exposed to magnetic fields of $\geqslant 0.2\ \mu$ or cumulative exposure of $\geqslant 0.4\ \mu$T years. The preliminary results of a similar cohort of adults do not point to an increased cancer risk, either. The number of children exposed to stronger magnetic fields may be too small to draw final conclusions, but that among the adults is not (8,554 cancer cases observed during the follow-up time). An association between the occupational exposure to electromagnetic fields and leukaemia and brain cancer obtained earlier in a Finnish study and some other studies is not confirmed in several more recent studies.

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NO ABSTRACT

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CONSERVATIVE TREATMENT FOR T1T2 SUPRAGLOTTIC SCC
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From 1974 to 1983, 240 previously untreated patients (pts) presenting with T1 or T2 (AJC 1992) supraglottic SCC were treated either by partial surgery (PS = 163 pts: 53 epilarynx, 110 vestibule) or by definitive irradiation (XRT = 77 pts: 52 epilarynx, 25 vestibule). There were 130 supraglottic laryngectomies, 27 hemilaryngopharyngectomies and 6 subtotal laryngectomies while 62 pts had postoperative XRT at primary site and 71 on the neck. There was no postoperative death and local failures occurred in 8% of cases, neck recurrences in 8%, distant metastases in 10% while 31% of pts developed metachronous cancers. The 3 yr survival was 75% (81% for endolarynx vs 50% for epilarynx). The final larynx preservation rate was 93%. In pts treated by XRT, there was no treatment related death and all the 9 local failures (12%) were T2 tumors arising the arytenoid or denuding the epiglottic cartilage. The 3 yr survival was 45% and the larynx preservation was achieved in 90% of pts. We recommend PS for (1) tumors of the laryngeal surface of epiglottis, (2) tumors of suprahyoid epiglottis denuding the cartilage, (3) limited but infiltrating tumors of lateral epilarynx and, (4) tumors reaching the arytenoid, all other cases being suitable for XRT.

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ASSESSMENT OF VOICE RESULTS IN GLOTTIC CARCINOMA TREATED BY IRRADIATION, CO_2 LASER RESECTION AND CORDECTOMY BY MEDIAN THYROTOMY
R. García-Tapia, J. Alcalde, S. Fernández, A. Huarte
The different types of treatment for T1a T1b vocal cord carcinoma: radiotherapy, cordectomy by median thyrotomy and endoscopic CO_2 laser resection offer from the oncologic point of view nearly the same results. When choosing the therapeutical procedure the functional results, regarding voice quality, are of main importance.

This study is directed to establish the differences of voice quality between patients treated by radiotherapy, conventional cordectomy and CO_2 laser resection.

Since the T1 vocal cord carcinomas is not a homogenous group of tumors and because the treatments are also different in some aspects comparison between the three groups could be erroneous. To avoid it we select a group of patients, treated by each one of the treatment types, of nearly the same characteristics on size and degree of infiltration. (Phonatory results by objective acoustical, etc.)

Phonatory results by objective acoustical analysis, visual evaluation by stroboscopy and perceptual evaluation by the patient and voice experts are presented.

The relationship between all degree of surgical resection on voice quality are discussed.

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SUPRAGLOTTIC CANCER-COMBINED RADIOTHERAPY/CHEMOTHERAPY AND/OR NEW FRACTIONATION SCHEDULES. DO THESE APPROACHES IMPROVE THE RESULTS COMPARED TO CONVENTIONAL RADIOTHERAPY? A REVIEW OF THE SITUATION IN 1995
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The principal goals in the management of laryngeal cancer are eradication of disease with preservation of function. The optimal treatment should be chosen for each patient. Several points will be emphasized.

—The results of conventional radiotherapy in several studies, including results of supraglottis in Institut Curie. The effects of dose-time-fractionation on local control.

—The results of clinical trials using altered fractionation schedules such as hyperfractionation, accelerated fractionation, treatment with split course, or with concomitant boost-Studies comparing altered schemes to conventional radiotherapy will be reviewed.

—The role of chemotherapy as part of combined modality programs and as part of larynx preservation. Results of clinical trials, especially with induction or concomitant chemoradiotherapy will be discussed.

—The value of cell kinetics measurements to predict radiosensitivity: labeling index, length of S-phase, potential doubling time and therapeutic implications.

