PG 7.03 SPEAKER ABSTRACT

Optimizing neoadjuvant chemotherapy through the use of early response evaluation (PET)

F. Lordick. *3rd Medical Department, Klinikum Braunschweig, Braunschweig, Germany*

Metabolic imaging and early response assessment by positron emission tomography (PET) are gaining importance in guiding neoadjuvant treatment of localized esophago-gastric cancers. The most consistent and validated results have been obtained during neoadjuvant treatment of adenocarcinoma of the esophago-gastric junction (AEG). It was demonstrated that PET is highly accurate for identifying non-responding tumors within 2 weeks after the initiation of neoadjuvant chemotherapy when a quantitative threshold for metabolic response is used [Weber WA et al. JCO 2001; Ott K et al. JCO 2006]. In consecutive phase II studies the metabolic activity, defined by the standardized uptake (SUV) of 18-FDG before and during chemotherapy, was measured. Significant decreases of the SUV after only two weeks of induction chemotherapy were observed. A drop of >35% 2 weeks after the start of chemotherapy revealed as an accurate cut-off value to predict response after a 12 weeks course of preoperative chemotherapy. It was further noticed that the metabolic response to induction chemotherapy revealed as an independent and important prognostic factor in locally advanced AEG. This suggests that PET can be used to tailor treatment according to the chemosensitivity of tumours. The concept was realized in the MUNICON-1 and -2 trials [Lordick F et al. Lancet Oncol 2007, Lordick et al. ASCO-GI 2011]. These trials prospectively confirmed that responders to induction chemotherapy can be identified by early metabolic imaging using FDG-PET. Continued neoadjuvant chemotherapy in the responding population resulted in a favourable outcome: MUNICON-1 showed that chemotherapy can be discontinued at an early stage in metabolic non-responders, thereby saving time and reducing side-effects and costs. Compared to previous studies one could delineate that the outcome of metabolic non-responders was at least not compromised by the early discontinuation of chemotherapy. MUNICON-2 showed that the addition of neoadjuvant radiation therapy in metabolic non-responders does not lead to an evident improvement of the poor prognosis, thus showing that early metabolic non-response indicates a dismal tumor biology.

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PG 7.04 SPEAKER ABSTRACT

When is neoadjuvant radiochemotherapy the treatment of choice?

A. Van der Gaast. *Department of Medical Oncology, Erasmus University Medical Centre, Rotterdam, Netherlands*

The incidence of esophageal and esophageal–gastric junction tumors is rapidly increasing not only due to ageing of the population but also due to an increase of the incidence of adenocarcinomas in the last decades. For patients with resectable tumors a surgical resection is generally the treatment of choice. However, despite careful staging and patient selection the prognosis of these patients after a surgical resection is poor and characterized by local recurrences and distant metastases. One of the reasons is that in 20% to 30% of patients an irradical resection is performed. Furthermore a resection carries a substantial risk of postoperative morbidity and mortality especially in non-specialized centers.

Preoperative chemoradiotherapy may increase the number of radical resections and therefore the prognosis of these patients. We have performed a phase III study (CROSS trial) comparing chemoradiotherapy followed by surgery versus surgery alone. The preoperative chemoradiotherapy regimen consisted of weekly administrations of carboplatin targeted at an AUC of 2 and paclitaxel 50 mg/m2 q. 5 and concurrent radiotherapy 23 fractions of 1.8 Gy, 5 days per week, total doses 41.4 Gy. A total 368 patients with adenocarcinomas or squamous cell carcinomas of the esophagus and esophagogastric junction were randomized. The preoperative chemoradiotherapy regimen was well tolerated and postoperative complications and in-hospital mortality (4% in both treatment arm) were comparable. A radical resections was achieved in 92% of patients in the chemoradiotherapy arm versus 69% in the surgery alone arm. Median overall survival was 49.4 months in the preoperative chemoradiotherapy followed by surgery arm versus 24 months in the surgery arm. Overall survival was significantly better ($p = 0.003$) in the chemoradiotherapy followed by surgery arm (HR 0.657; 95% CI 0.495–0.871).

