A Probabilistic Analysis of Cancer as a Markovian Process in the Curable Phase

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Abstract: *After diagnosis of cancer one can know about its stages and according to that treatment of a cancer patient is generally started. The main part of any cancer treatment is to prolong the advancement of cancer to further sites of human body and thus to increase the survival rate of the patient. In this paper, attempt was made to study the transiting behavior of a cancer patient from one stage of cancer to another through a Markov process. The stages of cancer were divided into two phases viz. curable and incurable. As long as the patient remains in the curable phase the treatment given to the patient will be more effective. The paper primarily dealt with the conditions of the curable phase of cancer. The different probabilities of going to a cancerous stage for the first time provided it was in a healthy stage initially were calculated. The different waiting time distributions from one stage to an advanced stage were calculated through different cure time distributions. The expected number of visits to the healthy state 0 from an unhealthy state as calculated in this paper will help in knowing about the effectiveness of the treatment given to a cancer patient.*

Keywords: Stages of cancer, States of Stochastic process, Curable phase of cancer, Incurable phase of cancer, Markovian process, Cure time distribution

1. Introduction

Cancer diagnosis is the first and foremost step of cancer management. Cancer diagnosis is mainly a combination of careful clinical assessment and diagnostic investigation including endoscopy, imaging, histopathology, cytology and laboratory studies. Once diagnosis of cancer is confirmed, it is necessary to ascertain the staging of cancer to make choices of therapy, for prognostication, to facilitate the exchange of communication, to determine the time to stop therapy and to standardize the design of research treatment protocols (Devita et.al. 1982, Bose 1982).

With sufficient multiplication of cancerous cells, the cancer becomes apparent to the individual or to the physician. Generally it takes the form of a lump that may be seen or felt in the organ of origin. Sometimes, even before detection, the cancer may spread to lymph nodes or if very rapid in nature, it may be detectable as distant metastases. But even after malignancy has started, it may still be possible to prevent progression to the invasive form of the disease. Timely recognition and excision of dysplasia or carcinoma in situ can prevent the progression of cancer to invasive cancer. With invasive cancer, removing cancer surgically or destroying cancerous cells by radiation or chemotherapy in some cases may cure it. Thus with early detection, there is a greater chance of the curative treatment to be successful (Goyal et. al.2001).

Cancers can be classified either in accordance to the affected types of cells and organs of the body or in terms of spreading of cancerous cells to different organs of the body. Now classification of cancers in terms of spreading of cancerous cells to different organs can be well understood from the following figure (National Cancer Control Programmes, 2002):
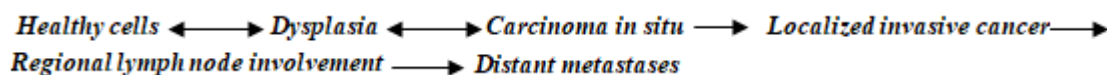

Figure 1: Different phases of cancer development

Here dysplasia is the first indication of abnormality in the character of cells. Carcinoma in situ is used to refer to the changes in cell nuclei but with no penetration of the underlying membrane that holds them in the tissue of origin. Localized invasive cancer is the abnormal cell growth involving areas underlying the tissue of origin. Regional lymph node involvement is the extension of cancerous cells to the regional lymph node that drains the area. Distant metastases are due to the spread of cancerous cells through the blood vessels or lymphatic system that affect other organs rather than the organ of origin (National Cancer Control Programmes, 2002).

It has been observed that complete remission is possible only when the patient is diagnosed in the early stage of cancer i.e. in any of the stages viz., dysplasia or carcinoma in situ. Thus we have placed the first three stages of cancer development i.e. the stages viz., healthy cells (H), dysplasia (D) and carcinoma in situ (C) under a phase to be termed as the **Curable phase**. When the patient reaches the stage of localized invasive cancer (L) then there is every possibility of going forward to any of the stages viz., regional lymph node involvement (R) and distant metastases (DM). In such a situation, restoration of functional health viz., physical, developmental and psychosocial aspects of the patient becomes the main look out of the Physician. Thus all these three stages have been placed under a phase to be named as the **Incurable phase**. The last stage of the curable phase i.e. the carcinoma in situ (C) is the **border stage** between the curable phase and the incurable phase as from this particular stage a patient either may remain in the curable phase or advances to the incurable phase. Obviously the last stage of the incurable phase i.e. the stage of distant metastases (DM) is the stage of no return or the ultimate stage for the cancer

patient with almost no chance of survival. The life of the cancer patient gets automatically accelerated from the time he enters the incurable phase. In this phase the patient goes through a sequence of transitions viz., a stage with accelerated cancer situation and then to a stage to be followed by death (Klein, et al. 1984).

