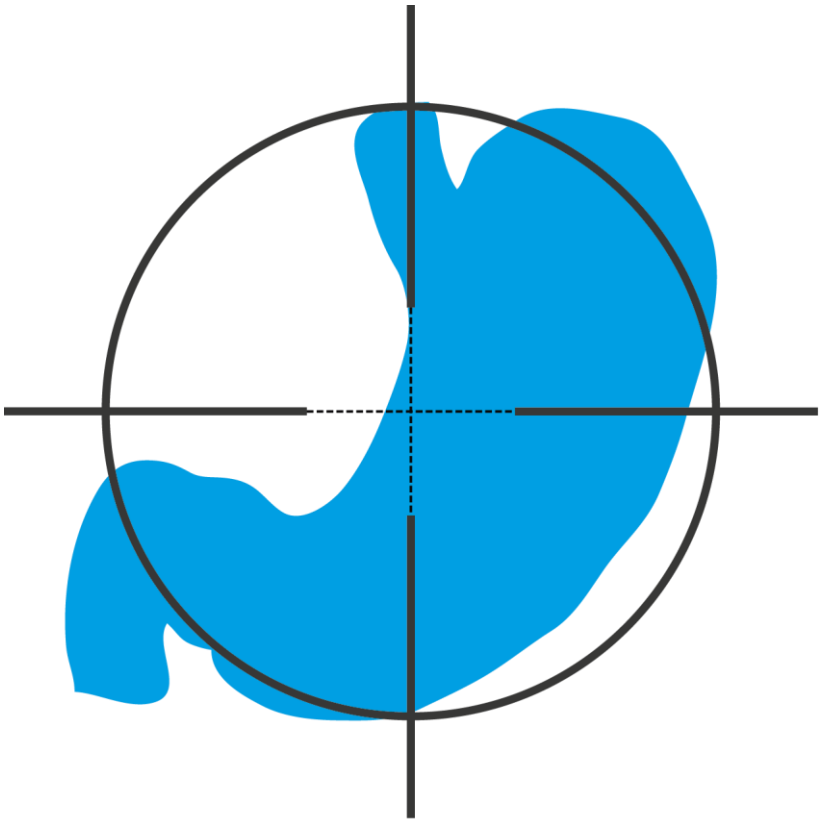
Evaluation of PET and Laparoscopy in STagIng advanced gastric Cancer: a multicenter prospective study



PLASTIC-study

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PROTOCOL TITLE

Evaluation of PET and Laparoscopy in STagIng advanced gastric Cancer: a multicenter prospective study

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SUMMARY

Objective: To evaluate the impact and cost-effectiveness of FDG-PET/CT (PET) and diagnostic laparoscopy (DLS) in addition to initial staging by CT and gastroscopy in patients with advanced gastric cancer.

Hypothesis: The study hypothesizes that performing DLS and PET for advanced gastric adenocarcinomas results in a reduction in the number of futile gastrectomies performed and a favorable cost-effectiveness. According to the literature, in 27% of patients a futile gastrectomy can be prevented, and the annual cost-reduction is an estimated €916.438.

Study design: The study design is a prospective observational study.

Study population: The study population consists of patients with a surgically resectable, advanced gastric adenocarcinoma (cT3-4b,N0-3,M0), who are scheduled for treatment with curative intent after initial staging with gastroscopy and CT.

Intervention: The intervention to be investigated in this study is the addition of both PET and DLS to the initial staging with gastroscopy and CT of patients with an advanced tumor (cT3-4).

Usual care / comparison: Both PET and DLS were recently included in the new Dutch guidelines for the treatment of gastric cancer, as staging modalities for advanced (T3-4) tumors after initial staging. The costs of the study population will be compared to retrospective data of patients who underwent curative surgery (gastrectomy) after initial staging with CT alone.

Outcome measures: The primary outcome of this study will be the proportion of patients in whom the PET or DLS lead to a change in treatment strategy from curative to palliative intent. The accuracy of each modality will be analyzed separately. Secondary outcome parameters will be diagnostic performance, morbidity and mortality, quality of life, cost-reduction and cost-effectiveness.

Sample size: Based on the expectation that 22% of patients will have a change in treatment strategy, at least 239 patients will be needed for this study to demonstrate that addition of the diagnostic modalities in the new guideline are break-even in comparison with the situation before the new guideline. Approximately 543 patients will be eligible for the study in 36 months.

Cost-effectiveness analysis: A state-of-the-art cost-effectiveness analysis and budget impact analysis will be performed on the additive value of PET and DLS by both prospective and retrospective data collection

1. INTRODUCTION AND RATIONALE

Gastric cancer treatment

Gastric cancer is the fifth most common type of cancer worldwide[1]. In the Netherlands, each year approximately 1500 patients are diagnosed with gastric cancer[2]. Curative treatment consists of gastrectomy with perioperative chemotherapy[3]. Unfortunately, as most tumors are already metastasized or irresectable, only around 500 (33%) eventually undergo a curative gastrectomy[4]. In addition, the prognosis of patients who underwent curative treatment remains relatively poor, with a 5-year overall survival rate of 20-40%, which is mainly due to tumor recurrence[3, 5]. As a result, the corresponding disease burden of gastric cancer is large, and has been estimated to be 19 Years-of-Life-Lost and 21 Disability-Adjusted Life-Years per patient[6].

