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RESEARCH PAPER

Model-Based Monitoring of Patient Response to Staged Thyroidectomy

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Abstract

The goal of this study is to develop a model-based control chart for monitoring patient behavior in a staged thyroidectomy considering risk factors and clinical prescription. prospectively collected data are gathered from the thyroid surgery unit of a hospital located in Tehran, Iran for 80 staged thyroidectomy patients discharged from 2009 to 2013. A risk-adjusted state-space model is developed based on the staged thyroidectomy. Variables to be included in the model are determined as a part of the model building process. Performance criteria, clinical prescription and patient risk factors are three variable components for the model. The appropriate risk factors are directly involved in the model and no scoring system is used for the model construction. Model identification is performed in two steps; model order selection and parameter estimation. In the first step, Hankel singular value decomposition (HSVD) is used for detecting the model order and in the second step, unknown parameters are estimated by the prediction error minimization (PEM) method. For monitoring patient responses, a group individual (GI) control chart is introduced and applied to a real-world problem. Results indicate that the suggested control chart can monitor the staged thyroidectomy patient's behavior with an acceptable accuracy. Also, computer-aided diagnosis (CAD) systems can be developed based on the proposed identification and monitoring method.

Keywords:
Surgical Operation;
Staged Thyroidectomy;
Risk Adjustment;
Model Identification;
Model-Based Control Chart

Introduction

Statistical modelling is a simplified, mathematically-formalized way to approximate reality which makes data analysts able to understand and interpret the information more strategically. Monitoring is a periodic tracking of any running process by systematically gathering and analyzing data [1]. A substantial application of statistical modelling and monitoring is for surgical operation analysis. One of the surgical operations is thyroid cancer surgery and its most common type is thyroidectomy [2]. Sometimes, thyroidectomy is performed at two different stages; first, excision of the dominant lobe and removal of the second side later. This is called staged thyroidectomy [3]. Despite considerable attention to staged thyroidectomy accreditation, statistical modeling and monitoring of this process have not been addressed adequately. However, these techniques can help surgeons ensure surgical process quality and inform them

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about critical events. In modelling and monitoring the staged thyroidectomy two main features should be considered; risk adjustment and cascade property.

Risk adjustment includes considering the staged thyroidectomy patient's inherent differences through some risk factors [4]. The use of appropriate risk factors and risk adjustment models play a key role in predicting costs and pays for performance (P4P) in medical centers [5]. Studies [6-10] applied risk adjustment for analyzing therapeutic processes. Juhnke et al. [5] provided a comprehensive review of papers that considered patient risk factors published from 1980 to 2016. They divided risk score calculation systems into three categories: patient death, patient mortality, and patient health status risk score calculation systems. In recent years, De Cassai et al. [11], Howard et al. [12], and Knuf et al. [13] contributed to the development of such scoring systems and Zeng [14] provides some examples of performance criteria and risk factors widely used in some applications of HSR.

All mentioned research used risk scores but none of them attempted to model the risk-adjusted (RA) processes by considering the relations between the performance criteria, the decision variables, and the risk factors. The use of the scoring systems usually overestimates the operational risk [5]. Moreover, using different scoring systems leads to different results and consequently raises issues and problems among physicians [15].

