Secondary lung lesions after head and neck cancer: Diagnosis, differentiation, screening, survival
Geurts, T.W.

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Chapter 7

Screening for lung cancer after curative treatment of head and neck squamous cell carcinoma?

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Screening for lung cancer after curative treatment of h&n squamous cell carcinoma?

Abstract

Whether pulmonary screening for second primary lung cancer after curative treatment for head and neck cancer (HNC) is meaningful, is a heavily debated issue. The objective of this report was to review screening strategies and to explore the conditions and possibilities of running a randomized trial on pulmonary screening after curative treatment for HNC.

Review of the available literature and as well as population-based data from the regional cancer registry were used to provide feasibility information. A screening tool should ideally be inexpensive, commonly available and patient-friendly. Chest X-ray has been shown unreliable and detects less than half of malignant lesions. CT and PET/CT are able to detect many more pulmonary lesions than chest X-ray, but false-positives and overdiagnosis are major problems. Due to much higher cost, use of PET screening will certainly be not appropriate at this time. Using the most realistic option, which would be CT screening, the evidence available thus far suggests that the mean gain in life expectancy, if any, is small and will most probably not exceed 1-2%.

It is doubtful that post-treatment CT screening will be cost-effective for patients who have been curatively treated for head and neck cancer. Our conclusion is that, unless wide international collaboration is established providing swift accrual, a properly designed randomized controlled trial does not seem to be feasible.
Introduction

Although many (patient information) websites state that all cancer survivors should have follow-up care, the intention is often unclear. Follow-up care can be important to address ongoing problems due to cancer or its treatment, and to check for physical and psychosocial effects after treatment ends. However the implication of early detection of other types of cancer or recurrence is questionable.

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide, with over 600,000 new cases per year. Survival figures have not improved considerably over the past two decades despite newer aggressive surgical and chemotherapeutic regimens.1,2 A considerable number of patients develop a second primary carcinoma in the oropharyngeal cavity, lung or esophagus. Within a time span of 5 years after treatment, 10-20% of patients are diagnosed with a secondary cancer in the aerodigestive tract.3-7 Besides, depending on initial tumor stage, 5-20% of patients will develop distant metastases, of which the majority occurs in the lungs.8-10 The development of (second primary) lung malignancy has a profound impact on survival of head and neck cancer patients and more adequate interventions and treatment may improve outcome considerably.

Although evidence for survival benefit is lacking, chest X-rays have been part of follow-up programs of head-and-neck cancer patients for many years. Trends of better overall survival in asymptomatic patients have been suggested in selected patients, if lung lesions were detected at an early stage.11,12 In the absence of data from adequately controlled trials, the usefulness of lung imaging follow-up in head and neck cancer patients is questionable. Secondly, the method of pulmonary screening by chest X-ray is imperfect and other methods of screening (like CT, PET/CT) should be considered. The objective of this report was to evaluate the available methods (chest X-ray, CT or PET/CT) for pulmonary screening and explore the conditions and possibilities of running a controlled trial on pulmonary screening strategy after curative treatment for HNSCC.

Methodology

Study designs
Screening in this population of patients with HNSCC can be defined as the systematic testing of those who are asymptomatic with respect to pulmonary (or esophageal) malignancy. The purpose of screening is to prevent, interrupt, or
delay the development of advanced disease in the subset with a preclinical form of the target disease through early detection.\textsuperscript{13} There are important differences between screening for preclinical cancer and the diagnosis of clinically overt cancer.\textsuperscript{14} In the case of diagnosis, patients being evaluated are symptomatic and are seeking help from medical providers. In the case of screening, the individuals being tested are asymptomatic and are being told that they should be screened to avert an avoidable cancer death. Because of these differences, the burden of proof for the effectiveness should be higher for screening interventions than for diagnostic and treatment interventions in those who are symptomatic. Randomized controlled trials are particularly appropriate for screening because they eliminate early-detection biases and the potential for confounding by variables associated with access to screening. Due to lead time bias and length time bias, survival from the target disease can be misinterpreted easily.\textsuperscript{15} As shown in Figure 1 and 2, the effectiveness of screening can only be evaluated in adequately controlled trials with survival from the time of random assignment to a follow-up strategy (with or without screening).

**Endpoints**

In studies of cancer screening, disease-specific mortality is often used as endpoint, but the validity of this endpoint is strongly dependent on the assumption that causes of death can be accurately determined. Misclassification in this respect may lead to either over- or underestimation of screening effectiveness.

