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Date:
2017-08-01

Citation:
Tamjid, B., Phan, P., John, T., Mitchell, P. & Gan, H. (2017). Outcomes for patients with synchronous and metachronous primary lung cancer after diagnosis of head and neck cancer. Head and Neck, 39 (8), pp.1544-1549. https://doi.org/10.1002/hed.24751.

Persistent Link:
https://hdl.handle.net/11343/293004

Title: Outcome of patients with synchronous and metachronous primary lung cancer after diagnosis of head and neck cancer

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Key Words:
Head and Neck cancer, NSCLC, Synchronous primary lung cancer, Metachronous primary lung cancer

Word Count:
Abstract contains 150 words.
Manuscript contains 2376 words (excluding references, tables and figures).

Abstract

Background: Not-infrequently patients with Head and Neck Cancer (HNC) are also diagnosed with synchronous (SLC) or metachronous primary lung cancer (MLC) which complicates the treatment decisions and prognosis.

Methods: Patients were identified from a database of HNC patients with second primary NSCLC.

Results: 34 eligible patients (15 SLC, 19 MLC) were identified. 13/15 with SLC received curative intent treatment for HNC first. 6/15 were in complete remission, 5/15 had died and 4 were alive with progressive disease.
Median time between two diagnoses was 47 months in MLC group. 12 patients had died, 3 were alive with disease and 4 lost to follow-up. Median survival from the time of lung cancer diagnosis was 13 months with a trend to better survival with SLC (15 vs 11 months, p=0.11).

Conclusion: Aggressive multidisciplinary management of second primary lung malignancies in HNC patients can result in respectable long-term disease control particularly in SLC patients.

Introduction

Head and neck squamous cell carcinoma (HNC) is the sixth most common cancer worldwide [1] and its incidence in Australia has been steadily rising since the 1980s, with 3,121 new cases diagnosed in 2011 alone.[2] Even though human papillomavirus (HPV) has been increasingly identified as a causative agent of HNC, smoking remains a major risk factor in this group of cancer patients.[3] The overall 5 year survival rate for HNC is approximately 64%, which has remained steady in the last decade despite advancements in the treatment of HNC.[2]

As smoking is a common contributing factor to many malignancies, it is not infrequent that patients with HNC are diagnosed with second primary cancers during their diagnostic workup or subsequent surveillance. In a large analysis of 13 cancer registries, the 20-year cumulative risk of a second cancer was as high as 36 percent.[4] The most common smoking related second malignancies are: non-small cell lung cancer (NSCLC) (45%) and oesophageal cancer (10%).[4-6] One percent absolute risk of synchronous primary lung cancer and six percent 5-year cumulative risk of metachronous second primary lung cancer have been reported.[7, 8] Importantly, the diagnosis of a second malignancy has substantial adverse impact on survival and second malignancies are the second most common cause of non-HNC related death in long-term survivors.[9]

The presence of a synchronous or metachronous primary lung cancer also greatly complicates the treatment options and overall prognosis of these patients. There is no clear consensus in the literature regarding outcome and

management of patients with such second primary lung cancers (SPLC) in HNC patients and more research is required in this field. Our paper describes the local experience of HNC with synchronous and metachronous primary lung cancer between 1990 and 2012.

Method

Patients were identified from a database of patients with HNC at the Austin Hospital, Melbourne, Australia between January 1990 and December 2013. Patients were deemed eligible for this review if they were 18 years or older, had histologically confirmed HNC and were known to have a synchronous or metachronous primary NSCLC based on Austin Hospital records. We applied Warren and Gates classical criteria to define a SPLC.[10] In brief, a diagnosis of NSCLC was accepted for pulmonary lesions with a non-squamous histology. Where histological confirmation of NSCLC was not available or where the histology was of squamous cell cancer, the diagnosis of NSCLC was accepted if there was radiological consensus that the pulmonary lesion was more consistent with a SPLC rather than a metastatic lesion from HNC. The lung cancer was considered to be synchronous (SLC) if the diagnosis of NSCLC was made within 6 months of diagnosis of HNC. If the diagnosis of lung cancer was made after 6 months of HNC it was classified as metachronous lung cancer (MLC). Demographic data, smoking status, tumour histology, stage at diagnosis, and treatment details were collected using a standardised template. Lung cancer histology was defined according to the World Health Organization pathology classification.[11] Data were extracted by two reviewers (BT and PP). The study was approved by the Austin Health Human Research Ethics Committee.

