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Natural History and Management of Fanconi Anemia Patients with Head and Neck Cancer: A 10-year Follow-up

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Abstract

Objective—To describe the management and outcomes of Fanconi anemia (FA) patients with head and neck squamous cell carcinoma.

Study Design—Cohort study.

Methods—Demographic information, prognostic factors, therapeutic management, and survival outcomes for FA patients enrolled in the International Fanconi Anemia Registry (IFAR) who developed head and neck squamous cell carcinoma (HNSCC) were analyzed.

Results—35 FA patients were diagnosed with HNSCC at a mean age of 32 years. The most common site of primary cancer was the oral cavity (26/35, 74%). Thirty patients underwent surgical resection of the cancer. Sixteen patients received radiation therapy with an average radiation dose of 5050 cGy. The most common toxicities were high-grade mucositis (9/16, 56%), hematologic abnormalities (8/16, 50%), and dysphagia (8/16, 50%). Three patients received conventional chemotherapy and had significant complications while three patients who received targeted chemotherapy with cetuximab had fewer toxicities. The 5-year overall survival rate was 39% with a cause-specific survival rate of 47%.

Conclusions—Fanconi anemia patients have a high risk of developing aggressive HNSCC at an early age. FA patients can tolerate complex ablative and reconstructive surgeries, but careful post-operative care is required to reduce morbidity. The treatment of FA-associated HNSCC is difficult secondary to the poor tolerance of radiation and chemotherapy. However, radiation should be used for high-risk cancers because of the poor survival in these patients.

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Keywords

Fanconi anemia; head and neck; squamous cell carcinoma

INTRODUCTION

Fanconi anemia (FA) is a rare recessive disorder (1–2:100,000 births)[1,2] caused by mutations in one of at least 19 known genes (FANCA/B/C/D1/D2/E/F/G/I/J/L/M/N/O/P/Q/R/S/T)[3] with patients with mutations in the same gene forming each of the 19 complementation groups (FA-A to FA-T). The proteins encoded by these genes act together to protect genomic integrity, and the mechanism of their function is under intense study in many laboratories. It has been shown that the FA pathway is involved in interstrand crosslink repair[4–6] although it clearly responds to conditions of replication stress.[7,8] Eight of the FA gene products interact in a core complex that localizes to the sites of damage or stalled replication forks.[5] The FANCL component of the core complex monoubiquinates two other FA gene product, FANCD2 and FANCI[9,10] which in turn activate effector pathways including nucleases, translesion polymerases and homologous recombination machinery.[6,11,12] Because of its function in DNA repair, FA belongs to a group of hereditary disorders called caretaker gene diseases, which also include ataxia-telangiectasia, nucleotide excision repair syndromes, Bloom syndrome, hereditary nonpolyposis colorectal cancer, and hereditary breast/ovarian cancer syndromes.[13]

FA is characterized clinically by bone marrow failure that can affect any of the hematopoietic lineages, congenital malformations (short stature, radial ray anomalies, café aulait spots, cardiac and renal anomalies), sensitivity to DNA cross-linking agents and increased risk of malignancy.[1] The correlation between genotype (the complementation group and the actual mutation) and phenotype is very poorly understood. The severity of the phenotype is determined in part by the patient's specific complementation group, and the type of pathogenic genetic variants inherited.[14] Previous studies have established that patients in group FANCC have a more severe FA phenotype characterized by earlier onset of bone marrow failure and poorer survival compared to groups FANCA and FANCG.[15] Biallelic mutations in BRCA2 and PALB2 results in the most severe phenotype of tumor predisposition. Because of these phenotypic differences among complementation groups FA is a heterogeneous disorder; patients may be severely affected, with multiple congenital anomalies and severe aplastic anemia, or may have a mild phenotype with no major malformations or hematologic abnormalities.[16,17]

Leukemia, specifically acute myeloid leukemia (AML), historically has been the most common cancer in FA patients, but patients are also at a significantly increased risk of developing solid tumors, with a 28% cumulative incidence of solid cancers by the age of 40.[15] In particular, head and neck squamous cell carcinomas (HNSCCs) are significantly more common in FA patients relative to the general population[18] with some reports calculating a 500–700 hundred-fold risk increase.[19] As hematopoietic stem cell transplantation (HSCT), preleukemia detection, leukemia therapies and other recent advances have improved the survival of FA patients into adulthood,[20] an increasing number

of these patients are developing HNSCCs. One hypothesis of cancer development in FA patients relates to the defects in DNA damage repair, and consequent increases in the genomic instability in the epithelial cells of the head and neck region.[21,22]

The standard treatment for HNSCC in the general population incorporates a combination of surgery, radiation and chemotherapy, depending on the tumor characteristics and clinical stage. Adjuvant radiation and chemotherapy therapy is often recommended to treat patients with higher stage tumors. Definitive radiation with or without chemotherapy is also used to treat certain HNSCCs depending on the location of the primary site and the initial cancer stage. However, even in the general population (without genomic instability), radiation and chemotherapy are known to potentially induce numerous side effects and complications including mucositis, dysphagia, taste changes and fatigue. Other more severe complications including osteonecrosis, fibrosis, and esophageal stenosis exist as well, but are relatively rare. The management of FA patients with HNSCC is often difficult because of their sensitivity to both radiation therapy and chemotherapy agents (particularly cisplatin and mitomycin C).[1] Therefore, these therapeutic modalities are commonly avoided in the treatment plans for FA patients with HNSCC. Because of the complexity of treating FA patients with HNSCC, a comprehensive evaluation of these patients is very important. An understanding of how to manage these patients has not been previously well⁻ elucidated, secondary to the rare occurrence of FA in the general population and, thus, the small number of FA-associated neoplasms. Other studies evaluating neoplasms in patients with FA have been based on individual case reports or have been limited by small patient numbers, limited follow-up, and unconfirmed FA diagnoses. In this study, we reviewed the records of patients reported to the IFAR for the occurrence of HNSCC over a 10-year period and defined its clinical course, management and outcome. No other previously published study has comprehensively evaluated FA patients with HNSCCs over such a long follow-up period. The goal of this study is to help the treating physician care for FA patients with head and neck cancer.

