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Impact of cancer cell growth rate on the quality of life of animals

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Abstract---It is widely known that cancer cells grow much more rapidly and cause pain, ultimately leading to a low quality of life for the patients in many different ways. How this effect can happen in the case of animals was tested using a simulation study on cancer in canines. Basic assumptions on differences in the growth of normal and cancer cells and pain, affecting the quality of growth and cell growth limits were set for the simulation. The results showed that cancer cells grow at least eight times faster than normal cells. The cancer cell growth was positively correlated with pain score. Thus, it was established that cancer induces pain. The pain score due to cancer was 4.8, representing moderate to severe pain, and that of the normal cell was 2.0, representing no pain. Since the pain was assumed to represent the quality of life in canines, it was concluded, cancer-induced pain leads to poor quality of life for canines under the simulation conditions. Some limitations of this study have also been stated.

Keywords---cancer growth rate, cells, simulation study, animals, quality of life.

Introduction

There is no doubt that cancer, as in the case of any chronic disease, affects the physical, physiological, and psychological well-being of the affected individuals even during post-cure stage of life. Such impact was seen more in the case of elder people, those with low income or with co-morbidities in the survey studies of Zebrack, Yi, Petersen, and Ganz (2008). However, in this research, the quality of life was measured in terms of the pain of cancer affected canines. Experience of recurring moderate to severe pain as the first sign of cancer and its effect on the quality of life were highlighted by Mantyh (2006). Such pain increases with the advancing stage of cancer. The high prevalence rate of pain among over 70% of cancer patients was mentioned by Portenoy and Lesage (1999). Thus, undoubtedly, pain is intimately related to incidence and post-cancer problems affecting the quality of life of patients in several ways. Most research works deal

with this problem in relation to some other variable like demographic factors, treatment interventions and self-care. Thus, there is a serious dearth of research in pain as a sole variable of quality of life affecting cancer patients.

Animal models are used for modelling epidemiology, symptoms, effect of interventions using new therapies and behaviour of individuals. Metastasis of cancer growth towards bone produces pain and reduce the quality of life of the patient. Animal models researched in the case of immunocompromised and immunocompetent host systems were discussed by Slosky, Largent-Milnes, and Vanderah (2015) and by Zhu, et al. (2015). These two articles also review past research on the topic. So, there is much justification for using animal models to study cancer-induced pain. The experience of traumatic pain in animals is similar to human beings. Therefore, the aim of this research is to estimate the impact of cancer cell growth rate on the quality of life of animals.

Literature Review

Two aspects are considered in this literature review: pain due to cancer, leading to a decline in quality of life and animal models to study this phenomenon.

Pain due to cancer and quality of life

Already, in the Introduction section, it was established that pain is due to cancer affects the quality of life. A Chinese study by Wang, et al. (1999) also showed functional health and quality of life severely affected by moderate to severe pain. Theobald (2004) asserted that pain is one of the most common symptoms experienced by cancer patients, and it leads to insomnia. Cancer, pain, insomnia, fatigue, depression and anxiety interact to produce a complexity of problems requiring multiple treatment plans. Without a doubt, any one or more of these symptoms affects the quality of life. Pain being the initiator of other symptoms, reduction of pain becomes the primary intervention strategy. Caffo, et al. (2003) and noted that irrespective of type of surgery, breast cancer patients might feel pain even when there is no recurrent causes leading to poor quality of life. Costa, Monteiro, Queiroz, and Gonçalves (2017) observed inverse relationship of pain with quality of life. Patients described the sensory aspect of pain mostly as jumping and the impact on daily life as troublesome. With metastasis and the advanced stage of the disease, the pain increased.

As early as 1989, Ferrell, Wisdom, and Wenzl (1989) described the pain as a cause of decreased quality of life among cancer patients. In the evaluation, the authors used and found pain associated with psychologic well-being, physical well-being, general and specific symptom control, and degree of social support, worry and nutrition. It was observed by Khalili, Farajzadegan, Mokarian, and Bahrami (2013) that pain affects the coping strategies of women with breast cancer due to which there is stress, and these factors affect the quality of life. In the studies of Tavoli, Montazeri, Roshan, Tavoli, and Melyani (2008), cancer patients with pain suffered from lower levels of functioning, emotional functioning, depression and global quality of life with cancer patients without pain. Higher pain permanence and consistency were associated with higher depression levels and lower quality of life.