Statistical analysis

Descriptive statistics were used to analyse demographics and baseline characteristics. Median follow up was calculated from the date of diagnosis of HNC to the last follow up or death if known. Differences in frequency of events were compared by Chi-square test. Progression free survival (PFS) after treatment was calculated from the date of the first cycle of chemotherapy, radiotherapy or surgery to documented relapse or death from any cause. Overall survival (OS) was defined from the date of diagnosis of lung cancer until documented death or last known follow-up. OS and PFS were described by Kaplan-Meier analyses and compared with the log-rank test.

Results

A total of 597 patients were identified as treated for HNC at our institution between 1990 and 2013, with 41 of these patients also having a diagnosis of lung cancer. Seven patients were excluded due to likelihood of the lung lesion being a metastasis from HNC according to the reporting radiologist. Baseline patient, tumor and treatment characteristics are summarised in table 1. The median follow-up of all patients was 39 months (range 4 – 275 months).

The majority of patients were male 27/34 (79%). Median age at diagnosis of HNC was 65 years (range 47-88). All the patients had a smoking history with median 50 pack years (range 10-120) and 10/34 patients were current smokers at the time of diagnosis. The primary HNC was in the oropharynx in 17 patients (50%), larynx in 13 (38%) or in other anatomical locations (lip, scalp, parotid and nasopharynx) in 4 cases (12%). Surgery alone or in combination with adjuvant radiotherapy/chemotherapy was used in 13/34 cases. Radiotherapy as the sole treatment of HNC was used in the majority of cases (15/34) and it was combined with chemotherapy in 6 cases. Of these 34 eligible HNC patients, 15 had SLC and 19 had MLC.

Patients with synchronous lung cancer

Fifteen patients with synchronous lung cancers were included with a median age at diagnosis of 63 years (range 50-88). Only two out of 15 patients with SLC were symptomatic from the lung cancer primary and all were incidentally

diagnosed on staging of their HNC. Six out of 15 (40%) of these patients were active smokers. Histology of NSCLC was adenocarcinoma in eight, squamous cell (SqCC) in four and large cell in three patients. Thirteen out of 15 patients received treatment for HNC first followed by treatment for lung cancer. Only two patients had resection of lung cancer before receiving treatment for HNC.

For the definitive management of HNC, surgery alone was done only in one of the 15 patients, while five patients had surgery followed by adjuvant radiotherapy. Definitive radiotherapy was used in seven and two patients received chemoradiation for HNC.

All 15 patients were also treated with curative intent for the SLC. Twelve patients had surgery (10 had lobectomy and two wedge resection) for treating lung cancer. Two out of 12 patients who had surgery received adjuvant treatment. Adjuvant radiotherapy was given to one patient and another patient received adjuvant chemotherapy. Three patients received radiotherapy alone.

At the time of the last follow-up in the SLC group, 6/15 (40%) patients were in complete remission (CR) with no evidence of cancer recurrence, five patients had died (33%) and another four patients (27%) were alive with progressive disease. Of those who died, the cause of death was SPLC in three patients and recurrent HNC in two patients. Of the four patients alive with recurrent disease, three had recurrent NSCLC and one recurrent HNC. Median OS in the synchronous lung cancer group was 16 months.

Patients with Metachronous Lung Cancers

For the 19 patients with MLC, the median time between HNC and diagnosis of MLC was 47 months (range 11-259 months) and median age was 65 years (range 49-88). Eleven patients (57%) were incidentally discovered during surveillance of HNC while the remaining patients were experiencing symptoms at the time of MLC diagnosis. Only 4/19 (20%) of patients were active smokers at the time of diagnosis of NSCLC. The NSCLC histology was SqCC in 12, adenocarcinoma in six and one patient with large cell.

Fifteen patients underwent surgery, with lobectomy in 12 and wedge resection in three, along with post-surgical adjuvant radiotherapy in two patients and adjuvant chemotherapy in three. Radiotherapy alone for the treatment of MLC was used in 2/19 patients. Details of treatment of MLC are summarised in table 2.

At the time of last follow up in the MLC group, no patient was known to be disease free, 12 patients had died (63%), three patients were alive with disease (16%) and four patients had been lost to follow up (21%). Lung cancer was the main reason for death or progressive disease in the majority of patients with only one out of 12 deaths due to HNC. Of three patients alive with progressive cancer, one had progressive HNC. The median survival in the MLC group after diagnosis of lung cancer was 11 months.

