Management of Neck Metastasis from Unknown Primary

ศาสตราจารย์ ดร.นพ. พรชัย โอเจริญรัตน์

สาขาศัลยศาสตร์ศีรษะ คอ และ颔下
ภาควิชาศัลยศาสตร์
คณะแพทยศาสตร์ศิริราชพาณิชยการ
Definition

- Histologic evidence of malignancy in the cervical lymph node(s) with no apparent primary site of original tumour
- Diagnosis after a thorough physical examination, radiographic and endoscopic evaluation, and multiple surveillance biopsies
Definition

- **Exclude** patients in whom a primary becomes evident during or shortly after therapy and those who have a metastasis that is histologically related to a previous primary tumour.
Historical Perspectives

Dr. Hayes Martin 1944

- 218 carcinomas presenting as cervical adenopathy
- Incidence of unknown primary was 25%
- Nearly always secondary to a primary in the head and neck which could be treated
- A biopsy should be the last investigation
- A search for a primary tumour must be made
- Fine needle aspiration cytology (FNAC)
The purpose of this communication is to call to the attention of the medical profession in general not only to the needlessness but also to the possible harmfulness of excisional lymph node biopsy as the first or even as an early step in the diagnosis of cancer.

Am J Surg 1961
Diagnostic Steps

History

- Painless unilateral neck mass of weeks' to months' duration
- Male to female ratio ~ 6:1
- Average age is 60 years
- Significant history of alcohol and tobacco use
- Sun exposure and previous skin lesion
Diagnostic Steps

Physical Examination

- Complete head and neck exam (visualize & palpate)
- Flexible fiberoptic nasopharyngoscope
- Ipsilateral otalgia with normal otoscopy
  - direct attention to tonsil, tongue base, supraglottis and hypopharynx
- Unilateral serous otitis
  - direct examination of nasopharynx
Metastasis Location according to Various Primary Lesions

- Scalp, Skin
- Oropharynx, Hypopharynx
- Nasopharynx
- Oral Cavity
- Larynx, Tongue
- Hypopharynx
- G-I, G-U, Pulmonary
Diagnostic Tests

- Fine needle aspiration biopsy (FNAB)
- Chest X-ray
- Computed tomography
- Magnetic resonance imaging
- Ultrasonography
- Radionucleotide scanning
- Panendoscopy
- Open biopsy
Fine Needle Aspiration Biopsy

- Standard of diagnosis
- **Indications**
  - Any neck mass that is not an obvious abscess
  - Persistence after a 2 week course of antibiotics
- Small gauge needle
  - Reduces bleeding
  - Seeding of tumor
    - not a concern
- No contraindications
Complete head & neck examination

FNAB

Benign
- Hyperplasia
- TB
  - Observe
  - Treat

Malignant
- Further work-up

Non-diagnostic
- Repeat
- Non-diagnostic
  - Open biopsy
Roles of Imaging Studies

- To evaluate extent of disease in the neck
- To evaluate parapharyngeal areas
- To evaluate hidden areas – nasopharynx, base of tongue, retropharyngeal areas
- To evaluate opposite neck
Computed Tomography

Small tumour in the base of tongue
Radionucleotide Scanning

- 18F-Fluorodeoxyglucose positron emission tomography (FDG-PET)
- Area with increased glycolic rate of metabolically active cells.
- Increased in infection and inflammation as well as neoplasm.
- With negative clinical examination and imaging, PET detected primary tumours in 25% of the cases.
FDG-PET Scanning

Primary tumour at nasopharynx
Primary tumour at base of tongue (single arrow)
Panendoscopy

- **Indication**
  - FNAB positive with no primary on repeat exam
  - FNAB equivocal/negative in high risk patient

- **Directed Biopsy**
  - All suspicious mucosal lesions
  - Areas of concern on CT/MRI
  - None observed – nasopharynx, tonsil (ipsilateral tonsillectomy for jugulodigastric nodes), base of tongue and piriforms

- **Synchronous primaries** (10 to 20%)
Panendoscopy with biopsy

- 17% detection rate in the absence of physical or radiographic suspicion
- 52-56% detection rate if either clinical examination or imaging was suggestive
- 65% if both were suggestive
- Repeat panendoscopy is not useful
- Sites of primary tumours are tonsillar fossae and base of tongue in 82% of patients
Open Excisional Biopsy

- Only if complete workup negative
- Occurs in ~5% of patients
- Be prepared for a complete neck dissection
- Frozen section results (complete node excision)
  - Inflammatory or granulomatous – culture
  - Lymphoma or adenocarcinoma – close wound
Molecular Diagnostic Tests

- Detection of Epstein-Barr virus in metastatic lymph nodes by *in-situ* hybridization
- Biomarkers: cytokeratins, thyroglobulin, etc.
- Gene expression array
In situ Hybridization with an Epstein-Barr Virus–encoded Small RNA

