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Special Article

Second Primary Cancers in the Lung in Head and Neck Cancer Patients: a Challenge

G.B. SNOW,* N. DE VRIES,* N. VAN ZANDWIJK† and H.M. PINEDO‡

**Department of Otolaryngology/Head and Neck Surgery, Free University Hospital Amsterdam, †Department of Lung Diseases, Netherlands Cancer Institute, ‡Department of Medical Oncology, Free University Hospital Amsterdam, Amsterdam, The Netherlands*

SURVIVAL rates of head and neck cancer patients in recent years have reached more or less a plateau, which is in a large measure caused by the occurrence of second primary tumours, particularly in the lung. Survival rates might be improved by applying screening and preventive strategies during follow-up of these patients. From the point of view of clinical research in this group of patients it appears particularly feasible to test methods of screening for early lung cancer as well as methods of chemoprevention of lung cancer.

For analysis of the occurrence of multiple primary tumours it is common practice to use the criteria proposed by Warren and Gates [1]: 1. the neoplasm must be clearly malignant on histological examination, 2. each neoplasm mut be geographically separate and distinct and not connected by either submusocal or intraepithelial neoplastic changes, 3. the possibility that a second neoplasm represents a metastasis must be excluded. Furthermore it is generally accepted to regard solitary lung tumours appearing in patients treated successfully for laryngeal cancer as being primary lung malignancies if the index larynx tumour was T1 or T2 without lymph node metastases and without signs of local or regional recurrence [2]. Skin tumours, carcinoma *in situ* lesions or carcinomas found at autopsy as second primaries are usually not included for analysis.

The incidence of multiple primary tumours in head and neck cancer patients reported in various studies is in the range of 10–35% [3–6]. The great majority of the second primary tumours occur in the respiratory tract, the oesophagus and in the head and neck. This is likely to be so because the mucosa of these regions is exposed to the same carcinogenic agents, such as tobacco and alcohol. The incidence and location of the second primary within the respiratory and upper digestive tract is related to the location of the index tumour. In index tumours of the oral cavity and oropharynx, for instance, the second primary tumour is relatively frequent also in the digestive tract [6, 7], while in laryngeal cancer the second primary frequently appears in the lung.

The overall risk of the laryngeal cancer patient developing a second primary cancer in the lung is approx. 10% [8]. The following subgroups of laryngeal cancer patients carry an even higher risk of developing lung cancer: patients with supraglottic cancer as compared to those with glottic cancer [8–10], males versus females [8] and those continuing smoking versus those stopping [11]. Recently it has been demonstrated that the occurrence of lung cancer in head and neck cancer patients is also related to certain immunoglobulin allotypes: patients who lack immunoglobulin light-chain marker Km(1) are at higher risk than Km(1)-positive patients [12]. Furthermore there is a relationship to certain HLA antigens: head and neck cancer patients with HLA-B8, -DR3, DQw2 are especially at risk [13]. Since the prognosis of laryngeal cancer—especially stage I and stage II—is rather favourable, the prognosis of laryngeal cancer patients is in a large measure determined by second primary tumours in the lung.

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Approximately 70% of the second primary cancers in the lung in laryngeal cancer patients are squamous cell carcinomas [14]. Rarely these lung cancers are found simultaneously or within a period of 6 months from the diagnosis of the index tumour in the larynx. The great majority is found after 6 months and are thus considered to be metachronous [8]. Whereas bronchoscopy, often as part of panendoscopy, is an established procedure at the initial work-up of head and neck cancer patients, it is rarely carried out routinely during follow-up. The usual follow-up policy in this regard consists of half yearly chest X-ray only and not surprisingly it is often inadequate. The bronchial carcinomas usually are found beyond the curative stage and the survival rate of these patients is as poor as that of lung cancer patients in general. With the availability of the flexible fibreoptic bronchoscope regular bronchoscopy during follow-up of high risk patients has become feasible. Preliminary experiences with fibreoptic bronchoscopy with sputum cytology every 6 months in patients previously treated for laryngeal cancer demonstrate that a significantly higher number of lung cancers are diagnosed in a stage where curative treatment is possible as compared to historical controls [15].

A very interesting development is the application of photosensitization for diagnosis and treatment of early lung cancer. Haematoporphyrin derivative, a photosensitizing agent, injected i.v., is concentrated preferentially in tumours after a latent period of 48–72 hr. Violet light from a krypton laser causes haematoporphyrin derivative to emit fluorescence, facilitating tumour localization and identification. In the bronchial tree very small (1 × 2 mm) mucosal cancer lesions can be located by their fluorescence, even when invisible to the eye under white light examination [16]. Red light (630 nm) from a dye laser catalyses a photochemical tumour-destructive process by haematoporphyrin derivative. This treatment can be applied endoscopically. Cases of early lung cancer treated successfully by this method have been reported [17–19]. Taking into account that the majority of second primary lung cancers in laryngeal cancer patients occur centrally in the lung—defined as visible at bronchoscopy [14]—in this group of patients it appears particularly feasible to explore the considerable potential of photosensitization for both diagnosis and treatment of early lung cancer.