For the risk-adjusted monitoring of therapeutic processes, Koestier et al. [16] discussed some methods. Monitoring of therapeutic processes is usually done through the use of risk-adjusted control charts which was first introduced by Lie et al. [17] to adjust the risk of infants who had Down syndrome based on their mother's age. They were followed by many researchers such as Alemi and Olivier [18], Cook et al. [19], Sego et al. [20], Grigg and Spiegelhalter [21], Steiner and Jones [22], Szarka and Woodall [23], Paynabar and Jin [24], Shojaei and Niaki [25], and Tian et al. [26]. In recent years, Zhang and Woodall [27, 28, 29] proposed dynamic probability control limits for risk-adjusted Bernoulli CUSUM control charts and evaluated the effect of estimation error on its performance. Sparks [30] developed a joint monitoring with the combination of EWMA *p* chart and risk-adjusted control chart. Sachlas et al. [31], Begun et al. [32], and Roy et al. [33] provided some examples of using risk-adjusted control charts in healthcare. Ali et al. [34] investigated the effect of estimation error for risk-adjusted control charts. Ding et al. [35] proposed a new risk-adjusted EWMA control chart for monitoring the continuous survival times of patients. Rafiei and Asadzadeh [36] used DEA and NSGA-II approach for designing a risk-adjusted CUSUM control chart. Keshavarz et al. [37] and Keshavarz and Asadzadeh [38] considered unmeasurable categorical influential covariates in designing a risk-adjusted CUSUM control chart in phase I monitoring. Kazemi et al. [39] proposed a risk-adjusted multivariate Tukey's CUSUM control chart as a robust chart. Also, Grigg and Farewell [40], Woodall [41], Cook et al. [42], and Woodall et al. [43] reviewed the use of risk-adjusted control charts in health services. However, none of these methods comprises the cascade property which doesn't make them suitable for monitoring staged thyroidectomy.

Cascade property is a property of multi-stage processes, like the staged thyroidectomy in which the performance criteria of the second stage are also affected by the first stage [44]. To involve the inherent differences of patients in multi-stage therapeutic processes, some studies proposed risk-adjusted models with spotting on the cascade property. Among these studies, are Funatogawa et al. [45, 46], Funatogawa et al. [47], and Funatogawa and Funatogawa [48], who tried to model such processes using autoregressive (AR) models taking into consideration the mixed effects, and Funatogawa and Funatogawa [49], who proposed models based on mixed-effects with a linear state-space approach for the therapeutic processes considering the latent variable. Sibanda [50] provided a graphical O/E model for such issues and Rastgoomoghadam et al. [51] continued to use a similar approach for modeling thyroid cancer surgery based on Sibanda [50]. Recently, Kazemian et al. [52] considered the risk factors of patients and used

the linear state-space approach to model the therapeutic process of glaucoma disease. Sogandi et al. [53] also proposed a method to monitor the multi-stage therapeutic processes using a linear state-space model and risk-adjusted control chart considering logistic regression. They used control charts with dynamic probability control limit (DPCL) for this purpose. The mentioned studies usually assumed the inherent differences of the patients randomly and did not consider the effects of each patient's risk on the outcomes. In addition, their methods, due to consideration of many model assumptions especially for the dimensions of the model variables, have limited applications in the real world.

Considering the literature review, it appears that despite few studies aimed at risk-adjusted modeling and monitoring multi-stage therapeutic processes, none of them meets the needs of staged thyroidectomy. Therefore, accurate and applicable modeling of staged thyroidectomy and providing a model-based control chart is a topic that requires more research to address real-world problems. So, the aim of this study is to propose a model-based method for monitoring patient responses to staged thyroidectomy. A state-space model (SSM) is considered as a vehicle to address this issue and a group individual (GI) control chart is suggested for monitoring purposes. The suggested model considers the lab test error, the between stages transition error, the patient risk factors, and the surgery team interventions, simultaneously. Besides, the introduced monitoring procedure is a novel graphical approach for visual control of the patient response to the staged thyroidectomy. All thyroid cancer surgery units can evaluate and approve their therapeutic process using computer-aided diagnosis (CAD) systems designed based on the suggested modelling and monitoring scheme.

The rest of the paper is organized as follows. In Section 2.1, the staged thyroidectomy process is described and the proposed model is presented. System identification, model parameters estimation and design of control chart are discussed in Section 2.2. The performance of the proposed method is evaluated in Section 3 and the application of the proposed method to a hospital data set are discussed. Finally, concluding remarks and future research areas are presented in Section 4.

Theory

Setting

A state-space model is developed to simulate and forecast patient behavior using data related to patients who had staged thyroidectomy from 21/4/2009 to 23/10/2013 in a hospital located in Tehran, Iran. The condition of the data set is presented in Table A.1. For data gathering, a pathology request form is designed based on the thyroid cancer structured reporting protocol of the royal college of pathologists of Australasia [54]. Moreover, this form complies with the 5th national audit report of the British Association of endocrine and thyroid surgeons [55]. The form is presented in Table A.2.