In this paper, I have tried to analyze the behavior of the disease cancer though a stochastic process by defining the three stages under curable phase as states 0 (i.e., H),1 (i.e., D), 2 (i.e., C) and the three stages under incurable phase as 3 (i.e., L), 4 (i.e., R), 5 (i.e., DM) respectively.
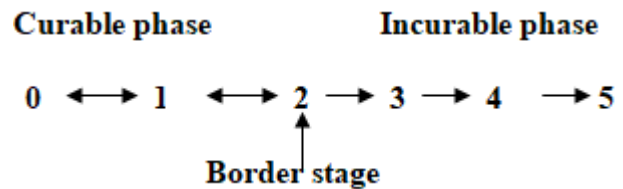
Figure 2: Transition graph between different states of curable and incurable phases

Now with the help of the transition graph in Fig 2, we can define a stochastic process $\{X(t), t \geq 0\}$ with state space $S = \{0, 1, 2, 3, 4, 5\}$, where $X(t) = i$, $(i = 0, 1, 2, 3, 4, 5)$ represents the stage of a cancer patient at time t (Biswas, 1993; Medhi, 1998). The corresponding transition matrix in this case is given by

$$
R = \begin{array}{c} \\ 0 \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{array}
\begin{array}{c} \begin{array}{cccccc} 0 & 1 & 2 & 3 & 4 & 5 \end{array} \\
\left(\begin{array}{ccc|ccc}
1-\lambda_h & \lambda_h & 0 & 0 & 0 & 0 \\
\mu_d & 1-(\lambda_d+\mu_d) & \lambda_d & 0 & 0 & 0 \\
0 & \mu_c & 1-(\lambda_c+\mu_c) & \lambda_c & 0 & 0 \\
\hline
0 & 0 & 0 & 1-\lambda_l & \lambda_l & 0 \\
0 & 0 & 0 & 0 & 1-\lambda_r & \lambda_r \\
0 & 0 & 0 & 0 & 0 & 1
\end{array} \right)
\end{array}
$$

where λ_h, λ_d, λ_c, λ_l and λ_r are the failure rates of transitions from states 0, 1, 2, 3 and 4 respectively and μ_d, μ_c are the cure rates at states 3 and 2 respectively.

2. Assumptions

For ease of analysis the following assumptions were made under the model studied in this paper:
1) The patients considered for the study are either in stage D or in stage C initially.
2) The stages H, D and C are to be defined as states 0, 1 and 2 respectively.
3) The system is to be analyzed assuming that it transits between states 0, 1 and 2.
4) C is the border state between the curable and the incurable phases.
5) Treatment of any patient is to be started immediately after diagnosis.
6) The treatment process is terminated as soon as the patient enters the incurable phase.
7) Spreading rates λ_i (i = 0, 1, 2) of the disease are constant but different at different states.
8) Cure time distribution applied to the patient to control the disease is general in nature but varies from state to state.

3. Stochastic Process

The cancer patient is kept under constant observation in the time interval $(0, t]$, $t \geq 0$. Now let $X(t) = i$ $(i = 0, 1, 2)$ be the state of the cancer patient at time t and hence $\{X(t), t \geq 0\}$ will be a stochastic process with state space $S = \{0,1,2\}$. The transitions of the process are of the types $i \rightarrow i+1$ $(i = 0,1,2)$ and $i \rightarrow i-1$ $(i = 1, 2)$. The corresponding transition matrix is

$$
C = \begin{array}{c} \\ 0 \\ 1 \\ 2 \end{array}
\begin{array}{c} \begin{array}{ccc} 0 & 1 & 2 \end{array} \\
\left(\begin{array}{ccc}
1-\lambda_0 & \lambda_0 & 0 \\
\mu_1 & 1-\lambda_1-\mu_1 & \lambda_1 \\
0 & \mu_2 & 1-\mu_2
\end{array} \right)
\end{array}
$$

4. Analysis

In this curable phase, the system is analyzed by assuming that the patient transits between the states 0, 1 and 2. The life times (or times to failure) of the cancer patients have independent exponential distributions with parameter λ_i $(i = 0, 1, 2)$. Let $t_1, t_2, ----$ be the epochs at which the patient transits from one state to another so as to start the treatment immediately.

