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Benefits and toxicities of accelerated radiochemo- versus accelerated radiotherapy in advanced head and neck cancer - Results of a German randomized study

S. Staar¹, H.E. Eckel¹, V. Rudat², A. Dietz², M. Flentje³, M. Schroeder⁴, P. Volling⁵, P. Schneider⁴, H. Stuetzer¹, R.P. Mueller¹. ¹University of Cologne, Radiationoncology, Head and Neck Surgery, Medical Statistics, Cologne, Germany; ²University of Heidelberg, Radiationoncology, Head and Neck Surgery, Heidelberg, Germany; ³University of Wuerzburg, Radiationoncology, Wuerzburg, Germany; ⁴City-Hospital, Head and Neck Surgery, Kassel, Germany; ⁵Ev. Hospital, Head and Neck Surgery, Oldenburg, Germany

Purpose: Concurrent chemo- and radiotherapy is proven highly effective in advanced head and neck cancer but associated with increased acute toxicities, especially mucositis. In a randomized phase III study the efficiency and toxicities of accelerated radiochemo- (RCT) versus accelerated radiotherapy (RT) were evaluated.

Materials and methods: This multicentric study opened in 7/1995 and closed patients accrual in 4/1999 with 263 randomized pts. with stage III+IV unresectable carcinomas of the oro- and hypopharynx without any pretreatment. Pts. were randomized either for RCT (2 cycles of 5-FU(600mg/sqm/d)/carboplatin (70mg/sqm), d1-5, 29-33, arm A) or RT only (arm B). Total RT-dose in both arms was 69.9Gy in 38d with a concomitant boost (weeks 1-3: 1.8Gy/d, weeks 4-6: Bid RT with 1.8Gy/1.5Gy). In both arms, there was a second randomization for prophylactic G-CSF (263µg s.c., d15-19) to test the effect on mucosal toxicity. Primary endpoint of the study was 1-year survival with local control (SLC).

Results: This analysis is based on 240 pts. (113 RCT-pts., 127 RT-pts., median FU 22.3 months), qualified for protocol and starting treatment. There were 178 oro- and 62 hypopharyngeal carcinomas, 96% in stage IV. The overall response rate (CR+PR) was 92.4% for RCT and 87.9% for RT (p=0.29). 1- and 2-year locoregional tumor control (LRC) was 69% and 51% after RCT versus 58% and 45% after RT (p=0.14). Median time of continuous LRC was 32 months after RCT versus only 14 months after RT with significant better 1y-SLC of 58% after RCT v 44% after RT (p=0.05). Oropharyngeal carcinomas showed highly better SLC after RCT (60% v 40%, p=0.01), the smaller group of hypopharyngeal carcinomas had no statistical benefit of RCT v RT (p=0.84). Regarding acute toxicities, RCT produced higher rates than RT, especially severe mucositis (68% v 52%, p=0.01). Patients with prophylactic G-CSF developed reduced mucosal toxicity (p=0.07), but also showed significantly reduced LRC (p=0.007), a completely unexpected result. Multivariate Cox regression analysis revealed initial hemoglobin level <13.5g/dl, G-CSF-application, and N2c-3- status as bad prognostic factors for SLC.

Conclusion: Accelerated RCT is more efficient than accelerated RT for patients with advanced oropharyngeal carcinomas. The increased acute toxicities are tolerable. Prophylactic G-CSF may reduce mucosal toxicity but may result in significantly decreased locoregional tumor control.

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Radiotherapy with or without mitomycin C in the treatment of locally advanced head and neck cancer. Results from the IAEA multicentre randomised trial

C. Grau^{1,2}, J. Agarwal², K. Jabeen², R. Jayatilake², A. Khan², T. Hadjiva², I. Wahid², S. Turkan², K. Nair², J. Overgaard^{1,2}. ¹Aarhus University Hospital, Experimental Clinical Oncology, Aarhus University Hospital, Denmark; ²IAEA-CRP E3.30.13 study group

Single agent MMC has previously been shown to improve the outcome of radiotherapy in single institution trials without increasing the normal tissue toxicity. In 1996 the International Atomic Energy Agency (IAEA) initiated a two-armed randomised multicentre trial where head and neck cancer patients were treated with primary curative radiotherapy (66 Gy in 33 fractions with 5 fractions per week) with or without a single injection (15 mg/sqm) of MMC at the end of the first week of radiotherapy. A total of 558 patients were recruited in the trial from Feb 1996 to Dec 1999 from eight centres in Europe and Asia. Patients had stage III (n=264) or stage IV (n=294) squamous cell carcinoma of the oral cavity (n=255), oropharynx (n=170), hypopharynx (n=80) or larynx (n=53). Many of these patients had very advanced tumors. Prognostic factors like age, gender, site and stage were well balanced between the two arms. The first results six months after study closure showed that MMC was very well tolerated in combination with primary radiotherapy. Acute morbidity data were available from 393 patients. The haematological side effects of MMC were very modest (<5% grade 3-4) and did not require any specific interventions. Furthermore,

