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Radiochemotherapy (RCT) of locally advanced oesophageal cancer – preoperative RCT vs. definitive RCT alone

T. Hoelscher[1], C. Petersen[1], M. Dawel[1], C.H. Koehne[2], D. Ockert[3], Th. Herrmann[1], M. Baumann[1]. *[1] Dep. of Radiation Oncology, Medical Faculty of the TU Dresden, Dresden, Germany; [2] Dep. of Internal Medicine I, Medical Faculty of the TU Dresden, Dresden, Germany; [3] Dep. of Visceral and Thoracic Surgery, Medical Faculty of the TU Dresden, Dresden, Germany*

Background: Since 7-96 neoadjuvant RCT has been performed at the University Hospital in Dresden, Germany for selected patients (pts.) with locally advanced oesophageal cancer without distant metastasis.

A retrospective comparison of preoperative RCT vs. definitive RCT alone will be presented to compare the efficacy of both treatment strategies.

Material and methods: Between 9-95 and 10-02 131 pts. have been treated in a curative setting. 61 with preoperative RCT and 70 with definitive RCT. Preoperatively 40 Gy have been administered. Pts. being further inoperable or pts. with definitive RCT received 60 - 66 Gy. Simultaneous chemotherapy consisted in CDDP and 5-FU. The main endpoint of this analysis was overall survival.

Results: According to overall survival no significant difference in this intent-to-treat analysis was observed between preoperative and definitive RCT: 303 days vs. 315 days (Fig. 1).

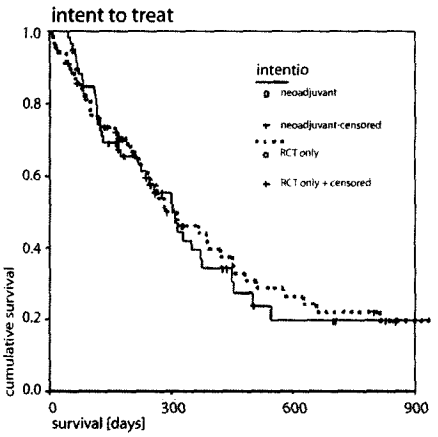

Fig. 1. "Intent to treat" analysis of 131 pts. with advanced oesophageal cancer treated with preoperative RCT or RCT alone.

27 of 61 pts. (44%) were successfully operated after preoperative RCT. Pts. treated with neoadjuvant RCT according to protocol had a higher 2-years survival rate compared to pts. got definitive RCT (42% vs. 28%, Fig. 2). However, this difference is not significant (p=0,26, log-rank). Pts. not eligible to receive successful surgery had a much poorer survival, although they received a cumulative dose of 66 Gy.

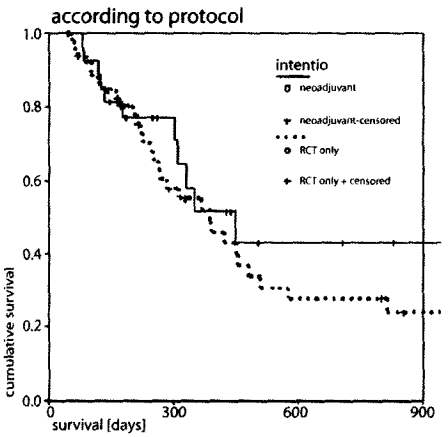

Fig. 2. Survival of 78 pts. treated "according to protocol" either with preoperative RCT or RCT alone.

Conclusions: The decision process for pts. with locally advanced oesophageal carcinoma receiving a preoperative RCT needs to be carefully evaluated. This is demonstrated by the fact that pts. who did not receive surgery had a poorer survival in this concept compared with pts. treated with RCT alone. An intensive interdisciplinary approach with high surgery competence of the centre is mandatory.

