Original Research

Management of patients with synchronous head-and-neck and lung cancers: SYNCHRON GFPC 15-01 Study

Nicolas Paleiron[1], Radj Gervais[2], Gaelle Rousseau-Bussac[3], Laurence Bigay Game[4], Anne Marie Chiappa[5], Regine Lamy[6], Florian Guisier[7], Hervé Le Caer[8], Gilles Robinet[9], Acya Bizieux[10], Christos Chouaïd[3] and the GFPC*

[1]Service des Maladies Respiratoires, Hôpital d'Instruction des Armées Clermont Tonnerre, Brest, France; [2]Centre Anti-Cancéreux François-Baclesse, Caen, France; [3]Centre Hospitalier Intercommunal de Créteil, Créteil, France; [4]Centre Hospitalier Universitaire (CHU) de Toulouse, Toulouse, France; [5]CH de Quimper, Quimper, France; [6]CH de Lorient, Lorient, France; [7]CHU de Rouen, Rouen, France; [8]CH de Draguignan, Draguignan, France; [9]Institut de Cancérologie de Bretagne Occidentale, Brest, France; [10]CH de La Roche-sur-Yon, La Roche-sur-Yon, France

ABSTRACT

Purpose: Few data have been published on the management of patients with synchronous head-and-neck cancer (HNC) and lung cancer (LC). This observational study was undertaken to describe the management of these patients in multiple centers.

Materials and Methods: All patients consecutively diagnosed with synchronous HNC and LC in 26 French centers were included. Information was collected on patients' clinical characteristics, management, and outcomes. Those characteristics and treatments were analyzed descriptively. Kaplan–Meier progression-free and overall survival probabilities were estimated.

Results: The study included 132 patients: 83% male; median age: 63.7 (range: 62.1–65.4) years; all current or former smokers; Eastern Cooperative Oncology Group performance status: 0 or 1 for 21.9% or 65.9% of the patients, respectively; cardiovascular comorbidities: 63%; chronic obstructive pulmonary disease: 33%; and previous cancer: 11%. HNC histology was 98% squamous: 23.5% oral cavity, 26.5% oropharyngeal, 22.0% hypopharyngeal, and 28.0% laryngeal. LCs were mainly localized (47.7% Stage I and 9.9% Stage II): 38% squamous, 49% adenocarcinomas, and 13% others. LC diagnosis impacted HNC management for 38% of the patients, with a median time from HNC diagnosis to first HNC treatment of 40 days. HNC impacted LC management for 48% of the patients, with a median time from LC diagnosis-to-LC treatment interval of 41 days.

Conclusions: Synchronous LC at HNC diagnosis impacted management and outcomes of both cancers. Specific recommendations should be elaborated to improve the management of these patients.

KEY WORDS: Head-and-neck cancer, lung cancer, management, patient care, synchronous cancers

INTRODUCTION

The synchronous discovery of lung cancer (LC) and head-and-neck cancer (HNC) is not uncommon because of the shared risk factors for these two locations.[1-8] The criteria defining a second primary tumor were established by Warren and Gates in 1932, as follows: (1) both tumors are malignant; (2) the two cancers are anatomically separated by normal mucosa; and (3) the possibility that one tumor represents a metastasis of the other is excluded. The index tumor is the first one diagnosed, and the second is any malignancy discovered thereafter. Second tumors are classified as synchronous when they are diagnosed at the same time as the index tumor, for example, during assessment of the tumor site and staging of the index tumor, or within 6 months after discovery of the index tumor. Synchronous cancers imply a global approach for the management of both.[9-12]

The prognosis depends on the initial staging of the two tumors and the patient's comorbidities. HNC patients' overall survival (OS) has not improved dramatically in recent decades, despite the introduction of new surgical procedures, improved radiotherapy techniques, and the use

Access this article online

Website: www.cancerjournal.net

Quick Response Code:

DOI: 10.4103/jcrt.JCRT_784_20

Cite this article as: Paleiron N, Gervais R, Rousseau-Bussac G, Game LB, Chiappa AM, Lamy R, *et al*. Management of patients with synchronous head-and-neck and lung cancers: SYNCHRON GFPC 15-01 study. J Can Res Ther 2021;XX:XX-XX.

