Second Malignant Tumors After Treatment of Nasopharyngeal Carcinoma: Four Case Reports and Literature Review

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ABSTRACT

The purpose of this study was to identify the histopathology, location, and latency interval for the development of second malignant tumors (SMT) after successful treatment for nasopharyngeal carcinoma (NPC). Of 55 patients, four developed SMT after successful treatment of NPC in a single institutional series for an incidence of 7%. An additional 31 patients with SMT after treatment for NPC were identified from the literature. At minimum, all patients were treated with radiotherapy to the primary site. The histopathology of SMT included sarcoma (69%), squamous cell carcinoma (17%), adenocarcinoma (6%), meningioma (6%), and lymphoma (3%). SMT occurred at various sites in the head and neck, but most (51%) arose in the sinonasal cavity. For the entire group, the mean latency interval between treatment for NPC and the development of SMT was 11.8 years. These findings indicate that the development of SMT in patients achieving long-term survival after treatment for NPC may be radiation induced. Long-term follow-up for these patients is important to assess for this potentially late complication.

KEYWORDS: Nasopharyngeal carcinoma, second malignant tumors

Nasopharyngeal carcinomas (NPC) differ in many aspects from other head and neck squamous cell carcinomas (SCCs). Their epidemiology is unique in that the incidence is 15 to 50 cases of NPC/100,000 persons in southern Chinese populations and in Southeast Asia, compared with less than

1/100,000 in Europe and North America.^{1,2} In addition to genetic predisposition, the Epstein-Barr virus, high consumption of dry-salted fish containing nitrosamines, and occupational exposure to hydrocarbons, fumes, and smoke are other unique etiologic factors.³ Traditionally, the mainstay of therapy

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for NPC has been external beam supervoltage radiation to the primary tumor and at-risk nodes. More recently, concomitant chemoradiotherapy using platinum-derived agents has been used to treat patients with advanced NPC.⁴

It is well known that patients with head and neck SCCs have an increased incidence of developing a second malignant tumor (SMT) possibly due to the "field cancerization" effect of tobacco and alcohol abuse.⁵ Given that the risk factors for NPC are different than those for head and neck SCC, the risk of developing an SMT may also vary. Likewise, patients treated for NPC may have a high long-term risk for developing radiation- or chemotherapy-induced malignancies. To identify the histopathology, location, and latency for the development of SMT after successful treatment for NPC, we reviewed the literature and added four cases of our own to the analysis.

METHODS

A search of the tumor registry database from the PennState Milton S. Hershey Medical Center identified 55 patients treated for NPC between 1976 and 1998. Four (7%) of these patients (three males, one female; mean age 54 years; range, 29 to 66 years) developed SMT after successful treatment of NPC. A MEDLINE search of the English literature from 1966 to 1999 for NPC and SMT identified 31 patients, for a total of 35 patients.⁶⁻¹⁷

RESULTS

Our four patients received 70 Gy of radiation to the nasopharynx, and two received concomitant chemotherapy. The histopathology of the SMT consisted of an osteosarcoma of the clavicle, an adenocarcinoma of the hard palate and maxillary sinus, an SCC of the tongue, and an SCC of the external auditory canal. The mean latency between treatment for NPC and presentation of the SMT was 15.5 years (range, 11 to 25 years). After undergoing treatment for the SMT, three patients have no evidence of disease and one patient is alive with distant metastases to the brain (Table 1).

Of the 31 patients with SMT obtained from the literature, there were 19 males and six females. The gender of six patients was not recorded. The mean age was 46.9 years (range, 21 to 70 years). The mean dosage of radiation to the nasopharynx was 65.7 Gy (range, 33.6 to 81.9 Gy) in 30 patients. In one patient, the amount of radiation administered was not recorded. The mean latency between treatment for NPC and presentation of the SMT was 11.6 years (range, 6 to 32 years).

