

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

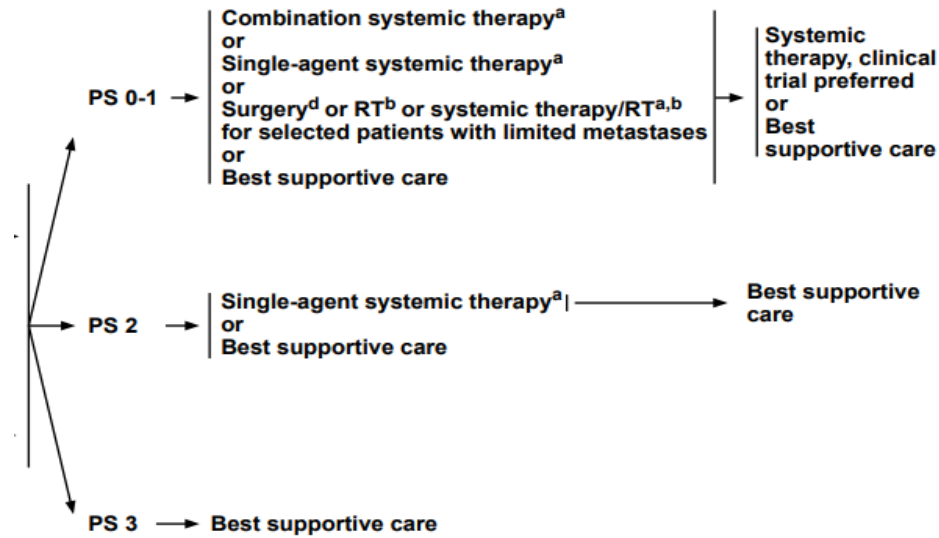
- HPV+ OPSCC has a better prognosis than HPV-disease, but not treated significantly differently (subject of ongoing clinical trials)
- Retrospective data suggests distant mets in HPV+ OPSCC significantly later than HPV-
- HPV+ OPSCC have atypical patterns of failure

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 oligometets

Background

- No clear treatment paradigm metastatic HPV+ OPSCC pts:
 - Chemo \pm 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)



NCCN 3.2019

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 \geq 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