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Chemoradiotherapy after surgery for adenocarcinoma of the stomach. Final results of a prospective, phase II, single-institutional program

F. Arias de la Vega[1], R. Vera[1], M.A. Domínguez[1], B. Larrinaga[2], J.J. Iñigo[3], P. Romero[1], P. Villafranca[1], E. Martínez[1], J. García-Foncillas[4], A. Manterola[1]. *[1] Hospital of Navarre, Oncology, Pamplona, Spain; [2] Hospital of Navarre, Pathology, Pamplona, Spain; [3] Hospital of Navarre, Surgery, Pamplona, Spain; [4] University of Navarre, Oncology, Pamplona, Spain*

Background: To evaluate the effect of surgery plus postoperative (adjuvant) chemoradiotherapy on the survival of patients with resectable adenocarcinoma of the stomach., we begun at the Hospital of Navarre in 1993, a phase II prospective study.

Material and methods: Forty six patients with pathological N+ or T3-T4 gastric cancer, were treated with postgastrectomy chemoradiotherapy. There were 33 men, and 13 women. By stage, there were 5 p. stage IB (11%), 9 p. stage II (19.5%), 12 p. stage III-A (26%), 9 p. stage IIIB (19.5%), and 11 p. stage IV (24%). R0 gastrectomy 37 p. (80%), R1 (residual microscopic disease) 8 p.(17%), and 1 p. had R2 resection. Treatment were similar than the used by Macdonald trial (1), and consisted of 425 mg of fluorouracil per square meter of body-surface area per day, plus 20 mg of leucovorin per square meter per day, for five days, followed by 4500 cGy of radiation at 180 cGy per day, given five days per week for five weeks, with modified doses of fluorouracil and leucovorin on the first four and the last three days of radiotherapy. One month after the completion of radiotherapy, two five-days cycles of fluorouracil (425 mg per square meter per day) and leucovorin were given one month apart.

Results: With median follow-up of 96 months, the median overall survival was 46 months. Five-years overall survival was 45%, and 5-Years specific-survival was 54%. Local recurrence occurred in 23% of the patients, and regional or distant metastases in 40%.

Toxicities: grade 3-4 toxic effects occurred in 16 p. (35%). Cumulative hematological toxicity precluded full chemotherapy in 9p (20%). There were not any toxic-related death.

Conclusion: In our series, patients with T2N0 stage were excluded for treatment. Nevertheless, our results are similar to the ones published by MacDonald, and it indicates that this combined treatment- now standard treatment for gastric cancer- can be administered safely in a Tertiary Hospital, and also that the results of the Intergroup can be reproduced in the clinical practice.

Reference

[1] Macdonald JS, Smalley SR, Benedetti J, et al: chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med,345:725-29; 2001.

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Treatment of pancreatic tumour cells with IC261 and spindle poisons alone or in combination leads to different effects on cell growth

C. Brockschmidt, A. Hillenbrand, M. Stoeter, D. Henne-Bruns, U. Knippschild. *University of Ulm, Department of Visceral- and Transplant Surgery, Ulm, Germany*

Background: For patients with advanced pancreatic cancer the established chemotherapies did not extend the median survival beyond several months. New approaches have to be developed. It has been shown, that the inhibition of Casein kinase 1 Delta (CK1δ) has similar inhibitory effects on the growth behaviour on tumour cells as spindle poisons.

Methods: Panc Tu 1 and Panc 89 cells were either treated with the CKId specific inhibitor IC261, the spindle poisons nocodazol and taxol, alone or in combination were analysed by FACS analysis at different time points. Additionally, RNA and protein levels of various proteins involved in cell cycle control and apoptosis were analysed by TaqManTM and Western Blot analysis, respectively.

Results: Our FACS analysis of different pancreatic tumour cells treated with IC261, nocodazol or taxol at different time points revealed a cell cycle arrest for IC261 or nocodazol treatment, whereas in the case of

taxol treatment cell death was induced. Synergistic effects were seen in a combined treatment of IC261 with nocodazol. In contrast IC261/taxol treatment suppressed the induction of cell death of taxol. For cell cultures undergoing different treatment we detected the changes in RNA and protein levels for proteins involved in cell cycle arrest and apoptosis.

Conclusion: Our results show, that treatment of different pancreatic tumour cells with spindle poisons or the CK1δ specific inhibitor IC 261 differently effects cell growth. Furthermore, combination of spindle poisons with IC261 can enhance or modulate the effects of spindle poisons alone. If these results could be validated in an animal model, new therapeutic options might arise.

