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METACHRONOUS TUMORS IN PATIENTS WITH OROPHARYNGEAL CARCINOMA: ITS INCIDENCE AND INFLUENCE ON SURVIVAL

C.A. Reguero, J. Romero, M.V. Ruiz, I. González, A. de la Torre, S. Rodríguez, F.J. Valcárcel, G. Aragón

Department of Radiation Oncology, Clínica Puerta de Hierro, 28035 Madrid, Spain

We analyzed a series of 245 patients with oropharyngeal carcinoma with no prior or coincident history of other malignant tumor.

The probability of developing a second malignant tumor (SMT), the probability of dying of oropharyngeal cancer, and the probability of dying of second tumor were calculated by the Kaplan-Meier method.

A total of 28 SMTs occurred in 245 patients. Of these tumors, 9 developed in head and neck (3 in the larynx, 4 in the oral cavity, and 2 in distant oropharyngeal subsites), 5 in the oesophagus, 8 in the lung, two in the bladder, and five in other sites.

The actuarial probability of developing a SMT within five years from treatment was 15%, and the probability of developing a second tumor within ten years from treatment was 36%.

The actuarial probability of dying of oropharyngeal cancer within three years from treatment was 54%.

The probability of dying of SMT within three years from treatment was 8%. Three-year survivors had a 20% probability of dying of second cancer within the following seven years.

These results suggest that three-year survivors should be considered eligible for chemoprevention trials.

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CERVICAL NODE METASTASES OF AN UNKNOWN PRIMARY SITE. "IN SITU HYBRIDIZATION" FOR EPSTEIN-BARR VIRUS RNA IN DIAGNOSING OCCULT NASOPHARYNGEAL CARCINOMAS

J. Temvall, M. Dictor, M. Siven, E. Rambech

Departments of Oncology and Pathology, University Hospital, S-221 85 Lund, Sweden

After time-consuming and costly investigations, patients with neck metastases from an occult primary often receive unnecessarily large radiation volumes to treat possible origin in the nasopharynx.

A colorimetric antisense EBER1 oligonucleotide probe specific for Epstein-Barr virus was hybridized in situ (ISH) to metastatic tissue from 18 nasopharyngeal (NPC), 54 oral and pharyngeal, and 12 occult carcinomas. All 16 nonkeratinizing NPC were positive for EBER1. Both cases of keratinizing NPC and all 54 other metastases were negative. A single positive case of nonkeratinizing occult carcinoma indicated its origin from NPC.

We conclude that, in our population, NPC appears to be a less common origin of occult carcinoma than previously considered. EBER1-ISH in the proper clinicopathologic context allows exclusion of NPC with a high degree of accuracy and nasopharynx can consequently be excluded from the radiation volume. Conversely, a positive ISH in occult carcinoma metastatic to upper and mid-cervical nodes, allows omission of a further extensive diagnostic work-up.

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RADIATION THERAPY OF HEAD AND NECK LYMPHOEPITHELIOMA AND TRANSITIONAL CELL CARCINOMA

K. Skłodowski, J. Rogozińska-Szczepka, R. Tarnawski

Centre of Oncology, MSC Institute, Gliwice, Poland

Standard radiation treatment strategy for head and neck patients with lymphoepithelioma (LE) and transitional cell carcinoma (TCC) is not established probably because of the aggressive nature and better radiosensitivity compared to the squamous cell cancer (SCC). Between 1980-92, 152 patients with LE or TCC of the nasopharynx and tonsil were irradiated alone. In retrospective study, using multivariate analysis, following factors were investigated as a prognostic: sex, age, tumor and nodal stage, hemoglobin level, radiation fields size, total dose, dose per fraction and overall treatment time. The influence of secondary treatment for loco-regional relapse or distant metastases on survival was also evaluated. Tumor stage and total dose have only had a detrimental influence on outcome. Chemotherapy as a secondary treatment for relapse has prolonged overall survival significantly compared to the group of patients with no treatment. Prognostic factors in radiotherapy of LE and TCC are similar like for SCC, however an unimportance of the overall treatment time in the irradiation of LE and TCC should be discussed.