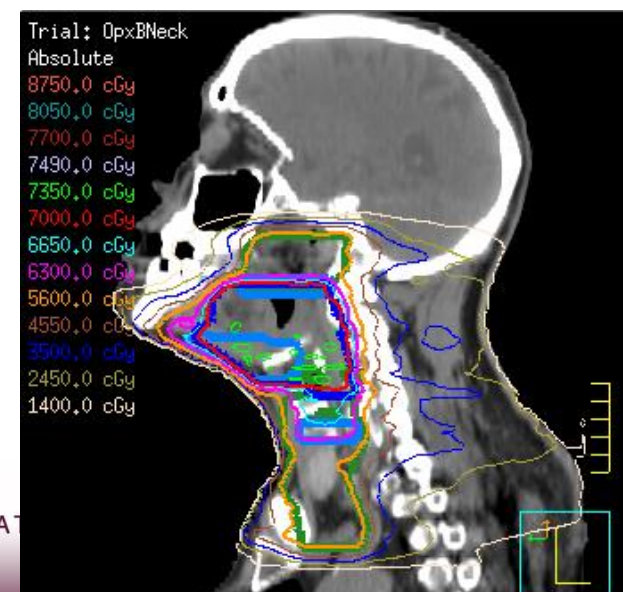
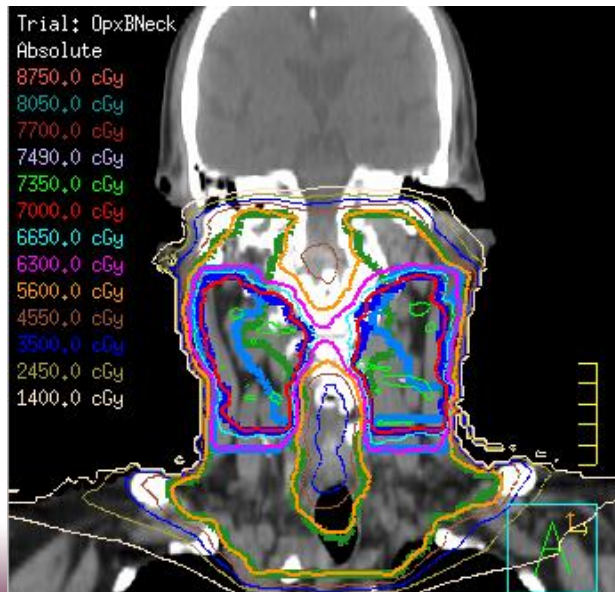
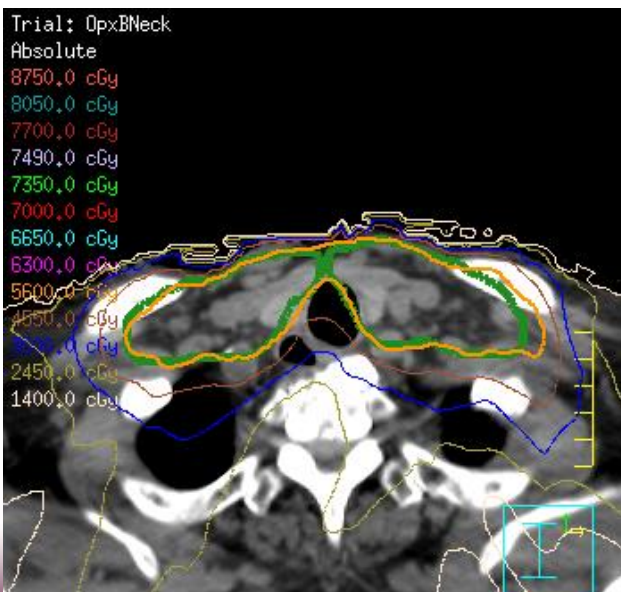
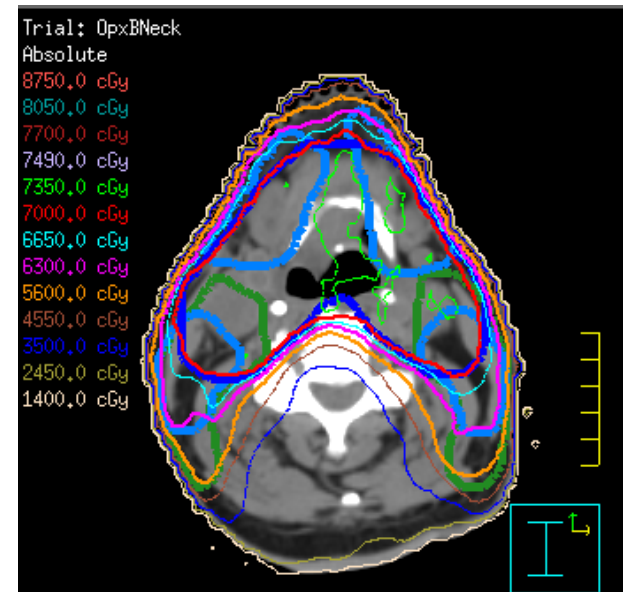
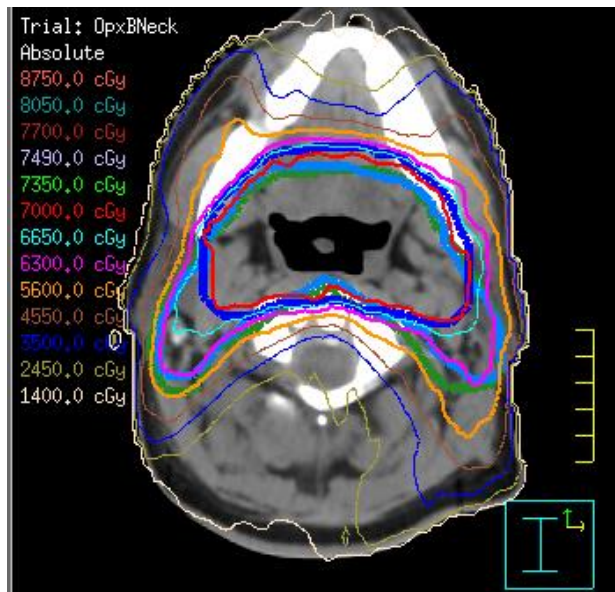
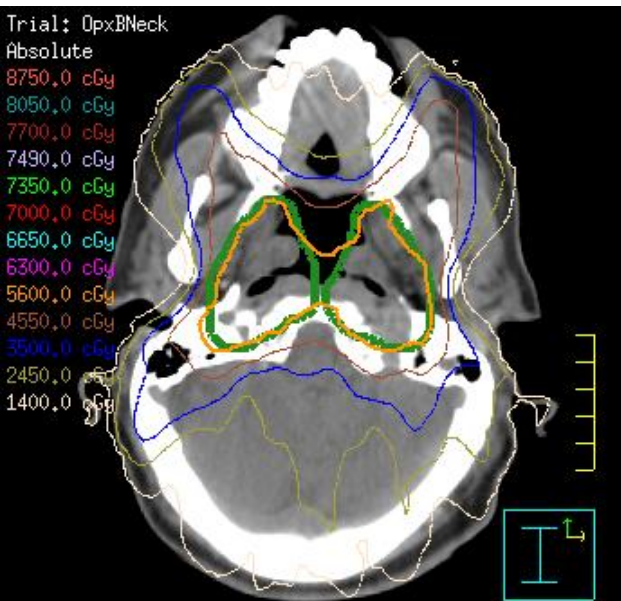
Case 1