Now according to assumption (8), the cure time distribution is general but is different at different states. Thus the epoch at which the patient enters a certain state loses its predictive nature (Medhi, 1998).

Let $X_n = i$ be the state of the process at the nth transitions occurring at time epoch t_n. Therefore, $\{ X_n, t_n, n = 0, 1, 2, ----- \}$ is a Markov Renewal Process with state space S = {0,1,2} and with Semi Markov kernel $Q(t) = \{ Q_{ij}(t) \}$, where

$$Q_{ij}(t) = \Pr\{ X_{n+1} = j, t_{n+1} - t_n \le t | X_n = i \}.$$

Thus $Q_{ij}(t)$ is the probability that the patient is in state j as an effect of nth transition provided he was in state i initially and is given by

$$Q_{ij}(t) = \Pr\{ X_n = j, t_n - t_{n-1} \le t | X_{n-1} = i \}.$$

$$= \begin{cases} \lambda_i \exp(-\lambda_i t)\overline{G}_i(t) & \text{for } i = 1; j = i + 1 \quad (1) \\ \exp(-\lambda_i t)\ g_i(t) & \text{for } i = 1,2; j = i - 1 \quad (2) \end{cases}$$

$$Q_{ii}(t) = \Pr\{ X_n = i, t_n - t_{n-1} \le t | X_{n-1} = i \}$$
$$= \exp(-\lambda_i t)\ \overline{G}_i(t) \text{ for } i = 1,2 \quad (3)$$

where

$g_i(t)$ = Probability density function (p.d.f)

$G_i(t)$ = Cumulative distribution function (c.d.f)

$\overline{G}_i(t)$ is the reliability function of cure time distribution in state i.

Now

$$Q_{00}(t) = \exp(-\lambda_0 t) \quad (4)$$

$$Q_{01}(t) = \lambda_0 \exp(-\lambda_0 t) \quad (5)$$

$$Q_{10}(t) = \exp(-\lambda_1 t)\ g_1(t) \quad (6)$$

$$Q_{11}(t) = \exp(-\lambda_1 t)\ \overline{G}_1(t) \quad (7)$$

$$Q_{12}(t) = \lambda_1 \exp(-\lambda_1 t)\ \overline{G}_1(t) \quad (8)$$

$$Q_{21}(t) = \exp(-\lambda_2 t)\ g_2(t) \quad (9)$$

$$Q_{22}(t) = \exp(-\lambda_2 t)\ \overline{G}_2(t) \quad (10)$$

Now we have defined $P_{ij}(t)$ as the waiting time distribution for a cancer patient in the state i before going to the state j i.e., $P_{ij}(t)$ is the probability that a patient is found in state j in (0,t] provided he enters the state i initially. Thus

$$P_{ij}(t) = \Pr(T_{ij} \le t) =$$

$$\Pr(t_{n+1} - t_n \le t | X_n = i, X_{n+1} = j)$$

Now $P_{ij}(t)$'s can be obtained by using the concept of renewal equations as follows (Biswas, 1993; Medhi, 1998):

$$P_{00}(t) = Q_{00}(t) + Q_{01} \copyright P_{10}(t) \quad (11)$$

$$P_{10}(t) = Q_{10}(t) + Q_{12} \copyright P_{20}(t) \quad (12)$$

$$P_{20}(t) = Q_{21} \copyright P_{10}(t) \quad (13)$$

Here $\copyright$ stands for convolution.

On using Laplace transformations (Spiegel, 1986) on (11), (12) and (13), we have

$$P_{00}(s) = Q_{00}(s) + Q_{01}(s)\ P_{10}(s) \quad (14)$$

$$P_{10}(s) = Q_{10}(s) + Q_{12}(s)\ P_{20}(s) \quad (15)$$

$$P_{20}(s) = Q_{21}(s)\ P_{10}(s) \quad (16)$$

On using (16) in (15), we have

$$P_{10}(s) = \frac{Q_{10}(s)}{1 - Q_{12}(s)Q_{21}(s)} \quad (17)$$

Consequently on using (17) in (16), we have

$$P_{20}(s) = \frac{Q_{10}(s)Q_{21}(s)}{1 - Q_{12}(s)Q_{21}(s)} \quad (18)$$

5. The probability of 1st visit to the border state 2 of the curable phase

As mentioned in assumption (4), carcinoma in situ (C) i.e. state 2 is the border state between curable and incurable phases. From this state, the patient may either remain in the curable phase or advances to the incurable phase. As long as the patient remains in the curable phase the treatment will be more effective. Thus tried to find what will be the probabilities that the patient visits the state 2 for the first time provided it was in state i initially ($i = 0,1$).

