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Phase II Study of RAD001 Monotherapy in Patients With Unresectable Adenoid Cystic Carcinoma

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Background: To examine the efficacy and toxicity of RAD001 when used as a treatment in patients with progressing unresectable adenoid cystic carcinoma.
Methods: Patients with histologically confirmed adenoid cystic carcinoma, with at least one measurable lesion were eligible for the study. Other eligibility criteria included; documented disease progression according to RECIST criteria within12 months prior to the entry, not amenable to curative-intent treatment, ECOG PS 0 or 1, and adequate organ function. RAD001 was given at a dose of 10 mg daily every 4 weeks. Response was assessed according to RECIST (v 1.0) every 8 weeks. Primary end-point was 4-month progression-free survival rate (PFSR). Hypothesis was that 4m-PFSR would be improved from 50% to 65%.
Results: A total of 34 patients were enrolled. Thirty one patients were evaluable for response. Partial response was not achieved. Twenty seven patients (87.1%) had stable disease and 4 patients (12.9%) showed disease progression. Overall disease control rate was 87.1%. Fifteen patients (48.4%) showed tumour shrinkage within SD. Pre-treatment and post-treatment (after 8 weeks) PET was available in 18 patients. All these 18 patients showed SD on RECIST criteria. Among them, 8 patients showed early PR metabolic response (>25% reduction from baseline SUVmax) and 9 patients showed SD metabolic response and one patient showed PD metabolic response (>25% increase from baseline SUVmax). The PFS was 11.7 months (95% CI, 8.1–15.2 months) and 4-month PFSR was 65%. Mean treatment duration was 6.4 months (range 0.4–23.2 months).
The most common AEs (all grades) were: stomatitis (82%), anemia (67%), asthenia (36%), leucopenia (33%). The major Gr 3/4 toxicities were: asthenia (6%), infection (6%), leucopenia (3%). Dose adjustment was done in 8 patients (24%).
Conclusions: RAD001 showed promising efficacy and good tolerability in unresectable adenoid cystic carcinoma.
Clinicaltrial.gov: NCT01152840

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A Prospective Study Evaluating the Influence of Smoking on Effective Hemoglobin Level and Outcome in Patients With Squamous Cell Carcinoma of the Head and Neck

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Background: Patients with head and neck cancer and a high hemoglobin level have been shown to respond better to irradiation compared to patients with low hemoglobin. The hemoglobin level is, however, a crude indicator of the amount of oxygen available to the tissue and may be influenced by a number of factors, smoking being of major importance.
The aim of the present study was to examine the effect of smoking on available oxygen to tumours and the effect on outcome in head and neck cancer patients treated with radiotherapy.
Material and Methods: A total of 233 patients with squamous cell carcinoma of the larynx, pharynx and oral cavity completed questionnaires on smoking habits and venous blood samples were collected prior to treatment to determine the amount of total hemoglobin, carboxy-hemoglobin, p50 and tumour unloading capacity. Patients were treated with primary curative radiotherapy 62−68 Gy/, 2 Gy/fx, 5 fx/week. All but 12 patients had a history of smoking, 36 were long term quitters, 23 recent quitters, 54 smokers and 108 heavy smokers (>1 pack/day).
Results: The amount of carboxy-hemoglobin increased with increasing smoking habits. There was no relationship between total hemoglobin and carboxy-hemoglobin, but effective hemoglobin and carboxy-hemoglobin was linearly correlated. Thus, the oxygen utilization in a tumour in a heavy smoking patient was found to be on average 20% lower than in non-smoking patients.
Actuarial 5-year univariate analysis showed that the heavy smoking patients had a significant reduced probability of loco-regional control (45% vs 65%, p = 0.002), disease-specific (56% vs 78%, p = 0.002) and overall survival (39% vs 66%, p = 0.0003) compared to non-smoking patients. In a multivariate analyses stratifying by site, the independent prognostic factors were found to be heavy smoking, T and N classification, age and gender, however moderate smoking did not influence the outcome after radiotherapy.
Conclusion: The effect of smoking on radiotherapy outcome in head and neck cancer patients can be explained by a reduced tumour oxygen supply caused by the increased carboxy hemoglobin concentration. The data strongly advocate that smoking should be avoided in order to improve the therapeutic efficacy of radiotherapy.
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Tumoural MRNa Profile of Angiogenesis/hypoxia Effectors in Patients With Operable Squamous Cancer of the Larynx

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Background: Tumour hypoxia and angiogenesis have been implicated in disease progression providing the basis for targeted anti-angiogenic therapeutic interventions. The aim of the present study was to explore the prognostic impact of angiogenesis and hypoxia related mRNA expression in patients with localized squamous laryngeal cancer.
Patients and Methods: We retrospectively analysed mRNA levels of Vascular Endothelial Growth Factor (VEGF)-A, -B, -C and the relevant receptors VEGFR 1, 2, 3 as well as the Hypoxia-Inducible Factor 1a (HIF1a) by means of quantitative real-time polymerase chain-reaction that was performed on RNA samples extracted from formalin-fixed paraffin-embedded squamous laryngeal carcinomas of patients with localized disease. We performed distributional and receiver-operating curve analyses that revealed the median mRNA relative expression value as the cut-off for VEGF-A, -B, -C, -R2 and HIF1A, and the 32nd and the 80st percentiles for VEGF-R1 and -R3 respectively. We studied their correlation with clinicopathologic parameters, relapse and death.

