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Phase II analysis of Taxol and Capecitabine in the treatment of recurrent or disseminated, squamous cell carcinoma of the head and neck region.

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Background: No standard chemotherapy has yet been agreed upon for recurrent or disseminated head and neck cancer, but most regimes tested so far contains Cisplatin; a drug that demands hospitalisation and have a high toxicity profile in this group of patients. We wanted to find a drug regime that could be administered on an outpatient basis and with a more tolerable toxicity. This is the preliminary results from a phase II study with Taxol and Xeloda.

Material: The study started to include patients 3 years ago. 50 patients have been included in the study of which 40 are evaluable. Patients with recurrent or disseminated squamous cell carcinoma are eligible. 42 males and 8 females entered the study: The median age was 55 years (32-73 years). 53% had pharyngeal, 29% oral, 12% laryngeal tumours and a few nose, maxillary and unknown primary tumours. Most patients had inoperable locoregional tumours but 15 patients had distant metastases in lung, lever or bone.

Methods: The treatment consisted of Pacilitaxel (Taxol) 75 mg/m^2, once every third week and Capecitabine (Xeloda) 825 mg/m^2 p.o. b.i.d. for 2 weeks.

Results: Patients who have had at least 3 series were evaluable for response. All patients were evaluable for toxicity, one patient died before treatment. 5 patients had 12 series, 5 had 9 series, 13 had 6 series and 17 patients had 3 series. The overall response shows 1 CR, 14 PR; 12 NC, 9 PD; 4 patients are still in treatment. The patient with complete response had 6 series chemotherapy, and has so far been free of symptoms and disease for more than 1* year. *Toxicity* was moderate. Hair loss after 2 to 3 series was observed in all patients. Hand-and-foot syndrom grade 2-4 were observed in 90%, but reversible even under continous treatment. Three patients had GI toxicity of grade 3+4, of which one had to have his treatment stopped. No heart toxicity was recognized. Blood toxicity was a minor problem. 3 patients had WBC toxicity grade 4 and 6 patients had a neutrophile count grade 4.

Conclusion: Toxicity was tolerable, hair loss and hand-and-foot syndrome were common, but expected. One patient had gastrointestinal toxicity grade 4 and treatment was terminated. The overall response was better than in most series.

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Oxaliplatin plus capecitabine in advanced neuroendocrine tumours (NETs): Is the new WHO classification applicable to daily practice?

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Background: WHO has recently suggested diagnostic criteria for classifying NETs, based on histological evaluation. Consequently *poorly-differentiated* and *well-differentiated* NETs are treated by chemotherapy and biotherapy respectively. We have applied the suggested diagnostic criteria in order to choose an adequate treatment and to check its consistency in efficacy and prognosis.

Methods: Twenty-seven patients (pts) with advanced NETs were treated with oxaliplatin and capecitabine. 15 pts had *well-differentiated* NETs progressing after biotherapy (octreotide or lanreotide), 10 pts had untreated *poorly-differentiated* NETs and two pts had Merkel carcinoma.

The plan of treatment was oxaliplatin e.v. 130 mg/mq day 1 and capecitabine 2000 mg/mq per os day 2-15 every 28 days, for a maximum of 6 cycles.

The median age was 60 years (range 28-71). The primary site of disease was lungs 8, pancreas 7, bowel 3, kidney 2, skin 2, unknown 2 and others 3. Eighteen percent of pts had more than two metastatic sites. At baseline, serum cromogranin A levels were increased in 20 (74%) pts and NSE in 7(26%) pts. Six (40%) pts, with well-differentiated NETs, had carcinoid syndrome consistent in diarrhoea (4) and flushing (5).

Results: In 15 pts with *well-differentiated* NETs the objective responses were 3 PR, 6 SD, 3 PD. Two pts are still in treatment and one patient was lost to follow-up. Biochemical responses were 20% and symptomatic responses were about 50%.In 10 pts with *poorly-differentiated* NETs the objective responses were: 2 PR, 1 SD, 6 PD. One patient was not evaluable because is still in treatment. Biochemical responses were 20%. No responses were observed in Merkel cells carcinoma. The adverse events were mild: nausea and vomiting grade 1-2 in 25% of patients, asthenia grade 3 in 5% of pts and thrombocytopenia grade 1-2 in 20% of pts.

