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Thyroid cancer in Denmark 1996–2002

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Introduction. Since 1st of January 1996 a prospective registration of all new thyroid cancer patients in Denmark has been performed in a common database – DATHYRCA. The five Danish university centres of head and neck oncology and one department of general surgery are responsible for the treatment of thyroid cancer in Denmark. According to guidelines from the National Board of Health all departments treating thyroid cancer are obligated to participate in The DATHYRCA registration. Recently a complete crosscheck between The DATHYRCA Database and The National Cancer Registry has been carried through for the years 1996–2002. October 2005 new national guidelines concerning treatment of thyroid cancer in Denmark was initiated and for the time being, new European guidelines are on their way.

Objectives. To present incidence and outcome for thyroid cancer patients in Denmark and to estimate effects on treatment strategy on differentiated thyroid carcinomas (DTC) by introduction of the Danish and European thyroid cancer guidelines.

Methods. A population based study of prospectively registered data. Analyses were performed in The Clinical Data Management System – Medlog.

Results. From 1996 to 2002 a total of 965 patients with histologically verified primary thyroid cancer of clinical significance were registered in The DATHYRCA Database resulting in an incidence of 2.6 per 100.000/year. Male/female ratio was 1/2.7. Lymph node metastases were present in 33% of cases and distant metastases in 7%. The histological distribution was 63% papillary-, 18% follicular-, 7% medullary-, and 8% undifferentiated carcinoma. The 5-year disease specific survival rates were as follows: Papillary carcinoma – 96%, follicular carcinoma – 87%, and medullary carcinoma – 83%. The 3-year survival rate for undifferentiated carcinoma was 9%. From 1996 – 2002 ninety percent of the Danish DTC patients were treated with total or near-total thyroidectomy and 59% received thyroid ablation therapy. When the high risk definitions from the Danish thyroid cancer guidelines are applied to the DTC patients from The DATHYRCA Database it results in 71% total or near-total thyroidectomies and 71% thyroid ablation therapies. The figures by applying the European guidelines are 82% and 39%, respectively.

Conclusions. The Danish national thyroid cancer database – DATHYRCA is well functioning. The introduction of Danish thyroid cancer guidelines seems to decrease the extent of thyroid surgery and increase the use of thyroid ablation therapy. And finally, introduction of European guidelines would result in a smaller decrease in the extent of thyroid surgery and a large reduction in the use of thyroid ablation therapy.

In vitro analysis of thyroid iodine concentration (TIC) in benign and malignant thyroid tissue using X-ray fluorescence analysis (XRF) and Secondary Ion Mass Spectrometry (SIMS)

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Objective. Outcome of radioiodine therapy in thyroid cancer depends on the thyroid ability to store and concentrate iodine. TIC in normal thyroids is well documented while information regarding malignant thyroid tissue is scarce. The study objective was to investigate TIC in benign compared to malignant tissue.

Material and methods. Tissue samples from normal thyroids and from patients with papillary cancer were collected and frozen in connection with surgery. Both benign and malignant tissue was sampled from the cancer patients. The iodine concentration was analysed using an XRF system with a ²⁴¹Am source. When irradiating iodine containing tissue, characteristic X-rays are emitted with intensity proportional to the amount of iodine in the sample. SIMS was used on glutaraldehyde fixed tissue as a histological tool for localization and quantification of iodine.

Results. The mean TIC in healthy thyroid tissue was 0.5 ± 0.2 (±SD) mg/mL. For the cancer patients, the TIC was 0.9 ± 0.8 mg/mL in benign tissue while no iodine could be detected in the malignant samples. These findings were consistent with the results from the SIMS investigation that showed a 100 times higher TIC in benign compared to malignant tissue. Moreover, in benign thyroid tissue iodine was predominantly located in the follicle lumen.

Conclusion. We found that TIC in papillary cancer tissue was considerably lower than in controls with no thyroid disease. It is our opinion that the XRF and SIMS techniques might be of value in future studies refining radioiodine treatment in thyroid cancer patients.

Neck dissections for thyroid cancer at the Turku University Hospital Department of Otorhinolaryngology between 1996 and 2005

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Background. Approximately 340 new cases of thyroid cancer are diagnosed per year in Finland, 29 of them in the Hospital District of Southwest Finland (453 000 inhabitants). Most cases are of differentiated type,

majority papillary in which cervical metastases are common. Lymph node dissection should be performed for patients with clinically positive nodes to improve loco regional control.

Objective. The aim of this report is to review our surgical experience of neck dissections for thyroid cancer.

Materials and methods. Medical records of all patients who underwent neck dissection for cervical metastases of thyroid carcinoma at our hospital between 1996 and 2005 were retrospectively reviewed. Data was analysed for clinical presentation, radiological examinations, histological findings, extent of thyroidectomy, types of neck dissection, radio-iodine treatment, outcome, and complications.

Results. Between 1996 and 2005 130 patients underwent surgery for thyroid cancer at the departments of surgery in the Hospital District of Southwest Finland. A total of 24 patients (15 women and 9 men) underwent 27 neck dissections for management of cervical metastases of thyroid cancer at the Department of Otorhinolaryngology in Turku University Hospital. Mean age of the patients at the time of operation was 45 years. One patient had a bilateral operation and two were operated twice. 22 of the operations were modified radical, three radical, one selective and one other type of neck dissection. Detailed results will be presented later.

Conclusions. At our hospital thyroid surgery and cervical lymph node dissections are done at different departments, surgical and otorhinolaryngological respectively. Selected patients with cervical metastases of thyroid cancer are directed to the Department of Otorhinolaryngology for neck dissection where a total of 70–80 patients have a neck dissection for head and neck cancer yearly. We conclude that neck dissection for thyroid cancer metastases should be carried out systematically by an experienced head and neck surgeon.

Fine needle aspiration biopsy in thyroid cancer – the prognostic value of class III findings

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Background. Although the fine needle aspiration biopsy (FNAB) has become the generally accepted investigation modality in evaluation of the risk for thyroid malignancy, a wide grey zone, class III category in Papanicolaou classification, between the clearly benign and malignant cytologic findings still exists. To estimate the risk of malignancy in that group we reviewed the data from all patients, who had undergone thyroid surgery in North Karelia Central Hospital in 2001–2004. Part of the patient material was collected prospectively as a part of a larger thyroid surgery study, while a part of the material was collected retrospectively. In addition to the cytologic findings also other possible prognostic factors were evaluated.

Results. Class III cytology was found in 52 of the 228 operated patients (22.8%). The large proportion of goiter (123/228, 53.9%) in this material is explained by the high prevalence of endemic goiter in this area. 42 of the 52 (80.8%) patients had a follicular and 10 a papillary atypia. The final histopathologic diagnosis revealed altogether seven malignant tumours (7/52, 13.5%): six of them in the papillary (6/10, 60%) and only one in the follicular atypia group (1/42, 2.3%). Ten elderly patients with follicular FNAB cytology were followed up, during at least 2 year follow up with US and FNAB no malignant lesions were revealed.