Submitted: 10-Jun-2020
Revised: 20-Sep-2020
Accepted: 21-Dec-2020
Published: ***

*GFPC Study Group: V. Blanc (Arcalib), R. Gervais (Caen, France), F. Vinas, C. Chouaïd (Créteil, France), L. Bigay Game, E. Noel Savina (Toulouse, France), AM Chiappa (Quimper, France), R. Lamy (Lorient, France), F. Guisier, S. Bota (Rouen, France), H. Le Caer (Draguignan, France), G. Robinet (Brest, France), A. Bizieux, M. Marcq (La Roche-sur-Yon, France), E. Huchot, M. André (Saint-Denis de la Réunion, France), R. Corre (Rennes, France), T. Urban (Angers, France), G. Le Garff (Saint-Brieuc, France), J. Crequit (Beauvais), J.-B. Auliac (Créteil, France), P. Thomas (Gap, France), J. Le Treut (Aix-en-Provence, France), A. Vergnenègre (Limoges, France), O. Bylicki (Clamart, France), H. Berard (Toulon, France), S. Vieillot (Perpignan, France), S. Loutski (Creil, France), L. Falchero (Villefranche-sur-Saone, France), S. Chouabe (Charleville, France), J. Vella Boucaud (Reims, France), G. Valette, L. Saramon, R. Marianowski (Brest, France), J. Rousset, N. Paleiron (Brest, France).

For correspondence:
Prof. Christos Chouaïd,
Service de Pneumologie, Chi Créteil, 40 avenue de Verdun, 94010, Créteil, France.
E-mail: christos.chouaid@chicreteil.fr

of chemotherapy.[13] LC, particularly non-small-cell LC, which represents almost 85% of LCs, remains a considerable public health problem.[14-16] Its management is complex, and the time between the first symptoms, the suspected diagnosis, its confirmation, an extended work-up, and starting treatment is a sequence that involves a wide range of specialists. The HNC–LC association frequency varies according to the series but seems to markedly impact patient survival.[17] In a retrospective study on 937 Asian HNC patients treated between 2000 and 2009, the cumulative incidence of synchronous primary malignancies was 7.2%. Multivariate analyses retained age >60 years, hypopharyngeal index tumor site, or being a heavy drinker as being independently associated with the development of synchronous primary malignancies. Among 830 patients analyzed retrospectively, 350 (42.1%) had synchronous cancers.[13] Only 42.7% of the patients with synchronous cancers had clinical signs, while 26.9% were asymptomatic. In a population-based cohort study on 64,673 patients in the National Cancer Institute Surveillance, Epidemiology, and End Results Registry (1979–2008), the standardized incidence ratio of synchronous primary malignancies was 5.0, corresponding to 2.62 excess cases per 100 patients, and the head-and-neck site had the highest excess risk of a second cancer, followed by the esophagus and lung.[18]

Few published data are available on the management of patients with synchronous HNC–LC. The aim of this observational study was to describe the clinical picture at diagnosis and the management of these patients in multiple specialized centers.

MATERIALS AND METHODS

This prospective, observational study was conducted in 26 French centers that had to include at least five consecutive patients satisfying the following criteria: age >18 years, histologically confirmed HNC (nasal fossa, oral cavity, nasopharynx, oropharynx, hypopharynx, or larynx), and discovery of LC during the initial extended work-up or within the following 6 months. Noninclusion criteria were the patient's explicit refusal to allow collection of personal and medical information, and a clinical picture with evidence of lung metastases (multiple large disseminated pulmonary nodules and perfectly round lesions).

The primary objective was to determine the management modalities for the patients (time to treatment onset and types of interventions). The secondary objectives were to describe these tumors at baseline, prognoses, progression-free survival (PFS), OS, and therapeutic changes necessitated by the concomitant presence of the two cancers. For each patient, the following information was collected: demographic characteristics, meaningful medical and surgical history, LC and HNC risk factors, date(s) of diagnoses, the stage of each tumor, and the dates treatments were initiated for each tumor. Finally, the patient's treating physicians had to state whether the concomitant diagnoses of the two cancers had modified the management that would have been applied to each of the locations, i.e., time to starting treatment or management modalities.

