# Abstracts of Theses from the Nordic Countries

Abstracts of Nordic 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.

## Development of a generalized Gaussian model for absorbed dose calculation and dose planning in therapeutic electron beams

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A model is developed to calculate the spatial absorbed dose distribution in heterogeneous media from high energy electrons in therapeutic use. In this model the multiple scattering of electrons is considered by the solution of the transport equation in the small-angle approximation of Fermi and Eyges. The continuous slowing down approximation is used in order to take energy losses into account. The model is applied on the dose contribution from electrons which ideally should be stopped in a collimator but instead are scattered out through the collimator edge and thereby contaminate the beam. It is shown that a high density material in the collimator minimizes the fluence of these electrons and that their mean energy is approximately 40 per cent of the mean energy of the incident electrons. For dose planning it is shown that single scattering events at large angles has to be considered for an accurate description of the dose distribution. This is done by correction terms to the small-angle multiple scattering distribution. These terms are derived from experimentally verified data obtained in the simulation of the electron transport using the Monte-Carlo method. An empirical correction function for the range straggling is also introduced. A computational algorithm is developed for the determination of the spatial distribution of absorbed dose in multiple parallel slab geometries. A method of dividing a broad beam into a number of narrow pencil beams is used to calculate the dose in arbitrary heterogeneous media. The assumption of semi-infinite slab geometry for each pencil beam is thereby used. This approximation introduces a limitation in computational accuracy, which is shown to depend on neglecting the change of the range of electrons scattered through lateral boundaries between different media. The accuracy of the present generalized Gaussian model for electron beam dose planning is investigated in anatomical phantoms. The mean error is generally of the order of 2 to 5 per cent, but maximum errors in small volumes of 20 per cent are obtained in special cases.

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## Interleukin 1, tumour necrosis factor-alpha (cachectin) and the pathogenesis of cancer cachexia

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Losses of body weight and lean tissue frequently occur in patients with cancer. Yet the causes of cancer cachexia remain unknown. Many aspects of the host response to cancer, such as anorexia, reduced skeletal protein content and increased hepatic protein content and synthesis are similar to those seen during acute infection, surgical injury or trauma. During many of these inflammatory states, there is an accelerated synthesis and release

of the monokines, interleukin 1 (IL-1) and tumour necrosis factor-alpha (TNF). This study has examined whether the host response to cancer could also be explained by the synthesis and release of IL-1 and/or TNF-alpha.

The first approach employed was to administer to healthy nontumour-bearing mice (C57/Bl6j or C3H/HeJ) the recombinant-derived monokines, IL-1 (alpha and beta) or TNF-alpha in an effort to replicate the host protein changes which occur in cancer. The second approach was to examine whether IL-1 and TNF production were increased in weight-stable mice (C57/Bl6j) bearing a methylcholanthrene-induced sarcoma and hospitalized patients with cancer. Production of these monokines was compared to either mice experiencing experimentally induced inflammation or hospitalized patients with fever.

Administration of TNF-alpha and IL-1 to healthy animals resulted in increased hepatic protein and RNA content, plasma protein and albumin synthesis and serum amyloid P concentrations similar to that seen in cancer and other inflammatory diseases. IL-1, but not TNF-alpha, reduced spontaneous food intake. Neither IL-1 nor TNF-alpha had any direct effect on skeletal protein balance either when administered in vivo or added to in vitro preparations.

In mice with an experimental sarcoma, neither TNF-alpha nor IL-1 could be detected in the blood, although both could be detected in mice during endotoxinemia and IL-1 could be observed during peritoneal and subcutaneous abscesses. In sarcoma-bearing mice, the capacity of either peritoneal or splenic macrophages to synthesize IL-1 in vitro was reduced with increasing tumour burden, but the capacity to synthesize TNF-alpha was maintained.

It can be concluded that IL-1 or perhaps TNF-alpha could be the signal for the anorexia and hepatic protein changes observed during cancer. However, either the monokines must exert their effects where they are locally produced or they circulate in the blood at insufficient levels to be detected with the present assays. Although IL-1 production may explain the anorexia seen in inflammatory diseases, its synthesis appears to be down-regulated in cancer. And finally, the decreased muscle protein content and synthesis observed in cancer appears to be independent of monokines and a direct result of associated anorexia.

