Six Sigma Approach for a First Evaluation of a Pharmacological Therapy in Tongue Cancer

A. Sorrentino[1], A. Scala[2(✉)], A. Fiorillo[3], I. Latessa[2], V. Abbate[1], and G. Dell'Aversana Orabona[1]

[1] Maxillofacial Surgery Unit, Department of Neurosciences, Reproductive and Odontostomatological Sciences, University Hospital of Naples 'Federico II', Naples, Italy
ariannascala7@gmail.com
[2] Department of Public Health, University Hospital of Naples 'Federico II', Naples, Italy
[3] Department of Advanced Biomedical Sciences, University Hospital of Naples 'Federico II', Naples, Italy

Abstract. Tongue cancers are among the most frequent malignancies in the population and their influence can be affected by many risk factors. Patients undergoing tongue surgery face different complications and can experience a long length of hospital stay (LOS). The aim of this paper is to compare two pharmacological therapies in order to understand which one decreases the LOS. At the University hospital of Naples "Federico II" two antibiotics were employed: Cefazolin plus Clindamycin and Ceftriaxone. Six Sigma methodology was employed to analyse two group of patients treated with these two different antibiotics: 55 patients treated with the antibiotic Cefazolin plus Clindamycin and 66 patients with the antibiotic Ceftriaxone. This is the first time that this methodology is used in order to compare two antibiotics in the oncology field. The results obtained show clearly and with a statistical evidence that patients treated with Ceftriaxone experienced a lower LOS (−28.6% in terms of percentage between medians). Reducing the LOS for patients means limiting the number of complications and, therefore, reducing the hospitalization costs. It would be valuable for both hospital and patients: the former would save money that they could invest in other important care activities; the latter would experience a higher quality of care with fewer complications.

Keywords: Six sigma · Statistical approach · Healthcare · Drugs

1 Introduction

Tongue cancers are the malignant neoplasms that occur on the dorsal surface, ventral surface, borders and anterior part of the tongue. These pathologies enter in the bigger group of oral cancers that, actually, represent the sixth most common cancer [1].

The incidence of tongue cancer is influenced by multiples variables, such as poor oral hygiene, persistent inflammations, smoking [2], alcohol abuse [3], infections [4].

T. Jarm et al. (Eds.): EMBEC 2020, IFMBE Proceedings 80, pp. 1028–1037, 2021.
https://doi.org/10.1007/978-3-030-64610-3_115

Nowadays, the incidence of this malignancies has increased during last years [5] especially in young population. In this study we considered all surgeries that previewed an asportation of the tongue [6] or part of it, with or without reconstruction.

Many approaches have been proposed in literature in the last years to improve and simulate processes a process, to compare biomedical technologies and to aid clinicians in decision making: Health Technology Assessment [7–10], Lean Six Sigma [11, 12] and data analysis and processing with several algorithms and different machine learning techniques [13–22] proved their reliability in the healthcare context. Six Sigma is a methodology of quality management and process improvement that combines the use of statistics with a five-step procedure: "Define, Measure, Analysis, Improve, Control" referred to in the acronym DMAIC. Through this problem-solving strategy with a fixed structure, it is possible to analyse a process in order to improve its performance by reducing the "natural variability" and the systematic "control" of the critical variables to obtain a better result.

From the literature it emerges that the DMAIC strategy has been successful in the healthcare field, such as in first aid [23] and eye surgery [24]. DMAIC cycle was applied in order to improve patients' access to clinical care, adopting strategic choices aimed at reducing patient missed appointments [25]. Furthermore, studies show that the Six Sigma methodology is often associated with Lean Thinking. This approach seeks to implement performance to meet customer needs by eliminating wastes and reducing costs [26, 27]. The use of Lean and/or Six Sigma methodologies has reported multiple benefits in the healthcare, in fact many studies have applied these methodologies to improve clinical decision-making processes and quality management in laboratory medicine, to reduce the risk of healthcare–associated infections in surgery departments [28], while others conducted studies to introduce pre-hospitalization, aimed at carrying out the tests and examinations required for prosthetic hip and knee surgery [29, 30], or new clinical pathways [31].

