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The risk of second primary tumors in head and neck cancer: a systematic review

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Abstract

Background: Second primary tumors (SPTs) are a common cause of reduced life expectancy in patients treated for head and neck cancer (HNC). This phenomenon forms an area to be addressed during posttreatment follow-up.

Methods: We conducted a systematic review of literature following PRISMA guidelines, from 1979 to 2019, to investigate incidence of SPTs, synchronous and metachronous, in HNC population.

Results: Our review includes data of 456,130 patients from 61 articles. With a minimum follow-up of 22 months, mean incidence of SPTs was 13.2% (95% CI: 11.56-14.84): 5.3% (95% CI: 4.24-6.36) for synchronous SPTs and 9.4% (95% CI: 7.9-10.9) for metachronous SPTs. The most frequent site for SPTs was head and neck area, followed by the lungs and esophagus.

Conclusion: Although with wide variations between studies, the rate of SPTs in HNC patients is high. Given the impact in the prognosis, we must develop strategies for the early diagnosis of SPTs.

Introduction

Head and neck cancers (HNCs) are the sixth most common malignancy worldwide. Approximately two thirds of HNC patients present with locally advanced disease[1]. The survival rates for early stage disease are high, but despite advances in treatment options, about 40% of locally advanced cases will recur after front-line treatment. More than 50% of these patients will develop a loco-regional recurrence within two years, and a 20-30% of those patients will develop distant metastases[2]. In contrast, most HNC patients are tobacco and alcohol consumers who have a significant risk of second primary tumors (SPTs), which may be detected either at the point of diagnosis or during follow-up[3]. SPTs are a major cause of mortality in HNC survivors[4–6]. It is postulated that this phenomenon is the result of "field cancerization" which denotes the entire aerodigestive epithelium having been exposed to chronic carcinogenic insults and is therefore predisposed to develop multiple premalignant and malignant lesions[7]. SPT risk is about 2% to 4% per year, a rate of about 10-20% overall lifetime risk[1,8].

The complexity of organizing follow-up for HNC patients includes the technical expertise required (e.g. flexible naso-laryngoscopic examination, imaging studies), the comorbidities experienced by the patients and the psycho-functional disruptions caused by both the disease and treatment[9]. The main objectives of follow-up in HNC is the evaluation of clinical response and adverse effects of treatment, the early detection of a recurrence or SPTs and the restoration of the patient to their premorbid health status to the maximal extent possible[2]. In general, a HNC surveillance program must consider

several aspects: the index disease recurrence rate, the optimal method for monitoring, and whether earlier detection of recurrence has the potential to result in successful salvage treatment and/or improved survival[10].

Two important factors that should be considered: first, the influence of persistent tobacco and alcohol use on the risk of SPTs in the aerodigestive tract, and second, the differences between HPV positive patients and negative patients in terms of SPT incidence. For example, Leon et al[11] carried out a matched case-control study in 514 patients with HNC and found that the odds ratio of SPT for patients who continued to smoke was 2.9 and for patients who continued to use alcohol it was 5.2. With respect to HPV status, it has been reported that patients with HPV-positive oropharyngeal cancer have a lower risk of appearance of SPTs than HPV-negative patients, particularly in those locations related to tobacco use or alcohol consumption[12]. Thus, Morris et al[13] reviewed 75087 patients with HNC and found that before the 1990s, hypopharynx and oropharynx cancers carried the highest risk of SPT, since then, during the HPV era, SPT risk associated with oropharyngeal cancer has declined to the lowest risk level of any subsite. A recent retrospective study in a large cohort of HNC patients also showed that patients with HPV-related tumors has a lower risk of development of SPTs[14].

This review aims at defining the average rate for SPTs in HNC patient population and the pattern of synchronous and metachronous tumors.

In order to evaluate the incidence of SPT on the long-term follow-up of the HNC patients, we performed a review of relevant articles on this issue.