Cancer-related pain was attributed to three causes by McGuire (2004): as a direct effect of tumour involvement, due to diagnostic/therapeutic procedures and side effects or toxicities of treatments provided. More than one of these pain types can be seen in many patients. The adverse effects the individual causes on quality of life could also be different. The majority of patients, especially at the end-stage disease, suffer from significant pain, the severity of which interferes with several aspects of the patient's quality of life. The intensity of pain is correlated with depression and anxiety also. These observations were reported by Cleeland (1984). According to Cleeland (1989) severe pain among cancer patients can divert the attention to be paid to family, friends and leave a feeling for being destined to die. Loss of sleep, appetite, and a reduction of activity are also affected, leading to increased impairment, directly measurable indices of disease status. It was also noted by Daut and Cleeland (1982) that pain, when present in any cancer, was usually moderate severity and interfered with activity and enjoyment of life to a moderate to a severe extent. A greater degree of interference with activity and enjoyment of life was noted, with cancer as the cause compared to any other cause.

Conservative breast surgery (CBS) is used as a surgical technique to improve the psychophysical outcome of women who underwent surgery for breast cancer (BC). CBS enhances the impact of local treatment on postoperative body image adjustment. However, it affects patients' quality of life in a similar way as mastectomy. It was noted by Amichetti and Caffo (2003) that generally, intermittent pain started about three months after the completion of therapy. The patients described the pain as aching, tender or cramping. Physical, physiological and autonomy aspects of quality of life were affected by pain. Mid-term morbidity after SN biopsy and axillary lymph node (ALN) dissection in breast cancer patients was evaluated by Barranger, et al. (2005). The results showed significantly lower mid-term morbidity in the case of SN biopsy than ALN dissection. However, the global Quality of life self-rating score was about 7.5 and thus very good. Therefore, these surgical procedures do not affect the quality of life. Thus, undoubtedly, pain caused by any type of cancer or even some of the surgical and therapy procedures affects the quality of life. The extent to which quality of life is affected is related to the severity of pain. Now how animal models have been used in these aspects are examined below.

Animal models

The major advantages of animal models in pain and quality of life studies were outlined by Gregory, et al. (2013). Studying intact animals allows the examination of the multidimensional nature of pain. A number of animal models describe pain phenotypes that are mediated by distinct mechanisms. Animal models of pain mimic distinct clinical diseases to evaluate underlying mechanisms and potential treatments better. Outcome variables measure multiple parts of the pain experience, reflexive hyperalgesia, sensory and affective dimensions of pain and impact of pain on function and quality of life. Various methods of inducing pain may be used on animals for studying such effects. The progress and challenges in developing animal models of pain were discussed by Mogil (2009). Poor record of translation so far, improvement of accuracy and relevance of current pain assessment methods, need for superior alternative models, inadequate attention

to spontaneous pain and excess attention on hypersensitive states of pain and inadequate attention to the impact of co-morbidities were discussed in this respect.

In their study, de C Williams, Gallagher, Fidalgo, and Bentley (2016) had used agent-based simulation to assess the pain behaviour in which 10000 simulations were done. The need for skeletal metastases to improve the understanding of pain and quality of life problems and lack of ideal models with adequate clinical relevance, reproducibility and replicability was highlighted by Simmons, et al. (2015), who also discussed the strengths and weaknesses of current models. In an agent-based simulation study, Wakeland, Gallaher, Macovsky, and Aktipis (2004) increased the simulation size from 1000 to 10000 for greater precision. In another thesis study, Nyre (2016) used 3000 trial runs. A total of 536399 patients were assigned to an agent-based simulation study by Pförringer, Breu, Crönlein, Kolisch, and Kanz (2018). In a review Davidsson, Holmgren, Kyhlbäck, Mengistu, and Persson (2006), simulation sizes of 1000 or more were noted in about 10% of the studies. Some limitations related to nature and complexity of samples were regarded as the reason for majority of the studies using low simulation sizes. Use of simulation sizes reaching 1000 was reported by Railsback, Lytinen, and Jackson (2006) in another review. These research works demonstrate the wide applicability of agent-based simulation modelling including healthcare. The number of times the simulation done is usually very high which may ensure better predictability and precision. Thus, there is adequate justification to test the cancer-induced pain status on canines through agent-based simulations as a forerunner of real-world study. This is the topic of the present study. In this study, the simulation size was 1000, which is quite reasonable considering the reviewed works on simulation sizes above.

