$. This is a first order linear differential equation whose solution will be $R_0 = k.e^{\frac{st}{3}}$. By taking initial conditions, at time $t = 0, R_0(0) = R_0$, gives $k = R_0(0)$. The solution can be taken as $R_0(t) = R_0(0)e^{\frac{st}{3}}$. Since the volume ($V = \frac{4\pi}{3}\ {R_0}^3$) of the tumour spheroid is directly proportional to the radius, we get $V(t) = V(0)e^{st}$. Let us consider the time taken by the tumour to doble its volume is t_d . Then the equation $V(t) = V(0)e^{st}$ will become $2V(t) = V(0)e^{st_d}$. Taking natural logarithms on both sides and solving, we get $s = \frac{ln\ 2}{t_d}$. The advantage of the mathematical modeling is to predict the result with out going for the experimental work. The proliferation rates can be calculated from available tumour doubling times and other parameters depending on the proliferation rate can be estimated with out waiting for a lengthy time.

In the experiments, the time taken for the cells to double their size assuming no cell loss is considered as potential doubling time t_{pot} and if there is cell loss, the time taken to double their size is considered as doubling time t_d . In this study, the time taken to double the size of the tumor with or with out cell loss is considered as t_d.In some experiments, instead of giving single value to doubling time, a range of values is used. In such cases, interval estimate of the proliferation rate is calculated. Since availability of a particular type of tumour cell is a constraint to the investigator, the numbers of tumours are less than 30, it is considered as small sample with size $n < 30$. In sampling theory, by considering the characteristics of the sample, we can make inferences about population parameter.The experimental results are used to estimate the unknown parameter (mean proliferationrate) of the tumour population in the form of interval estimate. While finding interval estimates, the confidence levels of 90%, 95%and 99% are considered. With respect to 90% confidence level, we can say the interval estimate will include the true population parameter 90% of the time and 10% ($\alpha = 0.10$) of the time it may not be.In these cases, α is considered as Significance level.The same assumption applies to 95% and 99% confidence interval estimates also with ($\alpha = 0.05$ & 0.01) respectively. Since $n < 30$, student's t distribution is used with the formula [Mean of the sample $\pm$ (t).(standard error of mean)] with degrees of freedom $(n - 1)$. To visualize and to have clear nature of the tumour cells of similar type, scatter diagrams are obtained with the help of MATLAB.

4. Results and Conclusions

1.The experimental data related to doubling times of various histological types of human tumours by Malaise et al, (1973) published in European journal of cancer,vol 9, 305-312 with reference from the book "An introduction to radiobiology "by A.H.W. Nias is taken for estimating of their corresponding proliferation rates and are shown in the table 1.

2. The proliferation rates of human tumours by using experimental potential doubling time data of human tumours by E.H. Cooper, A.J. Bedford and T.E. Kenny in 'cell death in normal and malignant tissues' from "Advances in cancer research; volume 21" are shown in the table 2.

3. The experimental doubling times of primary and metastatic human tumours from the book "The biology of cell reproduction "by Renato Baserga are used to calculate proliferation rates which are shown in the table 3.

4. Clinical data related to tumour doubling times from Esmael Mehrara et. al which contains range of values for doubling times and some similar type of tumours with different researchers is taken to calculate proliferation rate range in the table 4.

5. Much more detailed information on doubling times of cell lines from various panels based on extensive research work is taken from website of National cancer institute of United States of America,to calculate proliferation rates and shown in the tables 5&6.

6. For the nine panels of tumours with 61 different cells mentioned in the table 5 and table 6, Interval estimates of population parameter (mean proliferation rate of the panel) is obtained by calculating sample mean, sample standard deviation and standard error of the mean with confidendence levels 0.90, 0.95& 0.99 respectively which are shown in the table 7.

7. For the purpose of comparision between different panels and to visualize variations with in the panels, scatter diagrams of 9 panels were obtained with the help of MATLAB which is shown in the figure 8.

8. From the data in the tables 4, 5, 6 and 7 it was clear that even for the tumours of similar type, the doubling times are not same. But they may lie between certain limits. The same observation can be seen even for proliferation rates as they have been calculated from tumour doubling times. The results can be clearly seen in the scatter diagrams in the figure 8 which are scattered between certain limits without coincidence.

9. The advantage of mathematical modeling is to predict the result with out going for the experimental work. If the proliferation rates are known, the rate in change of volume over a period of time can be estimated with the initial volume of the tumour.

