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RADIATION NECROSIS OF THE MANDIBLE AFTER RADIOTHERAPY OF 921 OROPHARYNX AND ORAL CAVITY CARCINOMAS

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With megavoltage radiotherapy (RT) incidence of bone radiation necrosis of the mandible (BRN) has been decreased, but it is still a serious complication. The purpose of this study was to evaluate over a 15 year period of time, incidence and predictive factors of BRN after treatment of 921 carcinomas of the oropharynx and oral cavity.

The mean age was 58.3 years. 881 were male and 40 female. RT technique was homogeneous using to lateral opposed fields treated at each session. 815 patients (pts) were treated using a Cobalt 60 unit and 46 with 10 Mv photons. Total dose ranged from 40 to 82 Gy (mean dose of 68 Gy). Dose per fraction ranged from 1.8 to 5.0 Gy. For 67 pts a boost was delivered with brachytherapy. 321 pts received chemotherapy (neoadjuvant or concomitant). For 210 pts surgical resection of the tumor was performed before RT. 303 pts were toothless, the others received fluoride applications.

60 patients (6.5%) developed BRN with a mean delay of appearance of 12.3 months (5 to 63). Surgical resection of the mandible was necessary for 28 patients (46%). Uni and multivariate analysis showed that factors associated with a high incidence of BRN were a total dose over 70 Gy, a dose per fraction > 3 Gy, a boost given with brachytherapy and a combination of surgery and radiotherapy.

We concluded that BRN is rare complication but incidence could be decreased with optimisation of technical parameters of radiation therapy.

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LOCOREGIONAL CONTROL AND DISEASE SPECIFIC SURVIVAL AFTER ACCELERATED HYPERFRACTIONATED RADIOTHERAPY IN THE TREATMENT OF SUPRAGLOTTIC CARCINOMA

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Materials and Methods: The records of 165 patients undergoing BID radiation for carcinoma of the supraglottis from 1981–1992 were reviewed. Patients received 66 to 72 Gy in 1.6 Gy bid fractions and received a planned 7 to 14 day break. Median follow-up was 56 months. Five-year actuarial local control, regional control and disease-specific survival rates are reported.

Results: For T_1, T_2, T_3, and T_4 tumors, local control was: 95%, 86%, 77% and 42%, respectively ($P = 0.002$), and disease-specific survival was: 79%, 88%, 78%, and 40%, respectively ($P = 0.0004$). For N_0, N_1, N_{2-3} disease, local control was: 86%, 73%, and 54%, respectively ($P = 0.005$), and disease-specific survival was: 86%, 53%, and 54%, respectively ($P = 0.0001$). Regional control by T and N stage was non-significant. With surgical salvage, T_1, T_2, T_3, and T_4 ultimate local control was: 95%, 92%, 88%, and 51%, respectively ($P = 0.001$). The laryngeal preservation rate for the entire group was 83% and for T_1, T_2, T_3, and T_4 tumors was: 96%, 87%, 78%, and 56%, respectively. Total treatment time greater than 43 days resulted in a decreased local control: 87% versus 70% ($P = 0.002$), and decreased disease-specific survival: 84% versus 69% ($P = 0.01$).

Conclusions: Accelerated hyperfractionated radiotherapy resulted in excellent locoregional control, disease-specific survival, and laryngeal preservation rates for T_{1-3} and node negative patients. T stage, N stage and total treatment time were predictors of outcome. T_4 tumors or node positive neck disease, even N_1, portended a poor prognosis, and therefore these patients should be entered into protocols that include adjuvant therapy.