The serum thyroglobulin level (TG) is the main performance criterion which is considered as the output variable which should be monitored at each stage of the staged thyroidectomy. In the present study, the nonlinear behavior of the patient's response to the treatment is captured by including the velocity and acceleration of TG. This is an effective way to linearize a nonlinear model. Therefore, in addition to TG, TG^2 and TG^3 statistics are also defined as output variables. By considering these output variables, the staged thyroidectomy can be interpreted as a multivariate two-stage therapeutic process.

After a time period determined by the surgeon, patients should be treated with a certain amount of radioactive iodine to eliminate the remnants of cancerous tumors which were not removed and also those spread beyond the thyroid. The time interval between stages of surgery and when the radioactive iodine receive varies for different patients depending on the body

resistance, tumor size, invasion rate, and so on. These time intervals are input variables to be determined by the surgery team. Besides, variables such as relevant medical treatment, level of invasion, and radioactive iodine dose can also be considered as other input variables.

Among the risk factors for the staged thyroidectomy are sex, weight, age, tumor size, previous thyroid operation, family history, and hyper/hypothyroidism history. In addition to the patient risk factors, the type of operation can also be considered as an operational risk factor. The schematic picture of the staged thyroidectomy, along with the output variables (**y**), the input variables (u), and the risk factors (z) are shown in Fig. 1. In Fig. 1, z_k represents the k^{th} risk factor, u_{kt} represents the k^{th} input variable at stage t, and y_{kt} represents the k^{th} output variable at stage t.

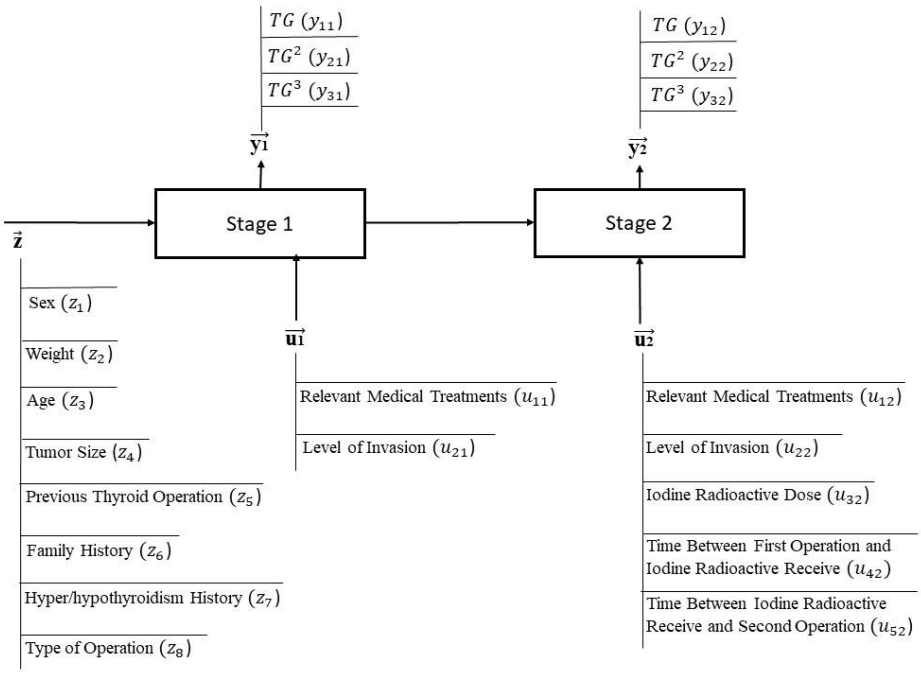

Fig. 1. A representation of the staged thyroidectomy

Based on the patient data set, the both values of the risk factor 'age' and the output variable 'TG' in stage I of the staged thyroidectomy is shown for 80 patients in Fig. 2.