Histological type	Doubling time (days)	***Proliferation rate (s)***
Embryonal tumour	27	**0.02567**
Malignant lymphoma	29	**0.02390**
Sarcoma	41	**0.01690**
Squamous cell carcinoma	58	**0.01195**
Adenocarcinoma	83	**0.00835**

Table1. Table showing estimated proliferating rates of various histological types of human tumours.

Lymphomas	Number of tumours measured	Potential doubling Times (days)	***Proliferation rate (s)***
Hodking's disease	10	1.8	**0.38508**
Recticulum cell sarcoma	13	1.6	**0.43322**
Lymphatic lymphoma	12	1.6	**0.43322**
Histiocytic - lymphocytic	5	4.0	**0.17329**
Burkitt tumour (1)	26	1.4	**0.49510**
Burkitt tumour (2)	23	1.9	**0.36481**
Carcinoma of bladder	32	15.0	**0.04621**
Carcinoma of colon	31	10.4	**0.06665**
Carcinoma of the breast	38	43	**0.01612**

Table2. Table showing estimated proliferating rates of human tumours corresponding to their potential doubling times

Type of Tumour	Mean volume doubling Time in days	***Proliferation rate (s)***
Primary tumours		
Squamous cell carcinoma of the lung	84	**0.00825**
Adenocarcinoma of colon and rectum	632	**0.00110**
Carcinoma of the breast	96	**0.00722**
Sarcoma of bone	63	**0.01100**
Metastases in the lung, from		
Adenocarcinoma of colon and rectum	95	**0.00730**
Carcinoma of the breast	73	**0.00950**
Ewing's sarcoma	17	**0.04077**
Sarcoma of bone	30	**0.02310**
Melanoma	53	**0.01308**
Lymphoma	27	**0.02567**

Table3. Table showing estimated proliferation rates of primary and secondary tumours calculated from their mean volume doubling time.

S.No	**Reference**	**Tumour**	Sample Size (n)	Doubling time range (t_d)	**Proliferation Rate range** (s)
1	(Nishida, Kaneko et al. 1999)	Pancreatic carcinoma	12	18-232	**0.0030 - 0.0385**
2	(Furukawa, Iwata et al. 2001)	Pancreatic carcinoma	9	64-255	**0.0027 - 0.0108**
3	(Wang, Some et al. 2000)	Adenocarcinoma (lung)	8	72-131	**0.0053 - 0.0096**
4	(Winer-Muram, Jennigs et al. 2002)	Adenocarcinoma (lung)	15	(-1350)-964	**-0.0005 - 0.0007**
5	(Winer-Muram, Jennigs et al. 2002)	Bronchioalveolar(lung)	9	36-1092	**0.0006 - 0.0193**
6	(Winer-Muram, Jennigs et al. 2002)	Squamous cell lung carcinoma	16	(-1214)-225	**-0.0006 - 0.0031**
7	(Winer-Muram, Jennigs et al. 2002)	Non small cell lung carcinoma	6	48-698	**0.0100 - 0.0144**
8	(EI Sharouni, Kal et al. 2003)	Non small cell lung cancer	18	8-171	**0.0040 - 0.0866**
9	(Wang, Sone et al. 2000)	Small cell lung cancer	4	54-132	**0.0052 - 0.0128**
10	(Blomqvist, Wiklund et al. 1993)	Sarcoma(lungmetastases)	21	7-1172	**0.0006 - 0.0990**
11	(Nakajima, Moriguchi et al. 2002)	Hepatocellular carcinoma (well differentiated)	19	38-274	**0.0025 - 0.0182**
12	(Saito, Matsuzaki et al. 1998)	Hepatocellular carcinoma (well differentiated)	15	76-720	**0.0010 - 0.0091**
13	(Nakajima, Moriguchi et al. 2002)	Hepatocellular carcinoma (moderately differentiated)	9	17-91	**0.0076 - 0.0408**
14	(Saito, Matsuzaki et al. 1998)	Hepatocellular carcinoma (moderately differentiated)	5	94-380	**0.0018 - 0.0074**
15	(Nakajima, Moriguchi et al. 2002)	Hepatocellular carcinoma (poorly differentiated)	5	20-78	**0.0089 - 0.0347**

Table4. Table showing number of tumours, doubling time range and their proliferation range including references