![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.](#)
Since exact classification of mortality is often difficult in this population of patients, all-cause mortality should be used as endpoint, which depends only on the accurate determination of deaths and when they occur. Furthermore, although a statistically significant effect on all-cause mortality may be unlikely with screening (because the target disease usually is responsible for only a small proportion of all deaths), it is useful to examine all-cause mortality along with disease-specific mortality for other reasons. First, examination of all-cause mortality may reveal major deficiencies in a study, such as flaws in the randomization or ascertainment of vital status. Second, examination of all-cause mortality helps ensure that a major harm or benefit of screening is not being missed. Third, examination of all-cause mortality puts the magnitude of expected benefits from screening into an appropriate perspective for decision making.\textsuperscript{16,17}

**Screening tools**

Data for this review were identified by searches of MEDLINE, PubMed, and references from relevant articles using combinations of search terms “head and neck cancer”, “lung cancer”, “pulmonary lesions” and “screening”. Since radiological and metabolic imaging techniques have progressed considerably, only relevant papers published in English from the last decade were included.
Review of screening tools

Many authors have evaluated several techniques (chest X-ray, sputum cytology, CT scanning of the chest, PET/CT or triple endoscopy) for pulmonary screening in head and neck cancer patients (Table 1).\textsuperscript{5,10,11,18-35} Detection of lung lesions is highly dependent on the method used for screening. On the other hand, a screening tool should ideally be inexpensive, commonly available and patient-friendly. The question is which diagnostic tool would be most appropriate for screening for curable new cancer manifestations in head and neck cancer patients.

Chest X-ray has been shown unreliable and detected less than half of malignant lesions in the lung cancer screening projects.\textsuperscript{36} In studies concerning HNSCC patients, sensitivity of chest X-ray was very low (Table 1), i.e. between 28 and 36%.\textsuperscript{10,18,22,25,35} Whereas detection of malignant lesions is inadequate, the specificity of chest X-ray is high (93-99%).\textsuperscript{25,28}

Sputum cytology has been used as a supplement to bronchoscopy and to annual chest x-ray. Twice-yearly bronchoscopy and sputum cytology in patients with laryngeal cancer was reported to be both ineffective and unpleasant.\textsuperscript{37} The addition of sputum cytology to chest x-ray has not been specifically studied in head and neck cancer patients, but two randomized trials were unable to demonstrate a lung cancer mortality reduction in populations of heavy smokers.\textsuperscript{38}

Within these data, especially squamous cell cancers were detected by sputum cytology. For innovative sputum tests using polymerase chain reaction (PCR) based assays (which can detect a few clonal cancer cells containing a specific DNA mutation, microsatellite alteration, or CpG island methylation among an excess background of normal cells), no data on screening are available yet. Although CT scanning can detect many more stage I lung cancers than chest radiography, and most of those suspect lesions measure ±1 cm in greatest dimension, the number of lesions to be evaluated is also much higher.\textsuperscript{15,39}

A number of studies in HNSCC patients reported results of CT-screening (Table 1) using varying techniques of sectioning and contrast-enhancement. CT scan of the chest showed abnormalities in approximately 20% of patients with HNSCC.\textsuperscript{10,18,19,22,25-29,33,35,40} These were proven to be malignant in around 15% of these patients, either by radiological progression during follow-up or by biopsy.\textsuperscript{10,18,19,22,25-29,33,35,40} The positive predictive value (PPV) was in the order of 60%.\textsuperscript{10,18,19,22,26-29,35,40} Sensitivity may be estimated around 80%, but could be much lower.\textsuperscript{10,19,22,27}
<table>
<thead>
<tr>
<th>Author</th>
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<th>Methods</th>
<th>n</th>
<th>imaging abnormalities</th>
<th>meta2nd/primary</th>
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<th>sensitivity</th>
<th>specificity</th>
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<th>NPV</th>
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<td>11</td>
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<td>5</td>
<td>4.9%</td>
<td>100%</td>
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</tbody>
</table>

| methods   | follow-up with or without screening method |
| n         | number of patients in report             |
| imaging abnormalities | number of patients with abnormal scans |
| meta2nd/primary | number of patients with malignant lesions (either metastasis or second primary) |
| 2nd primary | number of patients with second primary lung cancer |
In the evaluation of screening tests, screen detected cases are considered true-positive and interval cases - those that are not detected at screening but diagnosed by other means during the interval between screens - are considered false-negatives. Since few studies had adequate follow-up of patients with negative CT scans or performed repeat scans after 3-6 months, false-negative cases may not have been discovered and sensitivity may have been overestimated.

