Secondary lung lesions after head and neck cancer: Diagnosis, differentiation, screening, survival
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Chapter 1

General Introduction
Epidemiology

In 2002, approximately 874,000 new cases of cancer of oral cavity, pharynx and larynx were diagnosed worldwide, the fifth highest incidence of all cancers. Ninety percent of these cancers are of squamous cell carcinoma origin (HNSCC). In Europe, in the period 1995-1999 49,569 people were diagnosed with head and neck cancer, with a 5-year survival of approximately 40%. In 2005 in the Netherlands, 2157 patients developed carcinomas of the oral cavity, oropharynx, nasopharynx, hypopharynx and larynx, accounting for approximately 3% of all newly diagnosed cancer patients.

Due to the introduction of new surgical techniques, advanced radiotherapy techniques and the use of concurrent chemo-radiation, a significant improvement of loco regional control of HNSCC has been observed over the last decades. However, this improvement has not been translated into a positive influence on overall survival. This may be associated with development of distant metastases and second primary carcinomas. The reported incidence of distant metastases ranges from 4% to 26% in various clinical studies and from 37% to 57% in post-mortem studies. Depending on the primary site and duration of follow-up, the incidence of second primary malignancies in the upper aero digestive tract, lungs and esophagus, varies between 14% and 47%.

The incidence of secondary malignancies (all sites) in patients surviving HNSCC has been reported 3-7% per year. In a large cohort study on HNSCC patients, a meta-analysis and a systematic review of the literature percentages of second primary lung cancer range from 23% to 33% of all secondary malignancies. According to Chuang et al, estimating the risk of second primary cancers in head and neck cancer patients, second primary lung cancer contributed to the highest proportion of the second primary carcinomas with a 20-year cumulative risk of 13%. In HNSCC patients, pulmonary metastases account for 66% of distant metastases and the incidence of pulmonary metastases in curatively treated HNSCC patient’s ranges from 1.6% to 25% depending on tumor stage.

Five-year overall survival of metachronous second primary cancer (head and neck, lung and esophagus) in HNSCC has been reported to be as low as 9%. It must be noted that these figures are based on retrospective studies in heterogeneous groups of patients with second primaries in the esophagus as well. Both figures of relatively high risk and low survival are a potential opportunity for improving survival by early diagnosis and curative treatment of secondary pulmonary malignancies.
Secondary pulmonary malignancy

**Pulmonary metastases**

Distant metastases from HNSCC are found at various sites, but most frequently in the lungs (66-83%) followed by metastases in bone (22-31%) and liver (6-10%).\(^{17,25,26}\) Because imaging techniques varied, the incidence of multi-organ distant metastases at first presentation differs between the series described. Calhoun et al. reported that almost 80% of patients developing distant metastases had distant metastases involving only one organ system.\(^{25}\) Leon et al.\(^{8}\) found multi-organ distant metastases in 31% of 64 out of 1244 HNSCC patients. Because of improved detection techniques, it may be expected that in this ‘PET/CT’ era higher percentages of multi-organ distant metastases will be reported.\(^{26}\)

There are many factors, which influence the development of distant metastases, for example, primary site, advanced tumor stage, loco regional control of the primary tumor, histological differentiation, immunologic capacity and extra capsular spread of lymph node metastases.\(^{8,17,27-29}\) Multivariate analysis of factors influencing development of distant metastases (including pulmonary metastases), identified neck stage and loco regional control as the most significant risk factors.\(^{12}\)

Among sites, hypopharynx and supraglottis were associated with the highest incidence of distant metastases.\(^{8,12}\)

Clinically it is impossible to distinguish pulmonary metastases from second primary lung cancer. Frequently used parameters for estimating that a secondary pulmonary malignancy is a metastasis are multiplicity, peripheral and/or bilateral localization in the lungs, sharp edges of the nodule at imaging and an interval of 2-3 years or less between primary head and neck carcinoma and secondary pulmonary malignancy.\(^{23,30-34}\) However, most second primary lung cancers are also found within the same time interval.\(^{35,36}\) Some authors, because of these figures, advise a rigorous evaluation of the chest until a period of 2-5 years after primary treatment of HNSCC.\(^{8,28,35-39}\)

As reliable differentiation of secondary pulmonary malignancies on the basis of clinical criteria seems impossible, there is considerable need for more specific methods for discrimination.

