

Results. One flap failed due to insufficiency of perforators, and two developed major edge necrosis requiring revisions. Three others were re-explored, but salvaged. During the follow-up time one patient has died from the disease, and one is permanently hospitalized. All others have been eligible for follow-up, 12 have reached 1 year. Three have required minor revisions, debulking or intraoral scar release. All have resumed normal or soft diet. The donor site was closed directly in all but one, which was skin grafted. One patient devel-

oped a seroma and minor wound rupture. None complained of donor site pain or functional problems, but most had some dog-ear formation.

Conclusions. The anterolateral thigh flap is especially suitable for intra-oral reconstruction due to its thinness and pliability. The donor morbidity is minimal. In our practice, during the last two years, the ALT has mostly replaced the radial forearm flap in reconstructions of the head and neck region.

Abstracts from the 17th Annual Meeting of the Scandinavian Society for Head and Neck Oncology, Gothenburg, Sweden, 22–24 April 2005

Oral tongue cancer in Finland between 1995 and 1999

Mäkitie, A.,* Koivunen, P.,[†] Keski-Säntti, H.,* Törnwall, J.,* Pukkila, M.,[‡] Laranne, J.,[§] Luukka, M.,[¶] & Grénman, R.[¶]

*Helsinki University Central Hospital, Helsinki, [†]Oulu University Hospital, Oulu, [‡]Kuopio University Hospital, Kuopio, [§]Tampere University Hospital, Tampere, and [¶]Turku University Central Hospital, Turku, Finland

Introduction. Management of oral tongue cancer (OTC) remains a challenging problem. The purpose of this study was to investigate the used treatment approach and the outcome of OTC in a nationwide study.

Methods. Retrospective clinicopathological data of all patients who were diagnosed for a cancer of the oral tongue between 1995 and 1999 at the five University Hospitals in Finland with a population of 5.2 million inhabitants were reviewed. The mean follow-up time for the whole patient series was at least 5 years.

Results. A total of 235 patients (125 men, 110 women; mean age 61.6 years; range 24–90 years) were included. The T categories were as follows: T1, $n = 79$; T2, $n = 102$; T3, $n = 38$; T4, $n = 15$. In the majority (77%) of the patients the tumour was located in the lateral border of the tongue. Fifty-nine (25.1%) patients presented with neck node metastases. Surgery of the primary tumour was performed in 218 (92.8%) patients and in 69 (29.4%) patients consisted of resection of the tumour with reconstruction of the surgical defect. An ipsilateral neck dissection was performed in 114 (48.5%) cases and a bilateral neck dissection in nine (3.8%) cases. Pre- or postoperative radiation treatment was given to 131 (55.7%) patients. The rate for locoregional recurrences was 27.8%. Twenty-seven patients (18%) with N0 neck disease had regional recurrences. The 3- and 5-year disease-specific survival (DSS) rates for the whole patient series were 74% and 64% respectively. The 3- and 5-year DSS rates for stage 1 tumours were 88% and 74%, for stage 2 tumours 74% and 62%, for stage 3 tumours 79% and 71% and for stage 4 tumours 33% and 33%, respectively.

Conclusions. In the present study the surgical treatment approach seems effective in controlling early stage OTC but the frequent locoregional recurrences and the modest survival, in spite of combined radiotherapy and surgery, point out the need to consider new strategies in the management of advanced stage disease.

Risk Factors and Prognosis in Early Tongue Cancer

Westerborn, A.,* Reizenstein, J.,[†] Karlsson, M.,[‡] Adamsson, Gun-Britt[§]

*Örebro University Hospital, Department of Otorhinolaryngology, Head & Neck Surgery, Örebro, Sweden, [†]Örebro University Hospital, Department of Oncology, Örebro, Sweden, [‡]Örebro University Hospital, Department of Pathology, Örebro, Sweden, [§]Center of Head & Neck Oncology, Örebro University Hospital, Örebro, Sweden

Cancer of the oral tongue carries a bad prognosis with 30–40% local and regional recurrences even with T1–T2 tumours. Several different treatment strategies have been advocated without improving survival. Many studies have tried to find prognostic factors influencing outcome and pattern of recurrence.

Method. 1988–2001 we treated 137 patients with cancer of the tongue; 88 patients with T1–T2 tumours are analyzed here. In 1994–95 we changed treatment pattern to do RT postoperatively instead of preoperatively. Surgery was the primary treatment in 43 cases (single treatment in 23 and combined with RT in 20). TNM: T1 ($n = 24$) and T2 ($n = 19$). Three patients were N+. Forty-five patients did not have primary surgery (40 ext RT in combination with surg ($n = 21$) and brachytherapy ($n = 18$). TNM: T1 ($n = 8$) and T2 ($n = 29$). Nine patients were N+ (all T2).

Results. Forty-three patients had primary surgery (post op external RT in 17, brachytherapy in 5) with 11 recurrences (4 local, 6 regional and 1 locoregional). Forty-five patients were treated with ext RT (40) or brachytherapy ($n = 4$) or neck ($n = 1$). This was combined with brachytherapy ($n = 14$) and surgery ($n = 21$). Eleven recurrences (6 local, 4 regional and 1 locoregional). Five patients were never free of disease. In group 1 (surgery) recurrence rate was 26% and in group 2 (ext RT) 38%. Of 88 patients 14 were <40 y (3 died of disease), 29 were 41–60 y (dod: 7) and 45 were >60 y (dod: 18). Of 29 reexams of surgical specimens the growth pattern graded 1–2 ($n = 21$) and 3–4 ($n = 8$). Grading according to Batsakis, 3–4 is less well delineated. Tumor thickness: <5 mm 5 pat, 5–9 mm 15 pat, >10 mm 10 pat.

