Chapter 13

Head and Neck Squamous Cell Carcinoma in Fanconi Anemia Patients

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Introduction

Head and neck cancers are among the most common tumors to develop in patients with Fanconi anemia.[1,2] Although these tumors are histopathologically similar to those in patients without FA, the frequency, distribution, and clinical course are significantly different and must be taken into account when considering cancer management in patients with FA (Table 1). This chapter provides an overview of head and neck squamous cell carcinomas (HNSCC) in the general population in contrast to those occurring in FA patients, with a focus on aspects of prevention, treatment, and surveillance in FA patients.

Head and Neck Cancer in the General Population

Head and neck cancer is a group of diseases linked together by a common histopathology, squamous cell carcinoma (SCC). These diseases can occur anywhere in the mucosal linings of the upper aerodigestive tract, beginning in the oral cavity and nasopharynx, and extending to the oropharynx, larynx or hypopharynx. About 30,000 new patients present annually with head and neck cancer in the United States and about 30% succumb to their disease. Internationally, head and neck

cancer is a significant health concern as one of the five most prevalent malignancies.[3]

Head and neck SCC development has been closely associated with the use of tobacco and alcohol.[4,5] Betel nut chewing, a common practice in Southeast Asia, has also been linked to the pathogenesis of head and neck cancer.[6] More recently, cancer-causing viruses, such as the human papillomavirus (HPV) and Epstein-Barr virus (EBV), have been suggested to play a role in the pathogenesis of these tumors.[7,8] Since a detailed review of head and neck cancer is not feasible in this chapter, we recommend consulting the following reference textbooks: (Shah, Jatin P., and Snehal G. Patel, 2003. *Head & Neck Surgery & Oncology*, 3rd Edition. Edinburgh: Mosby; and Harrison, Louis, et al., 1999. *Head and Neck Cancer: A Multidisciplinary Approach*. Philadelphia: Lippincott Williams & Wilkins Publishers, 1999.)

Head and Neck Cancer in Patients with Fanconi Anemia

Three separate reports have shown a 500- to 700-fold increase in the incidence of head and neck cancer in patients with FA.[1,2,9,10] The cumulative risk for developing head and neck cancer is approximately 14% for patients surviving to the age of forty.[2] This may be an underestimation of risk as the relative risk increases with age, and many FA patients succumb to other diseases before the age of 20. The impact of increased survival resulting from bone marrow transplantation protocols on the incidence of head and neck cancer in FA patients remains to be determined. Moreover, as head and neck cancer may be the presenting manifestation of FA, testing for FA should be considered in younger SCC patients (<40 years of age), especially if

they have atypical findings (e.g., borderline anemia) or an atypical response to cytotoxic treatment.

The presentation, distribution and course of head and neck cancer are also altered in patients with FA. These patients present at a younger age, and there is an increased prevalence of oral cavity tumors. In general, FA patients develop HNSCC at a high rate without associated risk factors. The biological behavior of FA-associated HNSCC is considered aggressive with early lymph node metastases and early soft tissue invasion, which is reflected in their overall worse outcome (Table 1).

Table 1: Summary of the characteristics of HNSCC in the FA population

	FA-associated HNSCC	**Non-FA HNSCC**
Cumulative incidence by age 40 years	14%*	0.038%
Age of presentation (median)	31 years	53 years
Tobacco and alcohol use	16%	>85%
Primary tumor site	Oral cavity: 65% Oropharynx: 10% Hypopharynx: 10% Larynx: 10% Unknown: 5%	Oral cavity: 27% Oropharynx: 24% Hypopharynx: 8% Larynx: 41%
Development of secondary primary tumors	63%	15%
2 year overall survival	49%	70%
Standard treatment	Surgery	Surgery, Radiation, Chemotherapy

* Considered an underestimation of risk as the relative risk increases with age, and many FA patients succumb to other diseases before the age of 20.

Symptoms are variable at presentation, with presence of a lesion being the most common complaint (Table 2). These patients typically present with multifocal changes, including premalignant and invasive lesions. There is a bimodal distribution of stage; about half of the patients present with early and the remainder with advanced stage disease. These tumors are quite aggressive, with two-year survival rates less than 50%. In addition, the majority of patients develop second primary tumors (63%), even after effective treatment of the index cancer. These factors clearly need to be taken into account in any treatment planning for head and neck cancers in patients with FA.