Discussion. We report in this material a low percentage of malignant findings in this patient group compared to some earlier reports with figures up to 30%. Some clinical findings like gender, age and the diameter of the nodule has been proposed as criteria for surgery since the risk of

malignancy was increased in males, patients over 40 years of age and large nodules (>30 mm). Our findings do not support these Conclusions. If our findings can be confirmed in other materials, a more conservative attitude in the treatment of follicular nodules seems warranted.

Papillary microcarcinomas in Denmark 1996–2002

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Introduction. Papillary microcarcinoma (PMC) is defined as a papillary carcinoma ≤10 mm in largest diameter. Autopsy studies have shown frequencies from 6–36% with a large geographic variation. Clinical significant PMC is often coincidentally found at benign goitre surgery and carry a good prognosis. However, aggressive behaviour might occur and metastases, regional as distant, are found. The level of treatment is controversial. Most available studies are based on institutional materials.

Purposes. To describe incidence, treatment and outcome for Danish patients with clinical significant PMC and to compare results to patients with papillary carcinomas with a largest diameter over 10 mm.

Methods. population based study of prospectively registered data. Analyses were performed in The Clinical Data Management System – Medlog.

Results. From 1996 to 2002 a total of 181 patients with PMC were registered to The Danish thyroid cancer database – DATHYRCA. The incidence was found to 0.5 per 100.000/year and the male/female ratio was 1/3.3. There was no significant difference between PMC and other papillary carcinomas (PC). The median age was 45 years (range: 11–80) and again no difference was found by comparison to other PC. The presence of regional metastases was 28% and distant metastases 1%. Again no significant difference was found by comparison to other PC. A total or near total thyroidectomy was performed in 65% of PMC and 86% of other PC. This difference was significant. Neck dissection was used in 26% of PMC and 24% of other PC. No significant difference was found. By disease specific survival (DSS) analysis no events were found in the group of PMC. The 5-year DSS for other PC was 95%. The difference was significant.

Conclusions. In a population based national study no significant differences concerning sex, age and frequency of metastases were found between PMC and other PC. The use of total or near-total thyroidectomy was significantly more predominant in the 'other PC' group. The prognosis of patients with PMC is extremely good.

Papillary micro carcinoma in the thyroid gland: Can Cyclin D1 and Galectin-3 predict the incidence of metastases

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Background. The diagnosis of papillary micro carcinomas generally offers an excellent prognosis, but is associated with regional lymph node metastases in considerable numbers.¹ Metastases have a negative impact on the rate of recurrence^{1,2} but currently no factor exists that can reliably

predict the cases with metastatic potential. Immunohistochemical analyses might be the solution.

Objectives. To determine whether cyclin D1 or galectin-3 are useful as markers for metastases.

Design. Population based retrospective analysis.

Participants. Registered in the Danish Thyroid Cancer Database with; Histological verified papillary thyroid carcinoma ≤ 10 mm, diagnosed from 01.01.96 to 31.12.02, patient alive at the time of diagnosis and no prior history of thyroid cancer. 169 patients.

Method. Slides from 131 patients were stained, and two times 100 cells at 200X magnification were counted with the use of a grid. Cells were graded as negative or positive.

Results. Cyclin D1 showed significantly higher median expression in cases with metastases (43 patients), than in those without (88 patients) ($P < 0.05$). The expression was overlapping with negative cases in the 'with metastases' group and high expression in cases in the 'without metastases' group. Galectin-3 was generally expressed very highly in papillary micro carcinomas but no difference was found in the median expression between cases with and without metastases ($P = 0.27$).

Conclusion. The clinical usefulness of cyclin D1 as a marker for metastases is doubtful, further investigation is needed in order to determine whether it could be a marker for a subgroup of the metastases. Galectin-3 does not appear useful as a marker for metastases.

References

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Extended histopathological examination of sentinel lymph nodes

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Objectives. To examine the residual tissue of sentinel lymph nodes and describe the histopathological changes compared to central HE-sections and our current histopathological protocol.

Design. This study was a method study where we tested our histopathological protocol to an extended histopathological protocol to find possible reasons for sampling errors.

Setting. Departments of Plastic Surgery and Pathology, Odense University Hospital.

Participants. Forty patients with T1/T2 cN0 oral cancer were included. 147 sentinel lymph nodes were examined.

Main Outcome measures. The results of our current histopathological protocol were compared to the results on an extended histopathological protocol after re-sectioning and re-classification of the lymph nodes according to the classification proposed by Hermanek.

Results. The central HE-sections detected 55% (12/22) of the lymph node metastases and our current protocol 77% (17/22).

Conclusions. Our current histopathological protocol seems to predict positive neck sides correctly. However, additional positive lymph nodes with micro metastases were detected after resection and re-classification.

References

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Sentinel node evaluation in oral squamous cell carcinoma

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Objective. To determine the feasibility of sentinel lymph node biopsy (SNB) in patients with oral squamous cell carcinoma (OSCC) and to determine its predictive value for detecting sub clinical metastasis.

Design. Prospective cohort study

Setting. Secondary care. One university hospital.

Participants. Thirty-five patients with OSCC T1-2N0M0 undergoing surgical treatment including resection of the primary tumour, SNB and selective neck dissection entered the study. Exclusion criteria were prior treatment of the neck either surgery or radiotherapy.

Main outcomes measures. The histology of the sentinel lymph nodes (SN) and the nodes of the selective neck dissection were compared. The presence of metastasis was divided into micro metastasis (<2 mm) and macro metastasis (>2 mm) according to the classification of occult metastases proposed by Hermanek *et al.*¹

Results. Thirty-four SNB procedures were performed. The identification rate for SN using lymphoscintigraphy was 97 % (34/35). 18 % (6/34) of the patients had sub clinical lymph node metastasis. Five patients had only micro metastases. One patient had both macro- and micro metastasis. Metastases were located in level IIA and III. No false negative SNs were found.

Conclusion. SNB is feasible and predicts lymph node metastasis. SNB has the potential of selecting between patients with N0 neck that would benefit most from selective neck dissection and prevent the morbidity of an unnecessary neck dissection.

Reference

- Hermanek P, Hutter R.V., Sobin L.H., *et al.* (1999) International Union Against Cancer. Classification of isolated tumour cells and micro metastasis. *Cancer* **86**, 2668–2673.

Management and outcome of patients with mucoepidermoid carcinoma of major salivary gland origin; a single institution 30-year experience.

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Background. Mucoepidermoid carcinoma (MEC) of major salivary gland origin is a rare head and neck tumour composed of both mucous and

epidermoid cells. For these malignant tumours the prediction of clinical outcome is difficult.

Objective and methods. The purpose of this study was to review 55 MECs of major salivary gland origin diagnosed at the Department of Otorhinolaryngology, Helsinki University Central Hospital, during the period from 1976 to 2005. Diagnostic criteria used were WHO classifications valid for each time point and criteria for grading were those of AFIP recommendations. Since 1993, even the degree of cell proliferation has been taken into account in determining grading of MEC cases.

