439 PUBLICATION

AN EPIDEMIOLOGICAL STUDY OF SQUAMOUS CELL CARCINOMAS OF HEAD AND NECK REGION

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Of 1518 patients admitting to Department of Radiation Oncology from 1978 to 1994 with cancers of head and neck region, medical reports of 1293 patients with squamous cell carcinomas were retrospectively evaluated. The patients were classified according their age, sex, tumor localization and stage of tumor at presentation. Staging was performed according to TNM classification by American Joint Commitee (AJC). 1181 patients (91.3%) were male and 112 (8.7%) were female, with a male:female ratio of 10.5:1. The tumor was localized in larynx in 919 (71.1%) patients, nasopharynx in 131 (10.1%), oral cavity in 59 (4.6%), lip in 54 (4.2%), oropharynx in 33 (2.5%), hypopharynx in 31 (2.4%), paranasal sinuses in 20 (1.5%), external auditory canal in 17 (1.3%) and nasal cavity in 5 (0.4%) and other regions in 24 (1.9%) patients. Peak incidence was similar for all localizations and was observed in the fifth decade. Larynx cancers were most commonly localized in the supraglottic region (59.5%), followed by glottic (39.7%) and subglottic (0.8%) regions. Seventy-four percent of glottic larynx carcinomas were either stage I or II. Invasion of cartilage was relatively more common with supraglottic carcinomas than with glottic and subglottic carcinomas. Male:female ratio for larynx carcinomas was 29.6:1.

440 PUBLICATION

ORAL TONGUE CANCER: LONG-TERM RESULTS WITH RADIATION THERAPY

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Background: Even with the advent of neoadjuvant chemotherapy or concomitant chemoradiotherapy, little progress has been made in therapy of oral tongue cancer. So it could be interesting to reassess definitive radiation therapy value in this pathology.

Purpose: Evaluate our long-term results in oral tongue cancer.

Materials and methods: Fourty-four patients with epidermoid oral tongue cancer were successively treated in our department from 1972 to 1979. There were 38 men, 6 women. Age ranged from 43 to 78 (mean 60). There were 17 T1, 20 T2, 7 T3 and 5 Np. They were treated with brachytherapy (24 cases) or radiation therapy + brachytherapy (20 cases) on their primary. Radical neck dissection was conducted before or after treatment of the primary in 22 cases. Endpoints were local control, metastasis, second primaries, survival and tolerance of treatment.

Conclusion: Despite a good local control with radiation therapy, distant metastasis and second primaries result in a very low survival. Alternative therapies (as retinoids?) are still awaited in this bad prognosis alcoholism and tobacco use induced pathology.

441 PUBLICATION

SECOND PRIMARY CANCER OF THE LARYNX IN PATIENTS WITH LUNG CANCER

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The incidence of synchronous or metachronous second primary malignancies (SPM) arising in the lungs following laryngeal cancer varies from 1.4–10.6% of cases. Conversely, to date, only 15 cases of a laryngeal SPM following lung cancer have been reported. We have conducted a prospective, preliminary study in 23 terminal lung cancer patients in a hospice setting in order to assess the incidence of a laryngeal SPM. No laryngeal tumors were observed. Even if under-diagnosed and under-reported, this entity is anecdotal in nature, even when considering the overall poor general survival rates of lung cancer. A lung SPM following laryngeal cancer may be explained by common risk factors such as smoking. However, this plausible theory of "field cancerization" does not seem to work both ways. Multimodality treatment or genetic factors may also play a role in the sequence of mucosal changes leading to neoplasia. Our results are presented in light of the general incidence of SPM in our country. Possible hypothesis for the lack of laryngeal SPM following lung cancer will be discussed.

442 PUBLICATION

CHARACTERISTICS OF IRRADIATION INDUCED CELL DEATH MODE OF A HUMAN SALIVARY CELL LINE

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Irradiation induced injury to the major salivary glands is a known complication of radiotherapy. We used HSG cell line, which is derived from an irradiated human submandibular gland, as an *in vitro* model for the studying this damage. Ninety-six h post irradiation of HSG cells at log phase stage of growth the LD_{50} was found to be 5–7.5 Gy, with a cell death rate of 75%, resulting from 10–20 Gy. In contrast cells at the confluent stage of growth demonstrated radioresistancy. However, irradiation latent damage was again observed when these irradiated cells were reinduced into log phase growth. Incubation of the HSG cells with INF-g for 2–24 h partially minimized the irradiation induced injury but incubation with TNF-a, Interleukin-6 or heat shock protein did not reduce the damage. In summary, irradiation induced damage to HSG cells is in accordance with the delayed reproductive cell death mode.