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OUTCOME OF PATIENTS WITH LARYNGEAL CANCER—A RETROSPECTIVE STUDY

M. Voordeckers, D. Van den Barge, V. Vinh Hung, G. Storme

Department of Radiotherapy, Oncologic Center A.Z.-VUB, Brussels, Belgium

Over a period of 17 years (1978-1995) 197 patients with laryngeal cancer were treated with external radiotherapy at our department. All tumor localizations (glottis: n = 102, supraglottis: n = 55, NOS: n = 40) and tumor stagings were included in this analysis. The mean follow-up time was 3.4 years (range: 1 month-14.5 years).

The purpose of this study was to evaluate the overall survival and disease free survival and to compare them with the data found in the literature. This study also served as a quality control program for the treatment of head and neck tumors.

The data obtained showed a global survival rate at respectively 5 and 10 years for the whole patient group of 49% and 35%. The disease free survival for the same period was 73% and 69%.

The subgroup analysis at respectively 5 and 10 years showed following distribution: glottis 98% and 85%, supraglottis 60% and 48%, NOS 51% twice.

Most of these data were comparable with the results found in the literature, except for the local control rate of the T1 glottic carcinomas. This group contained 54 patients.

The 5 years local control after radiotherapy (76%) was worse than most data found in the literature ($\pm 90\%$). Survival after salvage surgery (96.3%) was again comparable with other data.

Until now, no explanation was found for this discrepancy in our results for T1 glottis carcinomas and the results found in the literature. Further investigations will be performed.

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COMBINED SURGERY AND IRRADIATION IN THE MANAGEMENT OF LOCALLY ADVANCED PARANASAL SINUS CARCINOMA

R. Smees, G.P. Bridger, M. Baldwin, R. Fisher, J. Hyde

Department of Radiation Oncology, The Prince of Wales Hospital, Randwick NSW 2031, Australia

Purpose: To compare the effectiveness (in terms of the local failure rate and cancer-specific mortality) of radiotherapy alone and combined modality treatment of paranasal sinus carcinomas.

Methods and Materials: A retrospective study of 96 patients treated over the period, 1970 to 1991 adjusting for imbalance of known prognostic factors.

Results: Local failure rates of patients treated by combined modality treatment were significantly lower than those of patients treated by radiotherapy alone (5-year actuarial local failure rates, 34% (SE = 7%) and 75% (SE = 9%), respectively; $P < 0.001$). Although the former patients were prognostically far superior (fewer sites of involvement, better performance status, younger, lower grade) they still had significantly lower failure rates after adjusting for this prognostic imbalance ($P = 0.002$).

Conclusions: Combination of radiotherapy and surgery may be the preferred treatment of patients with paranasal sinus carcinomas.

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DISCORDANCE BETWEEN P53 PROTEIN EXPRESSION AND SUPPRESSOR GENE MUTATION IN H&N SQUAMOUS CELL CARCINOMA

H. Mineta^{1,4}, Å. Borg², M. Dictor³, P. Wahlberg¹, J. Wennerberg¹

Departments of ¹ORL, ²Oncology, and ³Pathology, Univ. Hospital of Lund, S-221 85, Sweden

⁴Department of ORL, Hamamatsu Med. School, Hamamatsu, Japan

Mutation of the p53 suppressor gene and/or overexpression of the p53 protein is a common event in carcinogenesis. The objective of this study was to compare immunohistochemical (IHC) detection of p53 with PCR-SSCP analysis of gene mutations.