Material. The majority of cases occurred in the parotid gland ($n = 48$, 87.3%), followed by the submandibular gland ($n = 7$, 12.7%). The male-to-female ratio was 1: 1.3. Mean age at the time of diagnosis was 53.5 years, range 25–84 years. The T categories were as follows: T1 $n = 19$; T2 $n = 18$; T3 $n = 9$; T4 $n = 9$. Fourteen (25.5%) patients presented with neck node metastases. Four (7.3%) patients had distal metastases at the time of diagnosis. Fifty-two (94.5%) patients out of 55 were treated with curative intent. All these patients underwent surgery and 25 (48.1%) patients received post-operative radiotherapy. For three (5.5%) patients the therapy was palliative. The follow-up time varied from 6 months to 9 years. The rate for locoregional recurrences was 27.5%. Five patients (8.9%) with N0 neck disease had regional recurrences. In a 5-year follow-up 17 (30.9%) patients had died of disease.

Conclusions. The outcome in the present study warrants consideration of an overview of our treatment protocol. Future challenges include determination of relationship of N0 neck treatment failures to grade and cell proliferation, as well as emerging molecular pathological data such as gene expression profiles of MEC.

Parotid carcinoma: Expression of kit protein

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Objectives. Our aim is to investigate the expression of kit protein (KIT) in parotid carcinomas in order to correlate the expression to histology and prognosis. Further we want to perform mutation analysis of KIT-positive adenoid cystic carcinomas.¹

Patients and methods. Formalin-fixed paraffin-embedded sections from 73 patients with parotid gland carcinomas were used for the study. The sections were stained with KIT polyclonal antibodies. Twelve KIT-positive adenoid cystic carcinomas were examined for c-kit mutation in codon 816.

Results. Of all carcinomas 25% were KIT-positive. 92% of the adenoid cystic carcinomas were KIT-positive. None of the adenoid cystic carcinomas had mutations in codon 816 of the c-kit gene.

Conclusion. KIT-expression does not seem to harbour significant prognostic information. Adenoid cystic carcinomas express KIT, but no mutations in codon 816 of the c-kit gene were identified.

Reference

- 1 Sørensen K.B., Godballe C., de Stricker K., *et al.* Parotid carcinoma: Expression of kit protein and epidermal growth factor receptor. *Journal of Oral Pathology and Medicine* (in press).

Salivary gland cancer in Finland 1991–96: an evaluation of 237 cases

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Objectives. To retrieve all salivary gland cancer (SGC) patients diagnosed in Finland 1991–1996 and to evaluate the incidence, histological type, location, treatment given and outcome.

Method. All SGC ($n = 286$) diagnosed in Finland 1991–1996 and reported to the Finnish Cancer Registry were retrieved. The histological re-evaluation and retrospective study was made of 237 salivary gland patients.

Results. The study population consisted of 125 males and 112 females. The mean age was 59 years (males 61 years, females 58 years). The follow-up was at least 5 years. The most common tumour location was the parotid gland, ($n = 152$, 64%), followed by the minor salivary glands, ($n = 46$, 19%), the submandibular gland, ($n = 38$, 16%) and the sublingual gland ($n = 1$, 0.4%). The most frequent histological types were adenoid cystic carcinoma ($n = 65$, 27%), mucoepidermoid carcinoma ($n = 45$, 19%) and acinic cell carcinoma ($n = 41$, 17%). Surgery alone and in combination with other treatment modalities was used in 209 (88%) cases. Radiotherapy was given to 136 (57%) patients of which 13 (5%) without surgery. The 5-year over-all survival rate was 56.5%, and in stages I-IV; 78%, 25%, 21% and 23%, respectively ($P < 0.001$, log-rank test). Of the most common tumour types the best 5-year relative survival rate was in the patients with acinic cell carcinoma (96%), followed by mucoepidermoid (79%) and adenoid cystic carcinoma (74%). **Conclusion.** In this material consisting of various salivary gland carcinomas, stage I, male gender and age were the most powerful predictors of patient outcome.

Impact of waiting time on tumor growth of head and neck carcinoma

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Introduction. Waiting time prior to radiotherapy is a major and increasing problem.¹ This study aim was to determine the impact of waiting time on tumor growth in an unselected population of patients with head and neck cancer referred to primary radiotherapy at the Department of Oncology, Aarhus University Hospital, Denmark.

Material and methods. In a consecutive cohort of head and neck cancer patients referred to the Head and Neck Centre from January 2000 to

May 2005, all patients with both a diagnostic scan (MR or CT) and a CT scan for treatment planning were identified. Altogether 654 patients were seen and 457 were treated with primary radiotherapy with curative intent. Ninety-one patients had two sets of scans and for 53 patients scans were comparable and tumor measurable. Tumor size, size and number of metastatic lymph nodes were measured by an experienced radiologist. For each patient the diagnostic and the planning scan were evaluated successively in order to discriminate developing lymph nodes. Endpoints were progressive disease measured by RECIST criteria, change in total tumor volume and change in TNM stage (UICC).

Results. For all patients median waiting time between scans was 32 days (5–95). For patients included in the study waiting time was 30 days (5–125) and for the remaining group 34 days (9–95). Thirty patients (57%) had a measurable increase in tumor volume with median 42% (6–550%). Evaluated by the RECIST criteria 16 patients (30%) had progressive disease (>20% increase in largest tumor diameters or appearance of new lesions). Twelve patients (23%) developed new lymph node metastasis and 10 (19%) progressed up to another stage according to the UICC classification. There was a significant correlation between increase in tumor volume and waiting time ($P = 0.02$) for all patients and for patients with low or moderate grade tumors ($P = 0.03$) but not for patients with highly differentiated tumors.

Discussion and conclusion. Studies analyzing the impact of delay on survival in squamous cell carcinoma in head and neck have shown various results. However, it is well established that prognosis depends on tumor size, lymph node metastasis and thereby TNM stage at beginning of radiotherapy. This study indicates a negative prognostic impact of waiting time. It is concluded that delay in start of treatment in patients with squamous cell carcinoma of head and neck does significantly increase tumor size, tumor volume and number of lymph node metastasis in a substantial part of patients. This may in turn be expected to negatively influence the prognosis.

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The continuum of care for patients with head and neck cancer

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Background and purpose. The clinical work up of patients with head and neck cancer is time consuming. A delay may affect survival negatively. The care of H&N patients in Stockholm was concentrated into one centre in 1998. The clinical delay was shown to increase during the first period after reorganisation (Sharp L, Lewin F *et al.* 2002). The purpose of this paper is to follow up the delay 5 years later and to define the most important causes of delays in clinical investigations.

Materials and methods. Two hundred thirty four patients referred to the Stockholm Head and Neck Centre (SHNC) in 2003 and registered by the coordination nurse were included in a detailed analysis of time intervals from referral to start of preoperative radiotherapy. All patients treated between 2000 and 2004 were registered with more limited information about different time intervals. Mean and median values of the different time intervals were calculated. Delays in comparison with arbitrarily chosen optimal values were calculated.

Results. The median time interval from referral to start of radiotherapy increased the first year after reorganisation but decreased to original values 2003. Around 90% of the calculated delays were caused by lack of

radiological capacity and/or radiation capacity; together in mean 31.4 days.

Conclusion. The delays in clinical work up caused a loss in estimated survival between 5% and 10%. This was caused by lack of capacity in diagnostic radiology and radiation treatment. Only the director of the hospital has the ability to address these problems and has consequently the full responsibility.

