Esthesioneuroblastoma

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Case Presentation

- 52 years old woman presented with complaints of progressive right eye exophthalmos, nasal obstruction (right greater than left), anosmia, and recurrent sinus infection for 2 years
- Past medical history: hypertension
- Past surgical history: tubal ligation, tonsillectomy
- Family history: cardiac disease
- Social history: 50 pack-year smoking history, quit 13 years ago. She drinks alcohol occasionally

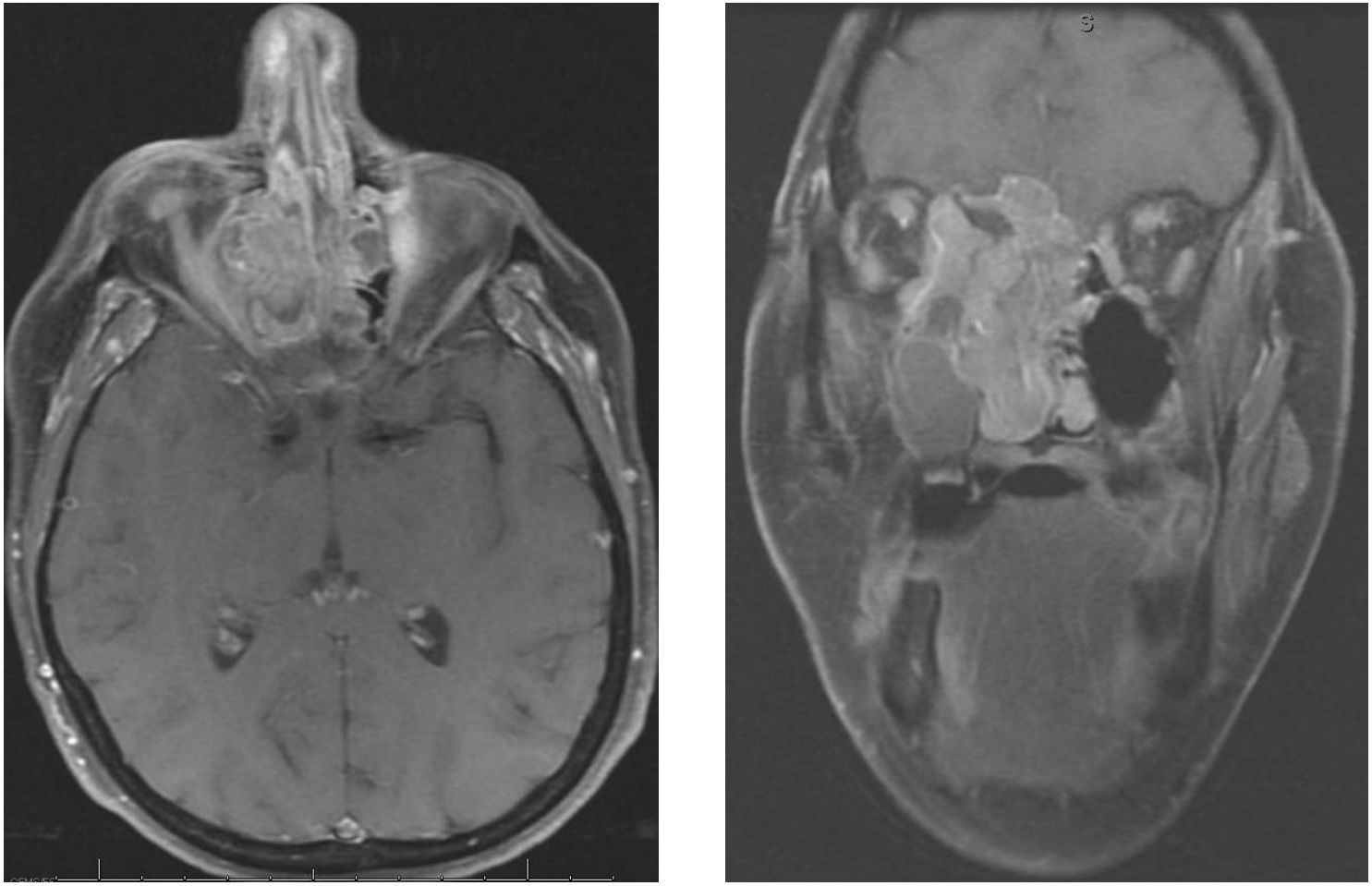
Physical Exam

- KPS 90%,
- Vitals: BP 110/66, P 77, T 37.1˚C, RR 16, SpO2 98%
- HEENT: Normocephalic, atraumatic. Pupils equal, round and reactive to light. Extra-ocular movements intact. Right sided exophthalmos.
  - Fiberoptic endoscopy reveals right nasal cavity obstruction by a polyp/mass, left sided septal deviation, otherwise normal.
- Oral exam: poor dentition. Gums, tongue, floor of the mouth, retromolar trigone, buccal mucosa, and hard palate are unremarkable. The tonsillar fossae, soft palate and base of tongue are unremarkable. No suspicious lesions appreciated on visual inspection or palpation.
- Neck: Neck is supple with no cervical or supraclavicular lymphadenopathy.
- Chest: Lungs clear to auscultation bilaterally.
- Heart: Regular rate and rhythm.
- Abdomen: Soft, nontender, nondistended, without organomegaly or masses.
- Extremities: No clubbing, cyanosis, or edema.
- Neurologic: Alert and oriented. Conversive. CN II-XII grossly intact.