Researchers have applied DMAIC cycle as an interesting and practical method to reduce the health and safety risks of clinicians using anticancer drugs and to optimize cost management within the department, an improvement project within the pharmacy department of a hospital, [32]. Other works have testified the efficiency of the processes designed through Lean Six Sigma methodology to reduce the dispensation error in the pharmacy department [33].

In this paper, the performance of two antibiotics, Cefazolin plus Clindamycin and Ceftriaxone, was compared investigating the postoperative LOS, measured in days, of patients undergoing surgery in the oral cavity (particularly on tongue), analysing the influence of some variables (American Society of Anaesthesiologists (ASA) score, age, gender) and employing Six Sigma methodology and DMAIC problem-solving strategy.

2 Materials and Methods

2.1 Dataset

The data were extracted from the medical records of the University Hospital of Naples "Federico II". In this phase, the dataset was made up of a sample constituted by 55

patients, treated with the antibiotic Cefazolin plus Clindamycin, and another one of 66 patients, treated with the antibiotic Ceftriaxone. The time range was from 2011 to 2018 for the first group and 2006–2018 for the second one since also patients that had used Ceftriaxone in the previous years were considered; it allowed to empower the statistical analysis including a greater number of patients.

For each patient, the following information was collected and analysed: gender and age; ASA score; admission diagnosis; prehospitalization; date of admission; date of surgery and date of discharge.

2.2 Define

In this phase, the purpose of the cycle is to define a multidisciplinary work team and divide the tasks of analysis. SIPOC (Suppliers-Inputs-Process-Outputs-Customers) scheme was a good tool to clarify the following main process characteristics:

- Supplier:
  - University hospital "Federico II" of Naples;
  - Clinical staff;
- Input:
  - Needs of patients;
  - Maxillofacial surgery;
- Process:
  - Arrival at the hospital;
  - Recovery;
  - Surgery;
  - Postoperative activities;
  - Discharge;
- Output:
  - Better recovery;
  - Improved outcome for patients;
- Customers:
  - Patients;
  - University hospital "Federico II" of Naples.

Moreover, the critical to quality (CTQ) was identified in the LOS.

A final statement summarizing the project was formalized: "Reducing the post-operative LOS of patients undergoing tongue cancer surgery".

2.3 Measure

After identifying the purpose of the study, the CTQs, the dataset and the methodology, the performance of the antibiotics was measured below. The descriptive statistic for the independent variable, according the dependent one (postoperative LOS), was carried out: the results for Cefazolin plus Clindamycin were, respectively, a mean of 15.67 days, a deviance of 8.36, and a variance of 69.96. Instead, the results for Ceftriaxone were an average of 12.56 days, a deviance of 8.90, and a variance of 79.23. The

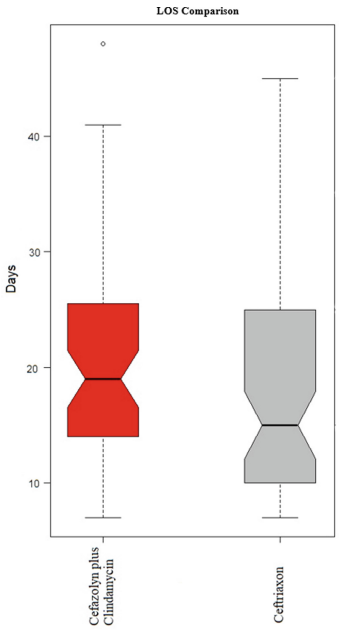

Fig. 1. Boxplot of LOS for the two groups

boxplot in Fig. 1 shows graphically the overall difference in LOS between the two groups.

2.4 Analyse

In order to evaluate statistically the effects of treatment on the group of patients on the basis of the defined categories, Mann Whitney and Kruskal Wallis tests were executed respectively for dichotomous and non-dichotomous categories since the test of Shapiro Wilk identified the data as not normally distributed.

