Chapter 14: Head and Neck Cancers in Patients with Fanconi Anemia

Introduction

Head and neck cancers are significantly more common in patients with Fanconi anemia (FA) than in the general population. Although the tumors in patients with FA have a similar microscopic appearance to those in patients without FA, the frequency, distribution, and clinical course differ and must be taken into account when considering cancer management in patients with FA.

Head and Neck Cancer in the General Population

Head and neck cancer encompasses a wide variety of tumors that typically begin in the squamous cells that line the moist, mucosal surfaces of the oral cavity, nasal cavity, pharynx (throat), and larynx (voice box). These tumors are often referred to as head and neck squamous cell carcinomas (HNSCC). Approximately 30,000 individuals are diagnosed with head and neck cancer in the United States annually, and about 30% of patients with head and neck cancer succumb to their disease. Increasingly, HNSCC is an international health problem, representing the fifth most common cancer type and cause of cancer-related death worldwide [1].

Good to Know

A **second primary cancer** refers to the presence of an additional, unrelated cancer in someone who was previously diagnosed with another type of cancer.

The vast majority of HNSCC cases (more than 90%) develop following exposure to carcinogens, including tobacco and alcohol [2, 3], betel nut (which is commonly chewed in parts of Southeast Asia for its stimulating effects) [4], and sexually transmitted viral pathogens such as human papillomavirus (HPV) [5]. Head and neck cancers are prototypic tobacco-related cancers, and the initial risk for the development of cancer and the subsequent risk for the development of second

primary cancers is directly attributable to the duration and intensity of tobacco exposure. Tobacco-related cancers can also occur in non-smokers as a result of secondhand (environmental) smoke exposure. Chronic consumption of alcohol is estimated to increase the risk for HNSCC by 2- to 3-fold in a dose-dependent manner. Moreover, individuals who use both tobacco and alcohol have up to 10-20 times higher risk for HNSCC than people who do not use tobacco or alcohol. Approximately 5% of HNSCC develop in individuals who do not smoke or consume alcohol. Emerging evidence suggests that HPV may play a role in the development of head and neck cancers, with HPV detected in more than 70-80% of cases of oropharyngeal cancer, which develops in the part of the throat that includes the tonsils and base of the tongue [22]. Unfortunately, the incidence of oropharyngeal cancer is increasing worldwide.

The incidence of HNSCC varies by geographic region. Southeast Asia has the highest incidence of carcinomas of the oral cavity and oropharynx due to the practice of chewing tobacco containing the betel nut. High rates of oral cancer are also reported in Brazil. The rates of laryngeal and hypopharyngeal cancer, which develops in the bottom part of the throat, are significantly elevated in Italy, France, and Spain due to the high prevalence of alcohol and tobacco use in those countries. Nasopharyngeal carcinoma frequently occurs in southern China and populations residing in nations that skirt the Mediterranean region, possibly due to infection with Epstein-Barr virus (EBV) and/or dietary habits. Because a detailed review of head and neck cancer is not feasible in this chapter, we recommend consulting reference textbooks [22 and 23].

Head and Neck Cancer in Patients with FA

By far, HNSCC is the most common solid tumor in patients with FA. The incidence of HNSCC in patients with FA is 500- to 700-fold higher than in the general population [6,7,8,9]. Approximately 1 in 7 (or about 14%) of patients with FA who survive to the age of 40 will be diagnosed with HNSCC during their lifetimes [10]. Some cases of FA remain undiagnosed until the appearance of head and neck cancer. Therefore, FA testing should be considered in patients younger than age 40 who develop HNSCC, especially if they have atypical findings such as borderline anemia or an atypical response to cytotoxic treatment.

Compared with the general population, the age of onset, distribution, and course of HNSCC is significantly different in patients with FA. Patients with FA tend to be diagnosed with HNSCC between the ages of 20-40, whereas individuals in the general population tend to be diagnosed between the ages

of 50-60. Patients with FA also have a higher proportion of HNSCC in the oral cavity, the vast majority of which involve the tongue, compared with the general population. Furthermore, a much higher proportion of HNSCC in patients with FA is diagnosed in advanced stages compared with the general population. Despite aggressive treatment, the outcome of HNSCC in patients with FA is significantly poorer than that in the general population. Moreover, even after cure of the primary HNSCC, patients with FA are more likely to develop second primary cancers than the general population (more than 60% vs. ~30%, respectively). The anatomic distribution of second primary cancer is also significantly different in patients with FA compared with the general population. Whereas patients with HNSCC in the general population tend to develop second primary cancers in the lung and esophagus, patients with FA develop second primary cancers in the genitourinary tract and skin. Interestingly, the pattern of second primary cancers in patients with FA resembles that observed in HPV-associated HNSCC in the general population [11].