MATERIALS AND METHODS

Fanconi Anemia Registry

The International Fanconi Anemia Registry (IFAR) was instituted in 1982 as a repository to collect clinical and genetic information from FA patients throughout the world. It currently has over 1200 families enrolled. The registry collects longitudinal medical and other pertinent information from these patients by contacting them or surviving family members.

Patient Data Collection

Overall, we identified and collected information on 35 FA patients with HNSCC. We obtained patient or family consent when appropriate and obtained all available histories, medical, surgical and radiation records from their respective treating hospitals. The diagnosis of FA was made by diepoxybutane (DEB) breakage test, as previously described.[23] FA complementation groups were documented when possible. HPV status of the tumors were previously reported.[24]

Statistical Analysis

The end points of interest were overall, cause-specific, and disease-free survival times. Overall survival time was calculated as the time elapsed in months between the date of biopsy or surgery and the date of death or of last follow-up. Cause-specific survival time was calculated as the time elapsed in months between the date of biopsy or surgery and the date of death due to HNSCC or the last follow-up. Disease-free survival time was calculated as the time elapsed in months between the date of surgery and the date of disease recurrence. The Kaplan-Meier method was used to estimate the overall, cause-specific and disease-free survival times. The log-rank test was used to detect any differences in HNSCC onset or survival between various patient subgroups.

RESULTS

Patient Demographic Information

Overall, we studied 22 female and 13 male FA patients who developed HNSCC (Table 1). Twenty-five patients were in complementation group FA-A, four in FA-C, and one each in FA-F, FA-J, FA-G and FA-P. Two patients are currently untyped. The median age for development of HNSCC was 30 years; the mean was 32 years with a range from 14 to 48 years. In five patients (14%), the malignancy preceded the diagnosis of FA. Patients' records were screened for environmental risk factors known to enhance the risk of HNSCC: 9 patients (26%) had a medical record indicating a history of tobacco use, alcohol consumption or both (Table 2). Thirteen of the 35 patients (37%) had undergone previous HSCT.

Tumor Location and Staging

For patients who had tumors with a known clinical stage, eight were stage I, three were stage II, one was stage III and 15 patients were stage IV. Of the 15 stage IV patients, 10 patients had N2b disease or greater. The TNM stages and tumor locations are summarized in Table 2. The sites of cancers included the oral cavity (26 cases), larynx (6 cases), oropharynx (1 case), and the esophagus (1 case). One patient had an unknown primary. The most common sub-site of oral cavity involvement was the tongue (n = 14), followed by the alveolar ridge (n = 4), the buccal mucosa (n = 3), the retromolar trigone (n = 2), and the floor of the mouth (n = 2). The most common sub-site of the larynx was the supraglottis (n=3).

Histological characteristics

Surgical pathology reports or paraffin-embedded specimens were obtained from the treating institution, and confirmed SCC in all patients. In 26 patients, information concerning tumor differentiation was available: 9 were well differentiated, 13 were moderately differentiated, and 4 were poorly differentiated. The size of the primary tumor ranged from 0.4 to 5 cm (median 2.6 cm). The depth of invasion of the primary tumor ranged from 0.14 cm to 4.5 cm with a median of 0.5 cm. Margin status was available for 24 patients: 18 patients had negative margins, 6 patients had microscopically positive margins, while 2 had close margins of less than 1 mm. Of 19 patients who underwent cervical lymph node dissection,

15 patients had positive lymph nodes. The average number of positive lymph nodes in the neck dissection specimens was 3 (range 1 – 10 nodes) with an average of 23 lymph nodes removed per patient. Extra-capsular spread (ECS) was identified in 6 of the patients' neck dissection specimens.

Human papilloma virus (HPV) analysis of the primary tumor was conducted for 20 of the 35 patients in this study. HPV was positive in 15 of the 20 patients (75%). All of the positive HPV tumors were typed as HPV-16. Thirteen of the HPV positive tumors were found in the oral cavity, while the remaining two tumors were found in the oropharyngeal region. There was no difference in survival outcomes for patients with HPV positive tumors compared to those with HPV negative tumors although such a difference was perhaps undetected due to the limited number of HPV negative tumors.

