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Abstracts of Theses from the Scandinavian Countries

Abstracts of Scandinavian theses on oncologic subjects are published under this heading. The full theses are as a rule published by the universities or as supplements to different journals. They can usually be obtained after contact with the author.

Clinical and prognostic features of advanced ovarian carcinoma

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From January 1981 to December 1986 a randomized study was performed at the Finsen Institute and Bispebjerg Hospital comparing sequential versus alternating combination chemotherapy in patients with advanced ovarian carcinoma. A total of 301 patients were included in the study. The treatment results were analysed and the prognostic influence of some variables were studied by univariate and multivariate statistical methods. Thirty-three percent of the patients were classified as low-risk patients defined by other histologic subtype than clear cell or mucinous carcinoma, good performance status, low alkaline phosphatase before treatment, well-differentiated tumour, few remaining metastases, and small residual tumour after the primary operation. This group had a 3-year survival rate of 62%. The high-risk group included 27% of the patients and had a 3-year survival rate of 7%. A control operation ('second look') was as a rule performed after the postoperative chemotherapy and included bilateral salpingo-ophrectomy and omentectomy. This control operation gave in itself prognostic information and patients characterized not only by well-differentiated tumour and good performance status at the start of the treatment but also by small residual tumour burden at the control operation had a comparatively long survival. It is uncertain whether the second operation in itself had a therapeutic effect but comparisons with ultrasound and CT scanning showed that these methods were inferior to the second operation for response evaluation. This is important as treatment of advanced ovarian carcinoma is still in an experimental and developing stage.

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Immunophenotyping in acute leukaemia, myelodysplastic syndromes and hairy cell leukaemia—The use of monoclonal antibodies against myeloid differentiation antigens

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During one period cells from all patients (a total of 106 patients) with clinical suspicion of acute leukaemia were phenotyped by monoclonal antibodies against myeloid differentiation antigens. By comparison with established morphological and cytochemical routine diagnostic methods it could be shown that the immunophenotyping could accurately differentiate acute leukaemia from other conditions and also distinguish between acute myeloid and acute lymphatic leukaemia. As in other reported studies there was some correlation between FAB classification and phenotype but essentially within the monocytoid cell type. The more rare cases of acute mixed leukaemia could be detected and accurately characterized. It was also found that 3 cases of advanced myelodysplastic syndrome had a phenotype indistinguishable from acute myeloid leukaemia and these patients rapidly progressed to overt acute leukaemia. In another study phenotyping of bone marrow cells was performed in 74 patients with myelodysplastic syndrome and it could be shown that in some cases of refractory anaemia with sideroblasts (RA-S) and also in some more advanced cases the phenotype was, astonishingly, normal. The number of cells with expression of the immature differentiation antigens CD13 and CD33 was generally increased and patients with more than 60% CD13 + CD33 positive cells had shorter survival. The use of the antibody NAT-9 (which detects an antigen on mature myeloid cells) was of great value for differentiation between acute leukaemia and other conditions but also due to the fact that the number of NAT-9 positive cells decreases as one of the first signs of progression of myelodysplastic syndrome. The prognostic value of phenotyping in AML is not completely clear but expression of immature myeloid antigens has in some investigations been found to be a negative prognostic factor. In a prospective phenotyping of 109 AML patients (of whom 89 had complete induction treatment and could be included in the statistical analysis) there were significantly better remission rates if the number of CD13 +, CD33 + or HLA − DR + cells were low. In a Cox multivariate analysis both low age ($p = 0.001$) and high ratio CD33/CD13 ($p = 0.03$) were good prognostic factors. The positive prognostic value of CD33/CD13 decreased with increasing age. The immunologic identification of hairy cell leukaemia cells is difficult due to lack of specific antibodies. However, by combination of a CD11c and a CD20 antibody in a double-stained assay it was possible to detect hairy cell leukaemia cells in blood, bone marrow and spleen. In some cases the number of CD11c/CD20 + cells was different from the number of acid phophatase tartrate resistent cells.

