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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.

6528 POSTER

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.

Conclusions: Our study demonstrated that lymph node size is a strong independent prognostic factor for patients undergoing chemoradiotherapy for esophageal squamous cell carcinoma. The results indicate that revisions of the current staging system for esophageal cancer should include N staging based on lymph node size, as is currently practiced for head and neck cancer.

6530 POSTER

Dosimetric Comparison of Liver Tumour Radiotherapy in All Respiratory Phases and in One Phase Using 4DCT

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Liver tumours exhibit significant intrafractional motions due to respiration therefore 4DCT as well as gated radiotherapy are introduced into treatment. We could delineate target volume on all respiratory phases and radiation is delivered during free breathing cycle. However the 4DCT technique synchronizes image acquisition with respiratory phase what allows us to delineate our target on the basis of one respiratory phase and deliver gated treatment choosing specific phase for irradiation. Up to now littlie is know about comparison of both techniques in terms of target and normal tissue dose distribution.
In the present paper we analyzed data of 20 patients treated for liver metastases, irradiated to the total dose 36 Gy in 3 fractions. We chose only tumours, which were clearly separated from the liver tissue. We used 4DCT to characterize tumour motion and create treatment volumes. For all patients we delineated two GTV, one based on all 10 respiratory phases (GTV 4D) and based on one phase (GTV GAT). To create PTV's we added the same 0.5 mm to GTVs. Two treatment plans were performed (4D and GAT) and dose volume distributions were analyzed in respect to target and normal tissue. Various tumour motions was included, motion along the superior–inferior direction was greatest mean 1.5 cm (range 1−3), to the side mean motion was 0.9 cm (0.6−1.3). GTVs volumes were larger in 4D than in GAT, mean 14.9 vs 27.6 cm3, also PTV 37 vs 61 were larger.
We achieved similar dose distribution in PTV4D mean 36.7 Gy SD $\pm$ 0.2 and minimum 34.9 Gy $\pm$ 0.3 for 4D plan, and PTVGAT for GAT plan mean 36.7 Gy SD $\pm$ 0.3 and minimum 34.9 Gy $\pm$ 0.3, but when we look at the dose distribution in PTV4D in the GAT plan, we found decrease in minimum dose to 12.3 Gy (2.2–24.3), and mean 33.9 Gy $\pm$ 2.3, what could be explain by differences in target volumes related to tumour movement. Radiotherapy delivered using GAT gave lower liver doses than using 4D with reduction of mean volume receiving 5 Gy by 9.3% SD $\pm$ 4.7, V10 Gy 6.7% SD $\pm$ 4.2, V20 Gy 4.8% SD $\pm$ 2.7 and reduction of mean kidney volume receiving 5 Gy by 12% SD $\pm$ 10, V10 Gy 7% SD $\pm$ 9, V20 Gy 2.8% SD $\pm$ 5.6. Moreover doses to the other normal tissues were also lower. We also found correlation between GTV volume reduction with GAT, GTV motion and doses to the normal tissues.
Gated radiotherapy allows us to decrease GTV and PTV volumes in comparison to volumes delineated on all respiratory phases. Decreased target volumes are responsible for improvement in dose distribution in normal tissue especially in the liver and kidney.

6531 POSTER

Impact of Planned Dose Distribution on Sites of Locoregional Failure for Oesophageal Cancer Patients After Exclusive Chemoradiotherapy

