Malignant Multiple Neoplasms in Head and Neck Squamous Cell Carcinoma

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Introduction: The incidence of multiple malignant neoplasms in the upper aerodigestive tract is high and ranges from 7% to 20%. We make a retrospective study to evaluate the incidence of multiple malignant neoplasms in head and neck squamous cell carcinomas, their main characteristics and survival.
Material and method: We studied 103 multiple malignant neoplasms from an oncological database of 1330 patients with head and neck squamous cell carcinomas. We use the SPSS v.15 for analysis of the results.
Results: The incidence of multiple malignant neoplasms in our series is 7.73%. Tumours of the hypopharynx are the primary tumours most often associated with multiple malignant neoplasms (21.34%), followed by tumours of the oropharynx (15.38%). Lung tumours are the multiple malignant neoplasms most often associated (29.03%). The 5-year global survival is 33% from diagnosis of the second primary tumour, 78.02% of which are metachronous with an average of 40 months between the diagnosis of the primary tumour and the presentation of the second tumour.
Conclusions: Multiple malignant neoplasms are very frequent in the head and neck area which shows the importance of thorough regular check-ups of these patients as the presence of multiple malignant neoplasms considerably worsens the prognosis.

Key words: Multiple malignant neoplasms. Head and neck squamous cell carcinoma. Metachronous. Second primary tumours.

Neoplasias malignas múltiples en el cáncer escamoso de cabeza y cuello
Introducción: La frecuencia de neoplasias malignas múltiples en el tracto aerodigestivo superior es elevada y varía de un 7 a un 20%. Valoramos la frecuencia de segundos tumores primarios en carcinomas escamosos de cabeza y cuello, y determinamos sus principales características y la supervivencia.
Material y método: Realizamos un estudio retrospectivo con 103 segundos tumores primarios de una base de datos de 1.330 pacientes con carcinomas epidermoides de cabeza y cuello. Empleamos el programa SPSS v.15 para el análisis de resultados.
Resultados: La frecuencia de segundos tumores primarios en nuestra serie es del 7,73%. Los tumores primarios que más frecuentemente asocian segundos tumores primarios son los de hipofaringe (21,34%), seguidos de los de orofaringe (15,38%). El segundo tumor primario más frecuentemente asociado es el de pulmón (29,03%). La supervivencia general es del 33% a los 5 años del diagnóstico del segundo tumor primario. El 78,02% de los segundos tumores primarios son metacrónicos, con una media de 40 meses entre el diagnóstico del tumor primario y la aparición del segundo tumor primario.
Conclusiones: Los segundos tumores primarios son muy frecuentes en el área de cabeza y cuello, lo cual resalta la importancia de un control periódico y exhaustivo de estos pacientes ya que su aparición conlleva un ensombrecimiento importante del pronóstico.

Palabras clave: Neoplasias malignas múltiples. Carcinomas epidermoides de cabeza y cuello. Metacrónicos. Segundos tumores primarios.

INTRODUCTION

The incidence of multiple malignant neoplasms in the upper aerodigestive tract is high and varies from 7% to 20%.[1] The number of cases appears to have increased over the years. There may be multiple causes for this: people are living longer on average, greater survival of patients treated for cancer, longer and more comprehensive follow-up of patients, increased exposure to carcinogens, etc.

The appearance of a second primary tumour is the main cause of treatment failure as of the second year from diagnosis and treatment of the initial tumour.[2] Tumours developing in the aerodigestive tract present an incidence of appearance of second tumours that is greater than neoplasms in other locations.[3,4] Among other reasons, this could be accounted for by the association of smoking and

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alcohol use in this type of patients with the appearance of these tumours. All the statistics point to the larynx as the most common location of the primary tumour and to the nose, sinuses, and nasopharynx as the least common locations. Insofar as second primary tumours are concerned, those located in the lung and in the head and neck have the highest incidence.[5]

We use the term primary tumour (PT) for the one diagnosed first and the term second primary tumour (SPT) for any other malignant neoplasm discovered simultaneously or subsequently to the PT.