Surgical Management and Complications

Thirty patients (86%) underwent surgical resection of their primary HNSCC, with 19 simultaneously undergoing a total of 21 neck dissections (8 modified radical neck dissections, 11 selective neck dissections, and 2 radical neck dissections). One patient died several days after a diagnostic biopsy, and a second patient had widely metastatic disease at presentation. One patient was diagnosed with an unknown primary and did not undergo a primary cancer resection. Of the 30 patients who underwent surgery, 9 (29%) underwent flap reconstruction, including 6 free flap reconstruction (2 jejunal free flaps, 2 fibular free flaps, and 2 anterior lateral thigh free flap), 1 regional flap reconstruction (gastric pull-up) and 2 local flap reconstructions (tongue flap and buccal fat pad). The remaining patients had primary closure of their defects. One patient had two sequential free flaps for a secondary primary tumor (an anterior lateral thigh free flap for reconstruction of the hypopharynx and a fibular free flap for reconstruction of the mandible). Seven patients had a total of 9 postoperative complications, including 2 wound infections requiring hardware removal, 1 acute respiratory distress syndrome, 1 hematoma after fibular free flap reconstruction, 2 pharyngocutaneous fistulas, 1 marginal mandibular nerve weakness, 1 abdominal sepsis after total esophagectomy and 1 aspiration pneumonia after supraglottic laryngectomy.

Patient Radiation Doses and Complications

Sixteen patients received radiation therapy--13 patients underwent adjuvant post-operative radiation therapy, one patient received neoadjuvant radiation therapy and two patients received palliative radiation therapy. Among these 16 patients who received radiation therapy, 69% (11/16) had stage IV cancers, 19% (3/16) had stage I tumors and 6% (1/16) had stage III cancer. Tumor staging was unknown for one patient who received radiation (Table 3). The total radiation dose ranged from 2500 cGy to 7020 cGy, with a mean dose of 5050 cGy. For patients from whom we were able to collect daily fraction data, doses ranged from 170 cGy to 200 cGy per treatment. Total length of treatment ranged from 31 days to 70 days.

The most prevalent complications during radiation treatment were high-grade mucositis (9/16), hematologic abnormalities (8/16), and dysphagia (8/16). Other complications included asystole/ cardiac arrest, wound site breakdown, fibrosis, local edema, sepsis,

tracheal stenosis, and radiation pneumonitis (Table 3). Eleven patients did complete the planned radiation dose while for five patients (n=2 FANCA, 1 FANCC, 1 FANCJ), radiation therapy needed to be prematurely halted or interrupted due to toxicities associated with the treatment, primarily due to mucositis (Table 3). Patient complementation group or severity of FA phenotype (younger age at diagnosis of FA, history of HSCT, or younger age at diagnosis of SCC) did not correlate with poor tolerance of radiation although it is possible that such associations could not be detected due to a relatively small sample size.

Chemotherapy and Complications

Three patients received conventional chemotherapy while another three patients received targeted chemotherapy with cetuximab (Erbitux). One patient who received conventional chemotherapy in addition to adjuvant radiation was not known to have FA until the development of treatment-related complications including mucositis, persistent myelosuppression, hemorrhage, dysphagia, tracheal stenosis, and recurrent aspiration pneumonia. One patient received conventional chemotherapy without radiation for tumor recurrence and treatment complications are unknown. Three patients received targeted chemotherapy with cetuximab in addition to adjuvant or neoadjuvant radiation therapy. Of these three patients treated with cetuximab, only one patient was reported to have complications, which included pancytopenia, dysphagia and folliculitis.

Second Primary Cancers

Patients with FA have a tendency to develop multiple malignancies. Overall, 12 (48%) of the 35 patients with HNSCC developed multiple malignancies, with 5 developing more than 2 primary malignancies. Of these patients, 9 developed a second primary SCC, including anal SCC (n = 2), cervical SCC (n = 2), vulvar SCC (n = 2), a second head and neck primary tumor (n = 2), and cutaneous SCC (n = 1). One patient developed a total of 4 malignancies (myelodysplastic syndrome, breast carcinoma, HNSCC, and anal SCC) before the age of 40 years, and was not diagnosed as having FA until after her third malignancy, when she was found to have anemia during her preoperative workup.

Survival outcomes

Follow-up and outcome information was available for all 35 patients. Thirty (86%) of the patients died during the study period. Sixteen patients (64%) died as a consequence of HNSCC. Overall survival time ranged from less than 1 month to greater than 410 months (34 years). The median follow-up, based on the 5 patients who were alive at last follow-up, was 178 months (14 years). Seventeen (49%) of the patients had recurrence of their tumor, with a median disease-free interval of 22 months. Among all patients with stage I cancers, 88% (7/8) experienced tumor recurrence and 100% (3/3) of stage II cancers, 0% (0/1) of stage III cancers, and 27% (4/15) of stage IV cancers recurred. Eight patients were known to have had a local recurrence and 3 had a neck recurrence while 6 patients developed recurrence both locally and regionally. Four patients progressed to have distant metastases. Twelve of the patients who experienced tumor recurrence underwent surgical resection. Of these 12 patients, two patients received adjuvant chemoradiation, two patients were treated with adjuvant chemotherapy, and one patient received postoperative radiation alone. One patient received radiation therapy without surgical resection for tumor recurrence. Of the 11

patients with early stage cancers at initial presentation (Stage I and II), 6 patients died of recurrent locoregional disease. Of the 16 patients who underwent radiation therapy, 15 patients died with 4 patients dying from complications while receiving radiation therapy (three from sepsis, and one from cardiac arrest). The 2-year cause-specific, disease-free and overall survival rates, based on Kaplan-Meier survival estimates, were 79%, 75%, and 71%, respectively. The 5-year cause-specific, disease-free, and overall survival rates, based on Kaplan-Meier survival estimates, were 47%, 43%, and 39%, respectively (Figure 1). HPV status, complementation group, history of radiation therapy or chemotherapy, and site of primary tumor did not significantly affect HNSCC onset or survival in this cohort.