Material and methods

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) method was used to conduct a systematic review of the current literature[15]. The search strategy aimed to include articles concerning the develop of SPTs in patients treated for HNC. A PubMed internet search updated to April 1, 2019 was performed for English language publications between the years 1979 and 2019 using the following search criteria in the title or abstract: “head and neck cancer,” coupled with “second primary cancer” or “second primary tumor” or “second primary malignancy”, “metachronous” and “synchronous”. The search results were reviewed for potentially eligible studies. When there was any information in the abstract about the study addressing SPTs in HNC patients, the full text article was searched. All review articles were also checked in full. References from any full text articles were cross-checked to ensure inclusion of all relevant publications (Figure 1). Studies were selected if they met the following inclusion criteria: (1) patients treated for HNC (mucosal squamous cell carcinoma), (2) information on the percentage of SPTs in these patients and (3) on the location of the SPTs are included in the text. Studies in which the percentage of SPTs was analyzed in patients with non-head and neck primary tumors, or when HNC data were analyzed together with primaries from other locations, were excluded. The same applied to articles in which only a specific type of SPT was analyzed. This last criterion was included because the objective of our study was to assess the incidence of all possible SPTs and not only in one location (for example, in lung).

Results

Our search criteria identified, 5540 papers and after removal of duplicates, 61 papers were selected for data review and are summarized in Table 1[5,6,16-74]. Most of the studies were retrospective. Our review includes 456,130 patients from these 61 articles during a period of 40 years (1979-2019). As can be seen in Table 1, data on the percentage of synchronous and metachronous tumors were not available in all articles, and some of them only reported the total percentage of SPTs. The mean rate of SPTs was 13.2% (95% CI: 11.56-14.84)). The mean rate of synchronous SPTs was 5.3% (95% CI: 4.24-6.36). In the case of metachronous SPTs, with a minimum follow-up of 22 months in the included studies (range 22-252 months, median 55 months), the mean rate was 9.4% (95% CI: 7.9-10.9). The large difference in SPT rates observed in Table 1 could be explained by several reasons: there is great variability between the studies, in terms of the location of tumors, the characteristics of the patients, as well as the duration of follow-up (since the incidence is cumulative, the duration of the follow-up is critical and may explain much of the observed difference) and the diagnostic methods used to detect SPTs. In 24% of the studies panendoscopy was the method used to screen for SPTs and in 15% some type of imaging test, but in 61% of them there is no data about which tests were used to diagnose SPTs.. In several studies, a hospital or regional tumor registry was used for the collection of the data, which explains the large proportion of SPTs found outside the aerodigestive system, with the consequent higher rate compared with studies using panendoscopy alone. In order to extract more information on the data available, we divided them in different ways (Table 2). Studies were coded as

prospective or retrospective, observing that the main bulk of patients were included in retrospective studies. A lower percentage of synchronous SPTs were observed in retrospective studies, 3.6%, compared with 8.5% in prospective studies, but the overall percentage of SPTs was higher for retrospective studies (13.4% vs 10.8%). The percentage of synchronous SPTs was higher in prospective studies, given that almost all studies in this group were conducted during the first two decades of the present review i.e. when the main diagnostic method used for diagnosing SPTs was panendoscopy. In more recent retrospective studies, other methods such as PET/CT were used, which makes it easier to detected SPTs in distant locations during follow-up. When we divided the studies by the time periods (1979-1998 vs. 1999-2019), we observed that majority of them were published during the last two decades and there was a difference in total percentages of SPTs (11.1% vs. 14.8%) between the two time periods. The great difference in the number of patients is most likely due to the ease with which large patient registries can now be accessed and obviously the better diagnostic techniques.

Discussion

It is known that HNC survivors have increased morbidity and mortality risk compared with the healthy population and this relates to treatment sequelae, coexisting pulmonary, cardiac, and liver diseases as well as development of SPTs secondary to smoking and alcohol use[75]. SPTs that often arise from the aerodigestive epithelium, are a major cause of mortality in HNC survivors[4]. The criteria defining a SPT were established by Warren and Gates in 1932[76] 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 metastasis from the other is excluded. The index tumor is the first diagnosed tumor, and the SPT is any malignancy discovered thereafter. SPTs are classified as synchronous if they are diagnosed at the same time as the index tumor, e.g. during staging of the index tumor, or within six months after discovery of the index tumor. If the SPT is discovered after a follow-up period of six months, it is classified as metachronous.

It is remarkable that the great majority of the patients in our review belong to retrospective studies from the last 20 years (more than 420,000 patients). This fact is important at the time of analyzing the data since being the majority retrospective studies, it is necessary to consider the possible selection bias, or of another type that could have been produced in such studies. Chuang et al[62] performed a study to assess the risk of SPT, they calculated the standardized incidence ratios (SIRs). The number of SPTs observed was compared to the expected number of cancers to estimate the SIRs. For all cancer sites combined, the SIR of SPTs was 1.86 and the 20-year cumulative risk was 36%. Lung cancer contributed the highest proportion of SPTs with a 20-year cumulative risk of 13%. They suggested that patients with HNCs are at increased risk of developing a SPC of the oral cavity and pharynx, esophagus, larynx and lung. Using SIRs is the most appropriate method for reporting the SPTs, but this methodology is used in only a few studies.