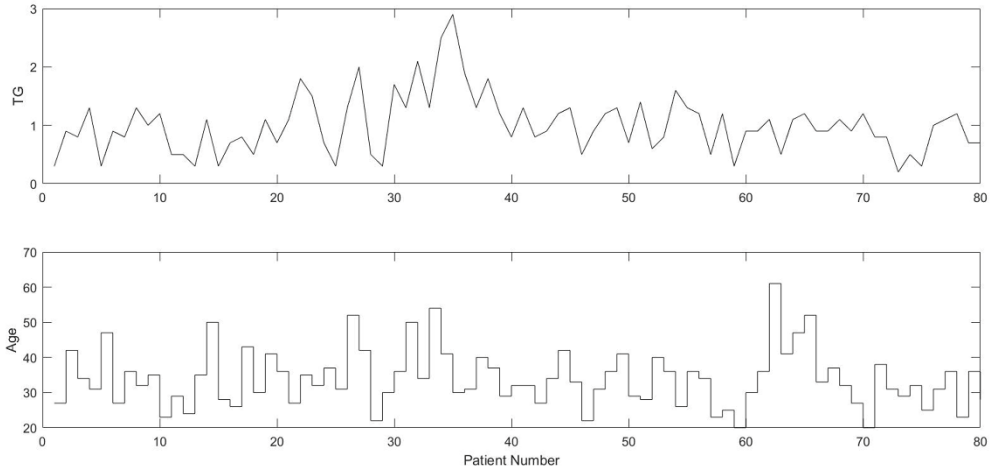

Fig. 2. Simultaneous change of age and TG in stage I of the staged thyroidectomy

The primary use of state-space models is to estimate the values of the latent variables [56]. Latent variables are those characteristics of the process that cannot be directly observed and measured. In other words, these characteristics of the process are latent in the various stages and their values can only be estimated through statistical relations. Among these variables are the actual condition of patients after surgery, the actual range of pain in patients, the unmeasurable risk factors, etc. The interested readers are invited to study Commandeur and Koopman [56] for more information about state-space models.

Assuming a multivariate normal distribution for errors and considering a linear relationship between each surgery stage, the risk-adjusted state-space model for the staged thyroidectomy is defined as in Eq. 1. The structure of the model considers two key errors; the observation error and the transition error.

$$\begin{gathered} Q_t = [z_t \dots z_t]_{8\times 5} \quad , \quad M_t = Q_t \times u_t \, , \quad g_t = \left[\acute{u}_t \;\; \acute{z}_t \; \acute{M}_t\right]'_{1\times 21} \\ \begin{cases} y_t = Cx_t + \omega_t; & t = 1. \dots . 160 \\ x_t = Ax_{(t-1)} + Hg_t + \nu_t; & t = 2i, i = 1,2, \dots ,80 \\ x_t = Ax_{0i} + Hg_t + \nu_t; & t = 2i-1, i = 1,2, \dots ,80, \end{cases} \end{gathered} \tag{1}$$

where z_t (8×1) is the risk factors vector at state t, u_t (5×1) is the input variables vector at state t, y_t (3×1) is the output variables vector at state t, x_t $(m \times 1)$ is the latent variables vector at state t, C $(3 \times m)$ is the observation matrix that determines how the latent variables are observed as output variables, A $(m \times m)$ is the state transition matrix governing the thyroid surgery stages progression dynamics, H $(m \times 21)$ is the effect matrix that captures the effects of the risk factors and input variables on the latent variables, x_{0i} $(m \times 1)$ indicates the zero state latent variables vector for patient i, ν_t is the state transition error vector at state t, and ω_t is the observation error vector at state t. Moreover, i is the counter of patients and t is the counter of states. It is clear that the total number of states is twice the total number of patients in the two-stage thyroid cancer surgery ($\max\{t\} = 2 * \max\{i\}$). Eq. 1 is a risk-adjusted state-space model with periodically linear parameter varying.

Statistical Methods

In Eq. 1, despite the vectors g_t and y_t which are known for all states, the latent variable (x_t) and the matrices C, A, and H are unknown. So, it is necessary to estimate their values. This is called model identification. In model identification, two steps should be taken; determining the dimension of the latent variable, which is called model order selection, and estimating the values of the model unknown parameters.