DISCUSSION

The propensity for patients with FA to develop cancer is well documented. Kaplan et al.[25] suggest that there are 2 major defects that play a role in the development of malignancies in patients with FA: defective chromosomal stability and immunodeficiency. Chromosomal studies[26] in patients with FA have shown an increased spontaneous instability. Aberrations, such as breaks, fragments, radials, and dicentric chromosomes have been described.

The best-described malignancies associated with FA are hematologic in origin.[27] Previous reports also suggest that patients with FA are predisposed to solid tumors, particularly HNSCC and SCC of the anogenital region. Lustig et al.[28] reviewed the literature and identified 17 cases of HNSCC associated with FA. In their report, they concluded that these carcinomas occurred in young patients (<30 years), were equally common in females as in males, and originated from the tongue (n = 9), gingiva (n = 3), pyriform sinus (n = 1), postcricoid region (n = 1), and the upper third of the esophagus (n = 1). Another previous study by Kutler et al.[15] of 754 subjects with FA determined the cumulative incidence of developing a solid tumor approaches 28% with the cumulative incidence of developing HNSCC is 14% by 40 years of age.[18]

Not only are patients with FA strongly predisposed to the development of HNSCC but they also have an earlier onset of HNSCC. Patients with phenotypically mild FA who have no bone marrow failure or leukemia development and who survive into the third decade of life are at a significant risk of developing HNSCC. In addition, as the life expectancies of more severely affected patients with FA increase with improvements in HSCT, the number of patients developing HNSCC will most likely increase as well. A history of HSCT is thought to increase FA patients' risk of developing subsequent solid malignancies, particularly HNSCC.[29,30] In one study by Rosenberg et al.,[22] the age-specific hazard of SCC was 4.4-fold higher in patients who received HSCTs than in those who did not (P = .003), and SCCs occurred at significantly younger ages in the former (respective medians, 18 vs. 33 years, P = .004). In this cohort, 13 of the 35 patients (37%) had a previous history of HSCT prior to developing HNSCC.

In this study, FA patients developed HNSCC at a very young age compared to the general population, with a mean of 32 years in our population versus 63 years as reported in a general population.[31] In addition, HNSCC developed often without history of tobacco use or alcohol consumption, common risk factors for HNSCC in the general population (twenty-six

percent in our FA population versus 75–85% in a general HNSCC population[31]). However, even a very small amount of alcohol consumption that perhaps would not be reported by patients may be quite carcinogenic in this patient population.[32–34] Based on reports in the literature that document development of HNSCC at ages as young as 13 (average 28) in FA patients,[29] increased screening and awareness of HNSCC should be maintained in this population starting at a young age. Based on the age distribution in this study, screening of the oral cavity and oropharynx should start prior to 15 years of age. This would include a detailed evaluation and physical examination of the FA patient by an expert in head and neck diseases every 3–4 months. In addition, fiberoptic evaluation of the larynx and hypopharynx should also be done in order to find early cancers of the larynx and pharynx. However, in patients with FA with a history of pre-cancerous leukoplakia or recurrent oral lesions, head and neck examinations are recommended every 6 to 8 weeks. Early identification of HNSCC and, thus, early therapeutic interventions may be translated into improved survival, or at least may reduce the necessity for more aggressive surgical approaches. Conversely, patients who develop HNSCC at young ages may be appropriate candidates for screening for FA.

HNSCCs in FA patients were most commonly located in the oral cavity (26/35, 74%), particularly in the tongue (14/35, 40%). This finding is similar to the findings in the review by Lustig et al.,[28] who found a 52% incidence of tongue carcinoma. The affinity of FA-associated SCC to the oral cavity and especially to the tongue is striking because the incidence of tongue carcinoma in the general population is only 10% to 20%.[35,36] The development of multiple primary malignancies, particularly SCC, is another common finding in patients with FA. The reason for the strong propensity for patients with FA to develop multiple oral cavity SCCs and secondary SCCs of the mucous membranes is unclear. Kennedy and Hart[37] noted that patients with FA have a marked predisposition for carcinomas of the mucous membranes of the anogenital and oral areas. In their review,[37] they found that 5 (36%) of 14 patients developed carcinoma in more than 1 mucosal site.

A hypothesis for predisposition to multiple SCCs is the possible increased susceptibility of the oral cavity and genital region to local predisposing factors, including viruses. The virus association is interesting because the mucous membranes are a common route for oncogenic viral infections, especially HPV. The immunosuppression associated with persistent bone marrow failure and the underlying genetic instability in these patients may predispose these patients to viral infections. In addition, studies have demonstrated an interaction between the HPV16 E7 oncoprotein and the FA pathway.[38–40] It has also been hypothesized that the FA pathway contributes to repair of DNA damage induced by HPV16 E7, providing one explanation for why FA patients are predisposed to HPV-associated HNSCCs.[41]

In FA patients from North America, a high percentage (84%) of HNSCCs were found to be positive for high-risk HPV DNA. Consistent with the role of HPV in these cancers, mutations in p53, a tumor suppressor that is inactivated by HPV 16 E6, were not found in HNSCCs from these patients.[24] However, in patients from European countries, HNSCCs were negative for HPV DNA and more than 50% of these tumors had p53 mutations.[42] Based on this conflicting data, it remains unclear whether HPVs play a role in HNSCCs arising in FA patients. In this study, which is based on previously published data,[24] 15 of the

20 HNSCCs (75%) that were tested for HPV were positive. In addition, the oncogenic HPV-16 was identified in all positive samples. Interestingly, 13 of the HPV positive tumors were found in the oral cavity, while the remaining two tumors were found in the oropharyngeal region. This is inconsistent with the literature from the general population, where HPV positivity is related to the oropharyngeal region rather than the oral cavity.[43,44] The reason for this difference is not known at this point. Because of the possible high rate of HPV-positivity in FA-associated HNSCC as well as the propensity for them to develop anogenital cancers, both male and female FA patients should be considered candidates for the HPV vaccine.