**Second primary lung cancer**

Not only pulmonary metastasis but also second primary lung cancer is a major problem in curatively treated HNSCC patients. For some patients, treated for early stage disease like T1N0 glottic laryngeal cancer, the risk of dying of an as yet
undetected second primary lung cancer is higher than the glottic cancer itself.\textsuperscript{40} Patients who continue smoking are at the highest risk of developing secondary malignancy.\textsuperscript{24} Tobacco smoke is the single most important etiologic factor in the development of lung cancer. It is estimated that 90\% of all lung cancers are attributed to smoking.\textsuperscript{41} Non-small-cell lung cancer (squamous cell carcinoma, adenocarcinoma and undifferentiated subtype) accounts for 80\% of second primary lung cancer.

Smokers tend to have a five-fold increased risk of second primary cancer of the aero digestive tract, whereas alcohol abuse is associated with a doubled increased risk.\textsuperscript{24} Schwartz et al.\textsuperscript{23}, found an estimated 5-year incidence of second primary lung cancer of 3\% for non-smokers vs. 26\% (20 pack years or less) to 42\% (20-40 pack years) for smokers. Alcohol is also a well known risk factor for development of second primary cancer, especially in the upper aero digestive tract: 5\% incidence for non-consumers vs. 32\% for consumers.\textsuperscript{23} Large (multicentre) studies reported second primary lung cancer in 7\% of patients with laryngeal carcinomas during long term follow up (>10 years).\textsuperscript{12,42,43} Even in patients with carcinoma in situ of the larynx, there is an increased risk (10\%) of developing secondary malignancies of the lungs.\textsuperscript{44,45} In a large prospective study on 2063 HNSCC patients 351 (17\%) patients presented with a second primary lung carcinoma after follow up.\textsuperscript{46} Patients with index tumors in the oral cavity developed second primary tumors in other head and neck mucosal sites in 42\% of the cases, whereas 24\% of larynx carcinoma patients developed second primary lung cancer. Hypo-pharyngeal and oropharyngeal cancer developed second primary lung carcinomas in 26\% and 20\% respectively.\textsuperscript{46} Therefore it becomes evident that reported percentages of second primary lung carcinoma are varying considerably among the reported series. This may be due to incorrect differentiation between second primary lung carcinoma and pulmonary metastases, differences in epidemiology and different follow up protocols.

Differentiation of secondary pulmonary malignancy

Differentiating second primary lung carcinomas from lung metastases of HNSCC is, as mentioned, a challenge, since second primary lung carcinoma of the squamous cell type and HNSCC metastases have similar histological appearance. Billroth was the first to develop clinical criteria to categorize a second primary
tumor. In 1932, Warren and Gates modified these criteria of diagnosis of second primary tumor and formulated the following definitions: 1. both tumors are diagnosed as malignant on histological examination, 2. the tumors must be anatomically separate and 3. the possibility of the second primary neoplasm being a metastasis must be excluded. The last criterion of Warren and Gates is the most difficult one to deal with in practice, especially when both carcinomas have similar histology. Supplementary criteria and characteristics have been postulated and in this respect frequently described characteristics of second primary lung cancer in the literature are: solitary lesion, central (endobroncheal) localization in the lung and interval of more than three years between primary HNSCC and secondary primary lung cancer. However, none of these criteria are absolute.

Like in adenocarcinoma, small cell carcinoma or a large cell undifferentiated carcinomas, histology can help to differentiate if from primary head and neck squamous cell carcinoma. Since two thirds of the second primary lung carcinomas are squamous cell carcinomas and only 18-23% adenoarcinomas, histological differentiation is only possible in a minority of cases. This relatively high proportion of squamous cell carcinomas in second primary lung carcinoma in HNSCC patients is understandable in view of the common etiologic factor of continued tobacco abuse but it hampers correct classification of these lesions. Promising results have been obtained by comparing tumor pairs on the more detailed DNA level, using molecular analysis.

Clinical Diagnosis

Among HNSCC patients with advanced stage disease and without loco regional control, metastases are a natural evolution of the primary tumor. In curatively treated patients, both distant metastases and second primary carcinomas may develop over time. It may be expected that this last group would benefit from follow up after treatment for their primary HNSCC assuming cure from their secondary cancer.

