Oligometastatic HPV-Positive Oropharyngeal Cancer

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Learning Objectives

• Follow-up of HPV+ Oropharyngeal (OP) H&N cancer patients
• Patterns of failure of HPV+ OP cancer patients
• Work-up of recurrent/metastatic HPV+ H&N cancer
• Special considerations for oligometastatic HPV+ OP cancer
Background

- HPV+ OPSCC has a better prognosis than HPV-disease, but not treated significantly differently (subject of ongoing clinical trials)
- Retrospective data suggests distant mets in HPV+ OPSCC significantly later than HPV-
- HPV+ OPSCC have atypical patterns of failure
Background

• 11% of HPV+ OPSCC develop distant metastases
  – Majority (2/3) have polymetastatic disease, minority (1/3) have oligometastatic disease
  – Oligometastatic HPV+ OPSCC have been shown to have better OS than polymetastatic pts
  – Retrospective data point to two distinct populations: “indolent” phenotype and a “disseminated” phenotype
    • indolent have prolonged DFS and more likely to have oligomets
Background

• No clear treatment paradigm for metastatic HPV+ OPSCC pts:
  – Chemo ± immunotherapy

• KEYNOTE-048:
  – PDL-1+: Pembrolizumab
  – PDL-1-: Pembro/cisplatin/5-FU

• Checkmate 141 (~25% known HPV+) after progressing on cetuximab: benefit for nivolumab vs. investigator’s choice (2 yr OS 16.9% vs 6%)
  – Ablation/removal of metastatic sites (surgery vs stereotactic RT)
Follow-up Paradigm

- **Currently same as HPV negative H&N cancer**
- H&P q1-3 months for 1 year, then q2-6 months for 1 year, then q4-8 months years 3-5
  - Clinical oral exam and LN palpation, fiberoptic evaluation (NPL)
- Imaging: PET/CT ≥ 12 weeks post-RT. Further imaging based on signs/sx
- Labs: TSH q6-12 months, CBC, CMP
- Supportive care
  - Regular dental evaluations and cleanings (at least q6 months)
  - Speech/swallow evaluations and rehabilitation
  - Lymphedema evaluation and PT
  - Nutritional eval until back to baseline
  - Psychosocial support/Distress screening
  - Smoking cessation and alcohol counseling PRN
Controversy

• Current f/u paradigm is based on HPV- H&N cancers, where predominant pattern is local failure within < 5 years of treatment
• HPV+ OPSCC have shown predominantly distant metastatic failure and at longer intervals
• Metastatic HPV+ OPSCC has been described in: brain, kidney, skin, skeletal muscle, axillary LNs, intraabdominal LNs, pericardium, peritoneum
  – Not caught by typical clinical exam
  – Role for more intensive clinical exam and/or more intensive imaging f/u?
Controversy

• Retrospective data indicates ≥ 5 LNs is a/w increased risk of distant failure and poorer OS for HPV+ OPSCC → different f/u based on such factors?
• Early data for limited mets treated w/SBRT indicate possibility of deferral/delay of systemic treatment
• Oligomet pts represent a more favorable subset of pts within metastatic H&N cancer
Controversy

• SBRT to metastatic sites is often well tolerated with minimal acute and late grade 3 toxicity. May be worthwhile if it provides a clinically meaningful benefit such as:
  – Prolonged DFS (and OS)
  – Improved QoL
  – Delay of systemic treatment
  – Improved response to systemic therapy (including immunotherapy) and/or synergistic effect
Case 1

• 54 yo M never smoker presented w/dysphagia and weight loss.
• CT & PET showed a large BOT mass with extension to lingual surface of epiglottis and invasion of extrinsic muscles of tongue, with bilateral enlarged nodes
• Staging: cT4a N2c M0, Stage IVA (AJCC 7th); cT3 N2 M0, Stage II (AJCC 8th) p16+ SCC of BOT
• Treated with chemoRT to 70 Gy completed in 2015.
• NCCN guidelines followed for follow-up (no routine chest imaging)
Case 1

- NED x 3 years, but has significant neck fibrosis, xerostomia. Up to date on care.
- 2018 – CXR for unrelated work-up incidentally noted suspicious nodule.
- Chest CT showed new RML and LLL nodules, bx showing p16+ SCC.
- Patient wished to avoid any systemic therapy.
Previous Treatment Plan
New Imaging Findings
Treatment Strategy & Outcome

• 2018 - Completed 50 Gy in 5 fractions lung SBRT to LLL and RML lesions
• NED x 1 year without any systemic therapy (patient preference)
Case 1 Learning Points

• Lung mets caught incidentally, not on routine f/u imaging study (as per NCCN)
  – Do HPV+ OPSCC pts need further imaging f/u and/or more extensive imaging f/u than HPV- pts?