The main treatment modality for FA patients with HNSCC is surgery because of the potential risks associated with primary radiation therapy and chemotherapy. The main preoperative problem in patients with FA is the bone marrow failure that is associated with the disorder, requiring preoperative consultation with a hematologist and the possibility of blood and platelet transfusion before surgery. A hematologist should also be available post-operatively to help manage any complicating hematologic abnormalities. However, no patient in this study had severe bone marrow failure during post-operative hospitalization.

This study shows that FA patient can tolerate large complex surgeries with free flap reconstructions without significant morbidity or mortality. Indeed, one patient underwent two separate free flap reconstructions without experiencing life-threatening complications.[45] However, she did develop a pharyngocutaneous fistula during the post-operative period of the second surgery, which resolved with local wound care. Other postoperative complications included wound infections, hematomas, pharyngocutaneous fistulas and aspiration pneumonia, which are not very different than the complications in the general population. In this study of FA-associated HNSCC, there were postoperative complications in 7 of 30 patients (23%) who underwent surgical resections, but most patients tolerated surgery well, with minimal long-term morbidity.

In a literature review by Lustig et al.,[28] the authors concluded that in the 5 patients who were treated for HNSCC by radiation therapy as primary or adjuvant treatment, all of them tolerated it without difficulty. In contrast, post-operative radiation therapy was used in 16 patients in this study with mixed success. Patients suffered complications even at low doses of radiation, and no minimal safe dose of radiation was seen in this cohort, as complications arose in one patient at 2500 cGy. Compared to a target minimum dose of 5760 cGy for post-operative patients in the general population,[46] FA patients in this cohort received a mean dose of 5050 cGy. This decreased average dose was due to the intolerance of these FA patients to the toxicity of the treatment, requiring termination or interruption of therapy in 5 patients. Since FA patient tumors carry FA mutations, the tumors themselves may be more sensitive to radiation, and consideration of lower doses of radiation to achieve cure in FA patients may be appropriate.

Radiation treatment for head and neck cancers is associated with numerous complications in the general population, with the most common being high-grade mucositis, dysphagia, dry mouth, and taste changes. High-grade mucositis is reported to range from 34% to 57% in the general population.[47] Mucositis was seen in 9/16 (56%) patients in our cohort, suggesting it

poses a significant risk in FA patients. In addition, pancytopenia, which is a rare complication in the general population, was experienced at high rates (8/16) in this cohort of FA patients. The pancytopenia is of particular concern in dealing with post-radiation complications in these patients as it can lead to bleeding complications, fatigue, poor wound healing, and infection. Due to the underlying stem-cell problems in these patients, time to recovery of normal blood counts may also be delayed. In this cohort, two patients developed sepsis, one had recurrent pneumonia, and two had bleeding complications.

Based on this case series, it is clear that FA patients should not be precluded from receiving post-operative radiation therapy. However, it is important to be aware of the complications that may present in FA patients, particularly hematologic abnormalities and high-grade mucositis. Therefore, we recommend frequent monitoring of hematologic counts throughout radiation therapy. In particular, careful monitoring of WBC counts is needed to avoid potential infections and sepsis. Close monitoring of mucositis should be performed especially since severe mucositis can limit completion of radiation therapy. For patients with significant complications, temporarily suspending therapy may be needed to avoid worsening of the complications and to allow for recovery. In developing radiation treatment plans, longer courses at lower daily doses may be considered in order to decrease risk of developing significant toxicities. The addition of chemotherapy to radiation in three patients in this cohort resulted in significant complications (including interruption or cessation of therapy in two); suggesting special care may need to be taken in considering chemotherapy in addition to radiation in FA patients. Three patients received targeted chemotherapy with Erbitux (cetuximab), which they tolerated well, but all three died of recurrent or metastatic disease.

The 5-year cause-specific and overall survival was poor in this patient population (47% and 39%, respectively) with a median overall survival length of 42 months. Five-year disease-free survival was also poor (43%) with a median disease-free interval of 22 months. Compared with other studies evaluating outcomes for patients with oral cavity SCC younger than 35 years, the outcome for those with FA-associated HNSCC is significantly worse. In a previous study of patients younger than 35 years with oral cavity carcinoma, the 5-year survival was 57.3%.[48] Another study[49] analyzing 12 patients younger than 35 years showed a 2-year survival of 57%. The underlying genomic instability in patients with FA may increase the likelihood of developing genomic alterations that select for a more aggressive phenotype or allow for the development of an early recurrence. Therefore, aggressive therapy should be considered in all FA patients with a balance between appropriately aggressive oncologic surgery and post-operative radiation. Special considerations with regard to blood counts, infections and side-effects should be a part of the normal post-therapy evaluation of FA patients. Advancements in targeted therapies like Erbitux, may also improve the treatment of these patients, but more studies concerning the efficacy in these patient are needed.

