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POSTER

Predictive value of p53 and PCNA expression for occult neck metastases in patients with clinically node-negative oral tongue cancer

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Background: In an attempt to identify molecular markers predictive of occult neck metastases, we investigated whether positive p53 or proliferating cell nuclear antigen (PCNA) immunoreactivities on deparaffinized sections of the primary tumor are correlated to the presence of occult neck node metastases in oral tongue cancer patients with clinically negative cervical nodes (N0).

Materials and Methods: Between 1986 and 1997, 37 clinically N0 patients who underwent functional supraomohyoid neck dissection (32 male, 15 female; mean age 54 years) were selected for p53 and PCNA staining.

Results: p53 and PCNA immunoreactivities were detected in 68% and 32%, respectively. There was no correlation between p53 or PCNA and other clinicopathological factors, such as tumor differentiation, tumor type, tumor size and T-stage. Although tumor differentiation ($p=0.03$) and tumor size ($p=0.03$) were significantly correlated with occult neck metastases of oral tongue cancer by univariate analysis, no correlation was found between p53 or PCNA and the presence of occult neck metastasis. Tumor size (>2 cm) was the most important risk factor in multivariate analysis ($p=0.05$).

Conclusions: p53 and/or PCNA expression are unsuitable as biological markers predictive of lymph node metastases of oral tongue cancer, and thus that p53 or PCNA positive status are not a reliable parameter for selection of elective neck dissection in the management of N0 oral tongue cancer patients.

Publication

Head and neck and endocrine cancer

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PUBLICATION

Role of CT imaging in predicting response of nasopharyngeal carcinoma to definitive radiation therapy

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Purpose: To investigate the role of post-treatment CT scans in assessing response of nasopharyngeal carcinoma (NPC) to definitive radiotherapy.

Material and Methods: Between March 1999 and October 2003, a total of 132 consecutive patients with newly diagnosed NPC were studied in this IRB approved protocol. Sixty-one patients with early stage disease (AJCC stage I or II) were treated with radiation only; 71 patients with locally advanced disease (stage III or IV) but no evidence of distant metastasis (DM) were treated with concurrent chemoradiotherapy. All patients received CT scans of the head and neck, nasopharyngoscopy, and biopsies of primary sites at 4–6 months after completion of radiotherapy. Clinical response of the primary tumor as determined by comparison of pre- and post-treatment CT scans was correlated to pathology results.

Results: The median follow-up time for all patients was 25 months (range 9 to 40 months). Radiological progression was seen in 5 patients, stable disease in 18 patients, and radiographic partial (rPR) and complete responses (rCR) were seen in 67 and 42 patients respectively at 4–6 months of follow-up.

Biopsies of the nasopharynx were positive in 6 patients. For patients with rCR, 2 patients (4.8%) had positive biopsies. Four patients with residual disease (rPR, stable, or progressive disease) following treatment had positive biopsies. The positive and negative predictive values, sensitivity, and specificity of CT scans in evaluating the NPC response to radiotherapy were 0.04, 0.95, 0.67, and 0.32, respectively.

Conclusions: Pathologic CR for nasopharyngeal carcinoma is usually evident at 4–6 months after definitive radiotherapy; however, there is no correlation between pathologic and radiographic response. Although longer follow-up is required to define the relationship between radiographic and pathologic responses with respect to disease control, we find CT scan at

4–6 months after radiation treatment to be neither sensitive nor specific in predicting the response of primary NPC to radiation treatment.

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PUBLICATION

Surgical treatment craniofacial malignant tumors

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Introduction: The management of craniofacial malignant tumors is associated with high risk of morbidity and mortality.

Materials and Methods: Between 1996 and 2001 69 patients, 39 males and 30 females aged from 8 to 74 years have been operated on by cooperative team of Herzen Cancer Research Institute and Burdenko Neurosurgical Institute. Craniofacial carcinomas were found in 35 cases, mesenchymal tumors in 16 cases, malignant osteoblastoclastomas in 2 cases, other tumors in 16 cases. In all cases preoperative biopsy was performed to plan the extent of treatment. Combined therapy, included preoperative or and postoperative radio and chemotherapy. Block resections were performed in 32 Patients, in other cases tumors were removed by fragments. For reconstruction of defects free vascularized flap technique was used (muscular, musculocutaneous, omentum vascularized flaps) in 22 cases. In 5 cases temporal muscle and periosteum flaps were sufficient for effective closure of defects. In 5 cases intraoperative radiotherapy was performed after block resection before plastic procedure.

Results and Conclusions: During the follow up period (3 to 6 years), out of 32 patients who underwent block resections 15 died, 17 survived, 17 of them survived more than 5 years. Out of 37 patients who underwent tumor removal by fragments 30 died, 7 survived, 7 of them survived more than 5 years. The multidisciplinary approach to this problem is necessary, including fundamental investigation of biological behavior of these tumors, complex of modern diagnostic techniques, radio and chemotherapy and cooperative surgical team, including craniofacial, plastic and skull base surgeons. Our experience demonstrates that craniofacial block resection improve survival rates in patients with craniofacial malignant tumors.