Neck metastasis of undiff. nasopharyngeal cancer

Neck metastasis of unknown primary SCC
Immunohistochemistry

- **CK7 + CK20 +**
  - Urothelial tumors
  - Ovarian mucinous adenocarcinoma
  - Pancreatic adenocarcinoma
  - Cholangiocarcinoma

- **CK7 + CK20 -**
  - Lung adenocarcinoma
  - Breast carcinoma
  - Thyroid carcinoma
  - Endometrial carcinoma
  - Cervical carcinoma
  - Salivary gland carcinoma
  - Cholangiocarcinoma
  - Pancreatic carcinoma

- **CK7 - CK20 +**
  - Colorectal Carcinoma
  - Merkel cell carcinoma

- **CK7 - CK20 -**
  - Hepatocellular carcinoma
  - Renal cell carcinoma
  - Prostate carcinoma
  - Squamous cell and small cell lung carcinoma
  - Head and neck carcinoma
Molecular Markers of Adenocarcinoma Characteristic of the Site of Origin

<table>
<thead>
<tr>
<th></th>
<th>Breast</th>
<th>Ovary</th>
<th>Prostate</th>
<th>Gastric</th>
<th>Pancreas</th>
<th>Colon</th>
<th>Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mammaglobin 1**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TFF 2**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pepsinogen C*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surfactant A*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metallothionein 1L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

|          |       |       |          |         |          |       |      |
| Lipophilin B* |     |       |          |         |          |       |      |
| Glutathione peroxidase 2* |     |       |          |         |          |       |      |
| KIAA0876 |       |       |          |         |          |       |      |
| PR Domain 10 |     |       |          |         |          |       |      |

| GAPDH    |       |       |          |         |          |       |      |

Gene Expression Profiling by Microarray Analysis
Identifying Tumor Origin Using a Gene Expression-based Classification Map
Squamous cell carcinoma
Undifferentiated carcinoma
Poorly diff carcinoma
Neuroendocrine carcinoma

FNAB

Squamous cell carcinoma
Undifferentiated carcinoma
Poorly diff carcinoma
Neuroendocrine carcinoma

Multiple endoscopies & biopsy

No primary found

Treatment of neck

Melanoma

Search for primary

No primary found

Treatment of neck

Lymphoma

Open biopsy

Diagnosis confirmed

Work-up and treatment
FNAB

Adenocarcinoma

Upper neck
- Imaging for salivary gland
  - Primary found
    - Treatment of primary and neck
  - No primary found
    - Treatment of neck

Lower neck
- Thyroglobulin
  - Positive
    - Thyroidectomy & neck dissection
  - Negative
    - Metastatic Work-up
      - Systemic Rx
Treatment of Metastatic Squamous Cell Carcinoma

- Principles for treatment:
  1) rule out nasopharyngeal cancer first
  2) the most important prognostic factor is the N-stage extent of the disease
  3) extracapsular spread is associated with a worst prognosis and relapse of disease
Treatment of Metastatic Squamous Cell Carcinoma

- **N1:**
  neck dissection or irradiation alone

- **N1 with extracapsular spread, N2 or N3, suspicion of residual microscopic disease of the neck, previous excisional biopsy:**
  neck dissection with postoperative radiotherapy

- **Inoperable disease or with distant metastases:**
  combined chemotherapy and radiation
Extended Neck Dissection
Extended Neck Dissection
Prophylactic Mucosal Irradiation

**Pro**

- Lower incidences of relapse when the entire pharyngeal axis was irradiated

**Against**

- Additional morbidity to the therapy
- Later primary manifestation may be related to the thoroughness and aggressiveness of the initial investigation rather than to the treatment modality
- The rate of primary development is roughly the same regardless of the treatment modality
Prophylactic Mucosal Irradiation

M.D. Anderson Experience

- Radiotherapy to the neck and naso-oral hypopharynx except when there is a strong suggestion that the nasopharynx is a primary site in which case the hypopharynx may be spared
- The nasopharynx may be omitted when disease is limited to the lower nodes
- Favours treating both sides of the neck
Prognostic Factors

- Site of metastasis - jugulodigastric vs supraclavicular
- Nodal status - N1 vs N2/N3
  - single vs multiple nodes
  - unilateral vs bilateral
- Pathology - type of tumour
  - extranodal spread
- Appearance of subsequent primary tumour
- Previous open biopsy
Conclusion

- 1-2% of SCC presents as neck metastases of unknown primary
- Thorough history and physical, FNAB, and imaging should all be done prior to panendoscopy
- Panendoscopy with directed biopsies, and tonsillectomy is recommended
Conclusion

- Close follow-up and aggressive approach is best for favorable outcomes

- Intensity-modulated radiotherapy for risk-adapted individually tailored radiotherapy plans

- Molecular diagnostic tools in the near future
“In medicine you uncover the unknown.

In politics you cover the known.”
Thank you for your attention