Prevention of Head and Neck Cancer

Patients with FA have the highest risk for HNSCC amongst all patients with inherited genetic syndromes (e.g., Li-Fraumeni syndrome, Bloom's syndrome). Unlike individuals with an inherited mutation in the retinoblastoma gene (*RB*), nearly all of whom develop tumors of the retina, not all patients with FA develop HNSCC. Like the association between radiation exposure and the development of high-grade sarcomas in patients with an inherited *RB* mutation, a co-factor(s) is likely required for FA patients to develop HNSCC. The precise cause(s) of and co-factor(s) for the increased risk of HNSCC in patients with FA have yet to be defined. The type of FA mutation and severity of manifestations have not been clearly associated with the development of HNSCC. One study [24] suggests that bone marrow transplantation increases the risk for HNSCC development in patients with FA, and primarily attributed the increased risk to the development of acute and/or chronic graft-versus-host disease (GvHD). An association between GvHD and HNSCC has also been suggested in patients without FA [12]. Tobacco and alcohol consumption are less commonly reported in patients with FA than in the general population, but remain major risk factors for the development of HNSCC in patients with FA. Most studies support a role for HPV in gynecological malignancies, but its precise contributions to HNSCC in patients with FA remain controversial. Some studies [25, 26] suggest that HPV may be a major contributor to HNSCC development in patients with FA, whereas other studies [27, 28] dispute these

results. Laboratory studies show that mutations in genes that cause FA increase susceptibility to HPV-induced carcinogenesis [29, 30]. Overall, the scientific literature suggests that multiple factors contribute to the development of HNSCC in patients with FA, although the precise contributions of individual factors remain to be defined. The following measures should be considered to minimize the risk of HNSCC:

- ***Abstaining from alcohol and tobacco.*** The causal link between tobacco and alcohol exposure and the development of HNSCC is well-established. Relatively few patients with FA admit to tobacco and/or alcohol use, but this is likely an underestimation of the actual prevalence of tobacco and/or alcohol use in this population. The use of tobacco and tobacco products should be discouraged categorically, including exposure to secondhand smoke. While it is best to abstain from alcohol use, individuals who consume alcohol should restrict their intake to no more than one drink equivalent per month. The chronic use of alcohol-containing mouthwashes should also be discouraged.
- ***Maintenance of oral hygiene.*** Although the evidence is not yet conclusive, several reports suggest that poor oral hygiene and chronic, repeated trauma may promote the development of HNSCC. Therefore, maintenance of proper oral hygiene and routine dental evaluations are recommended. This subject is discussed in detail in *Chapter 10*.
- ***HPV vaccination.*** While there is controversy about the role of HPV in the development of HNSCC in patients with FA, most studies agree that HPV is associated with the development of anogenital cancers as well as non-cancerous conditions such as genital warts. Therefore, all patients with FA should consider HPV vaccination. The timing of vaccination and the need for boosters remains to be defined. In general, HPV is typically transmitted by direct sexual contact; therefore, HPV vaccination is routinely recommended for preteen girls and boys in the general population who have not yet undergone puberty. Both HNSCC and genitourinary tract cancers have been reported in pre-pubertal and sexually inactive patients with FA. Given these factors, patients with FA may need to undergo HPV vaccination at an earlier age than the general population.

Other factors that are associated with the development of HNSCC in the general population include marijuana use and sexual transmission of HPV infection. Therefore, patients with FA should abstain from marijuana use and practice safe sex, including the use of condoms. The use of oral appliances,

braces, and dental X-rays do not need to be restricted in patients with FA given the lack of evidence to suggest a causal association with HNSCC (for more information, see *Chapter 10*).

