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Concomitant radiochemotherapy for advanced oropharyngeal cancer; tolerance and early results

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Purpose: To estimate tolerance and effectiveness of the concomitant radiochemotherapy for advanced unresectable oropharyngeal cancer.

Method: Cisplatinum 20 mg/m^2/day d. 0–4, 5-Fu 450 mg/m^2/day d. 0–6; than every week (days 13, 20, 27 etc) 5-Fu 450 mg/m^2 one-day. Conventional fractionation 2 Gy daily starting day 1, total dose 66 Gy. In case of CR of the primary and only PR of lymph nodes – MRND 4. Inclusion criteria: unresectable squamous cell cancer (SCC) of the oropharynx T3–4 and/or N2–3, no distant secondaries, perf. status 0–1 WHO, age < 70.

Material: Fifty seven patients entered the study (52 M and 5 F, age 17 to 69 years). Stage: T2N2–3 – 10 pts, T3–4N0–1 – 12 pts, T3–4N2–3 – 35 pts. Patomorphology: SCC G2 – 26 pts, poorly differentiated SCC – 31 pts. Tolerance: skin and mucosal reactions EORTC/RTOG classification: G3 in 27 pts. Breaks in radiation in 23 pts (in 2 over 10 days). All completed radiotherapy in planned total dose. Neutropenia was observed in 18 pts.

Results: CR was obtained in 41/57 pts (72%). CR of the primary and PR of lymph nodes: in 6 pts. During the observation (from 6 to 41 months) 11 pts failed. Recurrence at the primary was observed in 3 pts. Recurrences at the primary site and in the lymph nodes – in 4 other. Four patients failed due to distant secondaries. At present 34/57 (60%) patients are alive with NED.

Conclusions: Tolerance of concomitant radiochemotherapy in patients with unresectable oropharyngeal cancer is acceptable. Early results suggest high activity of this regimen.

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Hiperfractionated vs. standard radiotherapy of advanced laryngeal cancer

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Objectives: We begun treating patients with advanced laryngeal cancer with hyperfractionated radiotherapy in 1987 and this study analyses the results and the optimal time dose ratio for this particular type of fractionation.

Material and Methods: between 1987 and 1993, 106 patients (pts.) with T3 and T4 larynx squamous cell carcinoma entered in a prospective non-randomised study comparing standard 2 Gy/day, 10 Gy/week (ST-group B), vs. hyperfractionated 2× 1.2 Gy/day, 12 Gy/week (HF-group A) radiotherapy. Total doses administered were: 70–72 Gy and 74–84 Gy for standard and hyperfractionated schedules respectively. Distribution of pts. accordind to T category: T3 – 14 pts. in group A and 21 in group B; T4 – 45 pts in group A and 26 in group. B.

Results: 5 year actuarial survival: 68% for T4 in group A (HF) and 28% in group B (ST), for T3: 75% in group A and 73% in group B. Local failure was the mos frequent (45% of failures) followed by loco-regional failures (12%). A logistic regression was performed for some fractionation parameters. Total dose (TD), overall treatment time (OTT) and the dose intensity (>1.7 Gy/day vs. <1.7 Gy/day) were found to be significant ($p < 0.02$) for local control at 3 years.

Conclusions: Hyperfractionated radiotherapy is a valid therapeutic option for the advanced laryngeal cancer. Significant survival diferences were for T4 tumours but not for T3. TD, OTT and dose intensity are therapeutic factors with significant prognostic value.

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A retrospective analysis and long term follow up on patients receiving radiation treatment for T1–T4 laryngeal carcinomas at Uppsala University during 1978–1987

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Laryngeal carcinoma affects approximately two hundred patients annually in Sweden. The treatment of choice is radiation treatment and if this treatment fails, the patient is admitted to surgery.

