

## Early-stage cancer treatment, driven by context of molecular imaging (ESTIMA)

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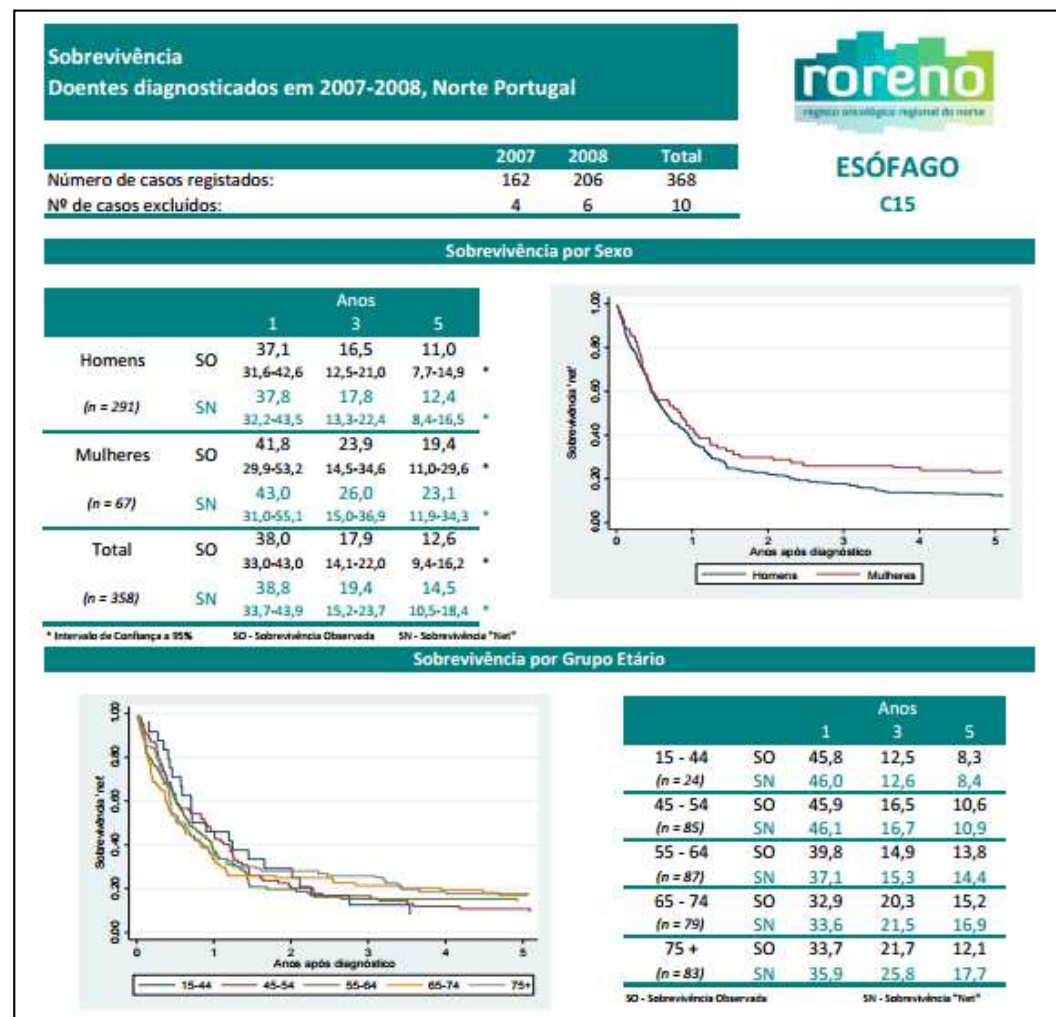
# Epidemiology of esophageal cancer

- Esophageal cancer is the 7th most commonly occurring cancer in men and the 13th most commonly occurring cancer in women world wide - 8<sup>th</sup> overall, 2014 data (*World Cancer Report 2014*); 5-year survival: 12%

- Several risk factors associated both to adenocarcinoma (e.g. smoking, obesity; gastroesophageal reflux) e and squamous cell carcinoma (e.g. smoking; alcohol consumption).

- Different incidence between countries, sex and habits.