Comparison between SLC and MLC

There were no significant differences in median age or gender between these two groups. More MLC patients had stopped smoking at the time of diagnosis of lung cancer (80% versus 60%, p=NS). The type of treatment modality for HNC was similar for both groups. However, there was a significant difference in NSCLC stage at diagnosis between patients with SPLC and MLC, with more early stage NSCLC in the SLC group compared to the MLC group (Stage 1/2/3 of 67%/27%/7% compared to 25%/50%/25%, p=0.028 two sided).

From the time of diagnosis of HNC, patients with SLC had significantly shorter median survival compared to those in the MLC group (16 versus 66 months, p=0.008). The median time between diagnosis of HNC and SLC was 1 month and 47 months after diagnosis of HNC in MLC group.

However, considering the median survival from the time of lung cancer diagnosis, this was 13 months in the overall population, with a trend to better survival with synchronous NSCLC (SLC median survival 15 months vs 11 months for MLC (P=0.11).

Discussion

Overall, outcomes in patients with both HNC and lung cancer appear worse than those diagnosed with either of these cancers alone. Previous studies found 0-20% five-year survival for patients who were diagnosed with SPLC,[12-14] which is inferior to the 15-73% five-year survival for stage I-III NSCLC diagnosed in the absence of HNC.[15] It is also inferior to the survival of patients who are diagnosed only with HNC, where 5-year survival is 65% (stage I-II HNC 70-90% and locoregionally advanced HNC 40%) with HPV positive patients having even better prognosis (80%) compared to patients with HPV negative HNC.[2, 5, 16, 17] In a large study of 36,000 HNC patients on SEERs registry, second primary cancers were the leading cause of non-HNC death (12%), and the most common site of second primary was lung (53%).[9] SPLC after diagnosis of HNC has been reported in some studies to have a 19-26% five-year survival.[18-21]

The current study showed significantly shorter OS of 16 months in SLC patients compared to 66 months in MLC group from the time of HNC diagnosis. However, from the time of NSCLC diagnosis, median survival trended shorter in MLC group compared to SLC group with 11 months versus 15 months (p=0.11). Patients with synchronous lung cancer were significantly more likely to have early-stage disease than those with MLC and consequently might be expected to have better survival. All of the patients with SLC were diagnosed on HNC staging, while over 40% of MLC were diagnosed on the basis of symptoms.

A similar pattern of survival from diagnosis of HNC was reported by Dequanter *et al*, for patients with HNC and SPLC (14 synchronous and 25 metachronous). In this study those with MLC had significantly better survival compare to patients with SLC (92.9 months versus 15.7 months; p=0.0045).[22] In a large study by Griffioen *et al*, [6] including 181 patients with 40 SLC and 141 MLC, patients with SLC were more likely to have early-stage lung cancer as compared to patients with MLC (45% vs. 28%, respectively; p = 0.036), consistent with our findings. Similarly, a high proportion of MLC were detected because of symptomatic disease, which in the Griffioen study which included a high proportion of patients with metastatic lung cancer. This is in contrast with the SLC population where the majority of patients were asymptomatic and diagnosed incidentally on staging imaging, as seen in our study. Lung cancer specific survival was 10 months in MLC group and 19 months in SLC after diagnosis of SPLC with a trend toward improved survival in SLC patients (P=0.09).[6]

Overall, our data and the literature have implications for the management of patients with HNC and SLC and MLC. In SLC group, patients appear to be equally at risk from NSCLC-related death and HNC related death. However, long term disease survival is possible with aggressive treatment of both malignancies in carefully selected patients. Our data suggest that 40% of patients can be successfully treated with this approach. Treatment decisions are likely to be complex and a multidisciplinary approach will be vital. In general, treatment of HNC preceded that of NSCLC in our series, which probably reflects the fact that patients were already substantially along their treatment pathway for HNC when diagnosed, and because the staging of HNC cancer was generally more advanced

than that of the SPLC. With regard to our data in MLC, the poorer prognosis of this group at the time of lung cancer diagnosis argues for the importance of smoking cessation and surveillance for MLC and other smoking related cancers. The long median time of 47 months (range 11-259 months) between their initial HNC diagnosis and their subsequent MLC suggests that surveillance intensity may need to be maintained for 5 years or perhaps even longer. Although there are competing potential causes of death, the risk of lung cancer is 6% and the early diagnosis of MLC is of paramount importance. Screening for lung cancer with yearly low-radiation dose CT scans has been shown to reduce lung cancer mortality by 20% for participants with a risk of lung cancer around 1 - 2%.[23] The much higher risk of MLC in HNC patients argues for routine lung cancer screening during follow up.