Let

$H_{i2}(t)$ = Probability that the patient visits the state 2 for the first time provided it was in state i initially ($i = 0,1$).

$H_{i2}(t)$'s can be obtained by using the concept of renewal equations as follows:

$$H_{02}(t) = Q_{01} \copyright H_{12}(t) \quad (19)$$

$$H_{12}(t) = Q_{10} \copyright H_{02}(t) + Q_{12}(t) \quad (20)$$

On using (20) in (19), we have

$$H_{02}(t) = Q_{01} \copyright Q_{10} \copyright H_{02}(t) + Q_{12}(t) \quad (21)$$

On using Laplace transformations in (20) and (21), we have

$$H_{12}(s) = Q_{10}(s)\ H_{02}(s) + Q_{12}(s) \quad (22)$$

And consequently $H_{02}(s)$ as

$$H_{02}(s) = \frac{Q_{12}(s)}{1 - Q_{01}(s)Q_{10}(s)} \quad (23)$$

On putting (23) in (22), we have

$$H_{12}(s) = Q_{12}(s)\left\{ 1 + \frac{Q_{10}(s)}{1 - Q_{01}(s)Q_{10}(s)} \right\} \quad (24)$$

6. Expected number of visits to the healthy state 0 during the treatment interval (0, t]

Cure of cancer will be effective only when the patient returns to the healthy state during the treatment period. Thus it becomes necessary to know about the nature of transitions of a cancer patient to the healthy state 0 from an unhealthy state. For this purpose I define the probability N_{i0} as

N_{i0} = The expected number of visits to the healthy state 0 from an unhealthy state
i ($i = 1,2$)
Now

$$N_{10}(t) = Q_{10} \copyright \{ 1 + N_{00}(t) \} + Q_{12} \copyright N_{20}(t) \quad (25)$$

with

$$N_{00}(t) = Q_{01} \ⓒ \ N_{10}(t) \qquad (26)$$

$$N_{20}(t) = Q_{21} \ⓒ \ N_{10}(t) \qquad (27)$$

On using Laplace transformations in (26), (27) and (25) we have

$$N_{00}(s) = Q_{01}(s) \ N_{10}(s) \qquad (28)$$

$$N_{20}(s) = Q_{21}(s) \ N_{10}(s) \qquad (29)$$

$$N_{10}(s) = Q_{10}(s) \ \{1 + N_{00}(s)\} + Q_{12}(s) \ N_{20}(s) \qquad (30)$$

Finally on using (28) and (29) in (30), we have

$$N_{10}(s) = \frac{Q_{10}(s)}{1 - Q_{10}(s)Q_{01}(s) - Q_{12}(s)Q_{21}(s)} \qquad (31)$$

Now on using (31) in (28) and (29), we have

$$N_{00}(s) = \frac{Q_{01}(s)Q_{10}(s)}{1 - Q_{10}(s)Q_{01}(s) - Q_{12}(s)Q_{21}(s)} \qquad (32)$$

$$N_{20}(s) = \frac{Q_{21}(s)Q_{10}(s)}{1 - Q_{10}(s)Q_{01}(s) - Q_{12}(s)Q_{21}(s)} \qquad (33)$$

Now $P_{ij}(t)$, $H_{i2}(t)$ and $N_{i0}(t)$'s can be obtained by taking inverse Laplace transformations of the corresponding Laplace Transforms. However with different forms of $g_i(t)$ and $\overline{G}_i(t)$, exact expressions for $P_{ij}(t)$, $H_{i2}(t)$ and $N_{i0}(t)$'s may also be obtained.

7. Different Cure Time Distributions

As mentioned earlier, to prevent the disease cancer, it is necessary to prevent the unusual growth of cells as far as possible through proper treatment. The treatment can take different forms and it is always tailored to the need of the individual patient. Depending upon the severity of the disease and the types of ailments present at the starting time of the treatment, it is necessary to adopt different combinations of treatment as suggested by the Doctor to treat the patient more effectively. In general, cure rates are functions of time. Therefore, though it is customary to use constant failure time so as to have mathematical flexibility, one can make use of any other cure time distribution other than exponential distribution. In the following section, I have considered three different cure time distributions viz., Exponential (Mukhopadhyay, 2000), Uniform (Mukhopadhyay, 2000) and Rayleigh (Miller, 1981) distribution.