The follow-up time for patients included in this review is difficult to analyze as many studies do not provide data about the mean follow-up or only give a minimum

follow-up times that patients should have in order to be included in the study. There were 20 articles given data about median follow-up. The median follow-up time is 4.6 years. However, as expected, for prospective studies the duration was shorter (2.6 years). As mentioned, these differences in follow-up periods could have influenced the reported rates of SPTs, as the incidence is cumulative between 3-7% per year[62].

There are some articles in which the method used to detect SPTs is panendoscopy (bronchoscopy, esophagoscopy, direct laryngoscopy and examination of the nasopharynx). Hujala et al[59] reviewed 203 consecutive patients with HNC and reported a 3.9% rate of synchronous SPTs. During the follow-up they found a 9.3% of metachronous SPTs. However, other authors including Hordijk et al[41] have questioned the usefulness of this procedure given the small number of tumors it detects (between 1-2%) and conclude that "panendoscopy should therefore be performed only as this diagnostic procedure is part of a well-documented prospective study". Dhooge et al[48] analyzed the use of panendoscopy in patients treated with HNC to evaluate the usefulness of each of their procedures. They found a 3.4% rate of synchronous SPTs. They conclude that rigid bronchoscopy should not be performed if chest radiograph is normal. Also, they do not recommend esophagoscopy as a screening procedure in every HNC patients, and instead advocate direct oro-hypopharyngo-laryngoscopy. Rodriguez-Bruno et al[66] suggested that routine panendoscopy should not be performed in nonsmoking patients since that in their retrospective study of 64 patients, they found 12.1% of synchronous SPTs in smoking patients and no synchronous SPTs were discovered in nonsmoking patients. Priante et al[77] analyzed the efficacy of a single

initial triple endoscopy in patients with HNC. The diagnosis of SPTs was more frequent in the intervention group than in a control group who underwent routine clinical examination. Although in the triple endoscopy group 50% of the SPTs were diagnosed earlier, at the time of initial evaluation, there was no impact on prognosis. These conclusions should be taken with caution as the number of patients is very limited. It is important to realize that many studies report on a period with less advanced imaging techniques through which SPTs were not detected by imaging, but by panendoscopy. The importance and yield of panendoscopy were probably higher in the past than now following contemporary imaging in the diagnostic work-up. On the other hand, new endoscopic techniques, e.g. narrow band imaging (NBI)[78], may detect SPTs earlier, even as a synchronous instead of a metachronous tumor. Studies with image-enhanced endoscopy have shown very promising results in the detection of SPTs. Lugol's stain isolates abnormal mucosal islands within otherwise normal tissue, especially in the esophagus, enabling targeted biopsy. When combined with NBI, it is reported to have a sensitivity of 94.7% and a specificity of 90.4% to detect early stage esophageal lesions[79]. Bugter el al[80] carried out a systematic review on the diagnostic yield of Lugol chromoendoscopy for esophageal SPTs in patients with HNC, showing that on average, 15% of the patients with primary HNC that underwent Lugol chromoendoscopy were diagnosed with an esophageal-SPT, which compares favorably with the prevalence of retrospective non-screening studies (1%-6%).

On the other hand, molecules such as DNAs, RNAs, proteins, metabolites, and microbiota, could be found in saliva. Therefore, salivary diagnostics has drawn

significant attention for the detection of specific biomarkers of cancer. Interestingly, salivary biomarkers signal not only for oral and pharyngeal disorders but also for tumors in different organs, suggesting that oral fluids may represent a substantial reservoir of molecular and microbial information, potentially useful to develop saliva-based biomarkers indicative of both local and systemic diseases[81,82].

The location of the index tumor is an important factor, but its impact remains difficult to analyze due to the contradictory data found in the literature. Some authors have shown that the index tumor site is related to the risk of developing a SPT: Jones et al[47] demonstrated that patients with oral cavity and oropharyngeal cancer had a significantly higher incidence of SPTs than patients with laryngeal or hypopharyngeal index tumors, as well as Haughey et al[83] and Rafferty et al[53]. Conversely, Patrucco and Aramendi[70], and Hujala et al[59], showed that the larynx is the location with the highest risk of developing a SPT. Within larynx, the greatest risk for SPTs is connected with supraglottic primary tumors, according to Leon et al[49]. As the annual rate of SPTs in most studies is constant (between 3 to 5%), the locations with the highest rate of cure will be those with a higher cumulative incidence of SPTs.