Work Up

- Right nasal mass biopsy: olfactory neuroblastoma
- MRI orbit, face, neck ± contrast: study limited due to motion artifacts. Large tumor centered in the right nostril and ethmoid labyrinth with extension into the right orbit, anterior cranial fossa, right maxillary sinus, and likely left ethmoid labyrinth. There is a suspicious 2.6cm right level 2 lymph node.
- PET/CT: hypermetabolic mass in the right nasal cavity and right ethmoid labyrinth with extension to the right orbit and anterior cranial fossa. Hypermetabolic right level 2 lymph node. No obvious distant metastases.

MRI orbit, face, neck



T1 fat suppressed post gadolinium

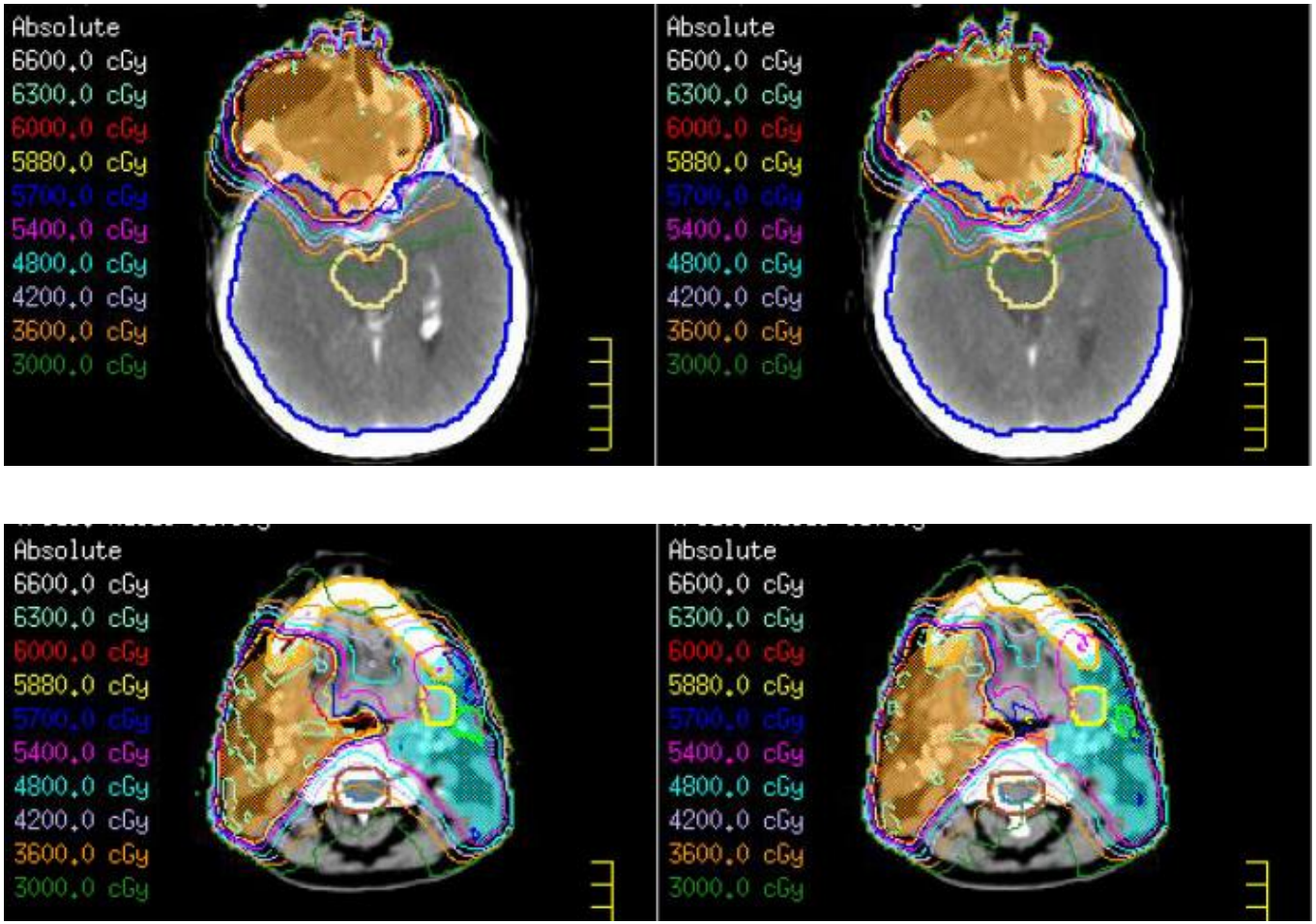
Treatment

- Patient underwent craniofacial resection of the primary tumor, right modified radical neck dissection level 2-4, right orbital exenteration with free flap reconstruction.
  - Final pathology: olfactory neuroblastoma, original Kadish C / modified Kadish D, Hyams Grade 4, grade 1-2, + bone and dural invasion, 3/19 LN positive (right level 2 and 3), +ENE, negative margins, +LVI, -PNI.

Treatment

- She then received adjuvant radiation therapy to a total dose of 60Gy/30fx with concurrent cisplatin
- Radiation volume delineation
  - CTV60 Gy: post-op tumor bed, right neck level 1a-5
  - CTV54 Gy: left neck level 1b-4
  - PTV = CTV + 3mm

RT Plan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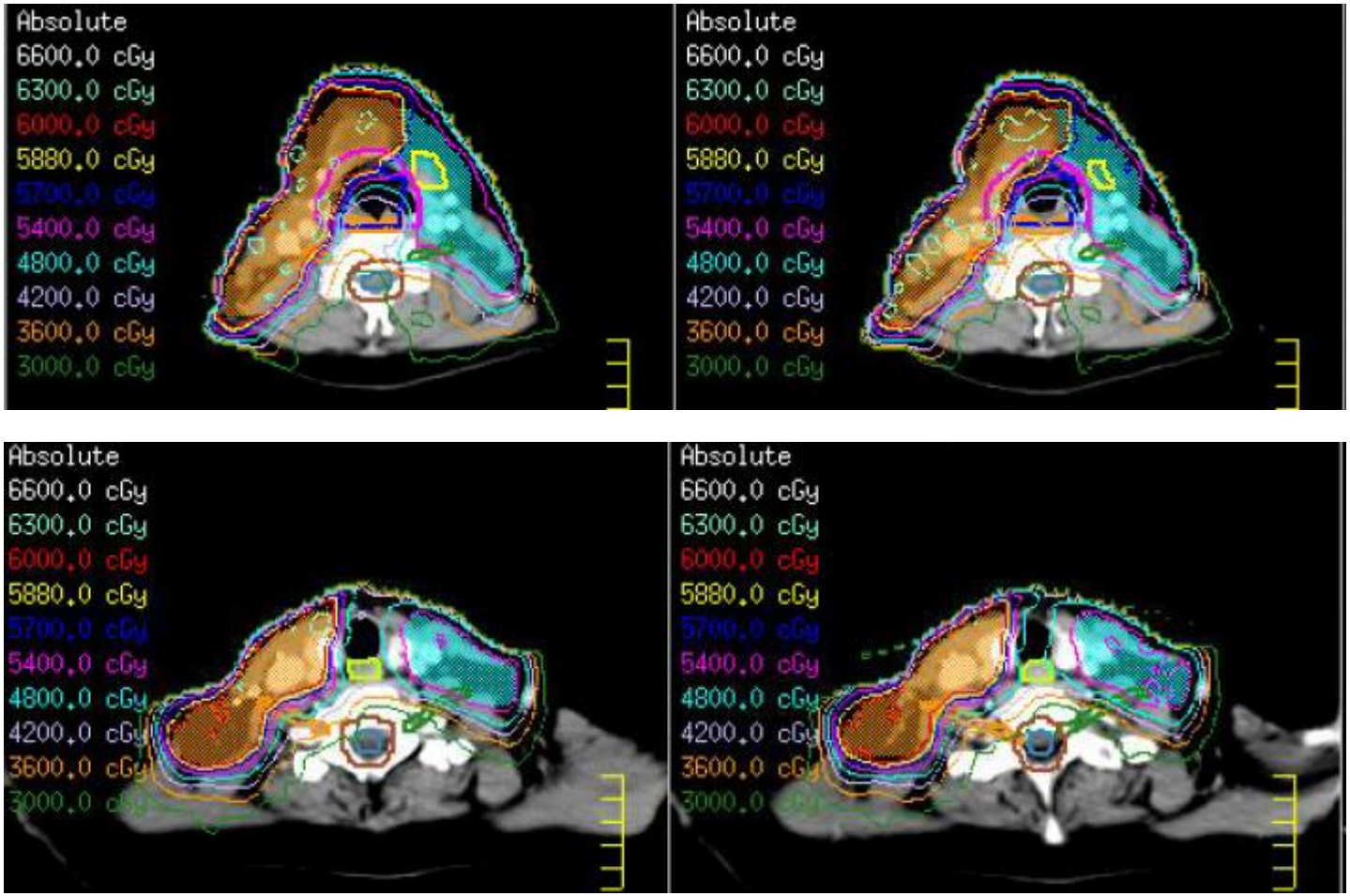
RT Plan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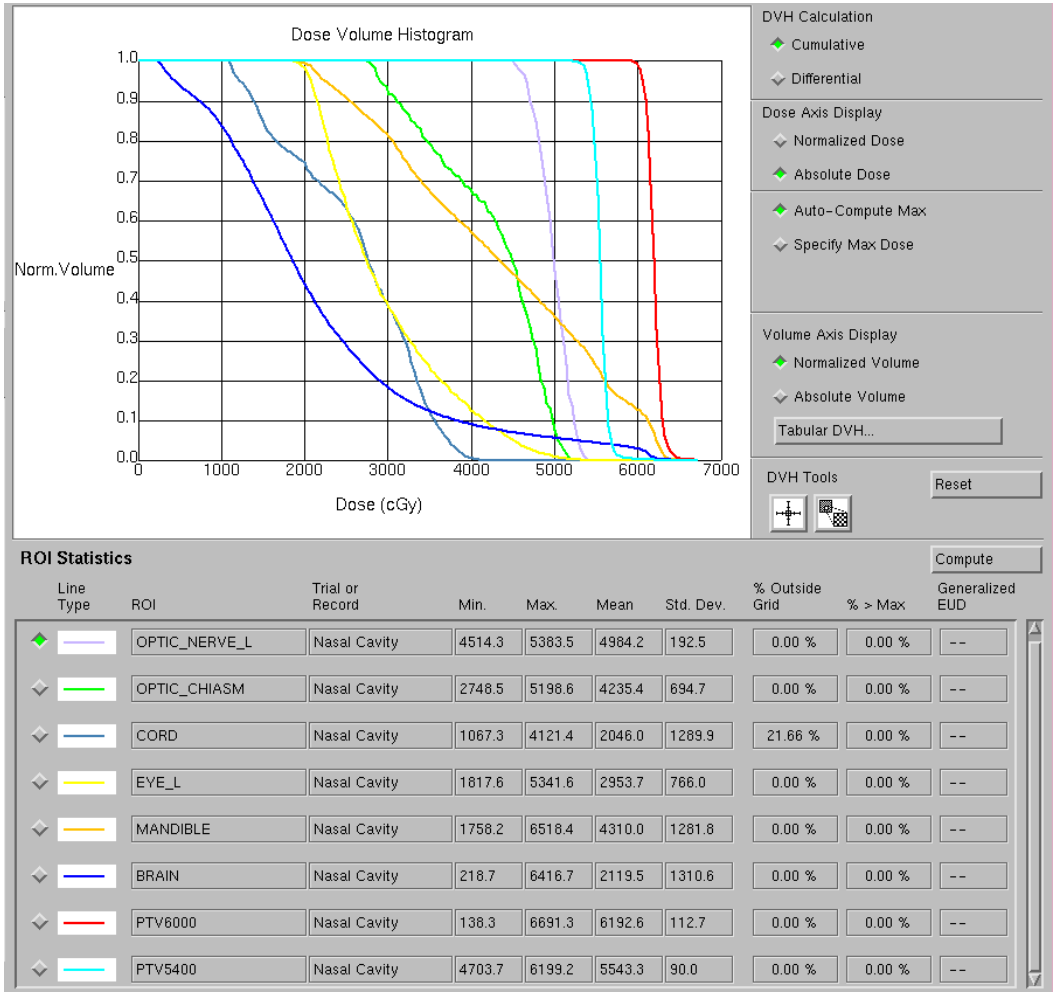
DVH



