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Tumour growth in waiting time for radiotherapy in head and neck cancer

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Aim: Waiting time prior to radiotherapy is a major problem. The aim of this study is to determine the impact of waiting time on tumour growth in an unselected population of patients with head and neck cancer referred to primary radiotherapy.
Material and methods: In a consecutive cohort of head and neck cancer patients referred to the Head and Neck Centre in Aarhus from 2000 to 2003, medical records were searched to identify patients with a diagnostic scan (MR or CT) and a CT scan for treatment planning. Thirty-three patients were identified having comparable scans. Tumour size, size and number of metastatic lymph nodes were measured by a skilled radiologist.
Results: Median waiting time between the two scans was 28 days (5–124 days). Nineteen patients (58%) developed an increase in total tumour volume with a 14% median volume increase (3–315%). Evaluated by the RECIST Criteria 18% had progressive disease (>20% increase in largest tumour diameters). Three patients (9%) developed lymph node metastasis and 5 patients (15%) progressed to a higher stage during the waiting time.
Discussion: Several studies have shown that the prognosis depends on tumour size, lymph node metastasis and stage. This study thereby indicates a negative prognostic effect of waiting time. In Denmark a significant increase in professional delay (from first visit to a doctor until beginning of treatment) for head and neck cancer patients has been reported, from 50 days in 1992 to 70 days in 2002. In the present work we focused only on a minor part of this delay. The impact of the total waiting time can be expected to be fare above the present findings.
Conclusion: Delay in the initiation of radiotherapy does significantly increase tumour size, tumour volume and the risk of lymph node metastasis in a substantial part of patients with head and neck cancer, resulting in worse prognosis. It is therefore important to emphasise that waiting time should be hold as short as reasonable achievable.

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Herpes simplex virus-1 (HSV-1) infection during head and neck radiotherapy. Incidence and therapeutic considerations

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Background: The aim of the study was to investigate the incidence and role of herpes simplex virus-1 (HSV-1) infection in mucositis during head and neck cancer radiotherapy.
Patients and Methods: Sixty patients with malignant head and neck tumor, eligible to receive radiotherapy entered the study. Thirty-one patients received fluconazole antifungal prophylaxis and 29 did not. Median total dose was 60 and 66 Gray respectively in each patient cohort. Sixteen patients (26.6%) received concomitant chemotherapy. Mucositis was recorded weekly. Smears from the ulcers of mucositis were stained with Papanicolaou and APAAP immunocytochemical method to identify HSV-1.
Results: Forty-eight patients developed ulcerative mucositis. Twenty-three patients (38%) completed radiotherapy with severe mucositis. Nine patients interrupted RT due to mucositis. Smear was available from 29 patients. HSV-1 infection was identified in 14/29 patients (48.2%). Mucositis healed or was reduced after one week of antiviral treatment in 11 of those 14 patients. Ulcerations recurred after quitting antivirals.
Conclusions: The incidence of HSV-1 infection was 29.1% (14 HSV-1 positive of 48 patients with ulcerations). Healing or reduction in the grade of mucositis after one week of antivirals supported the hypothesis that HSV-1 infection aggravated radiation mucositis. Dose and duration of antivirals during radiotherapy need to be further evaluated.

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A dose-volume histogram analysis of the PTV in patients with advanced head and neck cancer treated with concomitant chemoradiotherapy

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Background: Irradiated volume and delivered dose are considered as major factors for acute toxicity in head and neck cancer (HNC). We investigated the relationship between various parameters derived from planning target volume (PTV) dose-volume histogram (DVH) analysis and the risk of acute toxicity in patients undergoing concomitant radio-chemotherapy (RT-CT) for advanced HNC.
Material and method: From September 2001 to December 2003, 80 stage III and IV HNC patients were treated with a concurrent association of RT-CT to a prescribed target dose of 70 Gy in 35 daily fractions. Chemotherapy consisted of an association of carboplatin and 5 fu at weeks 1, 4 and 7. Acute toxicity according to the RTOG scoring system was prospectively recorded throughout the course of treatment. 3-D treatment planning based on computed tomography was done in all patients with contouring of gross tumour volume (GTV) consisting of primary tumour and involved lymph nodes. The PTV was defined by a 5–10 mm margin depending on clinical condition and tumour location. DHV were calculated for the PTV.
Results: The mean PTV volume was 79.5 cm^3 (range 11.2 – 255.6) without significant difference between tumour locations ($p = 0.56$) but with a significant trend ($p < 0.0001$) towards higher AJCC stages. Maximal dose (Dmax) deviation from ICRU dose in PTV ranged between 0 and 7% in 17 patients (pt) and was >7% in 63 pt. Mean dose (Dm) deviation ranged between −5% and <0% in 17 pt, *0% and $\leqslant$7% in 57 pt and >7% in 6. There were no differences in Dmax and Dm deviations between AJCC stages. Only weight loss during treatment was significantly correlated with higher PTV volume ($p = 0.01$) but objective mucosal reactions ($p = 0.029$) and xerostomia ($p = 0.04$) increased significantly with AJCC stage. Objective and functional mucositis, epithelitis, xerostomia, weight loss and Karnofsky index changes during treatment were not correlated with Dmax and Dm deviations.
Conclusion: A partial relationship between acute toxicities and irradiated volume was demonstrated by analysing DVH. Homogeneity in dose distribution obtained with 3-D conformal radiotherapy approach could have minimised toxicity variations due to differences in delivered dose.