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THE IMPORTANCE OF OVERALL TREATMENT TIME FOR THE OUTCOME OF RADIOTHERAPY OF ADVANCED HEAD AND NECK CARCINOMA IS DEPENDENT ON TUMOR DIFFERENTIATION

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Five hundred and one patients with advanced supraglottic and pharyngeal carcinoma with histopathological grading were treated with planned split-course (191 pts in the DAHANCA 2 protocol) or continuous radiotherapy (310 pts in DAHANCA 5). Irradiation were given with 2 Gy/fx, 5 fx/wk to a dose of 66–68 Gy in 91/2 or 61/2 weeks, respectively. Locoregional tumor control was significantly better in patients characterized by female sex, small T-classification, no nodes, poorly differentiated tumors and treatment given with short overall time. Overall, split-course and continuous treatment resulted in a 5-year loco-regional control of 30% and 42% ($P = 0.007$), respectively. However, the detrimental effect of split-course were only found in moderately and well differentiated tumors where the 5-year tumor control were 41% and 21% after continuous and split-course treatment, respectively ($P = 0.0009$). In contrast, poorly differentiated tumors gave tumor control values of 43% for continuous and 41% split-course treatment ($P = 0.69$). A Cox multivariate analysis confirmed that, among others, overall treatment time were a significant prognostic parameter in moderately and well differentiated tumors ($P = 0.0002$), but not in poorly differentiated ($P = 0.93$). It is suggested that the ability to accelerate repopulation may be lost by dedifferentiation. *Supported by the Danish Cancer Society*

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LARYNGEAL CARCINOMA:—TREATMENT INTERRUPTION AND OUTCOME

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Two patient groups have been identified from a data base of 965 patients with carcinoma of the larynx. One group of 393 patients had squamous cell carcinoma of the larynx arising in the glottis—no nodal involvement; the other group of 163 patients had tumours arising in the supraglottic region. The second group was a more heterogenous group some patients had nodal involvement at the time of presentation. All patients were treated on a linear accelerator. Patients were treated using a variety of dose-fraction-time schedules.

Mathematical modelling using linear quadratic equation was carried out. This shows that a break in treatment if a week reduces the local tumour rate for glottic tumours by 12% or about 25 per day. Local tumour control rates increased as the effective dose was increased. The data for tumours arising in the supraglottic region is not so convincing though it does show that prolongation of treatment time reduces local tumour control rates. The effects of longer times can be nullified by increasing the effective dose. The supraglottic subject, however, is very heterogenous, and the groups within the subset are small.

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RANDOMIZED PHASE II STUDY OF WEEKLY CISPLATIN WITH OR WITHOUT AMIFOSTINE IN PATIENTS WITH ADVANCED HEAD AND NECK CANCER

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High dose single agent cisplatin (C) regimens yield high response rates in advanced head and neck cancer (HNC) but nephro-, neuro- and ototoxicity preclude further dose escalation. In weekly C regimens bone marrow toxicity causes frequent treatment delays jeopardizing the dose intensity of C.

In this study patients (pts) with HNC are randomized between C 70 mg/m^2/wk for six weeks with or without amifostine (AMI) 740 mg/m^2. AMI is administered as a 15 min infusion directly prior to C. C is administered in 250 cc 3% NaCl as a 1-hour infusion with standard pre- and posthydration. The antiemetic schedule consists of thietylperazine, ondansetron and dexamethasone.

Up till 3/95 53 pts are randomized; 39 are fully evaluable for response and toxicity, one pt is not evaluable and 13 too early for evaluation.

Characteristics of the 39 fully evaluable pts: male:female ratio is 29:10; median age 52 years (range 36–68), median WHO performance status 1 (0–2); locally advanced disease 30 pts, locally recurrent 7 pts metastatic disease in 2 pts. Eighteen pts were randomized to C + AMI and 21 to C. In total these 39 pts received 210 C administrations, median 6 per patient (range 3–6), equal in both treatment arms. In the C alone arm 5/21 pts had treatment delays because of bone marrow toxicity versus 0/18 in the C + AMI arm. Thrombocytopenia grade 3 + 4 was

also more frequent in the C alone arm: 5/21 versus 1/18. Other differences observed in favour of the C + AMI arm are: hypomagnesaemia > CTC-grade 1 in 2/18 versus 8/21. Side effects of AMI were short lasting hypotension in 7 pts and occasional sneezing. Other toxicities are until now not different between both treatment arms. A CR was observed in 2 and a PR in 21 pts (RR%: 60%). The study will continue to 60 evaluable pts. In case of significant reduction of toxicity by the addition of AMI further dose escalation of C is planned.