- 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)

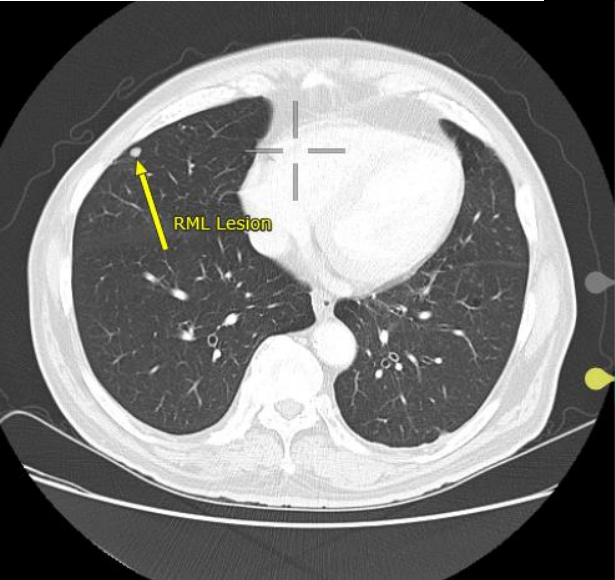
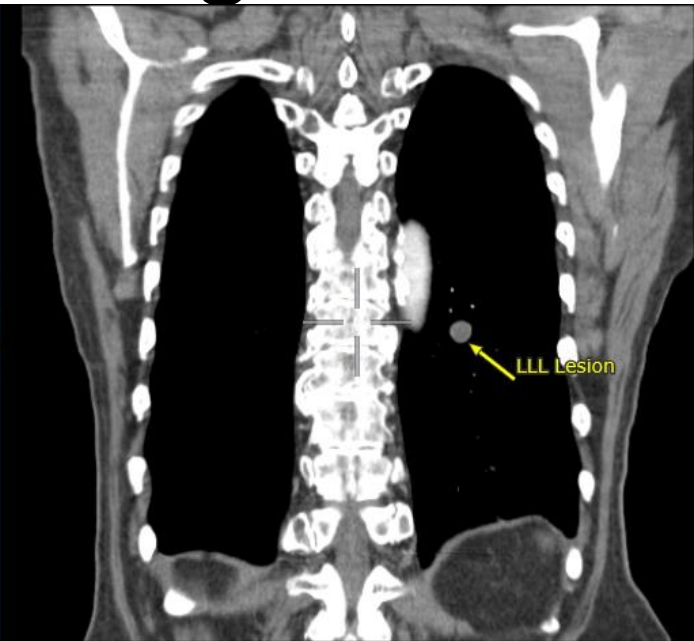
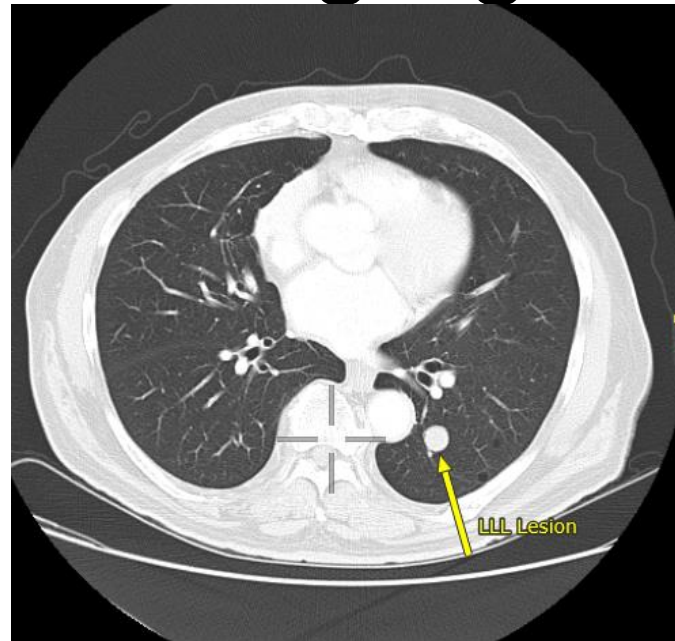
Case 1

