Secondary lung lesions after head and neck cancer: Diagnosis, differentiation, screening, survival
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Citation for published version (APA):

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Summary

Chapter 1
Patients surviving HNSCC are at considerable risk of developing second primary lung carcinoma or pulmonary metastases. Percentages of second primary lung cancer range from 23% to 30% of all secondary malignancies in HNSCC patients and pulmonary metastases account for 66% of all distant metastases, with an incidence of 1.6 to 25% depending on tumour stage. Due to tobacco abuse, patients with a history of laryngeal cancer are at the highest risk of developing second primary carcinoma in the lungs.

Chest X-ray imaging has been used for a long period of time as a standard procedure to detect secondary lung malignancies, even though sensitivity remains low. Although more sensitive, CT scan has a low specificity in detecting secondary lung cancer. Spiral-CT can identify very small lung cancers in high-risk individuals, with a resectability rate of 96%. \(^{18}\)F-FDG PET/CT is even more sensitive, but specificity is relatively low. Differentiation of lung lesions (second primary lung carcinoma vs metastasis) on the basis of clinical criteria is unreliable, which creates a considerable need for more specific diagnostic methods, like new imaging modalities or advanced molecular biological techniques on pre-treatment tissue specimens, ideally obtained by minimally invasive procedures.

Despite improvements of imaging techniques, the value of screening for secondary lung lesions in HNSCC patients is still questionable. Screening is mainly driven by very limited chances of cure of symptomatic (secondary) lung cancer due to presentation as advanced stage of disease. Important points in the screening discussion are reliable differentiation between second primary lung cancer and metastases, together with evaluation of survival characteristics. Furthermore, it addresses the need of testing the feasibility of a prospective randomized controlled clinical concerning the value of screening for secondary lung carcinoma.

Chapter 2
Similar histologies of primary head and neck and lung squamous cell carcinoma make it difficult to differentiate between second primary lung cancer and metastatic disease. Of 44 patients with secondary lung carcinoma, lesions were analyzed and distinguished by molecular biological techniques determining loss of heterozygosity (LOH). We used 12 markers on 11 chromosome arms in the LOH analysis. For interpretation of the LOH results a novel decision algorithm was
developed, based on biological insight and on our observation that multiple LOH on different chromosome arms are not independent. Clinical scoring (stage of the primary HNSCC, loco regional recurrence free status at time of pulmonary lesion, radiological presentation of the lung lesion and time interval between HNSCC and secondary lung carcinoma) suggested 38 patients with metastases and 6 with second primaries. LOH analysis indicated metastatic disease in 19 cases and second primary SCC in 24 cases (in one case LOH analysis was inconclusive). For 25 patients LOH supported the clinical scoring and in 18 cases it did not. These 18 discordant cases were all considered to be second primary tumors by LOH analysis. This analysis demonstrates that a considerable number of lung lesions (in this study 50%) clinically interpreted as metastases, are suggested to be second primaries by LOH analysis.

Chapter 3
Chapter 2 showed that clinical and histopathological criteria are unreliable for differentiation between second primary lung cancer and metastasis, while patterns of allelic loss (LOH) might be more useful. TP53 mutation analysis was used for validation of an allelic loss marker panel and the LOH decision algorithm (see also chapter 2). Tumor pairs of 39 patients were analyzed for p53 mutations and for patterns of allelic loss using 12 microsatellite markers on 11 chromosome arms. Results were related to immunohistochemical p53 expression. Distant metastases were diagnosed in 15 cases and second primary tumors in 23 cases indicated by LOH (Loss of Heterozygosity) analysis. In one case LOH analysis was inconclusive, TP53 mutation analysis was informative in 15 cases of 39 analyzed. Based on the p53 mutation status alone, nine tumors were diagnosed as second primaries and six as distant metastases. In all 15 cases the LOH analysis was in concordance with the TP53 mutation analysis. The immunohistochemical analysis of p53 expression could be completed in 25 patients with 5 being diagnosed as second primary tumor (SPT). All 5 cases were also identified as SPT’s by LOH analysis. We concluded that the TP53 mutation data validate the suitability of the LOH marker panel and decision algorithm for differential diagnosis of DM and SPT in the lung. LOH analysis can theoretically be exploited in almost all cases and is less laborious than TP53 mutation analysis. In 20 % (5 out of 25) of the cases the correct diagnosis SPT could be diagnosed using immunohistochemical analysis as single read-out. Based on this data we present a novel algorithm for differential diagnosis of lung cancer in treated head and neck cancer patients.
**Chapter 4**

This chapter describes the survival characteristics of patients with molecularly defined lung lesions after curative treatment for HNSCC. Therefore lung resection or biopsy specimens of 36 patients, curatively treated for HNSCC between 1978 and 2002, were defined as second primary squamous cell lung cancer or metastasis by LOH analysis. Twenty-two of them underwent surgical resection, resulting in a median overall survival of 23.1 months for second primary lung cancer (SPLC) (n=14) and 25.1 months for lung metastases (n=8). Fourteen patients, SPLC (n=6) and metastases (n=8), did not undergo surgical resection and their median overall survival was 3.7 and 4.4 months respectively. Our data suggest that survival after resection of metachronic lung lesions following curative treatment of HNSCC is similar for lesions characterized as second primary squamous cell lung cancer and those characterized as metastases.