Although the large number of patients and the long 10-year follow-up make the IFAR database unique, there are potential limitations. One problem is the possibility of selective reporting. Another is that there was no prospectively defined study design; reporting of malignancy development was determined by the participating physicians even after the

subjects were entered into the registry. A third consideration is the completeness and accuracy of data reporting; no audits of reporting centers were performed. However, by using this registry, we have been able to evaluate HNSCC in this rare population of patients with a known genetic disease characterized by chromosomal instability.

CONCLUSION

To our knowledge, this registry-based study represents the largest reported series of HNSCCs associated with FA. Patients with FA have an increased incidence of aggressive HNSCC that frequently develops at an early age and has a very poor prognosis. Primary surgery remains the mainstay for treatment; radiation therapy has been used in high stage cancers, but its success has been limited by severe mucositis and pancytopenia. Careful screening of the head and neck in patients with FA is essential to discover lesions at an early stage. There is also a tendency for the development of multiple SCCs of the mucous membranes of the aerodigestive and anogenital tracts in the setting of FA. Further studies of FA patients' responses to various treatment modalities should be conducted to establish appropriate therapeutic guidelines in order to achieve favorable oncologic outcomes while limiting toxicity. Additionally, the strong association between FA and SCC makes FA an excellent framework to study the role of chromosomal instability in the initiation and progression of SCC in all patients.

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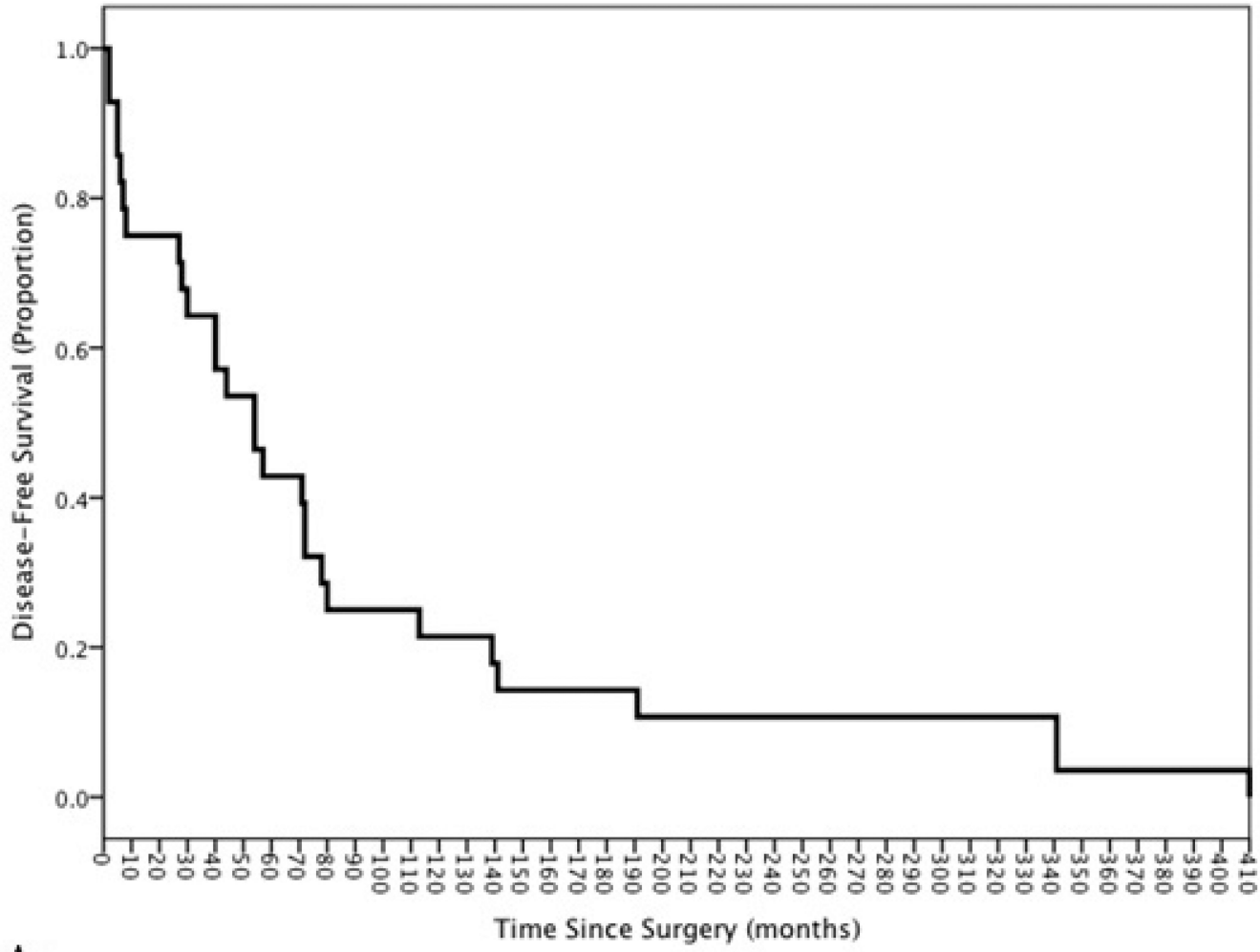