Now when cure time distribution is exponential with parameter μ_i and of the form

$$g_i(t) = \mu_i \exp(-\mu_i t), \ i = 0,1,2; \ \mu_i > 0 \ ; \ t \geq 0,$$ the following values were obtained

$$P_{00}(s) = \frac{1}{(\lambda_0 + \mu_0 + s)}$$

$$\left[1 + \frac{\lambda_0 \mu_1 (\lambda_2 + \mu_2 + s)}{(\lambda_1 + \mu_1 + s)(\lambda_2 + \mu_2 + s) - \lambda_1 \mu_2} \right]$$

$$P_{10}(s) = \frac{\mu_1(\lambda_2 + \mu_2 + s)}{\{(\lambda_1 + \mu_1 + s)(\lambda_2 + \mu_2 + s) - \lambda_1 \mu_2}$$

$$P_{20}(s) = \frac{\mu_1 \mu_2}{(\lambda_1 + \mu_1 + s)(\lambda_2 + \mu_2 + s) - \lambda_1 \mu_2}$$

$$H_{02}(s) = \frac{\lambda_1 (\lambda_0 + \mu_0 + s)}{(\lambda_0 + \mu_0 + s)(\lambda_1 + \mu_1 + s) - \lambda_0 \mu_1}$$

$$H_{12}(s) = \frac{\lambda_1}{(\lambda_1 + \mu_1 + s)}$$

$$\left[1 + \frac{\mu_1(\lambda_0 + \mu_0 + s)}{(\lambda_0 + \mu_0 + s)(\lambda_1 + \mu_1 + s)(\lambda_1 + \mu_1 + s) - \lambda_0 \mu_1} \right]$$

$$N_{00}(s) = \frac{\lambda_0 \mu_1 (\lambda_2 + \mu_2 + s)}{\left[(\lambda_0 + \mu_0 + s)(\lambda_1 + \mu_1 + s)(\lambda_2 + \mu_2 + s) - \lambda_0 \mu_1 (\lambda_2 + \mu_2 + s) - \lambda_1 \mu_2 (\lambda_0 + \mu_0 + s) \right]}$$

$$N_{10}(s) = \frac{\mu_1 (\lambda_0 + \mu_0 + s)(\lambda_2 + \mu_2 + s)}{\left[(\lambda_0 + \mu_0 + s)(\lambda_1 + \mu_1 + s)(\lambda_2 + \mu_2 + s) - \lambda_0 \mu_1 (\lambda_2 + \mu_2 + s) - \lambda_1 \mu_2 (\lambda_0 + \mu_0 + s) \right]}$$

$$N_{20}(s) = \frac{\mu_1 \mu_2 (\lambda_0 + \mu_0 + s)}{\left[(\lambda_0 + \mu_0 + s)(\lambda_1 + \mu_1 + s)(\lambda_2 + \mu_2 + s) - \lambda_0 \mu_1 (\lambda_2 + \mu_2 + s) - \lambda_1 \mu_2 (\lambda_0 + \mu_0 + s) \right]}$$

Similarly when cure time distribution is uniform of the form $g_i(t) = \dfrac{1}{a_i}$, $0 \leq t \leq a_i$

in the interval $(0, a_i)$ the different calculated values are

$$P_{00}(s) = \frac{1}{(\lambda_0 + s)} \left[1 - \frac{1}{a_0(\lambda_0 + s)} \right] \left[1 + \frac{\lambda_0}{a_1(\lambda_1 + s) - \dfrac{a_1 \lambda_1}{a_2(\lambda_2 + s)} \left(1 - \dfrac{1}{a_1(\lambda_1 + s)} \right)} \right]$$

$$P_{10}(s) = \cfrac{1}{a_1(\lambda_1 + s) - \cfrac{a_1\lambda_1}{a_2(\lambda_2 + s)}\left(1 - \cfrac{1}{a_1(\lambda_1 + s)}\right)}$$

$$P_{20}(s) = \cfrac{1}{\left[a_1 a_2(\lambda_1 + s)(\lambda_2 + s) - a_1\lambda_1\left(1 - \cfrac{1}{a_1(\lambda_1 + s)}\right)\right]}$$