Table 2: Presenting symptoms and frequency in FA patients with HNSCC

Presenting Symptoms	**Frequency**
Oral lesion	37%
Pain	17%
Dysphagia	14%
Odynophagia	14%
Loose dentition	14%
Ulcer	7%
Neck mass	3%
Oral bleeding	3%
Hoarseness	3%

Prevention of Head and Neck Cancer

The precise cause of this increased risk for head and neck cancer in patients with FA remains to be defined, but may be related to increased susceptibility to human papillomavirus (HPV) infection and/or its carcinogenic effects. A study by Kutler et al. showed that 83% of

FA head and neck SCC patients have HPV DNA present, compared to a 20-30% incidence in head and neck cancer patients from the general population.[11] Another study found contradictory results. Thus, this observation requires further study to establish a causal relationship between HPV and squamous cell carcinoma development in FA; however, it potentially provides a mechanism for preventative approaches in this population. A study published in *The New England Journal of Medicine* has suggested that vaccination against HPV type 16, the most common type of HPV in head and neck cancer in the general population and possibly in some FA patients, can effectively prevent tumor development.[12] The role of chemopreventative drugs and vaccinations is under investigation and should only be used as part of an appropriate protocol. This includes vaccination against the human papillomavirus.

At present, the most prudent preventative measures in FA patients include:

1. **Abstinence from tobacco/alcohol exposure:** Tobacco and alcohol exposure, especially in combination, is the most significant factor associated with SCC head and neck cancer development in the non-FA population. Fewer than 20% of FA patients with head and neck cancer report any tobacco/alcohol use, but this is significantly higher than the rate observed in FA patients without head and neck cancer. Accordingly, abstinence from tobacco and alcohol, including exposure to secondhand smoke, should be strictly avoided by FA patients. In addition, mouthwashes containing alcohol should be avoided.

2. **Maintenance of proper oral hygiene:** Although the evidence is not as compelling, several reports suggest that poor oral hygiene and repeated trauma may

promote head and neck cancer development. Accordingly, maintenance of proper oral hygiene and routine dental evaluations are recommended.

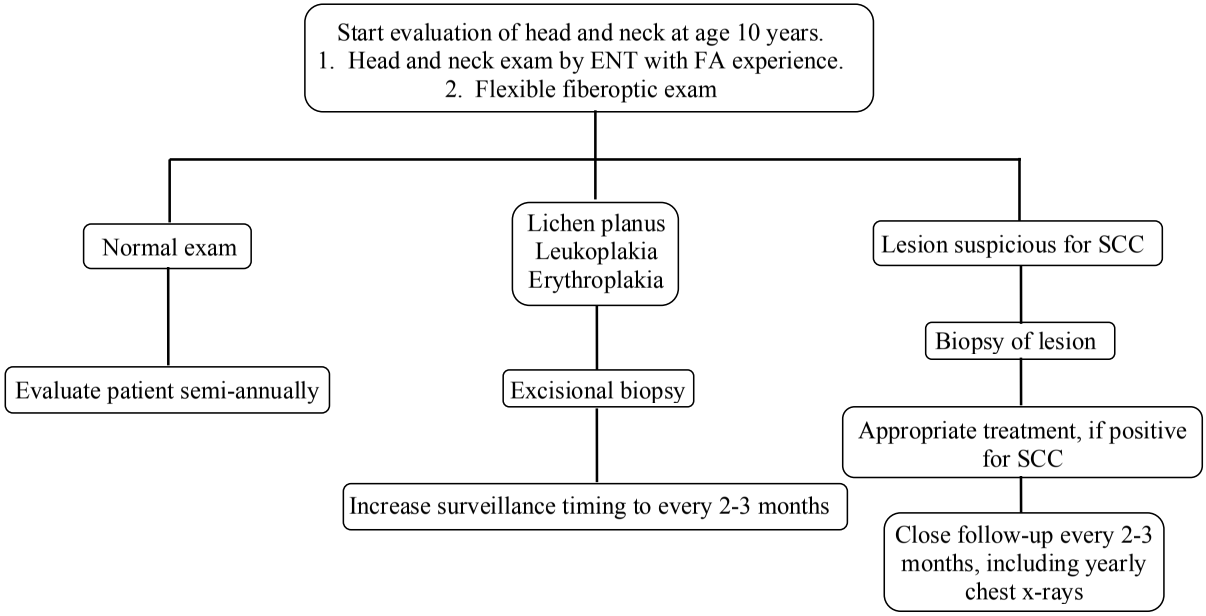
3. **The use of oral appliances:** Given the lack of evidence to suggest a causal association with head and neck cancer, the use of oral appliances, including braces, need not be restricted in FA patients.