Our study was a retrospective study and included patients over the last two decades. In particular, for the MLC patients, histological evidence was not available about tumour subtype but we have shown the data based on the clinical information that was used to guide patient care at the time. Additionally, although data of lung cancer treatment was available, detailed staging information could not always be retrieved.

In conclusion, second malignancies such as SLC and MLC present difficult diagnostic and management problems in HNC patients. We believe that such patients, in particular patients with SLC, should be discussed and managed in tertiary hospitals with multidisciplinary approach on an individualized basis. Whilst acknowledging that these patients often do poorly, aggressive

management can still result in respectable long term disease control rates. Our data also argues for the importance of secondary prevention and early diagnosis of lung cancer in patients who achieve long term disease control after their initial HNC diagnosis given the well documented rate of MLC.

References

1. Ferlay, J., et al., *Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008.* Int J Cancer, 2010. **127**(12): p. 2893-917.
2. Registries, A.I.o.H.a.W.A.A.o.C., *Cancer in Australia: an overview, 2012.* Cancer series no. 74. Cat. no. CAN 70. Canberra: AIHW., 2012.
3. Sturgis, E.M. and K.K. Ang, *The epidemic of HPV-associated oropharyngeal cancer is here: is it time to change our treatment paradigms?* J Natl Compr Canc Netw, 2011. **9**(6): p. 665-73.
4. Chuang, S.C., et al., *Risk of second primary cancer among esophageal cancer patients: a pooled analysis of 13 cancer registries.* Cancer Epidemiol Biomarkers Prev, 2008. **17**(6): p. 1543-9.
5. Rose, B.S., et al., *Population-based study of competing mortality in head and neck cancer.* J Clin Oncol, 2011. **29**(26): p. 3503-9.
6. Griffioen, G.H., et al., *Second primary lung cancers following a diagnosis of primary head and neck cancer.* Lung Cancer, 2015. **88**(1): p. 94-9.
7. Jain, K.S., et al., *Synchronous cancers in patients with head and neck cancer: risks in the era of human papillomavirus-associated oropharyngeal cancer.* Cancer, 2013. **119**(10): p. 1832-7.
8. Milano, M.T., et al., *Second primary lung cancer after head and neck squamous cell cancer: population-based study of risk factors.* Head Neck, 2012. **34**(12): p. 1782-8.
9. Baxi, S.S., et al., *Causes of death in long-term survivors of head and neck cancer.* Cancer, 2014. **120**(10): p. 1507-13.
10. Warren, S., Gates, *IA survey of the literature and a statistical study.* Am J Cancer, 1932. **16**: p. 1358.
11. Travis, W.D., *Pathology and genetics of tumours of the lung, pleura, thymus and heart*. Vol. 7. 2004: Iarc.
12. Lin, K., et al., *Second primary malignancy of the aerodigestive tract in patients treated for cancer of the oral cavity and larynx.* Head Neck, 2005. **27**(12): p. 1042-8.
13. Rennemo, E., U. Zatterstrom, and M. Boysen, *Impact of second primary tumors on survival in head and neck cancer: an analysis of 2,063 cases.* Laryngoscope, 2008. **118**(8): p. 1350-6.
14. Priante, A.V., E.C. Castilho, and L.P. Kowalski, *Second primary tumors in patients with head and neck cancer.* Curr Oncol Rep, 2011. **13**(2): p. 132-7.
15. Groome, P.A., et al., *The IASLC Lung Cancer Staging Project: validation of the proposals for revision of the T, N, and M descriptors and consequent stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours.* J Thorac Oncol, 2007. **2**(8): p. 694-705.
16. Rischin, D., et al., *Prognostic significance of p16INK4A and human papillomavirus in patients with oropharyngeal cancer treated on TROG 02.02 phase III trial.* J Clin Oncol, 2010. **28**(27): p. 4142-8.
17. Ang, K.K., et al., *Human papillomavirus and survival of patients with oropharyngeal cancer.* N Engl J Med, 2010. **363**(1): p. 24-35.