$$H_{02}(s) = \cfrac{\lambda_1\left(1 - \cfrac{1}{a_1(\lambda_1 + s)}\right)}{\left[(\lambda_1 + s) - \cfrac{\lambda_0}{a_1(\lambda_0 + s)}\left(1 - \cfrac{1}{a_0(\lambda_0 + s)}\right)\right]}$$

$$H_{12}(s) = \cfrac{\lambda_1}{(\lambda_1 + s)}\left(1 - \cfrac{1}{a_1(\lambda_1 + s)}\right)\left[1 + \cfrac{1}{a_1(\lambda_1 + s) - \cfrac{\lambda_0}{(\lambda_0 + s)}\left(1 - \cfrac{1}{a_0(\lambda_0 + s)}\right)}\right]$$

$$N_{00}(s) = \cfrac{\lambda_0\left(1 - \cfrac{1}{a_0(\lambda_0 + s)}\right)}{\left[a_1(\lambda_0 + s)(\lambda_1 + s) - \lambda_0\left(1 - \cfrac{1}{a_0(\lambda_0 + s)}\right) - \cfrac{a_1\lambda_1(\lambda_0 + s)}{a_2(\lambda_2 + s)}\left(1 - \cfrac{1}{a_1(\lambda_1 + s)}\right)\right]}$$

$$N_{10}(s) = \cfrac{\cfrac{1}{a_1(\lambda_1 + s)}}{\left[1 - \cfrac{1}{a_1(\lambda_1 + s)} \times \cfrac{\lambda_0}{(\lambda_0 + s)}\left(1 - \cfrac{1}{a_0(\lambda_0 + s)}\right) - \cfrac{\lambda_1}{(\lambda_1 + s)}\left(1 - \cfrac{1}{a_1(\lambda_1 + s)}\right)\left(\cfrac{1}{a_2(\lambda_2 + s)}\right)\right]}$$

$$N_{20}(s) = \cfrac{1}{a_2(\lambda_2 + s)} \times \cfrac{1}{\left[a_1(\lambda_1 + s) - \cfrac{\lambda}{(\lambda_0 + s)}\left(1 - \cfrac{1}{a_0(\lambda_0 + s)}\right) - \cfrac{a_1\lambda_1}{a_2(\lambda_2 + s)}\left(1 - \cfrac{1}{a_1(\lambda_1 + s)}\right)\right]}$$

When cure time distribution is Rayleigh with the form

$$g_i(t) = \beta_i t\left[\exp\left(-\frac{1}{2}\beta_i t^2\right)\right] \quad t > 0,\ \beta_i \geq 0,\ i = 1,2$$

$$P_{10}(s) = \frac{\beta_1 R_1'(\lambda_2 + s)^2}{(\lambda_1 + s)^2(\lambda_2 + s)^2 - \beta_2\lambda_1(\lambda_1 + s)R_1 R_2'}$$

$$P_{00}(s) = \frac{1}{(\lambda_0 + s)}\left[1 + \frac{\beta_1\lambda_0 R_1'(\lambda_2 + s)^2}{(\lambda_1 + s)^2(\lambda_2 + s)^2 - \beta_2\lambda_1(\lambda_1 + s)R_1 R_2'}\right]$$

$$P_{20}(s) = \frac{\beta_1\beta_2 R_1' R_2'}{(\lambda_1 + s)^2(\lambda_2 + s)^2 - \beta_2\lambda_1(\lambda_1 + s)R_1 R_2'}$$

$$H_{02}(s) = \frac{\lambda_1 R_1(\lambda_0 + s)(\lambda_1 + s)}{(\lambda_0 + s)(\lambda_1 + s)^2 - \beta_1\lambda_0 R_1'}$$

$$H_{12}(s) = \frac{\lambda_1 R_1}{(\lambda_1 + s)}\left[1 + \frac{\beta_1 R_1'(\lambda_0 + s)(\lambda_1 + s)}{(\lambda_0 + s)(\lambda_1 + s)^2 - \beta_1\lambda_0 R_1'}\right]$$

$$N_{00}(s) = \frac{\beta_1 R_1'\lambda_0(\lambda_2 + s)^2}{(\lambda_0 + s)(\lambda_1 + s)^2(\lambda_2 + s)^2 - \beta_1 R_1'\lambda_0(\lambda_2 + s)^2 - \beta_1 R_1 R_2'(\lambda_0 + s)(\lambda_1 + s)}$$