Surveillance for Head and Neck Cancer

The high incidence of head and neck cancer in patients with FA, combined with the ineffectiveness of available treatment approaches, underscores the need for aggressive surveillance. Surveillance should begin by the age of 10-12 years (based on literature reports of the earliest age at presentation with head and neck cancer) on a semiannual basis by an experienced professional; i.e., an ear, nose and throat specialist, an oral surgeon or other doctor experienced in head and neck cancer detection and treatment (Figure 1).

Since head and neck cancer in patients with FA commonly occurs in the oral cavity, the surveillance approach should focus on this region. However, as part of the routine screening, a flexible fiberoptic examination should be performed which includes evaluation of the nasopharynx, oropharynx, hypopharynx, and larynx. The use of routine esophagoscopy for screening is not mandated, but should be considered in any patient with odynophagia, dysphasia or other localizing symptoms. In these circumstances, evaluation could be performed either with endoscopy or barium swallow, with the specific findings guiding further evaluation and therapy. Focus should be on the cervical esophagus, which represents the region at highest risk for Fanconi-associated squamous cell carcinomas.

Figure 1: This flow chart describes the appropriate evaluation, surveillance, and diagnosis of head and neck lesions identified in the FA patient. The degree of dysplasia within the lesion should not influence decision-making regarding treatment. For example, even mild dysplastic lesions should be excised when feasible.



The head and neck examination should include not only the identification of malignant lesions, but also pre-malignant pathology. Lichen planus, leukoplakia, and erythroplakia should be specifically identified as part of the screening evaluation. When one of these lesions is identified in the head and neck region, an excisional biopsy should be performed, based on the size of the lesion. If an excisional biopsy cannot be obtained successfully, then a biopsy of the most representative/suspicious regions should be performed. In this patient population, the degree of dysplasia should not influence decision-making regarding treatment, and even mild dysplastic lesions should be excised, when feasible, to prevent the eventual progression to invasive cancer. The use of brush biopsies is not considered appropriate for the management of these patients, as there is a high incidence of false negative results due to non-representative sampling of the tumor.

Once a premalignant or malignant lesion is identified, the surveillance timing should be changed to once every 2-3 months, since this finding heightens the concern for development of subsequent premalignant and even invasive cancerous lesions. In patients who have been successfully treated for head and neck cancer, an annual chest x-ray should be included as part of the screening process.

Treatment of Head and Neck Cancer in Fanconi Anemia Patients

The core armamentarium used to treat patients with head and neck cancer in the general population includes surgery, radiation therapy, and chemotherapy. Many non-FA patients with advanced cancer of the head and neck will require multi-modality therapy to treat their tumors. However, in patients with FA, significant

sequelae can result from the use of radiation therapy and/or chemotherapy. Therefore, the use of these modalities must be individualized and only applied when absolutely required. Conversely, surgical therapy of head and neck cancer in patients with FA is reasonably well-tolerated. There does not seem to be an increased incidence of complications, including wound infections or long term sequela associated with surgical scarring. Accordingly, the consensus opinion is that surgical therapy needs to be entertained as the primary curative modality in all FA patients with head and neck cancer.

Surgery

Surgery in this patient population should follow dicta established for the general population with head and neck cancer, with a few modifications. In general, a wide complete excision of the primary tumor should be performed with adequate margins. The exact type of surgical resection required is dictated by the primary site, size, and the extent of the tumor. In general, oral cavity and pharyngeal tumors should be excised with at least one centimeter margins. The margins for laryngeal tumors need not be as comprehensive, due to the unique anatomy of the larynx.[13] Reconstruction of the primary site defect should follow dicta established for reconstruction in the general population with head and neck cancer, and should not be limited based on the presence of FA. Therefore, the standard application of free flaps for reconstruction should be considered as indicated, without restriction.

The management of clinically detectable cervical lymphadenopathy should follow dicta established for the general population. For lymph nodes greater than 3 cm, multiple lymph nodes on the same side of the neck or contralateral cervical adenopathy, a modified

radical neck dissection should be performed. In cases where a modified neck dissection is not feasible, a radical neck dissection can be considered.