MMC did not enhance the incidence or severity of acute or late radiation side effects. Confluent mucositis and dry skin desquamation was common, occurring in 56% and 65% of patients, respectively. Patient compliance to follow-up visit was a problem in many of participating centres from Asia. The overall 2-year locoregional tumor control, disease-specific and crude survival rates were 23%, 45% and 38%, respectively. Tumor stage and localization were significant parameters for loco-regional tumor control. There was no significant effect of MMC on locoregional control or survival. In conclusion, this large multicentre study did not show any influence of MMC on the outcome of primary radiotherapy in advanced head and neck cancer.

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Radiation therapy in elderly patients with head and neck cancer: a G.R.O.G.* study on 394 pts. (*Geriatric Radiotherapy Oncology Group - Italy)

L. Loreggian¹, P. Olmi², G. Ausili-Cefaro³, M.L. Friso¹, M. Pignataro¹, F. Pajar², A. Cerrotta⁴, V. Fusco⁵, L. Marmiroli³, G. Scotti¹. ¹Azienda Ospedaliera di Padova, Radiotherapy, Padova, Italy; ²University of Florence, Clinical Physiology-Radiotherapy, Florence, Italy; ³University of Rome - Pol. "A. Gemelli", Radiotherapy, Rome, Italy; ⁴National Institute of Tumors, Radiotherapy, Milan, Italy; ⁵Casa Sollievo della Sofferenza, Radiotherapy, S. Giovanni Rotondo, Italy

Aim of the study: a prospective study on patients aged more than 70 yrs with HN cancer to address the following questions: a) how elderly HNC patients are treated in Italy b) is the choice of therapy justifiable? c) are toxicity and late effects of RT in elderly patients well quantified and identified?

Materials and Methods: in 1997 the GROG performed a study involving 22 Italian RT Dpts. 394 pts (M=305;F=89) aged between 70 and 92 (mean 76.6) were enrolled in the study. Data concerning the type of education, family life, site and stage of disease, type and RT dose, early and late complications and response to treatment, were collected. Response to treatment, PS and late effects were collected 2 mts after the end of therapy and then at 6, 12 and 24 mts.

Results: data showed that elderly pts with HNC observed in Italian RT Departments usually present with a good KPS (=70 in 79%), live with a family (82%), have a high grade co-morbidity in <25% and a weight loss >5 kg in only 12%.

303 pts with primary SCC were evaluable: 62 pts with recurrent disease and 30 with a histology different from carcinoma were excluded. The site of neoplasm was: nasopharynx in 4%, oropharynx in 13%, hypopharynx in 6%, larynx in 47.5%, oral cavity in 21%, paranasal sinus in 5.5% and salivary glands in 3%.

Three pts were stage 0 (1%), 91 stage I (3%), 56 stage II (18%), 59 stage III (19.5%) and 96 stage IV (31.5%). 35 cases underwent surgery alone, 155 RT, 92 adjuvant RT and 18 palliative RT. In 3 cases no therapy.

If cure was the aim, a median dose of 66 Gy was delivered to the primary tumour (T) and 58 Gy to neck nodes (N); a median dose of 60 Gy was administered to T and 54 Gy to N if RT was considered adjuvant. Early toxicity was evaluated 2 mts after the end of RT: grade 3-4 toxicity involving at least 1 site was observed in 22 pts. Of the 155 pts treated with RT for HNC, 64.5% reached a CR and 14.1% a PR 2 mts after the end of RT. After a median follow up of 23 mts, 39.6% are alive with NED and 23.8% died with disease. Of the 92 pts treated with adjuvant RT, 76% reached a CR and 5.5% a PR 2 mts after the end of RT. After a median follow up of 20.2 mts, 62% are alive with NED and 16.3% died with disease.

Conclusions: a) RT in elderly pts with HN-SCC plays a major role in the global therapeutic strategy, alone or as adjuvant treatment. b) a treatment schedule including RT is justifiable, feasible and well tolerated also in elderly pts. c) tolerance to RT seems well quantified and identified.