Health care efficiency problem

The standard diagnostic work-up of patients with gastric cancer includes a gastroscopy to assess tumor size, location and to get tissue to further characterize the tumor. Furthermore, computed tomography (CT) of the thorax and abdomen is performed to detect metastases. However, the accuracy of CT for detecting metastasized disease (M1) is low: the sensitivity to detect peritoneal metastases is 22%-33% and to detect distant metastases is 14%-65% [7-9]. As a result, two situations may occur in practice:

1. Unexpected intraoperative peritoneal metastases are found at the onset of gastrectomy, occuring in approximately 19% of patients[10].
2. Early distant metastases present shortly after treatment with curative intent, including neoadjuvant chemotherapy and surgery, occurring in approximately 10% of patients[10].

Both situations are undesirable, as they express unfavorable treatment decisions and overtreatment, which lead to a reduced quality of life in patients and an increase in health care costs.

Standard of care: new Dutch guideline

To reduce the number of patients ending up in one of the above mentioned situations, the new Dutch guidelines for the treatment of gastric cancer recently included two new staging modalities in addition to initial staging of advanced (T3-4) tumors: diagnostic laparoscopy to detect peritoneal metastases and FDG-PET/CT to detect distant metastases[11]. However, as the guidelines also indicate, the evidence for both staging modalities is weak, and additional research is warranted to investigate the cost-effectiveness and applicability in the Dutch situation.

2. OBJECTIVES

The aim of the current study is to evaluate the impact and cost-effectiveness of diagnostic laparoscopy and FDG-PET/CT in patients with advanced gastric cancer. The combination of diagnostic laparoscopy and FDG-PET/CT in patients with advanced (cT3-4) tumors is estimated to prevent unnecessary surgery in 27% of patients, but evidence is scarce.

3. HYPOTHESIS

The study hypothesizes that adding diagnostic laparoscopy and FDG-PET/CT to the diagnostic work-up of advanced gastric adenocarcinomas results in a reduction in the number of futile gastrectomies performed and a favorable cost-effectiveness. According to the literature, the number of prevented futile gastrectomies is estimated to be around 27%[10], and the annual cost-reduction is an estimated €916.438 for the Netherlands. This trial will consider the addition of both treatment modalities clinically relevant and cost-effective if it leads to a reduction in futile gastrectomies without unreasonable extra burdens for patients, and if it leads to an overall cost-reduction.

4. RESEARCH QUESTION

What are the clinical impact and cost-effectiveness of diagnostic laparoscopy and FDG-PET/CT in the diagnostic work-up of advanced gastric cancer?

5. STUDY DESIGN

Design

The study design is a prospective observational study. All patients with an advanced tumor that are candidates for curative gastrectomy, as determined by the local multidisciplinary team meeting (first MDT), will be included in this study. An advanced (cT3-4) tumor is defined as a transmural tumor invading the outer layer of the stomach, as described on CT (table 1)[12].

Intervention

The intervention to be investigated in this study is the addition of both FDG-PET/CT and, if indicated, diagnostic laparoscopy to the initial staging with gastroscopy and CT of patients with an advanced tumor (cT3-4).

Patients will undergo diagnostic laparoscopy and FDG-PET/CT according to the recently revised Dutch guidelines. All patients will first undergo FDG-PET/CT, followed by a diagnostic laparoscopy. This order was chosen as it is more applicable in clinical practice for the following reasons:

- FDG-PET/CT is non-invasive, whereas diagnostic laparoscopy is invasive and is accompanied by a higher risk for the patients
- FDG-PET/CT is scheduled easier and therefore likely results in less diagnostic delay
- In a theoretical model from a previous study, performing a FDG-PET/CT first resulted in more cost savings compared to a diagnostic laparoscopy approach first (difference $2168 per patient[10]).
- Assessing the FDG-PET/CT after diagnostic laparoscopy will be less reliable, due to uptake of FDG in postoperative inflammation.

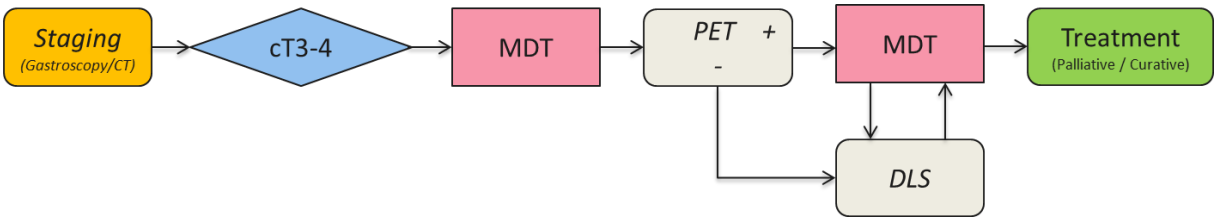

Figure 1. cT3-4: advanced tumor with clinical T-stage 3 or 4.; MDT: Multidisciplinairy Team; PET: FDG-PET/CT; DLS: Diagnostic Laparoscopy.

6. STUDY POPULATION

6.1 Population (base)

The study population consists of patients with a surgically resectable, advanced gastric adenocarcinoma (cT3-4b,N0-3,M0), who are scheduled for treatment with curative intent after initial staging with gastroscopy and CT. Differentiation between cT2 and cT3 tumors is not always possible with initial staging. In case there is considerable doubt whether a tumor is cT2 or cT3, patients may be included if deemed appropriate by the MDT.