From a chronological perspective, Moertel et al[6] classified second neoplasms on the basis of the time sequence of their appearance; they defined synchronous tumours as those diagnosed simultaneously with or within 6 months of diagnosis of the PT, and metachronous, as those diagnosed 6 months or more after diagnosis of the PT. In the case of simultaneous tumours, PT is considered to be the one giving rise to the symptoms.

In 1932, Warren and Gates[7] established the defining criteria for a second neoplasm:

– Each tumour must be histologically defined as malignant
– The possibility of a tumour being a metastasis from the other must be ruled out
– There must be no submucosal connection between the 2 nor between other tumours

A tumour located in the lung will be defined as an SPT, as distinct from a distant metastasis, when it presents as a solitary lesion and the histology study distinguishes it from the PT.

The hypotheses as to the aetiology of multiple cancers are subject to considerable discussion; some may be demonstrable in certain specific cases, but they can hardly ever be generalized. First of all, there is "individual predisposition," it can be proven on statistical grounds that a person who has had one cancer has a greater risk of presenting another one in comparison with the general population. Warren and Gates[7] report differences of up to 11-fold. Different epidemiological studies have shown that, after developing a PT in the head and neck, there is a greater risk of developing an SPT than in the general population.[8]

From an epidemiological point of view, the risk of developing a second tumour would vary according to the location of the index tumour, the histology, and exposure to tobacco and alcohol. Thus, tumours of the head and neck located in areas not directly related to smoking and alcohol use, such as neoplasms of the rhinopharynx or salivary glands, present an incidence of second tumours that is lower than that for index tumours located in the oral cavity, the oropharynx, the hypopharynx, or the larynx, epidemiologically related to smoking and alcohol use.[9] On the other hand, another series of possibilities has been discussed, such as: *a)* genetic or hereditary predisposition (in all the familial varieties of cancer, there is an excess of multiple cancers)[10]; *b)* depression of the immune system caused by the first cancer; and *c)* the carcinogenic effect of treatment for the first tumour.

The carcinogenic effect of radiotherapy administered to young people is fairly clear,[11] but the relationship between radiotherapy for cancer and the incidence of a second tumour is more controversial. Authors such as Wagenfeld et al[12] have published an incidence rate of 10% for radiation-induced tumours in patients after radiation for a glottal T1 tumour after 5-10 years of survival. For other authors,[13] treatment with radiotherapy decreases the incidence of second tumours. Tapperman and Fitzpatrick[14] attempted to explain this diversity of opinions by alleging that radiotherapy would initially eliminate the risk of second neoplasms by eliminating synchronous subclinical lesions, but long-term, it could increase the risk of second metachronous neoplasms. Donaldson[15] establishes 3 criteria for attributing any kind of aetiological role to radiotherapy. If all 3 criteria are not met, the second cancer is deemed to be incidental when:

1. There is no evidence of microscopic tumour in the area that has been radiated.
2. The tumour arises in an area that has received high doses.
3. A minimum of no less than 10 years has elapsed between radiation and the appearance of the second tumour.

On the other hand, the age and time of evolution are important factors; thus, young patients, with a longer life expectancy, who have been treated for cancer have more possibility of developing a second tumour than an elderly patient with a short life expectancy.[16] The same can be said of primary tumours offering a higher survival expectancy (for instance, tumours of the larynx or oral cavity vs tumours of the pharynx).

We have undertaken this study to determine the incidence of second tumours in squamous cell carcinoma of head and neck and we have defined the main characteristics and survival rates for this type of patient.

MATERIAL AND METHOD

We have carried out a retrospective study of the period 1980-2004; to do so, we have used our department's oncology database We collected 1331 patients diagnosed as having head and neck squamous cell carcinoma in this period. Of this total, 103 patients who met the criterion of having developed an SPT during the course of their illness were included in the study.