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Photodynamic therapy with Foscan® (temoporphin) in primary squamous cell carcinoma of the head and neck

C. Hopper. National Medical Laser Centre, London, UK

Aims: This prospective non-randomised Phase II study investigated the complete response (CR) rate to Foscan-mediated photodynamic therapy (Foscan PDT) in patients with primary head and neck cancers; duration of CR and survival time; and tolerability and safety of Foscan PDT.

Method: 114 patients with primary (Tis, T1, T2) squamous cell carcinoma (SCC) of the lip, oral cavity, oropharynx or hypopharynx and Karnofsky status = < 70 received Foscan (0.15 mg/kg IV), followed four days later by single non-thermal illumination of the tumour with red light (20 J/cm2,

irradiance 100 mW/cm², wavelength=652 nm). Response was determined after 12 weeks. Follow-up for 2-5 years is on-going.

Results: 85% of patients achieved CR (95% CI: 76-90%) through application of PDT alone, and a further 6% of patients who initially had a partial response achieved a CR with other adjunctive therapy, giving a total CR rate for PDT alone and PDT with adjunctive therapy of 91%. The majority of CRs (59%) were biopsy-confirmed (26 patients with clinical CR did not undergo biopsy). Mean duration of response was 621 days; one and two-year CR rates were 89% and 86% respectively, survival rates were 90% and 81% respectively. Censored mean patient survival time was at least 650 days (follow-up continues). The most common adverse event was local pain at treatment site. Mild to moderate photosensitivity reactions occurred in 13% of patients. Twelve patients died during the first year (none considered related to Foscan PDT). There were 23 non-fatal serious adverse events, of which 5 were considered related to treatment: two burns, one photosensitivity reaction, one excessive tissue necrosis, one increase in pain and dysphagia.

Conclusion: Foscan PDT is an effective treatment for small primary tumours of the oral cavity, yielding CR rates comparable to those published for surgery or radiotherapy. It is without major toxicity, preserves form and function and does not compromise future treatment options for recurrent, residual or second primary disease.

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"High" (60 mCi) vs. "low" (30 mCi) activities of ¹³¹I as adjuvant treatment for papillary thyroid cancer: the results of a prospective randomized trial

M. Gawkowska-Suwinska¹, M. Turska², J. Roskosz², D. Handkiewicz-Junak², B. Tuleja², Z. Wygoda², Z. Puch², B. Jarzab².
¹ Center of Oncology, Radiation Oncology, Gliwice, Poland; ² Center of Oncology, Nuclear Medicine, Gliwice, Poland

Purpose: To compare the effectiveness of 30 mCi vs. 60 mCi for ablation of thyroid remnants in papillary thyroid cancer (PTC) treated with total thyroidectomy.

Material/Methods: Since 1998 188 patients with PTC in a clinical stage T1-T3N0M0 have been randomly assigned to receive "high" or "low" ablative dose of ¹³¹I: 95 (50.5%) received 60 mCi, and 93 (49.5%) received 30 mCi. Post-therapeutic whole body scintigraphy (WBS), the uptake over the neck (UON), and serum thyroglobulin level (Tg) was obtained 6-12 months after ablation. Other routine imaging procedures included ultrasonography of the neck, and chest X-ray. Ablation has been considered as: very good if there was no uptake in WBS, and UON <0.09%, and Tg ≤ 4 ng/ml; good - if there was only scattered uptake over the neck on WBS, and UON =0.1-0.39%, or Tg =4.1-10 ng/ml; doubtful - if there was residual uptake over the neck, and UON =0.4-0.9%, or Tg =10.1-30 ng/ml; insufficient - if there was a distinct uptake over the neck, or UON ≥ 1%, or Tg <100 ng/ml; local recurrence or dissemination of disease - if WBS and/or other imaging procedures revealed a recurrent tumor or metastases, or Tg ≥ 100 ng/ml.

Results: In a group of patients who received 60 mCi ablation was considered very good in 82 (44%) patients, good in 12 (6%), there were no doubtful or insufficient results, and one (0.5%) early nodal recurrence. In a 30 mCi group ablation was considered very good in 62 (33%) patients, good in 21 (11%), doubtful in 9 (5%), insufficient in one (0.5%), and there were no local recurrences or dissemination. This difference is highly significant (p < 0.005) in favour of 60 mCi, as shown by non-parametrical distribution tests.

Conclusion: The results show a significantly higher effectiveness of 60 mCi for ablation of thyroid remnants in PTC treated with total thyroidectomy. Although long-term effectiveness of adjuvant radioiodine therapy has not been assessed in this study it can be postulated that "low" activities of ¹³¹I should not be routinely used, particularly for patients with high risk of locoregional relapse and/or distant dissemination.