Pulmonary follow-up for detection of secondary lesions can be performed in many ways: chest X-ray, Computed Tomography (CT-scan), Positron Emission Tomography (PET-scan), bronchoscopy, brushes, cytology etc. For a long period of time, chest X-ray has been used as a standard procedure for cost effectiveness and easy accessibility. Although specificity is high, its sensitivity in screening for lung malignancies is rather low (~35%). CT scan has proven to be more
accurate in detecting lung cancers. In the early Lung Cancer Action Project, CT detected almost 6 times as many stage I cancers as chest X-ray.\textsuperscript{58} Some recent studies reported high diagnostic accuracy also in \textsuperscript{18}F-FDG PET/CT in HNSCC patients, but high cost and low specificity are disadvantages for screening.\textsuperscript{26,57,59,60-62}

When secondary pulmonary malignancy is suspected on imaging, diagnosis should be confirmed by cytology or preferably by histology, either by CT guided biopsy, or fine needle aspiration or by bronchoscopy (washings, biopsies or brushes).

**Screening for secondary pulmonary malignancy**

Screening for secondary pulmonary malignancies in patients curatively treated for HNSCC is a heavily debated issue. Relevant scientific data are lacking. In the broader field of lung cancer screening, none of the randomized trials have demonstrated a reduction in overall mortality as a result of early detection of lung carcinoma.\textsuperscript{63} Furthermore, screening trials that use survival as an endpoint are subject to biases such as lead-time bias, length-time bias and overdiagnosis.\textsuperscript{64-66}

Lead-time bias refers to the ‘extra’ time in the preclinical period: it concerns the interval between the moment in time that the disease is detectable (and may be found by screening) and the time signs or symptoms occur. (Figure 1) The amount of lead time gained by screening is ‘extra’ compared to when survival is measured from the time of diagnosis by signs or symptoms and is also conditional to the coincidental selected screening moment and the time the disease is detectable by a specific screening method. Adjusting for lead-time bias is difficult because it is unknown and variable.

![Figure 1. Lead time bias. With screening the survival is advanced by lead time. The earlier the disease is detected: the longer the survival. Without screening the survival is measured from signs or symptoms.](attachment:image.png)
Length-time bias depends on the growth rate of the disease. Tumors with a slow growth rate have a higher chance to be detected by screening, as they are detectable over a longer period than fast growing tumors. (Figure 2) CT screening will present an over-representation of slowly growing tumors and an under-representation of rapidly growing tumors. In case of post treatment screening of HNSCC patients, there is a chance that second primary adenocarcinomas of the lung will be more frequently detected than for example metastatic squamous cell carcinomas, as the latter tend to have a more rapid growth.

Detection of preclinical disease that does not progress or even regress may lead to overdiagnosis. Another type of overdiagnosis refers to detection of preclinical disease that progresses, but not rapidly enough to produce signs or symptoms, before the individual dies from competing causes. This is most prevalent among individuals with slowly-growing tumors and short life expectancies because of age or co-morbidity. Lead-time bias, length-time bias and overdiagnosis contribute to an inappropriateness of survival measurements in screening trials. Other problematic aspects of screening are false positive screening results and costs. False positive screening may result in unnecessary invasive diagnostic procedures, including surgery.
Conclusions of reports on radiologic screening during follow up of HNSCC patients are discordant. Some suggest a survival benefit in screened populations or in patients treated for screen-detected secondary pulmonary malignancies.18-22,67,68 Others did not find a difference in survival or disease specific mortality for both symptomatic and asymptomatic patients, despite regular chest x ray screening.31,69,70 They conclude that survival is more dependent on the biological behavior of the tumor and co-morbidity than on the mode of detection.69 Large international randomized trials on lung cancer screening by CT are ongoing. Arguments for CT screening are its sensitivity, non-invasiveness, fast processing and low radiation dose (0.8-3.2 mGy).71 The (cost-) efficiency of screening seems to be more favorable for individuals with a high risk of developing a pulmonary malignancy. Johnson et al noted a 10-fold greater risk of a new primary tumor in smokers with a history of previous lung cancer.72 Schwartz et al found a 5-year incidence for developing second primary metachronous cancer (head and neck, lung and esophagus) of 3% in non-smokers and 26-42% in smokers treated for head and neck cancer.23 It may therefore be argued that the high risk of secondary pulmonary malignancy in head and neck cancer patients may render screening more (cost-) effective.35 Another argument favoring (CT) screening is the limited chance of curability in case of symptomatic (often advanced stage) lung cancer.73,74 Less than 10% of patients whose lung cancer was detected by the development of symptoms, had stage I disease.75 Many of those patients with early stage NSCLC can receive curative treatment by surgical resection or (stereotactic) radiotherapy.73,76,77 As Pastorino reported, Spiral CT may identify many more potentially curable pulmonary malignancies in high-risk individuals. More than 80% of stage I tumors were found in a group of high risk individuals (age: 50 years or older; smoking history: 20 pack years or more) with a resectability rate of 96%.78 Since there is no evidence yet that post treatment screening in HNSCC patients reduces mortality, clear recommendations concerning screening are difficult.