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INDUCTION CHEMOTHERAPY BEFORE RADIOTHERAPY IN OROPHARYNGEAL CARCINOMA. A RANDOMIZED TRIAL

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From 2/86 till 3/91 at Institut Gustave-Roussy in Villejuif and at Oscar Lambret Cancer Center in Lille 166 patients with squamous cell carcinoma of oropharynx were enrolled in a randomized trial of two arms. Arm A (A): radiotherapy (RT) alone; arm B (B): chemotherapy (CT) followed by radiotherapy. *Inclusion criteria:* oropharyngeal tumor exclusively (posterior wall, glosso-tonsilar sulcus excluded), T2, T3, T4; N0, N1, N2a, N2b; M0. *Exclusion criteria:* palliation treatment, age >70, pretreated patients, second cancer. *Treatment plan* Arm (A): radiotherapy 70 grays in 7 weeks, 5 fractions a week on the tumor site and in both sides of the neck. Arm (B) 3 CT cycles d1–d21, with CDDP 100 mg/m^2 IVP d1, 5 FU 1000 mg/m^2 d1 to d5 in 24 h continuous infusion, followed 15 to 21 days later by the same radiotherapy protocol. *Results:* all the patients enrolled in the study were included in the analysis even 10 pts classified N2c, 1 posterior wall, 1 70 older, 2 pts with general contraindication to CT and 1 with two primaries. Out of 83 pts in (B) 79 received CT; 5 had a grade III leukopenia and 6 a grade II, 4 had a grade IV mucositis. CT was stopped before the 3th cycle in 12 pts for toxicity (5), progressive disease (3), refusal (4). Regression was evaluated by CT scan and clinical examination on primary and nodes; we observed 57% objective responses (RC 19%, PR 38%). The 2 groups of 83 pts were well balanced in age, T, N and histology. With a median follow up of 36 months, the results at 72 months show that 37 patients died in (B) versus (46) in (A) without statistical difference (P = 0.12). Causes of death were: recurrences 28 VS 26, toxicity 2 VS 2, intercurrence 7 VS 1, second primary 8 VS 4, unknown 1 VS 4. Disease free analysis shows no difference and the 2 curves are similar, loco regional recurrence (LCR) 30 VS 21, LCR + MTS 0 VS 2, MTS 6 VS 6, second primary 6 VS 13.

In conclusion: chemotherapy with CDDP—5 FU does not improve the benefit of oropharyngeal carcinoma treatment comparatively to radiotherapy alone.

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CYCLIN D1 GENE AMPLIFICATION IN HUMAN LARYNGEAL SQUAMOUS CELL CARCINOMAS: AN INDEPENDENT PROGNOSTIC FACTOR

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The gene dosage of cyclin D1 gene (CCND1) was examined in 51 primary laryngeal squamous cell carcinomas and amplification of the gene was found in 9 cases (17.6%). CCND1 amplification did not correlate with the clinico-pathological parameters. In a median follow-up period of 29 months the overall survival rate was 71.4% for patients affected with tumors displaying normal CCND1 dosage, and only 25% for patients with tumors carrying amplified CCND1. In multivariate analysis, only CCND1 and tumor size retained a statistically significant prognostic value (P = 0.037, P = 0.041). This is the first report in which CCND1 amplification is identified as a significant independent prognostic factor in laryngeal squamous cell carcinoma.