Surveillance of Head and Neck Cancer

The high incidence of HNSCC combined with the poor outcome of advanced-stage disease in patients with FA underscores the need for HNSCC surveillance. Surveillance should begin at age 10, which is based on literature reports of the earliest age at diagnosis with head and neck cancer.

Selection of a medical care provider

The oral cavity of individuals with FA often contains multiple lesions. Distinguishing suspicious lesions from those that are non-cancerous requires the input of a health care provider with significant experience in the evaluation and management of head and neck cancer. Appropriate professionals may have dental, oral surgery, otolaryngology, or general surgery backgrounds supplemented with specialized training in head and neck cancer. Routine oral cancer screening by a general dentist can supplement but should not replace HNSCC screening by an experienced professional.

Components of examination

The sites at risk for development of HNSCC include all areas of the upper aerodigestive tract. Therefore, all mucosal surfaces of the head and neck region need to be examined thoroughly. The oral cavity, the most common site for HNSCC in patients with FA, and the proximal oropharynx (the back of the tongue) can be effectively evaluated through the mouth by visualization and palpation. Examination of the distal oropharynx (the back of the throat), nasopharynx (the uppermost part of the throat, between the nasal cavity and the soft palate), larynx, and hypopharynx (the bottommost part of the throat) requires the use of either a transoral mirror or a flexible fiberoptic laryngoscope. Although patients with FA have a higher rate of squamous cell carcinomas in the cervical esophagus (the uppermost part of the esophagus) than the general population, the routine use of esophagoscopy (visual examination of the esophagus using an esophagoscope) for screening is not advocated. Symptom-based evaluation for esophageal cancer needs to be considered. Any patient with odynophagia (painful swallowing), dysphagia (difficulty swallowing), or other localizing symptoms merits evaluation with a barium swallow study and/or esophagoscopy.

Good to Know

A **margin** refers to the amount of normal-appearing tissue surrounding the tumor when it is surgically removed. A positive margin indicates the presence of tumor cells near the edge of the tissue, which suggests that the cancer has not been completely removed.

A free flap refers to the transplant of a piece of tissue from one site of the body to another for the reconstruction of a defect.

The **extent or severity of HNSCC** is classified according to the TNM staging system, based on the size and configuration of the primary tumor (T), whether the cancer has spread to nearby lymph nodes (N), and whether the cancer has spread, or metastasized (M), to other parts of the body. For example, **N0** describes a cancer that has not spread to nearby lymph nodes, whereas **N1** indicates lymph node involvement.

The values for T, N, and M are then combined to assign an **overall stage** to the cancer. For most cancers, the stage is a Roman numeral from I to IV, where higher numerals represent more extensive disease.

Optimized medically means that a doctor has chosen the best treatment for a patient depending on his or her individual circumstances.

Frequency of screening

Patients with FA should begin undergoing screening for HNSCC at age 10. A qualified professional should perform a thorough head and neck examination every 6 months. If suspicious lesions are identified, they should be biopsied; further management should be dictated by the results from microscopic evaluation of the tissue. Once a premalignant or malignant lesion has been identified and appropriately treated, the frequency of surveillance examinations should be increased to once every 2-3 months. In patients successfully treated for HNSCC, an annual chest X-ray should be included as part of the screening processes to assess for distant metastasis.

Approach to biopsy

The oral cavities of patients with FA often have leukoplakia-like lesions (white or gray patches). Many of these lesions often grow bigger and then become smaller, but those that persist or progress require further attention. An experienced examiner should be able to distinguish lesions that need to be biopsied from those that can simply be followed over time. A brush biopsy may be used for screening, but a tissue biopsy is recommended to establish a definitive diagnosis.

Treatment of Head and Neck Cancer in Patients with FA

Surgery, radiation, and chemotherapy—either alone or in combination—are used to treat HNSCC in the general population. As a general rule, early-stage disease is treated with either surgery or radiation therapy, whereas advanced-stage disease requires combination therapy with surgery followed by radiation with or without chemotherapy or concomitant treatment with chemoradiation therapy. While all of these approaches can be used in the general population, significant negative aftereffects limit the use of chemotherapy and radiation therapy in patients with FA. Therefore, several modifications are required in the management of HNSCC in patients with FA.