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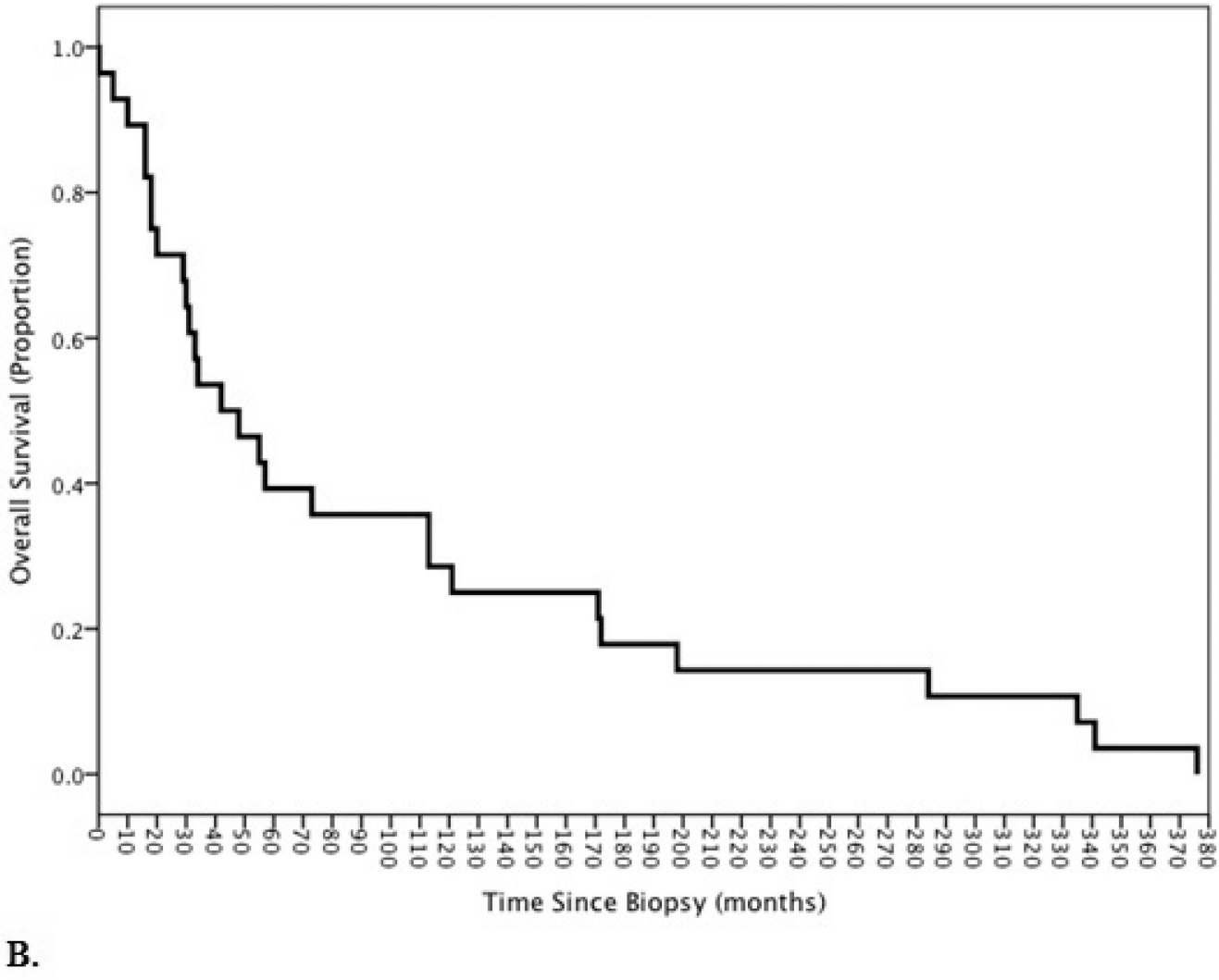

Figure 1.
Kaplan-Meier survival curves for Disease-Free Survival (A) and Overall Survival (B) for FA patients with HNSCC

Table 1

Characteristics of the Study Sample

Characteristic	Patients
Total No.	35
Sex	
Female	22
Male	13
Complementation group	
A	25
C	4
F	1
G	1
J	1
P	1
Untyped	2
Hematopoietic stem cell transplantation	
Yes	13
No	22
Primary tumor site	
Oral cavity	26
Larynx	6
Oropharynx	1
Esophagus	1
Unknown	1
Median age at FA diagnosis	10.4 (n=35)
Median age at HNSCC onset	30.1 (n=35)
Median lifespan	35.4 (n=30)