In this analysis an alpha of 0.05 is used as the cut-off value for significance. In Table 1, the variables and their categories influencing LOS for Cefazolin plus Clindamycin are reported. Table 1 shows that LOS for patients treated with cefazolin and clindamycin doesn't seem to be influenced by the gender and the age. Instead high ASA score seems to increase LOS.

Similarly, the effects of the variables on the LOS of patients undergoing Ceftriaxone therapy were statistically evaluated on the basis of the same grouping criteria and with the same statistical methods used in the previous case. In Table 2, the variables and the categories influencing the LOS and the p-value for Ceftriaxone treatment are reported.

From Table 2 it emerges that gender, age and ASA score don't seem to affect LOS in patients treated with Ceftriaxone in a statistically significant way considering a level of uncertainty of 5%.

Table 1. Variables influencing LOS for Cefazolin plus Clindamycin

Variable	Category	N	p-value
Gender	Man	27	0.853
	Woman	28	
Age	<51	12	0.172
	50 < Age < 61	16	
	>60	27	
ASA score	Low	17	0.009
	High	38	

Table 2. Variables influencing LOS for Ceftriaxone

Variable	Category	N	p-value
Gender	Man	35	0.056
	Women	31	
Age	Age < 51	14	0.074
	50 < Age < 61	14	
	Age > 60	38	
ASA score	Low	38	0.077
	High	28	

2.5 Improve

From the analysis conducted on the surgical wounds of patients operated for oral cancer, several different populations of bacteria were isolated, including Staphylococcus Spp and Gram-negative bacteria [34]. In 2011, according to our hospital guidelines and the evidences in literature of the success of an association of a first/second generation cephalosporin with other antibiotics, an association of cefazolin and clindamycin was introduced as antibiotic protocol [35]. This choice was driven by the action of the cefazolin on the main Gram-Positive bacteria such as Staphylococcus Aureus Metycillin-Sensible colonizing oral cavity.

Clindamycin is a lincosamide antibiotic that is active on anaerobic Gram-negative flora. As well, clindamycin can be used also in patients that are allergic to penicillin or that present infections due to resistant bacteria, such as Stphylococcus Aureus Metycillin Resistant. Clindamycin is active also on aerobic Gram-positive cocci, while it is generally resistent to aerobic Gram-negative bacteria, such as Pseudomonas and Legionalla. Clindamycin is used to prevent anaerobic infections including dental and first respiratory tract infections.

2.6 Control

After a normality test of Shapiro Wilk (with a level of uncertainty or an alpha equal to 0.05) attesting that the data were not normally distributed, some statistical tests with an

alpha of 0.05 were applied to the subgroups in order to enhance some statistically significant differences. Mann Whitney test was applied to the dichotomous groups while Kruskal Wallis was applied only on age since it was divided into three groups.

3 Results

Each category was studied through nonparametric statistical tests because the Shapiro Wilk test for the normality of data showed a p-value lower than 0.01. Table 3 shows all the results.

Table 3. Statistical analysis of LOS related to each variable and category

Variables	Category	Ceftriaxon [median]	Cefazolin plus Clindamycin [median]	Absolute difference [%]	p-value
All patients		10	14	28.6	0.028
Gender	Man	12	14	14.3	0.727
	Women	9	14.50	37.9	0.003
Age	<51	4.50	12	62.5	0.099
	50 < Age < 61	11	14	21.4	0.588
	>60	11.50	17	32.4	0.089
ASA score	Low	8	9	11.1	0.488
	High	12	17	29.4	0.099

The overall test showed that there is a statistically significant difference in LOS between patients who were treated with Ceftriaxon and those treated with Cefazolin plus Clindamycin (p-value = 0.028). As regards the categories, there was statistically significant difference in favour of Ceftriaxon in women. The biggest difference in terms of percentage between medians was obtained by the youngest patients (−62.5% for those younger than 51 years).

Moreover, a demographic study of the analysed population was conducted through a chi square test whose results are shown in Table 4.

Chi square test showed that the frequency of ASA score for the two groups was distributed differently in a statistically significant way.