6.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following inclusion criteria:

- Histologically proven adenocarcinoma of the stomach or esophagogastric junction (Siewert III), by gastroscopy.
- Underwent evaluation with computed tomography (CT) of the abdomen and chest.
- Surgically resectable, advanced tumor (cT3-4b,N0-3,M0), as determined by a multidisciplinary team meeting. Intention to perform a curative gastrectomy

T – Primary tumor	
T1a	Lamina propria
T1b	Submucosa
T2	Muscularis propria
T3	Subserosa
T4a	Perforates serosa / visceral peritoneum
T4b	Ingrowth in adjacent structures

N – Regional lymph nodes	
N0	No regional lymph node metastasis
N1	1-2 lymph node metastasis
N2	3-6 lymph node metastasis
N3a	7-15 lymph node metastasis
N3b	≥16 lymph node metastasis

M – Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

TNM7 classification UICC, www.uicc.org

6.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Siewert type I-II esophagogastric junction tumor
- Unfit or unwilling to undergo surgery

6.4 Sample size calculation

To calculate the sample size of this study, a break-even analysis was performed of the expected efficacy of the new guideline (figure 1). The costs of all diagnostic modalities were determined with help from the UMC Utrecht business office, and amounted to 1.500 euros for FDG-PET/CT, 750 euros for a biopsy to confirm a positive FDG-PET/CT, and 2.500 euros for diagnostic laparoscopy. The cost of gastrectomy along with all associated hospital costs was determined by the company X-IS, which is specialized in value-based healthcare, and was 25.000 euros. Based on the previous study by Smyth et al, it is expected that 27% of the patients will have a change in treatment strategy due to either FDG-PET/CT or diagnostic laparoscopy, and will not need to undergo gastrectomy[10]. In our sample size analysis, we included a safety margin of 5%, thus expecting that 22% of patients will have a change in treatment strategy. The lower border of the 95% CI of this 22% was used to calculate the break-even point for this analysis, to be sure for 97,5% that the new guideline is indeed cost-effective. Based on these figures, a minimum amount of 217 patients need to be included in this study (break-even point at 17%, based on the 95% CI [17% - 28%]). Taking into account a possible drop-out of 10%, the sample size of this study will be set at 239 patients. It must be stressed that the costs used for the sample size calculation are approximations and can deviate from reality, but are the best available. Taking that into account, and the fact that the study design is a prospective registration study without any risk or burden to the patient in addition to standard of care, this study will not be stopped after the sample size number is reached, but aims to include as many patients for 3 years to make the results as valid as possible.

7. TREATMENT OF SUBJECTS

7.1 Initial staging

Initial staging should be performed according to national guidelines, including at least a gastroscopy with tumor biopsies and a CT scan of the thorax and abdomen. Endoultrasonography (EUS) is advised if no differentiation between cT-stages can be made on the CT scan. After initial staging, patients will be discussed in the MDT. In case of a cT3-4 tumor (defined as a transmural tumor invading the outer layer of the stomach[12]), patients may then be approached to participate in this study. Differentiation between cT2 and cT3 tumors is not always possible with initial staging. In case there is considerable doubt whether a tumor is cT2 or cT3, patients may be included if deemed appropriate by the MDT. More information on the inclusion and registration of patients can be found in chapter 9.

Stage (depth of invasion)	New MDCT criteria
T1a (mucosa)	Tumour shows enhancement and/or thickening of the inner mucosal layer, as compared to the adjacent normal mucosal layer, with an intact low-density-stripe layer
T1b (submucosa)	Disruption of the low-density-stripe layer (less than 50% of the thickness) is visualised
T2 (muscularis propria)	Disruption of the low-density-stripe layer (greater than 50% of the thickness) is visualised without abutting on the outer, slightly high-attenuating layer
T3 (subserosa)	Discrimination between the enhancing gastric lesion and the outer layer is visually impossible, and a smooth outer margin of the outer layer or a few small linear strandings in the perigastric fat plane are visualised
T4a (serosa)	An irregular or nodular outer margin of the outer layer and/or a dense band-like perigastric fat infiltration is visualised
T4b (adjacent structures)	Obliteration of the fat plane between the gastric lesion and the adjacent organs or direct invasion of the adjacent organs

Table 1. New MDCT criteria for the tumour staging of gastric cancer (TNM-7)

Treatment of subjects will be performed according to standard of care as recommended by the Dutch national guideline[11]. In order to conduct all diagnostic modalities uniformly, the following protocols have been created:

7.2 FDG-PET/CT

Patient preparation and scan acquisition / reconstruction

Preferably, the FDG-PET/CT will be performed after a first MDT. Due to logistic reasons, performing the FDG-PET/CT before the first MDT is allowed as well, in case of high

suspicion of a cT3-4 tumor by the radiologist. Preparation of patients for FDG-PET/CT, scanning and image reconstruction may all be performed according to the institutional protocols of the participating centres, preferably incorporating EANM and/or NVNG guidelines[13].

In general, patients will have to refrain from strenuous exercise, and fast for at least 4 to 6 hours before the injection of FDG. Patients should be prehydrated by drinking approximately 1 L of water in the 2 h before injection. Fasting blood glucose should preferably be below 11 mmol/L. After the injection of FDG, patients should remain seated or lying and silent for 1 h in a warm room. The acquisition of a PET scan from eyes to thighs should be started 60 min (range 55 - 75 min) after the injection of FDG, being accompanied by a low-dose CT of the same scanning range.

In some institutions, all PET scans are made with a standard-dose diagnostic CT with intravenous contrast. This is allowed in this study, although it is not preferable from a perspective of radiation protection and kidney protection, since all patients have already undergone a diagnostic CT shortly before the PET/CT for standard staging of their gastric cancer.