18. Chen, M.C., et al., *Impact of second primary esophageal or lung cancer on survival of patients with head and neck cancer.* Oral Oncol, 2010. **46**(4): p. 249-54.
19. Jayaprakash, V., et al., *Previous head and neck cancers portend poor prognoses in lung cancer patients.* Ann Thorac Surg, 2011. **92**(3): p. 1056-60; discussion 1060-1.
20. Jones, A.S., et al., *Second primary tumors in patients with head and neck squamous cell carcinoma.* Cancer, 1995. **75**(6): p. 1343-53.
21. Di Martino, E., et al., *Survival in second primary malignancies of patients with head and neck cancer.* J Laryngol Otol, 2002. **116**(10): p. 831-8.
22. Dequanter, D., et al., *Second primary lung malignancy in head and neck cancer patients.* Eur Ann Otorhinolaryngol Head Neck Dis, 2011. **128**(1): p. 11-3.
23. National Lung Screening Trial Research, T., et al., *Reduced lung-cancer mortality with low-dose computed tomographic screening.* N Engl J Med, 2011. **365**(5): p. 395-409.

Figures legend

Figure 1. Patients flow diagram

Figure 1.

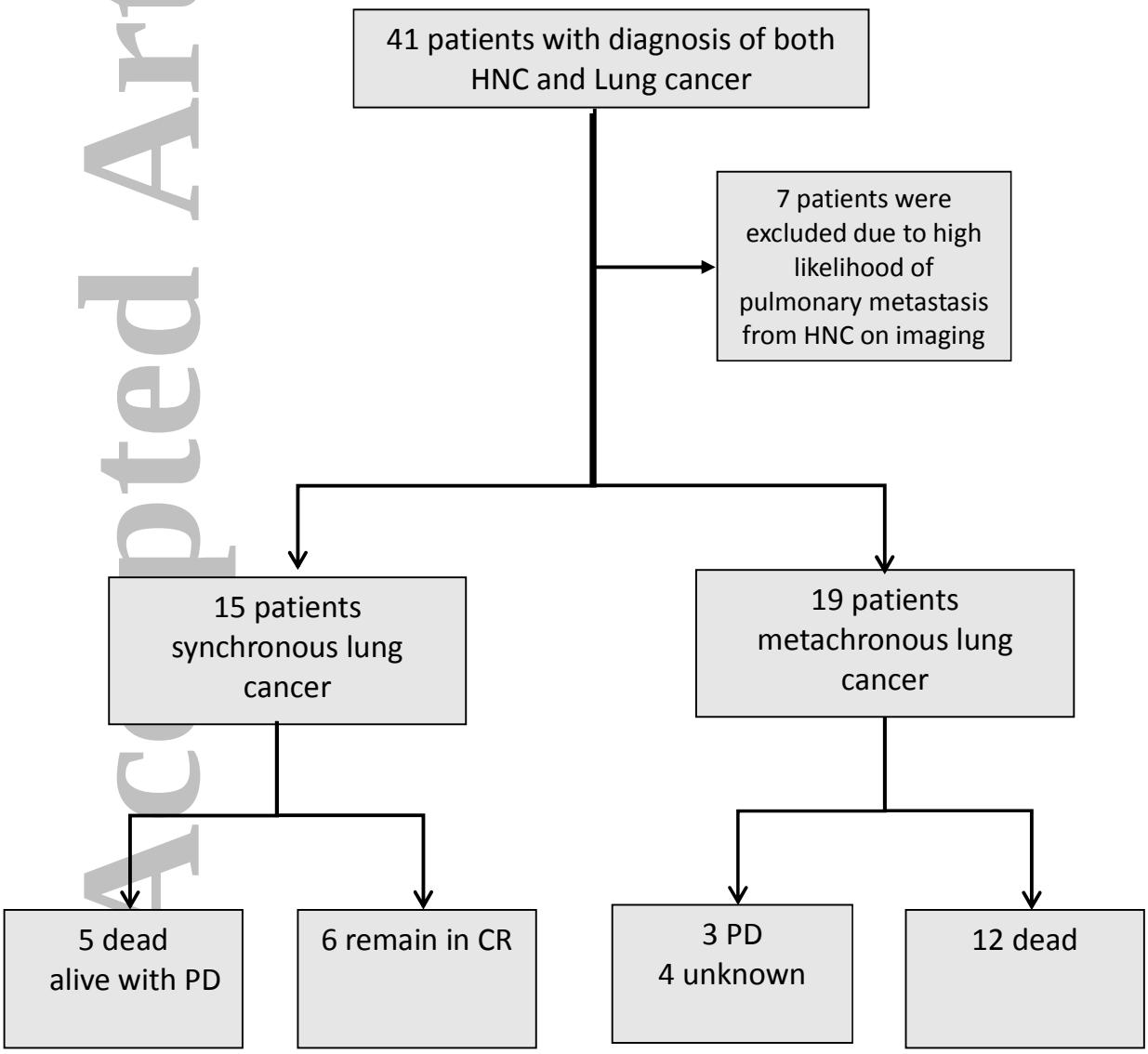
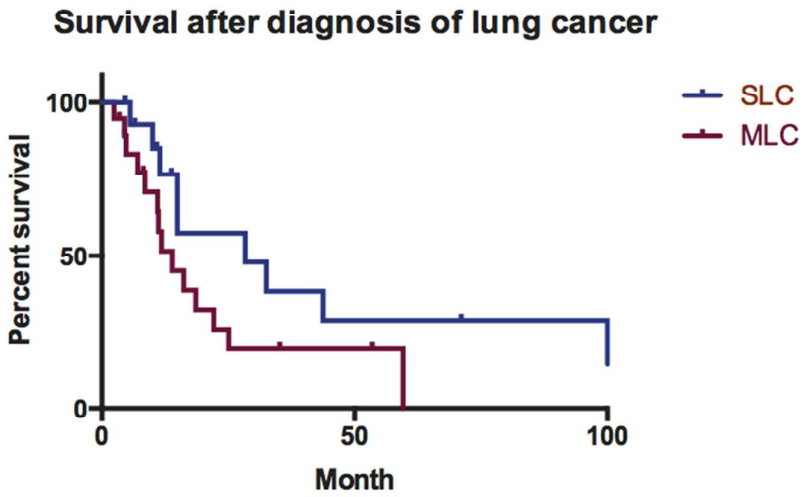