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## Bronchioloalveolar carcinoma
## A clinical study of surgically treated patients

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Bronchioloalveolar carcinoma was a quite uncommon pulmonary malignoma having an incidence of 3.7% of all primary pulmonary malignoma in this study. Tumours with a typical bronchioloalveolar appearance were very rare owing to very common overlap in microscopy between bronchioloalveolar and pulmonary adenocarcinomas. In the majority (64%) of bronchioloalveolar carcinomas, a pattern of adenocarcinomatous differentiation could be determined.

Patients with typical bronchioloalveolar carcinoma (BA) had previous pulmonary tuberculosis significantly more often than patients with the mixed form of bronchioloalveolar carcinoma (MBA) and patients with pulmonary adenocarcinoma (AD). Patients of the two latter groups had more previous pneumonias than BA patients. These infectious diseases or the scars and fibrosis caused by them may play a role in the aetiology of these pulmonary carcinomas. Many patients were asymptomatic and the diagnosis was made following a routine chest X-ray. The most common finding in the chest X-ray was a solitary peripheral nodule or infiltrate. Sputum cytology and bronchial washing cytology proved to be poor diagnostic methods. Fine needle biopsy was a good diagnostic method in those cases in which it was used. Because of the small number of aspiration biopsies performed, thoracotomy revealed the final diagnosis in the majority of cases. The peripheral location of the tumour allowed lobectomy, segmental resection or wedge resection to be used in most cases. There was no operative or hospital mortality after resection of the first primary tumour.

Local recurrence (second primary) was common (39% of cases) in patients with the typical form of bronchioloalveolar carcinoma (BA) and differentiation towards adenocarcinomatous direction increased the possibility of distant metastases (47% of MBA patients and 68.8% of AD patients). The majority of metastases (82%) were found before the 3-year follow-up and most local recurrences (65%) took place after this re-examination. Solitary bronchioloalveolar carcinoma proved to have a quite favourable prognosis: the 5-year survival was 57% for the typical form of the disease (BA) and 45% for the mixed form of the disease (MBA), compared with 17% for patients with pulmonary adenocarcinoma (AD) when solitary tumours were treated surgically.

The growth rate of bronchioloalveolar carcinomas proved to be slower than that of pulmonary adenocarcinomas. The presence of metastases did not correlate with the tumour doubling time. Actual survival times were similar to or shorter than the predicted survival times in those patients who died of pulmonary carcinoma. The surgical resection has probably been curative in those patients with actual survival times considerable longer than predicted survival times.

Carcinoembryonic antigen (CEA) and gastrointestinal cancer associated antigen (CA 19-9) seemed specific for malignancy in bronchioloalveolar carcinomas and pulmonary adenocarcinomas. Because of their fairly low sensitivity they proved to be unsuitable for screening these tumours. The sensitivity of the CA 19-9 test was even lower than that of the CEA test. Correlation between intensity of tissue expression and serum levels of CA 19-9 was poor. However, those tumours which produced high serum levels of CA 19-9 also stained positively by immunohistochemical method from histopathological specimens. A decline in high serum levels of CA 19-9 was found after resection of the primary tumour.

The resection lines of solitary tumours were free of residual carcinoma. One of four diffuse lesions revealed residual carcinoma in the bronchial resection line, and bronchopleural fistula occurred. It seemed that residual carcinoma in the bronchial resection line was associated with poor healing of the bronchial stump and that it increased the incidence of bronchopleural fistula. Routine frozen section of the bronchial resection line is preferred for detection of residual carcinoma. This allows the excision to be extended to carcinoma-free tissue and the healing of the bronchial stump is then more reliable.

Synchronous multiple primary tumours and the diffuse form of the disease seemed to be late manifestations. Survival of these patients and of most patients with metachronous multiple primary tumours after surgical treatment was poor. Operative and hospital complications were common in second operations. Lobectomy or more conservative resection is preferred because surgical mortality was found only after pneumonectomy. Patients with metastases or recurrences unsuitable for a second operation were treated with radiotherapy or chemotherapy without any objective response.

