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Find the GBC Outcomes Using Stochastic Analysis

A. Dinesh Kumar[1], M. Vasuki[2], V. Akilandeswari[3] & S. Niranchan Kumar[4]

[1]Assistant Professor, Department of Mathematics, Dhanalakshmi Srinivasan Engineering College, Perambalur, Tamilnadu, India. Pin: 621212. Email: dineshkumarmat@gmail.com.
[2]Assistant Professor, Department of Mathematics, Srinivasan College of Arts and Science, Perambalur, Tamilnadu, India. Pin: 621212. Email: vasuki.maths@gmail.com.
[3]Associate Professor, Department of English, Dhanalakshmi Srinivasan Engineering College, Perambalur, Tamilnadu, India. Pin: 621212. Email: mathsphd1@gmail.com.
[4]UG Scholar, Department of Mechanical Engineering, Dhanalakshmi Srinivasan Engineering College, Perambalur, Tamilnadu, India. Pin: 621212. Email: mathsphd1@gmail.com.

Abstract:
Gallbladder Cancer (GBC) is a rare disease of the hepatobiliary tract characterized by silent presentation, poor prognosis, and limited therapy. Current imaging modalities, clinical symptoms and laboratory values are of limited value in diagnosis and tumour markers are used as a clinical adjunct. Five year survival is 5% - 12% and a majority of patients survive less than 1 year. Early identification, negative nodal status, and extended cholecystectomy improve survival; adjuvant therapy does not appear to play a role. In this paper we evaluate the effects of stage and nodal status of GBC on survival by analyzing clinical and radiological factors leading to preoperative diagnosis and appropriate subsequent management by using gamma distribution.

Key Words: *Gallbladder Cancer, Mathematical Model, G Queue & Gamma Distribution.*

1. Introduction:

Gallbladder Cancer (GBC) is a rare disease of the hepatobiliary tract characterized by silent presentation, poor prognosis, and limited therapy. It is the most common malignancy of the biliary tract and the seventh most common gastrointestinal tract cancer, more so than cholangiocarcinoma [15]. It is found in 1% of all cholecystectomy specimens; twenty percent of GBC is diagnosed at the time of cholecystectomy for biliary colic or gallstones [1]. Although the pathological mechanism of GBC development is not understood, there is a known correlation with the presence of gallstones, possibly due to chronic inflammation. One to three percent of patients with cholelithiasis develop GBC over a 10 - 25 year progression [14] & [16]. Other gallstone related factors are also associated with increased risk of GBC; women are 2 - 3 times more at risk than men, and incidence increases with age and obesity [16]. GBC lacks specific symptoms and there is usually a low clinical suspicion for malignancy [16]. Diagnostic imaging has been problematic in the determination of GBC. Computed tomography (CT) and ultrasound (US) are the main modalities used in the diagnosis of GBC.

We consider a single server Markovian queue with two types of customers; positive and negative, where positive customers arrive in batches and arrivals of negative customers remove positive customers in batches. Only positive customers form a queue and negative customers just reduce the system congestion by removing positive ones upon their arrivals. We derive the queue length distribution to find the effects of stage and nodal status of GBC on survival by analyzing clinical and radiological factors leading to preoperative diagnosis and appropriate subsequent management by using gamma distribution.

2. Stochastic Model:

We consider a queue with two types of customers; positive and negative. Positive customers are ordinary ones who, upon arrival, join the queue with the intention of being served. In contrast to the positive customers, the arrival of negative customers removes some of the positive customers from the system, if any available, and then disappears; otherwise the negative customer is lost. Only positive customers can from a queue and negative customers just reduce system congestion. Such queues have been called G-Queue [5].

Since [3] introduced the notion of negative customers to represent the inhibitator signal in neural networks and commands to delete some transactions in distributed computer systems or databases, there has been a growing interest not only in networks of queues [3] [5] & [7] but also in single node queues with negative customers [6] & [8]. Interest in time delays in the G-queue has increased recently. From [4] derived the LSTs of the sojourn time distributions for the M/M/1 G-Queue under the combinations of various queueing disciplines and removal strategies. From [5] investigated the end to end delay in an open tandem pair of a G-queue with FCFS discipline and RCE removal strategy. Most papers assume that upon arrival to a queue, a negative customer removes an ordinary customer from the queue. Recently, several authors have generalized this concept, allowing a negative arrival to remove a batch of customers [7], a random amount of workload**,** or even all work in the system [8].