Hankel singular values decomposition (HSVD) is used for model order selection. The purpose of HSVD is to divide time series into a small set of components. The full description of HSVD is presented by Kung [57] and Danilov and Zygliavsky [58]. According to HSVD, the Hankel matrix is defined as follows.

$$H = \begin{bmatrix} y_1 & y_2 & y_3 & \cdots & y_{159} & y_{160} \\ \vdots & \vdots & \vdots & \ddots & \vdots & 0 \\ y_{159} & y_{160} & 0 & \cdots & 0 & 0 \\ y_{160} & 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \tag{2}$$

$SV_i = \frac{\lambda_i}{\sum_{i=1}^{d} \lambda_i}$ indicates the value of the dimension i for the latent variable where λ_i is the ith eigenvalue for matrix $O = HH^T$ and $d = max\{i;\ \lambda_i > 0\}$. One can use $ln(SV)$ instead of SV

[59]. By determining SV_i values, those dimensions with a low SV that do not provide significant information to the model are excluded.

Prediction error minimization (PEM) is used to estimate the values of the unknown matrices. PEM is a numerical optimization method that tries to minimize the loss function as a weighted function of the parameter estimation error. The full description of PEM is provided in Lijung [60]. The objective function of PEM is as follows.

$$V_T(\theta) = \frac{1}{2*80}\sum_{i=1}^{80}\sum_{t=1}^{2} \mathrm{e_{it}}(\theta)^T\, \mathrm{e_{it}}(\theta) + R\theta^2, \tag{3}$$

where θ is the set of unknown parameters, R is the regularization parameter, and $\mathrm{e_{it}}(\theta)$ is the estimation error in state t defined as $\mathrm{e_{it}}(\theta) = \mathrm{y_i}(\mathrm{t}) - \hat{y}_\mathrm{i}(\mathrm{t}|\theta)$ where $\mathrm{y_i}(\mathrm{t})$ is the real vector of the output variables of patient i in state t and $\hat{y}_\mathrm{i}(\mathrm{t}|\theta)$ is the estimated vector of the output variables of patient i in state t.

PEM tries to minimize the loss function value by performing numerous replications until the difference of the two consecutive values is less than ε_0 or the number of replications is greater than β. In the PEM, numerical iterations are done based on the least squares estimation which is about estimating parameters by minimizing the squared discrepancies between observed data and their expected values.

Large values of the estimation errors show that the patient response to thyroid surgery team prescriptions is not rational and has variation. The control chart should determine whether this variation should be considered as a random or assignable cause. For this purpose, a model-based GI control chart is suggested. For designing a GI control chart, defining a statistic and a control limit (CL) is vital. The individual statistic used in this study is $T_{it}^2 = \mathrm{e_{it}}^T \sum^{-1} \mathrm{e_{it}}$ for $i = 1,2,..,80$ and $t = 1\ and\ 2$ where $\sum$ is the variance of the estimation errors. So, the group individual statistics is as follows.

$$GX_i = \max_{1\le t\le 2}\left(\frac{T_{it}^2-3}{\sqrt{2*3}}\right);\quad i = 1.\ldots.80. \tag{4}$$

For a given value of type I error (α), the value of control limit for the GI control chart can be determined in phase I monitoring using Monte Carlo simulation.

Results and discussion

Three types of accuracy metrics are used for the performance evaluation of the model. The first metric is mean square error (MSE) defined as $MSE = \frac{1}{2*80}\sum_{i=1}^{80}\sum_{t=1}^{2} \mathrm{e_{it}}^T\, \mathrm{e_{it}}$. The second metric is the value of loss function (LF). This metric contains the effects of the model order, the fixed weights, and the regularization parameter used for estimation. The smallest MSE and LF values yield the better model accuracy. The third metric is a normalized root mean squared error (NRMSE) expressed as a percentage defined as fit percent (FP). FP is separately calculated for each output variable as $\mathrm{FP} = 100\left(1 - \frac{\|\mathrm{y}-\hat{\mathrm{y}}\|}{\|\mathrm{y}-\bar{\mathrm{y}}\|}\right)$ where, y is the measured output variable, $\hat{\mathrm{y}}$ is the estimated output variable, $\bar{\mathrm{y}}$ is the mean of the output variable, and $\|.\|$ indicates Euclidean norm of the vector. FP varies between negative infinity (bad fit) to 100 (perfect fit). If the value of FP is equal to zero, then the model is no better than a straight line equal to the mean of the data.