Conclusion. Generally older age groups present with more advanced disease. The younger age group does better and usually present with less advanced disease. Results indicate that tumour thickness <5 mm is a favourable prognostic sign as is growth pattern 1–2. A recurrence

rate of >40% in the group with tumour thickness 5–9 mm indicate that this group probably should receive more aggressive treatment, especially if combined with growth pattern 3–4. A good and representative biopsy is necessary for assessing prognosis and treatment options.

Brachytherapy of oral tongue cancer: a review of the literature and the Gothenburg experience

Mercke, C.,* Björk-Eriksson, T.,* Nyman, J.,* Hammerlid, E.,† Edström, S.,† & Fagerberg-Molin, B.‡

*Department of Oncology, University of Gothenburg, Gothenburg, †Department of Oto-Rhino-Laryngology, University of Gothenburg, Gothenburg, Sweden, and

‡Department of Oral and Maxillofacial Surgery, University of Gothenburg, Gothenburg, Sweden

There are several reports of improved local control in patients with tumours of the oral tongue following treatment with brachytherapy (BT), either alone or in combination with external radiation. The largest study of over 600 patients is from Institut Curie in Paris. Most patients, who had T1 and T2 disease were treated with an implant alone to a dose of 70 Gy over 6–9 days. Large T2 and T3 lesions received a combination of external radiotherapy and BT. Local control for T1, T2 and T3 tumours were 86%, 80% and 68% respectively. These results are similar to those obtained by Spiro *et al.*, who treated all their T1, T2 and T3 lesions with partial glossectomy alone. Local control was in their report 85% for T1, 77% for T2 and 50% for T3 tumours. Another subgroup of patients who seem to have benefited from BT include those who have undergone surgery for small lesions, yet found to have close pathologic margins, deep muscle involvement, perineural or lymphovascular invasion. When external radiotherapy and BT are combined at least two studies support the concept that in early stage oral tongue cancer patients the greater the proportion of dose given with BT the higher the probability of local control. Most data with BT for oral tongue cancer are derived from treatment with low dose rate, LDR. Mostly for radiation protection reasons but also for patient convenience, studies with high dose rate, HDR and pulsed dose rate, PDR, the latter trying to mimic the biology of LDR, are being performed. In three recent studies results are similar to HDR when compared with LDR with respect to local control and morbidity. In Gothenburg BT has been selected for patients with oral tongue cancer during 1995–1999 with the following characteristics: (i) T1-T2-T3 tumours with insufficient or close margins after surgery = 'barrier brachytherapy' and (ii) unresectable tumours, mostly T3-T4, together with external radiotherapy and if possible, induction chemotherapy. Techniques and results will be described.

Photodynamic therapy for treatment of malignant head and neck tumours

Lofgren, L.

Örebro University Hospital, Head and Neck Oncology Center, Örebro, Sweden

Objective. To review a prospective series of patients treated with photodynamic therapy (PDT) for recurrent and in some cases primary tumours of the head and neck during a period of 17 years.

Background. Photodynamic therapy is an evolving therapy for both primary and recurrent tumours of the head and neck. It is based on the

dual ability of specific drugs to accumulate in tumour tissue and to transfer light energy to oxygen in the normal triplet state so that it for a short time converts to highly toxic singlet oxygen.

Methods. Three different sensitizers were used including Hematoporphyrin derivative, Porfimer sodium, and Temoporfin. The choice of sensitizer was mainly decided by availability. Most treatments were carried out using a copper vapour pumped dye laser but lately we have used a semiconductor laser, which has simplified the treatment significantly.

Results. Eighty-seven photodynamic treatments for malignant head and neck tumours were carried out in 52 patients from 1987 to 2004. Sixty-seven treatments were carried out for recurrent or persistent cancer after radiation therapy failures and 20 were treatments for primary cancer. Forty per cent of the PDT treatments accomplished a complete response (CR) for three months or longer. If treatments, that for any reason were not adequate are excluded the CR was higher. Patients treated for primary tumours had a better outcome (CR = 65%) than those treated for recurrences. The largest treatment groups were nasopharyngeal cancer ($n = 16$) and laryngeal cancer ($n = 12$).

Conclusions. In appropriately selected cases PDT can achieve a CR in otherwise untreatable tumours and it can be used to avoid the severe handicap caused by resecting organs such as the soft palate. PDT can also be used for treatment of recurrent small tumours of the hypopharynx and larynx and the technique has a potential for becoming the primary treatment of choice for T1 vocal cord tumours.

Electroporation therapy for cancer in the head and neck

Lofgren, L.

The Head and Neck Oncology Center, Örebro University Hospital, Örebro, Sweden

Objective. To review a new selective technique for local ablation of head and neck tumours and to give an overview of the first clinical study in the Nordic countries.

Background. Electroporation, as a means of increasing the permeability of cell membranes, has been used in basic science since it was discovered in 1974. Erythrocytes exposed to an electrical field started to leak haemoglobin. The major use today is to introduce genetic material into cells. It has been shown that certain chemotherapeutic agents also can be introduced into cells by means of exposing cells *in vivo* to an electrical field (electrochemotherapy). A clinical study has been initiated at the department of Otolaryngology at Örebro University Hospital in conjunction with several other hospitals in Europe.