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PROGNOSTIC FACTORS FOR ORGAN PRESERVATION IN PATIENTS WITH ADVANCED LARYNGEAL CANCER
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The effectiveness of induction chemotherapy combined with radiation therapy as an organ preservation treatment strategy would be enhanced by improved methods to select for patients with a high likelihood of success. Detailed analyses of prognostic factors for chemotherapy response and ultimate organ preservation were undertaken in 166 patients randomized to 3 cycles of cisplatin/5-FU and definitive radiation (66–76 Gy). Overall tumor size and histologic pattern of growth were significant predictors of complete response after chemotherapy. Successful organ preservation was significantly associated with T class, performance status, and p53 overexpression. In patients with supraglottic cancers treated surgically, disease-free and overall survival were significantly associated with histologic growth pattern. Organ preservation after chemotherapy and radiation was predicted by performance status, prior tracheostomy and chemotherapy response. Until better molecular markers of chemo/radio sensitivity are available to optimize patient selection for organ preservation, histologic response to induction chemotherapy appears most reliable.

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NO ABSTRACT

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INHIBITION OF 3′, 5′-CYCLIC NUCLEOTIDE PHOSPHODIESTERASE AS A NOVEL CONCEPT IN TUMOUR THERAPY
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A wide spectrum of human and animal tumour cell lines exhibit significantly lower cAMP levels than normal cells, as a consequence of strongly enhanced activities of a cAMP-specific phosphodiesterase isoenzyme (PDE). Inhibition of this isoenzyme by selective inhibitors results in a long lasting, concentration-dependent rise of intracellular cAMP, accompanied by marked growth inhibition. At higher concentrations of the inhibitor (>3 μM), induction of apoptosis becomes apparent, as detected by flow cytometry, confocal microscopy and ELISA-based determination of fragmented DNA in intact cells. Thus tumour-associated overexpression of a cAMP-specific PDE-isoenzyme in proliferating tumours offers a novel cellular target for selective antineoplastic therapy.

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NEW CONCEPTUAL AND METHODOLOGICAL APPROACHES TO ANTICANCER DRUG DEVELOPMENT
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Although cancer chemotherapy and hormonal treatment may have significant palliative effects in the systemic treatment of malignant disease, major steps towards a cancer cure by drugs cannot be expected from these therapies. Therefore, the originally successful empirical approach to drug discovery should probably be substituted by a more rational drug design. Molecular genetics have produced enormous progress in our understanding of the principles of tumor development and tumor growth. For the first time in the history of anticancer drug development it now

appears that mechanism-based pharmacological interactions become a reality. Molecular targets can be defined for drug discovery programs and methodological advances, such as molecular diversity strategies including combinatorial chemical libraries and high throughput screening systems have increased the chance to find new lead compounds for more effective cancer therapy.

Drugs, which are meant to restore regulatory pathways in the biochemistry of signal transduction or cell division, will most likely be used as longterm chronic therapies. Therefore, oral bioavailability and high specificity for the target, i.e. low toxicity to normal tissues, will be required. In addition, the pretherapeutic diagnosis of the target in a given patient's tumor will be a prerequisite for adequate treatment. In clinical phase I-studies new pharmacokinetic or pharmacodynamic principles need to be defined as end points. The conversion of malignant tumors from an aggressive and destructive disease to a chronic condition with which the patient can live and age, is becoming a realistic concept. Unfortunately, the translation of new molecular biology concepts into useful cancer therapies is more difficult than the scientific community originally anticipated. One reason for this might be the lack of adequate pharmacological test systems. Human species specific therapies have no reasonable experimental equivalent in which the pharmacological behavior of a potential drug can be characterized. Despite all foreseeable pitfalls in the pharmaceutical development of new molecular targets, the gradual understanding of the fundamental processes opens up new avenues for anticancer drug development.

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NEW DRUG DEVELOPMENT AT THE END OF THE SECOND MILLENNIUM

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A limited number of cancer patients can be cured with currently available chemotherapy. Therefore, the search for and subsequent development of more effective and selective agents for cancer remains one of the major challenges in medicine today. Over the last decade our knowledge on the molecular basis of cellular processes like proliferation, differentiation, and apoptosis and their importance in cancer biology and treatment has increased dramatically. Also specific pathways of neoplastic transformation and processes involved in tumour vascularization have been elucidated. Key proteins involved in such processes are currently investigated as possible targets for therapeutic intervention. Among these the E2F transcription factor family, the cyclin dependent kinases, the tumour suppressor gene P53, the enzyme telomerase and others have attracted enormous interest recently. This is illustrated by the rapid growth of mechanism based screens. The availability of large chemical or natural product collections recently extended by combinatorial libraries and the presence of advanced technology allow high throughput screening of several thousands of compounds per week. Nevertheless, *in vitro* and *in vivo* models exhibiting presence or absence of such mechanisms will remain necessary to demonstrate activity at cellular and tumour level. Moreover, by studying drug activity in relation to the level of expression of different targets in tumour cell line panels, the advantages of both random and mechanism based approaches can be combined. Despite several advantages, the human tumour xenograft model in immunodeficient mice or comparable models cannot be used for such first line testing, because of the high costs and relatively large quantities of drug required. By performing limited "rodent only" toxicological research on potential anticancer agents and careful planning of subsequent steps of the drug development process significant unnecessary time loss up to several years between the discovery of a new drug and its ultimate use in clinical medicine can be avoided. This will certainly lead to an even more rapid clinical evaluation of exciting new concepts in the coming years. Several examples of new drugs already under clinical trial will be presented.