- More prevalent in northern Portugal than in the south





# Staging

Clinical history and physical examination;

Hematologic and biochemical tests;

Upper gastrointestinal endoscopy with histologic biopsy;

Electrocardiography;

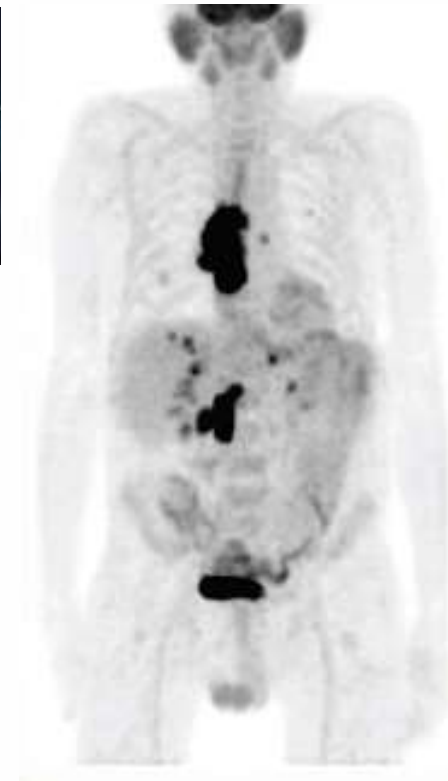
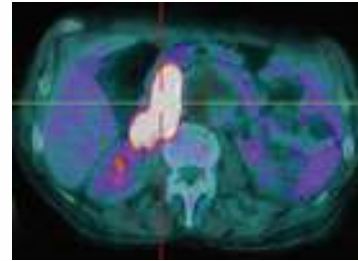
Pulmonary-function test;

Endoscopic ultrasonography (EUS);

Computed tomography (CT) of the neck, chest, and upper abdomen;

$^{18}\text{F}$ -FDG PET (fluorodeoxyglucose Positron Emission Tomography);

Bronchoscopy (if the tumour is related to respiratory tree)



# Treatment (loco-regional)

## Chemoradiotherapy + Surgery (CRT+surgery)

### Radiotherapy (day 1 - 31)

41.4 Gy /23 fraction to the planning target volume (PTV), 5 days per week

### Chemotherapy (day 1, 8, 15, 22 and 29)

Paclitaxel

Carboplatin

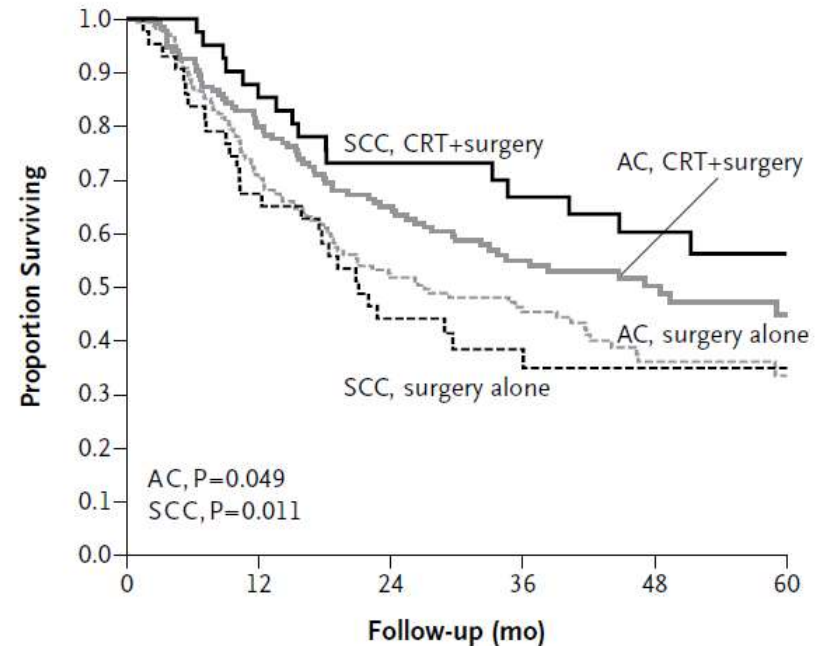
### Surgery

7 weeks after the end of radiation therapy

Complete pathological response after neoadjuvant chemoradiotherapy occurs in almost 50% for squamous carcinomas and 23% for adenocarcinomas

Complete pathological response in IPO-Porto series (n=61) is 45% for SCC and 7.7% ADC

B Survival According to Tumor Type and Treatment Group



No. at Risk

AC, CRT+surgery	134	107	87	53	34	18
AC, surgery alone	141	99	73	50	25	10
SCC, CRT+surgery	41	35	30	21	15	8
SCC, surgery alone	43	29	19	11	8	4
Total	359	270	209	135	82	40