Methodology

A numerical simulation methodology with some assumptions has been used for this research. The numerical simulations have been done using MS Excel and SIPMath Modeler add-in in MS Excel. The numerical simulations were done for two scenarios, (1) where the cancer cell growth rate would follow a normal distribution and (2) where the cancer cell growth rate would follow an exponential distribution. The following assumptions and criteria's were used in simulation:

- Pain has been used as the measure of the quality of life of animals (more pain equates to lower quality of life, and vice versa).
- The mean base number of cells for both normal and exponential growth scenarios was simulated between 0 and 200.
- The standard deviation for the base number of cells for both normal and exponential growth scenarios was simulated between 0 to 20.
- The growth rate for the base number of cells for both normal and exponential growth was simulated between 0% to 200%, where 100% indicates sustenance (i.e., neither growth nor decline).

The simulation was run as per the above criteria for normal and exponential growth for 1,000 cases. In computer simulation studies using agent-based modelling, it is common to use a large number of iterations for each variables. de

C Williams, Gallagher, Fidalgo, and Bentley (2016) used 100 repeated simulations for 10000 iterations for a pain study in an agent-based modelling. This and other studies reviewed in the literature review show that normally a large number of iterations are used for better precision of predictability. Hence, use of 1000 iterations in computer simulation studies is acceptable. Furthermore, the simulated number of cells for both normal and exponential growth were classified into pain ratings as per the table below.

Table 1
Cell growth range and associated pain ratings

Pain Score	Description	Cell Growth Range
1	Minimum	100 or less
2	Faint	100-200
3	Mild pain	200-300
4	Moderate pain	300-400
5	Severe pain	400 or more

Source: https://todaysveterinarypractice.com/wp-content/uploads/sites/4/2015/06/2015_0506_EO_Cancer-Pain_Table3.jpg

Thus, there is no or very little pain when there is no cancer due to causes other than the disease. Any serious quality of life problem may occur only when the cell growth exceeds 300 to give towards moderate or severe pain. The results have been compared for the two scenarios and reported in the next section. Finally, correlation analysis was undertaken between the simulated normal and exponential growth and their respective pain ratings. These are also reported in the next section.

Results

The summary statistics for the two scenarios are presented in Table 2.

Table 2
Summary statistics for the two scenarios of normal and exponential cell growth in the simulation study

Statistic	Normal Cell Growth	Exponential Cell Growth
Mean	104	808
Median	104	740
SD	2	409
Min.	96	35
Max.	113	3,206

There are distinct differences between the growth of a normal cell and of a cancer cell. Cancer cells grow eight times (808) that of normal cells (104). There is much larger variations in cancer cell growth (SD=409) compared to normal cells (SD=2). Maximum cell growth differs between 113 for normal and 3206 (about 33 times)

for cancer cells. These observations are in line with cancer cell growth patterns widely reported. Two graphs depicting the growth frequencies of normal and cancer cells are presented in Fig 1 and Fig 2.

