PROton versus photon Therapy for Esophageal Cancer – a Trimodality strategy (PROTECT) NCT050555648

A multicenter international randomized phase III study of neoadjuvant proton versus photon chemoradiotherapy in locally advanced esophageal cancer

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Background

For patients diagnosed with locally advanced esophageal (EC) and gastroesophageal junction (EGC) cancers neo-adjuvant chemoradiotherapy (nCRT) followed by surgical resection[1] and adjuvant immunotherapy is considered standard of care[2]. These treatments often result in severe, acute, and late, heart- and lung complications[3–7] which can be lethal[8]. Proton therapy (PT), in comparison with photon therapy (XT), allows for dose reductions to organs at risk (OAR) such as the heart and lungs due to the finite range of protons. This may result in fewer side effects[7], shortened postoperative hospitalization, improved quality of life (QoL)[9,10] and survival benefits.

A previous randomized phase II trial by Lin et al[7] including 145 patients undergoing either tri-modality treatment (48%) or definitive radio-chemotherapy (52%), showed a significant reduction in the total toxicity burden (TTB) and a postoperative toxicity score in patients treated with PT compared to XT. Noteworthy, no significant difference in neither survival nor QoL was observed. Overall survival as endpoint was not met due to challenges in recruitment caused by widespread insurance denial, the mix of patients who did or did not undergo surgery, and the small sample size. A further North-American multicenter randomized phase 3 NRG-GI006 trial (NCT03801876), comparing patients treated with PT versus intensity-modulated photon therapy (IMRT), using overall survival and grade 3+ cardiopulmonary toxicity as the primary endpoints, will randomize a total of 300 patients.

In parallel, the European PROTECT trial (NCT050555648) has been planned and opened, comparing neoadjuvant chemo-radiotherapy with either proton therapy (nCPT) or photon therapy (nCXT) combined with standard concomitant chemotherapy followed by surgery. The aim was to examine if PT based radiation dose reductions to critical OARs in the thorax, would result in lower rates of subsequent lung- and heart complications[11].

Study design

PROTECT is an unblinded randomized phase III study for patients with operable EC or EGC receiving nCXT (standard of care) or nCPT (intervention). The radiation dose is either 41.4 Gy in 23 fractions, five fractions per week or 50.4 Gy in 28 fractions, five fractions per week delivered concurrently with weekly carboplatin (AUC 2), and paclitaxel (50 mg/m^2), five cycles in total.

Patients will be randomized (1:1) to either nCXT or nCPT. Stratification for histopathology (adenocarcinoma versus squamous cell carcinoma), planned surgical technique (open versus minimal invasive/robotic or hybrid) and site (proton center and collaborating photon centers) will be performed. Each proton center and collaborating photon centers will declare a standard treatment dose of either 50.4Gy or 41.4Gy and hence, stratification for site will reflect total radiotherapy dose as well.

All patients will receive standard diagnostic work-up including esophagogastroduodenoscopy with biopsies, UICC TNM clinical staging 8th edition[12], diagnostic FDG-PET scan, and baseline lung and heart function tests. Patients will be seen weekly during radiotherapy, every second week after nCRT until surgery as well as post-operatively (up to three months), and at eight specified time points for 5 years of follow-up.

Statistical considerations

The primary endpoint is pulmonary complications within 90 days after completed surgery or radiotherapy for patients not undergoing surgery. Secondary endpoints include compliance with tri-modality treatment, other toxicities, concordance of observed pulmonary and cardiac complications with predicted complications from NTCP models, pathological complete response, TTB[11],

locoregional failure, disease-free survival, overall survival, health related QoL, patient reported outcomes and health economic assessments of PT and XT.

Sample size calculation is based on expected difference between nCXT and nCPT assessed via dual dose planning performed on 22 representative patients with an assumption of a ten percent reduction in pulmonary complication rate with nCPT (10% expected) compared to nCXT (20% expected), (80% power and two-sided type 1 error rate of 5%) leading to a total number of 396 patients (198 receiving XT and 198 PT).

Quality Assurance (QA) programs

Collaboration between centers in the PROTECT consortium will ensure that tri-modality treatment is optimally delivered. This set-up will allow for firm conclusions and for early translation of the study results into clinical practice.