# Objectives of the present project

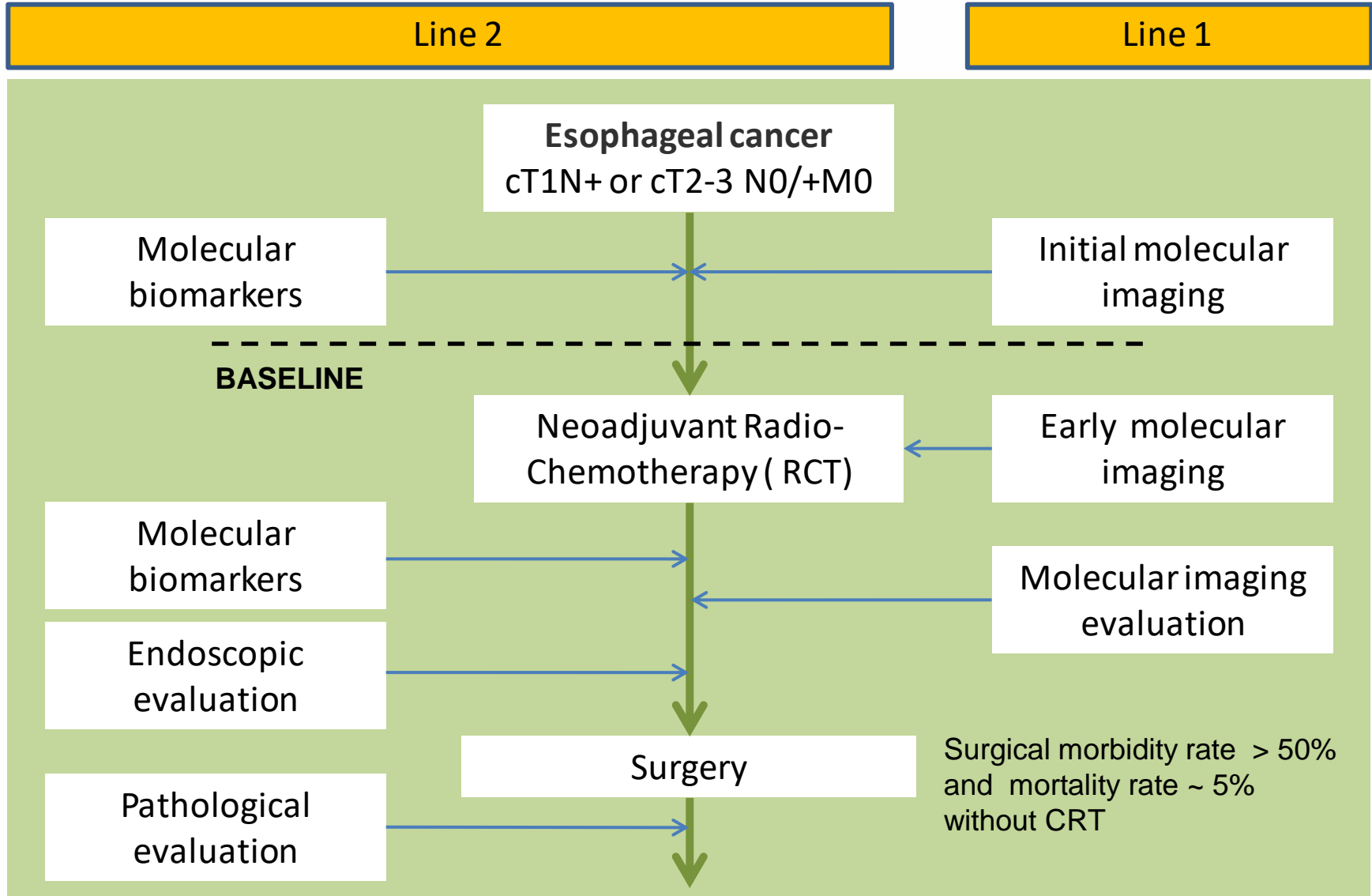
The objective of the ESTIMA project is to develop a *predictive model* of complete response to treatment of resectable esophageal cancer with *neoadjuvant chemoradiotherapy (CRT)*, based on several biomarkers to be defined, ***aiming to avoid the surgery procedure.***

The main project outcome will be the development and clinical validation of accurate criteria of complete tumor response to CRT based in *molecular imaging and biological evaluation biomarkers* (imaging, molecular, genetic, epigenetic, viral, etc.) aimed at improving the efficiency and efficacy of patient care.