- 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



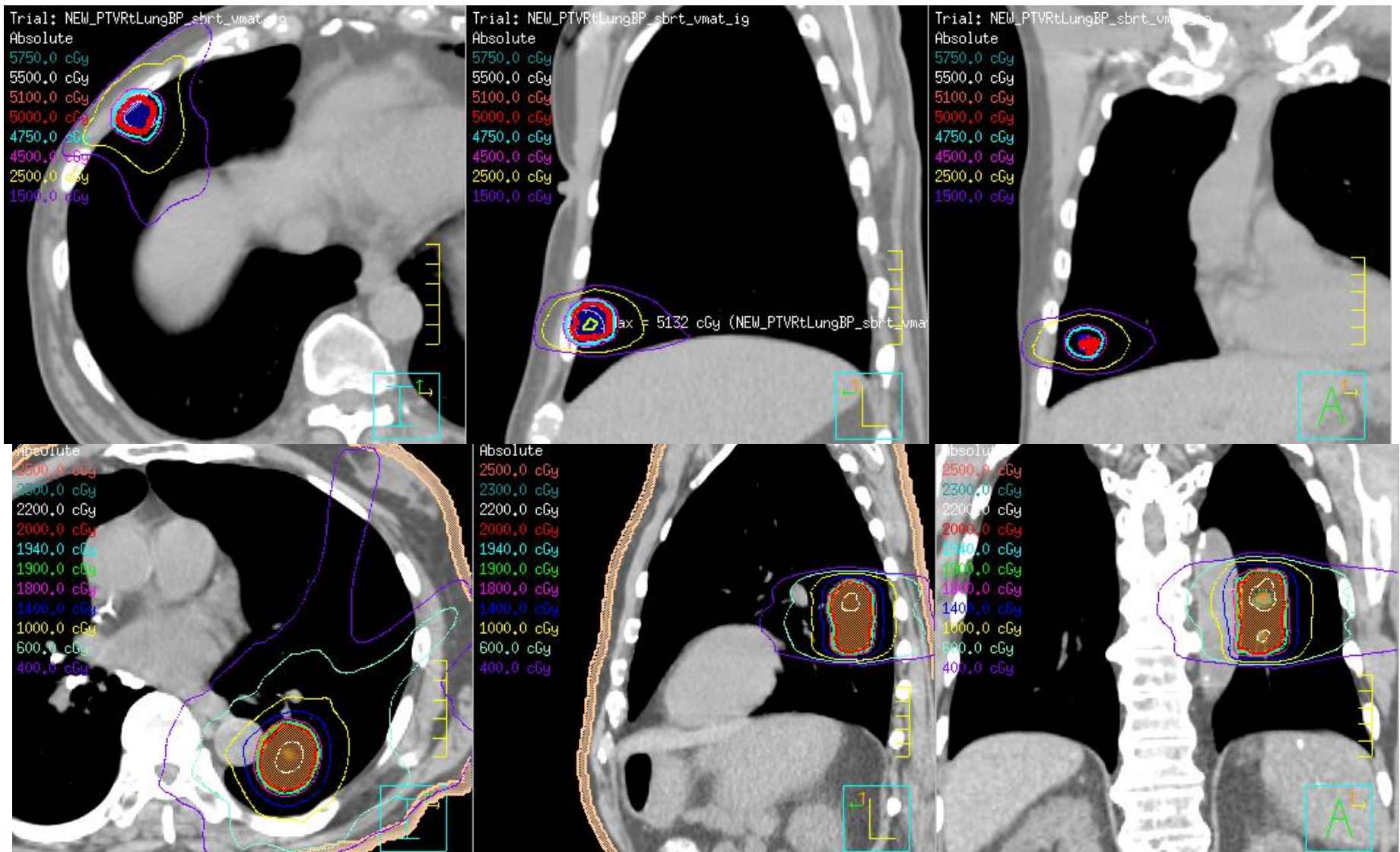
New Imaging Findings



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)