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Locally advanced laryngeal cancer: surgery and radiotherapy vs. radiotherapy alone. A multivariate locoregional control analysis in 2220 patients

R. Suwinski, K. Skladowski, J. Wydmanski, A. Sowa, T. Rutkowski, B. Maciejewski. Center of Oncology, Radiation Oncology, Gliwice, Poland

Purpose: To compare locoregional tumors control rate (TCP) of laryngeal cancer after radiotherapy alone (RTA) or after postoperative radiotherapy (PRT).

Material/methods: For the purpose of the analysis the data on RTA (1493 patients) and PRT (727 patients) were combined. A logistic analysis of the dose-response relationship, and multivariate Cox proportional hazard regression model of recurrence-free survival has been used. The presence of surgery has been considered as one of the variables included in the analysis.

Results: The presence of surgery, T, N stage, Hb concentration at the end of radiation course, total radiation dose and overall radiation treatment time (OTT) have significantly influenced the recurrence-free survival. It is predicted from the logistic model, that for a tumor in a clinical stage T3N0 to achieve the same cure rate as PRT, RTA would require an increase in total dose of as much as 32 Gy given in 2 Gy fractions (TCD50% 36 Gy vs. 68 Gy). It is, however, predicted that an increment in radiation dose of only 12 Gy, with simultaneous shortening of OTT by 14 days and increase in Hb of 1.5 g% may, in the same case, provide an isoeffect of dose escalation alone.

Conclusion: A large difference between TCD50% for PRT and RTA may indicate that surgery and PRT will so far remain a treatment of choice for a considerable proportion of patients with advanced head and neck tumors. The acceptable cure rates in organ-sparing therapy may likely be achieved by enhancing dose intensity of local treatment with concurrent increase (or prevention of decrease) of Hb concentration during radiotherapy.

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Growth patterns of pulmonary metastases of renal cell carcinoma and colorectal adenocarcinoma are distinct in angiogenesis

P. Sardari Nia¹, J.M. Hendriks¹, P.B. Vermeulen², G. Friedel³, E. Van Marck², P. Van Schil¹. ¹ University Hospital of Antwerp, Thoracic and Vascular Surgery, Edegem, Belgium; ² University Hospital of Antwerp, Pathology, Edegem, Belgium; ³ Klinik Schillerhoehe, Thoracic Surgery, Gerlingen, Germany

Objective: Metastatic disease needs angiogenesis to grow, but other vascularisation patterns which are not based on endothelial cell proliferation are described. The hypothesis of this study was that lung metastases (LM), present in a highly vascularised organ with a reduced hypoxic drive for angiogenesis, can demonstrate distinct growth patterns.

Methods: Tissue sections of 59 LM were analysed (13 pts with renal cell carcinoma (RCC) and 6 with colorectal carcinoma (CA). A hematoxylin-eosin and reticulin stain of all LM was done to evaluate growth patterns. Immunohistochemical staining with CD34 antibodies was done to count new formed blood vessels. Microvessel density across the LM was assessed.

Results: 2 growth patterns were found. A nodular growth pattern (NG) did not respect the lung parenchyma architecture, in contrast with the alveolar growth pattern (AG) in which tumor cells filled the alveoli. In each patient, all LM expressed the same growth pattern. The AG was present in 38% and 100% of the patients with RCC and CA respectively (p=0.07). The ratio of the microvessel density of the marginal zone over the central zone was at least 2 in 56% of the LM with an AG compared to 9% with a NG (p=0.02). The number of CD34-positive single endothelial cells was higher in NG than AG, indicating more angiogenesis in NG.

Conclusion: By co-opting existing alveolar wall capillaries, the alveolar growth pattern of pulmonary carcinoma metastases is less angiogenesis-dependent than the nodular growth pattern. Clinical implications are important since several angiogenesis-inhibitors are tested as anticancer agents, and lung metastases with a low angiogenesis intensity will probably not benefit from such treatment.

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Effects of adriamycin and interferon, applied in metronomic doses, on tumor volume, metastases and vessel density in murine renal cell carcinoma

N. Esser², S. Eisele¹, J. Fakler¹, M. Medinger¹, C. Laus¹, D. Marmé², C. Unger¹, J. Dreys¹. ¹ Tumor Biology Center, Medical Oncology, Freiburg, Germany; ² Tumor Biology Center, Molecular Oncology, Freiburg, Germany

Introduction: Chemotherapy is affecting tumor cells as well as endothelial cells. The application of low dose continuous (metronomic) chemotherapy may optimize the effect on the tumor endothelial cells, acting like an un-specific antiangiogenic regimen. Therefore, we evaluated clinically relevant