However, the results about sojourn time distribution even for single node G-Queues with batch arrival or batch removal are few to the author's best knowledge. In this paper, we use the first passage time arguments of Markov chains to

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derive the LST of the sojourn time distribution in single server Markovian G-Queues with a batch arrival of positive customers and/or batch removal by a negative arrival. The mathematical accessibility of our model compared with that of [4] represents a part of the motivation for the study of batch arrivals/removals. Furthermore, our model is related to the inventory systems with perishable products such as fruit, vegetables and meat, in which arrival and removal occur in batches and instantaneous removal of inventory usually depends on the length of time that the products spent it the system.

Now we describe the mathematical model in detail and derive the queue length distribution in equilibrium at the arrival instants of positive customers. We consider a single server queue in which positive customers arrive in batches according to a Poisson process with rate λ^-, which is independent of the arrival process of positive customers. We assume that each arrival of a negative customer removes a random number B of positive customers in the system. This is, upon a negative arrival, if there are k positive customers in the system, $min(B,k)$ positive customers are removed and the negative customer disappears. The service time distribution of all customers is exponential with mean $\frac{1}{\mu}$. For the notational simplicity, we let $\tilde{\mu} = \lambda^- + \mu$ and $\lambda = \lambda^+ + \lambda^-$. We assume that the batch size A of positive customers and the quota B of a negative customer take finite values to avoid calculations of infinite matrices. However, this assumption is not a strong restriction, since the supports of A and B may be arbitrarily large and one can apply our model to A and B taking infinite values by truncating the tail pats of the state spaces with sufficiently small tail probabilities. Let $P(A=n) = a_n$ and $P(B=n) = b_n, n = 1,2,\ldots$ with $a_n = 0, n \geq l+1$ and $ba_n = 0, n \geq m+1$ for some $1 \leq l, m < \infty$. We denote the means $\bar{a} = E(A)$ and $\bar{b} = E(B)$ and generating functions $A(z) = \sum_{n=1}^{l} a_n z^n$ and $B(z) = \sum_{n=1}^{m} b_n z^n$.

Note that the stationary distribution of the queue length in this system is invariant under the service discipline and removal strategies and concern only positive customers. This model is equivalent to the $M^A/M^B/1$ queue where customers arrive in batches with batch size A according to a Poisson process with rate λ^+ and the customers are served in batches of maximum size $\tilde{B}$ with $\tilde{b}_k = P(\tilde{B} = k), 1 \leq k \leq m$, where

$$\tilde{b}_k = \begin{cases} \frac{\lambda^- b_1 + \mu}{\tilde{\mu}} & k = 1 \\ \frac{\lambda^- b_n}{\tilde{\mu}} & 2 \leq k \leq m \end{cases}$$

and the service time distribution is exponential with parameter $\tilde{\mu}$. The necessary and sufficient condition for this system to be positive recurrent is given (See [11] & [12]) by

$$\rho = \frac{\lambda^+ \bar{a}}{\mu + \lambda^- \bar{b}} < 1$$

We assume that $\rho < 1$ throughout.

Now we turn our attention to the queue length distribution at the epochs of positive customers, which will be imperative in the upcoming sections. Let $\{N_n\}$ be the number of positive customers in the system at the epoch immediately before the arrival of the n[th] batch of positive customers. Let A_n be the batch size of the n[th] arrival of positive customers with the same distributions as A and D_{n+1}, where D_{n+1} is the number of positive customers departed from the system during the $(n+1)^{th}$ inter arrival period of the batch of positive customers. Then it a be seen that

$$N_{n+1} = \max(N_n + A_n - D_{n+1}, 0)$$

The probability d_n that n positive customers potentially leave the system during the inter arrival time of a batch of positive customers is given by

$$d_n = \begin{cases} p & n = 0 \\ \sum_{j=1}^{n} 1^b(j,n) p q^j & n \geq 1 \end{cases}$$