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PUBLICATION

Preliminary report of phase II study of neoadjuvant chemotherapy with paclitaxel, ifosfamide, and cisplatin (TIP) in locally advanced squamous cell carcinoma of the head and neck cancer (SCCHN) patients

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Background: Neoadjuvant chemotherapy has an increasing role in the treatment of unresectable advanced head and neck cancer. TIP regimen has been studied in recurrent and metastatic SCCHN, and produced high overall response rates. The goal of this study was to evaluate the efficacy and toxicity of TIP regimen as an induction chemotherapy for advanced SCCHN.

Methods: Patients with untreated SCCHN (exclude nasopharyngeal cancer) with WHO performance status ≤ 1 and good organ function were enrolled. All patients were given two cycle of TIP (paclitaxel 175 mg/m², cisplatin 60 mg/m² on day 1 and ifosfamide 1 gm/m² on day 1–3 plus mesna to decrease the urotoxicity of ifosfamide. Response evaluation after 2 cycles was performed. We continued another 2 cycles of TIP only in case of regression disease, then the patients received local treatment according their status.

Results: Twenty-seven patients with predominantly unresectable stage IV (25/27, 93%) were enrolled. The primary sites were maxillary sinus 10 patients (37%) followed by oropharynx 8 patients (30%), oral cavity 5 patients (19%), hypopharynx 3 patients (11%), and larynx 1 patient (3%). We observed 1 complete (4%) and 17 partial response (63%) after the chemotherapy. Six patients were stable disease (22%), and 3 patients (11%) were progression after 2 cycles of chemotherapy. All progression received palliative radiotherapy. Two partial response patients were eligible for a radical operation with free surgical margin. At the time of analysis 11 patients (41%) are still free from disease, 2 patients (7%) died in consequences of the tumor. The other 14 patients (52%) are living with disease. The most common toxicities of NCI-CTC grade 3–4 included: febrile neutropenia 4%, neutropenia 41%, anemia 4%, thrombocytopenia 7% of patients. No treatment related death occurred.

Conclusion: In locally advanced squamous cell carcinoma of head and neck, neoadjuvant chemotherapy with TIP produces a high rate of overall

response in these poor prognosis patients and may facilitate definitive local surgery or radiotherapy. Further follow up will be performed for survival rates.

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PUBLICATION

Postoperative radiotherapy after the partial laryngectomy in supraglottic cancer: an analysis of 79 patients

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Background: To evaluate treatment results and complication rates of postoperative radiotherapy after the partial laryngectomy for squamous cell carcinoma of supraglottic larynx.

Materials and Methods: Between January 1980 and July 2003, 79 patients with squamous cell carcinoma of supraglottic larynx who were treated with radiotherapy after the partial laryngectomy were evaluated. There were 77 (97.5%) male and 2 (2.5%) female with median age of 55 years (37–75 years). According to the 1998 TNM staging system of AJCC, the disease was T1 in 7 (8.9%), T2 in 35 (44.3%), T3 in 15 (19%), T4 in 20 (25.3%), Tx 2 (2.5%), N0 in 58 (74.7%), N1 in 10 (12.7%) and N2 in 11 (12.7%) patients. Bilateral neck dissection was performed in 13 (16.5%) and unilateral neck dissection in 18 (22.8%) patients. 48 (60.8%) patients did not undergo a neck dissection. The surgical margins were positive in 24 patients and close in 8 patients. The treatment field was confined only the larynx in 4 patients, neck lymphatics and the larynx in another patients. The median radiation dose was 50 Gy (48–70 Gy). Survival rates were calculated using the Kaplan–Meier method. Univariate analysis was performed using log-rank test. The median follow up time was 62 months for the surviving patients (17–260 months).

Results: 53 patients (67.1%) were still alive at last follow-up. 16 (20.3%) died of larynx cancer and 10 (12.7%) died of reasons not related to larynx cancer. Locoregional recurrence rate was 13.9%. The 5-year locoregional progression free rate, disease-free survival and overall survival rates were 84%, 77%, 72% respectively. On univariate analysis, histologically positive neck disease and grade II edema decrease the regional and local control respectively (79% $p = 0.01$ and 64% $p = 0.0001$). 67 (84.8%) patients had larynx edema and 18 (22.8%) had neck fibrosis. Tracheostomy could not be closed in 3 cases due to edema. Severe complication led to total laryngectomy in 1 patient. Cerebrovascular disease was seen in one patient.

Conclusion: Postoperative radiotherapy can safely be performed after the partial laryngectomy. Recurrence of tumor should be suspected in patients with continuous severe edema. The determination of radiotherapy treatment volumes according to high risk recurrence areas might reduce complication rates.

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PUBLICATION

Cryosurgery of larynx cancer T3N0M0 as a part of combined treatment

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Aim: To determine ability of using cryogenic method for treating larynx cancer T3N0M0 as an organ-preserving method.