395 POSTER

SURGICAL TREATMENT & FOLLOW-UP OF DIFFERENTIATED THYROID CANCERS: RESULTS FOR 290 PATIENTS

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Aim of the study: 1) Evaluation of the validity of the initial surgery with regard to the prognostic index (as defined by the E.O.R.T.C.)—2) Evaluation of the occurrence: of local recurrences (central compartment), of regional recurrences (lateral compartment) and of distant metastases—3) Impact of the former events on survival.

Material and method: 290 Patients (PTS) (110 M; 180 F) consecutively operated on from 1955 to 1994 in our Institution for differentiated thyroid cancer, placed on suppressive hormonal treatment with or without adjuvant I_{131} treatment (mean follow-up 9.7 yrs; 0.5 to 38 yrs). Histology: 212 papillary CA., 31 well differentiated & 47 moderately differentiated follicular cancer respectively. 26 PTS had various surgeries before referral, definitive surgery assured = 119 total thyroidectomies (TT), 36 bilateral subtotal lobectomies, 39 total unilateral and subtotal contralateral lobectomies and 93 unilateral lobectomies. 3 PTS: isthmusectomy or tumorectomy. 7 PTS: tracheotomy was mandatory. Recurrent nerve chain node dissection: 77 PTS, lateral neck dissection: 75 PTS. I_{131} was given to 140 PTS (10 for initial distant metastases, 32 for central node compartment invasion, 9 for locoregional subsequent recurrence, the remaining PTS for ablation of thyroid remnant). 34 PTS had additional external radiation.

Results: 235 PTS are alive, 55 PTS are dead (33 with recurrence). Among 208 PTS without either initial metastases or central compartment residual tumor after surgery, the Prognostic Index (PI) inferior to 50 (n = 94) predicts a 10 yrs Survival (S 10 yrs) of 99% versus 74% for 114 PTS with PI superior to 50 (p inf. to 0.0001). Among 6 deceased PTS in the PI inf. to 50 group, none died from CA (but one died with a recurrence). S 10 yrs of PTS with PI inf. to 50 with surgery less than TT (n = 62) is not different from S 10 yrs of same PI. PTS with TT (with or without I_{131}) (n = 21). Additional I_{131} for PI sup. to 50 PTS (n = 54) ensure a S 10 yrs of 84% versus 67% for PTS (n = 60) who did not receive I_{131} (P = 0.14 Logrank).

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REFLEX-OTALGIA: PROGNOSTIC RELEVANCE FOR RADICAL RADIOTHERAPY OF OROPHARYNX CARCINOMA

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In advanced diseases patients often claim reflex-otalgia (ReOt). Sometimes ReOt is the leading symptom, especially in the recurrence situation. Does this parameter have an impact on the probability of clinical CR under radical radiotherapy (RRT)? From Jan. 1991–Dec. 1994 36/76 pat (47%) treated with RRT for oropharynxca suffered from ReOt. 7/40 pat without and 8/36 with ReOt got simultan CDDP-therapy. The mean T-category for non-ReOt pat was 3.2, for ReOt pat 3.3. Also equal was the rate of N+ (72%). The mean age was 58 and 59 yr. 12.5% (non-ReOt) and 28 (ReOt) were female pat. The mean TD (Gy) was 72.1 (ICRU) for non-ReOt and 72.3 for ReOt pat. RRT was interrupted in 27% of non-ReOt (mean 11 d) and 31% of ReOt (mean 7.8 d) and stopped in 3 pat in either group. 75% (30/40) of the non-ReOt pat and 55.6% (20/36) of the ReOt pat (P = 0.01) have reached a clinical CR. CT- and/or MR-imaging strengthened the clinical findings. Our results proof ReOt as a significant clinical parameter for radioresponsiveness and tumour control.

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RISK FACTORS RELATED TO LOCOREGIONAL RECURRENCE IN SQUAMOUS CELL CARCINOMA OF THE SKIN

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A retrospective analysis was performed in order to identify the risk factors associated with development of locoregional recurrent disease in patients with primary squamous cell carcinoma of the skin. Step-wise logistic regression analysis was used which consisted of 1039 patients