Where $p = \frac{\lambda^+}{\lambda^+ + \bar{\mu}}, q = 1 - p$ and $b(j,n)$ is the j-fold convolution of the probability mass function $\{\tilde{b}_k, 0 \leq k \leq m\}$. Simple calculations yield

$$\tilde{B}(z) = \sum_{n=1}^{m} \tilde{b}_n z^n = \frac{1}{\tilde{\mu}}(\mu z + \lambda^- B(z))$$

and hence the probability generating function $d(z) = \sum_{n=0}^{\infty} d_n z^n$ is given by

$$d(z) = \frac{\lambda^+}{\lambda^+ + \mu(1-z) + \lambda^-(1 - B(z))}$$

Denoting $d_n = 0$ for $n \leq -1$ and $\bar{d}_n = \sum_{k=n}^{\infty} d_k, n \geq 0$, we deduce that the transition probability matrix $P = (p_{ij})$ of $\{N_n\}$ is given by

$$p_{ij} = \begin{cases} \sum_{k=1}^{l} a_k \bar{d}_{i+k} & j = 0 \\ \sum_{k=1}^{l} a_k \bar{d}_{k+i-j} & 1 \leq j \leq i+l \\ 0 & j \geq i \geq l+1 \end{cases}$$

Following similar procedures as those in [11], the stationary distribution $\pi = \{\pi_i, i = 0,1,\ldots\}$ of $\{N_n\}$ is given by

$$\pi_k = C \sum_{i=1}^{K} \sum_{j=0}^{n_i - 1} c_{ij} \left(\frac{d^j}{dx^j} x^k \,\middle|\, x = \alpha_i \right), k \geq 0$$

where $\alpha_i, 1 \leq i \leq K$ is the solution of the equation

$$\alpha^l = d(\alpha)(\alpha_1 \alpha^{l-1} + \alpha_2 \alpha^{l-2} + \cdots + \alpha_l) \quad (1)$$

with n_i being the multiplicity of α_i $(1 \leq i \leq K)$, such that $1 \leq n_i \leq l$ and $\sum_{i=1}^{K} n_i = l\, c_{ij}, 0 \leq j \leq n_{i-1} - 1, 1 \leq i \leq K$ are arbitrary constants, which are can be determined by the $l-1$ simultaneous equations:

$$\pi_j = \sum_{i=0}^{\infty} \pi_i p_{ij}, j = 1,2,\ldots,l-1 \quad (2)$$

under the constraint

$$\sum_{i=1}^{K} \sum_{j=0}^{n_i - 1} c_{ij} = 1 \quad (3)$$

and C, the normalizing constant (in $\sum_{i=0}^{\infty} \pi_i = 1$) is given by

$$C = \left[\sum_{i=1}^{K} \frac{c_{i0}}{1 - \alpha_i} + \sum_{i=1}^{K} \sum_{j=1}^{n_i - 1} c_{ij} \frac{j!}{(1-\alpha_i)^{j+1}} \right]^{-1}$$

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After simple but tedious algebra, we have from (2) and (3) the following linear system of equations for $\{c_{ij}, 0 \le j \le n_{i-1} - 1, 1 \le i \le K\}$:

$$Hc = e_l$$

where

$c = (c_{10}, c_{11}, \dots, c_{1,n_1-1}, c_{2,0}, c_{2,1}, \dots, \dots, c_{K,n_K-1})^t$ and $e_l = (0, 0, \dots, 0, 1)^t$ is the l unit vector and H is the $l \times l$ matirsx with its k[th] $(1 \le K \le l-1)$ row

$$h_k = h_{10}(k), h_{11}(k), \dots, h_{1,n_1-1}(k),$$

$\dots, h_{2,n_2-1}(k), \dots, h_{K,n_K-1}(k)$

and l^{th} row $h_l = (1, 1, \dots, 1)$ and for $1 \le k \le l - 1, 1 \le i \le K, 0 = j \le n_i - 1$

$h_{ij}(k) = \sum_{r=k+1}^{l} \alpha_r \sum_{n=0}^{r-k-1} (k - r + n)(k - r + n-1 \dots k-r+n-j+1 \alpha i k-r+n-j$

Special Cases:

(i) Let $l = 1$ that is $A \equiv 1$. In this case, (1) becomes

$$\tilde{\mu}\alpha\tilde{B}(\alpha) - (\lambda^+ - \tilde{\mu})\alpha + \lambda^+ = 0$$

and is has a unique solution $0 < \alpha < 1$, say α_0, and the stationary distribution is given by

$$\pi_n = (1 - \alpha_0)\alpha_0^n, n \ge 0 \qquad (4)$$

(ii) Let $l = 1$ & $m = 1$ that is $A \equiv 1$ & $B \equiv 1$. In this case, (1) becomes

$$\alpha^2 - (1 + \rho)\alpha + \rho = 0$$

and the stationary distribution is given by

$$\pi_n = (1 - \rho)\rho^n, n \ge 0 \qquad (5)$$

3. Example:

43 patients had primary GBC and 6 patients had cancer metastatic to the gallbladder. Initially, a list of all pathological reports containing mention of cancer in the gallbladder was reviewed to determine the series that were specifically carcinoma gallbladder. A retrospective review of charts and pathology reports was undertaken, comparing the pre-, intra- and post- operative diagnoses. Available radiology reports were reviewed and assessed qualitatively for suspicion of GBC or gallbladder masses. Data on palliative and adjuvant therapy were correlated through the tumor registry affiliated with the hospital site [2] & [9]. Statistical analysis of demographics and risk factors was performed. Clinicopathologic correlates of clinical presentation and laboratory values, including tumor markers, were determined. In 16 of 43 cases, chemotherapy was undertaken (38%). There was no consistency with regards to the type of agent used, although gemcitabine was frequently employed. Radiation was applied in 4 cases (9%) [10] & [13]. Thirteen of 43 patients were lost to follow-up. Of the 30 patients deceased or confirmed living, the 5-year survival rate was 13%. From the total 43 patients, there were 12 cases of early GBC (Stages 1 & 2) with an average survival of 55 months and a 5-year survival of 43%. In 23 patients with late GBC (Stages 3 & 4), the average survival was 9 months with no survival at 5 years. The average and 5-year survivals were calculated from the 30 patients whose survival outcomes were known. Survival probability in early and late stage GBC is seen in Figure (1) [17] & [18].

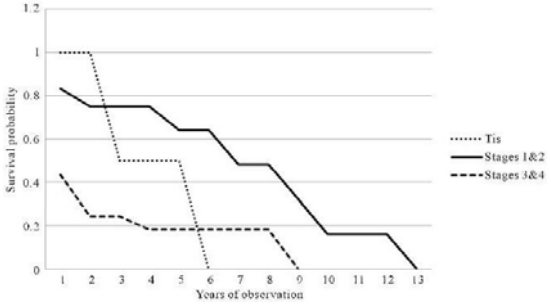
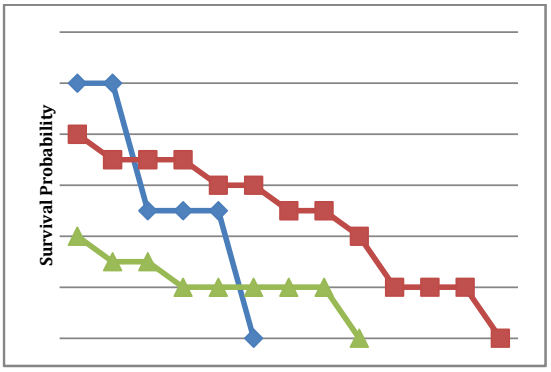


Figure (1): Kaplan Meier Survival Probability Graph for Carcinoma: Early (Stages 1 & 2) & Late (Stages 3 & 4) GBC



Blue Line: Tis
Red Line: Stages 1 & 2
Green Line: Stages 3 & 4

Figure (1): Kaplan Meier Survival Probability Graph for Carcinoma: Early (Stages 1 & 2) & Late (Stages 3 & 4) GBC (Using Gamma Distribution)

4. Conclusion:

Simple cholecystectomy for early GBC, and radical resection (determined by the grade, nodal status, and direction of spread) for cancers T1b or greater, are the surgical options for successful resection. There is still considerable overlap between the clinical presentation of GBC and more benign inflammatory conditions such as acute cholecystitis when laboratory values and clinical parameters are used for diagnosis. Improvements in imaging and preoperative planning are mandatory. Investigations into the use of tumor markers and genetics will become the key elements to improving outcomes in this insidious, lethal disease. Survival rates for advanced disease and node positive status can be improved by early diagnosis and curative resection. By using the stationary distribution of the queue length, the statistical results are nearly equal to the medical report. On comparing mathematical model with medical rapport, both results are coincides with each other.

5. References:

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