• SBRT to sites of oligometastatic disease allowed pt to have a >12 month interval w/o systemic therapy
SBRT for Oligometastatic Disease

• Multiple Phase II trials report an OS and/or PFS advantage to SBRT of oligomet cancer (SABR-COMET, Gomez trial, etc.)
  – Greatest benefit seen in 1-3 mets
  – Various histologies have shown benefit: less aggressive (i.e. prostate) to more aggressive (i.e. NSCLC)

• Can such a paradigm be followed for oligometastatic HPV+ OPSCC?
Case 2

- 41 yo M with 5 PY remote smoking hx with dysphagia/odynophagia
- Imaging reveals masses in the R BOT (2.5 cm), R level II and III LAD. Bx reveals p16+ SCC.
- Staging: cT2 N2b M0, Stage IVA (AJCC 7th)
cT2 N1 M0, Stage I (AJCC 8th)
- Treated with chemoRT to 70 Gy in 2014. NED x 3 years.
- 2017 - New subcutaneous lump on his anterior chest. PET/CT revealed a 1.4 cm lesion in the subcutaneous anterior chest, another 1.5 cm area in the subcutaneous skin of his R back. Bx showed SCC, p16+.
Case 2

• Placed on pembrolizumab. NED x 2 years.
• 2019 - Presented with ataxia and word-finding difficulties, brain MRI showed a left frontal mass with 2.7 cm with edema.
• Resection showed p16+ SCC, additional left parietal lobe lesion also identified (unresected).
Previous Treatment Plan
New Imaging Findings
Treatment Strategy & Outcome

- Received 5.5 Gy x 4 fx (22 Gy total) post-op SRS to cavity, 18 Gy x 1 fx to the intact lesion
- Placed on nivolumabab
- NED x 6 months
Case 2 Learning Points

• Presented with metastatic disease in atypical pattern of failure (subcutaneous metastases)

• Prolonged disease free interval prior to second presentation with brain metastases (in absence of other mets)

• Stereotactic RT may be synergistic with immunotherapy in metastatic HPV+ OPSCC
Conclusions

- HPV+ OPSCC has a higher predilection of disseminated mets (often to atypical sites), difficult to predict which pts and how to surveil them
- Metastatic HPV+ OPSCC respond more favorably to treatments and may benefit more from aggressive treatment strategies
- Oligomet HPV+ OPSCC represent 1/3 of metastatic HPV+ OPSCC patients. They may benefit the most from ablative treatments to metastatic sites with potential to:
  - Prolong OS and DFS
  - Improve QoL
  - Delay/defer systemic therapy and/or be synergistic with immunotherapy
Conclusions

• Unmet needs:
  – Prospective/RCT studies in polymetastatic and oligometastatic HPV+ OPSCC to determine ideal treatment strategies (single modality, multimodality, etc.)
    • Checkmate 141 included all H&N SCC who failed systemic therapy, only 25% known HPV+
    • KEYNOTE-048 included 21% HPV+ OPSCC pts
  – Revised imaging & clinical exam f/u strategies to detect mets earlier
Conclusions

• Unmet needs (cont’d):
  – Personalized Medicine:
    • Identification of noninvasive biomarkers (HPV DNA, ctDNA, etc.) to guide surveillance and treatment
    • Identification of genetic markers of tumor radiosensitivity to guide SBRT vs other options
  – With ongoing trials to deintensify HPV+ OPSCC treatment, how will that impact patterns of failure?
    • Do de-intensification trials need longer f/u?
  – What are differences between HPV Type 16 related OPSCC and HPV non-type 16 related OPSCC and how will that impact future treatment? Patterns of recurrence?
References