Outline

- Definition of squamous cell carcinoma of the head and neck
- Incidence in FA patients compared to non-FA population
- Characteristics of FA squamous cell carcinoma
- Prevention of SCC in FA patients
- Surveillance recommendations for SCC in FA patients
- Treatment of SCC in FA patients
Head and Neck Cancer - 2013

New Cases vs. Deaths

- Oral Cav: 5,200
- Larynx: 9,500
- Pharynx: 8,300

CA 53(1):5-26, 2003
Head and neck cancer rates

United States

Global
Mortality from head and neck cancer

United States

Global
Head and Neck Cancer

• Involved mucosal surfaces of upper aerodigestive tract
  – Diverse anatomical loci for involvement
    • Nasopharynx/paranasal sinuses
    • Oral cavity
    • Oropharynx
    • Larynx
    • Hypopharynx
Histology

- SCCa: 95%
- Minor Salivary
- Melanoma
- Lymphoma
- Sarcoma
Oral Pre-Malignant Lesions

• Leukoplakia: “white plaque”
  – Leukoplakia is a premalignant lesion found in the oral cavity.
  – The chance of transformation into oral squamous cell carcinoma varies from almost 0% to about 20%, and this may occur over 1 – 30 years.
Oral Pre-Malignant Lesions

- Erythroplakia “red plaque”
  - Far less common than leukoplakia
  - Much greater probability (91%) of showing signs of dysplasia or malignancy at the time of diagnosis.
  - Such lesions have a flat, macular, velvety appearance and may be speckled with white spots representing foci of keratosis.
Oral Pre-Malignant Lesions

- Oral dysplasia
- Precursor lesions of the upper aerodigestive tract
- Increased likelihood of progressing to squamous cell carcinoma.
- Presence of architectural and cytological changes:
Progression from hyperplasia to cancer
Squamous Cell Carcinoma

• Squamous cell carcinoma (SCC) of the head and neck
  – Irregular ulcers with raised margins
  – May be exophytic, infiltrative or verrucoid
  – Mimic benign lesions grossly
Squamous Cell Carcinoma
Squamous Cell Carcinoma
Squamous Cell Carcinoma
Clinical appearance
Factors predisposing to head and neck cancer

- Tobacco/alcohol exposure
- Betel nut
- Viruses (HPV/EBV)
- Genetic predisposing syndromes
  - Li Fraumeni
  - p16
  - Fanconi’s anemia
Tobacco & Alcohol - Risk for head and neck cancer

- Never smoker
  - >1ppd
  - <1ppd

- Never drinker

- 1-2 drinks/day

- >2 drinks/day

<1ppd
>1ppd
Never smoker
Prognostic factors

- Site
- Size (T-stage)
- Location (Anterior vs. Posterior)
- Cervical node status
- Histology (size, grade, depth of invasion, host/tumor interface)
Tumor location and survival

- Hypopharynx
- Pharynx
- Soft Palate
- Base of Tongue
- Tonsil
- Buccal Mucosa
- Hard Palate
- Floor of Mouth
- Gingiva
- Ant. Tongue
- Lip

Farr and Arthur (MSKCC:1955)
Head and Neck Squamous cell carcinomas

- Surgery
- Radiotherapy
- Chemotherapy
- Combined modality treatments
Head and neck cancer
Multimodality treatment

- Surgical oncology
- Radiation oncology
- Medical oncology
- Endocrinology
- Nuclear medicine
- Plastic & reconstructive surgery
- Dental and prosthetics
- Psychiatry
- Nutrition
- Nursing
- Diagnostic radiology
- Pathology
New Cancer Appearance after Treatment of H&N Primary

%/Yr

Year

Local Recurr  Neck Recurr  Distant Mets  2nd Primary
Case Report

• 33 year old FA male with a history of a BMT, who has a long history of oral leukoplakia, erythroplakia and oral dysplasia diffusely covering his oral epithelium.

• He was diagnosed with a left buccal squamous cell carcinoma, which developed within an area of erythroplakia. He underwent a resection of the buccal region and left neck dissection.

• He continued to have diffuse areas of both leukoplakia and erythroplakia.

• 7 years later, he developed a second left buccal squamous cell carcinoma and recently underwent re-resection of the buccal region.
Incidence in FA patients compared to non-FA population

Standardized Incidence Ratio (SIR) = 500 (95% CI: 300-781, p<0.0001).