Line Type	ROI	Trial or Record	Min.	Max.	Mean	Std. Dev.	% Outside Grid	% > Max	Generalized EUD
	OPTIC_NERVE_L	Nasal Cavity	4514.3	5383.5	4984.2	192.5	0.00 %	0.00 %	--
	OPTIC_CHIASM	Nasal Cavity	2748.5	5198.6	4235.4	694.7	0.00 %	0.00 %	--
	CORD	Nasal Cavity	1067.3	4121.4	2046.0	1289.9	21.66 %	0.00 %	--
	EYE_L	Nasal Cavity	1817.6	5341.6	2953.7	766.0	0.00 %	0.00 %	--
	MANDIBLE	Nasal Cavity	1758.2	6518.4	4310.0	1281.8	0.00 %	0.00 %	--
	BRAIN	Nasal Cavity	218.7	6416.7	2119.5	1310.6	0.00 %	0.00 %	--
	PTV6000	Nasal Cavity	138.3	6691.3	6192.6	112.7	0.00 %	0.00 %	--
	PTV5400	Nasal Cavity	4703.7	6199.2	5543.3	90.0	0.00 %	0.00 %	--

Esthesioneuroblastoma (ENB) Review and Selected Literature

Epidemiology

- Tumor arising from olfactory epithelium
- Also known as olfactory neuroblastoma or esthesioneurocytoma
- Rare tumors, account for ~3% of intracranial neoplasms
- Bimodal distribution, peak incidence at 11-20 years and 51-60 years of age
- Slight male predominance

Clinical Presentation

- Common symptoms include:
  - Nasal obstruction
  - Epistaxis
  - Headache
  - Visual changes
  - Rhinorrhea
  - Tearing
  - Proptosis
  - Neck swelling

Work Up

- H&P
- Imaging:
  - CT head with contrast: best for evaluation of skull base bone erosion
  - MRI head with contrast: best for evaluation of intracranial extension
  - CT chest or PET/CT to evaluate for metastatic disease
- Biopsy
- Labs: CBC, CMP
- Dental, swallowing, and nutritional evaluation

Kadish Staging System

- Most commonly used staging system
- Initially proposed by Kadish et al. (1976)
  - Kadish A: tumor confined to nasal cavity
  - Kadish B: tumor involves nasal cavity and paranasal sinuses
  - Kadish C: tumor spread beyond nasal cavity and paranasal sinuses

Modified Kadish Staging System

- Initially proposed by Morita et al. (1993)
  - Kadish A: tumor confined to nasal cavity
  - Kadish B: tumor involves nasal cavity and paranasal sinuses
  - Kadish C: tumor spread beyond nasal cavity and paranasal sinuses, including involvement of the cribriform plate, base of skull, orbit, or intracranial cavity
  - Kadish D: tumor with metastasis to cervical lymph nodes or distant sites

Other Proposed Staging Systems

- AJCC TMN staging system for nasal cavity and paranasal sinuses
- Dulguerov-Calcaterra staging:
  - Modification of TMN staging system proposed by Dulguerov et al. (1992)
    - T1: tumor involving the nasal cavity and/or paranasal sinuses (excluding sphenoid), sparing the most superior ethmoidal cells
    - T2: tumor involving the nasal cavity and/or paranasal sinuses (including the sphenoid) with extension to or erosion of the cribriform plate
    - T3: tumor extending into the orbit or protruding into the anterior cranial fossa
    - T4: tumor involving the brain

Hyams Grade

- Initially proposed by Hyams et al. (1982)
- Grades (I-IV) are assigned based on 6 histologic features:
  - Lobular architecture
  - Neurofibrillary matrix
  - Mitosis
  - Necrosis
  - Nuclear pleomorphism
  - Rosettes

Prognostic factors

- Poor prognostic factors identified in published retrospective series:
  - Higher stage
  - Higher grade
  - Positive margin
  - Positive nodal involvement
  - Age > 60
  - Male

Reported Outcomes by Kadish Stage

Author	n	Time (years)	OS	DFS
Elkon (1979)	97	5	A: 90% B: 70.8% C: 46.7%	-
Dulguerov (2001)	390	5	A: 72% B: 59% C: 47%	-
Jethanamest (2007)	311	10	A: 83.4% B: 49.0% C: 38.6% D: 13.3%	A: 90.0% B: 68.3% C: 66.7% D: 35.6%
Ozsahin (2010)	77	5	A: 80% B: 76% C: 52%	A: 68% B: 56% C: 43%
Konuthula (2017)	1167	5	A: 80.0% B: 87.7% C: 77.7% D:49.5%	

Treatment Options

- Treatment recommendations are based on retrospective series given the rarity of esthesioneuroblastoma
- Locally advanced or high grade tumors are treated using multimodality therapy with surgery, RT, and chemotherapy
- Surgery alone may be considered for small, low grade tumors limited to the ethmoids
- High risk of neck recurrence with Kadish Stage C without elective neck irradiation
- The role of chemotherapy is less clear, however there is emerging data supporting its efficacy

Surgery Alone

Biller HF, Lawson W, Sachdev VP, Som P. Esthesioneuroblastoma: surgical treatment without radiation. Laryngoscope 1990; 100: 1199–201.