We analyzed a series of data, such as gender, age on appearance of the PT, pathology report and staging of the PT, location of the SPT, survival and time of appearance between the PT and the SPT and its classification as:

– Synchronous: when the SPT appears within the first 6 months of the diagnosis of the PT. This group would also include simultaneous SPTs, ie, when both tumours were diagnosed at the time of presentation
– Metachronous: when the SPT is diagnosed more than 6 months after the PT

We used the SPSS v.15 software package for the statistical analysis, calculating absolute and relative frequencies with a 95% confidence interval (CI) and Kaplan-Meier survival tables.

RESULTS

Our series presents a 7.73% frequency of appearance for SPTs in a total of 103 patients. The frequency of appearance of the SPT according to the location of the PT is presented in Table 1. We observed that most SPTs occur in patients with a PT of the supraglottis (34.95%), followed by PT of the glottis (33.98%). However, if we analyze the frequency of said SPTs based on the total number of tumours with this location in the oncology database including 1331 patients, we find that the greatest percentage is found in patients with a PT of the hypopharynx (21.34%), followed by PT of the oropharynx (15.38%).

All patients were male, with a mean age of 58.60 years (interval, 41-81).

As regards the TNM of the PTs that went on to develop SPTs, we find that 35.29% were T3, followed by 29.41% T2, and 28.43% T1, and, finally, 6.86% were T4. Most (68.63%) were N0 and 13.72% were N1 and N2. Only 3.92% were N3. None of the patients presented distant metastasis at the time of diagnosis. All the PTs were squamous cell carcinomas. Insofar as the histopathology of the PT is concerned, 52.9% were G1 squamous cell carcinomas; 33.7%, G2; and 9.6%, G3. In 3.8% of the PTs it was impossible to record the grade of differentiation. In most cases, the histopathology of the SPT could not be studied.

Table 1. Frequency of Appearance of the Second Primary Tumour (SPT) According to the Location of the Primary Tumour (PT) in Patients With Head and Neck Squamous Cell Carcinoma (n=1331)

Location PT	*SPT, No.*	*Frequency SPT*[a]
Hypopharynx (89)	19	21.34%
Oropharynx (52)	8	15.38%
Subglottis (15)	2	13.53%
Oral cavity (63)	5	7.93%
Supraglottis (483)	36	7.45%
Glottis (580)	32	5.51%
Lip (21)	1	4.76%
Sinuses (9)	0	0%
Cavum (19)	0	0%
Total	103 (7.73%)	

[a]Frequency according to the total number of tumours in said location.

The distribution of patients with respect to the location of the PT is given in Table 2.

Insofar as treatment of the PT is concerned, 95.15% were treated surgically and 45.63% underwent radiotherapy versus 54.37% who did not receive radiation therapy. Only 8.74% received chemotherapy.

Table 2. Location of the Second Primary Tumour (SPT) According to the Location of the Primary Tumour (PT)

PT/SPT	*Hypopharynx*	*Oropharynx*	*Urinary Tract*	*Lung*	*Rectum*	*Thyroid*
Supraglottis	4	4	2	10	3	1
Glottis		3	5	11	2	1
Hypopharynx		5	2	5		1
Oral cavity	1	2			1	
Oropharynx	2	3				
Subglottis				1	1	
Lip				1		
Total SPT	7 (6.79%)	17 (16.50%)	9 (8.73%)	28 (27.18%)	6 (5.82%)	4 (3.88%)

PT/SPT	*Oesophagus*	*Stomach*	*Larynx*	*Oral Cavity*	*Trachea*	*Others*	*Total PT*
Supraglottis	3	1		2	1	5	36 (7.45%)
Glottis	2	2	4	1			32 (5.51%)
Hypopharynx	2	1	1	1	1		19 (21.34%)
Oral cavity			1				5 (7.93%)
Oropharynx	1		1		1		8 (15.38%)
Subglottis							2 (13.53%)
Lip							1 (4.76%)
Total SPT	8 (7.76%)	4 (3.88%)	7 (6.79%)	4 (3.88%)	3 (2.91%)	5 (4.8%)	