**Chapter 5**

The aim of this study was to evaluate a single institutional experience with resection of metachronous pulmonary malignancy in patients treated for squamous cell carcinoma of the head and neck (HNSCC). In the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, sixty-three consecutive patients, curatively treated for HNSCC, underwent surgical resection for malignant lung lesions between 1978 and 2006. Patient, treatment and outcome characteristics were retrieved from hospital dossiers. In 63 patients, 35 lobectomies, 4 pneumonectomies and 24 wedge resections were performed. Fifty-one patients (81%) having one lung lesion, the rest having multiple lesions (range 2-7). Median overall survival for the total group being 22.2 months. For pulmonary squamous cell carcinoma (n=52) 3-year survival was 35% (95% confidence interval 22-48) and for resected adenocarcinoma (n=10) 50% (95% confidence interval 18-75). Overall 5-year survival was 30% (95% confidence interval 19-42). In selected asymptomatic patients, curatively treated for HNSCC, resection of secondary pulmonary cancer is associated with favorable long-term overall survival, especially for adenocarcinoma lesions.

**Chapter 6**

The issue of psychological distress for the individual patient has been used to argue against routine radiological follow-up in curatively HNSCC patients. To substantiate this assumption we have investigated the psychological impact of annual lung cancer chest x-ray screening in a cohort of patients curatively treated for HNSCC. This cohort of one hundred and six patients consisted of 68 men and
Chapter 8

38 women, with a mean age of 56. The impact of the yearly chest radiograph was evaluated by means of a nine item questionnaire which was completed prior to the result of the radiograph. Remarkably, ninety percent of the patients were in favor of annual post treatment screening, 2% would not like to receive this screening and 8% had no preference. A majority (98%) considered the screening as an extra medical check and 76% felt re-assured. Although 21% of the patients were very nervous about the outcome of the screening, only 3% wanted to avoid the yearly chest x-ray for this reason. Annual post treatment screening of HNSCC patients for second primary lung cancer and metastatic recurrence caused no major burden for head and neck cancer patients. These results suggest that a screening program including thoracic imaging may psychologically be justifiable for this group.

Chapter 7

The issue of screening for secondary lung lesions in patients curatively treated for HNSCC is heavily debated. 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 after curative treatment for HNSCC. Therefore, a review of the available literature, as well data from the Dutch Cancer Registry was used to provide feasibility information. Although inexpensive, sensitivity of chest X-ray has proven to be very low (35%) detecting less than half of malignant lesions. CT and PET/CT are able to detect many more pulmonary lesions than chest X-ray, but false-positive findings and overdiagnosis emerge as major problems.

As the 5-year overall survival of HNSCC patients is approximately 37% and the median survival 3.5 years, in a randomized screening trial, the ‘drop-out rate’ would be close to 20%. Estimating that a new CT screening strategy could provide a relative improvement in survival for 10-15% of patients compared to the standard situation, 2000-3000 patients would be required. With a maximal estimated accrual rate of 400 patients per year in the Netherlands, enrollment for such a study would take at least 5-8 years.

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%. Therefore it is doubtful that post-treatment CT screening will be cost-effective for patients who have been curatively treated for head and neck cancer. Due to much higher cost, use of PET screening will certainly be not appropriate. Our conclusion is that, unless wide international
collaboration is established providing swift accrual, a randomized screening trial does not seem to be realistic.

Concluding remarks

This thesis demonstrates that clinical criteria are not appropriate for the differentiation of metastases and second primary lung cancer after curative treatment of head and neck cancer. We could demonstrate a more reliable distinction between these two clinical entities using LOH techniques (see chapter 2), with also the possibility to use immunostaining for P53 mutation as a first scan to diagnose a second primary lung cancer (as described in chapter 3). Although it has been hypothesized that early-stage second primary lung cancer gains better results by surgery than lung metastases, we were not able to prove a survival difference between the two molecularly defined groups of patients with resectable lesions.

The five years survival of 30% after resection of isolated secondary lung lesions in patients curatively treated for head and neck carcinoma is a result of a longstanding follow-up protocol and careful multidisciplinary selection of patients suitable for lung surgery. For this minority of HNSCC patients, screening probably contributed to adequate and timely treatment of second primary lung cancer or oligometastatic disease.

The (cost) effectiveness of a screening program can only be delivered by a randomized controlled trial. Although CT and PET/CT are able to detect many more pulmonary lesions than chest X-ray\textsuperscript{1-3}, false-positives and overdiagnosis remain major problems for such a screening trial.\textsuperscript{4,5} Searches for other screening methods, such as biomarkers in sputum and even markers in exhaled breath, may be more effective.\textsuperscript{6-8}

It may be expected that future investments in cancer prevention programs like smoking cessation with biochemical validation will be more cost effective in their contribution to a significant decrease of lung cancer as well as head and neck cancer.

References

Chapter 8