Materials and Methods: Paraffin embedded archival material from biopsies from previously untreated squamous cell carcinoma of the oral cavity was used. Nuclear overexpression of the p53 protein was detected using a monoclonal antibody which recognizes both wild-type and mutant protein. DNA for PCR-SSCP analysis was extracted from 8 μ sections by heating to 60° and incubation with Proteinase-K in 55°

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overnight. PCR-SSCP analysis was performed using standard methods. Four pairs of primers for exon 5 to exon 8 of the p53 gene were used.

Results: In 16 out of 26 cases studied informative results were obtained both from IHC and PCR analysis. Six out of 16 exhibited high (>70% staining nuclei) p53 expression and 4/16 p53 gene mutation. Discordant results were obtained in 6 cases (38%); two mutated cases had low (<10%) IHC staining and 4 cases with high IHC staining had no p53 gene mutation.

Conclusion: In one third of the cases IHC and PCR-SSCP analysis was discordant. Low p53 protein expression in mutated cases could be explained by production of a truncated protein. IHC staining without p53 mutation could be explained by mutations outside exons 5–8 or overexpression of wild-type p53.

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CELL CYCLE EFFECTS IN HEAD AND NECK CANCER AFTER TREATMENT WITH INTERFERON AND RETINOIC ACID

Ulf K. Zätterström, Maria C. Johansson, A. Källén, P. Wahlberg, J. Wennerberg

Departments of Oto-rhino-laryngology/Head and Neck Surgery, and Oncology, University Hospital

Department of Mathematics, University of Lund, Sweden

Combined treatment with retinoic acid and interferon reduces the growth rate of head and neck cancer. The object of the present investigation was to determine what cell cycle effects that are associated with this alteration in tumour growth rate. Two groups of xenografts grown in nude mice were compared: group 1 was treated with retinoic acid and interferon *in vivo*; group 2 served as controls. After three weeks BrdU was injected and tumours excised at regular intervals during 72 hours. From labelling data determined by flow cytometry the cell cycle was analysed by a computerised mathematical model. The results show that treatment with retinoic acid + interferon led to slowing of tumour growth rate that was associated with a prolongation of the G0/G1 phase and a shortening of the G2 phase. The findings give support to studies indicating that treatment with retinoic acid and interferon leads to cell differentiation with a larger proportion of cells resting in G0.

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HYPERFRACTIONATED IRRADIATION IN THE TREATMENT OF LARYNX CANCER T1aNoMo

V.S. Alferov, E.M. Zak, A.P. Kondratyeva

Department of Upper Respiratory and Digestive Tract Tumours, Cancer Research Center RAMS, Moscow, Russia

Early larynx cancer (glottic T1aNoMo) can be cured primary radiotherapy in 80–90%. Radiotherapy technique is important in obtaining of good results. We studied 120 patients who had received radiotherapy in two different regimes for T1a glottic carcinoma. Histologically all cases were squamous cell carcinoma. Traditional radiotherapy was used to treat 90 patients. All patients received irradiation 5 times a week 2 Gy a day, a total dose 66–70 Gy. We have cured 77.8% of patients; 21.1% had local relapse, 1.1%—regional metastases, 5-years survival after salvage surgery was 97.1%. 30 patients were treated with hyperfractionated irradiation. Single dose 1.1 Gy 2 times a day with 4 hours interval for 5 days a week, summary dose—66–70 Gy. 90% patients were cured; 10%—had local relapse. 5 years survival is 96.7%. Our results suggest that hyperfractionated irradiation is very important in obtaining of good results.

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EVALUATION OF THE EFFICACY AND SAFETY OF GM-CSF IN THE PHOPHYLAXIS OF MUCOSITIS IN PATIENTS WITH HEAD AND NECK CANCER TREATED WITH RT

N. Throuvalas, D. Antonadou, M. Pulizzi, G. Sarris

Radiation Oncology Department, Metaxa's Cancer Hospital, Piraeus, Greece

Introduction The presence of side effects during radiotherapy for Head and Neck cancer, like oral mucositis, is a major cause of morbidity that influences the overall treatment time and the probability of local tumor control.