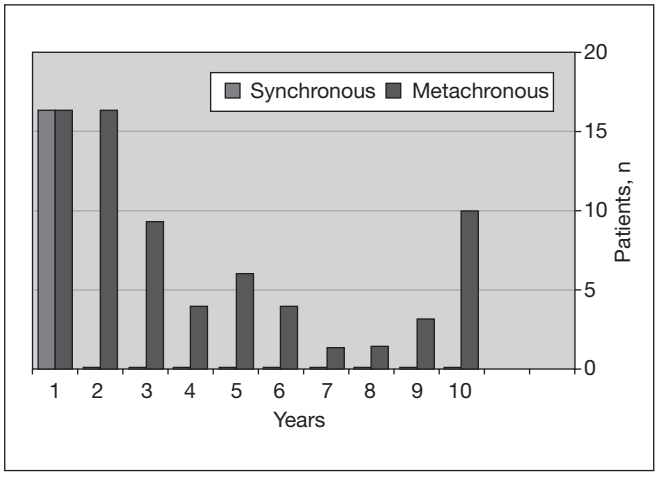

Figure 1. Time to appearance of the second tumour.

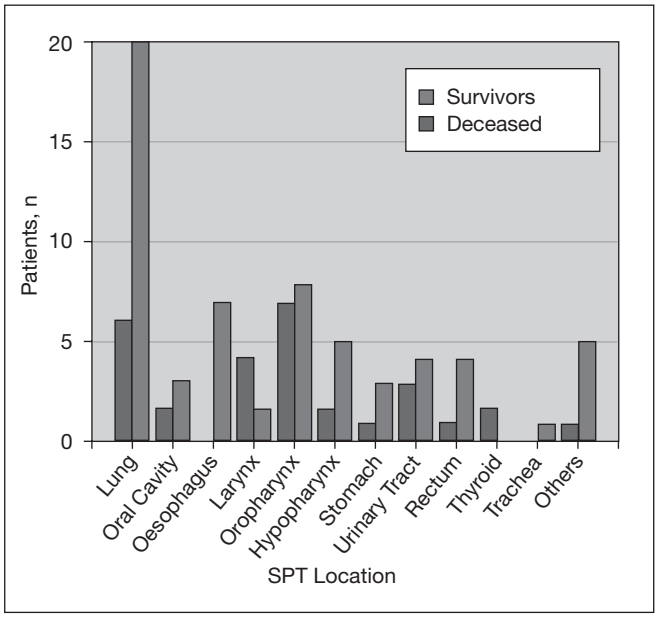

Figure 2. Survival according to location of the second primary tumour (SPT).

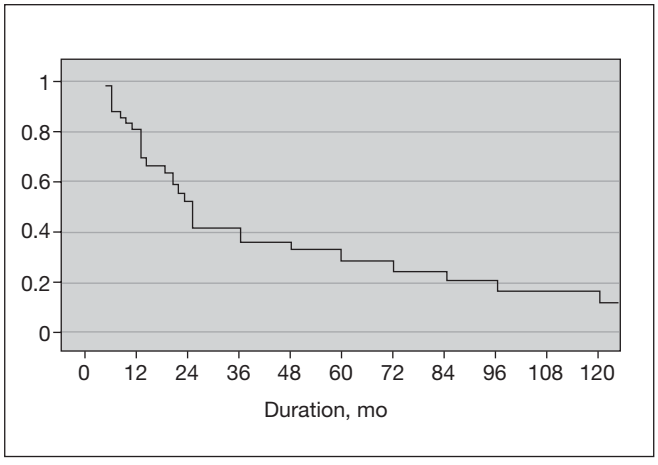

Figure 3. Overall survival curve of patients who developed a second primary tumour.