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An analysis of CDH1 –160 C/A promoter polymorphism and the risk of diffuse gastric cancer in Italy

A. Ruzzo[1], C. Spino[2], F. Graziano[3], E. Testa[3], A. Costagliola[1], F. Arduini[4], D. Santini[5], F. Andreoni[6], M. Magnani[1]. *[1] University of Urbino, Institute of Biological Chemistry "G. Fornaini", Urbino, Italy; [2] Biostatistical consultant, Ann Arbor; [3] Hospital of Urbino, Medical Oncology Unit, Urbino, Italy; [4] University of Ancona, Dept. of Hispopathology, Ancona, Italy; [5] University Campus Biomedico, Dept. Medical Oncology, Rome, Italy; [6] University of Urbino "Carlo Bo", Center of Biotechnology, Urbino, Italy*

The E-cadherin protein belongs to the family of calcium-dependent cell-cell adhesion molecule and it plays a fundamental role in the maintenance of cell differentiation and the normal architecture of epithelial tissues. Mutations in the E-cadherin gene (CDH1) have been frequently found in sporadic and hereditary diffuse gastric cancer. To date, polymorphisms in CDH1 have shown a functional role in experimental models. In particular, the C/A single nucleotide polymorphism (SNP) at position -160 bp relative to the transcription-start site of CDH1 promoter was found to be associated with impaired transcriptional efficiency of the gene; in fact, the *A*-allele has been shown to decrease the transcriptional efficiency by 68% compared with the *C*-allele in prostate cancer cell lines. Given the high incidence of gastric cancer in some areas of Central Italy, we have investigated the frequency of the CDH1 160 SNP in sporadic cases of diffuse gastric cancer and healthy controls who were natives of Central Italy.

The study population consisted of 91 patients with sporadic diffuse gastric cancer and 54 healthy controls for a total of 145 individuals. Seventy-four percent (40/54) of the cases were female, while 49% (45/91) of the controls were female. Genotype and allele frequencies differed significantly among cases and controls, with *A*-allele carriers occurring more frequently in diffuse gastric cancer patients ($p<0.0001$, logistic regression model controlling for the presence of the *A*-allele). *A*-allele carriers had a higher relative risk of diffuse gastric cancer (OR = 9.0, 95% CI 4.1-19.5) compared to *C*-only carriers. AC had an increased relative risk of diffuse gastric cancer (OR = 8.9, 95% CI 3.9-20.5) as did AA (OR= 9.1 95% CI 2.4-34.9) compared to CC genotypes.

-160 SNP	Controls	Cases
AA	3 (6%)	15 (16%)
CA	11 (20%)	54 (59%)
CC	40 (74%)	22 (24%)
Total	54	91

These data suggest an association between the SNP and diffuse gastric cancer susceptibility, but large epidemiologic studies are needed to confirm the etiologic role of the C/A SNP at position -160 of the CDH1 promoter.

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Intraluminal high dose rate brachytherapy in the treatment of carcinomas of the subhepatic region

J. Dvorak[1], J. Petera[1], Z. Papik[2], T. Kohlova[1], B. Melichar[1], Z. Zoul[1], R. Voboril[3], J. Mergancova[3], P. Jandik[3]. *[1] Oncology and Radiotherapy, [2] Department of Medicine, [3] Department of Surgery, Charles University Medical School and Teaching Hospital, Hradec Kralove, Czech Republic*

Background: The prognosis of carcinomas of the subhepatic region is poor, and therapeutic efforts are mostly limited to palliation. The aim of this study was to compare retrospectively the effectivness of administration of intraluminal high dose rate brachytherapy (ILBT) inserted via drains using percutaneous biliary, transduodenal or diahepatal approaches in the palliative treatment of carcinomas of the subhepatic region.