Of the detected malignant lesions (15%), at least 5% were classified as second primary lung cancer.\textsuperscript{10,18,19,22,27,28,33,35,40} There is probably some underestimation of this percentage, because only a minority of lesions was characterized using histological biopsy and molecular pathology. When analysis by loss of heterozygosity (LOH) or mutation status (TP53, p53) was used to classify malignant lesions as distant metastasis or second primary lung cancer, roughly half of the malignant pulmonary nodules in HNSCC patients were categorized as second primaries.\textsuperscript{41}

Positron emission tomography (PET), without or with combination with CT (PET/CT) may also be used for screening purposes, although this technology is expensive and is not currently available in every hospital. PET/CT picks up even more abnormalities than CT alone, on average 25-35\%.\textsuperscript{23,24,34} Some lesions were benign or inflammatory, 20-25\% was reported to be malignant including mediastinal lymphadenopathy, either by radiological progression or pathologic confirmation. The sensitivity of PET/CT may be somewhat higher than CT alone, but the available literature reported insufficient data for reliable estimation.\textsuperscript{42} The negative predictive value was reported to be high, in accordance with PET studies in other patient populations.\textsuperscript{43} The positive predictive value was reported to be around 60\%.\textsuperscript{24,43}

Pulmonary screening

\textbf{Assumptions on incidence and survival}

Based on the available literature, malignancy in the lungs will occur in 10-15\% of HNSCC patients.\textsuperscript{3,11,19,31} These lesions are either metastasis or second primary lung cancers. The incidence of pulmonary metastasis depends on the primary HNSCC tumor stage and is higher in patients with locoregionally advanced tumors.
Based on our own data\textsuperscript{12,41}, approximately half of screen-detected lesions are second primary lung cancers (thus 5-10\%). Surgical treatment of limited pulmonary disease (either resectable NSCLC or limited metastatic disease) was associated with favorable survival (5-year survival approximately 30\%).\textsuperscript{12,44-47} Only a limited proportion of patients with secondary lung lesions are eligible for thoracic surgery. In our series of HNSCC patients who were followed in a standardized program with yearly chest X-ray imaging, approximately 2\% of the total population of patients underwent surgical treatment for pulmonary malignancy.\textsuperscript{46} This figure is compatible with reports from other institutions.\textsuperscript{21,44,47}

Patients diagnosed with advanced second primary NSCLC or with widely disseminated disease after primary HNSCC obviously have a bad prognosis and 5-year survival is estimated at 2-7\%.\textsuperscript{3,49} In screened populations, a mix of early-stage and advanced second primary malignancies are diagnosed. Data on survival in screened populations are scarce; 5-year survival may be estimated at 15-20\%.\textsuperscript{4,11,31}

As chest X-ray has very low sensitivity, CT screening will pick up at least 2-3 times as many potentially curable lesions (either early stage NSCLC or oligometastatic disease).\textsuperscript{39} Furthermore, for slowly progressing lesions, CT on one occasion will probably identify lesions that would only become evident on chest X-ray several years later. At this time, screening by PET does not seem reasonable, due to insufficient data on overdiagnosis risks and much higher cost.

**Statistical considerations**

The intention was to explore the conditions of running a controlled trial on a pulmonary screening strategy using spiral CT instead of yearly X-ray after curative treatment for HNSCC. Sample size is dependent on several variables: the disease-specific mortality in the eligible population (mortality from HNSCC vs. pulmonary malignancy), the effectiveness of screening in reducing mortality from pulmonary malignancy, the duration and follow-up of the intervention, the compliance in each group, and the desired significance (\(\alpha\)) and power (\(\beta\)) levels.

Based on the results discussed above, it was assumed that in 10-15\% of patients treated with curative intent for head and neck squamous cell carcinoma, 2\textsuperscript{nd} primary tumors would develop in the aerodigestive tract, esophagus or lung, for which a curative therapy would be available, given early detection.

