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Phase I Study of Definitive Chemoradiation With Cisplatin/5-FU Plus Cetuximab in Unresectable Esophageal Cancer

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Background: The optimal treatment of locally advanced esophageal cancer is controversial. Most patients receive chemoradiation followed by surgical resection. However, many tumours are not resectable and are treated with definitive chemoradiation (dCRT). The results of dCRT including cisplatin and 5-FU are not satisfactory and need to be improved. This may be achieved with addition of the EGFR-antagonist cetuximab. This phase I study was performed to define the maximum tolerated dose (MTD) of 5-FU in combination with cisplatin, cetuximab, and RT in patients with unresectable locally advanced esophageal cancer.
Materials and Methods: Six patients (4 SCC, 2 adeno-carcinoma) with T3/T4 N+ diasease received dCRT of 50.4 Gy (5x1.8 Gy per week) to the primary tumour and regional lymph nodes plus a boost of 9 Gy to the primary tumour and involved lymph nodes. Four courses of cisplatin (20 mg/m^2 on days 1−4) and 5-FU (dose level 1: 750 mg/m^2 on days 1−4, N = 3; dose level 2: 1000 mg/m^2 on days 1−4, N = 3) were administered, two courses concurrently with RT. Weekly cetuximab was given for 14 weeks (initial dose of 400 mg/m^2 at one week prior to RT followed by weekly doses of 250 mg/m^2). The traditional 3+3 design was applied to specify the safe dose of 5-FU to be used for further studies. Dose-limiting toxicities (DLT: any grade >3 toxicity, dose reduction of chemotherapy or RT by >30%, interruption of treatment >2 weeks) were assessed from first admínistration of cetuximab until completion of RT. The primary endpoint (MTD/DLT) analysis includes all patients having either received the full scheduled chemoradiation or experiencing a DLT. A full safety evaluation was conducted for all patients at dose level 1, before any patients could be enrolled at dose level 2.
Results: Treatment at both dose levels could be safely administered, and no DLTs were observed in any of the 6 patients enrolled. Radio-immunochemotherapy could be administered as planned and dose modifications were minor and only due to organisational reasons or physician's/patient's request. In the three patients treated at dose level 2, only five adverse events of CTC grade 3 (nausea, infection, dyspnea, skin toxicity, allergic reaction) were observed.
Conclusions: Based on the favorable safety profile of this phase I study, an open-label randomized phase II study will be initiated using the regimen of dose level 2 to evaluate if loco-regional control and survival can be improved with the addition of cetuximab.

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Post- Chemoradiotherapy Standardized Uptake Value of FDG-PET as a Significant Predictor of Survival After Subsequent Surgery in Multimodality Treatment for Patients With Locally Advanced Esophageal Squamous Cell Carcinoma

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Background: Recent studies imply that positron emission tomography with fludeoxyglucose F 18(FDG-PET) significantly correlates with histopathologic response and survival in patients with esophageal cancer undergoing neoadjuvant chemoradiotherapy followed by surgical resection. Post-chemoradiotherapy (CRT) FDG-PET standardized uptake value (SUV) and rate of decrease in SUV are used to predictor of survival. To evaluate the rating system of FDG-PET after the completion of neoadjuvant CRT for the assessment of histopathologic response and prognosis in the multimodality treatment of patients with esophageal cancer.
Material and Methods: Sixty patients (51 men, 9 women; median age, 59.4 years) with locally advanced esophageal squamous cell carcinoma who received neoadjuvant CRT underwent FDG-PET before chemoradiotherapy and transthoracic en bloc esophagectomy in evaluation of pathologic response to CRT and postoperative survival.
Lack of FDG uptake was defined as primary tumours with SUVmax at least 2.5, and FDG-PET complete response after CRT(PET-CR) was defined as SUV <2.5 or SUV <3 with mild hyper metabolic activity around the primary tumour.
Results: After CRT, lack of FDG uptake was noted 18 patients, PET-CR was noted 22 patients and pathological CR was noted 26 patients. PET-CR indicated stronger correlation with postoperative survival than lack of FDG uptake. PET-CR and pathologic CR predicted for improved outcomes (2-year disease free survival 84% vs 35% P = 0.0002; log-rank test, 88% vs 48% P = 0.0035; log-lank test). On multivariate analysis, only PET-CR was found to be correlated with post-CRT disease free survival (HR 0.124 95% CI 0.024–0.647 P = 0.013).
Conclusions: FDG-PET predicted postoperative survival in advanced esophageal squamous cell carcinoma. With respect to influenced by esophagitis, when PET-CR defined as SUV <2.5 or SUV <3 with mild hyper metabolic activity around the primary tumour, FDG-PET seems to be the best available imaging modality for neoadjuvant chemoradiotherapy response assessment in squamous cell esohageal cancer.

