



DETECTION AND SPATIAL SIZING OF SUBCUTANEOUS CARCINOGEN NODULES IN THE ESOPHAGUS

Diogo de Oliveira Costa^{*1}, Alexandre Seiji Fukuda Ribas², Thiago Lopes Amaral³, Clara Fonseca da Justa⁴, Suélia de Siqueira Rodrigues Fleury Rosa⁵

^{*1}Laboratory of Engineering and Biomaterial – BioEngLab®, University of Brasilia, Brazil.

²Laboratory of Engineering and Biomaterial – BioEngLab®, University of Brasilia, Brazil.

³Laboratory of Engineering and Biomaterial – BioEngLab®, University of Brasilia, Brazil.

⁴Laboratory of Engineering and Biomaterial – BioEngLab®, University of Brasilia, Brazil.

⁵Laboratory of Engineering and Biomaterial – BioEngLab®, University of Brasilia, Brazil.

KEYWORDS: esophagus, cancer, biomaterial.

ABSTRACT

Esophageal Cancer (EC) is a malignant neoplasm with a high mortality rate and difficult diagnosis in the early stages of the disease, and this decreases the efficiency of its treatment. Its incidence is often linked to cultural and regional factors, such as the ingestion of food and/or drinks at elevated temperatures. Due to the low detection rate, we devised an instrumental catheter made of latex, which is a biosynthetic material, containing a matrix of electronic thermometers for measuring the intra-esophageal temperature, as well as preparing an on-board electronic apparatus, which combines an electronic circuit and a computer for correct data treatment. With this apparatus, we expect to obtain the thermal and pressure modeling for healthy tissues and tissues affected by EC.

INTRODUCTION

Esophagus cancer (EC) is a malignant neoplasm, with a high morbidity rate. Its incidence varies geographically. The consumption of alcohol, tobacco and high-temperature food and drinks, such as: coffee, tea and mate, makes the incidence of EC has a high degree of connection with cultural factors and regional. The malignant tumors present a high number of cases in which they cannot be completely removed, causing the patients not to be able to feed properly, which further worsens their health condition, leading to death [1-3] [21].

EC is basically classified into two types: epidermoid carcinoma and adenocarcinoma. Epidermoid carcinoma, which is the most commonly found, occurs in most of the cases in the upper and intermediate thirds; this metaplasia is formed in the esophageal mucosa. The adenocarcinoma usually occurs in the lower third. It is caused by a chronic gastroesophageal reflux and dysfunctions that replace esophagus cells by cells that resemble intestine cells. This is known as specialized intestinal metaplasia [4-5].

The medical and scientific community has been seeking new technologies to understand the growth of the cancer, such as mathematical modeling that allow for the prediction of an evolution of the EC and thus proposing a more effective treatment. This evolution of the mathematical modeling of the nodules had its beginning about 20 years ago, with the advancement of computer technology, microelectronics and nanoelectronics, which allowed for the creation of a very high set of support tools for the diagnosis of EC [10-12].

These computational tools have brought advances in the parameterization, which allowed for the simulation of the prognosis to a specific patient, making the treatment even more customized and best fitting for each patient. In spite of all the efforts, the complexity of the problem is high and this decreases the ability to predict mathematical models of *in vivo* tumors, which still makes this predictive factor low, and there is plenty of work to be done in this area in order to improve this aspect.

MATERIALS AND METHODS

Mechanical Changes in the Esophagus

The esophagus is a continuous muscular tube with approximately 250 mm in length, and is responsible for the direct connection between the oral cavity and the stomach. This organ is basically composed of three parts, where: the upper third is a striated muscle tissue, that is, it is a tissue with voluntary control; the lower third, which is the part closest to the connection with the stomach, it is composed primarily of smooth muscle tissue, being responsible for peristalsis, which lead the food in an involuntary way to the stomach; the middle third of the esophagus has a mix of the upper and lower portions: it is possible to identify in it both smooth and striated



muscles. This component has a high degree of lymphatic vascularization, making it highly sensitive to thermal variations. This sensitivity causes the esophagus to be a delicate organ; this, coupled with the fact of it being in direct contact with the bolus whenever food is ingested, whenever food is ingested, there is a very high possibility of injury that becomes difficult to cure, and may cause more serious problems, such as cases of infection and formation of carcinogenesis [6] [19-20].