Treatment team

Optimal treatment of HNSCC requires a treatment team that includes not only the **surgeon (cancer and reconstructive specialists), radiation oncologist**, and **medical oncologist**, but also specialized **dentists**, **oral surgeons, speech** and **language pathologists, nurses**, as well as many other professionals. This team should work in close collaboration with other FA specialists to provide comprehensive care. The involvement of multiple types of care providers in the care of patients with FA introduces the risk that medications prescribed by one physician might adversely interact with those prescribed by another. Therefore, it is essential that all subspecialists communicate with the primary physician, usually the hematologist/oncologist, to coordinate care.

Treatment approach

The following factors complicate the management of HNSCC in patients with FA:

- The tumors of patients with FA tend to be very aggressive and are often present in advanced stages.
- The healthy, non-cancerous cells of patients with FA are highly sensitive to treatments that crosslink DNA, such as the chemotherapeutic drug cisplatin and external beam radiation—two mainstays of HNSCC treatment for the general population.
- HNSCC cells in patients with FA are not as sensitive as non-cancerous cells to DNA-crosslinking agents. Therefore, HNSCC in patients with FA do not respond to sub-therapeutic doses of radiation. Thus, surgery is the preferred therapeutic modality in patients with FA.

Surgery

In contrast to the other treatment modalities, surgical therapy for HNSCC in patients with FA is reasonably well tolerated. Patients with FA exhibit no significant increase in the incidence of complications following surgical therapy, including wound infections or long-term negative side effects associated with surgical scarring. Accordingly, the consensus opinion is that surgical therapy should be considered the primary curative modality in all patients with FA who develop head and neck cancer.

A successful outcome following head and neck surgery requires a multidisciplinary preoperative assessment and optimization of the patient, intraoperative management, and postoperative care. To minimize the risks associated with surgery, patients with FA should be optimized medically by a hematologist who is experienced in the management of patients with FA. Depending on the extent of surgery and the anticipated outcomes, a pain management specialist and a psychiatrist should be consulted prior to surgery to help the patient cope with any negative aftereffects.

Surgery for HNSCC in patients with FA should follow the same parameters that have been established for the general population. In general, a wide complete excision of the primary tumor should be performed with adequate margins. Management of the neck also follows principles established for the management of HNSCC in the general population. The exact type and extent of surgical resection should be dictated by the primary site, size, and the extent of the tumor. In general, tumors of the oral cavity and pharynx should be excised with at least 1-cm margins. The margins for laryngeal tumors need not be as comprehensive, due to the unique anatomy of the larynx.

Reconstruction of the primary site defect should follow the guidelines established for reconstruction in patients with HNSCC in the general population, and should not be limited based on the presence of FA. Therefore, the use of free flaps for reconstruction should be considered as indicated, without restriction. In general, cancers that are classified clinically as N0 disease with high risk for occult metastasis or small volume N1 disease may be managed with a selective neck dissection, whereas modified neck dissection or even radical neck dissection may be required for more advanced disease. The specific details of surgical management are discussed elsewhere [22, 32].

Radiation therapy

Radiation treatment is associated with severe negative aftereffects in patients with FA, and many patients cannot complete a full course of radiation. The risk

of dying from the negative aftereffects of radiation is as high as 50%. Death may be due to local effects, but systemic effects such as bone marrow failure are also major contributors. Those who survive radiation treatment face severe side effects, including xerostomia (dry mouth syndrome), dysphagia (difficulty swallowing), esophageal stenosis (narrowing of the esophagus), laryngeal edema (swelling of the larynx), and wound breakdown. Therefore, radiation therapy should only be used in patients for whom it is absolutely required for disease control. If radiation therapy is to be utilized, patients must be optimized medically and monitored closely for signs for severe toxicity. Aggressive pretreatment optimization, combined with aggressive monitoring and early intervention can allow patients with FA to complete a full course of radiation treatment. It is important to keep in mind that tumor cells in patients with FA do not have increased susceptibility to the effects of radiation (unlike the tumor cells in most individuals in the general population). Therefore, if treatment with radiation is contemplated, it should be planned for the same doses used in the management of patients without FA.