Review of the data suggests that the most frequent site of SPTs is the head and neck area, followed by the lung and then, the esophagus. Rafferty et al[53] showed that the most common site, in their study of 425 patients, for the SPT was the oral cavity. They also found a high incidence of SPTs in the lungs. Jones et al[47] found that the most common SPT site was the lung for patients with oropharyngeal, hypopharyngeal and laryngeal index tumors. Schwartz et al[46] discovered that the esophagus was the most

frequent location for the synchronous SPT and the lung for the metachronous SPT. Within the head and neck area, the most frequent site for synchronous SPT was the pyriform sinus, and for the metachronous SPT the oral cavity. Hordijk et al[27] as well as Black et al[25], showed the majority of the SPTs were found in the head and neck region and lungs. Argiris et al[5] found that the most frequent site of SPTs was the lungs, esophagus and less frequently the head and neck.

Further, review of the literature reveals that SPTs is associated with a decreased overall survival[5,47–49,51,53]. SPTs may arise at unfavorable sites like lungs or esophagus. Often, they arise in previously irradiated or operated areas. Therefore, the choice of treatment of the SPT may be influenced by the treatment of the index primary tumor. Because of prior therapy, the full range of treatment options may not be available (e.g. radiotherapy dose). Moreover, general condition of the patient with a newly diagnosed SPT can be severely compromised after the first treatment which can also explain why these tumors cannot always be treated according to accepted guidelines[84,85].

Argiris et al[5] found that the causes of death in 324 HNC patients from their study, were: treated malignant disease, treatment-associated acute or late complications, SPT, comorbidities (cardiac and respiratory illness) and unknown causes. The cumulative incidence of SPT was 5%, 7%, and 13% at 3, 5, and 10 years, respectively. Accordingly, Rennemo et al[64] reported that 351 (17.0%) of 2063 patients with HNC developed SPTs, and the overall survival rates of these patients were 40.0% at 5 years and 25.0% at 10 years, which were significantly lower than those in the non-SPT group ($P<.001$), suggesting the need for early identification and management of SPTs to

improve overall survival rates of these patients.

With this review we hope to raise awareness of the problem of SPTs in patients with HNC. Many areas remain understudied including the impact of HPV related disease and the association with SPTs, the association between risk of SPTs and time from index primary tumor treatment and the role of continued diagnostic imaging in screening this high-risk population. By addressing these factors, a more evidence-based approach to follow up strategies could be developed for patients with HNC.

Conclusions

In this review, we found a mean rate of SPTs of 13.2% in patients treated for HNC, with a great discrepancy between studies. As SPTs significantly affect the prognosis of HNC patients, follow-up of HNC patients should involve screening for SPTs. Since the head and neck area and the lung are the sites more frequently involved, follow-up should include a full head and neck examination including flexible laryngoscopy and consideration of chest imaging in high-risk groups.

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Figure 1: Flow chart showing the process of the study selection for the systematic review.