S.No	Cell Line Name	Panel Name	Doubling time	*Proliferation rate (s)*
1	CCRF-CEM	Leukemia	26.7	**0.02596**
2	HL-60(TB)	Leukemia	28.6	**0.02424**
3	K-562	Leukemia	19.6	**0.03536**
4	MOLT-4	Leukemia	27.9	**0.02484**
5	RPMI-8228	Leukemia	33.5	**0.02069**
6	SR	Leukemia	28.7	**0.02415**
7	A549/ATCC	Non-Small Cell Lung	22.9	**0.03027**
8	EKVX	Non-Small Cell Lung	43.6	**0.01590**
9	HOP-62	Non-Small Cell Lung	39	**0.01777**
10	HOP-92	Non-Small Cell Lung	79.5	**0.00872**
11	NCI-H226	Non-Small Cell Lung	61	**0.01136**
12	NCI-H23	Non-Small Cell Lung	33.4	**0.02075**
13	NCI-H322M	Non-Small Cell Lung	35.3	**0.01964**
14	NCI-460	Non-Small Cell Lung	17.8	**0.03894**
15	NCI-H522	Non-Small Cell Lung	38.2	**0.01814**
16	COLO 205	Colon	23.8	**0.02912**
17	HCC-2998	Colon	31.5	**0.02200**
18	HCT-116	Colon	17.4	**0.03983**
19	HCT-15	Colon	20.6	**0.03365**
20	HT29	Colon	19.5	**0.03555**
21	KM12	Colon	23.7	**0.02925**
22	SW-620	Colon	20.4	**0.03398**
23	SF-268	CNS	33.1	**0.02094**
24	SF-295	CNS	29.5	**0.02350**
25	SF-539	CNS	35.4	**0.01958**
26	SNB-19	CNS	34.6	**0.02003**
27	SNB-75	CNS	62.8	**0.01104**
28	U251	CNS	23.8	**0.02912**
29	LOXIMVI	Melanoma	20.5	**0.03381**
30	MALME-3M	Melanoma	46.2	**0.01500**
31	M14	Melanoma	26.3	**0.02636**

Table5. Table showing cell line name, panel name with their doubling time and estimated proliferation rates.

S.No	Cell Line Name	Panel Name	Doubling time	*Proliferation rate* (*s*)
32	MDA-MB-435	Melanoma	25.8	**0.02687**
33	SK-MEL-2	Melanoma	45.5	**0.01523**
34	SK-MEL-28	Melanoma	35.1	**0.01975**
35	SK-MEL-5	Melanoma	25.2	**0.02751**
36	UACC-257	Melanoma	38.5	**0.01800**
37	UACC-62	Melanoma	31.3	**0.02215**
38	IGR-OVI	Ovarian	31	**0.02236**
39	OVCAR-3	Ovarian	34.7	**0.01998**
40	OVCAR-4	Ovarian	41.4	**0.01674**
41	OVCAR-5	Ovarian	48.8	**0.01420**
42	OVCAR-8	Ovarian	26.1	**0.02656**
43	NCI/ADR-RES	Ovarian	34	**0.02039**
44	SK-OV-3	Ovarian	48.7	**0.01423**
45	786-0	Renal	22.4	**0.03094**
46	A498	Renal	66.8	**0.01038**
47	ACHN	Renal	27.5	**0.02521**
48	CAKI-1	Renal	39	**0.01777**
49	RXF 393	Renal	62.9	**0.01102**
50	SN12C	Renal	29.5	**0.02350**
51	TK-10	Renal	51.3	**0.01351**
52	UO-31	Renal	41.7	**0.01662**
53	PC-3	Prostate	27.1	**0.02558**
54	DU-145	Prostate	32.3	**0.02146**
55	MCF7	Breast	25.4	**0.02729**
56	MDA-MB-231/ATCC	Breast	41.9	**0.01654**
57	MDA-MB-468	Breast	62	**0.01118**
58	HS 578T	Breast	53.8	**0.01288**
59	MDA-N	Breast	22.5	**0.03081**
60	BT-549	Breast	53.9	**0.01286**
61	T-47D	Breast	45.5	**0.01528**

Tabl6. Table showing cell line name, panel name with their doubling time and estimated proliferation rates