Table 1. Multivariate analysis

	HR	95% CI	Wald-p
Disease-free survival			
Node-positive	2.75	1.66–4.55	<0.001
Supraglottic localisation	0.62	0.41–0.94	0.023
Total laryngectomy	0.64	0.39–1.05	0.076
High tumoural VEGFR1 mRNA	2.00	1.22–3.28	0.006
Overall survival			
Node-positive	2.67	1.60–4.45	<0.001
High tumoural VEGFA mRNA	0.69	0.45–1.04	0.080
High tumoural VEGFC mRNA	1.49	0.98–2.26	0.061
High tumoural VEGFR1 mRNA	1.93	1.13–3.29	0.015
High tumoural VEGFR3 mRNA	1.56	0.96–2.53	0.073

Results: Clinical and mRNA expression data were available for 229 patients, mostly males (95%), smokers (86%) with locally advanced (T3/4 in 79%) node-negative (82.5%) glottic or supraglottic (89.5%) squamous carcinoma of the larynx were managed with total laryngectomy (85%) in the ENT Department, Papageorgiou Hospital from 1988 until 2008. At a median follow-up of 70 months, 34% of these patients had relapsed and 42% had died, resulting in median relapse-free survival (RFS) of 87.3 months (95% CI 69.5–105.2) and in median overall survival (OS) of 100.3 months (95% CI 82.6–118). We observed significant correlations between mRNA levels of VEGFR 1, 2, 3 with each other, the respective ligands and HIF1A. Significant associations were seen between high VEGFA, high VEGFR1 and advanced T stage (T3/4, p = 0.005 and p = 0.014 respectively), low VEGFB and alcohol abuse (p = 0.001), low VEGFC and supraglottic primary (p = 0.001). Relapse was significantly associated with high tumoural VEGFR1 mRNA (hazard ratio, HR 1.93, 95% CI 1.19–3.15,

p = 0.008), while death with high tumoural VEGFR1 mRNA (HR for death 1.71, 95% CI 1.02–2.87, p = 0.041) and VEGFR3 mRNA (HR for death 1.76, 95% CI 1.09–2.83, p = 0.02). In multivariate analysis, node-negative status, supraglottic primary and low tumoural VEGFR1 mRNA were favourable predictors of relapse-free survival, while node-negative status and low tumoural VEGFR1 were prognostic for prolonged survival (Table 1).
Conclusions: VEGFR1 mRNA expression in patients with operable laryngeal cancer provides adverse prognostic information and may justify targeted therapeutic interventions.

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DNA Methylation in Tumour and Normal Mucosal Tissue of Head and Neck Squamous Cell Carcinoma (HNSCC) Patients − New Diagnostic Approaches and Treatment

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Background: Cigarette smoke and alcohol consumption are considered to cause HNSCC. Despite advances in therapy, survival of HNSCC patients has not improved significantly during the last 20 years and recurrent disease is frequently observed. Interestingly, DNA methylation of cell cycle control genes, p16 and Ras association domain family 1A (RASSF1A) or death associated protein kinase (DAPK) gene was suggested to contribute to oncogenesis, metastasis and treatment failure.
Material and Methods: The possibility of detecting pre-malignant cells or malignant cells at diagnosis time in HNSCC patients was investigated. Fifty-nine biopsies obtained from 41 HNSCC patients were used. Forty-one were tumour biopsies and 18 of these biopsies were normal mucosal tissue, located at least five cm from the tumour margin. DNA methylation of p16, DAPK or RASSF1A was examined by multiplex methylation specific PCR (MSP). The ethical committee approved this study.
Results: Thirty-nine of 41 (95%) tumour biopsies showed DNA methylation of p16 gene. DAPK and RASSF1A methylation were detected in 7 (17%) and 8 (20%) of the tumour biopsies. In spite of normal mucosal phenotypes observed by the ENT specialist and confirmed by the pathologist, DNA methylation of p16, DAPK and RASSF1A were detected in these biopsies. Of the 18 distant normal mucosal tissue, 15(83%) showed methylation of p16 gene. Methylation of DAPK and RASSF1A gene in these normal mucosal biopsies were 2 (11%) and 4 (22%), respectively.
Conclusion: More than 80% of HNSCC patients carried pre-malignant cells or malignant cells in the normal mucosal tissues as indicated by DNA methylation. These cells were undetected by conventional macroscopic and microscopic examination. Thus, the low cost and simple molecular analysis such as multiplex methylation specific PCR in combination with histopathologically assessment will provide a better prognostic base for evaluation and treatment of HNSCC patients. Since DNA methylation was reversible by pharmacological means, the role of anti-methylation drugs in HNSCC need further investigation.