Method. Both primary and recurrent tumours with a maximum diameter of 4 cm can be included in the study. Bleomycin is injected directly into the tumour and surrounding normal tissue. After 8–10 min an applicator is introduced into the tumour and its surrounding and high voltage direct current (400–1500 volt, 400 A, 10 μ s) is applied between the applicator needles. The tumour will demarcate from normal tissue after about 3 weeks. The anticipated advantage is less damage or destruction of normal tissue and thus less loss of function of vital organs. We do not anticipate increased survival compared with other ablative methods. There is a maximized dose of Bleomycin per treatment (80 000 IE) and a lifetime maximum dose of 400 000 IE in this study. Experience has shown that pain can be quite severe but usually does not occur until the fifth to seventh day after the treatment. Morphine is effective for pain and Metronidazole may be given to reduce smell from the necrotizing tumour.

Conclusions. A new ablative technique presently is undergoing clinical evaluation.

Intensity modulated radiation therapy in the head and neck region

Bäck, A.,* Mercke, C.,[†] & Johansson, K.-A.*

*Department of Radiation Physics, and [†]Department of Oncology, Gothenburg University, Sahlgrenska University Hospital, Gothenburg, Sweden

Introduction. A great deal of experience with radiation therapy of head and neck cancers has demonstrated the need of a high absorbed dose to maximize the probability for local control and thereby cure. In spite of the development of 3D dose planning it has so far been difficult to protect normal tissue from unfavourable effects with external radiation techniques alone. Interstitial brachytherapy (BT) has good possibilities to accomplish a selectively high dose to the primary tumour but has limitations, at least for advanced tumours, to be used only as a part of the treatment and then often as a boost treatment after external radiotherapy. Inverse treatment planning and intensity modulated radiation therapy (IMRT) is an alternative approach to the traditional iterative method of treatment planning. IMRT makes it possible to shape the high dose region so that it conforms closely to the prescribed target volume, even for target volumes with concave shapes, and hereby spare organs at risk in complex treatment geometries. This leads to a possibility to escalate the absorbed dose to the tumour with minor effects on the dose to surrounding critical organs which in turn offers an opportunity to improve local control and survival while at the same time reducing complications. IMRT also makes it possible to use multiple target volumes with different prescribed doses for optimization of the dose distribution in the same treatment plan. A planning study with the purpose to evaluate the impact of the dose distribution of IMRT planning and treatment of tonsillar carcinoma using simultaneous integrated multitarget treatment (SIMT) is performed. The objective is to reduce complications and increase the quality of life for the patients.

Material and methods. The idea with IMRT is to use modulated fluence distribution of the incident beams. The optimal fluence distribution is usually determined using an automated optimization procedure sometimes called inverse planning. The dynamic MLC (multi-leaf collimator) technique was used for delivering the fluence modulated beams in this study. Two main advantages with the IMRT-technique will be used for the purpose of this study. First of all, the possibility to reduce complications by reducing the dose to healthy tissue and organs at risk, specifically the parotid glands and the minor salivary glands in the oral cavity and other critical tissues. Secondly, the high dose conformality of IMRT dose distributions will be used to create treatment plans that simultaneously deliver different dose levels to well defined volumes to do SIMT. We have a long experience in our clinic of combined induction chemotherapy, external radiation and BT for tonsil cancer patients with good results regarding tumour control. However, the frequency of complications for these patients is high with, for example, xerostomia and in some patients' tissue necrosis. In this study the radiation therapy part of the treatment will be optimized using the SIMT technique with the objective to reduce complications and increase the quality of life for the patients. The aims are (i) to investigate the possibilities of replacing a combined external treatment and a BT treatment with one single IMRT session and (ii) to create a dose gradient around the gross tumour volume (GTV) with a specific slope to mimic the differences in radiation sensitivity and decrease in tumour cell density around the GTV. The dose gradient was created by defining several target volumes around the GTV and delivering prescribed dose levels to those volumes. New target volumes and fractionated schedules for tonsil cancer treatments with the SIMT technique were designed using isoeffective dose calculations.

Results and conclusions. It was found in the planning study that the SIMT technique could reduce complications in several critical organs, for example parotid glands, mandibles and oral cavity while still give the same isoeffective doses to the target volumes with increased dose homogeneity compared with the doses created in a combination of external radiation and BT treatment. However, a clinical study is needed to confirm the theoretical results.

The neck diagnosis: diagnostic radiology with CT and MR

Berthelsen, B.

Department of Radiology, Sahlgrenska University Hospital, Gothenburg, Sweden

CT and MR are important in the assessment of head and neck cancer including regional lymph node metastases. Both imaging methods can be used in level classification of pathological nodes. For clinically known cervical metastases CT and MR can be helpful in demonstrating size, relationship to surrounding tissue, extranodal extension and invasiveness. The challenge however is the clinically silent lymph node metastases. Apart from identifying deeply sited metastases as in the retropharyngeal lymph nodes CT and MR are less successful. The most reliable imaging criteria of metastases in patients with a known primary tumour is nodal non-homogeneity or necrosis. The sensitivity and specificity of detecting necrosis are approximately 90% in both CT and MR. In homogeneous sharply outline nodes size is used as a criteria, usually with a maximum allowed diameter of 1.5 cm in level I and II nodes and 1 cm in the rest of the neck. Size alone however is inaccurate in approximately 25%. Using all imaging criteria, conventional CT is found to be slightly better than conventional MR in demonstrating cervical lymph node metastases. Imaging upstaging has been reported with a wide variation. In order to improve the tissue characterization different MR techniques have been attempted such as tissue specific MR contrast agent and functional imaging with varying results.