$$N_{10}(s) = \frac{\beta_1 R_1'(\lambda_0 + s)(\lambda_2 + s)^2}{(\lambda_0 + s)(\lambda_1 + s)^2(\lambda_2 + s)^2 - \beta_1 R_1'\lambda_0(\lambda_2 + s)^2 - \beta_1 R_1 R_2'(\lambda_0 + s)(\lambda_1 + s)}$$

$$N_{20}(s) = \frac{\beta_1 \beta_2 R_1' R_2'(\lambda_0 + s)}{(\lambda_0 + s)(\lambda_1 + s)^2(\lambda_2 + s)^2 - \beta_1 R_1'\lambda_0(\lambda_2 + s)^2 - \beta_1 R_1 R_2'(\lambda_0 + s)(\lambda_1 + s)}$$

8. Discussion

The forms of different $P_{00}(s)$ i.e., the waiting time distribution to remain in the healthy state and also $N_{00}(s)$ i.e., the expected number of visits to the healthy state 0 by a cancer patient during the treatment interval (0, *t*], under three cure time distribution viz., exponential, uniform and Rayleigh with the help of Laplace transformations were obtained. Now on using the Final Value Theorem, we have that as s → 0, t → ∝.

So to have a picture of the behavior of different $P_{00}(s)$ and $N_{00}(s)$, some simulated data with some pre assigned values of the different parameters under study viz., λ_0 = 0.5, λ_1 = 1.5, λ_2 = 2, μ_1 = 0.02, μ_2 = 0.002, a_1 = 0.06, a_1 = 0.006, β_1 = 0.0004, β_2 = 0.00008 with values of *s* taken as {4.1 (-0.1) 0.1} were obtained and the values were summarized in table 1 and table 2 respectively.

Table 1: Simulated values of $P_{00}(s)$ under different cure time distributions

s	Exponential	Uniform	Rayleigh
4.1	0.21778	0.19367	0.21739
4.0	0.22262	0.19843	0.22222
3.9	0.22769	0.20340	0.22727
3.8	0.23300	0.2086	0.23256
3.7	0.23855	0.21405	0.23810
3.6	0.24438	0.21976	0.24390
3.5	0.25050	0.22575	0.25000
3.4	0.25693	0.23204	0.25641
3.3	0.26370	0.23867	0.26316
3.2	0.27084	0.24564	0.27027
3.1	0.27838	0.25300	0.27778
3.0	0.28635	0.26078	0.28572
2.9	0.29478	0.26902	0.29412
2.8	0.30373	0.27774	0.30303
2.7	0.31324	0.28701	0.31250
2.6	0.32336	0.29688	0.32258
2.5	0.33416	0.30740	0.33334
2.4	0.34571	0.31864	0.34483
2.3	0.35808	0.33068	0.35714
2.2	0.37137	0.34361	0.37037
2.1	0.38568	0.35753	0.38462
2.0	0.40114	0.37257	0.40000
1.9	0.41789	0.38885	0.41667
1.8	0.43609	0.40654	0.43479
1.7	0.45596	0.42584	0.45455
1.6	0.47772	0.44697	0.47619
1.5	0.50166	0.47021	0.50000
1.4	0.52812	0.49589	0.52632
1.3	0.55753	0.52442	0.55556
1.2	0.59040	0.55631	0.58824

1.1	0.62739	0.59218	0.62500
1.0	0.66931	0.63283	0.66667
0.9	0.71724	0.67927	0.71429
0.8	0.77255	0.73286	0.76924
0.7	0.83709	0.76568	0.83334
0.6	0.91338	0.86926	0.90910
0.5	1.00495	0.95791	1.00001
0.4	1.11690	1.06626	1.11112
0.3	1.25687	1.20168	1.25001
0.2	1.43688	1.37580	1.42858
0.1	1.67696	1.60794	1.66668
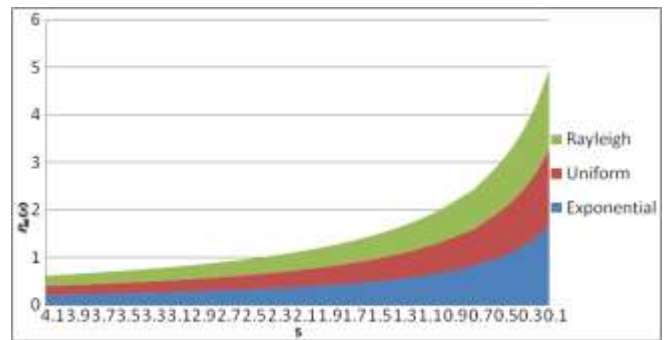
Figure 3: $P_{00}(s)$ under different cure time distributions