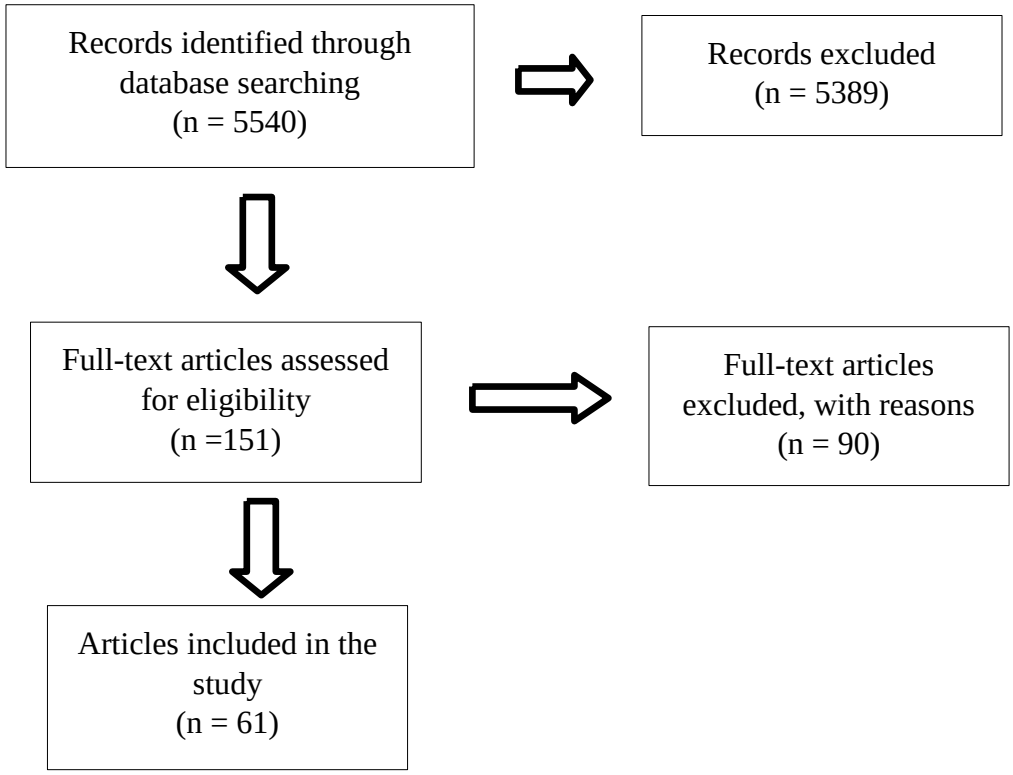

Table 1: Compiled findings in selected series describing multiple primary tumors in the head and neck.

Authors[Ref]	Year	N° patients	Study	% of ST	% of MT	% Total	Location of SPT
Weichert and Schumrick[16]	1979	825	R	2.3	4.2	6,5	Head and neck, lung, esophagus
Vrabec [17]	1979	1518	R	3.7	7.8	11.5	Head and neck, lung, esophagus, other locations
Gluckman [18]	1979	162	P	9.2	NA	NA	Head and neck, lung
Weaver et al[19]	1979	124	P	12.9	NA	NA	Head and neck, lung, esophagus
Shapshay et al [20]	1980	150	P	19	NA	NA	Head and neck, esophagus
Maisel and Vermeersch [21]	1981	449	R	8	4.7	12.7	Lung, esophagus
Atkinson et al [22]	1982	271	P	10.3	NA	NA	Head and neck, lung, esophagus
Deviri et al [23]	1982	1660	R	0.9	4.2	5.1	Lung, digestive tract, bladder
McGuirt [24]	1982	100	P	18	NA	NA	Head and neck, lung, esophagus
Black et al [25]	1983	645	P	8.9	NA	NA	Head and neck, lung and other locations
		577	R	6.2	14.7	20.9	
		5337	R	5.1	8.7	13.8	
Grossman et al [26]	1983	696	P	5.4	NA	NA	Head and neck, lung, esophagus
Hordijk and De Jong [27]	1983	1148	R and P	2	15.5	17.5	Head and neck, lung and other locations
Atkins et al [28]	1984	451	R	2.5	5	7.5	Head and neck, lung, esophagus, other locations
Leipzig et al [29]	1985	384	P	8.9	NA	NA	Head and neck, lung, esophagus
De Vries et al [30]	1986	210	R	1.9	15.7	17.6	Head and neck, lung, esophagus, other locations
Lau et al[31]	1986	105	P	8.5	NA	NA	Head and neck, lung, esophagus
Lundgren and Olofsson [32]	1986	295	R	1.4	11.2	12.6	Head and neck, lung, esophagus
Schuller and Fritsch [33]	1986	53	P	11.3	NA	NA	Head and neck, lung
Shikhani et al [34]	1986	1961	R	4.9	4.7	9.6	Head and neck, esophagus
Shibuya et al [35]	1987	1429	R	2.3	7.2	9.5	Head and neck, digestive tract