Figure 2. Survival after diagnosis of lung cancer



P= 0.11

Tables

Table 1. Patient Characteristics. N=34

Groups	Synchronous	Metachronous	All
Number of patients	15	19	34
Median age at diagnosis (range) - years	63 (50-88)	65 (49-79)	65 (49-88)
Sex			
Male	13	14	27
Female	2	5	7
Smoking status			
Current	6	4	10
Past	9	15	24
Head & Neck Cancer subtype			
Oropharynx	10	7	17
Larynx	4	9	13
Other	1	3	4
Clinical stage H&N cancer			
I	0	3	3
II	1	5	6
III	7	6	13
IV	5	2	7
Unknown	2	3	5
Clinical stage lung cancer			
I	10	4	14
II	4	8	12
III	1	4	5
Unknown	0	3	3
Treatment for H&N cancer			
Surgery	1	3	4
Surgery + adjuvant therapy	5	4	9
Radiotherapy	7	8	15
Radiotherapy + chemotherapy	2	4	6

Table 2. Lung cancer treatment details

	Synchronous (SLC) n=15	Metachronous (MLC) n=19	All
Histopathological subtype of lung cancer			
Adenocarcinoma	8	6	14
Squamous cell carcinoma	4	12	16
Large cell	3	1	4
Surgery			
Wedge resection	2	0	2
Lobectomy	10	12	22
Pneumonectomy	0	3	3
Surgery + adjuvant treatment			
Adjuvant radiotherapy	1	1	2
Adjuvant chemotherapy	1	2	3
Radiotherapy	3	2	5
Radiotherapy + chemotherapy	0	1	1
Chemotherapy	0	1	1
Further lines of treatment on progression of NSCLC			
2 lines	4	3	7
≥3 lines	1	2	3

Table 3. Details of treatment in SLC group		
Patient number	**Treatment of HNC**	**Treatment of SLC**
1	Chemoradiotherapy	Surgery + adjuvant radiotherapy
2	Radiotherapy	Radiotherapy
3	Surgery	Surgery
4	Surgery + adjuvant radiotherapy	Surgery
5	Surgery + adjuvant chemoradiotherapy	Surgery
6	Surgery + adjuvant radiotherapy	Surgery
7	Radiotherapy	Surgery
8	Radiotherapy	Surgery
9*	Chemoradiotherapy	Surgery + adjuvant chemotherapy
10*	Radiotherapy	Surgery
11	Surgery + adjuvant radiotherapy	Surgery
12	Surgery + adjuvant radiotherapy	Palliative chemotherapy
13	Radiotherapy	Surgery
14	Radiotherapy	Radiotherapy
15	Radiotherapy	Surgery
* Two patients had resection of lung cancer before receiving treatment for HNC.		