Results are expressed as *n* (%) for dichotomized variables and means 95% confidence intervals (CIs) for continuous variables quantitative in state of dichotomized. The times to starting treatments are expressed as medians then means (95% CI). PFS and OS probabilities were estimated using the Kaplan–Meier method. All statistical analyses were computed with R software.[19] In light of the descriptive design of this study, we did not determine the number of individuals required.

Patients received an information letter and gave their oral consent to participate. The study was approved by the Ethics Committee of the Military Hospital of Brest on January 11, 2016 (no. ID-RCB 2016-A00049-42). The authorization of the National Committee on Informatics and Liberty was obtained on March 14, 2016, and that of the Advisory Committee on the Handling of Health-Related Information on September 17, 2016.

RESULTS

The main characteristics of the 132 patients with synchronous HNC–LC managed in 26 French centers are reported in Table 1.

Their median age was 63.7 (62.1–65.4) years; 59.8% active smokers; 40.2% ex-smokers; 9.8% exposed to asbestos; mean body mass index 23.1 (22.3–23.9); 13.7% lost >10% of their body weight during the 3 months preceding diagnosis; Eastern Cooperative Oncology Group performance score performans status (ECOG PS) was 0 or 1, respectively, for 21.9% and 65.9%; and respectively, 63% or 33% had cardiovascular or respiratory comorbidity.

Initial characteristics and management

Head-and-neck cancers

The staging of HNC tumors is given in Table 2. The extension work-up comprised panendoscopy (81%), cervical (89%) and/or thoracic (92%) computed tomography (CT) scans, bronchial (64%) or esogastroduodenal fibroscopy (35%), positron emission tomography (PET)–CT scan (81%), and/or cervical magnetic resonance imaging (17%). Histological type was squamous cell cancer for 98.4%. The median intervals from histological HNC diagnosis to the therapeutic decision and treatment onset of were, respectively, 15 and 40 days. The main management modalities were surgery alone (37.1%) or with concomitant radiochemotherapy (35.6%) [Table 3].

Table 1: Clinical characteristics of 132 patients with synchronous head-and-neck and lung cancers

Characteristics	Value (%)
Men	109 (83)
Age (years), median	63.7 (62.1-65.4)
Smoking status	
Smoker	79 (59.8)
Former smoker	53 (40.2)
Comorbidities	
Cardiovascular	83 (62.9)
Pulmonary	44 (33.3)
Previous cancers	15 (11.4)
Head and neck	5 (7)
Lung	2 (1.5)
Prostate	4< (3.0)
Others	4 (3.0)
Weight loss during the preceding 3 months (%)	
>10	15 (13.7)
0-10	40 (37.7)
ECOG PS	
0	31 (21.9)
1	87 (65.9)
>1	16 (12.2)

ECOG PS=Eastern Cooperative Oncology Group performance status

Table 2: Local–regional extension of the 132 head-and-neck cancers or lung cancer stages

Head-and-neck extension	*n* (%)
Local extension	
T1	21 (15.9)
T2	32 (24.2)
T3	37 (28.0)
T4	24 (18.2)
Tx	18 (13.6)
Nodal extension	
N0	48 (36.4)
N1	24 (18.2)
N2	27 (20.5)
N3	11 (8.3)
Nx	22 (16.7)
Lung cancer stage	
1	63 (47.7)
2	13 (9.8)
3	38 (28.8)
4	20 (15.2)

Lung cancer

LCs were identified on thoracic PET or CT scans, rarely by bronchial endoscopy during the work-up for HNCs. The diagnosis was clinical, without histology for 18 patients because of age ($n = 4$), poor general condition ($n = 3$), comorbidities ($n = 9$), or inaccessible tumor ($n = 2$).

The median intervals between LC diagnosis and the multidisciplinary tumor meeting or treatment onset, respectively, were 16 and 41 days. The management interventions as a function of stage are detailed in Table 4.

Impact of having synchronous head-and-neck cancer–lung cancer

According to the physicians managing these patients, having synchronous cancers modified management of HNCs for 37.9% of them and that of LCs for 48.5% [Table 5].

Survival

OS at 1 year was 74.4% (95% CI: 63.7%–87.0%) and 50.4% (95% CI: 37.5%–67.8%) at 2 years. PFS rates at 1 and 2 years, respectively, were longer for HNCs, 88.5% (95% CI: 79.5%–98.6%) and 84.8% (95% CI: 74.0%–97.2%), than for LCs, 71.7% (95% CI: 58.8%–87.5% and 31.6% (95% CI: 18.0%–55.6%).