Chemotherapy in patients without FA

Systemic therapy is an integral component of the management for locally advanced and recurrent/metastatic HNSCC in patients without FA. In patients with resected HNSCC, cisplatin (100 mg/m^2 intravenously once every 21 days) administered concurrently with post-operative radiation therapy has been demonstrated to improve locoregional control and overall survival in randomized studies [13,14]. A pooled analysis of two phase III clinical trials demonstrated that patients with positive margins and/or extracapsular nodal spread (spread of the tumor beyond the lymph node) benefited the most from the addition of chemotherapy to post-operative radiation therapy [15]. Based on these results, treatment guidelines currently recommend adjuvant cisplatin-based concurrent chemoradiation therapy for patients with these high-risk adverse features.

In patients with stage III to IVB disease who are treated non-surgically with curative intent, the integration of platinum-based chemotherapy concurrently with radiation therapy has been demonstrated to improve locoregional control and overall survival in prospective clinical trials and meta-analysis, compared with radiation therapy alone. These studies demonstrated an absolute 5-year survival benefit of approximately 6.5% [16,17]. As a result, concurrent platinum-based chemoradiation therapy has become a standard option for non-surgical management of locally advanced HNSCC. However, the addition of cytotoxic

chemotherapy to radiation therapy has been associated with an increased incidence of adverse events, including mucositis (inflammation of the mucous membranes), dermatitis (inflammation of the skin), skin toxicities, and the need for feeding tube placement [16].

Cetuximab (Erbitux) is a monoclonal antibody that inhibits the epidermal growth factor receptor (EGFR) and is used for the treatment of patients with locally advanced HNSCC. Erbitux has been shown to improve locoregional control and survival when added to definitive radiation therapy in patients with oropharyngeal, laryngeal, and hypopharyngeal tumors in a randomized phase III trial [18]. Based on these results, Erbitux has been approved by regulatory agencies throughout the world to be used in this setting. Erbitux has a more favorable side effect profile than cytotoxic chemotherapy. Clinically relevant Erbitux-induced adverse events include skin rash, hypomagnesemia (abnormally low blood magnesium levels), grade 3-5 hypersensitivity reaction (in approximately 3% patients), and a small increase in the incidence of radiotherapy-induced mucositis. Blood toxicity is not usually observed with Erbitux/radiation therapy. Concurrent Erbitux and radiation therapy has not been directly compared to concurrent cisplatin and radiation therapy in large randomized studies. Studies evaluating the role of Erbitux in the post-operative setting are ongoing.

For patients with recurrent/metastatic disease, the cornerstone of treatment is systemic therapy with single agents (cisplatin, taxanes, 5-fluorouracil, or methotraxate), or platinum-based doublet regimens (the combination of a platinum-based drug with other chemotherapy agents) to ease pain. Erbitux has activity as single agent, and has also been shown to improve survival when added to first-line platinum/5-fluorouracil in a randomized phase III trial [19].

Chemotherapy in patients with FA

The use of chemotherapy—particularly DNA-damaging agents—in patients with FA is challenging, especially as it pertains to bone marrow failure and increased risk for normal tissue injury. The issue is further complicated by the lack of prospective trials, or even large retrospective series evaluating the safety and efficacy of cytotoxic agents in this patient population. Table 1 summarizes the published experience with the use of cytotoxic chemotherapy in patients with FA for treatment of multiple tumor types (the majority of which are HNSCC). Notwithstanding possible publication bias, the limited data demonstrate that standard doses and schedules of chemotherapy do not seem to be feasible in patients with FA. Furthermore, cytotoxic chemotherapy

at both standard and low doses is associated with severe, and in many cases fatal, toxicities and poor treatment outcomes. Kutler et al. recently updated one of the largest retrospective series of HNSCC in patients with FA ever reported. Of the 25 patients included in this report, 3 were treated with chemoradiation (cisplatin/carboplatin) at some point during the course of the disease; all 3 of the patients exposed to cytotoxic chemotherapy developed severe complications, including cytopenia and severe mucositis [20]. In addition, 2 patients underwent therapy with targeted chemotherapy (Erbitux) after developing non-resectable recurrence of their primary cancer; both tolerated Erbitux well, but died of recurrent disease.