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Sentinel Lymph Node Biopsy in Oral Cancer Patients − Single Centre Experience of 130 Cases

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Introduction: Oral cancer is one of the most common cancers in Indian subcontinent. Lymph node status is the most important prognostic factor and it has therapeutic implications. The only way to reliably assess lymph node status has been neck dissection but it is associated with significant morbidity. The other method of staging the neck like USG, CT scan and PET scan has low accuracy and high false negative rate. The Sentinel Lymph Node Biopsy (SLNB) is found to be most reliable alternative to neck dissection with >90% accuracy. We are presenting our experience of 130 cases of SLNB in oral cancer patients.
Methods: It is a retrospective analysis of prospective database from 1st February 2008 to 15 April 2011. In this period, patients of oral Squamous cell carcinoma clinically staged T1−4N0−1M0 (N1 − only soft non suspicious LN) underwent sentinel lymph node biopsy. All sites of oral cancer were included. The SLNB was performed either by blue dye or by combined technique. First phase was consist of validation and second was therapeutic phase. In validation phase, all patients underwent neck dissection after SLNB. The results of SLNB compared with final histopathology of remaining neck nodes. In therapeutic phase, no neck dissection was performed in SLNB −ve patients whereas SLNB +ve patients underwent MND I. The intra-operative assessment of SLN was done by Intraoperative touch cytology and its results were compared with histopathology.
Results: Total 130 patients were included in study. Mean age was 50 years and male: female ratio was 97:23. Sixty-two patients were in validation study and 68 underwent therapeutic SLNB. The identification rate was 100% in therapeutic phase. The mean SLN/patient was 2.95. The sensitivity, specificity, NPV and accuracy of SLNB in validation phase were 81.8%, 100%, 90.4% and 93.3% respectively. The sensitivity, specificity, NPV, PPV and accuracy of touch cytology in therapeutic phase were 88.88%, 98%, 96.07%, 94.11, 95.58% respectively. With a median follow up of 10 months in therapeutic phase, only 2 patents had neck nodal relapse and it was associated with local relapse.
Conclusion: Lymph node status is an important prognostic factor in oral cancer. The present evidence suggests SLNB has the best balance between accuracy and morbidity to stage the neck. It should be the preferred method of staging the neck in oral cancer to avoid the morbidity of neck dissection and high failure rate in observation group.

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Accelerated Clinical Pathways Have Caused a Significant Reduction in Time for Diagnosis and Treatment of Head and Neck Cancer in Denmark in 2010 Compared to 2002

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Background: Significant tumour progression has been observed during the waiting time for treatment of head and neck cancer. A meta-analysis of clinical observations in head and neck cancer has shown that the risk of local recurrence and death increases with increasing waiting time for treatment. A Danish study (Primdahl *et al.* Acta Oncol 2006) showed that compared to 1992, the waiting time before start of radiotherapy was significantly longer in 2002 (median 70 days versus 50 days). In 2008, the Danish national policy of fast track accelerated clinical pathways was introduced. Patients with suspicion of cancer are given the highest priority in the health care system. Local infrastructure has been improved by telephone hotline, reserved slots in ENT departments and radiology, fast pathology reporting, and multidisciplinary tumour boards and clinics twice weekly. The aim of the current study was to evaluate the potential influence of fast track by comparing waiting times in 2010 to the observations from 2002.
Patients and Methods: Charts of all consecutive new patients with squamous cell carcinoma of the oral cavity, pharynx, and larynx at the five Danish head and neck oncology centres from Jan-Apr 2010 were reviewed and compared to similar data from 2002. Number of patients was 253 (2010) vs. 221 (2002). Stage distribution 2010 vs. 2002 was stage I: 22% vs. 20%, stage II: 15% vs. 23%, stage III: 11% vs. 23%, and stage IV: 52% vs. 35%. Primary treatment was radiotherapy (73% vs. 81%), surgery (11% vs. 6%), combined treatment (4% vs. 1%), or palliative/none (12% vs. 12%).
Results: Total time from first health care contact (GP, ENT or hospital) to start of definitive treatment was median 41 calendar days in 2010 compared to 69 days in 2002 (p < 0.001). Median time used for diagnosis was 13 days compared to 17 days in 2002 (p < 0.001) and median time from diagnosis to treatment start was 24 days in 2010 versus 47 days in 2002 (p < 0.001). Significantly more diagnostic imaging was done in 2010 compared to 2002 (CT 59% vs. 21%; MR 43% vs. 16%; US 38 vs. 19%; PET 21% vs. 6%).
Conclusion: The study showed a significant reduction in time for diagnosis and treatment of head and neck cancer in Denmark in 2010 compared to 2002. More imaging was used and higher stages seen in 2010. Reducing waiting time by fast track clinical pathways is possible, but requires a substantial dedicated concerted effort of the involved health sectors.