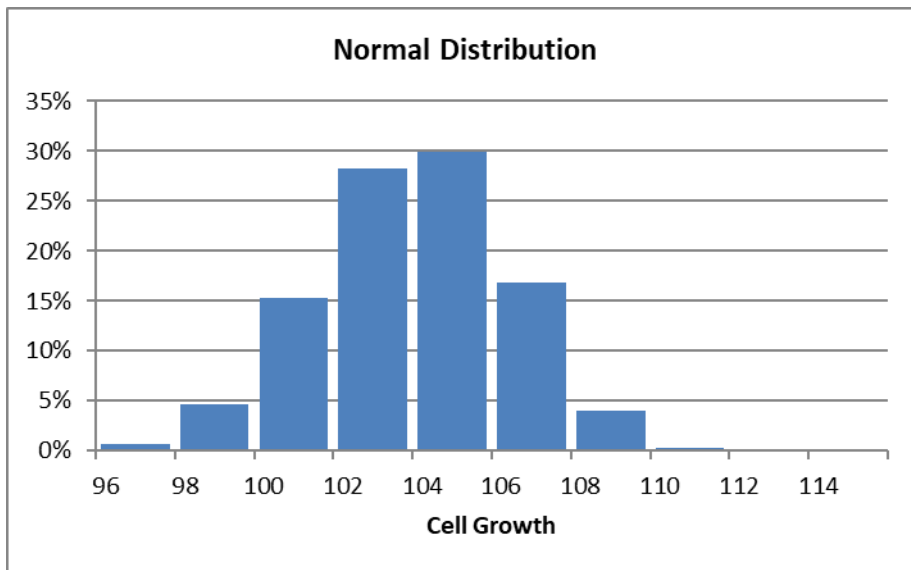


Figure 1. Histogram of the normal distribution of simulated cell growth values

Fig 1 shows that about 90% of normal cells are within the growth range of 108. Indeed, almost all normal cells grow within 110. There is a very low percentage of cell growths of 96, which was the minimum value noted in Table 2.

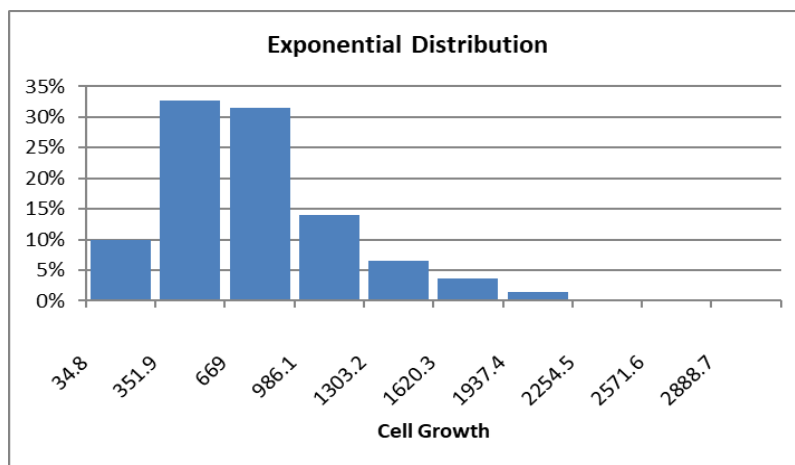


Figure 2. Histogram of the exponential distribution of simulated cell growth values

Fig 2 shows quite a different pattern of cell growth of cancer cells compared to normal cells in Fig 1. The growth of about 10% of cancer cells was only 35 well in the normal category. Cell growth in the range of 350 and 990 accounted for about 77%. An extremely high value of 1937 was noted for about 2% of cells. The

percentages of cell growth beyond this value were so low that they did not appear in the histogram. The correlations across the variables are presented in Table 3.

Table 3
Correlation matrix

	Normal Growth	Cell Exponential Growth	Cell Normal Score	Pain
Exponential Cell Growth	0.002			
Normal Pain Score	.427**	-0.045		
Exponential Pain Score	-0.004	.473**	-0.016	

** . Correlation is significant at the 0.01 level (2-tailed).

The results indicate that there is a moderate correlation between the exponential cell growth of cancer cells and respective pain ($r=.473$, $p<.001$), and similarly, a moderate correlation has been observed between normal cell growth of cancer cells and respective pain ($r=.427$, $p<.001$). Summary statistics of pain scores for normal and cancer cells is presented in Table 4.

Table 4
Summary statistics of pain scores (Table 1)

Statistic	Normal Score	Pain	Exponential Score	Pain
Mean	2.0		4.8	
SD	0.2		0.6	
Min.	1.0		1.0	
Max.	2.0		5.0	

Table 4 reveals that the mean pain score for the normal scenario is 2, and it is 4.8 for the exponential scenarios. According to the pain ratings given in Table 1, a score of 2.0 is slight pain and 4.8 almost nearer to severe pain. There is a 2.5 times difference between these scores. Therefore, it can be concluded that the quality of life can be expected to be about 2.5 times less in a scenario where the cancer cell grows at an exponential rate compared to a normal rate.