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Facing death—Physicians' difficulties and coping strategies in cancer care

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In the first part of the thesis earlier studies of physicians' stress and ways of coping are reported. There is a lack of systematic studies which show how doctors working with cancer patients adjust to this work. The aim of this investigation is to study cancer doctors' difficulties and coping strategies. The theoretical frame of the study embraces parts of psychoanalytical theory and coping models, emphasizing that both unconscious and conscious psychological processes play their part in the coping process. The second, empirical part of the study includes 23 physicians strategically selected out of a population of physicians who work with institutional care and who have daily contact with adult cancer patients. The main method of data collection has been a series of recorded interviews. The focus of the interview was the physician's perception of how he reacts, thinks, talks and acts in different phases of the cancer disease. To illustrate the defence strategies of the interviewers, the projective percept-genetic test, the 'Defence Mechanism Test' (DMT) is used. The 'Structural Analysis of Social Behaviour' (SASB) has been used to study the doctors' self image. The results indicate that the stated difficulties deeply affect the doctor as a human being. The statements reflect conflicting feelings and wishes in relation to authority, conflicting feelings and wishes in relation to frightening and injuring, conflicting feelings and wishes in relation to intimacy/distance. Thirty themes

of coping strategies frequently recur and they have been grouped into seven categories. Most of the doctors 'seek knowledge' and support from scientific literature. The majority of them state that attempting to 'solve a problem' is their main strategy. Most of the doctors 'seek support' as a part of their coping strategy. An interesting observation is that the doctors to a higher extent 'seek a relation' to their patients rather than to their colleagues. Almost one third use 'denial of the severity of a situation' as their main strategy. All the doctors consciously or unconsciously use 'diverting strategies', i.e. undertake tasks which are devoid of contact with patients, such as research and administration or other activities which allow them to avoid the patient. One third use 'projective manoeuvres' but this is never a main strategy. In the third part of the study the credibility of the results and their pedagogical and practical implications are discussed.

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Transrectal ultrasound and core biopsies for the diagnosis of prostate cancer—A study of pretreatment investigation strategy for patients with suspected prostate cancer

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Prostate cancer is the most common malignancy among Swedish men. In order to select patients to appropriate treatment, transrectal ultrasound (TRUS) and guided core biopsies is commonly used. The aim of this study was to define prognostically important factors in prostate cancer and the accuracy of TRUS and core biopsies as diagnostic tools. Fifty-one patients with localized prostate cancer were prostatectomized and followed up after a mean observation time of 73 months. The adverse influence on progression by tumor volume, Gleason grade, seminal vesicle invasion and lymph node metastases was statistically significant in the univariate analyses. However, tumor volume was the only parameter with an independent prognostic impact on progression. It is important to find a diagnostic method which can accurately determine these parameters in the pretreatment work-up. Thirty-four patients with localized prostate cancer were examined with TRUS prior to radical surgery. The ultrasound examination failed to detect 24% of the tumors, and was not reliable for the determination of tumor size and capsular penetration. TRUS cannot be used as the sole method for the diagnosis of prostate cancer. Biopsies might improve the results. Ultrasound-guided core biopsies targeting hypoechoic lesions suspicious for prostate cancer in combination with systematic biopsies sampling the whole gland were performed on 251 men. By adding the results of systematic biopsies to the results of target biopsies, additional information was obtained for the detection of cancer, on tumor volume and seminal vesicle invation. Grading was not improved. By taking multiple TRUS-guided biopsies considerable trauma is inflicted to the patient. A 1.2-mm cutting needle is commonly used for sampling. A thinner needle may possibly cause less pain. It was shown that a 0.9-mm core biopsy needle can be used without compromising diagnostic accuracy. The results obtained with two thinner needles, 0.8- and 0.7-mm, were unsatisfactory. Complications following TRUS-guided biopsies are infections, bleeding and urinary retention. A total of 347 consecutive men were extensively biopsied. We studied the impact of patient age, final diagnosis, number of biopsies taken, and different regimens for prophylactic norfloxacin treatment. The administration of antibiotics for 3 days, when the first dose was given before the examination began, was the only parameter statistically associated with a reduced risk for complications. Multiple biopsies can be taken without an increased risk for complications if prophylactic antibiotic treatment is given.