Fig. 3 presents $ln(SV)$ values for each dimension of the latent variable from HSVD.

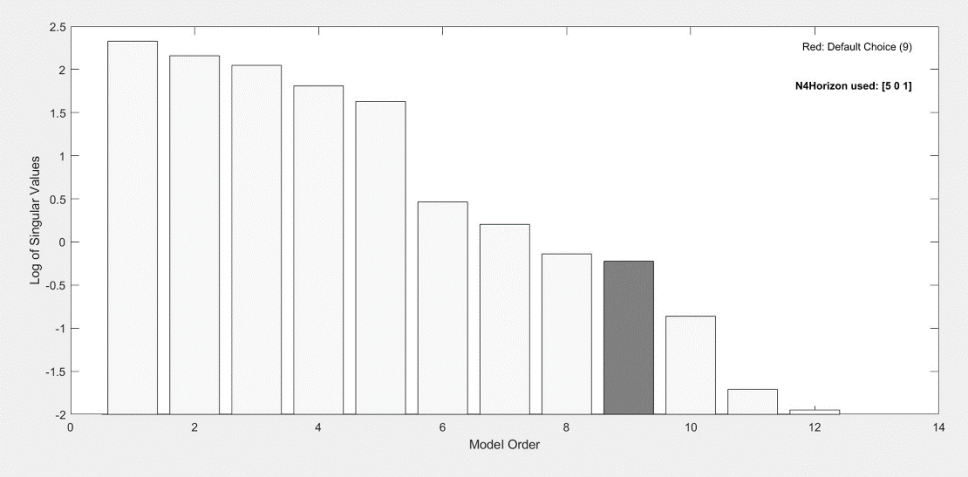

Fig. 3. $ln(SV)$ values for each dimension of the latent variable

Based on Fig. 3, there is no sudden decrease in the Hankel singular values for the staged thyroidectomy data. It reveals that the relation between the input variables and the output variables is complicated, so a high dimension latent variable is needed. The model order can be set as nine to obtain a proper accuracy. Table 1 presents the quality metrics by considering the various regularization parameters for the staged thyroidectomy patient data.

Table 1. Model accuracy for various regularization parameters for the staged thyroidectomy patient data

	Accuracy Metrics				
R	*MSE*	*LF*	*FP (TG)*	*FP (TG^2)*	*FP (TG^3)*
0	0.638	0.000	41.627	60.186	75.312
0.01	4.680	0.005	37.034	30.310	21.633
0.05	5.380	0.015	30.459	22.184	16.485
0.1	5.075	0.027	36.290	26.696	18.463
0.5	1.284	0.038	31.459	49.023	62.834
1	1.565	0.058	24.745	42.469	59.234
5	3.750	0.109	12.273	23.269	33.107
10	5.244	0.157	16.157	18.243	18.705
50	6.862	0.035	2.103	5.866	7.160
100	6.889	0.056	2.857	5.358	6.999

By adding the term $R\theta^2$ to the loss function, the values of the parameters which have little effect on the loss function are leaded to zero, so the parameters movement to the destructing values are stopped and the loss function matrix can be changed to a matrix with the better computational property. This procedure is called regularization. Since the problem is the loss function minimization, by considering the small value for the parameter R, fewer parameters lead to zero. Assuming the model order of nine, and considering various values for the regularization parameter, the best accuracy of the identified model is achieved by $R = 0$ when MSE equal to 0.638 and LF is about zero. This shows that in the staged thyroidectomy data, the model identification method is able to estimate all the parameters and no parameter is moved to zero. In this situation, the accuracy metric FP is estimated as 41.63, 60.19, and 75.31 for each output variable, respectively. Moreover, the comparison of the estimated output variable values and their actual values is given in Fig. 4. Visual comparison of the estimated values and real values indicates that the model identification method can estimate the output variables reasonably. It is clear that the model fitness is well for TG^2 and TG^3 and acceptable for TG.