Material and Method In this comparative pilot study 10 patients with Head and Neck cancer >T2N1M0 were enrolled either in group A (GM-CSF administration combined with RT) or in Group B (RT alone). All patients in both groups received 200 cGy/day 5 days/week. Treatment

duration was 6 weeks. Patients in group A received 1 mcg/kg/day 7 days/week, starting on week 3 till the end of the treatment.

Results GM-CSF administration was well tolerated for almost all patients. The radiation side effects that were statistically evaluated, were milder in group A than in group B (control group). During week 6 moderate pain was present in 41.7% of patients in the control group versus 5.9% (group A) ($P = 0.004$), severe pain 25% was present in 25% versus 0% ($P = 0.004$), extensive erythema was present in 41.7% versus 6.2% ($P = 0.009$). Similarly, 42.1% of patients in control group had food intake with the use of narcotics versus 0% in group A ($P = 0.008$).

Conclusion A comparative study with a larger number of patients will establish the use of GM-CSF in the prophylaxis of radiation mucositis.

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MATCHING HALF BEAMS IN HEAD AND NECK RADIOTHERAPY. PLANNING AND DOSIMETRY

A. Arellano, J. Cadenal, A. Melero, A. Castel, R. Ballester, V. Tuset

Radiation Oncology Department, Badalona, Barcelona, Spain

Introduction: In the treatment planning of the head and neck tumours, usually matching fields are necessary. There are inherent hazards with this technique in that overlapping of these portals may result in hot and cold spots at the field edges.

The use of linacs with independent collimators enables to eliminate the beam divergency, matching then the central axes of adjacent fields where there is no divergence. On the other hand, the 3D radiation treatment planning systems allow us to calculate the dose variation through the field's junction.

Technical description: We describe a technique consistent in three isocentric half-fields (two upper laterals and one lower anterior). Patients are immobilized with a thermoplastic mask. The upper limit of the lateral fields and the midline are outlined in the mask. It's not necessary to move either the patient or the treatment couch for the different fields of treatment. The SSD for each field is calculated at simulation and/or planification time. The lateral fields are shielded with individual focalized Cerrobend's blocks, leaving the half field limit free.

Conclusion: In this technique there isn't beam divergency at the junction's fields, so the homogeneity is maximal. A dosimetric study with a 3D planning system shows a good distribution of dose. The dose contribution of each half field in the other half field is <2%. The new linacs working with asymmetric collimators enable us to use the split matching technique in a simple, reproducible and accurate form.

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VINBLASTINE (VLB) IN DIFFERENTIATED THYROID CARCINOMA (DTC) EFFECT MONITORED BY DNA MEASUREMENTS

M. Auersperg¹, M. Us-Krašovec¹, A. Pogacnik¹, M. Hocevar¹, B. Palcic², D. Garner²

¹ Institute of Oncology, Ljubljana, Slovenia

² British Columbia Cancer Agency, Vancouver, Canada

Vinblastine (VLB) infusions 2 mg over 12–24^h were applied to 28 patients (21 females, 7 males, aged 32–85 years) with inoperable or metastatic DTC (follicular 13, papillary 8, Hürthle cell 7). Cytopunctures were performed before and sequentially after VLB infusions. Specimens were processed for Flow Cytometry (FCM) DNA studies (DAPI staining, PAS II cytometer) in all patients and for image cytometry analysis (Cyto-SavantTM cell image analyzer) in 12 patients.

In 17/27 patients (67%) a partial response was achieved. In responders, FCM DNA measurements, changes in DNA distribution pattern (increase in S, G₂ + M compartment, polyploidy, broad G₁ peaks and debris) were observed. Cytomorphological changes after VLB appeared later than changes in DNA histograms. Image cytometry data have also been analyzed in terms of DNA distribution diagrams, as well as changes in other nuclear (texture) features.

Our results show that VLB is effective in DTC, and that sequential DNA measurements can predict clinical effectiveness of VLB.