Time from first symptom to diagnosis and survival in patients with supraglottic laryngeal cancer

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A recent study from our department showed longer duration of symptoms in glottic cancer to lead to poorer prognosis. The aim of the present study was to see if the same correlation was found in supraglottic laryngeal cancer. This population has a broader variety of symptoms and are often diagnosed in more advanced stages. Three hundred sixty five cases of supraglottic laryngeal cancer stage 1–4 treated with curatively intended radiotherapy were included. The median age was 62 years (range 40–86), 29% were female, 71% male. At the first visit in a center patients were asked about start of symptoms. Median duration of symptoms before diagnosis was 115 days. Median time from diagnosis to treatment was 25 days. No significant difference in survival or recurrence free survival was found when patients were divided by 6 month duration of symptoms. This may be explained by the variety of symptoms of which only a few are experienced as warning symptoms. Another explanation could be that aggressive tumours present with rapidly progressing symptoms leading to short duration of symptoms before diagnosis. Further analyses will be performed.

Is expression of the epidermal growth factor receptor related to hypoxia in squamous cell carcinomas of the head and neck – an evaluation of the DAHANCA 5 study

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Purpose/Objective. Hypoxia and repopulation are the two main biological characteristics that can be manipulated in fractionated radiotherapy of squamous cell carcinomas of the head and neck (HNSCC). Carbonic anhydrase 9 (CAIX) is associated with tumour hypoxia and expression of the epidermal growth factor receptor (EGFr) is a poor prognostic factor for conventional fractionation but may predict the effect of reducing the overall treatment time of radiotherapy as means of overcoming radiation induced repopulation. Experimental data suggests that hypoxia is linked to tumour growth and its ability to repopulate and that it can be manipulated by inhibitors of EGFr. The current study addresses the hypothesis that expression of EGFr is related to hypoxic tumours and influences local control after fractionated radiotherapy.

Design. In the DAHANCA 5 trial, 414 patients with HNSCC were randomised to conventional fractionation with 66–68 Gy ± the hypoxic sensitizer nimorazole. Pre-treatment formalin fixed paraffin embedded tumour material from 320 patients were stained by immunohistochemistry and evaluated for the expression of EGFr and CAIX.

Results. Seventy-five percent of the tumours had high expression of EGFr (more than 50% of tumour area with positive staining) and 44% of the tumours had high expression of CAIX (more than 10% of tumour area with positive staining). EGFr or CAIX was not related to patient and tumour characteristics and high expression of EGFr and CAIX were not related, $P = 0.9$.

Conclusions. Expression of EGFr was not related to hypoxic tumours defined as tumours with high levels of CAIX. Probably, CAIX is not an optimal marker for hypoxia.

Recombinant erythropoietin β can enhance growth of squamous cell carcinoma *in vitro* and *in vivo*

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Background. Treatment of anaemia with recombinant human erythropoietin β (rHuEpo) has been hypothesised to improve outcome of curative radiotherapy among patients with head and neck squamous cell cancer (HNSCC). However, Henke *et al.*¹ showed that rHuEpo does not improve cancer control. In fact, incompletely resected patients with HNSCC receiving radiation in combination with rHuEpo showed poorer loco regional progression-free survival than patients receiving radiation in combination with placebo. Our objective was to examine the effect of recombinant erythropoietin β (rHuEpo) on the growth of human squamous cell carcinoma under different conditions *in vitro*, as well as *in vivo*, alone and in combination with surgical trauma.

Methods. *In vitro* a HNSCC-line without p53 mutation or cyclin D1 gene amplification were used. It expressed the EPO-receptor. The *in vivo*-effect of surgical trauma ± rHuEpo on growth of the cell-line above as a solid tumour xenograft on nude mice was evaluated by measuring the tumour volume growth. The animals were divided into three groups; A/ control + NaCl, B/ 'surgery' + NaCl and C/ 'Surgery' + rHuEpo. The surgical trauma was inflicted through a s.c. transection of the tumour with a needle. rHuEpo/NaCl (0.2 mL/g b.wt.) was administered by s.c. injection every third day starting from day of transplantation, and the tumour size was measured in two dimensions three times/week. The tumour growth was followed for at least two doubling-times.

Results. Under FCS- (foetal calf serum) deficient conditions *in vitro* rHuEpo in high but physiological concentrations stimulated cell growth. rHuEpo alone had no effect on the growth of xenografted HNSCC. However, a significant increase ($P = 0.0074$) in the tumour growth was observed after surgical trauma in combination with rHuEpo as compared to surgery alone.

Conclusion. (i) rHuEpo effects (in normal physiological concentrations) on HNSCC growth and might only be manifested *in vivo* and after cell trauma. (ii) Correcting anaemia with rHuEpo might contribute to poor outcome after incomplete surgical resection.

Reference

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Cell traffic in the lymphatic system can be inhibited by blocking the function of adhesion molecule CLEVER-1

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Objectives. The aim of this study was to unravel the mechanisms the malignant cells and lymphoid cells use when travelling in the lymphatic system. Although ~80% of cancers give rise to metastases via the lymphatic system, the mechanisms mediating this process have remained unknown. The mechanisms used in this process are most likely similar to the ones lymphocytes use in their recirculation but this cascade is poorly known as well. The first adhesion molecules in the lymphatic endothelium are described only a couple of years ago and their significance *in vivo* is not yet shown.

Design and setting. An *in vivo* rabbit model was used to investigate the role of lymphatic vessel endothelial adhesion molecule CLEVER-1 in the cell traffic in the lymphatic system.

Results. With the monoclonal antibody against CLEVER-1 we were able to inhibit the cell trafficking in the lymphatic system by 80% ($P = 0.03$).

Conclusion. CLEVER-1 is one of the first adhesion molecules described in the lymphatic endothelium. It has been shown to mediate cell binding *in vitro* and in this work we have shown that it is also important *in vivo* and by manipulating this binding we can inhibit the cell traffic in the lymphatic system. Hopefully this finding opens new possibilities to control the traffic of the metastasizing cells in the cancer patients in the future.

IL-6 production from monocyte is correlated with worsened survival in head and neck squamous cell carcinomas

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Introduction. Head and Neck Squamous Cell Carcinomas (HNSCC) are infiltrated with cells from the Mononuclear phagocyte system (MNP) which have the ability to bind and, if activated, kill tumour cells. IL-6 and MCP-1 are cytokines which play a role in the development and metastases of cancer.

Methods. An organ culture method was used by which small parts of tissues, either from Head and Neck Squamous Cell Carcinoma (HNSCC) or benign mucosa, could be maintained viable *in vitro* as Fragment (F)-spheroids. F-spheroids stimulate autologous monocytes to secrete interleukin (IL)-6 and monocyte chemotactic protein (MCP)-1 *in vitro*. We analysed the IL-6 and MCP-1 production from monocytes in co-culture with autologous F-spheroids in a cohort of patients from 1998–2005 all treated for HNSCC.

Results. We found an increased production of IL-6 by autologous monocytes, in co-culture with F-spheroids to correlate with more recurrences ($P < 0.05$) and to some extent an impaired general survival.

Conclusion. Monocytes in co-culture with autologous F-spheroids produce IL-6 and MCP-1. The IL-6 production is shown to be a prognostic factor *in vitro* in HNSCC.