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Radiochemotherapy comparing with radiochemotherapy and local hyperthermia in patients with unrecectable pharynx and larynx cancer: a phase I study

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Patients with primary advanced head and neck cancer not amenable to surgery require more aggressive regimes of radiation- and chemotherapy, or use of radiomodification. The purpose of the study was to test the hypothesis that radiochemotherapy in combination with local microwave hyperthermia (RCT-HT) leads to a better loco-regional control in patients with stage III-IV of squamous cell cancer of pharynx and larynx with lymph nodes metastases than radiochemotherapy (RCT) alone.
Methods: From December 2002 to May 2004, 65 patients with III-IV stage of squamous cell cancer of pharynx, hypopharynx and larynx with involved neck nodes were included into a prospective non-randomized study. The treatment protocol in the first group consisted of three courses of chemotherapy (5-FU+cisplatin) given in the 1-st, 5-th and 11-th week and conventional split radiation therapy (6–9 and 12–14 week), a total dose 68–72 Gy. In the second group, besides, patients were performed 6–8 sessions of local hyperthermia (915 MHz, 60–75 Wt). Heat was delivered for an hour up to 41.5–43^{0}C in the tumor after irradiation. 35 patients treated with radiochemotherapy were compared with 30 patients treated with radiochemotherapy and local microwave hyperthermia. Adverse effects (skin and mucosa toxicity, dysphagia, xerostomia and hematologic toxicity) were scored according to RTOG/EORTC criteria.
Results: CR+PR rate, achieved in one month after treatment, was 31 patients (88.5%) in the first group and 28 patients (93.3%) in the second group, respectively ($p = 0.16$). Progression was observed in 4 patients (11.5%) in the first and 2 (6.7%) in the second group. The 1-year progression-free survival was 54.2% and 60% ($p = 0.24$). RCT-HT patients more often developed 3+4 grade mucositis (45.5% vs 28%, $p = 0.034$)

and dysphagia (41.6% vs 24.1%, p = 0.046) compared to those with RCT. Hematologic toxicity was significantly higher in RCT-HT group. Stage 2–4 anemia developed in 43% and 25% (p = 0.004), respectively. No patient developed grade 3+4 neurotoxicity, ototoxicity or nephrotoxicity. Six month after treatment, 100% of survivors reported a dry mouth, with no difference between two groups. Lymph edema was observed in 47% patients in RCT-arm and in 76% in RCT-HT arm (p = 0.04).
Conclusion: Local microwave hyperthermia in combination with radiochemotherapy doesn't improve loco-regional control in patients with advanced pharynx and larynx cancer, but significantly increases toxicity of the treatment.

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A Phase II study of Sorafenib (BAY 43–9006) in patients with recurrent and/or metastatic head and neck squamous cell carcinoma (HNSCC) and nasopharyngeal cancer (NPC)

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Background: Sorafenib (Bay 43–9006), a novel bi-aryl urea, is a potent inhibitor of kinases of Raf-1 (c-Raf) and BRAF which are critical members of the RAS/RAF/MEK/ERK signalling pathway. In addition, Sorafenib inhibits other pro-angiogenic protein tyrosine kinases, including VEGFR-2/3 and PDGFR-β. Over-expression of these signal transduction and angiogenic markers has been associated with poor prognosis in epithelial malignancies. We conducted a phase II study to examine the efficacy of Sorafenib in advanced HNSCC and NPC.
Methods: Patients (pts) with advanced HNSCC and NPC with measurable disease, no more than one prior chemotherapy regimen for recurrent and/or metastatic disease, performance status (PS) ECOG 0–2, and adequate organ functions were eligible. Sorafenib was administered orally at 400 mg BID on a continuous basis, in 28-day cycles. Responses were evaluated every 8 weeks according to RECIST criteria.
Results: Twenty-three patients have been enrolled (13m/10f). One patient withdrew prior to beginning of treatment, 22 pts were evaluable for toxicity and response. Median age was 53 years (range 37 – 77); 87% had PS 0 or 1 and 13% PS 2; 70% HNSCC and 30% NPC; 15 pts had received prior chemotherapy, 4 had received prior erlotinib and 22 had received prior radiation therapy. One pt (4%) with HNSCC has a confirmed partial response, 9 pts (39%) (4 HNSCC and 5 NPC) had stable disease ranging from 2 to 6 cycles, and 12 pts (52%) had progressive disease. A total of 57 cycles had been administered (median number/patient: 2; range 1–6). No grade 4 toxicity was seen. Main haematological toxicity was grade 3 lymphopenia in 7 (30%) pts. Common grade 3 non-hematological toxicity included non-specific pain in 10 (43%), hyponatremia in 4 (17%), dyspnea in 4 (17%), and infection in 3 (13%) pts. Grade 1/2 non-hematolgical toxicity included fatigue in 21 (91%), hyponatremia in 15 (65%), hypertension in 9 (39%), mucositis in 9 (39%), and hand–foot syndrome in 7 (30%) pts respectively. One pt died of intracranial tumoral hemorrhage, deemed to be unlikely related to treatment. The median survival was 3.6 months with a 6-month survival of 12% (95% CI: 17–58%).
Conclusions: Sorafenib was well tolerated in this group of heavily pre-treated patients. Single agent Sorafenib has similar efficacy as single agent erlotinib or gefitinib in this patient population. Further evaluation of Sorafenib in combination with other agents may be are warranted in these tumor types.