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Introducing Perioperative Chemotherapy for Gastric Cancer in Norway

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Background: In 2006, perioperative chemotherapy with epirubicin, cisplatin/oxaliplatin and capecitabin was recommended in the National Guidelines for patients with resectable gastric cancer in Norway. We conducted a national audit related to clinical aspects, local organization and the implementation of this multimodal treatment.
Patients and Methods: All Norwegian departments of oncology were asked to submit aggregated data on gastric cancer patients who had started perioperative chemotherapy for cure; departments of surgery were asked to report on patients undergoing resection after preoperative chemotherapy. Data were retrospectively collected.
Results: All 20 departments of oncology and 20 of 21 departments of surgery responded. Of 336 patients operated on for gastric cancer and reported by surgeons, 144 (43%) received preoperative chemotherapy. 169 patients were reported by departments of oncology. 152 (90%) completed preoperative cycles; 92 (54%) started the postoperative cycles; and 68 (40%) completed all cycles. Toxicity grade $\geqslant$3, overall and haematological, increased during postoperative compared to preoperative cycles, 50% vs. 34% ($P = 0.012$) and 35% vs. 20% ($P = 0.012$), respectively. Surgical morbidity and mortality were 26 and <2%, respectively. R0 resection was achieved in 86% of surgically treated patients. Five per cent had a complete pathological response (ypT0) and 48% were node negative (ypN0). Within the first year, the National Guidelines were implemented in 19 of 25 hospitals (76%).
Conclusions: In this population-based series, the tolerance of peri-operative chemotherapy reported in the MAGIC trial was reproduced. Toxicity grade $\geqslant$3 was considerable and significantly increased related to postoperative cycles. The National Guidelines were rapidly adopted.
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Lymph Node Size Is a Strong Prognostic Factor for Patients With Esophageal Cancer Treated by Chemoradiotherapy

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Background: The 7th edition of the American Joint Committee on Cancer (AJCC) staging system does not include lymph node size in the guidelines for staging patients with esophageal cancer. Data from detailed evaluation of the size of lymph nodes in esophageal cancer patients undergoing chemoradiotherapy (CRT) have also not been available. The objective of this study was to determine the prognostic impacts of maximum lymph node diameter (ND), 3-dimensional total nodal volume (NV), and primary tumour volume (TV) on survival in esophageal squamous cell cancer patients treated with CRT.
Methods: Data from 215 consecutive esophageal squamous cell carcinoma patients who underwent CRT were reviewed retrospectively. Overall survival according to TNM stage, ND, NV, and TV was evaluated by Cox proportional hazards modeling and by time-dependent receiver operating characteristics (ROC) curve analysis.
Results: By multivariate analysis, T stage, ND, and NV were independently and significantly associated with survival ($P < 0.05$); however, TV and N and M stages according to the AJCC staging system were not significant predictors of survival. By time-dependent ROC curve analysis, ND and NV were consistently good prognostic factors for overall survival compared with the number of regional lymph nodes.