SEER population
Expected incidence: 0.038%

FA population
Cumulative incidence: 19%

21% incidence by age 40
# Characteristics of FA associated squamous cell carcinoma

<table>
<thead>
<tr>
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<th>FA</th>
<th>Gen. Pop.</th>
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<tbody>
<tr>
<td>Age- range</td>
<td>15 to 49</td>
<td>50-60’s</td>
</tr>
<tr>
<td>median</td>
<td>31 yr.</td>
<td>53 yr.</td>
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<tr>
<td>Female: male</td>
<td>2:1</td>
<td>1:2</td>
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<tr>
<td>Tob/ EtOH use</td>
<td>16%</td>
<td>&gt;85%</td>
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- FA: Field Cancer
- Gen. Pop.: General Population
Anatomic distribution of HNSCC

### FA-associated HNSCC
- **Oropharynx**: 10%
- **Hypopharynx**: 10%
- **Larynx**: 10%
- **Unknown**: 5%
- **Oral Cavity**: 65%

### SEER population
- **Larynx**: 41%
- **Oral Cavity**: 27%
- **Hypopharynx**: 8%
- **Oropharynx**: 24%
- **Unknown**: 5%
Prevention

• Tobacco/alcohol avoidance
  – Second hand smoke

• Role of HPV
  – Vaccination
HUMAN PAPILLOMA VIRUS AND FANCONI ANEMIA

CONTROVERSIAL TOPIC
HPV positivity
FA associated SCC vs. control SCC

FA-associated SCC

83% HPV Positive
N=25

Normal control SCC

36% HPV Positive
N=50

P<0.001
Types of HPV identified in FA-associated tumors

FA-Associated:
- HPV type 16
- HPV type 18
- HPV type 52

Normal control SCC:
- HPV type 67
- HPV type 33
- HPV type 16
Human Papillomavirus

- HPV-positive head and neck squamous cell carcinoma
  - Distinct Disease Entity?
  - Even though role of HPV in FA is controversial, it is an important risk factor in the general population.
Biology of Human Papillomavirus

• HPV is a small DNA virus
  – First identified in 1949
  – 120 genotypes of HPV
  – Infect exclusively basal epithelial cells in the mucosa or skin

• Replication
  – Occurs within the nucleus of the infected cell
  – Dependent on the S-phase for entry
  – Requires DNA machinery to replicate
Biology of Human Papillomavirus

- HPV subtypes divided into:
  - Low-risk – HPV-6 and HPV-11
  - High-risk (15 high-risk types are known) – HPV-16, -18, -31, -33, -35
- Each HPV type is associated with a specific clinical lesion
  - Cutaneous types: common wart
  - HPV-5 and -8: SCC of the skin
  - HPV-6 and -11 (low risk): benign lesions (anal warts or oral papillomas)
  - HPV -16, -18, -31, -33 and -45 (high risk): SCC of the mucosal regions
Biology of Human Papillomavirus

• HPV 16 is the most common type detected in oropharyngeal cancer
  – 90-95% of the HPV positive tumors.
HPV genome

- Small double stranded circular DNA
- 8000 base pairs
- Early Regions (E1-8)
  - Transcription, plasmid replication and transformation.
- Late Regions (L1 and L2)
  - Regulatory elements for transcription and replication
HPV genome
Propose mechanisms of HPV carcinogenesis

Two HPV viral proteins – E6 and E7 can incorporate into genome and inactivate p53 or retinoblastoma (Rb) tumor suppressor genes by increased degradation.
Mechanism of carcinogenesis

- **Disruption of p53 pathway**
  - Uncontrolled cell cycle progression
  - Usually mutated in HPV negative tumors
  - Usually not mutated in HPV positive tumors, but increased degradation leading to functional loss.

- **Disruption of the pRB pathway**
  - Failure of inhibition of E2F
  - Loss of cell cycle control
  - Upregulation of p16
    - Identified by immunohistochemistry in HPV + tumors
    - Very high correlation (>90%) - ? surrogatemarker
Mechanisms of HPV carcinogenesis
Papillomavirus life cycle and cancer induction in stratified squamous epithelium

1. Normal
2. Infection
3. Productive cycle
4. Persistent infection
5. Neoplasia
6. Pre-cancer
7. Cancer

Virus introduced into the skin through foreign body or microabrasion

E1 and E2 are expressed causing the population of dividing cells to expand. In the upper layers the capsid proteins are expressed, virions are assembled and shed.