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Capecitabine and cisplatin combination chemotherapy as salvage therapy for recurrent unresectable or metastatic squamous cell carcinoma of the head and neck

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Background: Head and neck squamous cell carcinoma (HNSCC) accounts for most malignant neoplasm of head and neck. About two thirds of the patients present with locally or regionally advanced disease, and in spite of combined modality including surgery, radiation, and chemotherapy, regional and distant progression occurs in 60% and 25% of these patients, respectively.
This prospective study was conducted to assess the efficacy and safety of the salvage chemotherapy of capecitabine and cisplatin for the patients with relapsed unresectable HNSCC.
Patients and method: Patients with measurable, metastatic or unresectable HNSCC who had received prior systemic chemotherapy (docetaxel and cisplatin regimen) and local treatment such as radiotherapy or surgery were eligible. Treatment consisted of cisplatin (75mg/m^2 as a 2 hours infusion on day 1) and capecitabine (1000 mg/m^2 orally twice daily, on day 2–15), repeated every 21 days.
Results: Twenty four patients were evaluable for toxicity and response. A total of 79 cycle with median of 4 cycles per patients were administered. The most common grade 3/4 hematologic adverse events were neutropenia and anemia, which documented in 5 (21%) and 4 (17%) patients, respectively. The most common treatment-related non-hematologic adverse event (all grades) were diarrhea (58%), hand–foot syndrome (45%), stomatitis (42%), and emesis (38%). However, the majority were tolerable in intensity. Treatment related mortality was absent. Overall The response rate was 42% with 1 complete response (4%) and 9 partial responses (38%). Five patients (21%) were stable disease and 9 patients(38%) presented progressive disease.
Conclusion: This regimen of capecitabine and cisplatin is an effective and tolerable treatment for patients with recurrent unresectable or metastatic HNSCC who are refractory to platinum/taxane-based chemotherapy.

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Weekly chemotherapy with cisplatin and docetaxel for recurrent metastatic head and neck cancer: a phase II study

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Background: A phase II study was conducted to evaluate the activity and toxicity of a weekly combination of cisplatin and docetaxel in patients with recurrent end-stage head and neck cancer.
Material and methods: From 07/2003 to 11/2004, 21 patients (5 female, 16 male, median age: 60 years) with proven recurrent unresectable head and neck cancer were enrolled. All 21 patients had metastatic neck disease. 7 patients presented additionally with distant metastases. 1 patient was previously treated by surgery alone, 2 had surgery and radiotherapy, and 18 surgery and radiochemotherapy. On an outpatient basis treatment consistent of 25 mg/m^2 cisplatin and 35 mg/m^2 docetaxel once a week for three weeks followed by one week without treatment for each cycle. A maximum of 5 cycles were given. The primary endpoint was median survival. Secondary endpoints were response rate (RECIST), time-to-progression, toxicity (NCI-CTC), and quality-of-life (EORTC QLQC30, QLQHN35).
Results: All 21 patients were assessable for toxicity and quality-of-life analysis. 19 patients were assessable for response analysis. The median number of weeks on chemotherapy was 9 (range: 1–15). 8 patients (38%) had a partial response and 8 patients a stable disease (38%). The median time to progression was 3.5 months (95% CI 2.0–5.0) and the median overall survival was 10.7 months (95% CI 6.4–15.0). The combination was well tolerated, a grade 3 hypohemoglobinemia occurred in 1 patient, and a grade 3 hand–foot skin reaction in another patient. The performance status did not decrease significantly during therapy. The quality-of-life scores did not show a significant alteration during therapy.
Conclusions: The combination of cisplatin and docetaxel, administered weekly in an outpatient setting in a lower dosage than in typical 3-week schedule, is an active regimen in recurrent end-stage head and neck cancer with comparable efficacy to a 3-week schedule. It appears to have a much more favourable toxicity profile in comparison to a 3-week regimen of cisplatin and docetaxel or to other taxane combinations. The work was supported by an unrestricted grant from Sanofi-Aventis