Ultrasound with FNAC and lymphscintigraphy in the detection of neck metastases

Margolin, G.

Department of Head and Neck Surgery, Karolinska University Hospital, Stockholm, Sweden

Presence of lymph node metastases is the single most important prognostic factor in head and neck cancer. If lymphatic tumour spread in the neck cannot be ruled out, the neck has to be treated. Palpation alone has a sensitivity of about 50%. With CT and MRI the sensitivity is higher, but even with advanced radiological techniques, 30% of the N+ patients are inappropriately staged as N0 pre-treatment. Ultrasound guided fine needle aspiration cytology (Ug-FNAC) has the highest sensitivity. In experienced hands the sensitivity is over 70% but this figure varies considerably down to less than 50%. The main reason for our difficulties to accurately detect occult metastases of the neck pre-treatment is that about 25% of the neck metastases are micro-metastases, identified only with histopathology after neck-dissection, and they don't change the structure of the lymph node (impossible to detect with radiological techniques or to catch with cytology). Another, more

recent prospect to detect occult lymphatic tumour dissemination is based on growing evidence that metastatic spread is not random but a stepwise process. The tumour cells initially propagate to one or two lymph nodes, the sentinel nodes, which primary drain the tumour area, and subsequently to other nodes of the neck. Using lymph scintigraphy, the sentinel node can be identified and biopsied. The result of the histopathological examination of this node represents the status of the rest of the nodes in 98% of the patients with breast cancer and malignant melanoma where this technique is widely used. In head and neck cancer the sensitivity and specificity of the sentinel node technique is still uncertain. The possible therapeutic implication on both surgery and radiotherapy of the neck using the sentinel node technique and individual lymph scintigraphy mapping will be discussed. The scientific problem of comparing different patients materials or studies that are using different modalities for staging such as palpation only, advanced radiological techniques or Ug-FNAC and sentinel node biopsy will also be touched upon.

New techniques in head- and neck radiotherapy

Björk-Eriksson, T.

University of Gothenburg, Department of Oncology, Gothenburg, Sweden

Today there is a rapid development of radiotherapy (RT) in the Scandinavian countries. This development of RT aims at improving the efficacy i.e. an increased therapeutic gain through both improved definitions of the target volumes and increased conformity/avoidance of normal tissue and organs at risk (OAR:s). The distinct areas where the development is easy to identify are

- Imaging for target definition for radiotherapy; CT, MRI, PET, SPECT, MRS and US
- Set-up and patient immobilisation
- RT verification; electronic portal image devices (EPID)
- RT planning and delivery; CT based dose planning 3 dimensional conformal RT (3D-CRT), stereotactic radiosurgery (SRS, γ -knife- or linear accelerator based), stereotactic conformal radiotherapy (SCRT), intensity modulated RT (IMRT) 4 dimensional RT (4D-CRT; gating and tumour tracking) and so on and so forth.
- "New" particles; protons and heavier charged particles.

In head- and neck RT there are well known difficulties to satisfactory cover the planning target volumes (PTV) to eradicate the tumour and avoid dose to the OAR:s aiming for the best possible quality of life. These challenging situations include eg 1) a primary tumour in combination with bilateral neck node (NN) metastases 2) a large pharyngeal primary tumour in combination with ipsilateral metastatic NN/-s 3) NN metastases in different levels of the neck and 4) tumours in close vicinity to OARs. Many of the improvements are of particular interest in head- and neck RT since they might help to improve the dose distribution in situations exemplified above. It is of importance to perform randomised studies even when new techniques are introduced in RT. However there are relatively few randomised studies of the effect of the introduction of new techniques in RT compared to the introduction of new drugs in medicine. This talk will therefore focus more upon describing and illustrate some of the new techniques and their potential benefit to the treatment of the neck and finally identify any possible pitfalls.

Impact on organ preservation, local control and survival with neo-adjuvant/concomitant chemotherapy, pre-operative radiotherapy and limited surgery for patients with advanced malignant tumours of the paranasal sinuses and nasal fossa (MTPSNF)

Björk-Eriksson, T.,* Petruson, B.,[†] Ekholm, S.,[‡] Mercke, C.*

*Department of Oncology, [†]Department of Otorhinolaryngology, and [‡]Radiology, Sahlgrenska University Hospital, Gothenburg, Sweden

Introduction. Radical treatment with surgery or radiotherapy (RT) of patients with advanced MTPSNF is often associated with serious side-effects with cosmetic or functional loss. This is a presentation of the impact on organ preservation, local control and long term survival with the addition of neo-adjuvant/concomitant chemotherapy (CHT), to pre-operative radiotherapy and limited surgery for patients with advanced MTPSNF.

Methods. From November 1986 to January 2002, 64 patients with mean age 62.3 years (range 21–85) and advanced MTPSNF were scheduled for treatment with neo-adjuvant/concomitant chemotherapy i.e. cisplatin (100 mg/m²) day 1 + 5-FU (1000 mg/m²) day 1–5, pre-operative radiotherapy (mean dose = 47.9 Gy, range 40, 8–51) and, in responding patients, limited surgery clearing the paranasal sinuses and nasal fossa. Patients were evaluated with physical examination and CT at regular intervals.