Materials and methods: 36 patients with primary larynx cancer T3N0M0, who had a radiation therapy (40 Gy) in first phase of combined treatment, with poor effect – reduction of tumor dimensions less than 50%. All patients had squamous cell carcinoma confirmed by cytological and histological examination. Low efficacy of radiation therapy was an indication to cryogenic treatment as an organ-preserving method. The zone of cryodestruction involved healthy tissue also. Cryosurgery was performed after making a laryngofissure with temporary tracheostomy. It was performed in minimum 3 cycles of freezing/warming. The laryngofissure was closed after cryodestruction.

Results: The follow-up ranged from 3 to 7 years. Recurrent disease was detected in 2 cases, these patients underwent laryngectomy. Metastases were revealed in 5 patients during follow-up and they had functional neck dissection of II-VI levels. Overall 3-years survival – 88.8% (32 patients), overall 5-years survival – 80.5% (29 patients). Satisfactory voice function was preserved in 32 (88.8%) patients. 29 (80.5%) patients continued to work at their previously jobs.

Conclusion: Cryogenic treatment of larynx cancer is an effective method for treatment of patients with locally-advanced larynx cancer T3N0M0, with poor effect after 40Gy radiation therapy. The obtained data show that cryogenic treatment is a perspective method on the final phase of combined therapy of larynx cancer, that allow us to improve complete response and to save larynx and its function.

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PUBLICATION

Assessing the feasibility of a randomized study of smoking cessation following active intervention in patients with squamous carcinoma of the Head and Neck: Results of a pilot study

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Introduction: Smoking is a major risk factor in the aetiology of squamous cell carcinoma of the head and neck (SCCHN) region. It also leads to many co-morbid conditions which are a common cause of death in patients who survive head and neck cancer. In addition, it compromises the tolerance to treatment of SCCHN. It is thought that those who continue to smoke have an increased risk of second primary or recurrent cancer. Many patients continue to smoke following their diagnosis. It is not clear whether active intervention could lead to better prognosis. A prospective randomized trial can possibly answer that question.

Aim: We set out to conduct out a population based pilot study in 2 Canadian centers with the aim of obtaining data on the number of patients who continue to smoke following diagnosis of SCCHN as well as interaction with other factors. The purpose of this study was to assess the feasibility of a phase III smoking intervention study in patients following treatment of SCCHN.

Materials and Methods: All newly diagnosed patients with head and neck cancer for a period of six months were asked to consent to the pilot study. There has been no refusal. A study questionnaire was completed with the aid of a trial nurse. No serum cotinin levels were done based on our previous experience which showed a good correlation between serum analysis and patient information.

Results: Demographics were typical for SCCHN patients the majority being males (75%), Caucasian (86%). Having high school or less education (80%), average age 64 years, 25% were employed and the majority also consumed alcohol.

Many significant differences were seen between the 3 groups of patients who are smokers, non smokers and the patients who are quitters. 32% of patients indicated that they continue to smoke at the time of diagnosis.

Summary and Conclusions: Based on the results of that population based study, a prospective Randomized study was not planned. Taking into consideration the small percentage who continue to smoke following diagnosis and the likely small benefit of smoking intervention in these patients such a trial would require a large sample size of 1200–1500 patients with long-term follow-up.

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PUBLICATION

Delay in referral of oropharyngeal squamous cell carcinoma to secondary care is associated with more advanced stage at presentation and poorer survival

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Squamous carcinoma of the oropharynx presents with symptoms common to many benign diseases, and this can cause delay in referral. We investigate delay in referral, and the effect of that delay, from symptom onset to the decision to refer from primary care, using a retrospective case notes based study of patients presenting at our institution with oropharyngeal squamous carcinoma over the last 10 years. Of 69 patients suitable for evaluation, 54 were male, 15 female (M: F 3.6:1). Stage grouping was II, III, IVA and IVB 9%, 24%, 52% and 15% respectively. Frequencies of presenting symptoms were: neck mass 49.3%, sore throat 33.3%, other 17.4%.

Using correlation analysis and ordinal regression, we examined the relationship between increased referral delay, clinical stage at presentation and survival.

Increasing delay in referral from primary to secondary care was positively correlated with more advanced disease stage at presentation ($r_s = +0.346$, $p = 0.004$). This was confirmed with ordinal regression modeling (delay estimate=0.045, $p = 0.042$). For every one-week increase in delay in referral, presenting stage increases by 0.045 of "a stage". Patients with delay of less than 6 weeks had significantly improved survival compared to those with a delay of greater than 6 weeks ($p = 0.032$) as illustrated in Fig 1.

Our results indicate that a prolonged delay before referral to secondary care is positively correlated with an advance in clinical stage at presentation to secondary care, also that the delay in referral can affect survival. Also, although sore throat is a symptom which is not referred to in the UK Dept. of Health urgent referral guidelines for Head and Neck cancer, since one third of patients presented with this symptom, we recommend that it should be so included.