

Study Protocol

Title: Real-world incremental costs of opportunistic upper gastrointestinal endoscopy added to colorectal cancer screening and the economic burden of gastric cancer management: an economic study.

NCT:

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1. Background and Rationale

Gastric cancer remains a major cause of cancer-related mortality in Europe[1], with diagnosis frequently occurring at advanced stages, leading to substantial clinical and economic burden. Opportunistic strategies integrating upper gastrointestinal endoscopy (esophagogastroduodenoscopy) (EGD) with organized colorectal cancer screening have been proposed as a pragmatic approach to improve early detection in intermediate-risk countries [2], [3], [4], [5].

In Portugal, a cost–utility analysis model by Areia et al. demonstrated that combining EGD with colonoscopy in individuals with positive fecal immunochemical testing (FIT) may represent a cost-effective strategy, whereas stand-alone gastric cancer screening was not [2]. However, evidence based on real-world cost data from clinical practice remains limited.

The number needed to screen (NNS) is defined as the inverse of the absolute risk reduction (ARR) in gastric cancer-related mortality between screened and non-screened populations. The ARR represents the attributable risk difference, calculated as the difference in mortality risk between individuals not undergoing screening and those undergoing endoscopic screening. [6].

Early-stage gastric cancer is associated with less intensive treatment and substantially lower healthcare costs compared to advanced disease, supporting the hypothesis that stage shift may result in economic benefit [4].

This study aims to estimate and compare:

1. the incremental direct medical cost per participant attributable to the addition of an opportunistic EGD performed during an already scheduled colorectal cancer screening colonoscopy following a positive FIT result.
2. the real-world costs associated with the diagnosis and management of gastric cancer over a 10-year period in the same institution.

2. Objectives

1. To estimate the total incremental cost of the opportunistic EGD screening component during the study period.
2. To estimate the mean and total real-world costs of gastric cancer management, overall and stratified by disease stage and treatment intent.

3. To describe treatment pathways and clinical outcomes of gastric cancer patients.
4. To identify major cost drivers of gastric cancer management.
5. To compare the total cost of opportunistic screening plus treatment of early-stage gastric cancer (stage I) with the cost of treatment of advanced-stage disease (stage II–IV or III–IV).
6. To estimate the potential cost savings associated with stage shift induced by opportunistic screening.
7. Estimated cost per stage shift (i.e., cost required to convert one advanced-stage diagnosis into an early-stage diagnosis).

3. Study Design

This is a real-world cost analysis based on two observational cohorts:

1. **Cohort A – Opportunistic screening cohort**

A cohort of FIT-positive individuals undergoing colonoscopy for colorectal cancer screening, with the addition of opportunistic EGD during the same procedure.

2. **Cohort B – Gastric cancer cohort**

A retrospective cohort including all patients diagnosed with gastric adenocarcinoma in the institution over a 10-year period.

The observational components will be reported according to **STROBE** guidelines, and the economic components according to **CHEERS** recommendations. When routinely collected healthcare data are used, **RECORD** principles will be followed.

4. Setting

The study will be conducted at Unidade Local de Saúde do Alto Alentejo, Portugal, including two centers participating in the opportunistic screening strategy.

5. Perspective, Time Horizon, and Currency

Perspective

The primary analysis will adopt the healthcare provider / National Health Service (SNS) perspective, including direct medical costs only.

Time Horizon

- **Screening cohort:** from February 2023 to February 2025.

- **Gastric cancer cohort:**
 - cumulative costs from diagnosis to death or end of 5-years follow-up.

Currency and Price Year

All costs will be expressed in euros (€) and adjusted to a common price year (March 2026), using appropriate inflation indices when necessary.

6. Study Population

Cohort A – Opportunistic Screening

Inclusion criteria

- Eligible participants were adults aged 50 to 75 years or older who had been referred for colonoscopy as part of the national colorectal cancer screening programme, following a positive FIT. To be included, individuals also needed to provide informed consent and agree to undergo an EGD endoscopy for the screening of potential upper gastrointestinal precancerous conditions or lesions.

Exclusion criteria

- Exclusion criteria included a prior diagnosis of gastric cancer, as well as any condition that would prevent the safe performance of the EGD or the collection of gastric mucosal biopsies. Previous EGD was not listed as an exclusion criterion.