4 Discussions and Conclusion

Six Sigma through DMAIC cycle provides researchers with a well-structured problem-solving strategy that is useful for a wide range of analysis, as testified previously by other studies [23, 24]. In this case, it was used to make a comparison between the LOS of two different antibiotics in the oncology field, taking into consideration three

Table 4. Demographic study through chi square test

Variables	Category	Ceftriaxon [N]	Cefazolin plus Clindamycin [N]	p-value
Gender	Man	35	27	0.666
	Women	31	28	
Age	<51	14	12	0.560
	50 < Age < 61	14	16	
	>60	38	27	
ASA score	Low	38	17	0.003
	High	28	38	

variables: gender, age and ASA score. The results obtained under the guidance of DMAIC show that patients treated with Ceftriaxone experienced a 28.6% lower LOS in percentage terms, while the group of patients treated with Cefazolin and Clindamycin presents in mean an increase of LOS in all patients. It is particularly evident in patients with a high ASA score, in women and in youngest patients (below the age of 51).

The novelty of this paper relies on the use of the Six Sigma methodology with the DMAIC cycle to handle a healthcare issue regarding the comparison of two antibiotics in the oncology field. This is an innovation because in literature Six Sigma is used to improve processes [11, 12], reduce costs [26, 27], introduce new clinical pathways [31], but it has never been used to compare two biomedical technologies. Further studies could include an increasing number of variables, both clinical and surgical, in order to evaluate also postoperative complications. Furthermore, Six Sigma could also be implemented as a Health Technology Assessment tool, capable of comparing two pharmacological therapies in order to understand which one makes the LOS and the complications decrease. Finally, using multiple linear regression or machine learning techniques could lead to the elaboration of a model capable of predicting the LOS, for each antibiotic, considering patient's characteristics. This model could be used as a useful decisional tool for doctors, for example, to facilitate the management of the entire department, to schedule unit personnel, to reduce LOS costs and to facilitate discharge planning.

Conflict of Interest Statement. The authors have no conflict of interest to declare.

References

1. Tsantoulis, P.K., Kastrinakis, N.G., Tourvas, A.D., Laskaris, G., Gorgoulis, V.G.: Advances in the biology of oral cancer. Oral Oncol. **43**, 523–534 (2007)
2. Khan, Z., Tönnies, J., Müller, S.: Smokeless tobacco and oral cancer in South Asia: a systematic review with meta-analysis. J Cancer Epidemiol (2014). Hindawi, 201. http://dx.doi.org/10.1155/2014/394696
3. Chuang, S.C., Jenab, M., Heck, J.E., et al.: Diet and the risk of head and neck cancer: a pooled analysis in the INHANCE consortium. Cancer Causes Control **23**(1), 69–88 (2012)