HNSCC derived spheroids increase lyophilised *S. pyogenes* (OK-432) activation of human monocytes *in vitro*

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Objectives. OK-432, penicillin-killed *S. pyogenes*, has been used in treating paediatric lymphangiomas and adult head and neck squamous cell carcinoma (HNSCC) in Japan. As stimulation of purified monocytes with OK-432 increases interleukin (IL)-6, tumour necrosis factor (TNF)- α and monocyte chemotactic protein (MCP)-1 production, we have studied this activation when monocytes are in co-culture with HNSCC derived spheroids. Furthermore, signalling pathways responsible for monocyte OK-432 activation were investigated.

Design. *In vitro* experimental design was employed. Participants. HNSCC spheroids together with monocytes were obtained from HNSCC patients subjected to surgery. In some experiments, blood was obtained from blood bank donors.

Main outcome measures. Monocyte cytokine syntheses were determined by mRNA quantification. Monocyte secretion of cytokines were determined by ELISA.

Results. HNSCC spheroids primed OK-432 monocyte responsiveness as measured by IL-6, but not MCP-1 or TNF- α secretion. Inhibition of Syk kinase by piceatannol decreased cytokine production. Monocytes not allowed to adhere *in vitro* had especially decreased TNF- α secretion compared to adhered monocytes, suggesting the requirement of a matrix surface for optimal monocyte activation by OK-432.

Conclusions. Purified monocytes are activated by OK-432. Present tumour cells do not inhibit this activation. Furthermore, OK-432 *in vitro* augments TNF- α production only when monocytes are stimulated upon adherence. The results imply that OK-432 is a target-seeking substance whereby only monocytes adhered to a target, e.g. a tumour cell, become fully activated by OK-432.

Human papillomavirus in oral and oropharyngeal squamous cell carcinoma: a risk factor for disease – and for recurrence after treatment?

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Objectives. The present study aimed to investigate the prevalence of high- and low-risk HPV (human papillomavirus) in a consecutive series of oral and oropharyngeal squamous cell carcinoma (OOSCC) matched with population-based, healthy controls.

Material and methods. From 131 patients with OOSCC, samples taken from the surface of the tumour and from the tonsillar fossa by cotton

tipped swabs were investigated together with exfoliated cells collected through a mouthwash. From 320 matched control persons, tonsillar fossa and mouthwash specimens were identically collected. All samples were tested for HPV DNA by nested PCR, and positive findings were HPV type-determined by DNA sequencing.

Results. Infection with high-risk HPV was shown to be a strong risk factor for OOSCC (OR = 63; 95% CI 14–480). Forty-seven (36%) of the cancer patients had one or more specimens positive for a high-risk HPV type (81% of which were HPV 16), while three (0.94%) of the control persons were positive for a high-risk HPV type. Seven (5.3%) of the cancer patients and 13 (4.1%) of the healthy controls were positive for any in a row of mucosal, muco-cutaneous or cutaneous low-risk HPV types. In total, 128 patients had planned curative treatment. After a median follow-up time of 22 months (range 0–36 months), 30 patients experienced a recurrence, two had an SPT, 12 were lost to follow-up, and there were 21 DICD (death from intercurrent disease). High-risk HPV-positive cases had an almost threefold increased relative rate (RR) of recurrence/SPT, but a lower RR of DICD compared to high-risk negative cases. There was no increased RR of recurrence/SPT related to smoking, but there was an association between smoking and DICD.

Conclusion. These results demonstrate a strong association between infection with high-risk HPV types and OOSCC, suggesting that they have a key role in the carcinogenesis. The estimated proportion of OOSCC cases attributable to HPV infections was 35%. High-risk HPV-positive cases had an almost threefold increased RR of recurrence/SPT. However, since DICD, is a competing risk, the RR for high-risk negative HPV cases might be underestimated due to DICD.

Establishment of a p53-mutated, terminal differentiation-deficient oral squamous cell carcinoma proliferative *in vitro* under serum free conditions

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The aim of this study was to establish an *in vitro* model where normal oral keratinocytes (NOK) and oral squamous carcinoma cells (SCC) could be investigated under the same conditions.

Methods. A tongue tumour biopsy was digested in dispase and collagenase and the resulting cell suspension was then pelleted, resuspended in 4 mL growth medium (Keratinocyte-SFM; GIBCO, Invitrogen Corporation) and then transferred into a cell culture flask. The medium was replaced every third day and the cultures were subcultured with a 1 : 3 split ratio weekly.

Results. The cell line LK0412 was established from a moderately differentiated HPV-negative SCC (T2N0M0), from the tongue of a non-smoking 54-year-old female. The LK0412 cells had a characteristic epithelial morphology and grew as an adherent monolayer. In the electron microscope, typical epithelial cell morphology such as presence of intermediate filament within the cytoplasm and desmosomes was observed. The LK0412 cells developed tumours in nude mice and generated soft agar colonies. The cell cycle distribution was analysed with flow cytometry and significant differences compared to NOK cultures were found in both S and G2/M phase. A mutation in the p53 gene was found at nucleotide position 734 in exon 7, substituting Glycine for Aspartic acid at codon 245 and the cells showed a high expression of the mutant p53 protein analysed by Western blot.

Conclusion. This newly established cell line, growing in serum free medium; provides together with normal oral keratinocytes a useful *in vitro* model for study pathogenesis and radiosensitivity of oral SCC.

Prospective study of 18FDG-PET in the detection and management of patients with lymph node metastases to the neck from an unknown primary tumour. Results from the prospective DAHANCA-13 study

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Objectives. Retrospective studies have indicated that 18F-FDG PET is a valuable diagnostic tool in the detection of a carcinoma of unknown primary (CUP) in patients with a metastatic neck lesion. We conducted a prospective study to evaluate the benefit of complementary FDG-PET scans to a national, standardized workup program for CUP and neck metastases.

Design. A prospective study (DAHANCA-13).

Participants. A consecutive cohort of patients with cervical lymph node metastases from SCC or undifferentiated CUP. 67 patients entered between 2000 and 2003. Patients underwent standardized diagnostic work-up according to national guidelines including panendoscopies, multiple mucosal biopsies and diagnostic CT/MR. 18F-FDG PET (281–534 MBq) was performed and pathological 'hot-spots' were further investigated to confirm a primary tumour.

Outcome measure. The detection rate of a primary tumour or distant metastatic disease. Survival data was analysed after a median follow-up of 40 months.

Results: In 60 eligible patients, a focal uptake on FDG-PET indicated a primary tumour or metastatic disease in 30 patients (50%). The focal activity occurred in the H&N in two-third, and below the clavicles in one-third. Additional investigations confirmed a primary tumour in 18 patients (30%): hypopharynx five, oropharynx five, nasopharynx two, lung one, axilla one, bone one, rectum one, and distant metastatic disease two. False-positive PET scans were predominant in the oropharynx. Three primary cancers went undetected by FDG-PET. A therapeutic change of treatment was made in 25% of the patients as a consequence of FDG-PET.

Conclusions. 18F-FDG PET has a high detection rate in CUP, detecting a primary tumour or distant metastatic disease in 30%. A change in treatment management due to PET was observed in 25%.