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## Gastrointestinal endocrine cells and carcinoids
### A histopathogenetic study with a comparison of silver-staining and immunohistochemical characteristics

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The principal aim of the present investigation was to study the histopathogenesis of mid-gut carcinoids, and, if possible, to obtain evidence for a not identical origin of appendiceal and other carcinoids of mid-gut type. Although carcinoids of the small-intestine, appendix and proximal colon usually are grouped together with the designation 'mid-gut' or 'classical' carcinoids, they are not in all respects identical, especially with regard to natural history. Further, the intestinal carcinoids mostly are considered to derive from the mucosal endocrine cells, but the origin of these tumours is still controversial. For this reason normal gastrointestinal endocrine cells and carcinoid tumours were characterized and compared by means of different silver-staining techniques, formalin-induced fluorescence (FIF) technique of Falck-Hillarp, immunohistochemistry, newly developed sequential staining methods for demonstration of peptide hormone/biogenic amine-containing cells and electron microscopically. The major immunological neuroendocrine markers used were antisera/antibodies to serotonin, neuron-specific enolase (NSE) and S-100 protein. A comparative examination of one fundic gastric carcinoid and a sample of intestinal adenocarcinomas was also performed because, it is well documented that these two types of tumours derive from epithelial endocrine and non-endocrine cells of the gastrointestinal mucosa. The results of this study suggest that the histopathogenesis of appendiceal and small-intestinal carcinoids is not identical. Evidence is presented indicating that appendiceal carcinoids develop from subepithelial neuroendocrine cells, in the mucosal stroma and are possibly related to the peripheral nervous system, and that small-intestinal carcinoids, like the fundic gastric carcinoids, are histo-genetically related to the intraepithelial endocrine cells of the gastrointestinal mucosa. Moreover, by means of a methodological piece of innovation, it became possible to accurately identify detectable amounts of serotonin and gastrin in the same cell in the antral mucosa from a patient with atrophic gastritis and multiple fundic gastric carcinoids. The method is considered to be of value for the further exploration of the gastrointestinal endocrine cells and tumours.

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## Epidemiology of polyps in the rectum and sigmoid colon
### A study of adenomas and hyperplastic polyps in a population of men and women aged 50–59 years

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The feasibility and acceptance of an endoscopic population screening examination with flexible fibersigmoidoscopy was demonstrated.

Reproducibility of size and localization of polyps at repeated endoscopy was good. A shortening of the sigmoid colon was observed at withdrawal of the endoscope during colonoscopy but not at sigmoidoscopy. This had no influence on the recovery of polyps in the sigmoid bowel segment.

Endoscopic population screening and histological examination of removed polyps showed that, in comparison to autopsy studies, the prevalence of adenomas and hyperplastic polyps was lower than expected for women, but not for men. This may be consistent with an overestimation of prevalence rates in younger age groups when based on autopsy studies. The prevalence of adenomas was higher in men than in women, whereas women showed a trend towards larger and more dysplastic adenomas —consistent with previous autopsy results.

Two years follow-up results indicated both growth and regression of polyps—growth and occurrence of new lesions seemed to be more common in the colon and proximal rectum, whereas regression was seen more often in the distal rectum. This indicated that the present model for population screening with initial examination only of the distal parts of the large bowel may not automatically be transferrable to an older age group.

DNA distribution and LD and G-6-PD activity within colorectal polyps showed a limited correlation to polyp size or degree of dysplasia. Prospective studies will be needed to further elucidate the prognostic value of these parameters in regard to risk of colorectal carcinoma.

Breath methane cannot be used as an adjuvant method in the identification of individuals with adenomas or development of dysplasia within a group of persons with adenomas.

A discriminant analysis model used on multivariate clinical information failed to differentiate satisfactorily between polyp-bearing and polyp-free individuals unless combined with information from the dietary registrations. Consequently, population screening of this type (with an aim towards secondary prevention) ought to be based on the single most important parameter —age, with a prospect of finding asymptomatic colorectal carcinoma in 1% in the 50–59-year age group.

A double blind model for registration of diet in persons with and without polyps was in agreement with epidemiological and case/control studies of patients with colorectal cancer, giving further evidence for the significance of dietary factors in colorectal carcinogenesis.

The present results, based on epidemiological, endoscopic and histological data, lend further support to the adenomacarcinoma sequence theory.

Our results add to the accumulated knowledge during the past decades, indicating factors of importance for primary and secondary prevention of colorectal cancer.

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# ERRATUM

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Rööser B., Pettersson H. and Alvegård T.: Growth rate of pulmonary metastases from soft tissue sarcoma.

On page 189, second column, line 16–17: 'between 6 and 99 months' should read 'between 1 and 99 months'. In the Table on page 190 it should be '(months)' instead of '(days)' in the last column.