For early detection based on either follow-up including spiral CT after 6 months of completion of HNSCC treatment (screening strategy) or follow-up without imaging (standard strategy), the following \(H_0\) and \(H_1\) hypotheses were made:
Screening for lung cancer after curative treatment of h&n squamous cell carcinoma?

H₀: Screening with spiral CT (after 3 months) has no added value (see endpoint)

H₁: The new screening strategy could provide a relative improvement of survival in about 10-15% of patients compared to the standard situation.

With the new method, the following assumptions on improvement in survival are suggested:

Screening strategy: 50% ‘curative’ at detection with a 5-year survival of 30%
50% palliative at detection with a 5-year survival of 5%

Standard situation: 10% ‘curative’ at detection with 5-year survival of 30%
90% palliative at detection with a 5-year survival of 5%

These assumptions translate, in the relevant group of patients (10-15% with 2nd primary), to 5-year survival estimates of 17.5% and 7.5% for the new screening strategy compared to the standard strategy respectively (or a hazard ratio of 0.673). To detect such an improvement with a sufficient power (e.g. 80%), 200 events should be observed (in this case disease specific deaths).

Sample size
To detect the difference in survival given these considerations with an accrual of 5 years and a follow-up of 10 years, 200 events would be required (corresponding to an enrollment of 106 relevant patients in each group) to provide 80% power (two-sided alpha 0.05). However, during the period of follow-up patients are at risk for other events and may not be evaluable for the early detection and subsequent therapy at stake. Assuming a drop-out rate of 15% annually, which actually means that after 5 years about half of the population is still at risk for the relevant event, 140 patients are required in each group (instead of 106). Again, assuming that in about 10% of the population a second primary malignancy would be detected early, these figures imply that the full population-to-be-screened should be 10 times bigger or consisting of 1400 patients in each group (2800 in total; 560 patients/year).

In this specific population of HNSCC patients, participants in a RCT on screening for second primary pulmonary malignancy must be asymptomatic with respect to the target cancer. In addition, participants should be healthy enough to undergo further evaluation of a positive screening CT and treatment for disease if it is eventually diagnosed, and should be likely to survive the duration of the study if they are cured. Finally, participants must be willing to be randomly assigned and to comply with the screening regimen and follow-up. Since a number of HNSCC
patients with a history of tobacco and alcohol abuse have psychosocial problems and comorbidities as restricted pulmonary function and cardiovascular disease, only a limited fraction of HNSCC patients will be eligible for such a trial. The incidence of invasive cancer of the oral cavity, oropharynx, hypopharynx, nasopharynx, sinuses and larynx in the Netherlands was 2157 in 2005\textsuperscript{50,51}. Of those patients, more than 30% were older than 70 years at diagnosis of HNSCC. It is estimated that approximately 70% of patients \( \leq 70 \) years would be eligible for a screening trial and that a proportion of around 50% of these patients would be willing to be randomly assigned to screening or not, to comply with the screening strategy and follow-up of their health. Thus, with a potential accrual of 400 patients per year in the Netherlands, the study would need to be open for at least 7 years, resulting in a total sample size of 2900 (compared to 2800).

In case the "early detection" would occur in 15\% instead of 10\%, then about 1900 patients would be required in total. On the other hand, if "early detection" would occur in only 5\% instead of 10\% of the screened population, more than 5000 patients would be required in total.

As the 5-year overall survival of HNSCC patients is approximately 37\% and the median survival 3.5 years, the ‘drop-out rate’ may likely be more close to 20\% in this group. In that scenario more than 3000 patients would be required at a 10\% manageable events incidence and more than 2030 in case of 15\% ‘manageable events’. With an accrual rate of 400 patients per year into the randomized trial, enrollment for such a study would take at least 5-8 years.

Discussion

Second primary cancer in the aerodigestive tract is a major problem in head and neck cancer affecting at least 10-15\% of the curatively treated patients within 5 years\textsuperscript{3,4,6,11,19,31}. Early detection of these lesions in asymptomatic patients may be important, as a potential gain in identification of early-stage second primary lung cancers for which a curative therapy would be available, could improve the prognosis of these patients. However, evidence is lacking that routine imaging improves life expectancy or quality of life. Awaiting the benefits, harms and costs of ongoing RCT’s (NLST, NELSON, Dante, and DLCST) on lung cancer screening, national authorities as the U.S. Preventive Services Task Force (USPSTF) and the National Institute for Clinical Excellence (NICE) do not recommend routine screening for pulmonary malignancy\textsuperscript{52-54}. 