Treatment of secondary pulmonary malignancy

Survival of patients with metastases of head and neck carcinoma without treatment is poor. Only 7% of patients survive more than one year.79 Primary lung cancer patients with stage I disease who refuse surgery were found to have a 5–year survival rate of 10 % (70% after surgery).80 For medically healthy patients, surgery remains treatment of choice in case of resectable secondary pulmonary malignancy. Reported mortality rates range from 0-4% and morbidity rates range from 10-17%.67 Favorable results largely depend
on careful selection of surgical candidates. This implies complete work up to assure that the secondary tumor is either an early-stage second primary cancer or oligometastatic disease. It is important to exclude extra thoracic disease or loco regional recurrence of the primary HNSCC.\textsuperscript{19} Many factors are thought to have impact on survival in patients with resection of secondary pulmonary malignancy, as the disease-free interval between index tumor and the secondary lung lesion(s), and the number of resected lesions.\textsuperscript{18,20,22} These factors reflect the biological aggressiveness of the tumor.

Site and stage of the primary head and neck cancer may influence survival after resection of secondary pulmonary malignancy as well. Nibu et al.\textsuperscript{19} and Mazer et al.\textsuperscript{22} reported that patients with squamous cell carcinoma of the oral cavity had poorer prognosis after surgical intervention of secondary pulmonary malignancy, than patients with primary HNSCC at other sites. Some report that nodal stage is of influence\textsuperscript{20,22}, but other reports find no correlation.\textsuperscript{18,67} The histology of the secondary pulmonary malignancy is also of importance, for biological behaviour and survival. For example, resection of adenoid cystic carcinoma in the lung is associated with far better survival probability than secondary pulmonary squamous cell carcinoma.\textsuperscript{18,20,81}

As mentioned above, many factors are thought to influence survival in patients with resection of secondary pulmonary malignancy in curatively treated HNSCC patients. Screening for secondary lung lesions as well as differentiation of these lesions and selection for treatment is therefore subject for serious scientific discussions.

**Aim and brief outline of thesis**

To address the major questions regarding diagnosis, differentiation, screening and survival of patients with secondary lung malignancies, we evaluated available data of head and neck cancer patients treated at The Netherlands Cancer Institute / Antoni van Leeuwenhoek Hospital (NKI/AVL). Pulmonary screening for secondary lung lesions has been part of a structured follow-up program of head and neck cancer patients for more than 30 years and forms the basis of this thesis.

Chapter 1 summarizes literature data on epidemiology of secondary lung lesions occurring after head and neck cancer treatment, clinical differentiation between metastasis and secondary pulmonary malignancy and screening. Chapter 2 describes the development of a molecular method to differentiate between metastasis and second primary lung cancer following curative treatment of head.
Introduction

and neck squamous cell carcinoma. In a series of 44 patients an algorithm for analysis of LOH (loss of heterozygosity) patterns is developed and placed in perspective against clinical and histological criteria. Chapter 3 uses TP53 mutation analysis for validation of the LOH algorithm. Chapter 4 describes survival characteristics after the LOH classification of lung resection or biopsy specimens of 36 patients, curatively treated for HNSCC. Chapter 5 deals with the clinical outcome of 63 patients, which were treated over the last three decades, with resectable secondary pulmonary malignancies after curative treatment for head and neck cancer. Chapter 6 focuses on the psychological impact of annual post-treatment screening of HNSCC patients for second primary pulmonary malignancy in a cohort of 106 patients. In chapter 7 the feasibility of a screening trial is methodologically and statistically analyzed based on the prevalence of head and neck cancer and expected lung lesions in the Netherlands. The thesis ends with a general summary and concluding remarks in Chapter 8.

References

Chapter 1


Project: overall design and findings from baseline screening