4. Gillison, M.L., Chaturvedi, A.K., Anderson, W.F., Fakhry, C.: Epidemiology of human papillomavirus-positive head and neck squamous cell carcinoma. J. Clin. Oncol.: Off. J. Am. Soc. Clin. Oncol. **33**, 3235–3242 (2015)
5. Shiboski, C.H., Schmidt, B.L., Jordan, R.C.: Tongue and tonsil carcinoma: increasing trends in the U.S. population ages 20–44 years. Cancer **103**, 1843–1849 (2005)
6. Gourin, C.G., Johnson, J.T.: Surgical treatment of squamous cell carcinoma of the base of tongue. Head Neck. **23**, 653–660 (2001)
7. Improta, G., Fratini, A., Triassi, M.: Health technology assessment: an essential approach to guide clinical governance choices on risk management. In: Risk Management for the Future – Theory and Cases (2012)
8. Improta, G., Triassi, M., Guizzi, G., Santillo, L.C., Revetria, R., Catania, A., Cassettar, L.: An innovative contribution to health technology assessment. Mod. Adv. Intell. Syst. Tools **431**, 127–131 (2012)
9. Improta, G., Parente, G., Triassi, M., Pitingolo, G., Cozzolino, S., Romano, M.: Evaluation of a set of indicators devoted to the service of health education: the case of the biotechnology centre of the A.O.R.N. Hospital "A. Cardarelli" in Naples ICIEMS. In: 2013 15th International Conference on Industrial Engineering (2013)
10. Improta, G., Russo, M.A., Triassi, M., Converso, G., Murino, T., Santillo, L.C.: Use of the AHP methodology in system dynamics: modelling and simulation for health technology assessments to determine the correct prosthesis choice for hernia diseases. Math. Biosci. **299**, 19–27 (2018)
11. Improta, G., Balato, G., Ricciardi, C., Russo, M.A., Santalucia, I., Triassi, M., Cesarelli, M.: Lean Six Sigma in healthcare: fast track surgery for patients undergoing prosthetic hip replacement surgery. TQM J. **31**(4), 526–540 (2019). https://doi.org/10.1108/TQM-10-2018-0142
12. Ricciardi, C., Fiorillo, A., Valente, A.S., Borrelli, A., Verdoliva, C., Triassi, M., Improta, G.: Lean Six Sigma approach to reduce LOS through a diagnostic-therapeutic-assistance path at AORNA Cardarelli. TQM J. (2019). https://doi.org/10.1108/TQM-02-2019-0065
13. Ricciardi, C., Cantoni, V., Green, R., Improta, G., Cesarelli, M.: Is it possible to predict cardiac death?. In: Mediterranean Conference on Medical and Biological Engineering and Computing, pp. 847–854. Springer, Cham (2019)
14. Romeo, V., Cuocolo, R., Ricciardi, C., Ugga, L., Cocozza, S., Verde, F., Elefante, A.: Prediction of tumor grade and nodal status in oropharyngeal and oral cavity squamous-cell carcinoma using a radiomic approach. Anticancer Res. **40**(1), 271–280 (2020)
15. Ricciardi, C., Amboni, M., De Santis, C., Improta, G., Volpe, G., Iuppariello, L., Cesarelli, M.: Using gait analysis' parameters to classify Parkinsonism: A data mining approach. Comput. Methods Programs Biomed. **180**, 105033 (2019)
16. Ricciardi, C., Cantoni, V., Improta, G., Iuppariello, L., Latessa, I., Cesarelli, M., Cuocolo, A.: Application of data mining in a cohort of Italian subjects undergoing myocardial perfusion imaging at an academic medical center. Comput. Methods Programs Biomed. **105343** (2020)
17. Ricciardi, C., Edmunds, K.J., Recenti, M., Sigurdsson, S., Gudnason, V., Carraro, U., Gargiulo, P.: Assessing cardiovascular risks from a mid-thigh CT image: a tree-based machine learning approach using radiodensitometric distributions. Sci. Rep. **10**(1), 1–13 (2020). https://doi.org/10.1038/s41598-020-59873-9
18. Romano, M., D'Addio, G., Clemente, F., Ponsiglione, A.M., Improta, G., Cesarelli, M.: Symbolic dynamic and frequency analysis in foetal monitoring. In: 2014 IEEE International Symposium on Medical Measurements and Applications (MeMeA), pp. 1–5. IEEE (2014)