DISCUSSION

The results of this multicenter, observational, prospective study showed that the synchronous LC–HNC diagnoses impacted almost a third of the managements of HNCs and half of the LCs. In this series, a majority of patients were in good general condition, with 87.8% having an ECOG PS of 0/1 and only 13.7% with >10% weight loss. The fortuitous LC discovery explains why the disease was still localized in 55.8% of the patients. HNC histology was almost always squamous, whereas LCs exhibited greater variability, including small-cell cancers, which should, in this context, incite systematic biopsies of the lung tumor.

Compared to published findings, the intervals until HNC management were acceptable, unlike those of LCs,[20,21] even though in this setting, no recommendations or consensus on practical management modalities have been formulated. In all published studies, the coexistence of two tumor sites led to higher morbidity. Among a series of 5846 patients who had undergone lobectomy, 354 with a previous HNC (68 synchronous and 286 metachronous), the lobectomy morbidity and mortality of those with HNCs were, respectively, 21% and 8% versus 13% and 2% without such prior events.[22]

Table 3: Management of the 132 head-and-neck cancers

Treatment	*n* (%)
Surgery	49 (37.1)
Concomitant radiochemotherapy	46 (34.8)
Chemotherapy alone	16 (12.1)
Radiotherapy alone	10 (T.6)
Chemotherapy followed by radiotherapy	9-6.8)
Best supportive care	2 (1.5)

Table 4: Management of the 132 lung cancers

Management	Stage I/ II (%)	Stage III (%)	Stage IV (%)
N	73	42	17
Surgery	29 (39.7)	12 (9)	
Lobectomy	1 (0.7)	2 (1.5)	-
Segmentectomy	25 (18.9)	8 (6.0)	
Wedge resection	3 (3.6)	2 (1.5)	
Radiotherapy	11 (8.3)	9 (6.3)	3 (2.2)
Conventional	≠4+64 (3.0)	6 (4.5)	2 (1.5)
Stereotaxic and local[a]	467 (5.3)	3 (2.1)	1 (0.7)
Chemotherapy	22 (16.6)	7 (5.3)	13 (9.8)
Radiochemotherapy	6 (4.5)	12 (9.0)	1 (0.7)
Concomitant	5 (3.5)	10 (7.0)	0
Sequential	1 (0.7)	2 (1.4)	1 (0.7)
Best supportive care only	5 (3.5)	2 (1.4)	0

[a]Endobronchial radiofrequency or curietherapy

Table 5: Treatment changes[a] due to synchronous head-and-neck cancer–lung cancer for the 132 patients

Impact of synchronous cancer	HNC management (%)	LC management (%)
Modified time to treatment	28 (21.2)	42 (31.8)
Modified chemotherapy chosen	21 (15.9)	28 (21.2)
Planned treatment canceled	19 (14.4)	24 (18.2)
Total changes	50 (37.9)	64 (48.5)

[a]A given patient could have one or more treatment modifications.
HNC=Head-and-neck cancer, LC=Lung cancer

Concerning changes of the planned treatment, ideally, each primary tumor should be treated according to the protocol that would have been applied to an isolated tumor. Keeping that in mind, there are two possibilities: either the protocol for each of the primary tumors can be respected, or it can be modified for one or both of the cancers. In a 9-year observational study including patients with synchronous HNCs,[23] the ideal treatment protocol was modified for 173/350 (49.4%) patients. Those modifications often resulted in poor prognoses for one or both of the synchronous primaries, particularly oropharyngeal, hypopharyngeal, esophageal, and LCs (64 patients). Such treatment changes usually occur when cancers are diagnosed simultaneously and when second cancers are diagnosed during treatment of the first. The reason for changing the therapeutic plan was the difficulty of implementing extensive surgical procedures for two simultaneous cancers in adjacent sites. Often, radiotherapy can include two cancer sites in the same radiation zone. In addition, in that study, patients with multiple cancers were often in poor general health, an additional argument further supporting changing the therapeutic plan.[24]

Some authors reported that LCs were the most common second primary tumors for patients with hypopharyngeal, oropharyngeal, and laryngeal index tumors.[13,16,20] Among a series of 77 patients with primary cancers of the larynx and lung, 35 were supraglottic, 27 glottic–supraglottic, and only 15 glottic.[25] LCs were detected after HNC diagnosis in 53 patients before in 6, and onset was synchronous in the remaining 18. Our data are consistent with those findings, but many of our patients had oral cavity cancers (23%), suggesting that this site is also associated with synchronous LCs.