Based on this study and meta-analyses preoperative chemoradiotherapy can be considered standard of care for patients with esophageal cancer. Important questions still remain such as are the results of definitive chemoradiotherapy comparable to the results of preoperative chemoradiotherapy followed by surgery and what is the role of delayed surgery for residual disease or recurrences after definitive chemoradiotherapy?

There is also a debate whether tumors arising of the esophageal-gastric junction should be treated with preoperative chemoradiotherapy (CROSS trial) or with preoperative chemotherapy as is suggested in the MAGIC and the FNCLCC and FFCD trial. Only in the POET trial preoperative chemotherapy was compared with preoperative chemoradiotherapy and although there was a trend for improved survival in favor of the preoperative chemoradiotherapy arm the difference in survival was not significant (hazard ratio adjusted for randomization strata variables 0.67, 95% CI 0.41–1.07). These issues will be further discussed.

Friday, 23 March, 12:00−12:30

Keynote Lecture II

PG 8.01 SPEAKER ABSTRACT

Writing and submitting an outstanding scientific manuscript

D.G. Haller. *Abramson Cancer Center, University of Pennsylvania Cancer Center, Philadelphia, United States of America*

Medical journals, such as the JCO, are complex enterprises, and require the close cooperation of authors, editors, reviewers and readers. Each journal decides its own territory, and the JCO has elected to represent a multidisciplinary hematology-oncology journal, rather than focusing on a single disease site or modality. Popular journals may receive more than 3000 original reports annually, but upper level journals publish only 10−15%. Editors monitor online accesses and other sources to determine reader's interest apart from original reports, especially editorials, reviews and guidelines or consensus statements. An important metric for journals, is the speed of manuscript review and publication. To sped publication time, most journals publish papers on-line ahead of print, which is the official Medline date for CVs and other purposes. When submitting MSS, authors should read the journal's information for authors, so that standard requirements are met. A popular metric of journal success is the Impact factor, which is a mathematical mean of the number of citations for the journal's original reports for two full years, divided by the number of papers published. This means that journals with high impact papers, but few papers published will have the highest impact factors. The JCO, which published about 650 papers per years, had an impact factor most recently measured at 17.793, the highest among peer-reviewed hematology-oncology journals. Why do we publish? Because they represent accomplishment in academic medicine, primary documentation of research data, evidence of expertise through writing an authoritative review paper or book chapter and are a major determinant in achieving academic promotion and career development. There are three key steps for getting published in any journal: Do good science, write well and submit what the journal publishes. For any clinical trial report, the trial must be registered when the study begins, in any recognized database, such as ClinTrials.gov, or the paper will not be reviewed or published by recognized journal. For more information read the JCO Editorial on this topic by Haller, November 2008: "Will your paper be publishable?" In preparing a manuscript, be aware of journal guideline for potential conflicts of interest; each journal may have their own specific policies, but general guideline may be found on the ICMJE and WAME websites. The intent of these policies is not to prevent authors with these relationships from publishing their work. It is merely intended that any relationships be identified openly so the Editors and peer reviewers can make informed decisions about submitted manuscripts. It remains for readers to determine whether the authors' outside interests reflect a possible bias in the conclusions presented, and not all potential conflicts of interest are financial, including personal relationships and academic competition. To qualify as an author, each listed author must have generated at least part of the intellectual content of the paper, and should have taken part in writing and revising the intellectual content. Solely entering patients on a trial does not qualify for authorship: acknowledgements are appropriate. All authors should be able to defend publicly in the scientific community the intellectual content of the paper for which responsibility is taken. If a communications firm or company writes your draft (ghostwrites), NEVER have them communicate with the journal directly, and always use their words as a draft. Medical writers should not be listed as authors, but should be listed under "acknowledgements". When preparing a manuscript, be wary of multiple papers from same research and avoid "salami science" – slicing data too thin. Avoid the "LPU": the "Least Publishable Unit", and republish only if there is substantial new data. Don't plagiarize yourself or violate previous copyright; when in doubt, consult ICMJE and WAME guidelines. For papers submitted to clinical journals, ask yourself

these editorial questions: is it new, is it true (validity, internal and external and does the evidence support the conclusions) and how will it affect patient care? For rejected manuscripts, read the reviews and consider appealing, but in doing so don't whine or get angry. Remember: every paper will find a home in the right journal!

