ORIGINAL ARTICLE

# Postoperative Clinical Radiosensitivity in Patients With Fanconi Anemia and Head and Neck Squamous Cell Carcinoma

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**Objective:** To describe the complications and adverse effects of postoperative radiotherapy in patients with Fanconi anemia (FA).

**Design:** Cohort study.

**Setting:** Patients with FA treated at community and tertiary care hospitals throughout the United States.

**Patients:** The study included patients with FA who were enrolled in the International FA Registry (IFAR) and who developed head and neck squamous cell carcinoma and received postoperative radiotherapy.

**Main Outcome Measures:** Demographics of patients with FA and adverse effects and dosages of radiotherapy.

**Results:** Twelve patients with FA (7 men and 5 women) were identified. They developed cancers at a mean age of 35.5 years (age range, 20-48 years). The sites of primary cancer were the oral cavity (n=8), larynx (n=2), pharynx (n=1), and unknown (n=1). The median radiation dose was 5590 cGy (range, 2500-7020 cGy). The most common adverse effects were mucositis (n=9), dysphagia (n=8), and pancytopenia (n=6). Other complications included esophageal stenosis, laryngeal edema, and wound breakdown. Radiotherapy could not be completed in 5 cases. Overall, 8 patients died, 4 during the course of radiotherapy. The postoperative disease-free survival time ranged from 0 to 55 months.

**Conclusions:** Patients with FA have a high rate of complications from radiotherapy. Common adverse effects, particularly mucositis, are especially prevalent and difficult to manage in this population. Pancytopenia is common and may lead to further complications, particularly bleeding and infection. Overall survival is poor. Further study of the response to radiotherapy in patients with FA should be attempted to establish appropriate dosages to balance treating disease while limiting adverse effects.

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FANCONI ANEMIA (FA) IS A rare recessive disorder (1-2: 100 000 births)[1] caused by mutations in 1 of at least 14 known genes in the FA pathway.[2,3] Genes in this pathway are involved in interstrand cross-link and double-strand break DNA repair.[4] Fanconi anemia is characterized clinically by aplastic anemia, congenital malformations (eg, short stature, hypoplastic thumbs, café au lait spots, cardiac and renal anomalies), sensitivity to DNA cross-linking agents, and increased risk of cancers.[1] Leukemias are the most common cancers in patients with FA, but patients are also at a substantially increased risk of developing solid tumors, with a 28% cumulative incidence of solid cancers by the age of 40 years.[5] In particular, head and neck squamous cell carcinomas (HNSCCs) are significantly more common in patients with FA,[6] with some reports calculating a several 100-fold increased risk.[7] As bone marrow transplantations (BMTs), leukemia therapies, and other recent advances have prolonged life in these patients,[8] an increasing number of patients are developing HNSCCs.

Standard treatment for HNSCC incorporates surgery in combination with radiotherapy and chemotherapy, depending on the tumor characteristics. Radiotherapy is known to potentially induce numerous adverse effects and complications in the general population, including mucositis, dysphagia, taste changes, and fatigue. Rarer complications of osteonecrosis, fibrosis, and esophageal stenosis exist as well.

In patients with FA, sensitivity to chemotherapy agents (particularly cisplatin and mitomycin C) is well known[1] and is therefore commonly avoided in postoperative therapy for HNSCC. Adjuvant ra-

**Table 1. Demographics of Patients With Fanconi Anemia (FA)**

| Patient No./Sex/ Age at Onset, y | FA Group[a] | Ethnic Group | Environmental Factors | Primary Site | TNM Stage[b] |
|---|---|---|---|---|---|
| 1/M/48.5 | J | W | None | Oral cavity (retromolar trigone) | T4N2bM0 |
| 2/F/30.2 | A | ME | None | Oral cavity (buccal gingiva) | T4N0M0 |
| 3/M/44.9 | A | W | Tobacco | Oral cavity (alveolus) | T3N2bM0 |
| 4/F/37.8 | A | AA | None | Oral cavity (alveolus) | T4N1M0 |
| 5/F/26.7 | C | AA | BMT | Oral cavity (alveolus) | T4N2cM0 |
| 6/M/28.1 | Untyped | W | Tobacco | Oropharynx | T3N2bM0 |
| 7/F/42.0 | A | H | None | Oral cavity (mandible) | T4N2bM0 |
| 8/F/40.9 | A | H | Tobacco | Unknown | TxN2bM0 |
| 9/M/29.8 | A | W | None | Larynx | T1N2bM0 |
| 10/M/20.9 | P | W | Tobacco | Oral cavity (tongue) | T4N2cM0 |
| 11/M/34.7 | A | W | None | Oral cavity (tongue) | T4N1M0 |
| 12/M/42.0 | Untyped | W | BMT | Larynx | T?N2bM0 |