Scan interpretation and follow-up

Scans are read, interpreted and reported by the nuclear medicine physicians of the respective participating centres. The report generally includes information regarding:

- primary tumor visible on PET: yes / dubious / no, SUVmax (if the tumor is not visible, the SUVmax of the stomach wall can be reported), and location
- locoregional lymph nodes visible on PET: yes / dubious / no, and location
- suspicion of distant metastases: yes / dubious / no, and location

The results of the PET/CT are discussed in the institutional MDT. If PET/CT identifies new lesions that are possible metastases, biopsy and/or additional imaging of a lesion is advised to confirm or exclude metastasis.

7.3 Diagnostic Laparoscopy

Diagnostic laparoscopy will be performed after FDG-PET/CT, prior to the initiation of treatment, and should be executed or supervised by a gastrointestinal or oncological surgeon. In a side-study, the influence of the type of hospital and execution by the surgeon or a resident on the quality of the laparoscopy will be investigated.

Surgery

During diagnostic laparoscopy, there are 2 goals:

1. To evaluate the resectability of the primary tumor (T-stage)
2. To evaluate the presence or absence of peritoneal metastases

To evaluate the resectability of the tumor, a thorough inspection of the stomach and tumor along with surrounding organs should be performed. To evaluate the presence or absence of peritoneal metastases, all 4 quadrants of the peritoneal cavity should be thoroughly inspected. In case of a tumor localized at the posterior wall of the stomach, it is advised to open the omental bursa and inspect it accordingly. In case of suspicious macroscopic lesions, biopsies will be taken and sent for pathological review. Macroscopic lesions will be scored according to the peritoneal cancer index (PCI, figure 2).

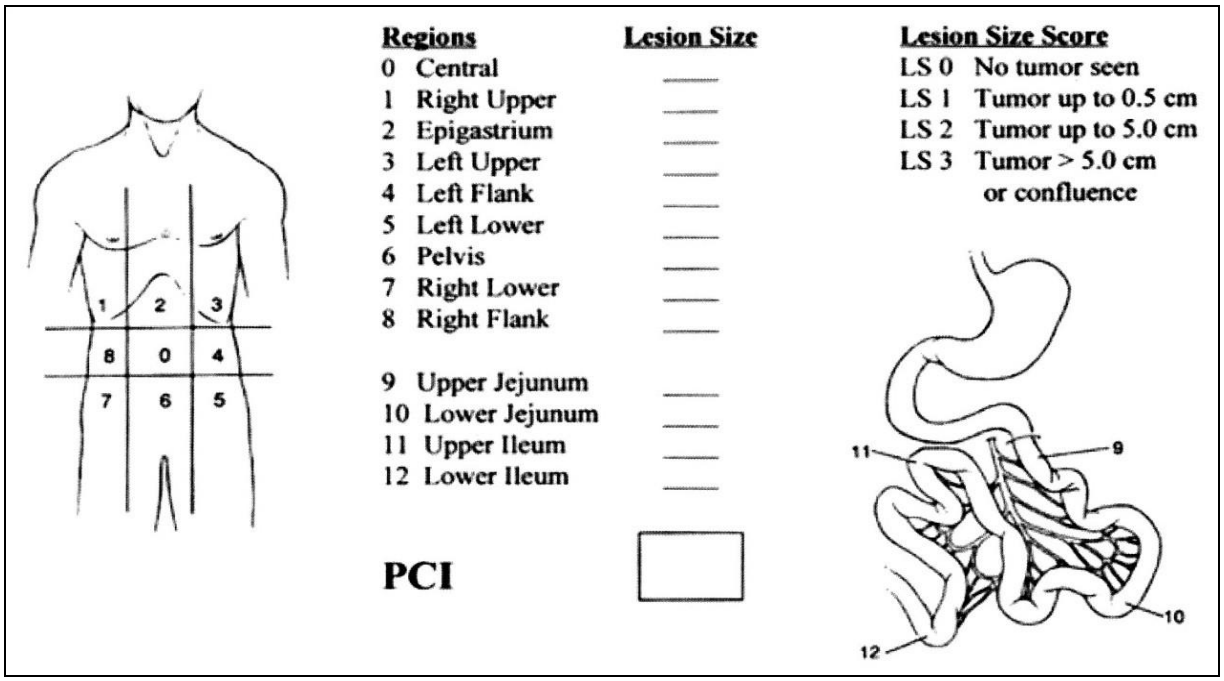

Figure 2. Peritoneal Cancer Index (PCI)

Although it is not part of the revised guidelines, all centers participating in this study are recommended to perform cytology of the peritoneal cavity, as this reflects microscopic M1-disease. In case of performing peritoneal cytology, at least 500ml of saline should be introduced and equally dispersed throughout the peritoneal cavity in all quadrants and the omental bursa if opened[14]. After collection, the samples will be sent for pathological review.

Pathology

Pathological review of potential peritoneal metastases and/or cytology will be analyzed by a dedicated gastrointestinal pathologist. Histological peritoneal samples should be sectioned and stained with haematoxylin & eosin (H&E). Peritoneal cytology should be evaluated with conventional smear cytology and with cell blocks of the remaining peritoneal lavage. If

necessary, additional immunohistochemical stainings will be performed (e.g. EpCam and/or calretinin)[15].