Friday, 23 March, 14:00–15:30

Session VII. Gastric Cancer

PG 9.01 SPEAKER ABSTRACT

Optimal surgery for gastric cancer: Is more always better?

W. Allum. *Department of Surgery, Royal Marsden NHS Foundation Trust, London, United Kingdom*

The extent of surgical resection for carcinoma of the stomach has been debated for many years. The aims of surgery are to obtain complete histo-pathological clearance of all possible sites of disease based on oncological principles. This has included radical resection of the primary site with combined organ resection as required and resection of associated lymph nodes. Detailed understanding of the natural history of gastric cancer has resulted in the Pichlmayr total gastrectomy "en principe" approach being super-ceded by a tailored approach according to tumour and patient characteristics. Careful tumour staging is fundamental to the selection of surgical intervention. Endoscopic therapy is recommended for well-differentiated, mucosal cancers less than 2 cm in size as the risk of nodal disease is 0–3%. Recently these criteria have been extended to include some larger and ulcerated cancers. Although extended lymphadenectomy has formed the basis of radical surgery, Japanese experience has also confirmed that for early gastric cancer involving the submucosa limited nodal resection can achieve the same outcome as standardized D2 lymphadenectomy. The approach to locally advanced T2, T3 and some T4 cancers has been defined by the Japanese Rules specifying proximal and distal margins as well as extent of lymph node resection. Translation of Japanese results to Western patients has not been straightforward. Two randomized controlled trials have shown limited or no benefit over conventional limited nodal dissection. However these studies have not been without criticism and individual specialist practice in the West now preferentially includes D2 lymphadenectomy in suitable patients. Extending conventional D2 lymphadenectomy has been evaluated but the results are not conclusive. Japanese RCTs have not shown an advantage but in selected cases several groups have reported a benefit. Historically radical gastric surgery in the West was associated with significant morbidity and mortality reflecting the comorbidity of the patient groups. Perioperative approaches have shown that outcome approaching that of radical surgery can be achieved with multimodal therapies for high risk patient groups for whom radical surgery would be contraindicated. Surgery for gastric cancer needs to be determined by a multidisciplinary team to ensure appropriate procedure selection for an individual patient. This allows all relevant information to be considered and to provide the best chance for high quality patient outcome.

PG 9.02 SPEAKER ABSTRACT

Is endosonography and laparoscopy essential before neoadjuvant therapy?

C. Schuhmacher. *Chirurgische Klinik und Poliklinik, TU München, München, Germany*

Clinical assessment of tumour stage is an essential step prior to multimodal therapy in gastric cancer. Based on recent literature indication for neoadjuvant chemotherapy excludes patients with mucosal or sub-mucosal cancer (early gastric cancer) or – in advanced cases – patients with a peritoneal seeding. Different radiological and nuclear imaging techniques are available for staging. Nevertheless, they do not provide sufficient resolution in order to evaluate the depth of infiltration of primary tumour in the hollow organ (T-category) or to accurately assess the peritoneal cavity (M-category). Only advanced clinical situations such as ascites formation or bulky intra-peritoneal masses will be detected by (noninvasive) imaging modalities (without direct inspection of the peritoneum). Thus, endoscopic ultrasound and diagnostic laparoscopy are the only diagnostic tools to address this clinical category with acceptable accuracy.

Several randomized trials are available for multimodal therapy of gastric cancer. Among these the EORTC 40954 trial is the only clinical study including both staging modalities, EUS and diagnostic laparoscopy (DL) into the pre-therapeutic staging process. The recently published French FFCD trial solely involved EUS in the clinical staging modalities and the pivotal MAGIC trial from UK did neither involve endoscopic ultrasound nor diagnostic laparoscopy.