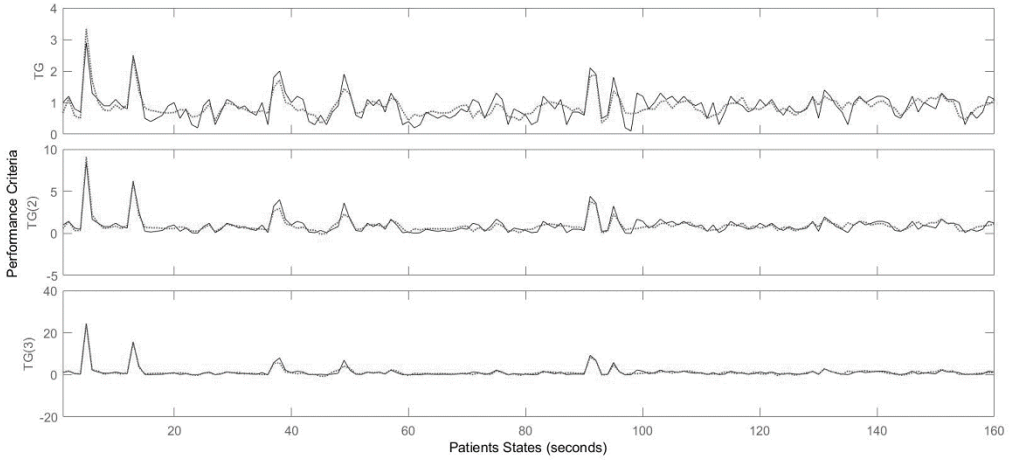

Fig. 4. Comparison of the estimated (dotted line) and actual (solid line) performance criteria values for the staged thyroidectomy patient data

The control limits for various type I error are obtained using Monte Carlo simulation. In the simulation, the actual model order is set to 9, the output variables dimension is set to 3, the number of replications is set to 1000, the number of states for each patient is set to 2, the matrices C, A, and H are fixed with their estimated values, and the error term follows a multivariate normal distribution. Table 2 shows the values of the control limits for the various type I errors.

Table 2. Values of the upper control limit for given type I error

Type I error	0.05	0.02	0.01	0.005	0.0027	0.002	0.001
CL	4.9723	5.8319	6.6052	7.3902	7.8290	8.2038	8.8964

Finally, monitoring the patient response to the staged thyroidectomy using a GI control chart is illustrated in Fig. 5, considering type I error equal to 0.005. Moreover, 14 other patients' data are gathered from the Hospital database in 2014 which were considered as the new samples. Their statistics are plotted in the GI control chart as represented in Fig. 5.

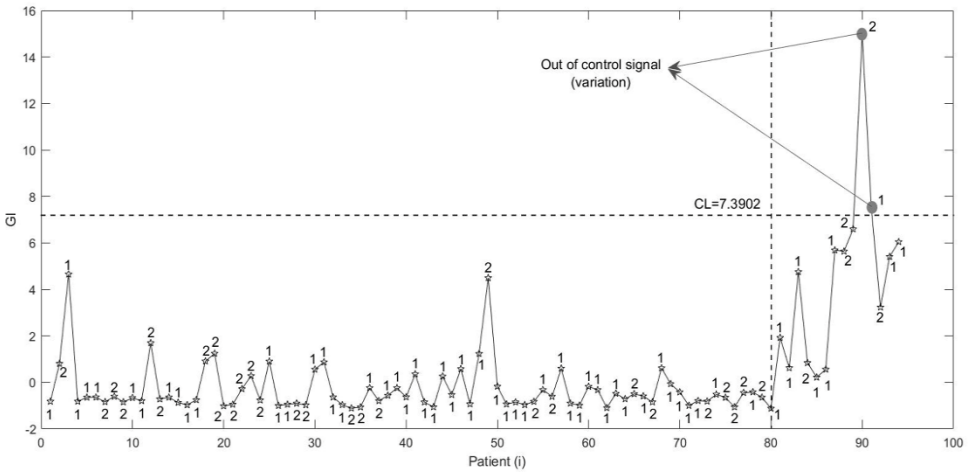

Fig. 5. GI control chart for the 80 staged thyroidectomy patient and the 14 new patient