The histopathology and anatomical sites of SMT from our four patients and the patients derived from the literature are summarized in Table 2. Of the 35 patients, 24 SMTs (69%) were sarcomas and consisted of the following subtypes: 12 malignant fibrous histiosarcomas (MFHs) (34%), 10 osteosarcomas (29%), one chondrosarcoma (3%), and one fibrosarcoma (3%). Other tumors included six SCCs (17%), two meningiomas (6%),

Table 1 Second Malignant Tumors After Successful Treatment for Nasopharyngeal Cancer: The PennState Milton S. Hershey Medical Center Tumor Registry Series

Age (yr)	Sex	XRT Dose (Gy)	Chemo	Histology	Site	Latency (yr)	Disease Status
29	F	70	Yes	Osteosarcoma	Clavicle	12	NED
57	M	70	No	Adenocarcinoma	Hard palate	25	AWD
64	M	70	No	SCC	Tongue	11	NED
66	M	70	Yes	SCC	External auditory canal	14	NED

SCC, squamous cell carcinoma; NED, no evidence of disease; AWD, alive with disease.

Table 2 Histopathology and Location of Second Malignant Tumors After Successful Treatment for Nasopharyngeal Carcinoma in 35 Patients

	Sinonasal Cavity	Mandible	Oral Cavity/Oropharynx	Clavicle	Brain	Ear Canal	Larynx/Neck	Total
MFH	10	2	0	0	0	0	0	12 (34%)
Chondrosarcoma	0	1	0	0	0	0	0	1 (3%)
Fibrosarcoma	0	0	0	1	0	0	0	1 (3%)
Osteosarcoma	6	2	0	1	0	0	1	10 (29%)
Adenocarcinoma	2	0	0	0	0	0	0	2 (6%)
SCC	0	0	4	0	0	2	0	6 (17%)
Meningioma	0	0	0	0	2	0	0	2 (6%)
Lymphoma	0	0	0	0	0	0	1	1 (3%)
Total	18 (51%)	5 (14%)	4 (11%)	2 (6%)	2 (6%)	2 (6%)	2 (6%)	35

MFH, malignant fibrous histiosarcoma; SCC, squamous cell carcinoma.

two adenocarcinomas (6%), and one Hodgkin's lymphoma (3%).

SMT involved the sinonasal cavity in 18 cases (51%), the mandible in five cases (14%), and the oral cavity/oropharynx in four cases (11%). The clavicle, brain, ear canal, and larynx/neck were each involved in two cases of SMT (6%).

SMT histopathology based on tumor site was also analyzed. Of the 18 cases of SMT involving the sinonasal cavity, 16 (89%) were sarcomas. Of these 16 sarcomas, 10 were MFH (56%) and six were osteosarcomas (33%). The remaining two SMTs were adenocarcinomas. Sarcomas also comprised all SMTs of the mandible, clavicle, and larynx. The lesions of the external auditory canal and oral cavity/oropharynx were exclusively SCCs, and both brain lesions were recurrent meningiomas.

DISCUSSION

The incidence of developing an SMT in our small series was 7%. Cooper and coworkers¹⁸ reviewed the Radiation Therapy Oncology Group database and identified five SMTs in 121 patients with NPC treated with radiation therapy alone for an incidence rate of 4.1%. Ingersoll et al.⁶ noted three out of 57 young patients (5.3%) developed SMT on long-term follow-up for treatment of NPC with radiation ther-

apy alone or in combination with chemotherapy. In larger series (>1000 patients), the incidence of SMT was lower—between 0.04% and 1.2%.^{9,19} Such variations in the incidence of SMT may partially be a function of sample size or may reflect other factors such as genetic predisposition, dose and administration techniques of radiotherapy and chemotherapy, occupational or environmental exposures, Epstein-Barr virus, or tobacco and alcohol use.

In general, head and neck SCCs, excluding NPCs, have a 5 to 21% incidence of developing an SMT of the upper aerodigestive tract.⁵ The increased susceptibility for developing an SMT is likely related to the field cancerization effect of tobacco and alcohol. Two of our patients with SMT had a history of tobacco and/or alcohol abuse: One developed an SCC of the tongue and the other developed an SCC of the external auditory canal. It is conceivable that the tongue cancer developed as a result of the tobacco and alcohol abuse. However, it is unlikely that a carcinoma of the external auditory canal would develop based on those risk factors.