7.4 Treatment

Preferably, results from the FDG-PET/CT and diagnostic laparoscopy will be discussed in a second MDT. In most of the cases, during this MDT treatment decisions will be made. In some cases, a second MDT may be omitted if the results of the FDG-PET/CT and diagnostic laparoscopy are negative. Occasionally, extra diagnostics will be required and the patient will be discussed during a third MDT.

After staging patients as described above (according to the Dutch national guidelines[11]), they will continue for treatment. No neo-adjuvant treatment or gastrectomy may be performed before completion of staging. Besides adherence to these guidelines, there are no restrictions on any specific treatment strategies, such as chemotherapy regimen or type / approach of resection. In particular, although positive peritoneal cytology is considered M1-disease according to the TNM-7[16], treatment of these patients will not be restricted in the study protocol due to limited evidence. In patients with limited peritoneal disease, clinicians are advised to consult the principal investigators of the PERISCOPE trial (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4250) for the possibility of hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreduction.

Patients with M1 disease (distant metastases or peritoneal metastases) will not undergo curative gastrectomy. Palliative gastrectomy or HIPEC may be performed at the discretion of the surgeon and according to the patient's preference, and will be documented. For patients with positive peritoneal cytology only no restrictions will be imposed for treatment.

The results from the FDG-PET/CT and diagnostic laparoscopy, and if applicable the change in treatment plan (e.g. from curative to palliative) will be recorded. Cost-effectiveness will be calculated, taking all relevant health-related costs into account, including costs arising from complications of medical treatment, and additional diagnostics arising from findings on FDG-PET/CT.

METHODS

7.5 Study parameters/endpoints

7.5.1 Main study parameter/endpoint

The primary outcome of this study will be the proportion of patients in whom the FDG-PET/CT and/or diagnostic laparoscopy lead to a change in treatment strategy from curative to palliative intent. This will include the proportion of patients in whom unnecessary gastrectomy is prevented, and the proportion of patients in whom the chemotherapy regimen is changed from a curative to a palliative regimen.

7.5.1 Secondary study parameters/endpoints

As secondary outcomes parameters, modality-specific performances will be scored:

- The diagnostic performance of both modalities to detect M1 disease. False negative is defined as pM1 at pathological evaluation or the occurrence of metastases within 6 months after performing the diagnostic test; false-positive is defined as a positive diagnostic test, but a negative result on pathological evaluation or follow-up.
- Incidental findings on FDG-PET/CT

Furthermore, the patients' extra burden of the diagnostic modalities will be evaluated:

- Morbidity and mortality of diagnostic laparoscopy
- Diagnostic delay (time between pre-diagnostic and post-diagnostic MDTs)
- The number of extra MDT's held besides the 2 which are routinely planned

Finally, the overall quality of life of patients and cost-effectiveness of the treatment modalities will be evaluated:

- Quality of life (EORTC-QLQ-C30, EORTC-QLQ-OG25, E Q-5D-5L)
- Cost-effectiveness

A subgroup analysis will be performed regarding the diagnostic performance of both diagnostic modalities for different tumor types (Lauren classification: diffuse, intestinal).

7.5.2 Comparison

Both FDG-PET/CT and diagnostic laparoscopy were recently included as staging modalities in addition to initial staging in the new Dutch guidelines for the treatment of gastric cancer of advanced (T3-4) tumors. However, the evidence for both staging modalities is weak, and additional research is warranted to investigate the cost-effectiveness and applicability in the Dutch situation. The additional value of each of these modalities will therefore be evaluated. The costs of the study population will be compared to retrospective and/or prospective data from the LOGICA study group, including patients who underwent curative surgery

(gastrectomy) after initial staging with gastroscopy and CT (without diagnostic laparoscopy and PET).

7.5.3 Data-analysis

The primary outcome measures will be presented as percentages. To objectify the performance of diagnostic laparoscopy and FDG-PET/CT, sensitivity and specificity will be calculated. For FDG-PET/CT, tumor biopsies will be the gold standard to exclude fals-positives, and follow-up at 6 months will be the gold standard to exclude false-negatives. The quality of life of patients will be compared to the literature and a retrospective cohort of patients who developed peritoneal metastases or distant metastases within 1 year after surgery. Differences are tested using linear mixed-effects modeling, taking relevant patient characteristics into account. Missing values will be imputed using multiple imputation techniques. Statistical significance is defined as $p<0.05$. Data-analysis of the cost effectiveness analysis is explained below.

7.5.1 Cost-effectiveness analysis

General considerations

Addition of both FDG-PET/CT and, if indicated, diagnostic laparoscopy to the initial staging with gastroscopy and CT of patients with an advanced tumor (cT3-4) is expected to result in cost-savings mainly due to reducing the number of unnecessary gastrectomies.

A detailed analysis of cost differences for the FDG-PET/CT and diagnostic laparoscopy group and standard of care (CT alone and gastrectomy for every patient) requires both prospective and retrospective data collection. The prospective data collection involves a detailed collection of all resources used after inclusion in the observational trial and ends after 36 months or death of the patient. This will include costs of all medical treatments, their associated complications, as well as costs arising from all extra diagnostics performed. These costs will be extracted from the hospital databases.

Retrospective data collection is needed to ensure a valid and detailed analysis of the complete clinical pathway for the comparative group, only gastroscopy and CT. Using retrospective data of patients who underwent curative surgery (gastrectomy) after initial staging with gastroscopy and CT enables to calculate total costs for the comparative patient group. Moreover, retrospective data enables us to calculate costs for palliative treatment within this group of patients as well.