Infection can proceed with integration of viral episome into host’s DNA. If it interrupts the E2 gene, overexpression of E6 and E7 occurs. Infected cells retain the capacity to proliferate indefinitely, which can lead to development of cancer.

- Epithelial stem cells
- Non-dividing squamous keratinocytes
- Cancer cells
- Transit-amplifying cells
- Antigen-presenting cells
- Cornified dead cells
GARDASIL™
[Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine]
HPV vaccine

- Based on recombinant expression and self assembly of the major capsid protein, L1
  - Gardasil (Merck & Co.)- targets subtypes 6, 11, 16, 18
  - Cervarix (GSK) – targets subtypes 16 and 18
- Vaccines significantly decrease the incidence of persistent HPV16 and HPV 18 infections in cervical dysplasia.
HPV vaccine

• Designed to initiate protective immunity against HPV -6, -11, -16 and -18
  – Humoral immune response
  – Efficacy through 5 years (booster ?)
  – Prevents HPV infection in unexposed patients.
  – No biologic role for treatment of existing HPV-associated OPSCC
HPV vaccine and oral cancer

• Animal models immunized against HPV16 have shown a reduction in the development of HPV-oral lesions.
• Further studies are coming.
Treatment of SCC in FA patients
Introduction

- **Head and neck procedures**
  - Large surgical incisions
  - Large amount of tissue dissection
  - Surgical complications
  - Post-operative morbidity
da Vinci System
da Vinci System
da Vinci Robotic Surgery
Surgery
Radiation Therapy

- 12 Fanconi anemia patients (7 male, 5 female) underwent radiation therapy.
- Average radiation dose was 5242 cGy (range 2500 to 7020).
- The most common toxicities:
  - High-grade mucositis (9/12)
  - Dysphagia (8/12)
  - Pancytopenia (6/12).
  - Other significant complications included esophageal stenosis, laryngeal edema, and wound breakdown.
Radiation Therapy

• Radiotherapy could not be completed in 5/12 cases.
• Overall 8/12 patients died, 4 during the course of radiation.
• Radiation should be used for high stage tumors and should be administered by physicians with experience treating FA patients.
Adjuvant therapy

- 3 patients received chemotherapy
  - Adjuvant chemo\XRT 1 patient
  - Primary treatment alone 1 patient
  - Chemo\XRT for recurrence 1 patient
Impact of secondary malignancies

- 12 of 19 (63%) developed multiple malignancies during their lifetime.
- 5 patients had >2 malignancies

Location of Second Primary

- **H&N**
- **Lung**
- **Esoph**
- **Skin**
- **GU/Anus**
- **Other**

Legend:
- **FA**
- **Gen Pop**
Outcome—More aggressive disease

- 10/19 (52%) had recurrence of their tumor with median disease-free interval of 10 mos.
  - PATTERNS OF RECURRENCE SIMILAR TO GP
  - Local recurrence: 7 patients
  - Regional recurrence: 6 patients
  - Distant metastases: 1 patient
- 5 of 7 stage I patients recurred locoregionally
- 14/19 (73%) died from all causes.
- 11/19 (58%) died with disease.
Overall survival

2-year OS: 48% vs. 70%
5 year OS: 27% vs. 63%

Follow-up time (months)
Treatment approach

- EARLY DETECTION
- Surgery is the preferred treatment
- Radiation can be used with care
- Chemotherapy in very limited circumstances
- ? Need for modification of treatment (use non-DNA damaging chemo modalities)
- Very close surveillance
Surveillance recommendations for SCC in FA patients

- Routine head and neck screening
  - Role of qualified examiner
  - Age of onset (12-14 years)
  - Frequency - Biannual

- Caveats
  - Increase frequency to every 3 months (or more) if premalignant lesion detected
  - Minimum of every 3 months if prior HNSCC
Post-treatment surveillance after treatment for cancer

• Routine follow-up is mandatory
  – Complete examination of upper aerodigestive tract mucosa
  – Chest X-ray annually

• Screening to include gynecological exam in women