The control limit values for the GA control chart, which are stated in Table 2, are general and applicable for any real staged thyroidectomy data risk adjust by state-space model. For the

current 80 staged thyroidectomy patient data, it can be seen that all samples are in control. Therefore, the control limits are set properly. Moreover, for the 14 new patient data, the value of GI_{90} and GI_{91} exceeds the control limit and an out-of-control signal is triggered. Therefore, some root-cause analysis should be performed at the 2nd stage operation of the 90^{th} patient and the 1st stage operation of the 91^{th} patient. This root-cause analysis could result in surgery team malfunctions, lack of TG test accuracy, the occurrence of metastasis, etc.

To the best of the authors' knowledge, there is no similar study for staged thyroidectomy. Comparing to the previous works on therapeutic processes [49-53], it should be noted that the proposed method takes into account fewer assumptions especially for the latent variable dimension and the number of stages of the therapeutic process. State-space models build on practical knowledge and physical laws of real systems [54]. One of the advantages of such a model is its applicability to model complex interactions between different stages of a process by defining a state variable. Therefore, it can state that the proposed model is more realistic than other alternatives. Moreover, the previous studies have mostly focused on phase II monitoring instead of parameter estimation in phase I. While present study tries to address parameter estimation and reaches better accuracy of estimation regarding the quality metrics. As the final point, it has to declare that the proposed model-based control chart is more graphical than the traditional scoring system already used.

In practice, the proposed modelling and monitoring scheme can be used as Computer-aided diagnosis (CAD) systems for staged thyroidectomy and other multi-stage surgical operations. CAD systems are among the most important current needs of the medical community. These systems work as physicians' medical assistants to improve the accuracy of prescriptions and evaluate the performance of the surgical team.

Conclusion

The monitoring scheme developed in this study increases the accuracy of therapeutic processes analysis, especially for the staged thyroidectomy because of considering the risk adjustment, the cascade property, the transmission error, and the test error simultaneously using linear state-space modeling. For this purpose, a risk-adjusted state-space model is proposed and its model order and parameters are estimated using HSVD and PEM methods, respectively. For parameter estimation, MSE metric is equal to 0.638 and LF metric is about zero. A GI control chart is introduced based on the identified model. Using a model-based control chart can help physicians to trace the process and evaluate patient responses to prescriptions.

For future studies, Use of other identification methods or different types of control charts can be a valuable area. Furthermore, Non-normal and non-linear state-space modelling of multi-stage multivariate therapeutic processes and the use of robust group multivariate control charts for monitoring such processes are interesting topics for researchers. In this paper, the staged thyroidectomy is investigated as an example of multivariate multi-stage therapeutic processes. Applying the proposed method for other clinical processes may provide a wide range of applications for practitioners. Designing application software based on the proposed model can also be helpful.

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Appendix

Table A.1. Condition of patient data set from 2009 to 2013

	Characteristics						
	Year		Sex		Age		Weight	
Condition	2009	5	Men	22	<20	2	<50	2
	2010	6			20 - 30	26	50 – 60	34
	2011	25			30 - 40	36	60 – 70	27
	2012	22	Women	58	40 - 50	12	70 – 80	15
	2013	22			>50	4	>80	2

Table A.2. Pathology request form for thyroid cancer

Sex: Male □ Female □ Weight: Age:
Date of First Operation: Date of Release (After Stage I):
Date of Iodine Radioactive Receive:
Date of Second Operation: Date of Release (After Stage II):
Type of Operation: Total Thyroidectomy □ Near-total Thyroidectomy □
Previous thyroid Operation: Yes □ No □
Tumor Size:
Relevant Medical Treatments (Intervention Before Stage I):
Relevant Medical Treatments (Intervention Before Stage I):
Family History:
Hyper/Hypothyroidism History:
Level of Invasion: Minimally □ Moderate □ Widely □
Number of Involved Lymph Nodes After stage I:
Number of Involved Lymph Nodes After stage II:
Serum Thyroglobulin (After Stage I):
Serum Thyroglobulin (After Stage II):
Iodine Radioactive Dose: