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● *Original Contribution*

MULTIPLE PRIMARY CANCER IN PATIENTS WITH CANCER OF THE HEAD AND NECK: SECOND CANCER OF THE HEAD AND NECK, ESOPHAGUS, AND LUNG

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Squamous cell carcinoma of the head and neck is complicated by a second primary carcinoma of the head and neck, esophagus (the upper aerodigestive tract, or UADT), or lung in 10–40% of patients. Routine panendoscopy will identify a simultaneous second primary in 9–14% of the patients. Metachronous second cancers most often involve the esophagus or lung, whereas synchronous second cancers are more common in the head and neck as occult lesions. For the highest-risk subgroups, second primary cancers occur in 4% of patients per year. In cancer of the floor of the mouth the excess mortality rate is 5–6% per year. Risk is independent of stage of the first primary and the survival impact is the greatest in groups of patients with early-stage disease. Head and neck cancer almost always results from the heavy use of tobacco for many years, either with or without the concomitant heavy use of alcohol, and these same agents are directly responsible for the second cancers of the UADT and lung. All head and neck cancer patients should be advised to avoid these agents. The clinician must diagnose and treat second cancers to extend the survival of patients with a good prognosis for control of the initial head and neck cancer. We need further progress in eliminating the use of known carcinogens in these patients, paradigms for cost-effective diagnosis and treatment of second primary cancers, effective treatment of the head and neck primary cancer devoid of long-lasting tissue toxicities, effective chemopreventive agents to retard established processes of carcinogenesis that place the patient at continued risk after cigarette and alcohol use has been eliminated, and continued efforts to control the medical illnesses to which these patients are susceptible.

Cancer mortality, Chemoprevention, Neoplasms, Multiple primary, Lung neoplasms, Head and neck neoplasms, Carcinoma, Squamous cell.

INTRODUCTION

Despite concerted efforts of surgery, radiotherapy, and chemotherapy to control head and neck cancer, at most 50% of patients are alive 5 years after diagnosis, and survival rates have not improved in recent years. The initially diagnosed cancer accounts for half of the deaths, with the other deaths equally divided between those due to a second primary cancer and those due to various other illnesses (1, 28, 41). The majority of head and neck cancers are attributable to extensive use of tobacco; concomitant use of alcohol is very often a significant cofactor. The two agents are also responsible for most of the second primary cancers among these patients, and for other illnesses leading to death, although the latter are complicated by the long-term effects of combined-modality therapy.

Most second primaries in head and neck cancer patients occur in the head and neck, esophagus, which together define the upper aerodigestive tract (UADT), or in the lungs. Cancers of the lung and esophagus, each of which has a very high mortality rate, represent as many as 82% of all metachronous cancers in patients with resectable Stage III or IV disease (38). In one series, the 2-year survival after diagnosis of a metachronous second primary of any UADT or lung origin was only 27% (33).

This paper examines the incidence, anatomic distribution, and survival impact of second primary cancers of the UADT with respect to specific head and neck cancer sites as first primary and as second primary cancer sites. The risk of second cancer as determined by the observed-to-expected (O/E) ratio is cited from case series. Salivary gland carcinoma and cancer of the nasopharynx, diseases

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not associated with excess second cancers of the UADT, are disregarded. Cancer of the lip is included in some series of oral squamous cancer, such as the Connecticut Tumor Registry (3, 44) and Hamilton County Ohio Tumor Registry (9, 10) series, but is often excluded from other series; it is discussed with these limitations to interpretation of the data.

METHODS AND MATERIALS

The problem of synchronous multiple primary cancers

Second primary cancers of the UADT and lung are often found with, or a short time after, presentation of head and neck cancer. Those found within the first 6 months, termed synchronous second primary cancers, were most likely present at diagnosis as simultaneous lesions, some of them evincible but missed by routine physical examination (7). In the Connecticut Tumor Registry (3, 44) and Hamilton County, Ohio, Tumor Registry (9, 10) series, respectively covering the years 1935–1982 and 1950–1983, 1–2% of patients with head and neck cancer were considered to have a second primary cancer in the UADT or lung at presentation (Table 1). Since the late 1970s, with the widespread introduction of fiberoptic endoscopy into clinical practice, considerable data have been accumulated on second primary cancers detected with routine "panendoscopic" inspection of the pharynx, larynx, esophagus, and tracheobronchial tree in patients undergoing initial evaluation of head and neck cancer. The available panendoscopic series have increased the 1–2% range to 9–14% (4, 10, 30, 43) (Table 1).

Panendoscopic assessment has revised the description of the anatomic distribution of second primaries in head and neck cancer patients (Table 1). The proportion of second primaries in the head and neck increased considerably, as does cancers of the esophagus. The relative proportion of lung cancers decreased, although the total percentage of patients with simultaneous lung cancer increased compared to preendoscopy (3, 9, 44) series.

Maisel and Veermersch only used endoscopy in patients in whom radiographs suggested lung or esophageal cancer or in whom a second head and neck primary was suspected, and found an 8% incidence of a second primary (20). The analysis of Gluckman *et al.* of their Hamilton County Registry series by location showed the second primary incidence to vary: 12.5% for the oral cavity, 18% for the pharynx, 18% for the oropharynx, 7.4% for the hypopharynx, and 5.7% for the larynx (10).

The Boston panendoscopy series (Shapshay *et al.*) was remarkable because of its high overall incidence (6%) of simultaneous esophageal carcinoma (30). The reason for this incidence is unclear. Sixteen esophageal cancers were identified in patients with index head and neck cancer in the oropharynx (3 cases), hypopharynx (4 cases), oral cavity (5 cases), larynx (3 cases), and nasopharynx (1 case). The high degree of discrepancy between this and the other

Table 1. Synchronous upper aerodigestive tract primary cancers in head and neck cancer

Investigators: geographic location	No. of patients with head and neck cancer	Second cancer incidence (%)	Second cancer location (%)		
			Head + neck	Lung	Esophagus
Tumor registry series					
Boice and Fraumeni (3) Winn and Blot (44) Connecticut tumor registry (1935–1982)	11,959	0.8	45	34	22
Gluckman and Crissman (9) Hamilton County, Ohio, tumor registry (1950–1983)	4,890	2.0	45	33	22
Prospective panendoscopy series					
Gluckman *et al.* (10) Cincinnati (Univ. Cincinnati)	259	10.4	70	15	15
Cohn and Peppard (4) Detroit	274	9	42	26	32
Shapshay *et al.* (30) Boston, VA (Boston Univ.)	150	14	52	5	43
Weaver *et al.* (43) Allen Park, VA (Wayne State Univ.)	124	13	69	13	19
All U.S. prospective panendoscopy series	807	9–14	42–70	5–26	15–43

VA = Veterans Administration.

series in this parameter could be ascribed to the scrutiny of the endoscopist, or to the arbitrary anatomic distinction between the hypopharynx and the cervical esophagus.

Distribution within the UADT and lungs of second primary cancers

Generalizations can be made regarding the proportion of second cancers found at each location at risk within the UADT and lungs (Table 2). Tumor registry series of head and neck cancer patients reveal that about one-third are located in the head and neck, one-third in the esophagus, and one-third in the lung (9, 11, 44). Oral cavity index primary tumors are more likely than other index tumors to be associated with a second primary within the oral cavity, which is about one-third of all second primaries for these patients (27, 37, 39, 44). With an oral cavity index, about one-half of second primaries are in the head and neck, one-third are in the lung, and 12–29% are in the esophagus. Index primary cancers of the tongue and the pharynx behave similarly to each other.

Although the three index sites of oral cavity, tongue, and pharynx display considerable overlap in distribution of second primaries, laryngeal cancer has a different pattern. For these patients, cancer of the lung accounts for 45–76% of all second cancers. Cancers of the oral cavity, pharynx, and esophagus are less common second primaries, and cancer of the larynx is fairly uncommon, perhaps because of the frequent extirpation of this organ by total laryngectomy. Esophageal and lung cancers account for one-half to two-thirds of all second primary cancers, regardless of the site of the head and neck index primary.

Synopsis of results by index site

Second primary cancers of the head and neck vary according to the risk of second primary cancer. This is a function of the anatomic site of the index cancer.

Lip. In lip cancer, the risk of metachronous second cancer is increased both for head and neck cancer and cancer at remote sites. The impact of second cancers is low within the UADT and lungs, and survival is a function to treatment of the index cancer.

Oral cavity. Both synchronous and metachronous second cancers occur at high rates when the index primary is of the oral cavity. Survival is inferior for oral cavity cancer patients with second cancers, and the greatest impact is from metachronous second cancers. Impact on survival from metachronous tumors continues for 10 years or longer. Oral cavity index cancers vary in risk by specific sites. The floor of the mouth entails a high risk of lung cancer. Second cancers of the oral cavity are more common than in other groups of head and neck cancer patients. This association is the greatest risk of any second primary affecting head and neck cancer patients.

Tongue. In tongue cancer, the rates for second cancers are comparable to those in oral cavity and pharyngeal cancers. Second cancers in the head and neck (excluding the larynx) are the most common, but up to one-third are second primary cancers in the lung. Lung cancer occurs 5 years after diagnosis at increased rates. Leukoplakia confers a much-increased risk of a second primary. It is not clear if tumors of the base of the tongue and oral tongue share risk profiles either with each other or with the adjacent pharynx and oral cavity. Impact on mortality from second cancers has not been studied in tongue cancer.

Oropharynx. Second cancers are seen to occur at high rates in patients with oropharyngeal cancer when careful panendoscopic staging is used and at higher rates than with any other site in the head and neck where close follow-up extends over many years. One known high-risk subsite is the faucial arch, comprising both the tonsillar pillar and the palate. There is evidence for shortened survival for all patients with second cancer as measured from initial diagnosis, but the most deleterious impact is in patients with a metachronous second cancer. In this group of patients, the greatest threat from cancer to survival after 3 years is a second primary cancer.

Hypopharynx. Of head and neck cancer patients, patients who present with cancer of the hypopharynx are reported to have, at 10% or less, the lowest incidence of a second primary in the UADT and lungs (9, 10). Survival is minimally affected because of poor survival from the first cancer (9). The risk of lung cancer over time may be high, similar to that in other head and neck sites. This may become important if treatment of the first cancer improves.

Table 2. Distribution of second primary cancers of the upper aerodigestive tract by site of initially diagnosed head and neck cancer

Index cancer	Second cancer distribution (ref(s).)				
	Oral cavity	Pharynx	Larynx	Esophagus	Lung
Oral cavity	29–35% (37, 39, 44)	15–23% (37, 39, 44)	5.7–11% (37, 39, 44)	12–29% (1, 9, 10, 37, 39, 44)	28–40% (1, 9, 10, 31, 39, 44)
Tongue	22% (44)	13% (44)	3–5% (28, 31, 36, 44)	25% (44)	36% (44)
Pharynx	19% (39, 44)	8.1–17% (39, 44)	8–11% (39, 44)	19–27% (9, 10, 39, 44)	27–40% (9, 10, 39, 44)
Larynx	7.7–17% (3, 39)	6.4–7% (3, 39)	0–4.2% (3, 24, 34)	10–19% (3, 9, 10, 20, 39–41)	45–76% (3, 9, 10, 20, 39–41)

Larynx. The incidence in laryngeal cancer of synchronous second primary cancer is similar to incidence in other head and neck cancers. The pattern of second cancers shows more second cancer in the lung than with other head and neck cancers. Lung cancer represents as many as 76% of cases. Glottic cancers differ from supraglottic cancers in the risk of a second primary, the latter showing a somewhat higher incidence when different series are compared (6, 8, 16, 23, 40, 41). In the series of Wagenfeld *et al.*, the risk per year of second cancer was 4% after supraglottic carcinoma, but only 1.3% after glottic carcinoma (40). The impact on survival affects all subgroups with a second cancer when compared with patients without a second cancer, but it is the most severe in patients with metachronous second primaries. The impact is evident by 5-year survival. The risk of lung cancer is comparable to other sites of higher risk.

Interaction of primary head and neck cancer by site with second primary in the UADT: Incidence, risk, and survival impact

Lip. Lip cancer accounts for 0.6% of all head and neck cancers in the United States. The cause is thought to be the carcinogenic effects of direct exposure to tobacco and ultraviolet light. The 5-year survival is 85% (44). Second cancers in the UADT and lungs were encountered in 4–6% of the patients in the Connecticut and Hamilton County tumor registries (10, 44). The O/E measure of risk was increased for development of second cancer in the lip (0.9), tongue (5.3), gum and not-otherwise-specified (NOS) oral sites (2.5), larynx (2.5), and esophagus (1.7) (44). Only 0.4% of patients developed a second cancer within 1 year of diagnosis, and the metachronous second cancers occurred over many years. These later cancers were most often diagnosed after 5 years. Lung cancers represented 57% (44) and 68% (10) of all the second cancers in the UADT and lungs, yet were only 19% (44) and 23% (10) of all second cancers because the preponderance of tumors originated in tissues outside the UADT and lungs.

Oral cavity. Second primary cancers occur in as many as 33% of patients with oral cavity cancer (1, 9, 10, 28, 31, 32, 37, 41). The Connecticut and Hamilton County series report that 7.9% and 13% of tumor registry patients developed a second primary in the UADT and lungs. Of second tumors in those areas, 50–60% are in the head and neck (29–35% in the oral cavity, 15–23% in the pharynx, 5.7–11% in the larynx) (37, 39, 44) 28–40% are in the lung (1, 9, 10, 37, 39, 44), and 12–29% are in the esophagus (1, 9, 10, 37, 39, 44). The incidence of a simultaneous second primary was 12.5% in a single panendoscopy series (44). Two hospital series give a similar breakdown of the site-specific incidence of second cancer. From the University of Cincinnati, the total incidence of a second primary was 15.2%, comprising 7.7% in the oral cavity, 5.0% elsewhere in the head and neck, 2.6% in the esophagus, and 6.4% in the lung (37). In the latter series, metachronous second cancers occurred in patients up to 15 years following the original diagnosis.

Not all sites in the oral cavity carry an equal risk for second primary cancer. The highest risk sites are the gum and NOS sites, the floor of the mouth, and the cheek for second oral cancer, and the gum and NOS sites and the floor of the mouth for second lung cancers (1, 37, 44).

The adverse impact on survival from a second primary is evaluable by comparing survival against that of patients without a second primary, and by examining the death rate from causes other than the index tumor, focusing upon deaths attributable to second primary cancer. In the Princess Margaret Hospital series, the survival of patients with a second primary cancer deteriorated over time following the initial diagnosis, without evidence of a plateau (17). When the excess mortality was examined, there was a 5.2% annual mortality from second primary cancer in the interval of 5 to 10 years following the initial diagnosis. For patients without a second primary cancer, the actuarial survival was 37% at both 5 years and 10 years. Note that 75% of the Princess Margaret Hospital patients with a second primary had a T1N0 or T2N0 initial cancer by TNM staging, versus 57% of series patients without a second primary. Total second-primary survival was higher at 5 years: 48.7% versus 37%. For survival at 10 years, having a second primary erased the survival advantage conferred by having an early-stage cancer at initial presentation in oral cavity cancer. Gluckman and Crissman also found poorer survival with a second primary cancer (9). Five-year survival for patients with a single primary was 26.9%, for those with a synchronous primary it was 20%, and for those with a metachronous primary it was 10.5%. For all cases with a second primary, the 5-year survival was 15.2% (9).

Tongue. About a fourth of oral and pharyngeal squamous cell carcinomas and a sixth of head and neck cancers arise in the tongue (44). Second primary cancers to index tongue cancer occurred in 4.8% of cases recorded in the Connecticut Tumor Registry, a rate similar to those of other head and neck sites analyzed (44). This is the only North American series including the risk of second cancer for this head and neck site. The risk at 10.1 (as measured by the O/E ratio) was high for the development of a second primary in the oral cavity or pharynx. The risk by site of the new cancer was 16.6 for the gum and NOS oral sites, 10.7 for the pharynx, and 9.0 for the tongue. The risk to the larynx was 3.1; to the lung, 2.9; and to the esophagus, 15.5. In the first 4 years from diagnosis, 71% of all second cancers in the oral cavity and pharynx, and 72% of all second cancers in the esophagus were diagnosed. Lung cancers were diagnosed both early and late compared with these sites: 8% in the first year, 44% in the second through fourth years, and 30% more than 10 years from the initial cancer diagnosis. In this series, only 21% of the patients lived beyond 5 years, and these 5-year survivors developed about half of all lung cancers.

Because tongue cancer comprises both lesions of the

oral tongue and pharyngeal lesions centered in the base of the tongue, unspecified tongue cancers were arbitrarily assumed to be evenly distributed between the two sites, in particular to assign second cancers of the tongue into the oral cavity or pharyngeal category for Table 2. Oral tongue lesions are not specifically dealt with in this section of the paper because of the absence of North American data. Jesse and Sugarbaker included the base of tongue in their extensive analysis of cancer of the oropharynx (14). Note that only 17% of cases in that series were staged T1N0 or T2N0, indicating that advanced cancers are perhaps more likely for this subset of patients than for patients with cancer of the oral tongue. In a large Japanese series of tongue cancers, 73% of all second primaries within the UADT and lungs were located in the oral cavity (31). The O/E ratio to develop a second primary was 110, which is extremely elevated.

In the Japanese series the presence of leukoplakia at the diagnosis of the initial cancer increased the risk of a synchronous or metachronous second primary 5-fold (31). No comparable North American data exist regarding second cancers in patients presenting with tongue cancer or other head and neck cancer in the presence of leukoplakia. Leukoplakia itself confers a risk of frank neoplasia elsewhere within the UADT and lungs, when it presents as laryngeal epithelial hyperplasia with dysplasia (5). Histologic confirmation is usually required to distinguish leukoplakia, a benign change in the epithelium of the UADT, from frank malignancy and from other whitish lesions of these tissues. Lesions with premalignant features such as severe dysplasia, require attention because of the risk of malignancy elsewhere in the UADT and the lungs. Simple resection of these lesions does not alter the risk of cancer elsewhere. The risk of direct progression is significant, and it is much greater in patients from the United States than in patients studied in India and elsewhere (Table 3) (11, 35).

Pharynx. The literature provides divergent figures regarding the incidence of second primaries in pharyngeal cancer. The discrepancies may be due to the considerable heterogeneity in the actuarial survival from the index pharyngeal cancer or to differences in the nature of follow-up or in the method of determining the presence of a second primary.

Oropharynx. Jesse and Sugarbaker reported a 37% incidence of second primary cancer in the UADT and lungs in patients surviving 5 years from the diagnosis of cancer of the oropharynx (14). In their series, primary cancers of the oropharynx were subdivided into tumors of the faucial arch (44% of cases), the base of the tongue (26%), the tonsillar area (16%), and the pharyngeal wall (13%). The series of Strong *et al.* at Boston University addressed cancer of the faucial arch and found 32% incidence of second cancer, or 15% simultaneous and 16% metachronous second cancers (36). Eighty-three percent of these second cancers were in the head and neck, 13% were in the esophagus, and 4% were in the lung. Strong *et al.* (36) reported a 3-year survival of only 18% with simultaneous second primary cancer, compared with Gluckman and Crissman's (Hamilton County) 5-year survivals of 23.8% in this category, 21.0% with a metachronous second primary, and 27.0% for patients without a second primary (9). Jesse and Sugarbaker reported that all local and regional failures occurred within 3 years in their oropharyngeal carcinomas, although 10% of distant metastases occurred after 3 years (14). Second primary cancer was the most likely cause of cancer death in patients followed for more than 3 years in their series, and only 34% of 5-year survivors who had a second cancer were alive 10 years from the initial diagnosis. The faucial arch may be at especially high risk to have an associated second cancer of the UADT and lungs, particularly elsewhere in the head and neck, where cancer is often occult (36). Second cancers in the lung and esophagus may be more common as metechronous lesions.

Hypopharynx. Survival is poor in hypopharyngeal carcinoma. In the Hamilton County series, patients without a second primary had a 5-year survival of 13%, with survival decreasing slightly, to 9.1%, for patients with a second primary (9). T1N0 disease accounted for only 6% of cases and Stage I or Stage II disease for 38% of cases reported by Shah *et al.* from Memorial Hospital (29). Second cancers are reported in 3.7–10% of the patients (9, 16, 20). About one-half of these are in the head and neck, and the remaining half are in the lung or the esophagus (20, 38). In a small cohort of 5-year survivors following radiotherapy with or without surgery or chemotherapy, the incidence of lung cancer was 1.9–7% (1, 9, 20). The risk of

Table 3. Rate of progression of leukoplakia to squamous cell carcinoma as a function of the study population

Chief investigator(s)	Population location	No. in study (follow-up in yr)	Percentage that developed cancer
Silverman and Rosen	San Francisco	257 (mean, 7.2)	17.5
Silverman and Rosen	India	4,762 (2)	0.13
Gupta *et al.*	India	410 (1–10)	2.2
Kramer	England	187 (1–16)	4.8
Einhorn and Wesall	Sweden	782 (1)	0.5
		691 (10)	2.4
		447 (20)	4.0

Adapted from Hong and Doos (11) and Silverman *et al.* (35)

lung cancer appears to be as high as other head and neck cancers that have better survival (see Table 4).

Larynx. Second cancers occur in cancer of the larynx to about the same extent that they do in cancers of the oral cavity and oropharynx. Gluckman and Crissman found 15.3% of patients to have a second primary, including 6.8% with a second primary in the lung (9). The 5-year survival for those with a single primary was 43.5%, and survival declined to 36.5% for those with a synchronous second primary and to 16.8% for those with a metachronous second primary, in a pattern similar to survival in oral cancer. Wagenfeld *et al.* observed an actuarial 5-year survival of 60% for supraglottic carcinoma, but 5-year survival was only 34% when other causes of death were considered (41). Of the excess mortality, the cause was second cancer in the UADT or lungs in about one half, and medical causes other than cancer progression accounted for the remainder. The death rate from a second primary in the lung was 7.4% at 5 years in the entire group. In patients with glottic carcinoma who had T1 disease Wagenfeld *et al.* found mortality from a second primary to be 4.2% at 5 years and 7.5% at 10 years (40). The incidence of a second primary was 1.3% per year for glottic primary tumors and 4% per year for supraglottic primary tumors. Patients with supraglottic primaries had a 3-fold greater occurrence of second primary cancers between the two Wagenfeld series. In the series reviewed for the present report, the incidence of lung cancer is 2.4–11.7% (3, 10, 13, 20, 38). For supraglottic primaries the incidence is 3.6–10.6%, and for glottic primaries it is 2.5–8% (8, 16, 24, 34, 41, 43). Note that among patients in treatment or follow-up for laryngeal epithelial hyperplasia, the presence of dysplasia is associated with an appreciable incidence of neoplasia (invasive cancers) elsewhere in the UADT or lungs (31).

Table 4. Incidence of and assessment of risk for second primary cancer in the lung

Index tumor	Incidence (ref.)	O/E ratio (ref.)
Oral cavity	2.2–7.6% (9, 10, 13, 20, 44)	2.0–3.2 (28, 32, 44)
Lip	1.0–3.4% (9, 10, 28, 44)	1.3–1.7 (1, 44)
Cheek	—	0.8 (1)
Palate	—	6.0 (1)
Floor of mouth	2.1–7% (28, 37)	4.0–6.25 (28, 37)
Tongue (oral plus pharynx)	0.6–1.7% (28, 31, 44)	2.9–3.0 (44)
Pharynx	1.5–11% (9, 10, 44)	2.9–6.0 (1, 44)
Oropharynx	0.8–over 10% (14, 36)	—
Hypopharynx	1.9–7.0% (1, 9, 20)	—
Larynx	2.4–11% (1, 3, 8–10, 13, 20, 27, 36)	2.6–3.2 (3)
Supraglottic larynx	3.4–10.6% (6, 23, 41)	5.0 (1)
Glottic larynx	2.5–8% (6, 8, 16, 40, 41)	3.0 (1)

O/E = observed-to-estimated ratio.

Table 5. Histology of second primary cancer of the lung in head and neck cancer

Investigator(s)	Histology (% of cases) Squamous cell carcinoma	Adeno-carcinoma	Other
Lefor *et al.* (1986) (17)	60	18	22
Mitchell (1979) (23)	75	12	12
Lyons *et al.* (1986) (19)	40	36	24
Malefatto *et al.* (1984) (21)	42	16	42

Synopsis of impact of second primary in the lung

Second primary cancers in the lung are found in as many as 5% of head and neck cancer patients at presentation when the evaluation routinely includes panendoscopy (4, 10, 13, 24, 30, 41, 43). The second primary in the lung is more often metachronous. In patients with resectable Stage III or IV head and neck cancers, Vikram *et al.* noted a 5.3% incidence of metachronous lung cancer (38). Second primary lung cancer occurs most often among survivors of laryngeal carcinoma, constituting 45–76% of all second cancers for that index primary. (Table 2), and in one series the incidence was 11.7% (13). Although squamous cell carcinoma is the most common histologic type of lung cancer in series of head and neck primaries (Table 5), increasingly other histologies are seen (17, 19, 21, 25), namely, adenocarcinoma, small cell carcinoma, and other tumor cell types.

The incidence of and risk for second primary cancer in the lung are shown in Table 5 by the index head and neck cancer. Data from the Connecticut Tumor Registry (3, 44)—in which the O/E ratio was 3.2 for index cancers of the gum or other mouth sites, 2.9 for the tongue, 2.9 for the pharynx, 1.7 for the lip, and 3.2 for the larynx—are comparable to values from hospital-based series. For laryngeal cancer, the O/E ratio ranges between 2.6 and 5. For the other head and neck cancer sites, the O/E ratio is generally lower except for the floor of the mouth, and for the pharynx in some series.

Synopsis of impact of second primary in the esophagus

Esophageal carcinoma accounts for as many as 43% of all second cancers at presentation, and in one series it was found in 6% of all patients studied with routine endoscopy.

The incidence in tumor registry series is 1% of head and neck cancer patients (3, 9, 43, 44). In the Princess Margaret Hospital Series, the annual incidence was 0.33% in cancer of the floor of the mouth (37). The highest-risk index primaries in tumor registry series were the tonsil and the palate, with O/E ratios of 44 and 38, 3 times the O/E ratio for the larynx (3, 9, 43, 44). Cancer of the supraglottic larynx confers a 6- to 10-fold greater risk than cancer of the true glottis (1, 28). In one series, cancer of the esophagus occurred in all subgroups at rates of 9–17% (9), but the incidence in cohorts of larynx patients has not been studied as a function of larynx cancer subside.

DISCUSSION

The problem of second primary cancers in the upper aerodigestive tract and lungs in patients diagnosed with a head and neck cancer is multifaceted and complex. The survival impact of second primary cancers is an important facet that remains to be fully clarified, despite good data on the incidence of occult second primaries. Because of the lack of convincing data about this parameter, routine panendoscopy has remained an inconsistent part of patient evaluation and treatment planning. The rationale for routine staging panendoscopy has been discussed at length elsewhere.

The problem of metachronous second primary cancer is another dilemma for the treating physician. The risk for the development of a second primary in the lung exceeds that of age- and sex-matched controls (as determined by O/E ratio data) by a factor of 3 to 6 or higher. Such figures for second primary cancer in the esophagus have not been calculated. Head and neck cancer is a group of closely related malignancies with somewhat differing patterns of second primary cancers. These differences also reflect subtle differences in host biology. For the clinician, these patterns of second primary cancer are important in guiding follow-up, but they do not define the best approach to cost-effective case management. Some direction is given as to the time to include surveillance for a second primary in the case management. Because second primary cancers are often occult, ideally surveillance would begin within 2 years of initial diagnosis in patients with oropharyngeal cancer and within 4 years in patients with cancer of the floor of the mouth, supraglottic larynx, or tongue. Patients with supraglottic tumors appear to be at a greater risk than patients with cancers of the true glottis. Patients with laryngeal cancer of any subsite require lifelong surveillance for lung cancer since second cancers occur at a steady rate for 10 years and longer.

For the clinical researcher involved with the design and implementation of cancer clinical trials, primary-risk intervention trials, and chemoprevention trials, the data here should prove helpful. For example, to prove an intervention successful in decreasing mortality from second primary cancers in T1 glottic carcinoma would probably require a large sample size of patients, and a follow-up per patient of 10 years, because the magnitude of the problem of mortality from a second primary cancer is 5–30% over 10 years. To prove an intervention successful in decreasing mortality from second primary cancers in patients with cancer of the oropharynx would probably require a briefer duration of follow-up. This is because the mortality from the index cancer is more significant within the first 3 years; for survivors of the first cancer, a second primary cancer may affect 37% of patients, with 60% mortality, again cumulative over 10 years or more.

The important steps in devising an appropriate schema for case management are: (a) proper evaluation of patients for the presence of synchronous second primaries and associated premalignant changes in the epithelial tissues of the head and neck; (b) advising the patient who has a relatively good prognosis based on the index cancer of the risk of a second primary cancer of the UADT and lungs; (c) advising all patients to discontinue use of all tobacco products and to discontinue alcohol consumption, offering any available assistance to break these habits (1, 36); and (d) incorporation of routine follow-up surveillance of the UADT.

In these patients, it is desirable to clarify the relationships between the continued use of alcohol and tobacco, the presence of preneoplasia, and the development of a second primary cancer. Such studies will probably require cohorts of survivors who have been closely followed for 10 years since diagnosis; patients who are typified by histories of cigarette use, use of other tobacco products, alcohol consumption, and the presence of premalignant changes and for whom the TNM stage of the initial primary is known.

Studies of methods to decrease the mortality of second primary cancer can be divided into (a) studies addressing the issue of synchronous second primaries as to the best form of case management, and (b) studies addressing the issue of metachronous second primaries, which mainly concern themselves with issues of early detection, prevention of second cancers, and the cost-effectiveness of specific methods of follow-up. Our ability to intercede when second primary cancers are still treatable is still limited. The data suggest that for patients with oropharyngeal primary cancers, the second primary is often present at the time of diagnosis as an occult lesion. Many second primary cancers that are not present initially, are potentially diagnosable early after the initial tumor has been treated, at a time that the clinician is still focusing upon the initial cancer. The same holds true for patients with cancer of the floor of the mouth, supraglottic larynx, or tongue, and possibly for patients with carcinoma of the hypopharynx who are responding well to treatment. As local control rates improve, there should be increased ag-

gressiveness and optimism on the part of the primary physician. However, for a patient who has a tumor of poor prognosis, the added cost and complexity of treatment may not be justified.

The head and neck cancer patient often has impaired immune functions and exposed UADT squamous epithelium to some extent affected by preneoplastic process. Both immune deficiencies and pathologic immune processes are seen in these patients (15, 26). It is important to consider if current treatments which interfere with host vascular supply and immunocompetency, without any specific impact upon preneoplastic characteristics of the tissues treated, might increase or decrease the risk of second primary cancers. Ideally, head and neck cancer therapies would be immunorestorative, and would have an ameliorating effect upon premalignant tissue characteristics and the host immunocompetence.