- Retrospective series comparing T1N0M0 Kadish A-B esthesioneuroblastoma patients treated with craniofacial resection (20 patients) versus neoadjuvant RT + extracranial resection (5 patients)
- Results:
  - Higher local recurrence with neoadjuvant RT + extracranial resection (60% vs. 12%)
  - Author argues that pre-operative radiation therapy does not appear to provide any advantage if adequate resection can be performed. Additionally, tumor shrinkage from RT may mask microscopic disease at the time of surgery.

Surgery + RT

Foote RL, Morita A, Ebersold MJ, et al. Esthesioneuroblastoma: the role of adjuvant radiation therapy. Int J Radiat Oncol Biol Phys. 1993;27:835–842

- Retrospective review of 49 patients treated at the Mayo Clinic between 1951-1990
  - Kadish Stage distribution: A - 4 patients, B - 13 patients, C - 29 patients, D - 3 patients
  - Treatment modality: GTR alone - 22 patients, GTR + RT - 16 patients
  - Median RT dose 55 Gy
- Results:
  - 5 years OS, DFS, and LC were 69.1%, 54,8%, and 65.3%
  - Only significant predictor of DFS was Hyams grade
  - Adjuvant RT improved LC over surgery alone 85.9% vs 72.7%, p=0.26; there was a higher proportion of high grade tumors in the adjuvant RT group

Foote RL, Morita A, Ebersold MJ, et al. Esthesioneuroblastoma: the role of adjuvant radiation therapy. Int J Radiat Oncol Biol Phys. 1993;27:835–842

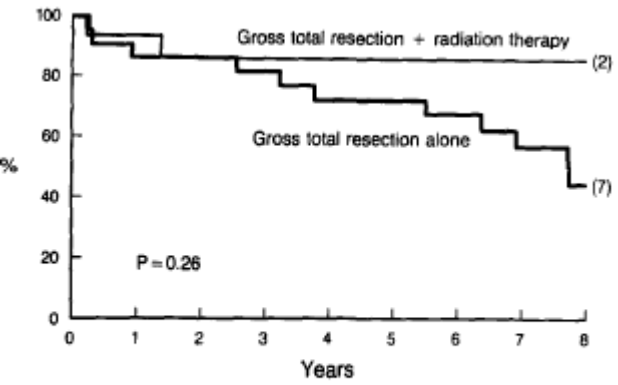


Fig. 3. Local control in patients with esthesioncuroblastoma, by initial treatment technique. Numbers in parentheses are number of patients followed at 8 years.

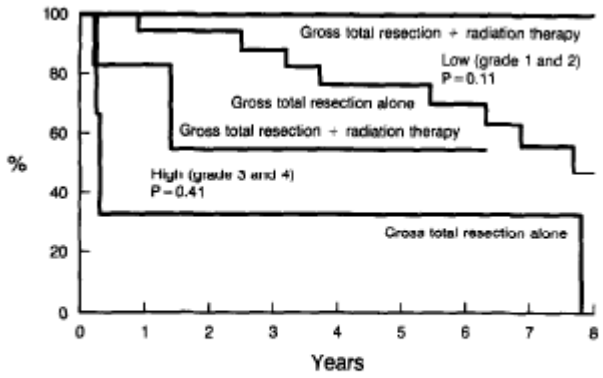


Fig. 4. Local control in patients with esthesioneuroblastoma, by Hyams' grade (low-grade vs. high-grade) and initial treatment (gross total resection alone vs. gross total resection and adjuvant radiation therapy).

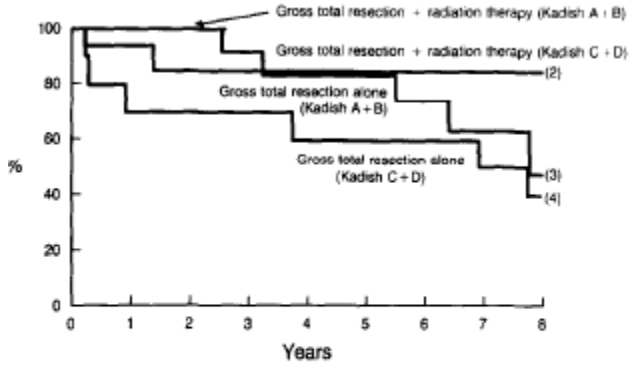


Fig. 5. Local control in patients with esthesioneuroblastoma, by Kadish Stage (A and B vs. C and D) and initial treatment (gross total resection alone vs. gross total resection and postoperative adjuvant radiation therapy). Numbers in parentheses are number of patients followed at 8 years.