The use of PET imaging in the treatment of head and neck cancer

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The combined FDG-PET/CT scan may influence staging of both primary tumours and metastases and also the search for occult primary tumours

in patients with neck metastases. FDG-PET is also utilized for follow-up of clinically cured patients and to detect recurrences or second primary cancers. However, the FDG-PET analysis is expensive and a cost-benefit analysis has to be performed when introducing a new technology. Other important issues are if there is an obvious clinical benefit of this technique and if it gives an improved therapy for the individual patient. We have investigated our first 80 cancer cases (104 investigations) (age range 18–87 years) to evaluate how the FDG-PET results influence treatment outcome. Main focus was on staging, search for recurrence or residual tumour, follow-up and search for unknown primary cancers. The majority of cases were squamous cell carcinomas ($n = 86$) but also malignant melanomas, adenoid cystic carcinomas, adenocarcinomas and salivary duct carcinomas were investigated. In parallel with the FDG-PET investigation all cases were examined also with either CT-scan or MRI or both. In summary: staging or assessment was altered in 24% following PET examinations; altered overall therapy or follow-up was modified in 32%, the surgical plan itself was adjusted in 12% and in 13.5% extensive surgery was avoided. 39 examinations were performed for staging. The FDG-PET detected all but two (T1) primary tumours. PET outcome changed staging in 5/39 cases (13%). In the T category, PET correctly staged the primary tumours whereas CT scan failed in one case. For N staging, PET and MRI upstaged one primary tumour as compared with the physical examination. Suspected metastases seen on MRI were down staged by PET in two cases and upstaged in one case. Treatment was changed or modified in 6/39 (15%) cases after considering the PET results. Surgery was avoided in 4/39 (10%). In two cases with very extensive cancers, therapy with curative intent was performed when PET excluded distant metastases. When a recurrence was suspected the PET investigation determined the further treatment in 52% of cases. PET analysis gave a correct diagnosis in all but one case (false positive) and in 7/33 (21%) cases planned surgery was altered. Occult primaries were detected in 7/18 (39%) cases and in 4/18 (22%) PET was the sole modality to do so. Our results suggest an important role for FDG-PET technique in staging, on suspicion of recurrence, and for detecting occult primary tumours. For economical reasons PET analysis for follow-up purposes may have to be restricted to patients with a high risk for cancer recurrence.

Cervical metastasis of unknown origin – a series of 72 patients

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Objective. Cervical metastasis from unknown origin is still a challenging problem because of the quite poor prognosis and the uncertainty of the primary site.

Design and setting. We analysed retrospectively all the 72 patients with cervical metastases of unknown origin diagnosed and treated between 1985 and 1995 in the five university hospitals of Finland. Main Outcome measures – Survival and some prognostic and clinical factors of the disease.

Results. The most common sites where the primary tumour was found in the follow-up or in autopsy were lung (8%), oral and pharyngeal region (7%) and skin (6%). When the lower neck nodes (regions IV, V, VI) were affected, the primary tumour was significantly ($P < 0.001$) more often found from the subclavicular sites. The disease-specific 5-year survival rate was 32%. In the multivariate analysis, nodal stage of N2c or N3 [adjusted relative hazard of death (HR) 2.43], other metastases found at the time of the treatment (HR 2.15) and age over 65 years (HR 2.12) were significantly associated with a poor prognosis. Median survival tended to be longer among the patients treated with surgery combined with radiotherapy (39.9 months) compared to treatment with radiotherapy alone (16.8 months), but the difference was not statistically significant ($P = 0.153$).

Treatment of cancer of the external auditory canal and middle ear 1992–2001. A Danish survey from DAHANCA

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Objectives. To evaluate the treatment of External auditory canal (EAC) and Middle Ear (ME) cancer, to compare radiotherapy and surgery as initial therapy, identify prognostic factors and to compare two different staging systems earlier presented by Moody¹ and Manolidis².

Design. Retrospective survey.

Setting. Nationwide. The five head and neck oncology centres in Denmark.

Participants. Seventy consecutive patients with primary cancer of EAC and ME admitted during 1992–2001, identified by diagnosis databases, central cancer registry, radiotherapy database and SNOP codes. Main outcome measures. Patient and tumour characteristics, treatment and recurrence data was recorded. Five-year Kaplan-Meier Crude survival (CS), Loco-regional control (LRC) and Disease-specific survival (DSS) probabilities were calculated using SPSS.

Results. Analysis shows five-year CS of 45% ($\pm 6\%$ SE) and LRC of 43% ($\pm 8\%$). ME involvement decreased 5-year LRC to 21% ($\pm 12\%$) compared to disease confined to EAC ($62\% \pm 10\%$) ($P = 0.001$). Node-negative patients had a 5-year DSS of 64% ($\pm 6\%$) compared to 25% ($\pm 15\%$) for node-positive ($P = 0.009$). As for histology Squamous cell carcinoma (SCC) 5-year DSS was lower ($43\% \pm 7\%$) compared to Basal cell carcinoma (100%) ($P = 0.007$).

Conclusions. We conclude that ME involvement, node metastasis, histology of SCC as well as high T-stages using Moody and Manolidis significantly decrease 5-year survival and disease control probability. The current data represent a surgically less aggressive approach with broader use of primary and adjuvant radiotherapy than generally reported for this rare disease. Our 5-year actuarial survival rates compare well with what other have found using more extensive surgery.

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Treatment outcome for squamous cell carcinoma of the nasal vestibule in Denmark 1993–2002

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Objectives. The current nationwide retrospective study from DAHANCA was performed to evaluate the prognostic factors and establish the basis for a national treatment strategy.

Design and setting. All patients diagnosed in the period 1993–2002 at the five head and neck oncology centres in Denmark were included.

Participants. The study group consisted of 174 patients (97 men and 77 women) with a median age of 69 years (range 36–94 years). Stage distribution according to UICC was T1: 109 patients (63%), T2: 30 patients (17%), T3: four patients (2%) and T4: 31 patients (18%). Only 10 patients had positive lymph nodes at the time of diagnosis (N1 three patients, N2 seven patients). Most patients (114) were treated with primary radiotherapy; 21 underwent surgery only, and 28 had surgery and post-operative radiotherapy. Eleven patients were not treated with curative intention.

Results. The overall 5 year loco regional control was 67%; overall 5-year survival was 58%, and the 5-year cancer specific survival was 78%. The UICC classification system was prognostic with 5-year actuarial local control values of 84%, 55%, 50%, and 58% for UICC T1, T2, T3, T4, respectively ($P < 0.004$). The Wang 1976 T-classification system seemed to better distinguish between the prognosis of various T-stages with 5-year values of 86%, 57%, and 50% for Wang T1, T2, T3, respectively ($P < 0.0001$). The 5-year lymph node control was 92% (N0), 67% (N1), and 43% (N2), respectively.

Conclusions. This nationwide survey resulted in one of the largest series of nasal vestibule cancer ever recorded. The majority of patients were treated with conservative small field radiotherapy, and the results were comparable to other series with more extensive treatment.

Prevalence and peak incidence of acute and late normal tissue morbidity endpoints in the DAHANCA 6 & 7 randomized trial with accelerated radiotherapy for head and neck cancer

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Objectives. The aim of this report was to describe the incidence and prevalence of acute and late morbidity in a randomized trial with accelerated radiotherapy.