Results. 59 patients completed the intended treatment protocol, one patient was Inoperable even at radical dose, one patient interrupted treatment due to alcohol abuse and 3 patients died during the treatment in myocardial infarction, WHO grade 3 and 4 toxicity were seen in ten more patients mainly nausea, infections and renal toxicity. Local recurrence-free survival and overall survival at 60 months were 65% and 55% respectively.

Conclusion. Neo-adjuvant/concomitant chemotherapy with cisplatin + 5-FU in combination with preoperative RT and limited surgery in patients with advanced MTPSNF has resulted in a high rate of organ preservation, local control and survival.

Mannose receptor and clever-1 direct the traffic of cancer cells on the lymph vessel endothelium

Irjala, H.,* Alanen, K.,[†] Grénman, R.,* Heikkilä, P.,[‡] Joensuu, H.,[§] & Jalkanen, S.[¶]

*Department of Otorhinolaryngology - Head and Neck surgery, Turku University Central Hospital, Turku, [†]Department of Pathology, Turku University Central Hospital, Turku, [‡]Helsinki University Central Hospital, Pathology, Helsinki, [§]Department of Oncology, Helsinki University Central Hospital, Helsinki, and [¶]Medicity Research Laboratory, National Public Health Institute, Turku, Finland

Background. Although approximately 50% of cancers give rise to metastases via the lymphatic system, the mechanisms mediating this process have remained unknown.

Methods. We investigated the role of two lymphatic endothelial molecules, the mannose receptor (MR) and CLEVER-1 in adhesion of malignant cells to the lymphatic endothelium, and analysed their expression in two clinical series consisting of squamous cell cancers of the head and neck ($n = 17$) and breast cancers ($n = 72$).

Results. Affinity of the tested head and neck cancer cell lines to the lymphatic endothelium varied greatly, but adhesion of all cell lines was dependent on both the MR and CLEVER-1. Almost all cancer specimens contained peritumoral vessels that expressed CLEVER-1 and the MR, and also the intratumoral lymph vessels often expressed them in both tumour

types. However, only intratumoral expression of these molecules seems to be essential for metastatic spread to the regional lymph nodes. Only eight (22%) of the 36 axillary node-negative breast carcinomas expressed the MR on the intratumoral lymph vessels when compared with 16 (50%) of the 32 node-positive carcinomas ($P = 0.017$), and all eight head and neck carcinoma patients with regional lymph node metastases at diagnosis had tumours that expressed CLEVER-1 on the intratumoral lymph vessels.

Conclusion. These data suggest an important role for both the MR and CLEVER-1 in directing the traffic of cancer cells within the lymphatic system.

Radiotherapy response in oral squamous cell carcinoma; the importance of apoptotic proteins as prognostic factors

Roberg, K. & Norberg-Spaak, L.

Division of Oto-Rhino-Laryngology, University Hospital, Linköping, Sweden

Background. Radiotherapy is a primary mode of treatment of squamous cell carcinoma (SCC) of the head and neck. Radioresistance and local recurrence are significant problems following radiotherapy and therefore it is a paramount need for predictive markers. Loss of growth control and a marked resistance to apoptosis are probably major mechanisms driving tumour progression. Apoptosis is thought to be a critical factor in radiation-induced cell death, and therefore the importance of apoptosis and apoptotic proteins was studied.

Methods. Cultures from oral tumour biopsies and oral SCC cell lines were treated with ionizing radiation (15 Gy/3 days). Proliferation and cell death were studied by cell counting, apoptosis by detection of caspase-3 activity and protein expression by Western blot analysis.

Results. In cell cultures sensitive for radiotherapy an increase in cell death and caspase-3 activity were measured. In tumour cells not sensitive for radiotherapy three anti-apoptotic proteins, Bcl-XL, survivin and EGFR were expressed in a higher degree compared with cells sensitive for radiotherapy. Moreover, the expression of pro- and anti-apoptotic members of the Bcl-2 family differed between the cell lines as well as the expression of p53 and hsp70 (heat shock protein).

Conclusion. Our results suggest that apoptosis and several pro- and anti-apoptotic proteins play an important role for the radiosensitivity in oral tumour cells.

Tumour associated macrophages secrete IL-6 within HNSCC tissue

Kross, K.W.,* Olsnes, C.,† Heimdal, J.H.,* Olofsson, J.,* & Aarstad, H.J.*

**Otolaryngology/Head and Neck Surgery, Haukeland University Hospital, Bergen, †Otolaryngology/Head and Neck Surgery, University in Bergen, Bergen, Norway*

Background. Tumour associated macrophages (TAM) probably play an important role during tumour establishment, growth, as well as development of metastases. It has been shown that the amount of TAM is associated with a worsened survival rate and neo-angiogenesis. IL-6 is a pleiotropic cytokine that modulates a variety of physiological events and can have a stimulatory function in cancer. IL-6 is a macrophage product, but is also secreted from head and neck squamous cell carcinoma (HNSCC) cells. We aimed at determining the source of the IL-6 secreted form HNSCC tumours.