As regards the time of appearance of the SPT, we have found that most of the SPTs were metachronous (78.02%), followed by synchronous (16.48%) and simultaneous (5.49%). The mean (standard deviation) for the time between diagnosis of the PT and the appearance of the SPT is 39.98 (46.61) months. Hence, in 67.96% (70 patients) the SPT was diagnosed within the first 5 years, whereas in 32.03% of the cases, the diagnosis of the SPT was made after 5 years had elapsed from the time of diagnosis of the PT. Figure 1 reflects the distribution of the cases according to the time of diagnosis of the SPT with respect to the PT.

The most commonly associated SPT was located in the lung (29.03%). It may be difficult to rule out metastasis for a pulmonary tumour if we rely on clinical and radiological criteria to guide our decision; histology may provide the definitive diagnosis. Head and neck locations come a close second: oropharynx (16.13%), hypopharynx (7%), oral cavity (5.38%), and larynx (6%).

On the other hand, if we compare survival according to the location of the SPT, we find that patients with SPTs located in the lung, oesophagus, stomach, and hypopharynx have a lower survival rate than those with SPTs located in the oral cavity, larynx, or oropharynx. Thus, patients with an SPT located in the lung have a survival rate of 23.1%; in the stomach, 25%; in the oesophagus, 0%; and 28% in the hypopharynx. All these findings are illustrated in Figure 2.

As regards overall survival, we see that 33% of the patients were alive 5 years after diagnosis of the SPT, whereas 67.01% were deceased. Death was due to the SPT in 40% and due to an indirect cause in 56.92%. The mean survival time of the deceased patients was 33.78 months since the time of diagnosis of the SPT. Figure 3 presents the survival information pertaining to these patients.

DISCUSSION

According to the data in our study, the frequency of appearance of SPT is 7.73%. This result is similar to that in the published literature.[17] The most common SPT is located in the lung (29.03%), a finding that coincides with most authors.[18] However, there are certain geographical variations; in fact, the most striking association is larynx-stomach in the Japanese literature. Given the high incidence of gastric cancer in that area, this association may be considered incidental. Following the publication of an in-depth study conducted with a group of patients with PTs in the head and neck, Licciardello et al[2] propose that the location of the PT might correlate with that of the SPT in the aerodigestive tract. In their revision, PTs of the oral cavity appear to be related to SPTs in the head and neck, whereas PTs of the larynx are more related to SPTs in the lung.

For Jones et al,[19] the location of the PT had a significant influence on the location of SPTs. When the PT was located in the hypopharynx, larynx, and/or oropharynx, the second neoplasm was more often located in the lung; whereas when the first neoplasm was located in the oral cavity, the second neoplasm was also located in the oral cavity. In our results, we observe (Table 2) that PTs of the supraglottis, glottis, or

hypopharynx most commonly present SPTs in the lung, whereas PTs of the oral cavity present SPTs most often in the larynx, the oropharynx or the hypopharynx.

According to our results, most of the SPTs are metachronous (71%) and the mean time of appearance between the PT and the SPT is about 40 months. We have found that more than half the SPTs (58.25%) are diagnosed within the first 3 years of follow-up and that 68% of all SPTs are diagnosed within the first 5 years after diagnosis of the PT. However, up to 32% of all patients develop an SPT after 5 years (as shown in Figure 1). This finding is significant as it underscores the importance of prolonged patient follow-up, given that a significant number may develop SPTs after the first 5 years.