Radiation therapy is the conventional treatment for NPC and is also a common treatment for other sites of head and neck cancer. An unrelated cancer arising within the radiation field can occur as a late sequela of radiation therapy.²⁰ Qian and colleagues²¹ have defined radiation-induced malignancies by the following criteria. (1) The patient must have a history of radiotherapy. (2) The sec-

ondary cancer must occur within the irradiated field. (3) There must be a latent interval of years to decades. (4) The second malignancy must be confirmed histologically. The patients reported here appear to meet all of these criteria. Therefore, patients cured of NPC may have a long-term risk of developing radiation-induced SMT. However, a study by the Radiation Therapy Oncology Group¹⁸ revealed that the incidence of SMT after successful treatment of NPC with irradiation is significantly less than after similar treatment for other upper aerodigestive tract malignancies (4.1 vs. 12.3%).

In this review, most SMTs were sarcomatous lesions. Of these mesenchymal tumors, MFHs and osteosarcomas were the most common. Previous studies have demonstrated a relationship between radiation exposure and the development of sarcomas. In a review of 3,223 patients, Ko and colleagues¹⁴ identified eight long-term survivors of NPC with a radiation-induced MFH of the maxillary sinus or nasal cavity for a prevalence of 0.38% and a 15-year cumulative incidence of 2.2%. SCCs also accounted for a significant number of second malignancies. Squamous cell malignancies of the upper aerodigestive tract also may be induced by radiation, but other variables such as alcohol and tobacco use must be considered as possible etiologic factors. The association of Epstein-Barr virus and SMT in a large retrospective study of patients with NPC was recently reported by Wang and coworkers.²² Although their results revealed an increased risk for secondary head and neck cancer, gastric cancer, and leukemia after irradiation for NPC, there was no significant association with the development of SMT and the presence of Epstein-Barr virus.

Another cancer often associated with radiation exposure is thyroid carcinoma. Interestingly, no cases of thyroid cancer occurred in our patients or those obtained from the literature. This finding may be related to the administration technique, dosage of radiotherapy to the neck, or both. It also may reflect that these populations were exclusively adult, whereas delayed or secondary thyroid carcinoma usually arises from head and neck irradiation of pediatric patients. Of the 35 patients in this

study, only four (11%) developed SMT in the neck or clavicular region.

Most SMTs (88%) developed between the brain and the mandible. The sinonasal cavity was the most commonly involved anatomical site, accounting for 18 of 35 cases (51%). Sarcomas predominated in the sinonasal cavity, and this site most likely received the largest dosages of radiotherapy during the treatment for NPC. The mandible was the second most common site, and all tumors were of the sarcoma variety. SCCs of the ear canal and oral cavity accounted for 17% of the lesions reported. As noted, the larynx, neck, and clavicular region were seldom sites for the development of SMT.

CONCLUSION

The development of an SMT after treatment of NPC is an important concern in patients achieving long-term survival. SMT may be a late radiation-induced complication because most of these neoplasms develop within the prior radiation field. Alternatively, this population of patients may be genetically predisposed to developing an SMT *de novo*. Sarcomas are the most common SMT and MFHs occur most frequently. The sinonasal cavity followed by the mandible are the sites most commonly involved. Given the long latency between treatment for NPC and the development of an SMT, routine, long-term follow-up is essential to assess for potentially late complications.

EDITORS' NOTE

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Commentary

Although the long-term recurrence of sarcomas after radiation treatment for primary carcinomas in the nasopharyngeal region is well known, the topic merits further discussion. The authors have added their four cases to a literature review and have made some positive statements. Certainly for those beginning their career in head and neck surgery, this is an important article to read and remember. Within this area of surgery, these patients are a unique group who must be followed for a very long time, if not forever, to detect this particular entity as early as possible. In this way, the dismal prognosis for these patients might be improved.

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