Broich G, Pagliari A, Ottaviani F. Esthesioneuroblastoma: a general review of the cases published since the discovery of the tumour in 1924. Anticancer Res 1997;17:2683–2706

- Retrospective review of 945 cases reported in literature
  - Kadish Stage distribution: A - 18.29%, B - 32.33%, C - 49.38%
  - Treatment could be classified in 898 cases: surgery alone - 25.17%, RT alone - 18.37%, combined surgery + RT - 43.21%, and chemotherapy - 13.2%
- Results:
  - Outcomes available for 477 cases, with 234 cases having 5 year follow up (20.51% surgery alone, 11.11% RT alone, and 68.38% surgery + RT)
  - Best survival rate with combined surgery + RT (72.5%) versus surgery alone (62.5%) and RT alone (53.85%)

Platek ME, Merzianu M, Mashtare TL, et al. Improved survival following surgery and radiation therapy for olfactory neuroblastoma: analysis of the SEER database. Radiat Oncol 2011; 6: 41

- SEER database analysis between 1973-2005 examining management strategies for of esthesioneuroblastoma
  - 511 patients identified
  - Treatment modalities: 61% surgery + RT, 22% surgery alone, 11% RT alone, 6% did not receive surgery or RT
- Results:
  - 5yr OS: 73% surgery + RT, 68% surgery only, 35% RT only, 26% for neither RT nor surgery, $p<0.0001$
  - At 10 year, there was no difference in OS between surgery versus surgery + RT when stratified by stage and treatment modality

Platek ME, Merzianu M, Mashtare TL, et al. Improved survival following surgery and radiation therapy for olfactory neuroblastoma: analysis of the SEER database. Radiat Oncol 2011; 6: 41

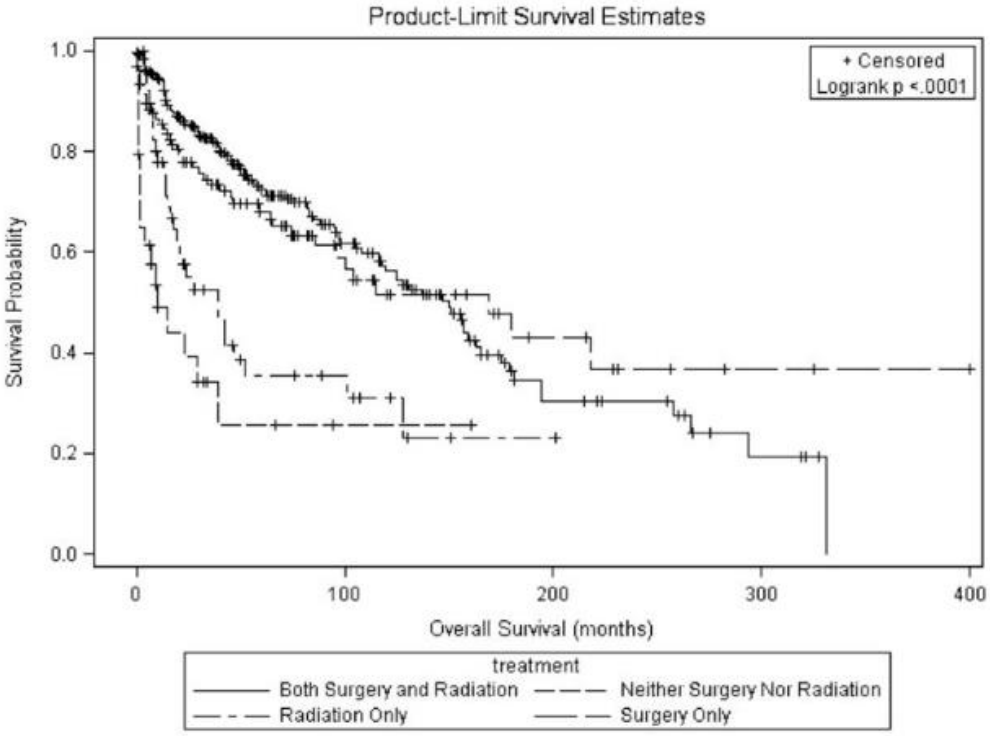
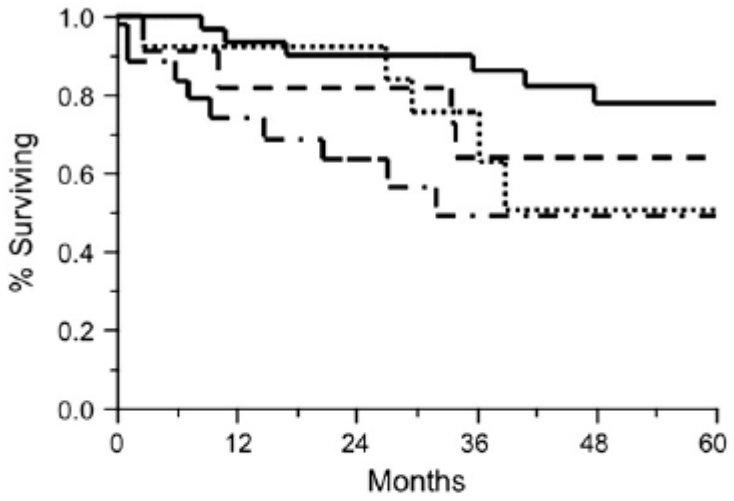


Figure 1
Overall Survival of SEER ONB Cases by Treatment Groups.

