

advanced NPC. However, the higher acute toxicity needs the use of conformal radiotherapy technique to reduce this toxicity. Longer follow-up and further investigations are required to evaluate this regimen.

**228** **Nasopharyngeal carcinoma in children and adolescents - 15 years experience at the benbadis hospital of constantine - long-term results of 284 patients** Poster

R. Djekkoun<sup>1</sup>, K. Boudaoud<sup>1</sup>, M.S. Bali<sup>1</sup>, N. Ferdi<sup>1</sup>, W. Boughrara<sup>1</sup>, B. Boudraa<sup>1</sup>, S. Taleb<sup>1</sup>, A. Djemaa<sup>1</sup>, T. Filali<sup>1</sup>  
<sup>1</sup>Centre Hospitalier Universitaire Benbadis, Oncology-Radiotherapy, Constantine, Algeria

**Purpose:** To report a retrospective analysis of epidemiologic, clinical, and therapeutic aspects of 284 children and adolescents with newly diagnosed nasopharyngeal carcinoma (NPC), and to evaluate the efficacy and toxicity of a sequential neoadjuvant Chemotherapy (CT) and bifractionated Radiotherapy (RT) regimen.

**Methods and Materials:** Between January 1990 and December 2004, 284 consecutive, previously untreated, children and adolescents less or equal to 20 years old were diagnosed with NPC and treated at the Benbadis University Hospital of Constantine. The median age was 14.6 years (6-20). The sex-ratio was 2.02 (190 males and 94 females). After excluding patients presenting with distant metastases (27 pts), 257 pts were identified as having only primary locoregional disease and they serve as the study population. 221 pts (86%) had locally advanced primaries (T3/T4) and 178 pts (69%) with cervical lymph node involvement (N2/N3). Histopathologically, undifferentiated type predominates, representing 96% of cases. All patients received neoadjuvant CT, 234 of them (91%) were treated combining Cisplatin and Epirubicin, 3 or 4 cycles every 21 days. The CT was followed by a loco-regional bifractionated external beam RT (1.6 Gy twice a day). The total radiation dose for the primary tumor was 70.4 Gy and for uninvolved regions was 45 Gy. All patients completed the scheduled treatment. Evaluation was repeated at completion of CT and of therapy.

**Results:** The objective response rate (OR) after neoadjuvant CT at the primary site was 95.7% (246 pts), with a 44.7% (115 pts) of complete response (CR) rate, 51% (131 pts) of partial response (PR) and 11 pts (4.3%) did not respond or progressed during CT. At completion of therapy, CR was recorded in 218 pts (84.8%), PR in 31 pts (12.1%) and progression in 8 pts (3.1%). The median follow-up time was 74 months (11 – 192). Patients failed rarely locally (16.3%), but generally distantly (28.4%) as first event. The median time for first relapse was 13 months. The actuarial 5-year and 10-year overall survivals (OS) were respectively 65.3% and 54.2%, and disease-free survivals (DFS) rates were respectively 51.7% and 43.8%. OS and DFS were plotted using Kaplan Meier method. Chemotherapy-related toxicity was mycosis Grade II-III in all patients and nephrotoxicity Grade I-II occurred in 19 pts (7.4%). Different late toxicity affecting quality of life was found, especially among patients less than 13 years of age (xerostomia, skin fibrosis, trismus, dental caries, hearing loss, hypothyroidism, and growth retardation).

**Conclusions:** NPC in children and adolescents is diagnosed late usually in an advanced stage of disease. However, this combined modality management is quite effective and results in good outcome with a satisfactory locoregional control and overall survival. It seems to give similar results to those in adults, but perhaps with more late induced toxicity.

**229** **Membrane-remodeling controls the death of microvascular cells engaged by radiotherapy** Poster

C. Niaudet<sup>1</sup>, S. Bonnaud<sup>1</sup>, S. Gouard<sup>1</sup>, M.H. Gaugler<sup>1</sup>, I. Corre<sup>1</sup>, F. Paris<sup>1</sup>  
<sup>1</sup>INSERM U601, Radiobiology, Nantes, France

This study aims at correlating the biophysical and molecular pathways through which a single high-dose irradiation can engage endothelium destruction.

p38-phosphorylation, ceramide generation, membrane remodeling and apoptosis quantification were assessed on the Human Microvascular Endothelial Cell line (HMEC-1), irradiated at 15 Gy.

We show here that generation of ceramide in the membrane of HMEC-1 appears in the five minutes following 15 Gy irradiation. The apoptosis wave detected within 24 hours is decreased by use of the pharmacological inhibitors of aSMase, desipramine and monensin (respectively from 52% and 32%). This is consistent with the in-vivo protection of microvasculature offered by knocking-out aSMase.

Ceramide is well known to induce the coalescence of rafts microdomains. We detected a deep relocalisation of the raft-marker ganglioside GM1, from a scattered, discreet pattern, to large areas on the cell membrane, following irradiation, and this membrane reorganisation could be mimicked by

addition of exogenous ceramide or bacterial SMase, or conversely be totally prevented by addition of desipramine.