Index date

- Date of the combined colonoscopy + EGD procedure.

Cohort B – Gastric Cancer

Inclusion criteria

- Patients with gastric adenocarcinoma, diagnosed and treated at Unidade Local de Saúde do Alto Alentejo between 2015 and 2020.

Exclusion criteria

- Other types of gastric tumors.
- Gastric involvement from metastatic disease of another primary tumor.

Index date

- Date of pathological diagnosis of gastric cancer.

7. Data Sources

Data will be extracted from routinely collected hospital databases, including:

- Electronic medical records;
- Endoscopy and pathology databases;
- Surgical and hospitalization records;
- Oncology treatment databases;
- Imaging and diagnostic services;
- Institutional mortality records.

When multiple sources are available, predefined rules will be applied to resolve discrepancies.

8. Variables Collected

For economic comparison purposes:

- Early-stage gastric cancer will be defined as stage I disease
- Advanced-stage gastric cancer will be defined as stage II–IV (or alternatively III–IV in sensitivity analysis)

Screening Cohort

- Demographics (age, sex).
- Procedure characteristics (EGD and colonoscopy completeness, sedation).
- Endoscopic findings and biopsies.
- Pathology results.
- Complications and related hospitalizations.
- Follow-up procedures directly related to screening.

Gastric Cancer Cohort

- Demographics.
- Tumor characteristics and stage at diagnosis (TNM/AJCC).
- Treatment intent (curative vs palliative).
- Treatments received (surgery, chemotherapy, radiotherapy, palliative).
- Number of consultations and hospital admissions.
- Dates of death and overall survival.

Data will be anonymized prior to analysis, and access to identifiable information will be restricted to authorized investigators only.

9. Costing Methodology

Costing Approach

A hybrid costing approach will be used, quantifying healthcare resource utilization at the individual patient level and multiplying by unit costs.

Unit Costs

Unit costs will be obtained from official national tariffs and/or institutional accounting systems. Alternative cost sources will be explored in sensitivity analyses.

Incremental Cost Definition for the Screening Strategy

The economic evaluation will estimate only the additional costs generated by the opportunistic EGD, assuming that colonoscopy, sedation, and baseline procedural infrastructure were already required for colorectal cancer screening.

Accordingly, the following incremental resources will be considered:

- EGD procedure and reprocessing;
- Disposable biopsy forceps;
- Specimen collection containers;
- Histopathological processing and analysis of gastric biopsies.

Costs related to colonoscopy performance, sedation, patient preparation, recovery, and baseline endoscopy unit operation will not be included, as these would occur regardless of the addition of EGD.

Direct estimation of marginal infrastructure costs (procedure room occupancy time, utilities such as electricity and water, and personnel time) may not be individually measurable within routine accounting systems. Therefore, these components will be considered implicitly incorporated within institutional procedure tariffs when applicable.

Cost Estimation – Gastric Cancer Cohort

Healthcare resource utilization will be collected at the individual patient level and will include:

- Surgical treatment episodes, including operating room procedures and consumables;
- Systemic therapy regimens, number of treatment lines, and cycles administered;
- Radiotherapy treatments (number of fractions or total dose);
- Hospitalizations related to cancer treatment or complications;
- Day-hospital oncology episodes;
- Outpatient consultations related to gastric cancer management.

Unit costs for surgical procedures, systemic therapy administration, hospitalizations, outpatient visits, and radiotherapy will be obtained from institutional accounting systems and/or official national tariffs.

Follow-up diagnostic examinations will be included in the economic model using a standardized surveillance schedule based primarily on NCCN recommendations, while acknowledging that real-world follow-up is heterogeneous and that ESMO recommends an individualized approach. In line with ESMO guidance, regular follow-up is considered appropriate for symptom assessment, psychological support, and early detection of recurrence, but ESMO does not define a detailed

surveillance timetable. Therefore, for costing purposes, a pragmatic NCCN-based schedule will be adopted.

For all patients undergoing curative-intent treatment, clinical follow-up visits will be assumed every 6 months during years 1–2 and annually during years 3–5, corresponding to a total of 7 follow-up consultations over 5 years. A complete blood count and basic chemistry panel will be costed at each scheduled visit as a standardized analytical assumption, although laboratory tests are described in the guideline as clinically indicated rather than mandatory.