Methods. We have studied the interaction between mononuclear phagocytes and autologous head and neck squamous cell carcinoma cells, by

using tumour cell fragment-spheroids as a vector of tumour cells. L-leucine-methylester (LLME), a substance selectively diminishing the secretion from TAM in tissue, was added to HNSCC tissue. We were able to establish fragment F-spheroids from malignant and benign tissue from HNSCC patients with and without LLME pre-treatment.

Results. F-spheroids treated with LLME showed a significantly decrease in IL-6 production. LLME showed no toxic side effects on the non-TAM cells.

Conclusion. TAM is an important factor in the production of IL-6 in HNSCC and seems to play a supporting role in tumour growth and development. This could have implications for future (immuno-) therapy for HNSCC.

Effects of low-dose cisplatin on Fas (CD95) expression and apoptosis induction in oral cancer cells *in vitro*

Sundelin, K.,* Roberg, K.,† & Håkansson, L.‡

**Otorhinolaryngology, Gothenburg, †Otorhinolaryngology, Linköping, and ‡Oncology, Linköping, Sweden*

Background. New treatment modalities including chemoradiotherapy, immunotherapy and treatment with selective monoclonal antibodies are intensively evaluated for advanced HNSCC. Besides being a potent cytotoxic drug, cisplatin has interesting immunomodulatory effects. The objective in the present investigation was to study effects of cisplatin at non-toxic levels on a therapeutically interesting Fas-receptor in oral cancer cells, and furthermore, investigate whether apoptosis induction is affected.

Methods. Two oral squamous cell carcinoma cell lines (UT-SCC-24A and UT-SCC-20A) were studied. Cisplatin was added to cell cultures at a low concentration (0.5 µg/mL) and 48 h later Fas expression was studied by immunohistochemical and ELISA techniques. Apoptosis was induced by an agonistic Fas-antibody (CH11) and caspase-3 activity was measured.

Results. Cisplatin stimulation enhanced expression of membrane-bound and cytoplasmic Fas in both cell lines as studied by immunohistochemical staining. However, the total amount of cell-bound receptor was enhanced only in UT-SCC-20A according to ELISA results. Furthermore, the apoptosis induction was not enhanced by cisplatin in UT-SCC-20A whereas in the other cell line (UT-SCC-24A), an enhanced caspase-3 activity was observed after cisplatin stimulation.

Conclusion. Low-dose cisplatin has modulating effects on Fas expression in both cell lines. The results indicate that cisplatin can contribute to re-distribution of cell-bound Fas and thereby enhance susceptibility to apoptosis. Still, other mechanisms, such as p53 status, can play an important role in cisplatin sensitivity.

The impact of brachytherapy on quality of life in patients with oral and oropharyngeal cancer

Peterson, K.,* Mercke, C.,† & Hammerlid, E.*

**Department of Otorhinolaryngology, Head and Neck Surgery, Gothenburg, and †Department of Oncology, Gothenburg, Sweden*

Background. Brachytherapy (BT) is used at Sahlgrenska University Hospital for many tumour sites in head and neck region. BT is most often delivered as a boost after external radiotherapy (ERT) with or without preceding surgery or chemotherapy using an interstitial implant with Ir 192. The possibility to give a higher local dose together with the radiobiologically short treatment time, could well increase patient cure. However, the higher dose and the dose distribution could create side-effects both acute and late, affecting health related quality of life (HRQL). In this prospective longitudinal 3-year study HRQL in patients with oral and oropharyngeal cancer treated with BT was studied.

Methods. Two groups of patients were included in the study: 30 patients with oral tongue cancer (67% male, mean age 54 years) and 60 patients with base of tongue or tonsil cancer (79% male, mean age 57 years). Patients' HRQL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30), and the Head and Neck cancer module (EORTC QLQ-H&N35). HRQL was measured at diagnosis and 3, 12 and 36 months after the start of treatment. HRQL scores were correlated to the characteristics of the BT: dose, dose rate, tumour target volume (cm³) receiving doses of 150% and 200%.

Results. After treatment the patients reported statistically and clinically significant problems with pain, problems with swallowing and dry mouth. Three years after treatment the oral tongue cancer patients still reported statistically increased problems with dry mouth. Patients with base of tongue or tonsil cancer reported statistically increased problems with dry mouth, eating solid food and problems with choking when swallowing. When correlating HRQL with the BT characteristics only single random correlations were found.

Conclusions. Three years after treatment there still was an impact on HRQL, i.e. some treatment related side-effects still persisted.

3DCRT combined with brachy-boost contra simultaneous integrated multi-target IMRT for nasopharyngeal carcinoma: comparison of dose distribution and tumour effect

Taheri-Kadkhoda, Z.,* Pettersson, N.,[†] Bäck, A.,[†] Björk-Eriksson, T.,* Mercke, C.,* & Johansson, K.-A.[†]

*Jubileumskliniken, Department of Radiotherapy, Sahlgrenska University Hospital, Gothenburg, and [†]Department of Radio-physics, Sahlgrenska University Hospital, Gothenburg, Sweden

Objectives. Forty patients with nasopharyngeal cancer (NPC) were treated at our centre with a combination of 3DCRT (60–68 Gy/30–34 fr or 61.2–64.6 Gy, 1.7 Gy/fr b.i.d.) and HDR/LDR brachyboost (6–12 Gy) ± CHT during 1991–2002. None of patients with T1 tumour (13), developed local recurrence while nine patients (22.5%) of 27 remaining patients with T2–T4 tumours developed persistent tumour/local recurrence (median follow-up of 45 versus 49 ms) suggesting inadequate dose distribution using 3DCRT + BT for tumour coverage in locally advanced tumours. Through a modelling study, we have evaluated dose distribution advantages of simultaneous integrated multitarget IMRT (SIMT) technique and its impact on TCP of nasopharyngeal carcinoma compared with combined 3DCRT + BT-boost.