Ozsahin M, Gruber G, Olszyk O, et al. Outcome and prognostic factors in olfactory neuroblastoma: a rare cancer network study. Int J Radiat Oncol Biol Phys. 2010; 78(4):992–997

- Retrospective review of 77 patients treated at 13 European and North American centers
  - Kadish Stage distribution: A - 14%, B - 38%, C - 48%
  - Treatment: surgery + RT + chemo - 16%, S + RT - 52%, surgery alone - 6%, RT alone - 14%, RT + Chemo - 12%
- Results:
  - Median follow up 72 months
  - Multivariate analysis showed independent predictors for outcome were T1-3, N0, R0/R1 resection, and RT dose ≥ 54 Gy

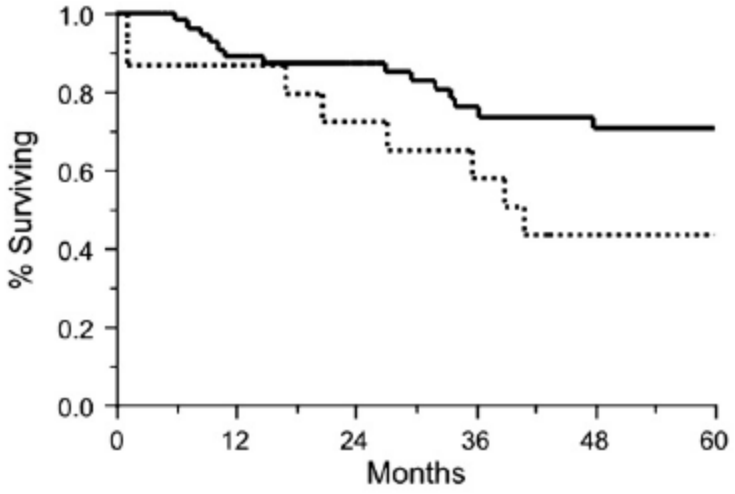
Ozsahin M, Gruber G, Olszyk O, et al. Outcome and prognostic factors in olfactory neuroblastoma: a rare cancer network study. Int J Radiat Oncol Biol Phys. 2010; 78(4):992–997



Patients at risk

R0	32	29	27	23	20	19
R1	13	12	11	8	5	4
R2	11	10	9	8	6	5
No surgery	21	16	11	8	7	6

Fig. 1. Overall survival at 5 years according to surgical margin (log-rank test, $p = 0.006$): R0 resection (solid line; $n = 32$), R1 resection (dotted line; $n = 13$), R2 resection (dashed line; $n = 11$), or no surgery (dashed/dotted line; $n = 21$).



Patients at risk

RT ≥ 54 Gy	57	49	44	32	28	27
RT < 54 Gy	15	13	11	9	7	6

Fig. 2. Overall survival at 5 years according to total radiotherapy (RT) dose in 72 patients treated with RT (log-rank test, $p = 0.08$): ≥54 Gy (solid line; $n = 57$) vs. <54 Gy (dotted line; $n = 15$).

Elective Neck Irradiation

Monroe AT, Hinerman RW, Amdur RJ, et al. Radiation therapy for esthesioneuroblastoma: Rationale for elective neck irradiation. Head Neck 2003;25:529–534

- Retrospective review of 22 patients treated at the University of Florida between 1972-1998
  - Modified Kadish Stage distribution: A – 1 patients, B - 4 p, C - 15 patients, D - 2 patients
  - Treatment modalities: definitive RT - 6 patients, preoperative RT - 1 patient, postoperative RT - 12 patients, salvage RT - 3 patients
  - Median RT dose: 65.5Gy - postop, 70Gy - definitive
  - 11 patients received elective neck RT, median dose 50Gy
- Results:
  - 5 years LC 59%, CSS 54%, OS 48% for entire cohort
  - Lower 5 years CSS with RT alone (17%) vs. craniofacial resection and post-operative RT (56%)
  - 4 neck recurrences (44%) in 9 patients not treated with elective neck RT vs. none in 11 patients treated with elective neck RT, p=0.02

Demiroz C, Gutfeld O, Aboziada M, et al. Esthesioneuroblastoma: Is there a need for elective neck treatment? Int J Radiat Oncol Biol Phys. 2011; 81:e255–e261

- Retrospective review of 26 patients treated at the University of Michigan between 1995-2007
  - Kadish Stage distribution: A - 1 patient, B - 10 patients, C - 5 patients, unknown - 1 patient; all N0
  - Treatment modalities: surgery + RT 46%, surgery alone 54%
  - Elective neck dissection or RT were not performed
- Results:
  - Adjuvant RT improves 5 years LC (100% vs 29%, p=0.005) and DFS (87.5% vs 31%), p=0.005
  - Neck failure observed in 7 (27%) patients (6 Kadish B, 1 Kadish C)
    - Level II neck was the most common site of recurrence
    - 3 patients recurred in the contralateral neck
    - 3/7 patients were successfully salvaged

Jiang W, Mohamed AS, Fuller CD. , et al. The role of elective nodal irradiation for esthesioneuroblastoma patients with clinically negative neck. Pract Radiat Oncol 2016; 6 (04) 241-247

- Retrospective review of 71 patients treated at MDACC between 1970-2013
  - Modified Kadish Stage distribution: A - 5.6%, B - 21.1%, C - 71.8%, D 1.4%
  - Treatment modality: surgery + RT - 65 patients, RT alone - 3 patients, chemo alone - 3 patients
  - Median RT dose 58 Gy
  - 22 (31%) patients received elective neck RT
- Results:
  - Elective neck RT improved 5 years regional control rate (100% vs 82%, $p<0.001$) but did not influence OS or DFS
  - Neck failure observed in 13 patients, 2/13 also had distant metastases
    - 92.3% of neck recurrences were Kadish C patients
    - Level II neck was the most common site of recurrence (84.6%)
    - 55% were successfully salvaged

Induction Chemotherapy/Chemoradiation

Modesto A, Blanchard P, Tao YG, et al. Multimodal treatment and long-term outcome of patients with esthesioneuroblastoma. Oral Oncol 2013; 49: 830–4