Materials and methods: Between February 1997 and February 2003, 51 patients, 32 females and 19 males, mean age 65 (range 41-90) years, were treated with ILBT. Seven patients had gallblader carcinoma, 31 bile duct carcinoma, and 13 pancreatic carcinoma. All patients were irradiated by the source of Iridium-192 using high dose rate remote afterloading device Gammamed 12i (Isotopen-Technik Dr.Sauerwein). Forty-four patients received the total dose 30-42 Gy (4-6 fractions) twice weekly and 7 patients 10-15 Gy (2 fractions) twice weekly in combination with external beam radiotherapy 45 Gy/25 fractions during 5 weeks. The dose reference point was selected 10 mm from the source axis in all cases. The mean length of irradiated volume was 4 cm (range 3-9 cm). Twenty-four patients received brachytherapy via a percutaneous biliary drain, 18 patients via a nasobiliary drain, 2 patients via a nasobiliary drain with the bile derived by a parallel duodenobiliary drain, 1 patient via a nasobiliary drain inside the metal-mesh self-expandible stent, 1 patient via a nasopancreatic drain in the duct of Wirsung and 5 patients after Roux-en-Y hepaticojejunoanastomosis via a diahepatal U drain. Twenty-six patients received additional treatment after brachytherapy: systemic chemotherapy in 15 cases and hepatic arterial chemotherapy in 6 cases.

Results: The mean survival time from the time of initiation brachytherapy to the last control in February 2003 was 276 days (range 42-678) in brachytherapy inserted via a percutaneous biliary drain, 282 days (range 34-965) in brachytherapy inserted via a transduodenal drain and 531 days (range 85-1271) in brachytherapy inserted via a diahepatal drain.

Conclusions: Transduodenal intraluminal brachytherapy is technically feasible. The survival was not significantly different in inoperable patients treated with brachytherapy inserted via a percutaneous biliary drain in comparison with transduodenal drain. Transduodenal insertion of brachytherapy is not competitive to the percutaneous approach but widens the options of the treatment of carcinomas of the subhepatic region. Intraluminal brachytherapy of pancreatic head carcinoma is feasible only via a transduodenal approach. We observed significantly longer survival in patients treated with diahepatal U drain after Roux-en-Y hepaticojejunoanastomosis compared with those treated by brachytherapy inserted by percutaneous biliary or transduodenal drains.

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Does the temperance prevent metachronous multiple squamous cell carcinoma of the esophagus after endoscopic resection?

Y. Shimizu[1], H. Tsukagoshi[2], M. Fujita[3], M. Hosokawa[4], M. Kato[1], M. Asaka[5]. *[1] Hokkido University Medical Hospital, Division of Endoscopy, Sapporo, Japan; [2] Keiyukai Sapporo Hospital, 2. Department of Internal Medicine, Sapporo, Japan; [3] Keiyukai Sapporo Hospital, Department of Pathology, Sapporo, Japan; [4] Keiyukai Sapporo Hospital, Department of Surgery, Sapporo, Japan; [5] Hokkaido University School of Medicine, Third Department of Internal Medicine, Sapporo, Japan*

Background: Alcohol consumption is regarded as the major risk factor of squamous cell carcinoma of the esophagus, and some authors reported that heavy drinking would predisposes a person to multiple esophageal carcinoma. We previously reported that metachronous multiple carcinoma of the esophagus frequently arise after endoscopic mucosal resection (EMR)(Gastrointest Endosc 2001; 54: 190-4). The aim of this study was to determine whether abstinence from alcohol prevents subsequent carcinoma of the esophagus after EMR.

Methods: Of 134 patients who underwent EMR for squamous cell carcinoma of the esophagus, 92 daily drinkers for whom temperance was recommended were studied. Those who reduced their drinking to 1 day a week or less were regarded as the temperance group, and others were regarded as the non-temperance group. All of the 92 patients were followed-up by periodic endoscopic examination with iodine staining.

Results: Twenty-seven of the 92 patients continued temperance, and were regarded as the temperance group. The median follow-up periods were 38 months (range, 13 to 81 months) in the temperance group and 43 months (range, 12 to 91 months) in the non- temperance group. Metachronous multiple carcinomas developed in 4 (14.8%) of the 27 patients in the temperance group and in 10 (15.4%) of the 65 patients in the non-temperance group. The cumulative proportion of metachronous multiple carcinoma-free subjects in the temperance group was similar to that in the non- temperance group ($P = 0.8681$).

Conclusion: The results suggest that there is no relationship between continuous alcohol consumption after EMR and occurrence of metachronous esophageal carcinoma. Alcohol may act as an initiator of the development of esophageal carcinoma rather than a promoter of esophageal carcinoma.