443 PUBLICATION

CISPLATIN AND IFOSFAMIDE IN ADVANCED POORLY DIFFERENTIATED CARCINOMA OF THE NASOPHARYNX

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From 1990–1995, 19 males and 8 females (median age 29 years) presented with advanced nasopharyngeal carcinoma. 12 had bony metastases and 15 advanced local disease. 20 patients received cisplatin 50 mg/m^2 and ifosfamide (with mesna) both 3 g/m^2, all daily for 2 days. There were 2 CRs (local disease) and 10 PRs (4 on bone scan, 6 of local disease), with an overall response rate of 60%. The median time to treatment failure was 30 weeks and median survival 60 weeks, with no difference between those with bone metastases and those with local disease only. 10 patients had nausea and vomiting, 3 headaches and 13 developed Grade III–IV neutropenia (median WBC 1.75). There were 2 admissions and 1 death from neutropenic sepsis. Cisplatin and ifosfamide is well tolerated and promising in this aggressive form of head and neck cancer seen in young patients in Africa and Asia.

Oncogenes and suppressor genes

444 EACR Award lecture

A MOLECULAR GENETIC VIEW OF CANCER PROGRESSION

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Cancer development is thought to be caused by a sequence of genetic changes, but the details of these genetic progression events are only partially understood and many important cancer genes still remain to be cloned. This presentation will highlight new strategies for dissecting the multi-step progression of breast and prostate cancer.

Comparative genomic hybridization (CGH) has enabled the identification of chromosomal regions likely to harbor important genes for tu-

morigenesis, metastasis and drug resistance as illustrated here by three examples of breast and prostate cancer research: 1) Amplification of the 20q13 chr region was found in breast cancer suggesting the location of a new important oncogene. 2) Distant metastases of breast cancer were often found to be remotely, if at all, clonally related with the primary tumors. Measurements of e.g. prognostic factors from the primary tumors may therefore not reflect the biological properties of metastatic tumor cells. 3) In prostate cancer, amplification of the Xq12 region, the site of the human androgen receptor (AR) gene, emerged in conjunction with the development of resistance to androgen deprivation. AR amplification was found in ≈ 25% of recurrent prostate tumors and apparently facilitated tumor cell growth in low androgen concentrations. These clinical implications of CGH illustrate the power of new genetic screening tools in dissecting the genetic basis of cancer progression.

445 ORAL

RECIPROCAL PATTERNS OF C-ERBB-2 THREONINE AND TYROSINE PHOSPHORYLATION IN HUMAN TUMOUR CELLS

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Overexpression of the c-erbB-2 receptor is implicated in the pathogenesis of human breast cancer, but the functional significance of this phenotype is unclear. We have developed phosphothreonine-specific antibodies recognizing the c-erbB-2 juxtamembrane consensus site for protein kinase C (PKC). Using these antibodies we show that a number of human cancer cell lines exhibit constitutive c-erbB-2 threonine phosphorylation. Unlike nonmalignant fibroblast cell lines, these tumour cells sustain little if any enhancement of receptor threonine phosphorylation following phorbol ester treatment. DNA sequencing reveals no abnormality of juxtamembrane domain structure in any of these cell lines. Hence, PKC may be constitutively activated in some human tumour cells.

446 ORAL

ENHANCED EXPRESSION OF C-MYC, N-MYC, C-HA-RAS 1, C-ERB B-2/NEU, C-FOS AND C-JUN IN HUMAN GERM CELL TUMORS

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The presence of c-myc, N-myc, c-Ha-ras 1, c-erb B-2/neu, c-fos, and c-jun was investigated in biopsy specimens from 20 patients with various types of germ cell tumors. The expression of the oncogenes was demonstrated by in situ hybridization.