Material and methods. Four patients with following stages (T1N0M0, T1N1M0, T2N2M0, T4N1M0) were chosen for our preliminary analysis. GTV (defined by MRI) and three sets of PTVs as well as 10 different organs at risk were delineated and taken into account in the optimization process. For each patient, SIMT-IMRT and 3DCRT plans including the dose distribution from the brachytherapy were made. Dose prescriptions in SIMT-IMRT for GTV, PTV-T and PTV-N were 72.6, 69.3 and 52.8 Gy in 33 fr versus 74 Gy (including HDR-BT 3Gyx2), 68 Gy/34 fr and 46 Gy/23 fr in 3DCRT + BT plan.

Results. Comparing with 3DCRT + BT, SIMT-IMRT plans provided better GTV coverage (V95 = 64–68% versus 98.6–100%) and increased the TCP for all patients. However, the increase of TCP was dependent on the tumour location.

Conclusions. In this study SIMT-IMRT was superior to 3DCRT + BT in terms of tumour coverage and increase in TCP. Modest increase in dose per fraction and decreasing the overall treatment time of the tumour with SIMT-IMRT technique were radiobiological advantages which

were taken into account in the TCP analysis. Based on above data, SIMT-IMRT technique seems to be a better treatment option than 3DCRT + BT for locally advanced nasopharyngeal carcinoma.

Screening and rehabilitation of olfaction after total laryngectomy in Swedish patients: results from an intervention study using the nasal airflow- inducing manoeuvre (NAIM)

Finizia, C.,* Risberg-Berlin, B.,[†] & Ylitalo, R.[‡]

*Department of Otolaryngology, Särskilda spec. Sahlgrenska University Hospital, Mölndal, [†]Division of Logopedics and Phoniatrics, Särskilda spec. Sahlgrenska University Hospital, Gothenburg, and [‡]Department of Logopedics and Phoniatrics, Karolinska Institute, Stockholm, Sweden

Objective. To examine the olfactory function in Swedish laryngectomized patients and to assess the results of the NAIM odour-rehabilitation technique using the validated Scandinavian Odor-Identification Test (SOIT). **Methods.** Twenty-four laryngectomized patients, 21 males and three females (mean age 68 years) answered olfaction and gustation and quality of life questionnaires and were tested with SOIT before and after four NAIM rehabilitation sessions.

Results. 72% of the patients with anosmia or hyposmia at baseline improved during intervention with the NAIM technique according to SOIT results. Before treatment 10 patients were categorized as smellers while 14 patients were non-smellers, i.e. having anosmia according to SOIT. Post-intervention, the patients' with anosmia improved their olfaction significantly according to SOIT and their self-estimation of olfaction, gustation and quality of life improved.

Conclusion. The SOIT odour-differentiation test is an effective and simple test for the assessment of olfaction acuity after laryngectomy in Scandinavian patients. The NAIM rehabilitation method is easy to learn and gives rapid and excellent results in improved smell, taste and quality of life. We recommend that olfactory and gustatory rehabilitation according to the NAIM technique should be incorporated into routine rehabilitation program for laryngectomees in Scandinavia.

Clinical outcome following radiotherapy and planned neck dissection in N+ head and neck patients. Is a neck dissection indicated?

Lagerlund, M.,* Ahlberg, A.,[†] Lundgren, J.,[†] Lewin, F.,[‡] & Friesland, S.,*

*Department of Oncology, Karolinska University Hospital, Stockholm, [†]Department of Otorhinolaryngology, Karolinska University Hospital, Stockholm, [‡]Department of Oncology, Karolinska University Hospital/St Olavs Hospital, Stockholm/Trondheim, Sweden

Background. A planned neck dissection (ND) following radiotherapy (RT) is standard procedure in patients with N+ head and neck cancer at our institutions. In many other centres this is not the case. The aim of this retrospective study is to evaluate if unnecessary ND are performed. It is a follow-up of our presentation last year in Oulu.

Methods. A review of the medical records in Stockholm between 1998 and 2002 was performed. Patients with squamous cell carcinoma of the head and neck with regional metastases receiving primary RT (60 Gy or more) followed by ND, were included. The follow-up time was between 2 and 7 years.

Results. A total of 156 patients were included in the study. Recurrence was found in 29% of the patients. The overall survival was 62% and the disease-free survival 76%. No relation between the palpatory findings in the neck after radiotherapy and the clinical outcome was found. Patients with viable malignant cells in the neck specimen (33%) relapsed in 52% compared with 18% if no malignant cells were seen in the neck specimen. Disease-free survival was 48% in the group with malignant cells in the neck specimen and 89% in the group with no malignant cells.

Conclusions. In our study ND relieves one-third of the patients from viable malignant cells and almost half of these patients survive their head and neck cancer disease. Our clinical examination cannot be used as a tool to decide if a ND should be performed or not. Viable malignant cells in the neck specimen after radiotherapy seem to be a strong negative prognostic factor. Further focus has to be put on this group of patients. Until further knowledge or better methods for preoperative evaluation are available we do not intend to change our present policy regarding a planned ND.