For stage II–III disease, contrast-enhanced CT of the chest, abdomen and pelvis will be assumed every 6 months during the first 2 years and annually thereafter until year 5, totaling 7 CT scans. For stage I disease, routine CT surveillance will not be included in the base-case analysis and imaging will be considered only if clinically indicated.

Routine endoscopic surveillance will not be included in the base-case model. In accordance with NCCN-based follow-up principles, upper gastrointestinal endoscopy will be considered only when clinically indicated, and routine endoscopy after total gastrectomy will not be assumed. Given persistent variation in practice regarding surveillance of the gastric remnant after subtotal gastrectomy, endoscopy may instead be explored in sensitivity analyses.

PET/CT will not be included as a routine surveillance examination and will be reserved for problem-solving in cases of suspected recurrence or equivocal findings on conventional imaging.

Because guideline recommendations for postoperative gastric cancer surveillance remain heterogeneous and several investigations are classified as clinically indicated, the study will use a base-case standardized schedule and test alternative surveillance intensities in sensitivity analyses.

Comparative Economic Analysis

A comparative analysis will be conducted to evaluate the economic implications of stage shift associated with opportunistic screening.

The following comparison will be performed:

- **Strategy A (Screening scenario):** Incremental cost of opportunistic EGD screening + cost of diagnosis and treatment of stage I gastric cancer.
- **Strategy B (No screening / usual care scenario):** Cost of diagnosis and treatment of advanced-stage gastric cancer (stage II–IV).

Mean per-patient costs will be estimated for each stage group using real-world data from the gastric cancer cohort.

The analysis will estimate:

- Cost difference between early-stage and advanced-stage disease
- Incremental cost required to detect one stage I cancer
- Potential cost offsets associated with earlier diagnosis

The previously defined number needed to screen (NNS) will be incorporated as an external effectiveness input in the comparative economic analysis and explored in sensitivity analyses. The NNS parameter will be explored in sensitivity analyses to account for uncertainty in screening effectiveness.

Costs from the screening cohort and gastric cancer cohort will be integrated analytically to model the economic impact of early detection.

Optional Societal Costs (Exploratory Analysis)

Indirect costs related to productivity losses due to work absenteeism and premature mortality may be explored in secondary analyses using publicly available national wage statistics. These estimates will be considered exploratory due to limitations inherent to retrospective data collection, and use of assumptions due to the general lack of available data.

The study does not directly estimate cost-effectiveness metrics such as QALYs, limiting full health economic evaluation.

10. Outcomes

Economic Outcomes

- Incremental cost per screening EGD.
- Incremental cost per early-stage gastric cancer detected.
- Total and mean incremental screening cost per patient.
- Total and mean cost per gastric cancer patient.
- Costs stratified by stage and treatment intent.
- Cost difference between early and advanced-stage disease.
- Estimated cost savings per patient associated with stage shift.

Clinical Outcomes

- Stage distribution at diagnosis.
- Treatment patterns.
- Overall survival.

11. Statistical Analysis

Costs will be summarized using means, medians, and interquartile ranges. Confidence intervals for mean costs will be estimated using non-parametric bootstrap methods. Missing data patterns will be described and addressed using appropriate methods.

12. Ethical Considerations

The study will be conducted in accordance with national regulations and approved by the institutional ethics committee. Data will be pseudonymized, and no direct patient contact will occur.

All participants in the opportunistic screening cohort provided informed consent at the time of inclusion in the screening programme. Patients in the gastric cancer cohort had previously provided informed consent for the use of their clinical data in research, including prior institutional studies (e.g., MGPT study).

The current study will use fully anonymized data, and no additional patient contact, intervention, or data collection beyond routine clinical records will be performed.

13. Strengths and Limitations

This study provides real-world cost data from routine clinical practice but is limited by its retrospective design and lack of a contemporaneous non-screened comparator.

14. Expected Impact

The results will inform decision-makers on the economic burden of gastric cancer and the potential budgetary implications of implementing opportunistic combined endoscopic screening strategies in intermediate-risk settings.

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