Conclusion: The WHO classification simplifies the identification of high risk pts and they are therefore treated accordingly. Oxaliplatine and capecitabine appears less effective in *poorly-differentiated* NETs than in *well-differentiated* NETs that have previously been given biotherapy. Thusthis chemotherapy regimen is well tolerated and feasible in advanced NETs especially in pts rapidly progressing after biotherapy.

Data management by scientific service I.T.M.O. - Italian Trials in Medical Oncology.

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Conformal radiotherapy for carcinoma of the nasopharynx: pattern of acute and late toxicities

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Purpose: to evaluate the toxicity of conformal radiotherapy (RT3D) alone or associated with chemotherapy in carcinoma of the nasopharynx (NPC).

Patients and Methods: Between 01/89 and 7/01, 51 patients aged from 18 to 86 years (median 47) were treated with curative intent for NPC. All patients received RT3D to a median total dose of 65 Gy with 2 Gy/d. Twenty patients received RT3D alone, 26 received RT3D preceded by chemotherapy (5FU: 600mg/m^2/d D1-5, CDDP: 40mg/m^2/d D2-4, Cyclophosphamide: 500mg/m^2/d D1 and D5, Doxorubicin: 50mg/m^2 D1), 5 received concurrent chemoradiotherapy (Carboplatin: 20mg/m^2 each day). Twenty-six patients were T1T2, 13 T3, 12 T4, 19 N0N1, 13 N2, 17 N3 and 2 Nx; 3 patients were M1. UCNT was present in 40 patients and SCC in 21 patients. The median follow-up was 48 months (range: 19-77). Acute toxicities and chronic toxicities were analyzed according to RTOG and LENT SOMA grades, respectively.

Results: All patients completed RT3D. Grade 2 and 3 acute skin reactions occurred in 14 and 5 patients, respectively. There was no Grade 4. Grade 2, 3 and 4 mucositis were observed respectively in 11, 18 and 7 patients. Acute Grade 3 and 4 dysphagia occurred in 7 and 8 patients, respectively. Weight loss (> 10%) was observed in 13 patients. Only 1 patient experimented Grade 2 fever and 1 Grade 4 thrombopenia. Chronic toxicity included Grade 2 (n=10), Grade 3 (n=13) and Grade 4 (n=2) xerostomia. At 24 months, there were 54.1% patients with Grade>2 xerostomia. There was one Grade 2 trismus. More questionable, Grade 2, 3 and 4 hear loss were observed in 5, 3 and 1 patients, respectively (12.6% at 24 months). Chemotherapy (neoadjuvant or concurrent) didn't increase acute or late toxicities.

Conclusion: Although retrospective, the results suggest that RT3D has acceptable toxicity. Grade 3, 4 acute and late toxicities were equivalent with addition of chemotherapy. IMRT could have the potential to decrease toxicities allowing concurrent chemotherapy addition and/or total dose escalation.

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Re-irradiation for locally recurrent nasopharyngeal carcinoma: treatment results and prognostic factors

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Purpose: To analyze the results and evaluate the prognostic factors in the retreatment of locally recurrent nasopharyngeal carcinoma.

Methods and Materials: Forty-one patients with locally recurrent nasopharyngeal carcinoma were re-irradiated at the University of Istanbul, Cerrahpa&sogon;a Medical Faculty, Department of Radiation Oncology, between 1979 and 2000. There were 32 males and 9 females with median age of 46 years (range: 15 to 67 years). Histologically, 9 tumors (22%) were WHO I (squamous cell carcinoma), 17 (41.5%) WHO II (nonkeratinizing carcinoma), 15 (36.6%) WHO III (undifferentiated carcinoma). According to the 1997 TNM staging system of the American Joint Committee on Cancer (AJCC), the recurrent disease was stage I in 5 (12.2%), stage II in 11 (26.8%), stage III in 6 (14.6%), and stage IV in 19 (46.3%) patients.