Abbreviations: AA, African American; BMT, bone marrow transplantation; H, Hispanic; ME, Middle Eastern; W, white.
[a] The complementation groups are discussed in the first paragraph of the "Results" section.
[b] All cancers are stage IV.

diotherapy is recommended to treat patients with high-stage tumors (stage III-IV). However, postoperative sensitivity to radiotherapy in patients with FA is not as well characterized. While some case reports mention radiation toxicity and complications,[9-11] others do not document adverse effects or suggest mild adverse effects.[12-14] Because of evolving treatments in radiation techniques and uncertainty in identifying safe dosages in an FA population, it is important to document radiation dose levels, adverse effects, and outcomes among patients with FA who have received radiotherapy. Given the sensitivity of such patients to DNA-damaging processes, understanding how patients with FA respond to radiation exposure is important in guiding their therapy.

## METHODS

### FA REGISTRY

The International FA Registry (IFAR) was instituted in 1982 as a repository to collect clinical and genetic information from patients with FA throughout the world. Approximately 1200 families are currently enrolled. The registry collects medical and other pertinent information from these patients by contacting them or their surviving family members on a regular basis.

### PATIENT DATA COLLECTION

Overall, we identified and collected information on 12 patients with FA and HNSCCs who received postoperative radiotherapy. We obtained patient or family consent when appropriate and obtained all available medical histories and medical, surgical, and radiotherapy records from their respective treating hospitals. The diagnosis of FA was made with the diepoxybutane breakage test, as previously described.[15] Fanconi anemia complementation groups were documented when possible.

### STATISTICAL ANALYSIS

The Kaplan-Meier method was used to calculate disease-free and overall survival rates. Disease-free survival was calculated in months from date of surgery without primary disease or recurrence of disease. Overall survival time was calculated in months from date of surgery until death or to date in surviving patients.

## RESULTS

### PATIENT DEMOGRAPHIC INFORMATION

Overall, we studied 5 female and 7 male patients who developed HNSCCs and received postoperative radiotherapy (**Table 1**). Patients with FA are subdivided into complementation groups based on their specific mutated FA genes. Seven patients were in complementation group FA-A, 1 patient was in FA-C, 1 in FA-J, and 1 in FA-P. Two patients are currently untyped. The median age for development of HNSCC was 36.3 years (mean age, 35.5 years; age range, 20.9-48.5 years). All 12 cancers were stage IV. The primary sites of cancers included the oral cavity (n=8), larynx (n=2), pharynx (n=1), and unknown (n=1). All patients underwent initial surgery, including lymph node dissection, and received postoperative radiotherapy. Patients' records were screened for environmental risk factors known to enhance the risk of HNSCC: tobacco use and previous BMT: 2 of the patients had undergone previous BMT, and 4 had a history of smoking (Table 1).

### RADIATION DOSES AND ADVERSE EFFECTS

The total radiation dose ranged from 2500 to 7020 cGy (**Table 2**), with a median dose of 5590 cGy. The dose per fraction ranged from 170 to 200 cGy. The number of fractions ranged from 20 to 39. The total treatment days ranged from 31 to 70.

The most prevalent complications during radiation treatment were high-grade (≥grade 3) mucositis (n=9), dysphagia (n=8), and hematologic abnormalities (n=6). Other complications included asystole with cardiac arrest, wound site breakdown, fibrosis, local edema, sepsis, tracheal stenosis, and radiation pneumonitis (**Table 3**). In 5 patients, radiotherapy needed to be prematurely halted or interrupted

**Table 2. Postoperative Radiation Doses**

| Patient No. | Total Dose, cGy | Dose per Fraction, cGy/No. of Fractions/ Duration of Treatment |
|---|---|---|
| 1 | 4000 | 200/20/33 d |
| 2 | 2500 | NA |
| 3 | 6100 | 55 d |
| 4 | 5600 | NA |
| 5 | Unfinished | NA |
| 6 | 5100 + chemotherapy | 52 d |
| 7 | 6460 | 170/30/70 d |
| 8 | 6180 | 200/30/39 d |
| 9 | Unknown | NA |
| 10 | 7020 + chemotherapy | 180/39/50 d |
| 11 | 4240 + chemotherapy | 200/20/28 d |
| 12 | 5580 | 180/22/31 d |

Abbreviation: NA, Not available.