The various esophageal lesions have in common the increase in cellular activity at the wound site; this increase results in considerable increase in local temperature, allowing for the quantification of the size of the lesion the evaluation of a possible carcinogen situation. The correct diagnosis and clinical understanding of cancerous tumors provide decision-making support in therapeutic behaviors [11]. With this, it is possible to characterize the evolution of the lesion and propose growth models, in order to predict future presentations with the goal of helping decide which is the best strategy to control the tumor growth for each particular patient.

Biomaterials

A biomaterial is defined as a synthetic or natural material used to replace, repair or help part of a living system. For its use, it is important to consider physiological factors so that it is not rejected by the body. Attention should also be paid to the safety of the system and the cost of the material.

Biomaterials are usually arranged in four subcategories: biocompatibility, ability to be sterilized, functionality and reproducibility. These can still be separated again in four other subgroups, where we can see the type of interaction that occurs between the material and the body in contact with it, namely: bio-inert — do not cause foreign body reaction in the body, and are in direct contact with the receptor tissue; bio-tolerated — moderately supported by the receptor tissue and usually involved by fibrous tissue; bio-active — there is direct connection to living tissue; and re-absorbable — slowly degradable and gradually replaced by the tissues [14-16].

Instrumental Catheter

The catheter is comprised of biomaterial based on natural latex extracted from the rubber tree *Hevea brasiliensis*; the material was centrifuged. It is a mechanical device, of a biocompatible, flexible material, with a cylindrical shape of 80 to 180 mm in length, which has an air inlet to be connected to a blower. This length dimension corresponds to the average size of the initial portion of the esophagus. For the construction of this device we chose the value of 150 mm, which is a median value for that portion in adults. The catheter has at one end a wire for mounting the module to a dental crown, which should be attached to the upper molar with the purpose of preventing the module from migrating to the stomach in the event of accidental disinflation.

The confection of the module begins by preparing the environment, the raw materials, the molds, and several steps follow, such as: filtering of latex, deposition of latex in a glass container, dipping the glass molds into a container with liquid latex, drying the molds in an oven and analysis of thickness. After reaching half of the thickness expected, we place the sensors and their wiring and repeat the same steps above. Finally, we remove the solidified latex from molds, assemble the module and make a final inspection. Some of the steps can be seen in Figure 1.



Figure 1 - Manufacture of the catheter for data capture inside the esophagus, where: (1) Aluminum with axial chamfers; (2) Mold being bathed in latex; (3) Placement of temperature sensors; (4) Final product after removal of the already hardened latex from the mold.



The materials used in the manufacture and packaging of the catheter, which cannot be heated, were sterilized with ethylene oxide. On the other hand, molds can be heated and sterilized with a steam autoclave.

This device is included in restrictive surgical techniques, being applied via endoscopy, empty, within the initial third of the esophagus, 30 mm after the passage of the upper esophageal sphincter and subsequently blown up until it reaches the esophageal walls.

The catheter has small temperature sensors that are within the structure of latex. This increases the robustness of the system because the sensors do not come into contact with the external environment. There is no device similar to this in the market, because it has a matrix of sensors, properly aligned, where it is possible to interpolate the values where there is no presence of sensors.

This system is less fragile and has a far lower cost than the existing perfusion system in the market, and allows for a faster response, appropriate to the study of the thermal response of the esophagus. In conjunction with the catheter, there is a control board connected to a computer, which, in turn, via software, is able to read and analyze the data collected from the patient through the catheter. The data obtained from various measurements can be interpreted more effectively through the advanced application data, processing and data analysis.

Most cases of esophageal cancer have effective treatment with cure, provided that it is discovered and treated in the early stages of the disease. For an effective treatment, a good diagnosis equipment is necessary in order to predict, measure and interpret correctly the thermal and vascular responses to heating.

Simple Thermal Analysis via Software

Based on THE reading of temperature sensors within the catheter, it is possible to diagnose changes in thermal patterns in the organ. This tool allows for the diagnosis and quantification of lesions due to the increase of local cellular activity. In the case of cancerous tumors, the increased vascularization increases this activity even more, which allows for fast diagnosis.