For this purpose, this prospective cohort study has two investigational lines:

- **Line 1-** Diagnostic *molecular imaging*, using FDG PET/CT studies performed before, during and after CRT – *treatment response (imaging); image descriptors*
- **Line 2-** Treatment - determination of *molecular and genetic profiles* and *pathological evaluation* (after CRT and surgery – adaptation of EURECA CC2 guidelines\*)

# Overview (road map)





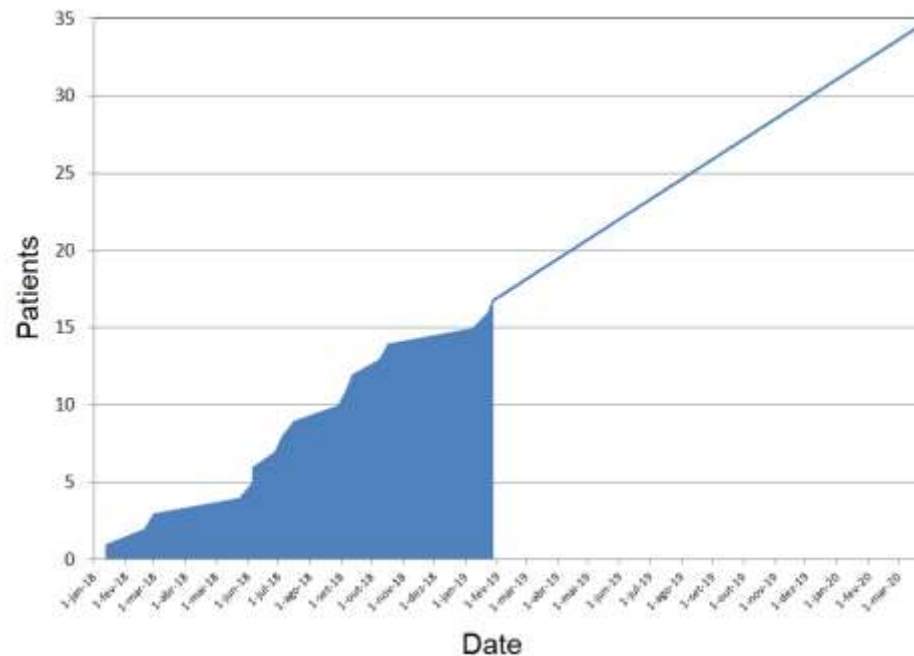
# Patient enrolment

## INCLUSION CRITERIA

- Age of 18 years to 75 years
- World Health Organization (WHO) performance status score of 0 or 1
- Diagnosis of squamous cells carcinoma, undifferentiated carcinoma or adenocarcinoma of esophageal or esophagus-gastric junction (Siewert I e II).
- Clinical Stage II or III (AJCC 7th edition) resectable disease
- Signed informed consent

## EXCLUSION CRITERIA

- Pregnant or lactating women
- Previous thoracic radiotherapy
- Impaired hematological, hepatic, renal or pulmonary functions
- Active infection or other medical conditions that prevent the planned treatment





# Research network

IPO-Porto

All clinical services of IPO-Porto following the patient pathway during their treatment (Gastroenterology, Pathologic Anatomy, Nuclear Medicine, Radiotherapy, Medical Oncology, Surgery, Epidemiology, etc.)

CI-IPO

**Cancer Genetics Group**, IPO Porto Research Center (CI-IPOP), Portuguese Oncology Institute of Porto (IPO-Porto), Porto, Portugal.

**Cancer Biology and Epigenetics Group**, IPO Porto Research Center (CI-IPOP), Portuguese Oncology Institute of Porto (IPO-Porto), Porto, Portugal.

**Molecular Oncology and Viral Pathology Group**, IPO Porto Research Center (CI-IPOP), Portuguese Oncology Institute of Porto (IPO-Porto), Porto, Portugal.

**Experimental Pathology and Therapeutics Group**, IPO Porto Research Center (CI-IPOP), Portuguese Oncology Institute of Porto (IPO-Porto), Porto, Portugal.

**Medical Physics, Radiobiology and Radiation Protection Group**, IPO Porto Research Center (CI-IPOP), Portuguese Oncology Institute of Porto (IPO-Porto), Porto, Portugal.

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## Major “heavy” equipment used in this project

### PET TOF Tomograph Siemens mCT

LSO High-Rez crystals: increased volumetric and spatial resolution  
Time-of-flight (TOF) technology: Increased image contrast  
Extended field of view (FOV) - 78 cm FOV  
Respiratory gating: Accurate quantification in thoracic tumors,  
Improved quality control and quantification  
Improved Reconstruction  
Harmonization of measured activity across patient scans (SUV)



### TrueBeam STx<sup>®</sup> linear accelerator (*co-financed by this project*)

High radiation output (FFF)  
Higher positioning accuracy  
Higher reproducibility  
Higher quality image guided treatment delivery  
Less late and acute radiotoxicity  
Sub-millimetric precision