Design. The DAHANCA 6&7 multicenter trial¹ randomized patients to receive either 5 or 6 weekly fractions of conventional radiotherapy.

Participants. The study included morbidity data of 1452 of the 1485 randomized patients with St. I-IV squamous cell carcinoma of the oral cavity, pharynx and larynx. The inclusion period was January 1992–December 1999. The prescribed dose was 62–68 Gy in 33–34 fractions. Median overall treatment time was 46 and 39 days in the 5 and 6 fractions/week arms, respectively.

Results. Accelerated radiotherapy caused a significant ($P < 0.05$) increase in the peak incidence of the following acute radiation endpoints: pain, use of analgesics, dysphagia, mucosal oedema, and mucositis. In contrast, loss of taste, xerostomia, and skin reaction was not different between the two groups. Accelerated radiotherapy did not influence incidence or severity of late radiation morbidity. The preliminary prevalence analyses showed that most endpoints (pain, analgesics use, dysphagia, loss of taste, hair loss, oedema, xerostomia) improved significantly during follow-up, whereas only fibrosis and mucosal atrophy increased in severity and prevalence over the 5 years. Osteoradionecrosis, perichondritis, and excess dental carries rates were identical in the two arms. Field size and irradiated anatomical area strongly influenced both acute and late reactions.

Conclusions. A moderate shortening of the overall treatment time with one week increases acute but not late toxicity. For all late endpoints except fibrosis and atrophy a decline in prevalence was observed as a function of time after radiotherapy.

Reference

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Electroporation therapy for treatment of head and neck cancer and cutaneous and subcutaneous foci of cancer – results after 1 year

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Objectives. The primary aim of these studies is to characterize local tumor recurrence through 8 months post-EPT/Bleomycin treatment in two groups of patients – one with cancer of the head and neck and one with cancer of the skin and subcutaneous tissue.

Design. This is an international, multicenter, observational study with 100 patients in each group. We are only reporting our own experience at this time.

Setting. Tertiary care university hospital. **Participants.** Ten patients with cancer of the head and neck (HNC) and 10 patients with cutaneous or

subcutaneous foci of cancer (SSC). **Main Outcome measures.** Local tumor recurrence through 8 months.

Results. Ten out of ten treated patients in the HNC group have been evaluated with biopsies at two months. All biopsies were negative for cancer. Four out of five treated patients in the SSC group were evaluated with biopsies at two months. Four were negative for cancer but one biopsy from a patient with a recurrent cancer in the external ear close to the canal showed cancer in situ and the patient was retreated. This patient recurred once again and was then successfully treated with surgery.

Conclusions. The results so far are excellent both regarding recurrence rate and functionality. EPT treatment seems to spare normal tissue including nerves and ducts. Further evaluation, preferably with a randomized study, is needed.

Reference

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Verrucous cancers in head and neck; a 10 year material Homøe, P.,* & Lajer, C.†

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Introduction. Verrucous cancer in head and neck areas represents a problem both diagnostically but also by choice of treatment. The dilemma is whether this low grade cancer type is best treated by surgery, radiotherapy or combination therapy.

Study design and methods. We have performed a retrospective analysis of all cases registered at our Department of Pathology between 1.1.1992 and 31.12.2001 with the histological diagnosis verrucous carcinoma in the oral cavity, pharynx, and larynx. We have investigated epidemiological data, treatment modalities and outcome.

Patient characteristics. In total we have registered 19 patients with histologically verified verrucous carcinoma. Medical records exist in 16 patients. Fourteen cancers were situated in the oral cavity predominantly in gingival and buccal mucosae and two were laryngeal cancers. Nine were males and seven were females. The age distribution ranged from 12 to 84 years at diagnosis with a median age of 66 years.

Results. The tumour size varied considerably. Five had only surgery, two had only irradiation and nine had combination therapy. Nine patients had recurrences with a range of 7 months–10 years, median 2 years. The seven recurrence free patients have been followed from 1 to 11 years with a median follow-up time of 5 years. The 5 years crude survival rate was 63%. Three patients died from cancer disease before 5 years, one after 1 year, one after 2 years and one after 4 years.

Conclusion. There is a need for a large-scale study of patients with verrucous cancers in the head and neck region in order to apply the best treatment modality. Such a study is best undertaken in a multicenter study due to small numbers with this histological type of cancer. Also uniform guidelines for the histological diagnosis need to be established.

Immediate reconstruction of the maxilla Bundgaard, T., & Kofod, T.

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There is no evidence in the literature suggesting that obturation after partial or total maxillectomy have a better prognosis than patients having their defect closed with immediate reconstruction. In the last decennium different reconstructive methods have been described. At the ENT Depart-

ment Aarhus University Hospital 23 patients with tumour in the maxilla in the period 2000–2005 inclusive have been treated with radical surgery and immediate reconstruction with a pedicled temporalis myofascial flap. Nine of the patients had a salivary gland tumour in the palate. Six of the patients had incorporated bone in the reconstruction, in order to improve dental rehabilitation. The procedure is with very few complications. The myofascial flap was epithelialized in 4 weeks. In 22 cases the functional result was fully satisfied. The patients reconstructed with osseous reconstruction, had undergone dental reconstruction with implants. The pedicled temporal myofascial flap is an easy and excellent way to reconstruct the maxilla, with good functional result. Closing the defect after partial or total maxillectomy is indicated, even in the elderly patients.

A randomized phase II study of simultaneous versus sequential 5-FU and cisplatin in patients with recurrent or metastatic head and neck cancer

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Objectives. To evaluate the treatment efficacy of simultaneous 5-FU and cisplatin versus sequential 5-FU and cisplatin in terms of response rates, time to progression (TTP), and toxicity in patients with advanced or recurrent squamous cell carcinoma of the head and neck.

Design. A randomized phase II study. Arm A: 5-FU (1000 mg/m²/24 h continuously day 1–5) and cisplatin (100 mg/m² day 1) in combination every 3 weeks. Arm B: 5-FU alone followed by cisplatin in case of progression.

Participants. Sixty-one patients were recruited in two hospitals over a 4 year period. Outcome measures: Toxicity, response rates and TTP. Secondary measures: survival rates.

Results. Fifty-eight patients were eligible for analysis. Significantly more patients with grade 3/4 leucopenia were observed during 5-FU-C compared to 5-FU alone, including one septic death. Also, more renal toxicity was noted in arm A. Only 15 patients received sequential cisplatin in arm B due to death, poor performance status, or patient refusal. The overall response rate to treatment in arm A was 14% (95% CI: 6–31%). The response rate for 5-FU alone in arm B was 17% (95% CI: 8–35%) while three additional partial responses were observed after sequential cisplatin leading to an overall response rate of 28% (95% CI: 15–46%) in arm B. The median TTP was 3.0 months for arm A and 3.8 months for arm B (5-FU alone) while the median overall TTP (with sequential cisplatin) was 2.3 months. Median survival rates were 4.1 months and 5.5 months in arm A and B, respectively ($P = 0.37$).