In this study we have retrospectively analysed a consecutive material of patients with a histopathological confirmed diagnosis of laryngeal carcinoma. These patients have received radiation treatment at the Department of Oncology, University Hospital, Akademiska sjukhuset in Uppsala, Sweden during 1978–1987. The study focuses on the outcome of radiation treatment in terms of survival and local recurrence rates. The patients have been followed up to a maximum of nineteen years from start of radiation treatment. Approximately 150 patients have been included and analysed.

Local control rates at five years were approximately: T1:86%, T2: 87%, T3: 76% and T4: 62%

The percentage of patients that died due to laryngeal carcinoma at 5 and 15 years after radiation treatment is approximately:

T1. 5 years: 4.%, 15 years: 4.%
T2. 5 years: 15%, 15 years: 34%
T3. 5 years: 23%, 15 years: 27%
T4. 5 years: 50, 15 years: 50%

The results of this retrospective study is that radiation treatment produces high accuracy of cure for patients with laryngeal carcinomas in low stages and that the five year survival is maintained at ten and fifteen years follow up for all stages except for laryngeal carcinomas in stage T2.

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Low-dose gemcitabine with radiotherapy in advanced head and neck an thyroid tumors: A phase II study

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Objective: Gemcitabine (GEM) is a radiosensitizing agent Phase I studies combining RT and low-dose GEM have shown interesting activity in head and neck and pancreatic cancer, in part with severe side effects In order to evaluate the toxicity and efficacy of a combination of RT and low-dose GEM in locally advanced or recurrent head and neck and thyroid tumors, a phase II study was performed with GEM 200 mg/m^2 i.v. weekly during RT.

Methods: 26 patients with locally advanced and progressive head and neck (n = 22) and thyroid carcinomas (anaplastic 2, medullary, follicular 1), median age 60 yrs (range 36–71), male/female 21/5, were treated with 2–10 cycles GEM in combination with RT (mean 42 Gy, range 18–67), 14 untreated, 12 pts pre-irradiated (60 Gy, 40–80). 26/26 pts are evaluable for toxicity.

Results: The most common side effects were mucositis and erythema, in 8 pts toxicities > gr. 2; 6 pts mucositis gr. 3; 1 Pt skin gr. 3; 1 leucopenia gr. 3. Until now, previously reported late toxicities such as pharyngeal Stricture was not observed. 20/25 are evaluable for response: 3 CR (15%; first line 3, pre-irradiated 0), 9 PR (45%; first-line 4, pre-irradiated 5), 6 NC (30%), 3PD (10%). In untreated pts the response rate is 70% vs. 50% in pre-irradiated pts. Interestingly, thyroid carcinoma responded well (3/4 PR, 1 NC). After a median follow-up of 44 (3–83) weeks the median time of progression is 29 (3–83) weeks.

Conclusion: Low-dose GEM in combination with RT has a high radiosensitizing potential with durable response in first-line treatment of locally advanced head and neck and thyroid tumors, but is also effective in pre-irradiated pts, with low acute toxicity. While these preliminary data are encouraging, further assessment is required to define the optimal dosage for combinations of GEM and RT, especially with lower dosages in first-line treatment of head nad neck and thyroid tumors.

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Apoptosis in relation to topoisomerase IIa, p53, p21 and p27 in head and neck cancers

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Aims: The aim of the study was to estimate the apoptotic index (AI) in 65 cases of head and neck carcinomas and to correlate it with the clinicopathological characteristics of the cases, the expression of Topoisomerase, p53, p21 and p27 proteins and patients survival.

Material: Sixty five patients with head and neck cancer (38 from larynx, 8 from tongue and 19 from other sites were included in the study. The tissue specimens were taken at initial diagnosis.

Methods: Cells undergoing apoptosis were detected by the in situ end-labeling method on paraffin sections and the AI was estimated by measuring the percentages of apoptotic nuclei using the CAS 200 image analysis system. Topoisomerase IIa, p53, p21 and p27 proteins were detected by immunohistochemistry.