**Table 3. Postoperative Complications of Radiotherapy (RT)**

| Patient No. | High-Grade Mucositis | Dysphagia | Cytopenia | Premature Termination or Interruption of RT | Other Complications | Status/ Disease-Free Interval, mo/ Postoperative Survival, mo |
|---|---|---|---|---|---|---|
| 1 | Y | Y | Y | Y | Sepsis | D/0/2 |
| 2 | N | N | N | Y | Recurrence, sepsis | D/2/2 |
| 3 | Y | N | Y | N | Graft site breakdown, mandibular hardware removal, recurrence | D/16/54 |
| 4 | Y | Y | Y | N | Hemorrhage, pleural thickening, sepsis | D/55/55 |
| 5 | N | Y | N | Y | Dyspnea, asystole/cardiac arrest | D/2/2 |
| 6 | Y | N | Y | Y | Tracheal stenosis, radiation pneumonitis, recurrent pneumonia, recurrence | D/4/12 |
| 7 | N | Y | Y | N | No other complications | A/21+/21+ |
| 8 | Y | Y | N | N | Hemorrhage, trismus, fibrosis, esophageal stenosis, oral dryness | A/25+/25+ |
| 9 | Y | Y | N | N | Recurrence | D/5/77 |
| 10 | Y | N | Y | N | Dermatitis, sepsis | D/10/10 |
| 11 | Y | Y | Y | Y | Wound breakdown, dermatitis, hemorrhage | A/15+/15+ |
| 12 | Y | Y | N | N | Laryngeal edema, fibrosis, esophageal stenosis, recurrence | A/33/129+ |
| **Total, No.** (%) | **9** (75) | **8** (67) | **6** (50) | **5** (42) | NA | NA/15.7[a]/33.7[a] |

Abbreviations: A, alive; D, dead; N, no; NA, not applicable; Y, yes.
[a] This number represents the average.

because of adverse effects associated with the treatment, primarily mucositis.

Disease-free survival ranged from 0 to 55 months (**Figure**, A). Five patients had a local or regional recurrence of cancer. Overall survival time ranged from 2 to 129 months (Figure, B). Overall, 8 patients died, 4 as a result of complications while receiving radiotherapy. Three patients died of sepsis. One died of cardiac arrest during the course of radiotherapy. Radiation to the head and neck is not known to cause cardiac arrest, and this patient likely had other underlying medical issues.

## COMMENT

Patients with FA, given their predisposition to sensitivity toward DNA-damaging processes such as radiotherapy, may have increased adverse effects. Case re-

ports to date have had differing accounts of radiation sensitivity for HNSCC in patients with FA. We sought to study such patients in our IFAR cohort to gain a better sense of the response of patients with FA to radiotherapy and to provide more insight into treatment-related adverse effects.

Overall, patients with FA developed HNSCC at a very young age compared with the general population, with a mean of 35.5 years in our population vs 63 years in a general population.[16] Also, HNSCC developed often without history of tobacco use, a common cause of HNSCC in the general population (4 of 12 cases in our population vs 75%-85% in general HNSCC cases[17]). These findings suggest that increased screening and awareness of HNSCC should be maintained in this population starting at a young age. Reports in the literature document the development of HNSCC at ages as young as 13 years (average age, 28 years) in patients with FA.[18] Conversely, patients who develop HNSCC at a young age may be appropriate candidates for screening for FA.

A history of BMT is thought to increase the risk for the subsequent development of solid malignant neoplasms, particularly HNSCC.[18,19] In this cohort, 2 patients had a history of BMT, suggesting that although this may be a risk, many patients without BMT develop HNSCC. Nevertheless, particularly rigorous screening for HNSCC should be performed in patients with FA who have a history of BMT.

Tumors were most commonly located in the oral cavity (n=8). This finding is consistent with reports in the literature that patients with FA are especially prone to develop HNSCC in the oral cavity.

The overall mortality was high in our patients (n=8): the mean overall survival was 33.7 months. Disease-free survival was poor, with a mean disease-free interval of 15.7 months. The patients had complications even at low doses of radiation, and no minimal safe dose of radiation was seen in this cohort, as complications arose in 1 patient at 2500 cGy. Compared with a target minimum dose of 5760 cGy for postoperative patients,[20] patients with FA in this cohort received a median dose of 5590 cGy and mean dose of 5278 cGy. This decreased average dose was attributable to the intolerance of these patients with FA to the adverse effects of the treatment, requiring termination or interruption of therapy (n=5). Since tumors in patients with FA carry FA mutations, the tumors themselves may be more sensitive to radiation, and consideration of lower doses of radiation to achieve cure may be appropriate.