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Studies on etiological factors in nasopharyngeal carcinoma

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Both Epstein-Barr virus (EBV) infection and certain dietary factors have been implicated as risk factors for nasopharyngeal carcinoma (NPC). The EBV-encoded latent membrane protein (LMP1), expressed in the majority of NPC cases, can morphologically transform human epithelial cell lines, suggesting an important role in the tumorigenesis of NPC. Epidemiological studies have implicated salted fish as a nasopharyngeal carcinogen. The aim of the present study was to investigate the impact of EBV and salted fish on the development of NPC by epidemiological and experimental studies. In the epidemiological study we showed that IgA antibody against EBV viral capsid antigen (IgA/VCA) and intake of salted fish were associated with a strong excess risk of NPC. The association persisted after adjustment for other dietary factors, occupational exposure and medical history. The combination of salted fish and EBV is strongly associated with NPC more than EBV or salted fish alone. The findings indicate that both EBV and salted fish may contribute to the tumorigenesis of NPC. The expression of LMP1 in NPC biopsies in relation to tumour proliferation was analysed by Western blot and immunohistochemistry. The observations that LMP1 expression correlated to tumour proliferation as determined by Ki67 and epidermal growth factor receptor (EGFR) expression indicate an effect of LMP1 on increasing tumour proliferation in vivo. In the in vitro studies, the LMP1 genes derived from both B-lymphocyte (B-LMP1) and NPC (C-LMP1) were transfected into a human keratinocyte line, Rhek-1. Expression of both B- and C-LMP1 in Rhek-1 cells resulted in morphological transformation of these cells. The C-LMP1 more effectively predisposed the Rhek-1 cells to a neoplastic change as indicated by increasing clonability in soft agar and tumorigenicity in SCID mice. Moreover, the C-LMP1 expressing sublines showed higher proliferation than those expressing B-LMP1. The proliferation of these cells correlated to the level of LMP1 expression. To investigate the carcinogenic effect of salted fish, Sprague-Dawley rats were fed with salted fish for a period of two years. In the groups treated with salted fish, three rats had nasopharyngeal tumours and four rats had nasal tumours. No nasal or nasopharyngeal tumours appeared in the control group. The difference in the occurrence of nasal and nasopharyngeal tumours between rats treated with salted fish and the controls was statistically significant. This finding further strengthens the hypothesis that Chinese salted fish is a nasopharyngeal carcinogen. We also analysed the nitrosamines in salted fish samples and in rats fed with such fish. N-nitrosodimethylamine (NDMA) was found in the salted fish samples, and in organs (livers and kidneys) of rats fed with salted fish for two years, indicating an accumulation of nitrosamines in these rats. In short-term in vitro cultures, salted fish extract decreased proliferation and induced differentiation of epithelial cells, as evidenced by a reduced growth rate, and increased the expression of differentiation-associated molecules in these cells. However, the expression of LMP1 protected these cells from the growth suppression, indicating a possible interaction between the viral protein and potential carcinogenic substances in salted fish. In summary, the

present studies demonstrated EBV and salted fish as risk factors for the development of NPC, and indicate a synergistic effect between these two factors. Expression of LMP1 in immortalized human epithelial cells in vitro leads to neoplastic transformation and the expression of LMP1 in NPC is associated with increased tumour proliferation in vivo. Salted fish studies established a rat NPC model and indicate that nitrosamines are a potential nasopharyngeal carcinogen in salted fish.