Discussion

The main point emerging from the results of this study is the abnormal growth of cancer cells more than eight times the growth of normal cells, causing moderate to severe pain. As pain is used as an indicator of the quality of life, it is also shown that increasing pain is associated with a decline in quality of life. The usefulness of animal models to investigate pain and its relationship with behavioural problems and decline in quality of life was discussed by Currie, et al. (2013) in a review of 38 animal models. Many animal models (40 models) developed for simulation studies on pain for different aetiological conditions were reviewed by Jaggi, Jain, and Singh (2011). In this respect, Xie and Zaidi (2016) observed that the rapid development of multi-modal pre-clinical imaging techniques and computer simulation tools have led to many pre-clinical simulation applications using laboratory animal models. These offer the facility to

test the effect of different variables on outcomes, as in the case of the effect of cancer cell growth on pain and its impact on the quality of life, studied in this paper.

The use of some drugs like morphine to relieve pain also can induce pain under certain conditions, as was shown, in a review, by Gach, Wyreńska, Fichna, and Janecka (2011). As was mentioned in the review of the literature section, several studies support the theory that pain due to cancer lowers the quality of life and animal models are useful to study this phenomenon in more detail. The results of this study endorse these findings. The abnormal growth of cancer cells is common knowledge. Jimenez-Andrade, Ghilardi, Castañeda-Corral, Kuskowski, and Mantyh (2011) pointed out that the individual cancer cell colonies have a limited half-life as they continuously proliferate, metastasise and undergo necrosis as the parent cancer cell colony are gradually drained off its blood supply. The mechanism of abnormal cancer cell growth is clear from this work. A more detailed biochemical mechanism of cancer growth and associated pain was provided by Schmidt, Hamamoto, Simone, and Wilcox (2010).

With respect to the difference between normal and cancer cells, Mason (2020) point out that normal cells have been genetically programmed to grow, differentiate and multiply and die as per the requirement of the body dictated by external signals. Cancer cells, on the other hand, are misshaped, appearing as a chaotic collection of cells consisting of many different forms, shapes and sizes with uncontrolled growth implying reaching a much higher number compared to normal cell numbers developed at the same time. This study has shown that cancer cells grow at least eight times faster than normal cells. Metastasis (ability to spread) was added to this list by Eldridge (2019). This ability enables the cancer cells to multiply several times more than normal cells, as the limitation of space does not exist. The properties contributing to high multiplication rates of cancer cells compared to normal cells were listed by Cancer cells continue to divide and multiply without any limit of cell density. They do not specialise or differentiate. They divide quickly to remain immature and undifferentiated. They do not respond to signals from other cells to stop growing and thus continue to grow when normal cells in the region have stopped growing. Cancer cells grow in a disorganised fashion as an irregular cluster. They invade other tissues or migrate over adjacent cells. They do not repair themselves and do not undergo apoptosis, and thus have a long life. Growth factor proteins and genes are implicated in these differences. All the above-discussed points establish the current findings on pain due to cancer as a factor impacting the quality of life in simulated data on animal models and thus support the conclusions of others reported in the literature.

Conclusion

The simulation study using canines as the animal model and pain as a proxy variable for quality of life showed that cancer cells grow at least eight times faster than normal cells. There is a positive correlation between cancer cell growth and the pain score of the same cells. The mean pain score of 4.8 for cancer cells categorises it as moderate to severe compared to 2.0, meaning no pain of normal

cells. Since the pain was considered as indicative of quality, canines affected with cancer suffer from moderate to intense pain and, thus, lower quality of life.

Limitations

There was a severe lack of literature precisely on the lines of this research. So, points derived from some related studies were used. The study had a very narrow scope of just doing some simulations and correlating the cell growth with reported scales for categorising pain. It is likely that temporary or short-duration pain may not affect the quality of life unless they are recurrent. This effect was not studied. Most literature deals with pain in animal models in relation to some other biochemical factor or treatment interventions. Here, these factors were not considered. This may be one reason for the inability to find literature on the topic studied. It would have been better to base the studies on true ranges of cell growth data. As this was not done here, it cannot be ascertained whether the cell growth values represent the real-world values.

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