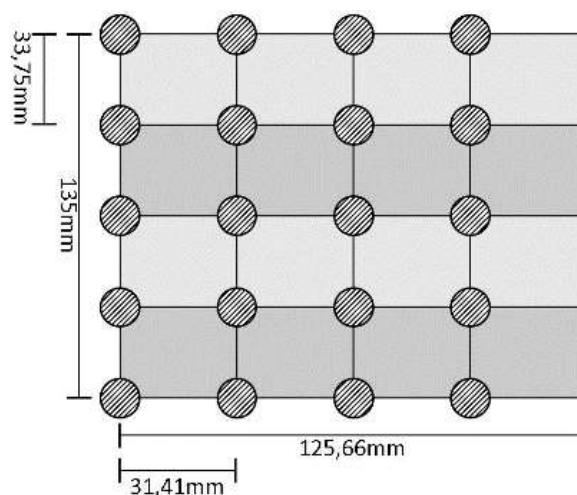


Figure 2 — Overview of the matrix arrangement of the sensors with the distances between them.

The instrumental catheter has an array of sensors arranged equidistantly from each other as shown in Figure 2 so as to allow for the interpolation of data and estimation of the values in regions where it does not have sensors. The matrix is constructed in such a way that when it is deposited on the material that is in a cylindrical mold, the matrix also assumes this form, but, in the software, the matrix is displayed in a planar form, which facilitates the interpretation of the data. Figure 3 shows a graph with random numbers of the readings of the sensors, where the reddish colors represent higher temperatures and bluish colors represent lower temperatures, where the specialist can also see in the side the numerical values of the temperatures of each sensor.

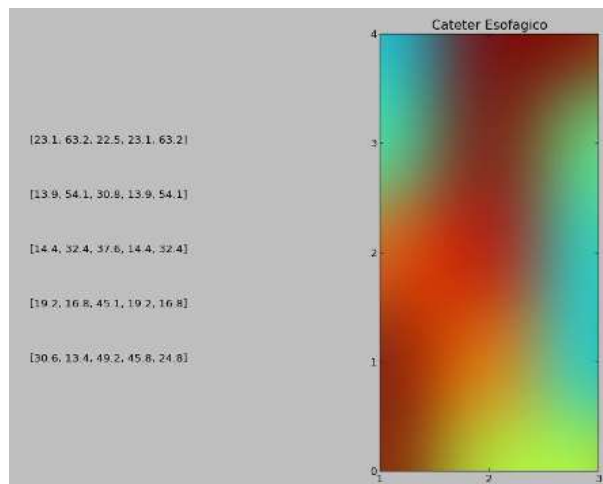


Figure 3 — Screen of the software of response to random data in the entries referring to thermal sensors. In the left side of the picture, we can see the numerical values, and in the right side, the interpolated and plotted matrix using color variation for thermal variation.

CONCLUSION

With the overall objective of this article, we came to the conclusion that esophageal lesions, which can evolve to carcinogenesis, has a direct connection with local temperature increase. With an initial proposal, the authors intend to develop an instrument to assist in the diagnosis of esophageal cancer in its early stages. From this premise, we developed an esophageal catheter with temperature sensors which allow the visualization of the thermal gradient of the esophageal walls to analyze the local variation in theoretically affected areas. Although we have obtained a numerical result, it needs to be validated with experimental data after a set of collections.

ACKNOWLEDGEMENTS

To all the staff at the University of Brasilia and colleagues of the Biomedical Engineering Laboratory – BioEngLab® for their support in all the research we perform.

REFERENCES

1. BARROS S. G. S., GHISOLFI, E. S., LUZ, L. P., BARLEM, G. G., VIDAL, R. M., WOLF, F. H., MAGNO, V. A., BREYER, H. P., DIETZ, J., GRÜBER, A. C., KRUEL, C. D. P., PROLLA, J. C. Mate (chimarrão) é consumido em alta temperatura por população sob risco para o carcinoma epidermóide de esôfago. *Arquivos de Gastroenterologia*, 37(1), p. 25-30, 2000.
2. ANDASARI, V., CHAPLAIN, M. Intracellular modelling of cell – matrix adhesion during cancer cell invasion. *Mathematical Modelling of Natural Phenomena*, 7, p. 29–48, 2012.
3. ITO, E., OZAWA, S., KIJIMA, H., KAZUNO, A., NISHI, T., CHINO, O., SHIMADA, H., TANAKA, M., INOUE, S., INOKUCHI, S., MAKUUCHI, H. New invasive patterns as a prognostic factor for superficial esophageal cancer. *Journal of Gastroenterology*, 47, p. 1279–1289, 2012.
4. GHADIRIAN P. Thermal irritation and esophageal cancer in northern Iran. *Cancer*, 60, p. 1909-14, 1987.
5. WOLF, K., TELINDERT, M., KRAUSE, M., ALEXANDER, S., TERIET, J., WILLIS, A. L., HOFFMAN, R. M., FIGDOR, C. G., WEISS, S. J., FRIEDL, P. Physical limits of cell migration: control by ECM space and nuclear deformation and tuning by proteolysis and traction force. *The Journal of Cell Biology*, 201, p. 1069–1084, 2013.
6. ROSA, S. S. R. F., ALTOÉ, M. L. Bond Graph modeling of the human esophagus and analysis considering the interference in the fullness of an individual by reducing mechanical esophageal flow. *Revista Brasileira Engenharia Biomédica*, vol.29, no.3, p.286-297, 2013.
7. MRUÉ F. “Reparo de lesões parciais do esôfago cervical utilizando biomembrana de látex natural com polilisina. Monografia do exame de qualificação da Faculdade de Medicina da Universidade de São Paulo – Ribeirão Preto, p. 33-35, 2000.
8. PROLLA J. C., DIETZ J., DA COSTA L. A. Diferenças geográficas namortalidade por câncer de esôfago no Rio Grande do Sul. *Revistada Associação Médica Brasileira*, 39, p. 217-220, 1993.