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Head and neck cancer patients have an even higher risk of developing pulmonary malignancy as compared to persons (smokers and former smokers) included in lung cancer screening trials. Chest X-ray has been used as a yearly or half-yearly screening tool for secondary pulmonary malignancy in many institutions worldwide. However, chest X-ray has been shown unreliable and detects less than half of malignant lesions.\textsuperscript{10,18,22,25,35,36} CT and PET/CT are able to detect many more pulmonary lesions than chest X-ray, but overdiagnosis could be a major problem. Particularly the high numbers of false-positive test results and consequences have illustrated the potential pitfalls of CT screening. Abnormal scans may lead to follow-up examinations with intravenous injection of contrast medium, invasive testing, including percutaneous needle biopsies or even surgery, in addition to increased anxiety. These procedures are associated with mortality and morbidity, anxiety, lost productivity, and medical and nonmedical costs. Thoracic surgery for benign disease is not necessarily benign.\textsuperscript{55} Overdiagnosis also relates to detection of preclinical disease that does not progress, as in low-grade bronchoalveolar lesions,\textsuperscript{56} and to the detection of preclinical disease that progresses but not rapidly enough to produce any signs or symptoms before the individual dies from competing causes.\textsuperscript{15} The later type is most prevalent among individuals with slow-growing tumors and short life expectancies caused by age or comorbidity. This downside particularly relates to screening for lung malignancy in HNSCC patients because a substantial proportion of screened lungs cancers have long doubling times\textsuperscript{57} and HNSCC patients (with history of tobacco and alcohol abuse) have high levels of competing mortality.

Costs and use of (limited) health care resources are also major issues. It is doubtful that post-treatment CT screening will be cost-effective for patients who have been curatively treated for head and neck cancer. In selected patients with previously resected stage IA NSCLC, the cost of surveillance CT was 47,676 dollars per QALY gained.\textsuperscript{58} However, factors that rendered surveillance CT cost ineffective were (1) age at entry into the surveillance program $\geq$65 years, (2) cost of CT greater than 700 dollars, (3) incidence of SPLC of less than 1.6\% per patient per year of follow-up, and (4) a false positive rate of surveillance CT greater than 14\%. Due to much higher cost, use of PET screening will certainly be not appropriate.

Ethical considerations primarily relate to smoking habits. The risk of lung cancer mortality can be reduced more effectively by quitting smoking than by screening. Furthermore, a true-negative outcome of screening may be interpreted as
sanctioning an unhealthy lifestyle (i.e. smoking), which may cause disease in the future. In the Danish Lung Cancer Screening Trial quit rates were higher among subjects with CT abnormalities that necessitated further evaluation.

To illustrate how the prevalence of disease, the sensitivity and specificity of screening CT, drive the trade-offs, we can consider the following estimations. In HNSCC patients, pulmonary malignancy may have an estimated prevalence of 10%. The screening CT has a sensitivity of 80% or less and a specificity of 90%. If 1,000 individuals are screened, we can expect 80 true-positive outcomes and 90 false-positive outcomes. For every case detected, at least one other patient will undergo further unnecessary testing, experience associated anxiety, and induce costs. In case of a lower prevalence, e.g. 5%, for every case detected more than 2 other patients will undergo unnecessary testing (ratio 1: 2.4).

The evidence available thus far suggests that the mean gain in life expectancy would be very small. If a CT screening strategy could indeed provide a relative improvement of survival of 10% in about 10-15% of patients compared to no screening, the overall survival benefit will not exceed 1-2%. However, potential harm due to false-positive testing and overdiagnosis is real and precludes adopting pulmonary CT screening for HNSCC patients on a wide scale. A randomized trial in this group of patients is the only option to elucidate the issue of usefulness of pulmonary screening. The international community of head and neck cancer surgeons should decide if this potential limited survival benefit justifies a collaborative RCT accruing at least 3000 patients.

On the other hand, it may be more effective to invest in antismoking programs or to evaluate other screening methods, such as PCR-based sputum tests and analysis of exhalation volatile compounds (eNOSE) (possibly combined with CT as the second step). If such (combination of) tests would prove to more accurately detect malignancy, this may be a better alternative for screening high-risk individuals.

References


Screening for lung cancer after curative treatment of h&n squamous cell carcinoma?


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