Results: Higher apoptotic index was found in tumors of advanced stage ($P = 0.03$) and in tumors with negative p53 expression ($P = 0.10$). Patients with

tumors showing higher AI had longer overall survival but the difference was not statistically significant. No significant correlation was found between AI and gender, age, site of disease and tumor grade as well as with topoisomerase IIa, p21 and p27 expression.

Conclusions: Our findings indicate that apoptosis is mainly related with advanced stage of disease and wild type p53 protein and does not seem to play an important role to the overall survival of the patients with head and neck cancer.

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Phase II study of paclitaxel (P) twice a week as a radiosensitizer, after paclitaxel-carboplatin (C) induction chemotherapy (IC) in stage IIId–IV head and neck carcinoma (HNC)

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To assess the tolerance and efficacy of combined fractionated radiotherapy (RT) with P, after IC, 29 patients (pts) with unresectable HNC were enrolled at a phase II study from 09.97 to 11.98. IC consisted of two courses of P 175 mg/m^2 and C AUC 6, every 21 days. 66.6 Gy were delivered 4 weeks after the IC (1.8 Gy daily, 5 fractions per week, one week rest at 45 Gy) to a volume encompassing the primary tumor and regional lymph nodes. Concurrent CT consisted of P 20 mg/m^2 over 1 hour twice a week. Characteristics of the pts were: median age 56 years (range 43 to 75), WHO performance status of 0–2 (11 PS0, 12 PS1, 6 PS2), primary site was: oropharynx 15, hypopharynx 12, larynx 2. All pts presented with AJCC stage III or IV. 29 pts received two cycles of IC and were evaluable for toxicity and response. The response was 52% (3 CR, 12 PR, 12 NC, 2 PD). The toxicity following IC was hematological with 4G1 and 1G2 anemia, 8G1–2 and 2G3–4 leucopenia, 1G2 thrombopenia. 19 pts completed the chemoradiotherapy (CRT), median (range) total dose of RT was 65.7 Gy (63–68, 8 Gy). 11 pts required interruption during RT (2–5 weeks). The median duration of RT was 9.3 (7–12) weeks. One patient did not receive CRT due to early progression and 9 pts are still under RT. All the 19 pts experienced mucositis (5G2, 14G3) and 9 required hospitalization. 12 CR (64%) and 2 PR (11%) were achieved. Median duration of response was 11+ months (range 6+–12+ months. This combined treatment is highly effective in poor prognosis unresectable HNC. The main toxicity (mucositis) is manageable.

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A phase III study of concurrent radiotherapy with carboplatin or weekly paclitaxel in patients with advanced squamous cell head and neck cancer (SCHNC)

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Introduction: Patients (pts) with advanced SCHNC have poor prognosis. Chemotherapy (CT) and Radiotherapy (RT) given concurrently increase local-regional control and survival rates compared with RT alone. From 5/98 we started a phase III study of the activity and toxicity of Chemoradiotherapy using Carboplatin or Taxol in the CT arm. We report our preliminary results of this study.

Methods: Thirty six pts with advanced (stage III and IV), inoperable SCHNC received RT to the primary and lumph nodes 1.8–2 Gy/day, 5 fractions/week, total 65/72 Gy. During RT, Carboplatin 400 mg/m$_2$ day 1, 22, 43 was administered in 19 pts (mean age 59.8 years) and Taxol 80 mg/m$_2$ weekly (as 1-hour infusion) in 17 pts (mean age 55.1 years). The two groups were similar with respect to age, sex, stage, PS of the pts, differentiation and site of primary tumor.

Results: 28 pts (77.8%) achieved a remission (CR:16, PR:12 pts). In the Carboplatin group we observed 12 responses (63.2%) with 6 CR (31.6%) and 6 PR (31.6%) and in the Taxol group 16 responses (94.1%) [$p < 0.05$] with 10 CR (58.8%) and 6 PR (35.3%). Grade III/IV neutropenia occurred in 3 pts of the Carboplatin group and 5 of the Taxol group and grade III/IV stomatitis in 2 and 4 pts respectively.