Data collection

Prospective data collection

In this prospective cohort we aim to collect all resources used within the hospital. These resources will be collected from start of the patient in the observational study up to 2 years or until death. These resources are used to assess the total costs for each possible branch and outcome as indicated in figure 2. A case report form (CRF) will be developed, ensuring a structured and uniform data collection. The acquired data will consist of all the health care professional visits, hospitalizations, imaging, pathology, biochemical investigations, medication and surgery and will be collected in relevant units in the CRF. In addition to the collection of resource use we aim to perform microcosting studies for the most essential cost components (gastrectomy and laparoscopy). For both, no reference prices are available at this moment in the Netherlands.

Retrospective data collection

To complement the prospective data collection, we aim to include in a retrospective approach at least 400 patients who underwent curative surgery after only gastroscopy and CT. A retrospective dataset of approximately 700 patients who underwent gastrectomy for cancer is available within the UMC Utrecht. For these patients also all resources used from CT scan until death will be collected using the previously outlined CRF. In addition, this trial can use data from the LOGICA-trial (Laparoscopic versus Open Gastrectomy for Cancer) for comparison of standard care.

Patient outcome analysis

Quality of life will be measured before inclusion in the observational study and thereafter using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires C-30 (EORTC-QLQ-C30) and STO-22 (EORTC-QLQ-STO22), and the EuroQol-5D-5L (EQ-5D-5L)[17-19]. These questionnaires will be completed at the moment of diagnosis at baseline, and after 3, 6, 9 and 12 months.

Costs

All individual units of care in both the prospective and retrospective cohort will eventually be linked to their unit costs. Reimbursement prices issued by the Dutch Healthcare Authority (NZA) and national reference prices will be used for this assessment as outlined in current Dutch pharmaco-economic guidance.

Analysis

Comparison to the costs of previous standard of care

We aim to reproduce the model developed by Smyth et al. to calculate total costs for the PET + laparoscopy group (figure 3)[10]. This model calculates the total costs of FDG-PET/CT and diagnostic laparoscopy pathway using a decision tree including various branches ending in surgery or no surgery. Total costs for each of these branches will be calculated using the resource use data obtained in part 1.1.

Outcomes of this decision tree can be compared with costing outcomes for only a CT scan and gastrectomy for every patient. For this assessment we make use of the total costs collected in the retrospective part of this research (part 1.2) and multiply this with the number of patients included in the prospective observational study.

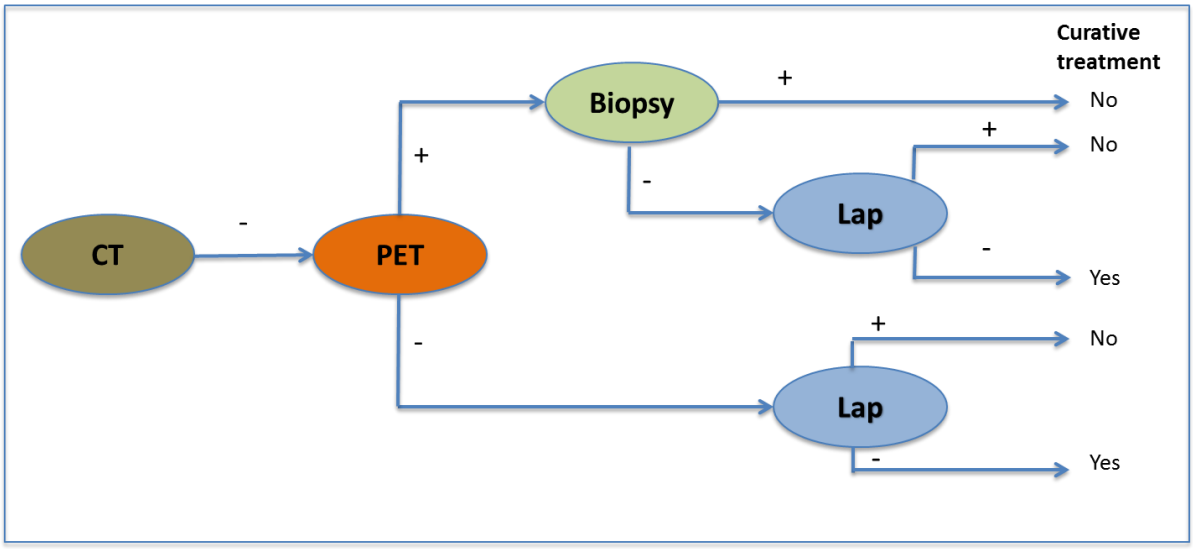

Figure 3. Decision tree for PET and laparoscopy (+ = distant metaseses)

Productivity loss

The majority of patients included in this observational study will probably be elderly (57% >68 years , 78% >60 years; own data). Inclusion of productivity loss questionnaires is therefore deemed unneccessary.

Budget impact

General considerations

Data collected will be used to perform a budget impact analysis (BIA) of implementing both FDG-PET/CT and laparoscopy as diagnostic modalities.

Costing analysis

The BIA adheres to the new guidelines (Zorginstituut, 2016) and applies the perspectives: societal, health insurance/third party payer and health care (Budgettair Kader Zorg (BKZ)). The BIA Prices will be linked to perspectives: societal-CEA based prices, BKZ-average rates according to NZa, for health insurance perspective also NZa average rates and, for example, for a local health care provider perspective specific passenger rates ('passantentarieven'). The BIA will be assessed through (decision analytical) modeling and analyzed in a probabilistic way.