In France, for LC patients, the mean interval between the first suspicious imaging and histological confirmation was 21.5 ± 17.6 days, and the interval between that imaging and a therapeutic plan was 13.5 ± 10.7 days. Those intervals seem shorter for metastatic stages than localized or localized advanced disease.[20,21] A more standardized approach based on the extension and functional work-up common to both cancers (including at least brain imaging and pulmonary function tests) followed by a tumor multidisciplinary meeting, could shorten the time to treatment onset.[25-27]

This analysis is limited to synchronous LC, i.e., LC diagnosed at the same time as the HNC or within 6 months of the diagnosis of HNC. Beyond 6 months, it is a metachronous tumor, realizing a completely different clinical situation. In an Australian study, monocentric analysis, over 12 years, among the 597 patients treated for HNC, 15 patients had a synchronous LC and 19 a metachronous LC, with a tendency for better OS for patients with a synchronous lesion (15 vs. 11 months, $P = 0.11$).[11]

In an another database analysis in the same period in The Netherlands, 181 eligible patients were identified, comprising 40 synchronous and 141 metachronous LC. Patients presenting with synchronous LC were more likely to have early-stage disease, as compared to patients with metachronous LC (45% vs. 28%, respectively; $P = 0.036$).[12]

This study has several limitations. Although the participating centers were asked to include all their consecutive patients meeting the inclusion criteria, it is possible that inclusion in each center was not exhaustive, with an overrepresentation of patients in good general condition. In addition, the extension work-ups of these synchronous tumors were somewhat heterogeneous, with a wide variety of management modalities, underscoring the clinical complexity of managing these patients.

Overall, our data and the literature have implications for the management of these patients with HNC and synchronous LC. A majority of LCs were diagnosed at an early stage, and patients seem to be equally at risk from LC- and HNC-related death. Treatment decisions are likely to be complex, but a multidisciplinary should make to avoid delays in the management of each cancer and allow a good coordination between the various stakeholders.

CONCLUSIONS

Herein, we described the clinical characteristics and treatment modalities for patients with synchronous HNC–LC. They confirmed the importance of obtaining histological confirmation of the malignancy of the two tumors and highlighted the impact of having these simultaneous cancers on suspicion-to-confirmation and treatment-onset intervals.

Acknowledgments

This study was an academic study conducted by the Groupe Français de Pneumo-Cancerologie.