S. No	**Panel Name**	**Average** $(\bar{s})$	**Standard deviation** (σ_S)	**90% Confidence Interval** $(\alpha = 0.10)$	**95% Confidence Interval** $(\alpha = 0.05)$	**99% Confidence Interval** $(\alpha = 0.01)$
1	Leukemia	**0.0259**	**0.0050**	**0.0218 -- 0.0300**	**0.0207 -- 0.0311**	**0.0177 – 0.0341**
2	Non-Small Cell Lung	**0.0206**	**0.0084**	**0.0154 -- 0.0258**	**0.0141 – 0.0271**	**0.0140 – 0.0272**
3	Colon	**0.0319**	**0.0057**	**0.0277 – 0.0361**	**0.0266 – 0.0372**	**0.0234 – 0.0399**
4	CNS	**0.0207**	**0.0059**	**0.0158 – 0.0256**	**0.0145 – 0.0269**	**0.0110 – 0.0304**
5	Melanoma	**0.0227**	**0.0064**	**0.0187 – 0.0267**	**0.0178 – 0.0276**	**0.0156 – 0.0298**
6	Ovarian	**0.0192**	**0.0045**	**0.0159 – 0.0225**	**0.0150 – 0.0234**	**0.0129 – 0.0255**
7	Renal	**0.0186**	**0.0073**	**0.0137 – 0.0235**	**0.0125 – 0.0247**	**0.0096 – 0.0276**
8	Prostate	**0.0235**	**0.0029**	**0.0106 – 0.0364**	**0.0000 – 0.0756**	**0.0000 – 0.2835**
9	Breast	**0.0181**	**0.0077**	**0.0124 – 0.0238**	**0.0110 – 0.0252**	**0.0073 – 0.0289**

Table7. Table showing average, standard deviation of proliferation rates with their confidence intervals

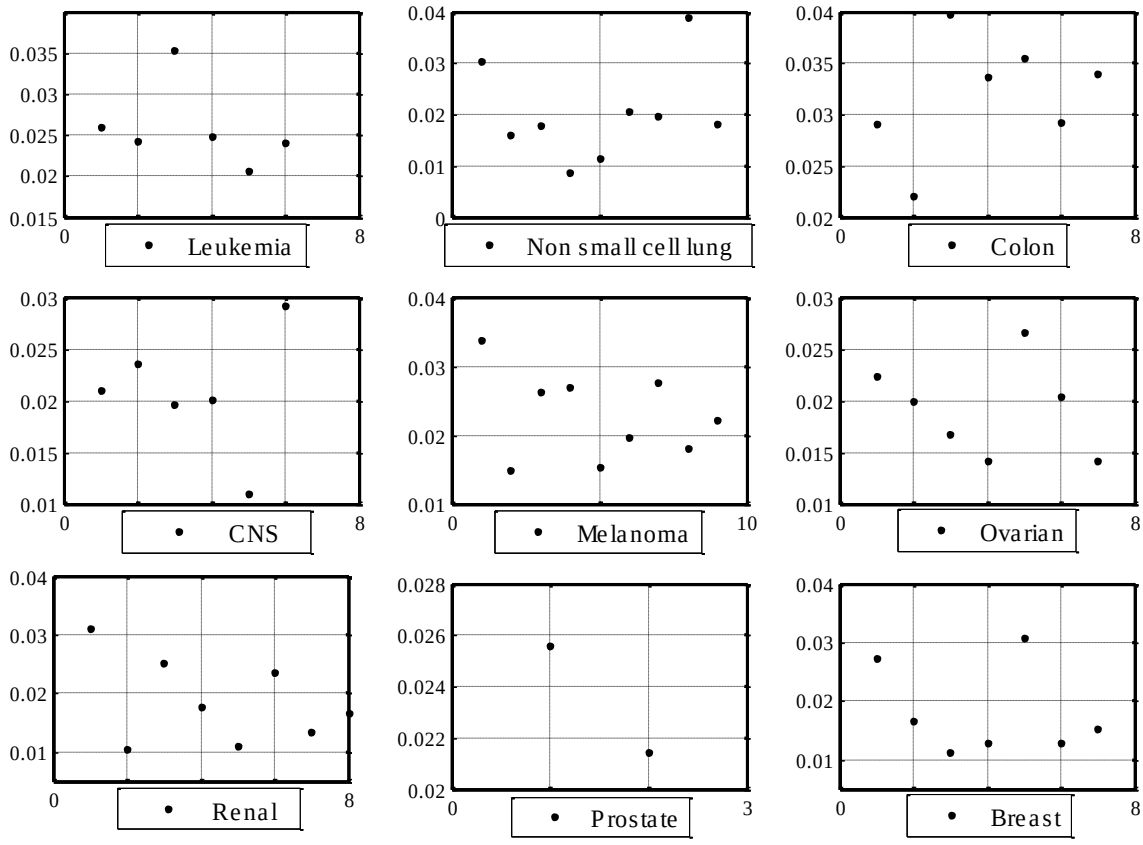

Figure8. Scatter diagrams showing proliferation rates of cell lines from different panels

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