Conclusions: Weekly Taxol given concurrently with RT seems to be safe and more active than Carboplatin/RT in pts with advanced SCHNC. Updated results about survival will be presented.

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Prognostic value of hematocrit level in radiotherapy of laryngeal cancer

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Purpose: The evaluation of importance of pre-treatment hematocrit level in radiotherapy of laryngeal cancer.

Material and Methods: In the group of 295 laryngeal cancer patients treated by definitive radiation therapy pre-treatment level of hematocrit was scored. The impact of hematocrit level on results of treatment was assessed using proportional hazard (Cox) regression and the logistic regression.

Results: In analysed group of patients median of pre-treatment hematocrit level was 42% (range 30%–52%). Logistic regression model and the proportional hazard regression showed that tumour control probability (TCP) was 0.2 and 0.8 for hematocrit level 30% and 52%, respectively ($p < 0.0002$). When both haemoglobin and hematocrit were introduced to model, hematocrit had lower p-value.

Conclusion: In radiotherapy of laryngeal cancer pre-treatment hematocrit level significantly affect TCP.

651 PUBLICATION

Phase II studies using electroporation therapy in patients with recurrent head and neck cancer: A safe and active treatment approach

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Electroporation is a process which temporarily increases the permeability of cell membranes, therefore enhancing the intracellular delivery of locally injected substances. Two Phase II studies were conducted in patients with recurrent or refractory head and neck cancer following standard curative therapy and who were not candidates for salvage therapy. A total of 41 patients were enrolled in two multicenter trials to evaluate the patient response of intratumoral (IT) administration of bleomycin or Electroporation Therapy (EPT), defined as IT bleomycin with electroporation. Patient responses were evaluated over 12 weeks by direct measurement of lesions as well as CT/MRI studies. Of the 41 patients enrolled, 31 had failed two or more prior treatment modalities, i.e. surgery, radiation, and/or chemotherapy. In protocol EPT-97-01, 23 patients were treated with IT bleomycin alone and crossed over to EPT (n = 15) if progressive disease occurred. In protocol EPT-97-02, 18 patients received EPT only. The significant side effects related to EPT therapy were necrosis of the tumors and overlying skin in cervical lesions associated with cellulitis [7%] and bleeding [12%] requiring increased wound care. No deaths attributable to the therapy were reported. In 33 patients who completed therapy receiving EPT there was a 64% objective response rate durable over 12 weeks. In summary, Electroporation Therapy is an efficient, safe, and well tolerated method of treating symptomatic recurrences of head and neck cancer that warrants further investigation.

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Head and neck cancer: Pretreatment and midtreatment PO_2 levels

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Purpose: In vitro studies have shown that fully hypoxic cells are 3 times more radioresistant than fully oxygenated cells. Accordingly, clinical studies have proven that pretreatment tumor hypoxia is an essential factor in predicting local tumor control, survival and the rate of metastases. In this ongoing study we compare pretreatment tumor pO2 levels with measurements taken during nonsurgical treatment when the size of the cervical metastatic node has decreased by 50%.

Methods: Using the Eppendorf pO2 histograph we measured pO2 levels in metastic lymph nodes of so far 10 patients with head and neck SCC who were being treated with nonsurgical management.

Results: A mean of 72.6 measurements per session was taken from each lymph node. The median tumor pO2 measurement fell from a mean of 13.9 ± 8.0 mm Hg to 7.3 ± 9.9 mm Hg Even more dramatic, however, was the substantial increase in the percentage of values less than 5 mm Hg, a rise from 29% to 52%.

Conclusions: While there is variability both in the pretreatment tumor pO2 and in the change in pO2 during treatment, there appears to be a