The use of biologic agents in patients with FA is an attractive alternative to cytotoxic chemotherapy, given the more favorable side effect profile of biologic agents. Nonetheless, Erbitux the only targeted agent approved for HNSCC) has only been used anecdotally in patients with FA. One recent case report describes the use of concurrent Erbitux and radiation therapy for the management of a recurrent squamous cell carcinoma of the tongue. The patient was able to complete 8 out of 10 planned doses of the biologic agent; however, the dose had to be reduced to 200 mg/m^2/week after the patient developed neutropenia (a toxicity not usually seen in non-FA patients) following the initial loading dose of 400 mg/m^2. The patient also developed grade 3 dermatitis (following 50 Gy of radiation therapy), mucositis (following 45 Gy of radiation therapy), and cholestasis, but all were clinically manageable. Unfortunately, the patient developed a rapid recurrence of HNSCC after completion of treatment and died with the disease [21]. Taken together, the data indicate a significant risk of complications in patients with FA receiving cytotoxic agents alone or in combination with radiation therapy.

Cytotoxic chemotherapy serves only as an adjunct to the cornerstone treatment—adequate surgery and/or radiation therapy—for patients without FA who have locally advanced disease. In patients with FA, the highest chance for long-term disease-free survival is achieved with adequate surgery (and/or possibly radiation therapy, as discussed elsewhere in this chapter). Because of the high incidence of complications related to cytotoxic agents in patients with FA, the risks of integrating cytotoxic chemotherapy to the treatment regimen outweigh the potential benefits in most situations. Therefore, the use of cytotoxic agents in patients with FA who have locally advanced or recurrent/metastatic head and neck cancers is strongly discouraged. For selected cases in which chemotherapy and/or biologic therapy are to be considered, it is recommended that treatment is delivered in centers with extensive experience managing head and neck cancers and FA.

Table 1. Cytotoxic chemotherapy in patients with Fanconi anemia.

Tumor type	N	Chemotherapy	Cycles	Outcome
SCC tonsil[33]	1 ¶	Cisplatin (40 mg/m2)	X1	Fatal myelotoxocity
SCC hypopharynx[34]	1 ¶	Cisplatin (100 mg/m2)	X1	Fatal myelotoxicity
SCC esophagus[35]	1 ǂ	• Cisplatin (33 mg/m2) • 5-FU (1000 mg/m2)	X1	• Severe diarrhea and myelotoxicity • Partial response allowing surgery
SCC tongue[36]	1 ǂ	• Cisplatin (8 mg) • 5-FU (60 mg)	X1	• Severe toxicity • No tumor response
SCC lung[37]	1 ǂ	• Carboplatin (AUC 3 d1) • Gemcitabine (1250 mg/m2 d1,8)	X2	• Pneumonitis • Partial response allowing surgery
SCC head and neck[10]	3 (2 ¶ + 1 ǂ)	N/A	N/A	All died with disease
SCC vulva[38]	1 ¶	Cisplatin (40 mg/m2)	X1	Fatal fungal sepsis

Chemotherapy was given as a single modality (ǂ) or concurrently with radiation therapy (¶).
Abbreviations: AUC, area under the curve; N, number of patients treated with chemotherapy in each report; N/A, not available; SCC, squamous cell carcinomas.

Rehabilitation and lifestyle modification

The treatment of HNSCC can be debilitating. Rehabilitation should be initiated as needed, to optimize the patient's functional, psychological, and vocational outcomes. The negative aftereffects of surgical tumor removal on speech and swallowing require intervention by physical and rehabilitation specialists (e.g., neck and shoulder exercises, speech and swallowing therapy, etc.). In addition, paralyzed vocal cords and stricture or obstruction of the pharynx also require intervention. Cosmetic restoration of the face is crucial to psychological rehabilitation. Following radiation therapy, patients may require management of xerostomia (dry mouth syndrome), dental care, and prevention of fibrosis-related complications such as trismus (reduced opening of the mouth due to spasm of the jaw muscles). Patients should be placed on long-term care specifically with respect to dental management. Monitoring of dentition should be maintained, and prevention measures for caries initiated, including the use of fluoride treatments in all patients. Following chemotherapy, patients may require management of kidney function, hearing, and damage to peripheral nerves.

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 patients with FA. 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 patients with FA, because 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.

Chapter Committee

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