Conclusions. Simultaneous 5-FU and cisplatin was more toxic and did not produce superior overall response rates or improved survival rates compared to sequential 5-FU and cisplatin. 5-FU alone has a favourable toxicity profile and may be adequate for palliative treatment in patients with recurrent or metastatic head and neck cancer.

The correlation between objective findings and quality of life in patients with cancer of the pharynx

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Objectives. In order to facilitate interpretation of morbidity data we wanted to examine the relation between objective findings and corres-

ponding endpoints of EORTC quality of life questionnaires C30 and H&N35.

Method and Material. Thirty-five recurrence free patients treated with radical radiotherapy >2.5 years ago (median 4.7 years) was examined with Functional Endoscopic Evaluation of Swallowing (with sensory testing in 14), saliva flow measurements and a dental examination with orthopan tomography. Patients filled out the quality of life questionnaire (QLQ) (EORTC C30 and H&N35).

Results. Dental status: Edentulous patients ($n = 7$) used all four answer categories (*not at all to very much*) for the question: 'Have you had problems with your teeth?' (HN Teeth). Only one patient did not answer the question. The answer to the question HN Teeth was more predictably dependent on problems with dental prosthesis. The degree of and carries was correlated to HN Teeth, but periodontitis was not. 'Have you had pain in your mouth?' was unrelated to any objective finding. **FEESST:** Overall score for the protection of airways (penetration and aspiration) correlated with HN Coughing. The swallowing scale only correlated with penetration of pureed food into the larynx. Some expected correlations were between the items of the HN Swallowing Scale and objective findings. **Saliva flow:** Stimulated and unstimulated whole mouth and selective parotid flow correlated with the Dry mouth and Sticky saliva item of the questionnaire.

Conclusions. Limited or no obvious correlation was found between the objective examinations and quality of life endpoints. Research in the physiology of side effects must be based on objective measurements, whereas research in the consequences for the patient must be based on patient oriented tools (questionnaires).

Drinking to cope, alcohol and cigarette use, and quality of life in successfully treated HNSCC patients

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Objectives. To study the association between self-reported coping by alcohol, reported alcohol and tobacco use and Quality of Life (QoL) in a sample of successfully treated Head and Neck Squamous Cell Carcinoma (HNSCC) patients.

Design. We employed a cross sectional Design.

Setting. The patients were interviewed in conjunction with a routine follow up visit at the outpatient clinic of the Department, and all Norwegian laryngectomised patients answered an anonymous questionnaire.

Participants. Sample I included all patients less than 80 years that had been diagnosed with HNSCC in Western Norway in the period from 1992 to 1997, and who were disease free in the year 2000. Sample II included all Norwegian laryngectomised patients.

Main outcome measures. The coping by alcohol use was assessed by the COPE questionnaire and the QoL was assessed by the EORTC-QLQ questionnaire.

Results. Actual level of alcohol consumption was not associated with QoL. Reported smoking level was inversely associated with symptom QLQ scales and HN QoL. High level of coping by alcohol consumption was on the other hand generally associated with lowered QoL with about 10% common variance. The associations were still present after adjustment for gender, age, levels of neuroticism and avoidance coping of the patients.

Conclusions. Level of coping by alcohol consumption is broadly inversely associated with level of QoL.

Modified acidic candy has reduced erosive potential in irradiated patients

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Objective. Patients unilaterally irradiated on head and neck area often have reduced saliva flow and consequently use acidic candies to relieve the symptoms of dry mouth. However, acidic candies may cause dental erosion, especially in this patient group. The aim of this study was to determine the erosive potential of acidic candies with calcium (modified), and without calcium (control), in irradiated cancer patients.

Methods. Twenty unilaterally irradiated cancer patients on head and neck area (26–70 years) and twenty healthy persons (21–29 years) participated in the study. The erosive potential of the candies was evaluated from saliva pH, candy-induced changes in saliva degree of saturation with respect to hydroxyapatite (HAp) and by dissolution of HAp crystals in candy-stimulated saliva. The HAp dissolved was determined from saliva pH changes upon contact with HAp crystals.

Results. No significant difference was found in the saliva flow when sucking control or modified candy in neither healthy or patients. However, the saliva became significantly more under saturated with respect to HAp in patients than in healthy with both control ($P < 0.01$) and modified ($P < 0.01$) candies. Interestingly the modified candy did not only have significantly reduced erosive potential in both groups ($P < 0.01$), but it also had slightly less erosive potential among patients than healthy when the erosive potential was determined with HAp dissolution.

Conclusion. Modified acidic candy with calcium has reduced erosive potential in patients unilaterally irradiated on head and neck area and may be a favourable stimulant for dry mouth relief.

Functional endoscopic evaluation of swallowing with sensory testing (FEESST) for the study of aspiration and swallowing function in irradiated pharyngeal cancer patients

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Introduction. Dysphagia after radiotherapy for pharynx cancer is a common problem with impact on morbidity and mortality. Sensitivity cannot be evaluated using video-fluoroscopy (VF) – the gold standard of

swallowing evaluation. We wanted to examine the swallowing function and sensitivity of irradiated patients using FEESST.

Methods and materials. Thirty-five recurrence free pharynx cancer patients, 10 women, 25 men, median age 61 years (44–82) treated with radical RT >2.5 years ago (median 4.9 years) with Functional Endoscopic Evaluation of Swallowing (with sensory testing in 14).

Results. Fifteen of 31 patients had reduced swallowing frequency, as an expression of reduced sensitivity of the pharynx. Sensitivity testing for touch was reduced in 29 of 31 at the base of the tongue and in 11 of 32 at the tip of epiglottis. Sensitivity to airflow was reduced (>4 mmHg) in nine of 14 patients. Penetration and aspiration were more pronounced with thinner boluses: Swallowing water 10 patients had penetration and six aspirated, two silent. The corresponding numbers with food were five and zero. Structural changes were observed in 25 of 32 patients. Swallowing function was normal in two and severely reduced in nine patients. 27 of 32 had residues of fluid in the vallecular regions and 29 had residues of fluid in the pyriform sinuses.

Conclusions. FEES(ST) was well tolerated and provided important information about protection of the airway and swallowing. Both functions were severely affected in the patients to such a degree that it is expected to affect morbidity and quality of life.

Ultrasound examination during follow up of head and neck cancer

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We here present data on 453 consecutive patients examined from 1999–2002 with Ultrasound examination in relation to routine clinical follow up after definitive treatment for head and neck cancer. Ultrasound examination was done the first 2 years of follow up. Patients enrolled in this study had received treatment with curative intent, either surgery, radiotherapy or a combination for malignant tumours originating in the head and neck region. Laryngeal glottic cancers in stage 1 were not entered in this study. The clinical follow up examination was performed by either an oncologist or an oto-rhino-laryngologist. The same day the patient had an Ultrasound performed by a radiologist. A minor proportion of the Ultrasound examinations were performed by oto-rhino-laryngologists. We here present data on the impact of ultrasound examination in the follow up of head and neck cancer patients.

Results. A total of 1331 Ultrasound examinations were performed in 453 patients. Twelve non-palpable relapses were found in the N-site during the 2 year follow-up period. Ten of these patients received curative intended treatment. Seven patients relapsed later during follow-up. Four patients were without disease at the end of follow-up.