High-dose irradiation is also known to induce the death-pathway p38 in microvascular endothelial cells. A 15 Gy irradiation is indeed able to activate rapidly a durable phosphorylation of p38 in HMEC-1, detected by immunofluorescence and phospho-blot. p38 blockade by MAPK inhibitor III or sh RNA decreased radiation induced death of HMEC-1 by respectively 30% and 43%. The p38-activator anisomycin leads to a durable activation of the pathway, and a wave of apoptosis 24 hours post-exposition, confirming the critical role exerted by this pathway in microvascular apoptosis.

We finally investigated whether these two concomitant phenomena, i.e. ceramide-induced raft coalescence and p38 death-pathway activation, could be connected. Disorganization of rafts by drugs as nystatin, hindered the radiation-induced rafts coalescence, the activation of p38 and the subsequent death-induction of microvascular cells (death-decrease by 35%).

In the present work, a cell-culture model allows us to arrange the cascade of until-then disconnected events leading to microvascular cells destruction: the 15 Gy-irradiation activates ceramide generation by aSMase, which leads to a thorough reorganization at the membrane surface, through rafts coalescence. These large platforms in turn strongly activate the p38 pathway, and hence the apoptosis of the endothelial cells.

**230** **Carotid vessel changes and risk factors in patients receiving radiotherapy for head and neck cancers** Poster

Z. Kadehçi<sup>1</sup>, N. Dagoglu<sup>1</sup>, A. Ucar<sup>2</sup>, H. Oflaz<sup>3</sup>, Y. Dizdar<sup>1</sup>, M. Altun<sup>1</sup>  
<sup>1</sup>Istanbul Medical Faculty, Radiation Oncology, Istanbul, Turkey; <sup>2</sup>Istanbul Medical Faculty, Radiology, Istanbul, Turkey; <sup>3</sup>Istanbul Medical Faculty, Cardiology, Istanbul, Turkey

**AIM:** Late effects of radiation on medium and large sized vessels including the carotid arteries have not been thoroughly studied. The role of interaction between radiation and known risk factors for atherosclerosis is unclear either. This study aims to evaluate the changes in carotid vessels, the interaction of these changes with risk factors and to determine the value of carotid vessel screening. **MATERIAL AND METHOD:** 81 patients suffering from head and carcinoma and Hodgkin lymphoma and had received external radiotherapy to the cervical region between 1981-2000, were consecutively recruited for the study. The study group included patients who had received high doses (50-70Gy) and relatively low doses (30-36Gy). Results were compared with a control group of 59 volunteers. All patients and controls were questioned for risk factors of an arterial disease. Changes in bilateral carotid arteries were evaluated by doppler ultrasonography. **RESULTS:** 68 patients received high dose (50-70Gy), and 13 low dose (30-36Gy) radiotherapy. 55 patients received concomitant chemotherapy and 19 (%23) undergone surgery. Smoking, hypertension and hypercholesterolemia were identified as risk factors. 35 patients (45%) had a history of smoking, 5(7%) had hypertension and 3(5%) had hypercholesterolemia. Median arterial thickness was higher in the radiotherapy group ( $p < 0.0001$ ). Smoking was a significant risk factor ( $p < 0.0001$ ), but sample sizes for hypertension and hypercholesterolemia were too small to reach a significant result. Chemotherapy was found to increase the thickness only for common carotid artery. Sample size for surgery may not be enough to reach significant difference. Radiation dose did not have a significant effect, however low dose group had only 13 patients. According to NASCET criteria, atherosclerotic plaques causing stenosis over 50% were detected in 10 patients. Three patients had advanced stenosis; one had endarterectomy prior to ultrasonographic evaluation and 2 had stent application. **DISCUSSION:** External radiotherapy to the cervical region caused thickening of carotid artery intima-media ( $p < 0.0001$ ). Considering 10 patients (12.3%) had stenosis and 3 necessitated therapeutic intervention, these results suggest screening with doppler ultrasonography after neck radiotherapy, especially for patients with known risk factors. This would be beneficial for early interventions or preventing possible complications. The frequency and timing of screening should be further evaluated.

**231** **Mitochondrial modulation of oxygen-dependent radiosensitivity in some human tumor cell lines** Poster

S. Anoopkumar-Dukie<sup>1</sup>, G.D. Sisk<sup>1</sup>, T. Conere<sup>2</sup>, A. Allshire<sup>1</sup>  
<sup>1</sup>University College Cork, Pharmacology & Therapeutics, Cork, Ireland; <sup>2</sup>Cork University Hospital, Medical Physics, Cork, Ireland

Oxygen-dependent radiosensitivity of tumour cells reflects direct oxidative damage to DNA but non-nuclear mechanisms including signaling pathways may also contribute. Mitochondria are likely candidates because not only do they integrate signals from each of the main kinase pathways but