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TAXOTERE: FROM PRECLINICAL TO CLINICAL PHARMACOLOGY

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Taxotere (Docetaxel) (TXT) is the first active hemisynthetic taxane with specific properties in part related to the hydrophobic domain (3′ phenyl group) and the polar functions of the C13 lateral chain. In the purified tubulin test as well as in experimental tumors TXT (1) is 2–12 times more active than paclitaxel (TAX); (2) retains activity in some tumors overexpressing Gp 170; (3) shows only partial cross resistance with TAX. In humans 100 mg/m^2/3 weeks has been defined as the optimal schedule with >80% neutropenia, anaphylactoid type reactions, and cumulative skin toxicity and fluid retention syndrome. The latter are in part prevented by corticoseroid premedication.

A striking activity was observed in patients with advanced breast cancer in pts with prior chemotherapy (CT) for metastatic progression RR was 50%; it was 48% in anthracyclin resistant pts and 39% in anthracyclin refractory pts with a response duration of 25–28 weeks in these studies. In pts with NSCLC whether previously treated or not RR were close to 20%. Other tumors (Head and Neck, pancreatic, NHL) appeared sensitive although confirmation is required. Taxotere appears a promising new agent which should be part of combination regimens in particular for breast cancer patients.

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THE ROLE OF LYMPH NODE DISSECTION IN BREAST CANCER SURGERY

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Axillary dissection has been a routine part of breast cancer treatment to provide accurate staging and information on which decisions about adjuvant treatment can be made and to provide local tumour control. The aim of this paper is to explore the opportunity not to perform an axillary dissection in all breast cancers.

Between 1987 and 1994, 1351 full axillary dissections were performed for five breast cancer subgroups by T category: pT1a, 100; pT1b, 197; pT1c, 574; pT2, 453 and pT3, 27.

Nodal positivity was 11%, 16.7%, 32.6%, 55.0%, 66.7% respectively. The total number of nodes involved and the type of involvement for each T category was compared with the next more advanced T category; interrelationships between clinical and pathologic characteristic were determined.

In conclusion our data suggest that only in selected patients (age, small size lesions, prognostic factors) axilla, performed only as a staging procedure, can be left untouched because of the low rate of lymph node metastasis. In these patients adjuvant systemic treatment can be planned on the basis of other factors.

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DOES EXTENSIVE SURGERY IMPROVE SURVIVAL IN GASTRIC CANCER?

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Experiences from Japan with extensive lymph node removal and much better survival as compared with the results following surgical therapy as it is conventionally performed in Europe has been put forward to support a more aggressive surgical approach to patients with gastric cancer. On the other hand, it has been argued that cancer with spread to distant lymph nodes is unlikely to be cured with techniques that only can provide local cancer control. Furthermore, previous trials from the western world have not been able to support the hypothesis that more extensive surgery prolongs survival. Instead higher post operative morbidity has argued in favour of more conventional techniques. However, a recent large German-Austrian randomized study (Siewert *et al.*, *Br J Surg*, **80**, 1015, 1993) did demonstrate that a subgroup of gastric cancer patients did benefit from more extensive lymph node dissection. The data pros and cons and their potential consequences are discussed.

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RESULTS OF SENTINEL NODE BIOPSY IN CUTANEOUS MELANOMA

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Lymphatic mapping and sentinel node (SN) biopsy is an exciting development that can give better regional tumor control, improve survival and spare patients unnecessary lymph node dissection. Lymphoscintigraphy, intra-operative gamma ray (Neoprobe®) and dye (patent blue) detection as means for SN identification in melanoma were studied in 55 patients with a primary tumor thicker than 1 mm according to Breslow (median 2.2, range 1.1–8). A total of 116 SN's were visualized in