Prognostic role of the neck metastasis in patients with tonsillar carcinoma treated with irradiation

Aziz, L.,* Grunditz, T.,* Mercke, C.,† Edström, Staffan*
*Otorhinolaryngology, Head and Neck Surgery, Gothenburg, and †Department of Oncology, Gothenburg, Sweden

Background. Tonsillar carcinoma is primarily treated with external radiation and brachytherapy in most institutions. Adjuvant neck dissection may be performed as well. However, the clinical significance of neck dissection is not secured. The aim of this study was to determine the prognostic significance of lymph node metastasis in patients with tonsillar carcinoma subsequently treated with irradiation and/or chemotherapy.

Patients and methods. Ninety-seven patients with carcinoma of the tonsil region confirmed by biopsy from the tumour were treated between 1988 and 2000 and followed up at least 3 years at Sahlgrenska University Hospital. All patients were treated with external radiotherapy (final dose 40–60 Gy) completed with interstitial irradiation. Sixty patients in this group received also chemotherapy before radiotherapy. Thirteen patients were subsequently treated with salvage neck surgery when persisting neck metastasis was verified.

Results. Mean age was 61 years. Seventy-six per cent were males and 24% were females. The 3-year survivals in those patients who treated with radiotherapy and/or chemotherapy in T stage were T1 87% ($n = 11$), T2 89% ($n = 28$), T3 50% ($n = 33$) and T4 57% ($n = 25$). In N stage survival rate was N0 60% ($n = 27$), N1 70% ($n = 11$), N2 73% ($n = 41$) and N3 66% ($n = 18$) respectively. The 3-year survival rates in stage II, III and IV were 78% ($n = 10$), 64% ($n = 14$) and 66% ($n = 71$). ($n =$ original number of patients). Survival rates were significantly influenced by T stage rather than by other variables ($P < 0.01$).

Conclusion. This study shows that the survival rate was significantly influenced by T stage in patients treated with irradiation/chemotherapy. As N-state did not have any prognostic significance, we conclude that neck dissection was not justified as an adjuvant therapeutic procedure in these patients.

Are neck recurrences more common today when neck dissections are largely selective and modified

Gertzén, H.O. & Adamsson, G.-B.

ENT, University Hospital Örebro, Örebro, Sweden

Background. In the literature there has been a lot of discussion about a less radical approach to neck dissection: Is selective and modified neck

dissection adequate treatment for node positive disease and how high is the incidence of neck recurrence?

Methods. Since 1988 the Head and Neck Oncology Center at the Örebro University Hospital has a register for head and neck cancer. N+ patients with primary tumours of the oral cavity, pharynx, larynx and salivary glands were collected from 1988 to 2001. The data includes surgery, radiotherapy, chemotherapy and a follow-up 2004 for recurrences and death.

Results. 1058 primary cancers of the oral cavity, pharynx, larynx and salivary glands were classified as N+ in 398 patients. 243 of these N+ patients had a neck dissection. The follow-up showed 16 patients with recurrence (6.6%). Six of these patients had a recurrence on the contralateral side of the neck. The other 10 patients are discussed in detail.

Discussion. The overall N-recurrence rate of 6.6% and a side-specific recurrence of 4% corresponds to the large cancer centres. In the most patients we could not find anything indicating that a more radical neck dissection should have been carried out. A scheme for selective neck dissection is discussed.

Conclusion. Our results compare well with those of others indicating that a more selective and modified approach is safe under the following conditions. The localization of the primary, the T-classification and the level and classification of N+ must be considered before a selective and modified neck dissection can be done.

Malignant mixed tumour of the parotid gland

Kontaxis, A.,* Alborn, T.,* Habermann, W.,*
Salzwimmer, M.,* Beham, A.,† & Rant, B.*

*ENT, and †Department of Pathology University Hospital Graz, Graz, Austria

Introduction. Malignant mixed tumours of the salivary gland are very rare, representing only 0.2% of all salivary gland malignancies. Three subtypes of malignant mixed tumours are described: Carcinoma ex-pleomorphic adenoma. Carcinosarcoma: this true biphasic cancer consists of malignant epithelial and malignant mesenchymal elements. This rare tumour is highly lethal, with a mean patient survival of 3.6 years. Rarest of all is the so-called benign metastasizing mixed tumour.

Case report. We report three cases of carcinosarcoma of the parotid gland, occurring at our hospital in the last 5 years. Due to this diagnose these patients underwent radical surgery followed by radiotherapy. One died in the third postoperative year with extensive local recurrence, one died in the first postoperative year with central nervous system metastasis, and one is alive and well since 5 years.

Discussion. Carcinosarcoma of salivary gland usually occur in preexisting pleomorphic adenomas. Tumour spread is characteristically haematogenous. Tumors metastasize especially to the lung, followed by hilar and cervical lymph nodes. Distant metastases were also rarely found in various soft tissue sites, bones, liver and the central nervous system. Patients were treated with various forms of surgery and occasionally with radiation therapy and/ or chemotherapy. In literature radical surgical excision together with radiation therapy and a neck dissection in case of nodal involvement is recommended. The adjuvant role of chemotherapy needs to be further evaluated because of the high rate of distant metastasis with these tumours.

Conclusion. Clinical experience of carcinosarcoma of the salivary glands is very poor due to the low incidence of this lesion. This tumour typically has an aggressive and often rapidly fatal progression. For this reason it is important to keep these patients in a rigid follow up.