The retreatment volume was confined to the site of recurrence in the nasopharynx. Treatment was delivered with 4-6 MV X-rays or Co-60 g rays. The re-irradiation dose ranged from 20 to 60 Gy, with a median of 50 Gy. Treatment was delivered at 1.8-2 Gy/ fraction/ day, 5-days/ week. Chemotherapy was used in 17 (41.5%) patients.

Results: Median follow-up was 23 months (range: 3 to 143 months). The 2-, 5-, and 10-year local progression-free rates were 39, 23, and 23% respectively. 14 (34.1%) were free of further local recurrence after retreatment. A total of 27 patients (65.9%) had local failures and 24 patients (58.5%) had neck failures with a median time to recurrence of 12 months and 13 months, respectively. The 2-, 5-, and 10-year actuarial overall survival following retreatment was 48, 28, and 11% respectively. On univariate analysis, age (p=0.0467), total re-irradiation dose (p=0.0008) were significant prognostic factors for local progression-free rate. For overall survival, age, total re-irradiation dose, stage, T stage were significant. On multivariate analysis only total dose (p=0.005) was significant for local-regional progression-free rate and total re-irradiation dose (p=0.021), interval to recurrence, stage were significant for overall survival.

Conclusion: Early diagnosis of local recurrence and adequate total dose by re-irradiation are crucial for improving the chance of local salvage and survival.

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Long time treatment outcome of accelerated hyperfractionated radiotherapy for stage II laryngeal cancer

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Purpose/objective: Laryngeal preservation was a very important issue in the quality of life of patients with laryngeal cancer. However, it has been considered that conventional fractionation radiotherapy (CFR) is not good enough for cases with relatively large volume tumor. To improve the local control and laryngeal preservation rate in stage II laryngeal cancer, we conducted a Phase II trial of accelerated hyperfractionated radiotherapy (AHFR) since April 1986. In this study, we analyzed long time treatment outcome of these group to compare with our historical control of CFR group.

Materials & Methods: From April 1986 to December 2001,we treated 83 cases of stage II laryngeal cancer with AHFR. The AHFR group was irradiated with a fraction dose of 1.5 Gy twice a day at least 6 hours apart, 10 times a week to a total dose of 72 Gy within 6 weeks. The CFR group consisted of 89 cases treated from December 1966 to December 2001. Pathological type of all cases in both groups was squamous cell carcinoma. We divided glottic T2 into T2a (no impaired vocal cord mobility) and T2b (with impaired vocal cord mobility). In AHFR group, there were 63 glottic (T2a 51, T2b 12), 17 supraglottic and 3 subglottic tumors. In CFR group, there were 76 glottic (T2a 59, T2b 17), 9 supraglottic and 4 subglottic tumors. Patient characteristics of age, gender, pathological differentiation, field size, anterior commissure involvement, and hemoglobin concentration did not differ between the two groups.

Results: Five-year actuarial local control rate (LCR) was 73.0% for AHFR group and 70.0% for CFR group (n.s.). Five-year LCRs were 76.1% and 73.9% for glottic cancers (n.s.), 73.3% and 76.6% for glottic T2a cancers (n.s.) and 88.9% and 64.7% for glottic T2b cancers (p

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Is the usefulness of routine triple endoscopy for head and neck cancer patients debatable?

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Background: The use of tobacco and/or alcohol is linked with the occurrence of head and neck squamous cell carcinoma, esophagus cancer and lung cancer. If this carcinogenic factor can induce the development of a cancer in one of these locations, it would seem reasonable that a second cancer could appear in another of those areas. The aim of the present study was to analyze the results obtained by the triple endoscopy during the initial evaluation of a primary carcinoma of the head and neck. Patients and methods: patients had no evidence of metastasis or of second primary cancer on the thoracic CT scan or chest X-ray. Second synchronous primaries were defined by a tumor located at a site distant from the margin of the first primary head and neck tumor, separated by normal mucosa. All patients had a triple endoscopy including nasopharyngoscopy, laryngoscopy, pharyngoscopy, bronchoscopy and esophagoscopy.