Table 2

Fanconi Anemia Patient Demographics

Patient No.	Gender	HNSCC Onset Age	FA Group	Environmental Risk Factors	Primary Site (Subsite)	T/N/M (Stage)
1	F	30.2	A		Oral Cav (Buccal gingiva)	T4N0M0 (IV)
2	M	42.1	A	HSCT	Larynx (Supraglottis)	T2N2bM0 (IV)
3	F	36.1	A		Larynx (Pyriform sinus)	T2N0M0 (II)
4	F	28.6	G	Tobacco/alcohol	Oral Cav (Tongue)	T1N0M0 (I)
5	F	36.8	A		Oral Cav (Lip)	
6	F	44.0	A		Oral Cav (Buccal/palate)	T1N0M0 (I)
7	F	Unknown	A		Oral Cav (Tongue)	
8	F	26.1	F	HSCT	Esophagus	T3N0M0 (III)
9	M	20.9	P	Tobacco/alcohol	Oral Cav (Tongue)	T4N2cM0 (IV)
10	M	48.5	J		Oral Cav (Retro Trigone)	T4N2bM0 (IV)
11	M	32.2	A	HSCT	Larynx (Supraglottis)	T2N2aM0 (IV)
12	F	42.1	A	Alcohol	Oral cavity (Alveolus)	T4N2bM0 (IV)
13	M	28.2	Untyped	Drugs/tobacco/alcohol	Oropharynx (Tonsil)	T3N2bM0 (IV)
14	F	15.4	A	HSCT	Oral Cav (Tongue)	T1N0M0 (I)
15	M	26.9	A	Substance abuse	Oral Cav (Tongue/floor)	T1N0M0 (I)
16	M	24.5	Untyped	HSCT	Oral Cav (Tongue)	T2N2bM0 (IV)
17	F	36.9	A	Tobacco	Oral Cav (Alveolus)	T4N1M0 (IV)
18	M	43.9	A		Oral Cav (Alveolus)	T4N2bM0 (IV)
19	M	34.8	A	Alcohol	Oral Cav (Tongue)	T4N1M0 (IV)
20	F	26.8	C	HSCT	Oral Cav (Submand/floor)	T4N2cM0 (IV)
21	M	29.9	A	Alcohol	Larynx (Supraglottic AE fold)	T1N0M0 (I)
22	M	23.2	A	HSCT	Oral Cav (Buccal)	T2N0M0 (II)
23	F	30.1	A	HSCT	Oral Cav (Tongue)	T1N0M0 (I)
24	F	29.2	A		Oral Cav (Tongue)	T4N0M0 (IV)
25	F	40.7	A		Oral Cav (Retro Trigone)	T2N2bM0 (IV)
26	M	24.2	A		Oral Cav (Tongue)	

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Patient No.	Gender	HNSCC Onset Age	FA Group	Environmental Risk Factors	Primary Site (Subsite)	T/N/M (Stage)
27	F	14.7	C	HSCT, alcohol	Oral Cav (Alveolus)	
28	M	47.1	A		Larynx (Post-cricoid region)	T2N0M0 (II)
29	F	24.7	C	HSCT	Oral Cav (Tongue)	T1N0M0 (I)
30	F	41.1	A	Tobacco/alcohol	Unknown	TxN2bM0 (IV)
31	F	31.6	A	HSCT	Oral Cav (Tongue)	
32	F	21.9	A	HSCT	Oral Cav	
33	F	29.0	C	HSCT	Oral Cav (Tongue)	T2N1M0 (III)
34	F	44.0	A		Oral Cav (Tongue/ Submand)	T1N0M0 (I)
35	F	33.9	A		Larynx	

Abbreviations: Oral Cav = oral cavity, HSCT = hematopoietic stem cell transplant, Floor = floor of mouth, Submand = submandibular, Retro trigone = retromolar trigone

Table 3

Post-operative Radiation Doses, Chemotherapy and Complications

Patient No.	T/N/M (stage)	XRT Total Dose (cGy)	Treatment days / # fractions / cGy per fraction	High-grade Mucositis	Dysphagia	Cytopenia	Premature termination/ interruption of XRT	Other Complications	Status/ Disease-free interval (mo)/ Post-op survival (mo).
10	T4N2bM0 (IV)	4000	33d / 20 / 200	X	X	X	X	Sepsis	D / 5 / 10
1	T4N0M0 (IV)	2500					X	Recurrence, sepsis	D / 2 / 16
18	T4N2bM0 (IV)	6100	55d	X		X		Graft site breakdown, mandibular hardware removal, recurrence	D / 71 / 172
17	T4N1M0 (IV)	5600		X	X	X		Hemorrhage, pleural thickening, sepsis	D / 139 / 171
20	T4N2cM0 (IV)	unfinished			X		X	Dyspnea, asystole/ cardiac arrest	D / 5 / 20
13	T3N2bM0 (IV)	5600 + cisplatin, bleomycin ,MTX	52d	X		X	X	Tracheal stenosis, radiation pneumonitis, recurrent pneumonia, recurrence	D / 28 / 33
12	T4N2bM0 (IV)	6460	70d / 30 / 170		X	X			D / 80 / 113
30	TxN2bM0 (IV)	6000	39d / 30 / 200	X	X	X		Hemorrhage, trismus, fibrosis, esophageal stenosis, oral dryness	A / 178+ / 178+
14	T1N0M0 (I)	+MTX		X	X			Recurrence	D / 6 / 18
9	T4N2cM0 (IV)	7020	50d / 39 / 180	X		X		Dermatitis, sepsis	D / 7 / 34
19	T4N1M0 (IV)	4240 + cetuximab	28d / 20 / 200	X	X	X	X	Wound breakdown, dermatitis, hemorrhage	D / 78 / 121
2	T2N2bM0 (IV)	5580	31d / 22 / 180	X	X			Laryngeal edema, fibrosis, esophageal stenosis, recurrence	D / 341/ 341
21	T1N0M0 (I)	+cetuximab						Recurrence, metastasis	D/141/198
33	T2N1M0 (III)	5000	31d / 25 / 200					Trismus, erythema	D / 27 / 31

Patient No.	T/N/M (stage)	XRT Total Dose (cGy)	Treatment days / # fractions / cGy per fraction	High-grade Mucositis	Dysphagia	Cytopenia	Premature termination/ interruption of XRT	Other Complications	Status/ Disease-free interval (mo)/ Post-op survival (mo).
34	T1N0M0 (I)	2500						Erythema	D / 26 / 73
26		+cetuximab							D / No surgery
Totals		5050 (avg)		9/16 (56%)	8/16 (50%)	8/16 (50%)	5/16 (31%)		/ 28 / 73 (med)/ (med)

Abbreviations: XRT = radiation therapy, mo = months, A = alive, D = deceased, MTX = methotrexate, avg = average, med = median