C-myc oncogene expression was found in 10/20 of tumors including 2 embryonal carcinomas, in one Leydig cell tumor, in 3 embryonal carcinomas with seminomas, in one immature teratoma with seminoma, in one immature teratoma with choriocarcinoma, in one embryonal carcinoma with immature teratoma, and in one mature teratoma. N-myc was observed in 8/20 of tumors including 2 embryonal carcinomas, in 3 embryonal carcinomas with seminomas, in one embryonal carcinoma with immature teratoma, in one immature teratoma with choriocarcinoma, and one immature teratoma with seminoma. C-Ha-ras 1 oncogene expression was found in 7/20 tumors including 2 embryonal carcinomas, in one mature teratoma, in the benign Leydig cell tumor, in 2 embryonal carcinomas with seminomas, and in one embryonal carcinoma with immature teratoma. Expression of c-erb B-2/neu oncogene could be identified in benign Leydig cell tumor only. C-fos was expressed in 12/20 tumors including in the benign Leydig cell tumor, in 4 pure seminomas, in 3 embryonal carcinomas with seminomas, in 2 immature teratomas, and in one immature teratoma with choriocarcinoma.

C-jun expression was observed in 14/20 tumors, including in 6 pure seminomas, in the benign Leydig cell tumor, in 2 immature teratomas, in one mature teratoma, in 2 embryonal carcinomas with seminomas, in one immature teratoma with choriocarcinoma, and in one embryonal carcinoma with immature teratoma.

The evidence of these oncogenes in human testicular cancer is consistent with the view, that alterations of these oncogenes play a role in the pathogenesis of this tumor type.

447 ORAL

CLASSICAL GENE AMPLIFICATIONS IN HUMAN BREAST CANCER ARE NOT RESPONSIBLE OF DISTANT METASTASES

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Tumour progression is a fundamental feature of biology of cancer. In breast cancer, no genetic events that are critical in the late stages of the tumorigenic process have been identified. To define the relationship between breast cancer progression and gene amplifications, we analysed 62 distant metastases (18 solid metastases and 44 pleural effusions), and 122 primary breast tumours for the three regions most frequently amplified in primary breast carcinomas (protooncogenes *MYC* and *ERBB2* and 11q13 chromosomal region). Surprisingly, *MYC* gene (and also *ERBB2* but at a lower level) was unfrequently amplified in metastases compared with primary breast carcinomas. Furthermore, the solid metastases did not show amplifications for any of these three regions.

These results suggest that protooncogenes *MYC* and *ERBB2* and 11q13 chromosomal region are mainly involved in the genesis of the tumour at its primary site and not in its progression.

448 ORAL

PCR-SSCP A SENSITIVE AND RAPID METHOD TO DETECT MUTATIONS IN THE P53 TUMOR SUPPRESSOR GENE OF PATIENTS WITH ADVANCED COLORECTAL CANCER

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Mutations in the p53 tumor suppressor gene, located on chromosome 17p, are known to be the most frequent genetic alterations found in human cancers. We used the polymerase chain reaction (PCR) followed by the single-strand conformation polymorphism (SSCP) analysis to screen for mutations of the p53 gene in patients of the European Saar-Lor-Lux area with colorectal cancer at various developmental stages. While we detected no mutations in all of 16 early-staged colonic polyp samples, we revealed 7 (13.7%) transition point mutations in exons 5 to 9 of the p53 gene in 51 late-staged colorectal tumours. These results show that the PCR-SSCP analysis technique provides both a sensitive and rapid method for the genetic staging of colorectal samples and confirm previous reports that p53 mutations are usually associated with an advanced development of colorectal cancer characterized by the transition from adenoma to carcinoma.

449 ORAL

BRCA1 GENE MUTATION CARRIER ANALYSIS IN FAMILIAL BREAST CANCER PATIENTS

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Myriad Genetics

BRCA1, the predisposing gene for familial breast and ovarian cancer localized on chromosome 17q21.3 has been recently cloned. The gene comprises 22 coding exons which span 100 kB of genomic sequence. The protein predicted is 1863 aminoacids long. 31 mutations have been identified in constitutional DNA of affected member from various family of which 22 were distinct. Not one of 22 transcribed exons seems to be a preferential target site for mutations. Overall germline BRCA 1 mutations account for 1–2% of all breast cancers and about 3% of ovarian cancers. The lifetime risk of breast and ovarian cancer in BRCA1 mutation carriers is high: the risk of breast cancer is about 50% by age 50 and 70% by age 70. The average risk of ovarian cancer is 40% by age 70. BRCA1 has never been found mutated in sporadic carcinomas, however, loss of heterozigosity in the region of BRCA1 has been observed in 40% of breast and about 60% of ovarian cancers. The lifetime risk to