## Publications so far (2017-2019)

- [1] Come J, Castro C, Morais A, Cossa M, Modcoicar P, Tulsidãs S, Cunha L, Lobo V, Morais AG, Cotton S, Lunet N, Carrilho C, Santos LL. Clinical and Pathologic Profiles of Esophageal Cancer in Mozambique: A Study of Consecutive Patients Admitted to Maputo Central Hospital, *J Glob Oncol*. 2018 Nov; (4):1-9. doi: 10.1200/JGO.18.00147
- [2] Gisele Pereira, Inês Domingues, Pedro Martins, Pedro H. Abreu, Hugo Duarte, and João Santos. Registration of CT with PET: a comparison of intensity-based approaches. In "International Workshop on Combinatorial Image Analysis (IWCIA)", 2018.
- [3] Inês Domingues, José P. Amorim, Pedro H. Abreu, Hugo Duarte, and João Santos. Evaluation of oversampling data balancing techniques in the context of ordinal classification. In *International Joint Conference on Neural Networks (IJCNN)*, pages 5691-5698, 2018.
- [4] Inês Domingues, Pedro H. Abreu, and João Santos. BI-RADS classification of breast cancer: a new pre-processing pipeline for deep models training. In *IEEE International Conference on Image Processing (ICIP)*, pages 1378 - 1382, 2018.
- [5] Jastin P. Soares, Miriam S. Santos, Pedro H. Abreu, H. Araújo, and João Santos. Exploring the Effects of Data Distribution in Missing Data Imputation In *International Symposium on Intelligent Data Analysis*, pp. 251-263 (2018).
- [6] Joana M.O. Santos, Sara Peixoto da Silva, Natália R. Costa, Rui Gil da Costa, Rui Medeiros "The role of microRNAs in the metastatic process of high-risk HPV-induced cancers, *Cancers* 2018, 10, 493
- [7] José P. Amorim, Inês Domingues, Pedro H. Abreu, and João Santos. Interpreting Deep Learning Models for Ordinal Problems. *European Symposium on Artificial Neural Networks, Computational Intelligence and Machine Learning*, 1(1):25(27), 2018
- [8] Marta Mercier, Miriam S. Santos, Pedro H. Abreu, C. Soares, Jastin P. Soares, and João Santos. Analyzing the footprint of classifiers in overlapped and imbalanced contexts. In *International Symposium on Intelligent Data Analysis*, pp. 200-212, 2018.
- [9] Miriam S. Santos, Jastin P. Soares, Pedro H. Abreu, and J. Santos. Influence of Data Distribution in Missing Data Imputation. In *Artificial Intelligence in Medicine in Europe (AIME)*, 2017.
- [10] Miriam S. Santos, Jastin P. Soares, Pedro H. Abreu, H. Araújo, and João Santos. Cross-Validation for Imbalanced Datasets: Avoiding Overoptimistic and Overfitting Approaches. *IEEE Computational Intelligence Magazine*, 13(4):59(76), 2018.
- [11] Natália R. Costa, Rui Gil da Costa, Rui Medeiros, A Viral Map of Gastrointestinal Cancers, *Life Sciences* 2018 Apr 15;199:188-200

### Submitted, accepted or being prepared for submission:

- Catarina Macedo-Silva\*, Vera Miranda-Gonçalves, Rui Henrique, Carmen Jerónimo, Isabel Bravo. Hypoxic microenvironment and epigenetic mechanism regulation: a critical role in radioresistance of esophageal cancer (review paper)
- Catarina Macedo-Silva, Vera Miranda-Gonçalves, Joana Lencart, Sofia Silva, Ana Lameirinhas, Rui Henrique, Isabel Bravo, Carmen Jerónimo. Role of JmJc-KDMs in hypoxic microenvironment: effect on ESCC radioresistance (original paper)
- Firass Ghareeb, Joana Lencart, Jorge Oliveira, João A. M. Santos, Characterization of extrafocal dose influence in the out-of-field dose distribution by Monte Carlo simulation and dose measurements, *Health Physics* (accepted)
- Natália Rios Costa e Rui Medeiros, Human papillomavirus and TP53 mutations in esophageal squamous cell carcinoma response to chemoradiotherapy: walk-ons or main actors? (under submission)
- Sofia Salta, Vera Miranda-Gonçalves, Catarina Macedo-Silva, Mónica Farinha, Davide Gigliano, Rita Guimarães, Olga Sousa, Rui Henrique, Carmen Jerónimo. A DNA Methylation-Based Test for Esophageal Cancer Detection (In preparation)
- Inês Domingues, Inês Lucena Sampaio, Hugo Duarte, Pedro H. Abreu and João Santos, Computer vision in esophageal cancer: a literature review (In preparation)

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