Results: A total of 487 patients with a squamous cell carcinoma of the head and neck was studied. A synchronous primary invasive carcinoma of the lung and the esophagus were diagnosed in 5 (1%) and 10 (2%) patients, respectively. In addition, 9 lesions were considered to be a regional extension of the primary tumor to the esophagus, and 9 in-situ carcinomas were observed. Interestingly, a significant relationship was found between the risk of second synchronous esophageal carcinoma and the initial location of the primary head and neck cancer ($\chi 2$ test: p = 0.002). Esophageal cancer was observed in 1.3% of the patients with an oropharynx tumor, 2% of the patients with a larynx tumor, 0% of the patient with an oral cavity tumor and 9.2% of the patients with an hypopharynx tumor.

Conclusion: The role of bronchoscopy and esophagoscopy in the presence of a normal thoracic CT-scan is questioned because of the presence of a second esophageal and/or lung primary tumor is relatively low for the overall incidence. Nonetheless, based on the same incidence criterion, it seems reasonable to schedule a routine esophagoscopy for patient with hypopharynx squamous cell carcinoma.

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Adjuvant chemo-radiotherapy in high risk head and neck elderly cancer patients (pts).

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Introduction: The loco-regional failure of pts with positive margins (+) and/or vascular/perineural invasion (VI/NI) and/or extracapsular spread (R+) is high and results in poor survival. Adjuvant chemo-radiotherapy (CT-RT), as recently shown, improves the treatment outcome but its applicability to elderly (EL) cancer pts is not established.

Patients and Methods: Forty EL pts (median age=73.5 yrs; range 70-78) were enrolled (35 m, 5 f; PS0 =26, PS1=12, PS2=2; site= oral c. 10, oropharynx 12, hypopharynx 8, larynx 10; pT N, 8 / pT N, 12 / pT N, 8 / pT N, 12) with the following poor-prognosis characteristics: (+)=6, VI=14, NI=16; R+=26. All pts were treatetd with CT (carboplatin 30 mg/m^2 d. 1⋄ 5 of the week 1,3,5) concomitant with RT (54 Gy + 10 Gy on high risk volumes; 1.8 Gy/d).

Results: No grade 4 toxicity was observed. Grade 3 toxicity: mucositis, 25%, neutropenia, 15%, dermatitis, 5%, thrombocytopenia, 2%. Median RT given dose = 52 Gy + 10. Thirty-two pts (80%) received 3 cycles of CT, 6 (15%) 2 cycles and 2 (5%) one cycle. Three-year estimates are as follows: disease-free survival = 58%, overall survival=64%, time to progression=64%, local control=79%).

Conclusions: The results confirm that adjuvant CT-RT can be performed successfully in EL pts who are physically healthy enough to receive such treatment. The results are better than those observed in a superimposeable previous group treated with RT alone and are very similar to those reported in a younger group with the same poor prognosis characteristics treated with CT-RT.

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Medullary thyroid carcinoma (MTC): genetic screening in Slovenia 1997-2002

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Background: MTC is a rare, endocrine tumor that occurs sporadically or is inherited. In hereditary MTC, germ line point mutations in RET proto-oncogene (RET gene) are responsible for the development of tumor and inheritance of settings MEN 2A, 2B and FMTC. Inherited MTC can be identified by genetic screening.

The aim of our study was to identify carriers of RET gene mutations in our patients with MTC and their kindred. The decision for therapeutic or prophylactic thyroid surgery was based on genetic testing results and clinical features.

Methods and patients: From 1969-2002, 105 (44 M (16-93y), 61 F (12-78y)) patients with MTC were treated and /or diagnosed at the Institute of Oncology, Ljubljana. From 1997 onwards, genetic testing was performed in 72 (29 M (16-93y), 43 F (12-77y)) of 105 (71.4%) patients with MTC and