For patients presenting without clinically detectable cervical adenopathy, elective nodal dissection should be considered for those who are at high risk for occult nodal metastasis. These high-risk regions include tumors of the oral cavity, oropharynx, and hypopharynx. For oral cavity tumors, the standard elective neck dissection consists of an ipsilateral supraomohyoid neck dissection extended to include level IV and should be performed in the majority of cases. For midline tumors, due to the high rate of nodal metastases bilaterally, a bilateral elective nodule dissection should be performed in all cases. For pharyngeal tumors, bilateral jugular nodal dissection consisting of levels 2-4 should be performed in all cases. If a suspicious node is identified during the course of an elective neck dissection, it should be sent for frozen section examination and, if metastatic disease is confirmed to be present within the node, a more comprehensive dissection of the cervical lymphatics should be undertaken.

External beam radiation

Adjuvant radiation therapy may be required in FA patients, especially those presenting with advanced disease. For the general population, advanced T-stage and the presence of nodal metastasis are significant indicators for the use of radiation therapy. In patients with FA, these same oncologic indicators exist; however, consideration must be given to minimize the sequelae of radiation therapy treatment. In the study by Kutler et al., four out of six patients who received radiation had significant treatment related sequela, two of whom died as a consequence of the treatment itself.[14] The selection

of patients for radiation should, therefore, be modified in patients with FA.[15] Bulky nodal metastasis and concern about incomplete resection of the disease are the most significant indicators to add radiation in this population. If radiation is to be given, a full course of radiation should be attempted, as it does not appear that tumors derived from patients with FA have the same degree of sensitivity to radiation as do non-tumorous cells from these patients.

Several considerations must be taken into account when treating FA patients with radiation. First, intensity modulated radiation therapy (IMRT) is recommended to decrease the toxic effects on non-cancerous tissues. Second, these patients must be monitored closely, not only for loco-regional problems but also for systemic sequelae such as bone marrow failure. To limit the risk for loco-regional problems, aggressive oral hygiene should be initiated in all patients undergoing radiation treatment, including routine brushing and oral/pharyngeal irrigation with a combination of salt water and baking soda solution. This solution can be made by boiling one quart of water and adding one teaspoon of salt and one teaspoon of baking soda. The irrigation should be performed at least every three to four hours on a daily basis during the waking hours. Third, aggressive observation of these patients for development of fungal infections should be maintained, and systemic antifungals initiated should evidence of infection be present. Delay or termination of therapy should be considered if significant and/or life-threatening side effects are becoming manifest. In addition to acute management, patients should be placed on long-term care specifically with respect to dental management. Use of fluoride treatments should be considered in all

patients. Monitoring of dentition should be maintained, and prevention measures for caries initiated.

Chemotherapy

Similar to the use of radiation therapy, the use of chemotherapy should be used with caution. Typically, chemotherapy protocols for head and neck cancer include a combination of cisplatin and 5-FU. These chemotherapeutic agents can have significant side effects in FA patients. Aggressive monitoring for these side effects, especially bone marrow failure, must be considered routine. In addition, monitoring for cisplatin effects on sensorineural hearing should also be a routine in these patients. If hearing sequelae develop as a consequence of the cisplatin treatment, cisplatin should be changed to carboplatin, which has similar efficacy but lower risk for ototoxicity. Recent studies have shown that, when given with radiation, cetuximab improves locoregional control in non-FA patients with head and neck cancer.[16] More importantly, these patients did not have increases in toxicities associated with radiation. The use of cetuximab in patients with FA and head and neck cancer is attractive, as its activity does not involve DNA damage. Nonetheless, the role for cetuximab in the treatment of FA patients remains investigational and should only be used under the recommendations and care of experienced oncologists.

Conclusions

Patients with FA have an increased risk for developing aggressive head and neck cancer, especially of the oral cavity. Until new therapeutic and preventative measures are available, strict abstinence from tobacco and alcohol, avoidance of second-hand smoke, maintenance of oral hygiene, and aggressive routine screening are the most immediate ways to reduce the development

and morbidity of head and neck cancer in this patient population. Early and frequent head and neck examinations, including careful oral cavity evaluations and flexible fiberoptic laryngoscopy are important surveillance measures. Appropriate surgical resection remains the mainstay of treatment for FA patients, since radiation and chemotherapy are poorly tolerated. If radiation and chemotherapy are required for advanced tumors, they should be used with caution and by physicians who have experience in identifying, preventing, and treating associated complications.

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