9. MELO, G., C. Metaplasia intestinal: esôfago de Barrett. *Revista de Medicina e Saúde de Brasília*, 2(3), p.177-82, 2012.
10. VOLKWEIS, B. S., GURSKI, R. R. Esôfago de Barrett: aspectos fisiopatológicos e moleculares da seqüência metaplasia displasia - adenocarcinoma. *Revista do Colégio Brasileiro de Cirurgiões Colégio Brasileiro de Cirurgiões*, 35(2), p.114-123, 2008.
11. FERREIRA J.,O., OLIVEIRA H., C., B.,e MARTINEZ M., R. Aplicação de uma metodologia computacional inteligente no diagnóstico de lesões cancerígenas. *Revista Brasileira de Inovação Tecnológica em Saúde*, v. 1, n. 2 p.04-09, 2011.
12. PIA D., DUMITRU T., ALF G., MARK A. J. C., Mathematical modelling of cancer invasion: Implications of cell adhesion variability for tumour infiltrative growth patterns, *Journal of Theoretical Biology*, Volume 361, p. 41-60, 2014. <http://dx.doi.org/10.1016/j.jtbi.2014.07.010>.
13. MONTEIRO, N. M. L., ARAÚJO, D. F. D., BASSETI SOARES, E., VIEIRA, J. P. F. B., SANTOS, M. R. M. D., JUNIOR, P. P. L. O. Câncer de esôfago: perfil das manifestações clínicas, histologia, localização e comportamento metastático em pacientes submetidos a tratamento oncológico em um centro de referência em Minas Gerais. *Revista brasileira de cancerologia*, 55(1), p. 27-32, 2009.
14. PREZIOSI, L.; TOSIN, A., "Multiphase modelling of tumour growth and extra cellular matrix interaction: mathematical tools and applications", *J. Math. Biol.* 58, 625 (2009).
15. ROSA, S. S. R. F. Desenvolvimento de um sistema de controle de fluxo esofágiano para tratamento da obesidade. Edgard Blücher, 2009.
16. MRUÉ, F. . Neo formação tecidual induzida por biomembrana de látex natural com polilisina. Aplicabilidade em neoformação esofágica e da parede abdominal. Estudo experimental em cães. Tese Doutorado Universidade de São Paulo, 2000.
17. TOKLU, E. A new mathematical model of peristaltic flow on esophageal bolus transport. *Scientific Research and Essays*, v. 6, n. 31, p. 6606–6614, 2011.
18. TRAWITZKI, L. V. V.; DANTAS, R. O.; MELLO-FILHO, F. Masticatory muscle function three years after surgical correction of class iii dentofacial deformity. *International Journal of Oral and Maxillofacial Surgery*, v. 39, p. 853–856, 2010.
19. MRUE F. Substituição do Esôfago Cervical por Prótese Biossintética de látex: estudo experimental em cães [dissertação]. Ribeirão Preto: Faculdade de Medi-cina da Universidade de São Paulo Ribeirão Preto; 1996.
20. Guyton A.C., Hall J.E. *Tratado de Fisiologia Médica*. 10ª edição, Ed. Guanabara Koogan S.A; 2002.
21. Machado, G. Esôfago. In: . [S.l.]: Rubio, 2005. cap. Aplicabilidade da Endoscopia Digestiva Alta nas Doenças Esofagianas, p. 37–68.