Table 2: Simulated values of $N_{00}(s)$ under different cure time distributions

s	Exponential	Uniform	Rayleigh
4.1	0.00219	0.02137	1.4E-06
4.0	0.00224	0.02099	1.5E-06
3.9	0.00229	0.02061	1.6E-06
3.8	0.00234	0.02023	1.7E-06
3.7	0.00240	0.01985	1.8E-06
3.6	0.00246	0.01948	1.9E-06
3.5	0.00252	0.01912	2E-06
3.4	0.00259	0.01875	2.1E-06
3.3	0.00265	0.01839	2.3E-06
3.2	0.00273	0.01804	2.4E-06
3.1	0.00280	0.01769	2.6E-06
3.0	0.00288	0.01734	2.8E-06
2.9	0.00297	0.01700	3E-06
2.8	0.00306	0.01666	3.3E-06
2.7	0.00315	0.01633	3.5E-06
2.6	0.00326	0.01600	3.8E-06
2.5	0.00337	0.01568	4.2E-06
2.4	0.00348	0.01536	4.5E-06
2.3	0.00361	0.01506	4.9E-06
2.2	0.00374	0.01475	5.4E-06
2.1	0.00389	0.01446	5.9E-06
2.0	0.00405	0.01417	6.5E-06
1.9	0.00422	0.01389	7.2E-06
1.8	0.00440	0.01361	8E-06
1.7	0.00460	0.01335	8.9E-06
1.6	0.00483	0.01309	9.9E-06
1.5	0.00507	0.01285	1.1E-05
1.4	0.00534	0.01262	1.3E-05

1.3	0.00564	0.0124	1.4E-05
1.2	0.00597	0.01220	1.6E-05
1.1	0.00635	0.01201	1.8E-05
1.0	0.00678	0.01184	2.1E-05
0.9	0.00727	0.01170	2.5E-05
0.8	0.00784	0.01158	2.9E-05
0.7	0.00850	0.01150	3.4E-05
0.6	0.00928	0.01145	4.1E-05
0.5	0.01022	0.01146	5E-05
0.4	0.01138	0.01154	6.2E-05
0.3	0.01283	0.01172	7.7E-05
0.2	0.01470	0.01202	9.9E-05
0.1	0.01720	0.01253	0.00013

Figure 4: $N_{00}(s)$ under different cure time distributions

From all the simulated values, it can be observed that as $s \rightarrow 0$ i.e., as $t \rightarrow \infty$, $P_{00}(s)$ increases in all the three cure time distributions. But on a close look, it is obvious that in a large time interval, the number of patients getting cured under exponential cure time distribution is more as compared to cure time distribution as Rayleigh and uniform respectively.

Thus exponential distribution will be a better cure time distribution compared to either Rayleigh or uniform cure time distribution in a large interval of time. Similarly, for small t i.e., in a finite time interval, exponential cure time distribution is giving better result than the Rayleigh and uniform cure time distribution in terms of number of patients getting cured.

Now in accordance with the aim to retain the patient in the state 0, i.e., in the healthy state with proper treatment as long as possible, it is better to have more number of patients visiting state 0 during treatment. By looking at the simulated values of $N_{00}(s)$, it can be observed that exponential distribution will be a better cure time distribution than Rayleigh and uniform distributions.

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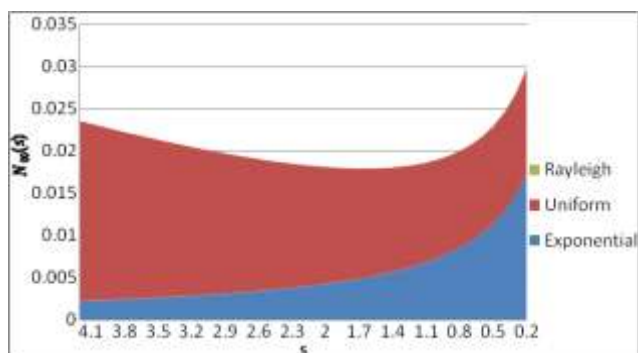
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