Treatment Plan



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?

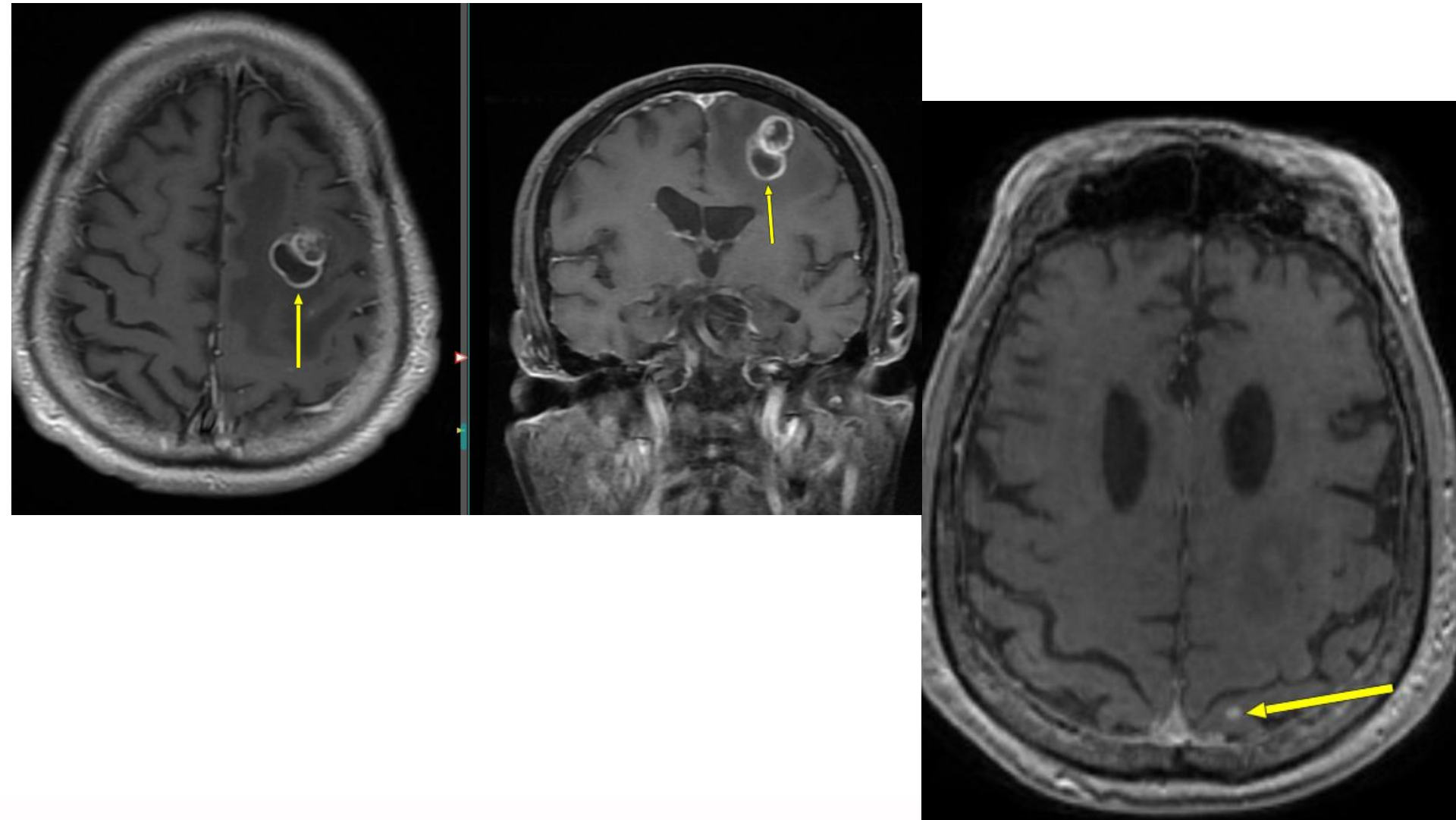
Case 2

- 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).