7.5.2 Side-studies

1. The influence of type of hospital (peripheral, tertiary referral) and execution by the surgeon or resident on the quality of diagnostic laparoscopy
2. Re-evaluation of cT-staging by a CT expert panel
3. Re-evaluation of cT-staging by review of the resection specimen
4. Re-evaluation of clinical decision making by MDT reports
5. Subgroup analyses of the impact of FDG-PET/CT and diagnostic laparoscopy according to histological subtype (intestinal, diffuse) and T-stage
6. Evaluation of the incidence and impact of positive peritoneal cytology

7.5.3 Time schedulde

The study will start on 01-08-2017, and will take 36 months. Before the start of the study, all preparations will be made. After start of the study, the first 30 months will consist of inclusion and follow-up of the patients. The last 6 months will consist of follow-up and analysis of results. The study will end at 01-08-2020.

8. PATIENT & DATA REGISTRATION

8.1 Local leading center

Each region of gastric cancer care will have one local leading center. This center will preferably be the center performing gastrectomies in its region. The local leading center will be responsible for adequate inclusion of patients, adherence to national guidelines and the research protocol, and for data entry. The local leading centers are the UMC Utrecht, AMC, VUmc, LUMC, Erasmus MC, Catharina, AvL NKI, Zuyderland MC, ZGT Almelo, Rijnstate, Gelre ZH, ETZ Tilburg, MC Leeuwarden, and the UMCG.

8.2 Inclusion of patients

After the multidisciplinairy team (MDT) of a region has decided that a high-risk patient will undergo FDG-PET/CT and diagnostic laparoscopy according to the new national guideline, the patient may be informed and included in the study. Informing and including patients may be done at any hospital, under responsibility of the local leading center.

Patients should be informed about the following facts:

1. Patients will not need to undergo extra interventions, diagnostics, or other big actions besides adherence to standard of care.
2. Patients will only be asked to fill in questionnaires regarding quality of life at baseline, at 3 months, 6 months, 9 months, 1 year, and each year thereafter up to 5 years after diagnosis. These questionnaires may be conducted in collaboration with POCOP to prevent double registration.
3. Patients' data will be anonymously used for research purposes.
4. Patients' data may be linked to other existing registries for research purposes, such as the Netherlands Cancer Registry (IKNL), DICA, and hospital data.

For inclusion of patients, the informed consent form should be used, available from the study website (www.plasticstudie.nl). After inclusion of the patient, the complete informed consent form should be sent to the local leading center and the coordinating researcher in the UMC Utrecht, accompanied by the hospital patient ID.

Directly after inclusion, the local leading center should register the patient in the electronic case report form (eCRF) by completing form 1. Completing form 1 will lead to a study identifying number, which should be stored and linked to the particular hospital patient ID in a separate file. To double check this procedure, the central coordinating investigator will also

receive an e-mail if a patient is registered and will check if the informed consent and hospital patient ID are provided.

8.3 Case report forms (CRF)

This study will use an electronic CRF (eCRF) as basis for the data registration. The eCRF's are available on the study website (www.plasticstudie.nl) and should preferably be filled out by researchers from the local leading center. To facilitate multidisciplinary collaboration, paper CRF's will be available from the study website (www.plasticstudie.nl). These paper CRF's will be ideal for other centers besides the local leading center collaborating in the MDT and performing diagnostic laparoscopies and FDG-PET/CT occasionally. All data from the paper CRF's eventually need to be recorded in the online eCRF's.

Standard operating procedure

As stated in paragraph 9.2, directly after inclusion a patient should be registered in the eCRF by completing form 1 (registration). This will allow for adequate registration and administration of the trial. Subsequently, form 2 (MDT 1, conclusion initial staging) should be completed, including all details of the first MDT after initial staging (fig. 4). Alternatively to online registration, the local center may send and e-mail to plastic@umcutrecht.nl with all details, and the central study coordinator will register the patient in the eCRF.

Patients will now undergo FDG-PET/CT and diagnostic laparoscopy according to national guidelines. The results of additional staging will preferably be discussed during a second MDT. After the additional staging, form 3 (PET), 4 (Diagnostic laparoscopy, if applicable) and 5 (MDT 2) should be completed (fig. 4).

After additional staging, patients will proceed for curative or palliative treatment. Depending on this decision, form 6 (curative treatment) or 7 (palliative treatment) may be completed. For patients undergoing curative treatment in the first case, but palliative treatment in a later phase, both forms may be completed. During follow-up at different time points since diagnosis, forms 8-13 (6 months, 1-5 years) should be completed (fig 4).

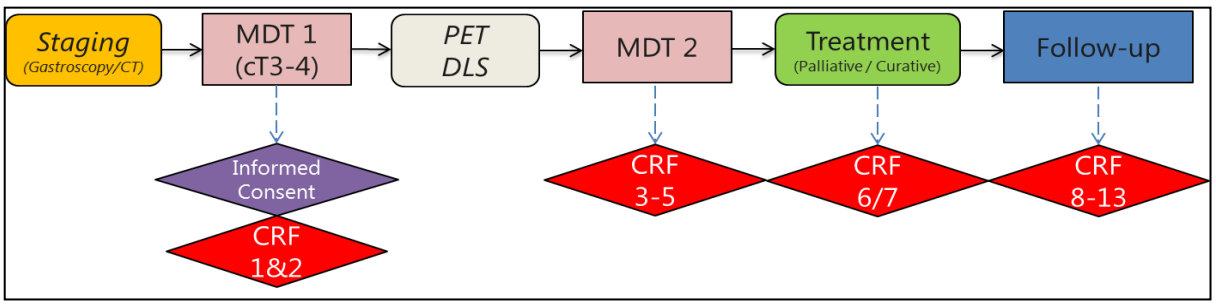

Figure 4. Points in time upon which CRF's should be completed.