Although EUS is known for high accuracy in discriminating clinical T-categories, the results of the EORTC 40954 trial reported less convincing numbers in this matter. 50% of patients in the surgery alone treatment arm revealed tumours with T-categories less advanced than pT3. This might be attributed to the high incidence of adenocarcinoma of the esophago-gastric-junction (AEG type II and III), a tumour location lacking serosal coverage.

In a prospective analysis of patients with locally advanced gastric cancer undergoing a diagnostic laparoscopy at the TU Munich, in 24% of all cases the diagnostic laparoscopy revealed findings, which beyond the standard imaging modalities, changed the initial stage of the disease.

In addition, detection of peritoneal seeding of gastric cancer will avoid unnecessary laparotomy and protect patients from a prognostically problematic tumour resection.

Retrieving peritoneal fluid for cytological assessment during the staging laparoscopy is an additional and highly useful diagnostic tool to rule out potential sources of therapy failure. Disseminated tumour cells result in a significant upstaging of the disease with dismal prognostic consequences even if no intra-peritoneal tumour growth is visible. These patients should rather be treated with a less toxic and yet lasting chemotherapy regimen including modern targeted antibody components.

Endoscopic ultrasound and diagnostic laparoscopy are essential in clinical staging of gastric cancer, especially in the context of multimodal therapy. Tomographic imaging modalities lack accuracy to detect both, early gastric cancer within the stomach wall and incipient peritoneal seeding.

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PG 9.03 SPEAKER ABSTRACT

Can adjuvant radiochemothrapy replace extended lymph node dissection?

E.P.M. Jansen. *Department of Radiation Oncology, Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands*

Surgical resection remains an essential part in the curative treatment of gastric cancer [1]. However, with surgery only, long-term survival is poor (5-year survival <25% in Europe). Randomized studies that compared limited (D1) lymph node dissection with more extended (D2) resections in the Western world, failed to show a survival benefit for more extensive surgery. 15-year follow-up of the Dutch D1D2 trial showed that D2 surgery was associated with lower locoregional recurrence rates and gastric-cancer related death rates than D1 surgery [2]. Centralization of gastric cancer surgery in Denmark increased the percentage of patients with at least 15 lymph nodes removed from 19 to 76 [3]. A substantial increase in survival was found with peri-operative chemotherapy in the MAGIC study [4]. In addition, the SWOG/Intergroup 0116 study showed that postoperative chemoradiotherapy prolonged 5 year overall survival compared to surgery only.[5] Since 54% of patients in this study had a D0 dissection, many judged chemoradiotherapy (CRT) to compensate for suboptimal surgery. Investigators from the SWOG concluded that surgical undertreatment undermined survival in their trial, but subgroup analysis did not have enough power to detect an association between D-level and outcome [6]. However, in a Korean study with almost 1000 patients who all underwent a D2 dissection, 544 patients received postoperative CRT accordingly to the SWOG regimen [7]. Although patients were not compared in a randomized trial, the study demonstrated a survival benefit with postoperative CRT (5 year OS 57.1% vs. 51%, $p = 0.02$). The percentage of patients that had >15 lymph nodes removed was >98% in both groups. Results of the already completed ARTIST trial from Korea (clinicaltrials.gov NCT 00323830), where 458 patients are randomized between postoperative capecitabine/cisplatin and capecitabine plus 45 Gy radiotherapy after D2 dissection, are eagerly awaited. At our institute phase I–II studies with adjuvant cisplatin and capecitabine based CRT have been performed in over 120 patients with resected gastric cancer. These studies demonstrated that intensive postoperative concurrent CRT has manageable toxicity [8–10]. Retrospective comparison of patients treated in these studies with those that had surgery only in the D1D2 study, demonstrated that postoperative CRT was associated with better outcome, especially after D1 or a R1 resection [11]. For daily practice it remains unclear whether patients with operable gastric cancer should have pre- (and post-) operative chemotherapy or postoperative CRT. To resolve this dilemma the CRITICS (ChemoRadiotherapy after Induction chemotherapy In Cancer of the Stomach) study was developed. The CRITICS study is a randomized phase III trial (clinicaltrials.gov NCT 00407186) in which all patients receive 3 courses of ECC chemotherapy and then have D1+ gastric resection. After surgery