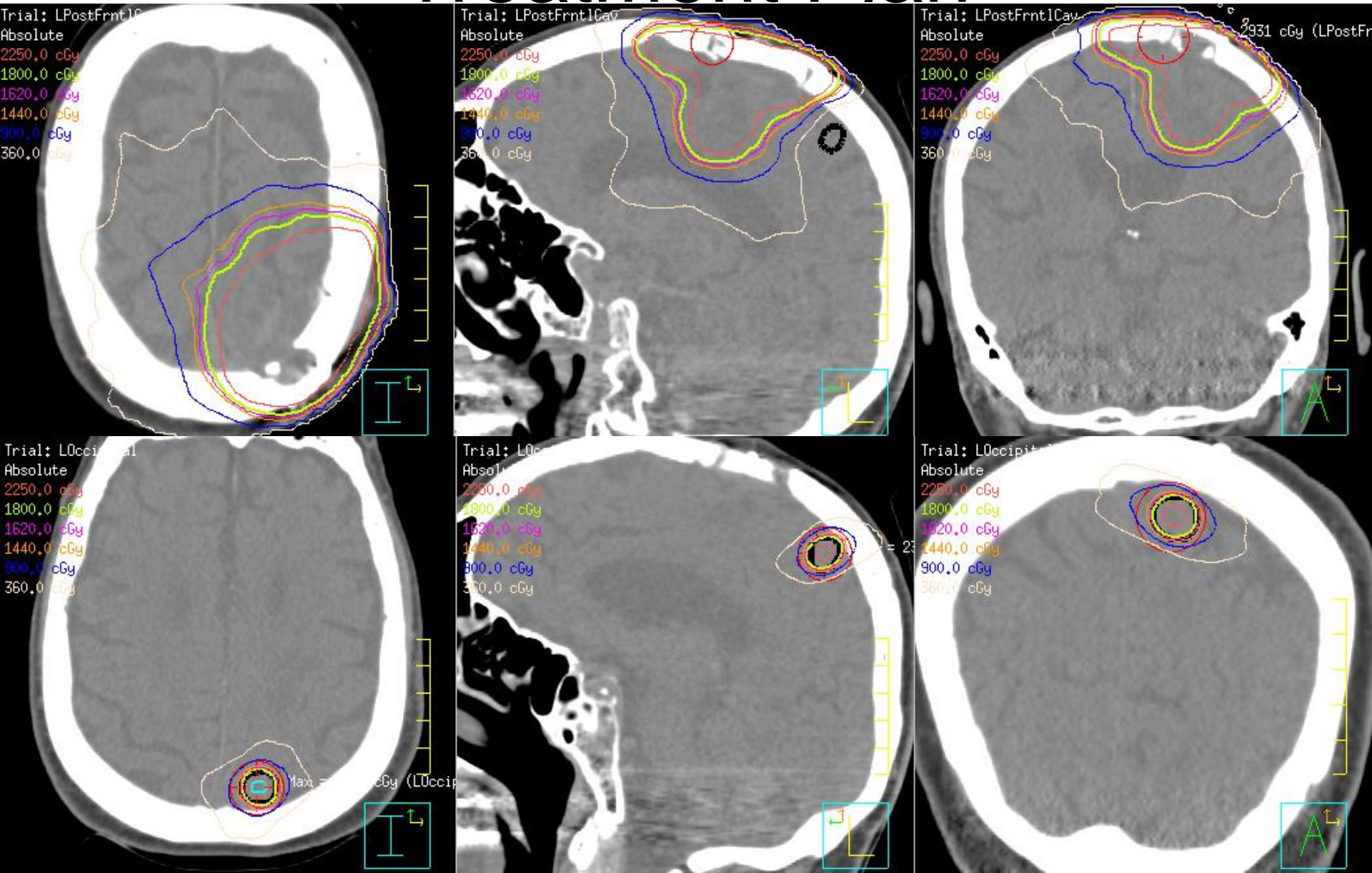
New Imaging Findings



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 nivolumab
- NED x 6 months

Treatment Plan



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

- Trosman, SJ, Koyfman, SA, Ward, MC, Al-Khudari, S, Nwizu, T, Greskovich, JF, ... & Burkey, BB. Effect of human papillomavirus on patterns of distant metastatic failure in oropharyngeal squamous cell carcinoma treated with chemoradiotherapy. *JAMA Otolaryngol Head Neck Surg* (2015);141(5):457-62. PMID:25742025
- Lee, NCJ, Kelly, JR, Park, HS, An, Y, Judson, BL, Burtness, BA, & Husain, ZA. Patterns of failure in high-metastatic node number human papillomavirus-positive oropharyngeal carcinoma. *Oral Oncol* (2018);85:35-9. PMID:30220317
- Bonomo P, Greto D, Desideri I, Loi M, Di Cataldo V, Orlandi E, Iacovelli NA, Becherini C, Visani L, Salvestrini V, Mariotti M, Livi L. Clinical outcome of stereotactic body radiotherapy for lung-only oligometastatic head and neck squamous cell carcinoma: Is the deferral of systemic therapy a potential goal. *Oral oncology* 2019;93:1-7. PMID:31109688
- Bates JE, De Leo AN, Morris CG, Amdur RJ, Dagan R. Oligometastatic squamous cell carcinoma of the head and neck treated with stereotactic body ablative radiotherapy: Single-institution outcomes. *Head & neck* 2019;41(7):2309-14. PMID:30788878
- Albergotti WG, Abberbock S, Mathews F, Ferris RL, Johnson JT, Duvvuri U, Kim S. Oligometastatic status as predictor of survival in metastatic human papillomavirus-positive oropharyngeal carcinoma. *Head & neck* 2018;40(8):1685-90. PMID:29756301
- Sun XS, Michel C, Babin E, De Raucourt D, Péchery A, Gherga E, Géry B, Florescu C, Bourhis J, Thariat J. Approach to oligometastatic disease in head and neck cancer, on behalf of the GORTEC. *Future oncology (London, England)* 2018;14(9):877-89. PMID:29578359