8.4 Questionnaires

In the eCRF, the e-mail address of the patient is registered. This will allow for automatic sending of quality of life questionnaires during the follow-up. In case the patient does not have e-mail, no questionnaires can be send. If a patient is also participating in POCOP, this can be noted in the eCRF and patients will not receive questionnaires twice.

8.5 Linking data to other registries

At the end of this study, the data from the eCRFs will be linked to existing registries. This will allow for a lower burden of registration for all participating centers. In order to make this link possible, it is important that the study identifying number generated by the eCRF and the hospital patient ID are registered together in the eCRF and in a separate file. This file will be managed by the central study coordinator of the UMC Utrecht.

At the end of this study, local centers will be asked to request their own hospital data from DICA for the specific patients included in this study. This is allowed by DICA if it is done by the hospital itself, and will allow for linking of the study data to perioperative surgical data.

Second, with the informed consents provided by the patients, the central coordinating center (UMC Utrecht) will request data on tumour characteristics and survival from the Netherlands Cancer Registry (IKNL).

Last, for the cost-effectiveness analysis, all data on DBC’s and interventions recorded per patient will be requested from the hospital financial department. This will be agreed upon at the start of this study to prevent problems afterwards.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (2008). As this study does not allocate patients to study interventions other than usual care, this study does not fall within the Medical Research Involving Human Subjects Act (WMO). A non-WMO declaration (METC 16-633/C) has been obtained from the Medical Review Board (METC) of the UMC Utrecht.

9.2 Recruitment and consent

Patients are recruited to participate in this trial at the outpatient clinic. The subjects will be fully informed about the study by a physician who explains the trial. Potential participants can contact the coordinating investigator or independent physician for any questions concerning the trial. The subjects will be asked to sign a brief informed consent form to confirm that they know that their information will be anonymously used for research purposes, and that they approve to receive quality of life questionnaires.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.

2. Nederlandse Kankerregistratie. Cijfers over kanker. 2015. Available at: http://www.cijfersoverkanker.nl/.

3. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20.

4. Dutch Upper GI Cancer Audit. DUCA Jaarrapportage 2015. 2016. Available at: https://www.dica.nl/jaarrapportage-2015/duca.

5. Dassen AE, Dikken JL, Bosscha K, et al. Gastric cancer: decreasing incidence but stable survival in the Netherlands. Acta Oncol 2014;53:138-142.

6. Hoeymans N, Melse JM, Schoemaker CG. Gezondheid en determinanten. Deelrapport van de VTV 210 Van gezond naar beter. 2010;RIVM rapport 270061006:http://www.rivm.nl/bibliotheek/rapporten/270061006.pdf.

7. Choi JY, Shim KN, Kim SE, et al. The clinical value of 18F-fluorodeoxyglucose uptake on positron emission tomography/computed tomography for predicting regional lymph node metastasis and non-curative surgery in primary gastric carcinoma. Korean J Gastroenterol 2014;64:340-347.

8. Seevaratnam R, Cardoso R, McGregor C, et al. How useful is preoperative imaging for tumor, node, metastasis (TNM) staging of gastric cancer? A meta-analysis. Gastric Cancer 2012;15 Suppl 1:S3-18.

9. Wang Z, Chen JQ. Imaging in assessing hepatic and peritoneal metastases of gastric cancer: a systematic review. BMC Gastroenterol 2011;11:19-230X-11-19.

10. Smyth E, Schoder H, Strong VE, et al. A prospective evaluation of the utility of 2-deoxy-2-[(18) F]fluoro-D-glucose positron emission tomography and computed tomography in staging locally advanced gastric cancer. Cancer 2012;118:5481-5488.

11. IKNL. Richtlijn Maagcarcinoom conceptversie. 2015.

12. Kim JW, Shin SS, Heo SH, et al. Diagnostic performance of 64-section CT using CT gastrography in preoperative T staging of gastric cancer according to 7th edition of AJCC cancer staging manual. Eur Radiol 2012;22:654-662.

13. Boellaard R, Delgado-Bolton R, Oyen WJ, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging 2015;42:328-354.

14. Lorenzen S, Panzram B, Rosenberg R, et al. Prognostic significance of free peritoneal tumor cells in the peritoneal cavity before and after neoadjuvant chemotherapy in patients with gastric carcinoma undergoing potentially curative resection. Ann Surg Oncol 2010;17:2733-2739.

15. Haverkamp L, Brenkman HJ, Ruurda JP, et al. The Oncological Value of Omentectomy in Gastrectomy for Cancer. J Gastrointest Surg 2016.

16. Brierley J, Gospodarowicz M, Wittekind C. TNM Classification of Malignant Tumours. : Wiley; 2009.

17. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727-1736.

18. Blazeby JM, Conroy T, Bottomley A, et al. Clinical and psychometric validation of a questionnaire module, the EORTC QLQ-STO 22, to assess quality of life in patients with gastric cancer. Eur J Cancer 2004;40:2260-2268.

19. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365-376.