Radiotherapy for head and neck cancers is associated with numerous complications in general populations, with the most common being mucositis, dysphagia, dry mouth, and taste changes. High-grade mucositis is reported to range from 34% to 57% in the general population.[21] Mucositis was seen in 9 of the 12 patients (75%) in our cohort (Table 3), suggesting an enhanced risk in patients with FA. Also, pancytopenia, which is a rare complication in the general population, was experienced at high rates (n=6) in our FA population. The pancytopenia is of particular concern when dealing with postoperative complications in these patients, as it can lead to bleeding complications, fatigue, poor wound healing, and infection. Because of the underlying stem cell problems in these patients, time to recovery of normal blood cell counts may also be delayed. In this cohort, 3 patients developed sepsis, 1 patient had recurrent pneumonia, and 2 patients had bleeding complications. Blood cell counts should be monitored closely during radiotherapy to avoid low white blood cell levels, thereby decreasing the risk of infectious complications.

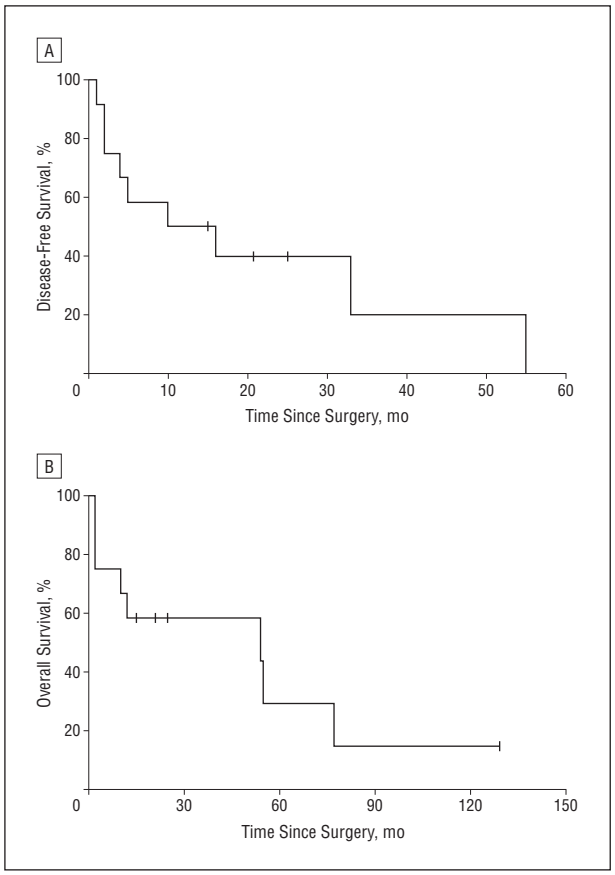


**Figure.** Kaplan-Meier survival curves for disease-free survival (A) and overall survival (B) among patients with Fanconi anemia and head and neck squamous cell carcinoma.

The addition of chemotherapy to radiotherapy in 3 patients in our cohort resulted in substantial complications (including interruption or cessation of therapy in 2 patients), suggesting that special care may need to be taken when chemotherapy is considered in addition to radiotherapy in patients with FA.

It is important to incorporate postoperative radiotherapy in stage III and IV HNSCC, as it has been shown to improve cancer-specific and overall 5-year survival rates.[22] Radiotherapy in patients with FA can be successful and was completed in 7 of 12 cases in this study. Based on our case series, however, it is important to be aware of the complications that may present in patients with FA who are receiving postoperative radiotherapy, particularly hematologic abnormalities and high-grade mucositis. We recommend frequent monitoring of hematologic counts during radiotherapy. In particular, careful monitoring of white blood cell counts is needed to avoid potential infections and sepsis. Close monitoring of mucositis

should be performed as well, as severe mucositis can limit the completion of radiotherapy. In patients with substantial complications, temporarily suspending therapy may be needed to avoid worsening of the complications and to allow recovery. In developing radiation treatment plans, longer courses at lower daily doses (150-180 cGy per fraction) may be considered to decrease the risk for the development of severe adverse effects.

Although our study was limited to 12 patients with FA, our findings suggest that there is an enhanced sensitivity to postoperative radiotherapy for HNSCC in patients with FA. Future reports and studies in patients with FA should be undertaken to determine whether particular FA groups are more prone to radiation complications and whether particular dose levels or radiation treatment parameters cause more complications. Uncovering minimal safe dosages and identifying risk factors for adverse effects of radiotherapy can provide valuable information in treating these patients. In future cases, it will be crucial to adjust radiotherapy to balance the risks of undertreating the cancer vs the complications of irradiation.

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