The American Cancer Society has proposed a follow-up plan for these patients, including examination of aerodigestive tract, yearly chest x-ray and complementary testing, such as oesophagoscopy or bronchoscopy, depending on the clinical findings.[20] Some authors even advocate performing panendoscopic screening during the evaluation of the index tumour in order to rule out synchronous tumours. However, Haughey et al[21] found that panendoscopy did not offer much of an advantage as a screening process in the detection of SPTs. Hence, it appears that screening with panendoscopy offers few benefits in comparison with screening by means of yearly chest x-rays and complementary testing in the light of the patient's symptoms. A prospective study of panendoscopy in this type of patient questions the cost-effectiveness of this procedure.[22] Nevertheless, despite the follow-up protocols for these patients, many SPTs are diagnosed as a result of the clinical symptoms they cause. In a study conducted by Shah and Applebaum,[23] in the course of the follow-up of patients who had developed a tumour in the head or neck, the usual chest x-ray detected a mere 34% of the lung tumours, whereas the remaining 66% were diagnosed on the basis of the symptoms the patient developed. Some authors have proposed follow-up with more aggressive protocols: chest x-ray every 3 months for 3 years and annually thereafter[24] or cytological sputum every 3 months and chest x-rays.[25]

Studies are under way to determine the effectiveness of new techniques for SPT detection, such as positron emission tomography (PET) or serial determination of certain serum tumour markers (anti-p53 antibodies, metalloproteases, …).[26,27] Stokkel et al,[28] in a prospective study in patients with tumours of the head and neck, concluded that the use of PET significantly increased the percentage of SPT detection. However, more studies are needed to determine the usefulness of PET in the diagnosis of SPTs.

According to our results and with reference to the oncology database including 1331 patients with squamous cell carcinomas of the head and neck, the PTs that most often develop an SPT are those of the hypopharynx (21.34%), followed by the oropharynx (15.38%), oral cavity (7.93%), supraglottis (7.45%), and glottis (5.51%). According to some studies, supraglottic tumours have a greater risk of presenting SPTs than glottic tumours. Wagenfeld et al[12] have stated that the incidence of multiple cancer in supraglottic lesions is 3 times greater than that of glottis lesions. Other authors[19] do not find such striking differences; nor have we on the basis of our own results.

On the other hand, the issue of radiotherapy prior to the SPT and the relation between radiotherapy and the incidence of an SPT is a matter of debate. Our results reveal that 47% of the patients who developed an SPT had received radiotherapy to treat the PT; however, these data must be interpreted with caution.

As we can see from the survival curve, these patients have a survival rate of 33% five years after diagnosis of the SPT, reflecting the fact that presenting a second neoplasm considerably worsens the prognosis with respect to those who present a single cancer, although much depends on the location of the second tumour. There are several reasons why prognosis is worse in these cases. On the one hand, many SPTs have an unfavourable prognosis (lung, oesophagus), on the other hand, the SPT is often diagnosed after it has reached advanced stages, and finally, radical treatment of the PT may hinder treatment of the second tumour.[12] All authors agree in pointing out that patients who develop an SPT have a lower survival rate than those who do not.[20,21] According to Dooghe et al,[29] an SPT has the same prognosis as recurrence of the PT. However, recent studies[30] highlight the poor survival rate of tumour relapse in the area of the oral cavity, whereas survival is 61% in the case of an SPT in this location.[31]

Development of an SPT is considered to be the main cause of failure and death in patients diagnosed with carcinoma of the head and neck in early stages.[19,32]

On the other hand, the location of the SPT also has a bearing on survival. As we see in our results, the patients with an SPT in the oesophagus, lung or stomach have lower survival rates than those who present an SPT in another location; this is consistent with the data found in the literature.[19]

In conclusion, we would point out the high incidence of appearance of an SPT in the area of the head and neck, as reflected in most of the series in the literature, with the resulting effect on survival and worsening of prognosis. It is important also to underscore the importance of periodic and comprehensive follow-up in these patients, given the possibility of their developing an SPT even 10 years after diagnosis of the PT; however, it is hard to establish the most appropriate technique that will diagnose these SPTs earlier, particularly if we consider cost-effectiveness. We must therefore pay close attention to the new studies using techniques such as PET or tumour markers to detect these neoplasms early.

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