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Background: Nearly half of the patients (pts) with an oesophageal cancer (OC) have locoregional failure (LRf) after exclusive chemoradiation (eCRT). We aim to evaluate the patterns of LRf with respect to the initial dose distribution at time of planning CT (t0).
Material and Methods: Twenty three pts with an OC who failed locally and/or regionally in their follow-up were exclusively reviewed. All the pts have been initially treated in a curative intent with Platin-based eCRT. Among them, 19 patients had available imaging performed at time of failure (tf). Co-image registration of CT or PET-CT at tf and planning CT at t0 was made for image fusion considerations. Each nodal failure (Nf) and each local failure of the primary tumour (Lf) has been outlined, as well as each nodal station (NS) including Nf. The dose planned to the PTV at t0 was compared to the recalculated dose delivered to invaded NS at tf using a non-parametric Wilcoxon's test.
Results: Fifteen pts had a squamous cell cancer and 4 pts had an adenocarcinoma. Clinical T-stage at t0 was either T2 (4 pts) or T3 (15 pts). Five pts were clinically staged N0 and 14 pts had N1 disease. The median number of involved NS at t0 was 2 (0−4). The median Dmean planned to the PTV was 50 Gy [42.7 Gy-64 Gy]. In the follow-up period, 12 pts were in complete response, 3 pts in partial response, 3 pts had a progressive disease (1 pt unknown). The median delay between diagnosis and LRF was 12.6 months [4.27–48.46]. Nine pts had a Lf, 6 pts had a Nf, 4 pts had Lf with Nf and 6 pts had a concomitant distant failure. All Lf were located at the epicenter of the primary tumour. Nf occurred inside NS included in the CTV at t0 for 7 pts. Among them, 5 pts had additional recurrent NS outside the CTV (3 pts in 1 NS, 1 pt in 2 NS and 1 pt in 4 NS). Nonetheless, 3 pts had Nf in NS outside the CTV only.
The mean doses recalculated to the NS at tf were more likely to be lower than the planned dose delivered to the PTV at t0: Dmean = 34.7 Gy vs. 48.6 Gy ($p = 0.0015$), Dmax= 41.3 Gy vs. 48.9 Gy ($p = 0.013$), Dmin = 23.1 Gy vs. 38.6 Gy ($p = 0.031$), D95= 28.0 Gy vs. 44.8 Gy ($p = 0.003$).
Conclusions: Our preliminary results suggest that patients with Nf could suffer from geographic misses when performing elective nodal irradiation (ENI). Moreover, increasing the dose to the primary tumour above 50 Gy could decrease Lf rates.

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Phase I/ II Study of Concurrent Chemoradiotherapy With Gemcitabine and S-1 for Unresectable Locally Advanced Pancreatic Adenocarcinoma

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Purpose: The primary objective of this study is to assess the efficacy and toxicity of concurrent radiotherapy with a combination of Gemcitabine (GEM) and S-1 for unresectable locally advanced pancreatic cancer.
Patients and Method: Chemotherapy-naive patients with histologically or cytologically proven unresectable locally advanced pancreatic adenocarcinoma were enrolled to this trial. The patients received gemcitabine intravenously over 30 min on days 1 and 8 and S-1 orally b.i.d. from days 1 to 14. Cycles were repeated every 21 days until disease progression. Patients were scheduled to receive gemcitabine (mg/msq/week) and S-1 (mg/msq/day) at five dose levels: 600/50 (level 1), 600/60 (level 2), 800/60 (level 3), 800/70 (level 4) and 1000/70(level 5). Radiation therapy was delivered through four fields as a total dose of 50.4 Gy in 28 fractions over 5.5 weeks, and no prophylactic nodal irradiation was given. Dose-limiting toxicity (DLT) was defined as grade 4 thrombocytopenia, grade 4 neutropenia, or grade 3 non-hematologic toxicity. Every patients were evaluated for response with RECIST criteria by a radiologist.
Results: Fifteen patients were enrolled in phase I study between 05/12 and 07/05. The maximum-tolerated dose was level 2, Gem 600 mg/ S-1 60 mg. Six patients experienced DLT (four patients with anorexia and two patients with Gr4 neutropenia). Fifteen patients were added to phase II study, and finally twenty one patients treated with the recommended dose of phase I were enrolled to phase II part. Treatment was well tolerated. Response rate(RR) was 52% and one year survival rate was 76%.
Conclusion: The chemoradiation therapy with a combination of GEM and S-1 can be one of the most promising options for unresectable locally advanced pancreatic cancer.

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Effective High Precision Radiotherapy in Advanced Cholangiocarcinoma/Klatskin Patients − a New Interdisciplinary Challenge

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Background: Owing to the fact that high precision radiotherapy like stereotactic body radiotherapy (SBRT) allows high dose radiation close to sensitive organs of risk phase 1 studies demonstrate good local tumour control rate in patients with advanced cholangiocarcinoma (CCC)/Klatskin tumours.
Aim of this study is to evaluate this therapy with regard to local control rate, toxicity, and overall survival in a larger cohort.
Material and Methods: 30 patients (p) with histological proven CCC/ Klatskin tumours, stage Bismuth III or IV, underwent SBRT. Planning target volume contained gross tumour volume, 2 mm set-up margin and movement margins based on 4 D list mode-detected PET/CT. All patients underwent SBRT with prescribed radiation dose to the 65% enclosing