It is well known that patients who continue smoking are at more risk to develop a second primary cancer in the lung than patients who stop smoking [11]. An intensive effort is therefore necessary to get the laryngeal cancer patient to stop smoking. However antismoking campaigns are at most only partially successful. It may be more effective to add to the average diet specific micronutrients, which have been suggested as possible late-stage inhibitors of cancer.

An increased susceptibility to chemically induced cancers has been well documented in vitamin A deficient animals, and epidemiological studies have shown an inverse relationship between food intake of vitamin A or β-carotene and cancer risk, particularly for lung cancer [20–23]. These data suggest that physiological levels of vitamin A and/or β-carotene may exert a protective effect against cancer development. Several mechanisms of action have been suggested. Both may be involved in cell differentiation, but carotene in addition has the capacity to capture certain organic free radicals to deactivate excited molecules, particularly excited or singlet oxygen, thus preventing one of the first steps of carcinogenesis [24]. Synthetic derivatives of vitamin A, i.e. retinoids, have been shown to have even more potent tumour inhibiting properties than β-carotene or vitamin A. A major problem, however, in prescribing synthetic retinoids is that the dosage should preferably be just below the dose at which hypervitaminosis will occur and this may complicate long-term usage. Recently another drug, *N*-acetyl-cystein (NAC) has attracted attention as a possible chemopreventive agent. This drug as a precursor of intracellular glutathione is widely used in the treatment of patients with chronic bronchitis and emphysema. Recently it also became popular for its potent antioxydant/detoxificant properties [25]. For instance, treatment of paracetamol poisoning with NAC is effective in preventing fatal liver damage [26]. *In vitro* studies show the ability of NAC to inhibit direct or indirect acting mutagens, such as aflatoxin, benzpyrene and cigarette smoke condensate [27, 28]. NAC has also been shown to prevent chemically induced lung tumours in mice at a relatively low dose [29].

In epidemiological studies generally tens of thousands of individuals are required to estimate risk reduction of intervention measures. Patients treated radically for laryngeal cancer, however, are at such a high risk of developing lung cancer that much smaller numbers are required for intervention studies. Moreover, high patient compliance is to be expected, as these patients already are kept under follow-up.

At a recent workshop meeting on 'Secondary primary tumours in the lung in head and neck cancer patients'* sponsored by the EORTC Head

*Participants: J. Castella (Hospital de la Sta. Creu i de St. Pau, Barcelona, Spain), O. Dalesio (statistician EORTC Data Centre, rue Héger-Bordet 1, 1000 Brussels, Belgium), J.G. McVie (Department of Internal Medicine, The Netherlands Cancer

and Neck Cancer Cooperative Group and the EORTC Lung Cancer Group the various aspects of second primary cancers in the lung in head and neck cancer patients as outlined above were discussed. A writing committee of representatives of both the EORTC Head and Neck Cancer Cooperative Group and the EORTC Lung Cancer Group was established to design a protocol for a Europe-wide randomized study to assess the value of aggressive screening for early lung cancer on the one hand and chemoprevention of lung cancer on the other hand in patients previously treated for laryngeal cancer.

Institute, Amsterdam, The Netherlands), S. Frustaci (Centro di Rifermento Oncologico, Aviano, Italy), G.J. Gerritsen (Department of Otolaryngology/Head and Neck Surgery, Free University Hospital, Amsterdam), G.J. Hordijk (Department Otolaryngology/Head and Neck Surgery, University Hospital, Utrecht, The Netherlands), P. Hugh-Jones (Chest Unit, King's College School of Medicine, London, U.K.), B. Luboinski (Department de Chirurgie Cervico-Fac., Institut Gustave Roussy, Villejuif, France), U. Pastorino (Istituto Nazionale Tumori, Milan, Italy), P.A. Rocmans (Department of Thoracic Surgery, ULB Hopital Erasme, Brussels, Belgium), G.B. Snow (Department of Otolaryngology/Head and Neck Surgery, Free University Hospital, Amsterdam, The Netherlands), N. de Vries (Department of Otolaryngology/Head and Neck Surgery, Free University Hospital, Amsterdam, The Netherlands), N. van Zandwijk (Department of Lung Diseases, The Netherlands Cancer Institute, Amsterdam, The Netherlands).

CONCLUSIONS

An increasing problem in head and neck cancer patients who are successfully treated for their head and neck cancer is the development of second primary cancers in the lung. Particularly patients with laryngeal cancer are at a very high risk: 10%! With the currently used policies during follow-up these lung cancers are nearly always detected too late. It is clear that more effort must be directed in laryngeal cancer patients to either preventing or diagnosing the second primary lung cancer earlier. Chemoprevention with vitamin A analogues and/or *N*-acetyl-cystein and regular fibreoptic bronchoscopy with sputum cytology possibly combined with haematoporphyrin derivative photosensitization, are to be considered.

Within the EORTC a writing committee has been established for a protocol of a Europe-wide randomized study to test the validity of these concepts.

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