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On the role or metalloproteases in tumor invasion and metastasis

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The metastatic process involves a series of linked sequential steps of which degradation of tissue barriers by preteases is believed to be one of the more important. The metalloproteases is a family of proteolytic enzymes of which several members are expressed at elevated levels in human tumors, and have been directly linked to metastasis in a number of tumor models. This thesis is focusing on experimental studies of metalloprotease expression in cell lines transformed by the *ras* oncogene alone, or in combination with the *plt* (polyoma T) or E1A oncogenes. Rat fibrosarcoma cell lines with large differences in invasive and metastatic capacity were generated and analysed, in an attempt to correlate the expression level of specific metalloproteases with the malignant properties of the cells. The stromelysin-1 mRNA level correlated with capacity to metastasise in athymic mice, for all cell lines tested. The most metastatic cell lines expressed interstitial collagenase and 92 kDa type IV collagenase in addition to stromelysin-1, suggestive of a cascade of proteases acting in concert. The expression of stromelysin-1 also correlated with the ability to penetrate a reconstituted basal membrane, but only in cells transformed by *ras* + E1A oncogenes, and not in cells transformed by *ras* + *plt* oncogenes. The lack of correlation was not due to differences in adhesive or chemotactic properties of *ras* + *plt* cells. Cell lines with low expression of stromelysin-1 were observed to express enhanced levels of this protease when grown as tumors in athymic mice. Two *ras* transformed fibrosarcome cell lines lacking the important transcription factor c-Jun were demonstrated to be tumorigenic, invasive and metastatic. Transcriptional activation of the stromelysin-1 gene in these cells appeared to involve other Jun-family proteins, in the absence of c-Jun. Stromelysin-3 is differentially expressed in breast tumors of different histological type and malignancy. A statistically significant correlation between high stromelysin-3 mRNA levels in the primary tumor and fatal metastatic disease was demonstrated. Stromelysin-3 may be a useful prognostic marker in human breast cancer.

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Thyroid cancer—Studies on etiology and prognosis

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This dissertation was performed to elucidate the importance of different prognostic and etiological fracors in thyroid cancer. Thyroid cancer constitutes about 1% of all malignant tumours and the incidence is increasing in Sweden. It is rare in children before the age of 10. During puberty the female to male ratio increases to be two to three times more common in females. The ratio remains constant until menopause and thereafter declines. The etiology of this gender-dependent incidence difference is unclear. Ionizing radiation is the only well-established risk factor for the disease, while the impact of other etiological factors is not clear. A retrospective study based upon medical records of 218 females and 91 males with papillary, mixed or follicular types of thyroid cancer was conducted. Prognostic factors were compared by multivariate analysis using Cox's semiparametric hazard model. Differences in prognosis between women and men were found. There was a higher relapse rate and mortality risk among men. Distant metastasis, age >50 years, regional lymph node metastasis, low or moderate differentiation, and tumour related symptoms at diagnosis were also independent factors related to increased tumour mortality risk. A population-based case-control study including 180 cases and 360 controls was carried out to identify risk factors for thyroid cancer. Information on exposure was obtained by mailed questionnaires. The first part of the study investigated connections between medical ionizing radiation and thyroid cancer. The results showed that diagnostic x-rays were a significant risk factor for papillary thyroid cancer in women between 20 and 50 years at diagnosis. Exposure to iodine-131 caused no increased risk for thyroid cancer. The result supports that external radiotherapy is a risk factor for tyroid cancer in women. The second part of the case-control study dealt with occupation and different exposures. Work with diagnostic x-ray investigations and work as a lineman was associated with thyroid cancer. Exposure to impregnating agents increased the risk. The third part of this study showed that one pregnancy increased the risk for papillary thyroid cancer. A medical history of asthma or allergy decreased the risk. Another case-control study using medical records as the source for assessment of exposure gave a non-significantly increased risk for thyroid cancer in patients who had been treated with external radiotherapy including the thyroid gland.

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