Masaki et al [36]	1987	3162		R	1.2	7.1	8.3	Head and neck, digestive tract, lung
Poppendieck [37]	1987	589		P	3.05	3.4	6.45	Head and neck. esophagus, lung
Parker and Hill [38]	1988	208		P	7.2	NA	NA	Head and neck, lung
Poppendieck and Schrader [39]	1988	712		R	7.1	7.9	15	Head and neck. esophagus, lung
Shaha et al [40]	1988	140		P	13	NA	NA	Head and neck. esophagus, lung
Hordijk et al [41]	1989	141		P	1.4	NA	NA	Head and neck, lung
Panosetti et al [42]	1989	9089		R	3.9	5.3	9.2	Head and neck. esophagus, lung
Panosetti et al [43]	1990	796		R	4.1	5.4	9.5	Head and neck, esophagus, lung
Choy et al [44]	1992	573		P	1.9	0.5	2.4	Head and neck. esophagus, lung
Esteller Moré et al [45]	1992	1212		R	3.13	NA	NA	Head and neck, esophagus, lung
Schwartz et al [46]	1994	851		R	7.75	11.28	19.3	Head and neck, esophagus, lung
Jones et al [47]	1995	3436		R	1	7	8	Head and neck, lung, other locations
Dhooge et al [48]	1996	127		P	3.4	NA	NA	Head and neck, lung
León et al[49]	1999	1845		R	4.6	11.7	16.3	Head and neck, lung, esophagus, other locations
Esposito et al[50]	2000	877		R	1.14	4.3	5.4	Head and neck, lung, esophagus, other locations
Nikolaou et al[51]	2000	514		R	1.48	6.29	8.17	Head and neck, lung, esophagus, other locations
Albright et al[52]	2001	23150	364<40 y	R	NA	NA	8.2	Head and neck, lung, esophagus, other locations
			22786≥40 y				21.3	
Rafferty et al[53]	2001	425		R	2.1	6.4	8.5	Head and neck, esophagus, lung
Stoeckli et al [54]	2001	358		R	6.4	9.8	16.2	Head and neck, esophagus, lung
Spector et al [55]	2001	2550		R	NA	NA	8.9	Head and neck, lung, esophagus, other locations
Holland et al[56]	2002	240		R	4.1	24.1	28	Head and neck, lung, esophagus, other locations
Gao et al[57]	2003	20074		R	NA	NA	17.6	Head and neck, esophagus, lung, other locations
Warnakulasuriya et al [58]	2003	59958		R	NA	NA	4.6	Head and neck, lung, esophagus, other locations
Argiris et al [5]	2004	324		R	NA	NA	8	Head and neck, esophagus, lung, other locations

Hujala et al[59]	2005	203	R	3.9	9.35	13.3	Head and neck, lung
Alvarez Marcos et al[60]	2006	633	R	NA	NA	11	Head and neck, lung, esophagus
Sjögren et al[61]	2006	359	R	1.9	25.7	27.7	Head and neck, esophagus, lung, other locations
Chuang et al[62]	2008	99257	R	NA	NA	10.9	Head and neck, esophagus, lung, other locations
Lopez Mollá et al[63]	2008	1330	R	NA	NA	7.73	Head and neck, lung, esophagus, other locations
Rennemo et al[64]	2008	2063	P	NA	NA	17	Head and neck, lung, other locations
Morris et al[65]	2011	75087	R	NA	NA	23.2	Head and neck, lung, esophagus, other locations
Rodriguez-Bruno et al[66]	2011	64	R	6.25	NA	NA	Head and Neck
Jégu et al [67]	2013	6258	R	NA	NA	21.1	Head and neck, esophagus, lung
Krishnatreya et al[68]	2013	4184	R	1.3	NA	NA	Head and neck, esophagus, lung
Lee et al[6]	2013	937	R	7.2	11.4	18.6	Head and neck, esophagus, lung, other locations
Tiwana et al[69]	2014	1658	R	3	24	27	Head and neck, lung, esophagus, other locations
Patrucco and Aramnedi[70]	2016	307	R	0.32	8.46	8.79	Head and neck, lung, esophagus, other locations
Adeel and Siddiqi[71]	2018	221	R	NA	8.14	NA	Head and neck, esophagus, lung
Boakye et al[72]	2018	109512	R	NA	NA	12.3	Head and neck, lung, esophagus, other locations
Leoncini et al[73]	2018	4005	R	NA	NA	8.6	Head and neck, lung, other locations
Silén et al[74]	2019	151	R	NA	NA	26	Head and neck, lung, esophagus, other locations

R: Retrospective, P: Prospective, ST: Synchronous tumor, MT: Metachronous tumor, NA: Not available, Y: Years.

Table 2: Analysis of the significant differences in Table 1.

Data		N° patients	Mean % ST	Mean % MT	% Total	Median follow-up
By years	1979-1998	39586	6	7.6	11.1	3.2 years
	1999-2019	420107	3.3	12.5	14.8	5 years
By type of study	R	448451	3.6	9.7	13.4	4.9 years
	P	7679	8.5	6.5	10.8	2.6 years
Global		456130	5.3	9.4	13.2	4.6 years