Radiotherapy guidelines are described in detail in the PROTECT RTQA guideline including target definition and delineation, radiation dose constraints to normal tissue, tolerances for daily image guidance, as well as treatment planning, robustness evaluation, and weekly 4DCT-based verification and adaptation. Completed and accepted pre-trial target delineation[13] and planning of benchmark cases[14], individual case reviews and site visits are mandatory prior to trial initiation. Delineations and plans of study patients are reviewed by the RTQA group.

Surgery follows the PROTECT surgery QA guideline and will be performed by surgeons specialized in upper gastrointestinal cancer with the main goal of achieving a complete resection of the tumor (R0-resection). This includes rules for surgery techniques, and documentation of individual surgery performance prior to trial initiation and during treatment with the purpose of ensuring high-quality surgery and validation of the scoring of the primary endpoint.

Patient involvement, health economics, and translational research

The PROTECT consortium is based on a collaboration between leading European proton therapy centers, their collaborating photon departments, and academic collaborators from eight European countries (Denmark, Germany, The Netherlands, Belgium, Switzerland, Italy, France, United Kingdom). The consortium is committed to strong partnerships with patients, patient organizations, and scientific networks.

Patient involvement and engagement has informed the design and content of the patient-facing material, trial recruitment and will inform dissemination activities. A key element of the PROTECT trial is the collection of patient-reported outcomes[15–17], in addition to clinical endpoints. Patient representatives have also helped inform an in-depth questionnaire on healthcare resource use, in order for health economic analyses to be undertaken. A within trial economic evaluation will estimate incremental cost effectiveness ratios, for cost per QALY gained, cost per complication avoided, and cost per TTB avoided thereby offering evidence for decision makers on the cost-effectiveness of proton therapy.

To maximize the impact of the trial a platform for translational research has been created. This includes novel NTCP models, LET calculations and collection of research blood samples (e.g., for circulating tumor DNA). Results from the PROTECT randomized trial will be combined with results from the Model-based Approach (MBA)[18] in the Netherlands to validate a novel MBA approach against the conventionally accepted high-level evidence from a randomized trial.

Conflict of interest

Hanna Rahbek Mortensen is Co-chair in Patient Involvement Work Package in PROTECT.

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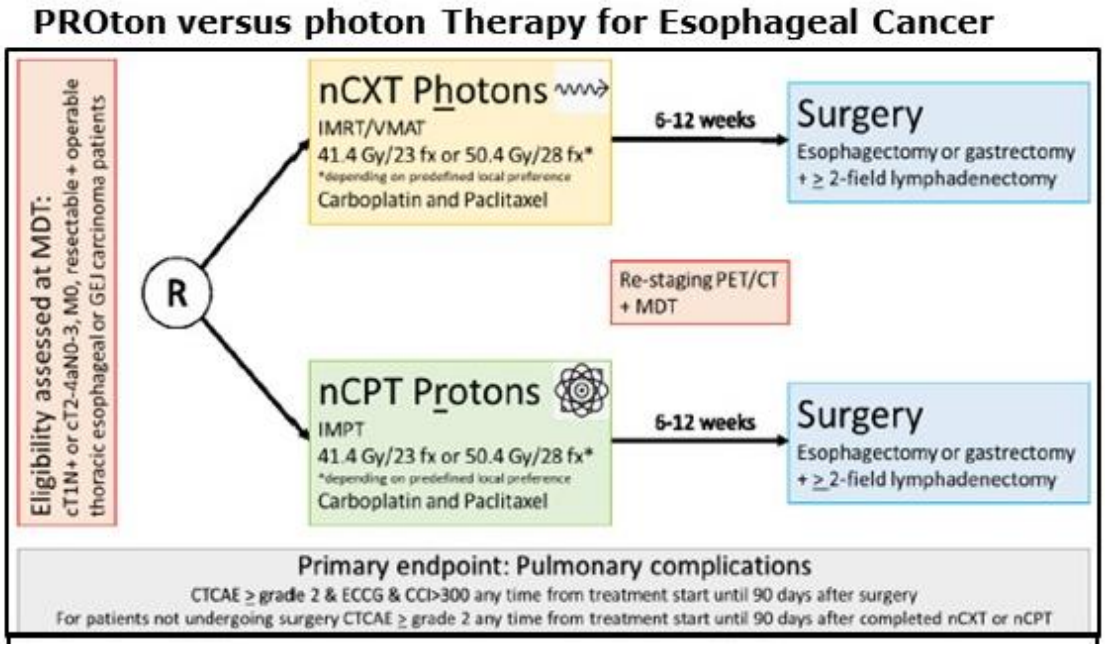

Figure 1: PROTECT study design.

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