- Retrospective review of 43 patients treated between 1998-2010
  - Kadish Stage distribution: A - 5, B - 13, C - 16, D - 9
  - Treatment modalities
    - 23 patients received neoadjuvant chemotherapy (2 regimens)
      - Cyclophosphamide/Vincristine/Epirubicin/Dacarbazine/Cisplatin
      - Cyclophosphamide/Doxorubicin/Vincristine
    - 31 patients treated with surgery
    - 39 patients received RT
  - 12 patients received bilateral neck RT
- Results:
  - 74% response rate to induction chemo (6 complete response and 11 partial response)
  - 2 patients who did not receive elective neck RT developed nodal relapse; none in patients receiving neck RT

Sohrabi S, Drabick JJ, Crist H, Goldenberg D, Sheehan JM, Mackley HB.. Neoadjuvant concurrent chemoradiation for advanced esthesioneuroblastoma: a case series and review of the literature. J Clin Oncol. 2011;29:e358–61

- Case reports of 2 patients with Kadish C, high grade ENB treated with induction concurrent chemoradiation
  - RT: 50Gy/25fx
  - Chemo: cisplatin + etoposide
- Both patients required hospitalization for treatment toxicity (neutropenic fever, grade 4 mucositis requiring feeding tube)
- Both went on to have surgery and were found to have complete pathologic response
- NED for 30 months and 24 months at the time of case report
- Induction chemoradiation may allow significant tumor downstaging and multimodal treatment for locally advanced disease but carries high risk of morbidity

References

1. Kadish S, Goodman M, Wang CC. Olfactory neuroblastoma—a clinical analysis of 17 cases. Cancer 1976;37:1571-1576.

2. Elkon D, Hightower SI, Lim ML, et al. Esthesioneuroblastoma. Cancer 1979;44:1087-1094.

3. Morita A, Ebersold MJ, Olsen KD, et al. Esthesioneuroblastoma: prognosis and management. Neurosurgery. 1993;32:706-714. discussion 714-715.

4. Dulguerov P, Calcaterra T. Esthesioneuroblastoma: the UCLA experience 1970-1990. Laryngoscope. 1992;102:843-849.

5. Hyams VJ. Olfactory neuroblastoma (Case 6) In: Batsakis JG, Hyams VJ, Morales AR, editors. Special tumors of the head and neck. Chicago: ASCP Press; 1982. pp. 24–29.

7. Jethanamest D, Morris LG, Sikora AG, Kutler DI. Esthesioneuroblastoma: a population-based analysis of survival and prognostic factors. Arch Otolaryngol Head Neck Surg. 2007; 133(3):276–280.

8. Dulguerov P, Allal AS, Calcaterra TC. Esthesioneuroblastoma: a meta-analysis and review. Lancet Oncol. 2001; 2(11):683–690.

9. Ozsahin M, Gruber G, Olszyk O, et al. Outcome and prognostic factors in olfactory neuroblastoma: a rare cancer network study. Int J Radiat Oncol Biol Phys. 2010; 78(4):992–997.

10. Konuthula N., Iloreta A.M., Miles B., et al. Prognostic significance of Kadish staging in esthesioneuroblastoma: An analysis of the National Cancer Database. Head Neck. 2017;39:1962–1968.

11. Resto VA, Eisele DW, Forastiere A, Zahurak M, Lee DJ, Westra WH. Esthesioneuroblastoma: the Johns Hopkins experience. Head Neck 2000; 22: 550–8.

12. Bell D., Saade R., Roberts D., Ow T.J., Kupferman M., DeMonte F., Hanna E.Y. Prognostic utility of Hyams histological grading and Kadish-Morita staging systems for esthesioneuroblastoma outcomes. Head Neck Pathol. 2015;9:51–59.

13. Van Gompel JJ, Giannini C, Olsen KD, et al. Long-term outcome of esthesioneuroblastoma: Hyams grade predicts patient survival. J Neurol Surg B Skull Base. 2012;73:331–6.

14. Broich G, Pagliari A, Ottaviani F. Esthesioneuroblastoma: a general review of the cases published since the discovery of the tumour in 1924. *Anticancer Res*1997;17:2683–2706.

15. Platek ME, Merzianu M, Mashtare TL, et al. Improved survival following surgery and radiation therapy for olfactory neuroblastoma: analysis of the SEER database. *Radiat Oncol* 2011; 6: 41.

16. Diaz EM, Johnigan RH, Pero C, et al. Olfactory neuroblastoma: the 22-year experience at one comprehensive cancer center. Head Neck 2005; 27: 138–49.

References

17. Demiroz C, Gutfeld O, Aboziada M, et al. Esthesioneuroblastoma: Is there a need for elective neck treatment? Int J Radiat Oncol Biol Phys. 2011; 81:e255–e261.

18. Monroe AT, Hinerman RW, Amdur RJ, et al. Radiation therapy for esthesioneuroblastoma: Rationale for elective neck irradiation. Head Neck 2003;25:529–534.

19. Jiang W, Mohamed AS, Fuller CD. , et al. The role of elective nodal irradiation for esthesioneuroblastoma patients with clinically negative neck. Pract Radiat Oncol 2016; 6 (04) 241-247.

20. Foote RL, Morita A, Ebersold MJ, et al. Esthesioneuroblastoma: the role of adjuvant radiation therapy. Int J Radiat Oncol Biol Phys. 1993;27:835–842.

21. Modesto A, Blanchard P, Tao YG, et al. Multimodal treatment and long-term outcome of patients with esthesioneuroblastoma. Oral Oncol 2013; 49: 830–4.

22. Sohrabi S, Drabick JJ, Crist H, Goldenberg D, Sheehan JM, Mackley HB.. Neoadjuvant concurrent chemoradiation for advanced esthesioneuroblastoma: a case series and review of the literature. J Clin Oncol. 2011;29:e358–61.

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