19. Romano, M., Bifulco, P., Ponsiglione, A.M., Gargiulo, G.D., Amato, F., Cesarelli, M.: Evaluation of floatingline and foetal heart rate variability. Biomed. Signal Process. Control **39**, 185–196 (2018)
20. Improta, G., Ricciardi, C., Amato, F., D'Addio, G., Cesarelli, M., Romano, M.: Efficacy of machine learning in predicting the kind of delivery by cardiotocography. In: Henriques, J., Neves, N., de Carvalho, P. (eds.) XV Mediterranean Conference on Medical and Biological Engineering and Computing – MEDICON 2019. MEDICON 2019. IFMBE Proceedings, vol. 76. Springer, Cham
21. D'Addio, G., Ricciardi, C., Improta, G., Bifulco, P., Cesarelli, M.: Feasibility of Machine Learning in Predicting Features Related to Congenital Nystagmus. In: Henriques, J., Neves, N., de Carvalho, P. (eds.) XV Mediterranean Conference on Medical and Biological Engineering and Computing – MEDICON 2019. MEDICON 2019. IFMBE Proceedings, vol 76. Springer, Cham (2020)
22. Romeo, V., Cuocolo, R., Ricciardi, C., et al.: Prediction of tumor grade and nodal status in oropharyngeal and oral cavity squamous-cell carcinoma using a radiomic approach. Anticancer Res. (2020). https://doi.org/10.21873/anticanres.13949
23. Improta, G., Romano, M., Di Cicco, M.V., Ferraro, A., Borrelli, A., Verdoliva, C., Triassi, M., Cesarelli, M.: Lean thinking to improve emergency department throughput at AORN Cardarelli hospital. BMC Health Serv. Res. **18**(1), 914 (2018)
24. Jin, X., Sivakumar, A. I., Lim, S.Y.: A simulation based analysis on reducing patient waiting time for consultation in an outpatient eye clinic. In: Proceedings of the 2013 Winter Simulation Conference: Simulation: Making Decisions in a Complex World, pp. 2192–220. IEEE Press (2013)
25. Improta, G., Guizzi, G., Ricciardi, C., Giordano, V., Ponsiglione, A.M., Converso, G., Triassi, M.: Agile Six Sigma in Healthcare: Case Study at Santobono Pediatric Hospital. Int. J. Environ. Res. Public Health **17**(3), 1052 (2020)
26. Improta, G., Cesarelli, M., Montuori, P., Santillo, L.C., Triassi, M.: Reducing the risk of healthcare associated infections through Lean Six Sigma: the case of the medicine areas at the Federico II University Hospital in Naples (Italy). J. Eval. Clin. Pract. **24**(2), 338–346 (2018)
27. Ricciardi, C., Balato, G., Romano, M., Santalucia, I., Cesarelli, M., Improta, G.: Fast track surgery for knee replacement surgery: a lean six sigma approach. TQM J. (2020). https://doi.org/10.1108/TQM-06-2019-0159
28. Montella, E., Di Cicco, M.V., Ferraro, A., Centobelli, P., Raiola, E., Triassi, M., Improta, G.: The application of Lean Six Sigma methodology to reduce the risk of healthcare associated infections in surgery departments. J. Eval. Clin. Pract. **23**(3), 530–539 (2017)
29. Improta, G., Balato, G., Romano, M., Carpentieri, F., Bifulco, P., Russo, M.A., Rosa, D., Triassi, M., Cesarelli, M.: Lean Six Sigma: a new approach to the management of patients undergoing prosthetic hip replacement surgery. J. Eval. Clin. Pract. **21**(4), 662–672 (2015)
30. Improta, G., Balato, G., Romano, M., Ponsiglione, A.M., Raiola, E., Russo, M.A., Cesarelli, M.: Improving performances of the knee replacement surgery process by applying DMAIC principles. J. Eval. Clin. Pract. **23**(6), 1401–1407 (2017)
31. Improta, G., Ricciardi, C., Borrelli, A., D'alessandro, A., Verdoliva, C., Cesarelli, M.: The application of six sigma to reduce the pre-operative length of hospital stay at the hospital Antonio Cardarelli. Int. J. Lean Six Sigma (2019). https://doi.org/10.1108/IJLSS-02-2019-0014
32. Chiarini, A.: Risk management and cost reduction of cancer drugs using Lean Six Sigma tools. Leadersh. Health Serv. **25**(4), 318–330 (2012)
33. Chan, A.L.F.: Use of Six Sigma to improve pharmacist dispensing errors at an outpatient clinic. Am. J. Med. Qual. **19**(3), 128–131 (2004)

34. Durand, M.L., Yarlagadda, B.B., Rich, D.L., Lin, D.T., Emerick, K.S., Rocco, J.W., Deschler, D.G.: The time course and microbiology of surgical site infections after head and neck free flap surgery. Laryngoscope **125**(5), 1084–1089 (2015)
35. Johnson, J.T., Yu, V.L., Myers, E.N., Murder, R.R., Thearle, P.B., Diven, W.F.: Efficacy of two third-generation of cephalosporins in prophylaxis for head and neck surgery. Arch. Otolaryngol. **110**, 224–227 (1984)