The development of malignancy within the UADT and lungs conforms well to the model of multi-step carcinogenesis. Initiation is the first somatic mutation, a result of carcinogen-induced changes in the genome that are in excess of cellular ability to repair the damage before mitosis takes place. In a second step called promotion, there is facilitation of the changes brought about by initiation, which results in the manifestation of intracellular phenotypic changes caused by an abnormally functioning, mutated genome. In the third step, progression, the dysplastic cell line develops the full complement of characteristics that constitute frank neoplasia as defined histologically and manifested as invasive cancer. Retinoids, which are synthetic compounds chemically related to vitamin A, have been studied in this context. They are able to interfere with carcinogenesis in animal tumor models and are also effective against human tumors *in vitro,* apparently acting at the promotion step of carcinogenesis. Retinoids both cause tumor regression and act as chemopreventive agents.

The initial clinical trials of retinoid therapy in head and neck cancer have been encouraging. Hong *et al.* demonstrated in a recent double-blind, placebo-controlled study that 13-*cis*-retinoic could cause temporary shrinkage of leukoplakia and reverse dysplasia (12). Synthetic retinoids and beta-carotene are capable of retarding carcinogenesis in animal models, and initial clinical trials of retinoids inhuman tumors are promising (18). These agents and other biologic-response modifier strategies are potential new tools in decreasing the risk of second primary cancers, but they are not yet ready for application in practice.

Our understanding of the processes of carcinogenesis is expanding rapidly. A broad front of scientific inquiry is addressing the major questions of genetic control of the maintenance of normal and dysplastic squamous epithelium, regulation of oncogene expression, and host repair of sublethal carcinogen-induced damage to the genome, and also the pathophysiology of promotion and tumor progression. It will require effective exchange between researchers from the clinic and the laboratory to develop effective chemoprevention of human tumors. Can we distinguish the critical microscopic histologic and cytologic features of preneoplastic tissue in clinical trials of new biologic-response modifier therapies? Can we identify favorable host characteristics responsive to external modulation, and can we develop therapies to restore or enhance these favorable histologic/cytologic, immunologic, and serologic (or other) parameters?

Problems in the early diagnosis of lung cancer are well known. Fontana *et al.* has reviewed this subject elsewhere (7). The patients with high-risk cancers, namely, laryngeal cancers and high-risk subsets of the oral cavity and pharynx, may benefit from routine fiberoptic bronchoscopy and sputum cytologic assessments at appropriate intervals, but this remains a subject for prospective study. Regardless of the specifics, lifetime follow-up and a paradigm of screening studies and risk intervention is badly needed.

Fiberoptic endoscopy, appropriately employed, should be useful in detecting occult head and neck and esophageal cancers in high-risk patients. Barium studies are inexact and miss cancers, but may be useful prior to endoscopy. Computed tomography and magnetic resonance imaging have not been thoroughly studied in this circumstance. Patients with head and neck cancer can be categorized according to the extent of the risk of second cancer. From the standpoint of cost-effective care, the patient with a lip cancer does not need the same scrutiny for early lung cancer as the patient with laryngeal cancer. The same is true for the patient with a carcinoma of the cheek. Patients with leukoplakia with or without an associated cancer of the oral cavity, larynx, or other head and neck site require individualized careful follow-up. Patients with leukoplakia containing dysplasia and prior or concomitant oral cancer need the most vigorous approach possible, including effective chemoprevention and other risk intervention if available.

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APPENDIX I

Diagnosis of multiple primary squamous cell carcinoma

The criteria set forth by Billroth (2) for multiple primary carcinoma are too strict to allow complete diagnosis in head and neck cancer. In these patients, any focus of cancer within the squamous epithelium of the upper aerodigestive tract may be a second primary cancer. A solitary focus of cancer in the lung may also represent a second primary.

Care in the selection of head and neck biopsy sites enables assessment of bordering epithelium; biopsies of the tumor margins and of any clinically suspicious areas are advisable. Local origin of head and neck cancer is strongly suggested whenever a focus of cancer is confluent with a zone of squamous dysplasia. The presence of tumor beneath normal-appearing mucosa is not adequate to define the site of origin. The diagnosis of multiple primary carcinoma of the head and neck is fairly straightforward, particularly if the lesions are synchronous.

The determination that lung cancer is a second primary is more difficult because the only direct visualization is through endoscopy and because lung metastasis occurs in perhaps 15% of all head and neck cancer patients. In this context, Warren and Gates (42) provide reasonable criteria for the diagnosis of multiple primary carcinoma, and those of Martini and Melamed (22) may be of valuable assistance.

The clinician must make an additional decision when a metachronous lesion may represent a second primary in head and neck cancer, namely, to rule out local recurrence in the initial tumor site (the oral cavity). No absolute guidelines will suffice for all cases, although the more certain the pathologic exclusion of tumor in the margins of the surgical specimen, the more confident the diagnosis of metachronous second primary cancer.