Financial support and sponsorship

This study received academic grants from Pierre Fabre and Boehringer Ingelheim.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Erkal HS, Mendenhall WM, Amdur RJ, Villaret DB, Stringer SP. Synchronous and metachronous squamous cell carcinomas of the head and neck mucosal sites. J Clin Oncol 2001;19:1358-62.
2. Schwartz LH, Ozsahin M, Zhang GN, Touboul E, De Vataire F, Andolenko P, *et al*. Synchronous and metachronous head and neck carcinomas. Cancer 1994;74:1933-8.
3. Douglas WG, Rigual NR, Loree TR, Wiseman SM, Al-Rawi S, Hicks WL Jr. Current concepts in the management of a second malignancy of the lung in patients with head and neck cancer. Curr Opin Otolaryngol Head Neck Surg 2003;11:85-8.
4. Tiwana MS, Hay J, Wu J, Wong F, Cheung W, Olson RA. Incidence of second metachronous head and neck cancers: Population-based outcomes over 25 years. Laryngoscope 2014;124:2287-91.
5. Jain KS, Sikora AG, Baxi SS, Morris LG. Synchronous cancers in patients with head and neck cancer: Risks in the era of human papillomavirus-associated oropharyngeal cancer. Cancer 2013;119:1832-7.
6. Hordijk GJ, De Jong JM. Synchronous and metachronous tumours in patients with head and neck cancer. J Laryngol Otol 1983;97:619-21.
7. Cohn AM, Peppard SB. Multiple primary malignant tumors of the head and neck. Am J Otolaryngol 1980;1:411-7.
8. Nikolaou AC, Markou CD, Petridis DG, Daniilidis IC. Second primary neoplasms in patients with laryngeal carcinoma. Laryngoscope 2000;110:58-64.
9. Moertel CG. Multiple primary malignant neoplasms: Historical perspectives. Cancer 1977;40:1786-92.
10. Kim JH, Rha SY, Kim C, Kim GM, Yoon SH, Kim KH, *et al*. Clinicopathologic features of metachronous or synchronous gastric cancer patients with three or more primary sites. Cancer Res Treat 2010;42:217-24.
11. Tamjid B, Phan P, John T, Mitchell P, Gan H. Outcomes for patients with synchronous and metachronous primary lung cancer after diagnosis of head and neck cancer. Head Neck 2017;39:1544-9.
12. Griffioen GH, Louie AV, De Bree R, Smit EF, Paul MA, Slotman BJ, *et al*. Second primary lung cancers following a diagnosis of primary head and neck cancer. Lung Cancer 2015;88:94-9.
13. Buckley JG, Ferlito A, Shaha AR, Rinaldo A. The treatment of distant metastases in head and neck cancer – Present and future. Orl J Otorhinolaryngol Relat Spec 2001;63:259-64.
14. Ettinger DS, Wood DE, Akerley W, Bazhenova LA, Borghaei H, Camidge DR, *et al*. NCCN guidelines insights: Non-small cell lung cancer, version 4.2016. J Natl Compr Canc Netw 2016;14:255-64.
15. Pfister DG, Spencer S, Brizel DM, Burtness B, Busse PM, Caudell JJ, *et al*. Head and neck cancers, version 1.2015. J Natl Compr Canc Netw 2015;13:847-55.
16. Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Levra MG, *et al*. Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v1-27.
17. Léon X, Ferlito A, Myer CM, Saffiotti U, Shaha AR, Bradley PJ, *et al*. Second primary tumors in head and neck cancer patients. Acta Otolaryngol 2002;122:765-78.
18. Lee DH, Roh JL, Baek S, Jung JH, Choi SH, Nam SY, *et al*. Second cancer incidence, risk factor, and specific mortality in head and neck squamous cell carcinoma. Otolaryngol Head Neck Surg 2013;149:579-86.
19. R Development Core Team. R: A Language and Environment for Statistical Computing. Foundation for Statistical Computing, Vienna, Austria; 2008. Available from: http://www.r-project.org. [Last accessed on 2020 Mar 1].
20. Pourcel G, Ledesert B, Bousquet PJ, Ferrari C, Viguier J, Buzyn A. Waiting times for cancer care in four most frequent cancers in several French regions in 2011 and 2012. Bull Cancer 2013;100:1237-50.
21. Leveque N, Brouchet L, Lepage B, Hermant C, Bigay-Game L, Plat G, *et al*. An analysis of treatment delays of thoracic cancers: A prospective study. Rev Mal Respir 2014;31:208-13.
22. Pagès PB, Mordant P, Cazes A, Grand B, Foucault C, Dujon A, *et al*. Prognosis of lung cancer resection in patients with previous extra-respiratory solid malignancies. Eur J Cardiothorac Surg 2013;44:534-8.
23. Panosetti E, Luboinski B, Mamelle G, Richard JM. Multiple synchronous and metachronous cancers of the upper aerodigestive tract: A nine-year study. Laryngoscope 1989;99:1267-73.
24. Jones AS, Morar P, Phillips DE, Field JK, Husband D, Helliwell TR. Second primary tumors in patients with head and neck squamous cell carcinoma. Cancer 1995;75:1343-53.
25. Rinaldo A, Marchiori C, Faggionato L, Saffiotti U, Ferlito A. The association of cancers of the larynx with cancers of the lung. Eur Arch Otorhinolaryngol 1996;253:256-9.
26. Gould M, Ghaus S, Olsson J, Schultz E. Timeliness of care in veterans, with non-small cells lung cancer. Chest 2008;133:1167-73.
27. Leong PP, Rezai B, Koch WM, Reed A, Eisele D, Lee DJ, *et al*. Distinguishing second primary tumors from lung metastases in patients with head and neck squamous cell carcinoma. J Natl Cancer Inst 1998;90:972-7.