- Leeman JE, Li JG, Pei X, Venigalla P, Zumsteg ZS, Katsoulakis E, Lupovitch E, McBride SM, Tsai CJ, Boyle JO, Roman BR, Morris LGT, Dunn LA, Sherman EJ, Lee NY, Riaz N. Patterns of Treatment Failure and Postrecurrence Outcomes Among Patients With Locally Advanced Head and Neck Squamous Cell Carcinoma After Chemoradiotherapy Using Modern Radiation Techniques. *JAMA oncology* 2017;3(11):1487-94. PMID:28542679
- Sinha P, Thorstad WT, Nussenbaum B, Haughey BH, Adkins DR, Kallogjeri D, Lewis JS. Distant metastasis in p16-positive oropharyngeal squamous cell carcinoma: a critical analysis of patterns and outcomes. *Oral oncology* 2014;50(1):45-51. PMID:24211084
- Palma, DA, Olson, R, Harrow, S, Gaede, S, Louie, AV, Haasbeek, C, ... & Senan, S. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet* (2019);393(10185):2051-8. PMID:30982687
- Ferris RL, Blumenschein G, Fayette J, Guigay J, Colevas AD, Licitra L, Harrington KJ, Kasper S, Vokes EE, Even C, Worden F, Saba NF, Docampo LCI, Haddad R, Rordorf T, Kiyota N, Tahara M, Lynch M, Jayaprakash V, Li L, Gillison ML. Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumor PD-L1 expression. *Oral oncology* 2018;81:45-51.
- Huang SH, Perez-Ordóñez B, Weinreb I, Hope A, Massey C, Waldron JN, Kim J, Bayley AJ, Cummings B, Cho BC, Ringash J, Dawson LA, Siu LL, Chen E, Irish J, Gullane P, Hui A, Liu FF, Shen X, Xu W, O'Sullivan B. Natural course of distant metastases following radiotherapy or chemoradiotherapy in HPV-related oropharyngeal cancer. *Oral oncology* 2013;49(1):79-85.
- Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet (London, England)* 2019;394(10212):1915-28.