Case Report: Recurrent Olfactory Neuroblastoma Nasal Cavity in Young Boy Refractory to Chemotherapy with Remission after Radiotherapy and Sparing of Left Eye

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Abstract

Olfactory neuroblastomas make up about 3-5% of malignant intra-nasal tumors and originate from the olfactory neuroepithelium lining the roof of the nasal vault. There exist no optimum treatment guidelines from randomized data due to paucity of patients. Treatment options range from minimal surgery to extensive cranio-facial resections and adjuvant radiotherapy. In this case a tumor engulfing optic nerve and globe was safely treated by 3D-CRT with complete remission and relative sparing of the eye as well as late toxicities were avoided. 3D-CRT permits increased dose to tumor sparing critical areas and is a feasible option in centres without IMRT.

Keywords:
Esthesioneuroblastoma, olfactory neuroblastoma, malignant tumors of nasal cavity, refractory olfactory neuroblastoma

Introduction

Malignant tumors of the nasal cavity are very rare and olfactory neuroblastomas (ONB), also called esthesio-neuroblastoma, are even rarer. They make up about 3-5% of malignant intra-nasal tumors and usually originate from the olfactory neuroepithelium lining the roof of the nasal vault in close proximity to the cribriform plate. ONBs occur in all age groups with a peak incidence in the age groups of 11 to 20 years and 51 to 60 years (1) with a slightly greater incidence in women. This tumor is locally aggressive with occasional metastasis. It was first described by Berger in 1924, and has no distinctive clinical picture, often presenting as chronic unilateral nasal obstruction or recurrent epistaxis. The other common clinical symptoms are hyposmia, rhinorrhea, headaches, and visual disturbances (1, 2). Since this condition is rare, there are no optimum treatment guidelines from randomized data. Treatment options range from minimal surgery to extensive cranio-facial resections and adjuvant radiotherapy. Modern conformal radiotherapy techniques allow high doses to be safely delivered to tumor volume with sparing of surrounding critical normal structures from acute and late toxicities. In this report, we present a case of an eight year old boy with tumor recurring after repeated surgeries and treated with conformal 3D-CRT leading to complete remission and sparing of vision.

Case History

An eight-year old boy presented with swelling in left naso-labial area in January 2009 which was diagnosed as a benign growth and he underwent a sub-labial excision at another center. No further treatment was advised. The boy had a recurrence in same site in April 2010 and underwent re-excision. Post-operative histo-pathological examination was suggestive of olfactory neuroblastoma. Patient was on follow up and again developed recurrence in same area. He then underwent re-surgery in Department of ENT, JIPMER in August 2010. Tumor excision was done via sub-labial route. Intra-op, a 4 x 3 cm nodular mass was noted on the left side of face in subcutaneous plane extending from medial canthus and infra-orbital rim; medially obliterating naso-facial groove; laterally extending to upper gingiva-
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Patient was then referred to Department of Medical Oncology, JIPMER where he received five cycles chemotherapy from Sept 2010 to January 2011 with CCG 3891 protocol (Doxorubicin, Cisplatinum, Etoposide and Cyclophosphamide).

Patient did not respond to chemotherapy with reappearance of swelling at same site and increase in size (Figure 1). Case was discussed in combined tumor clinic with ENT Surgeon, Medical and Radiation Oncologist. Re-surgery was not deemed possible. An MIBG study showed no disease metastasis, only local recurrence. CECT showed large recurrence involving almost entire left cheek, upper lip, orbit and left medial canthus; however left nasal cavity, left lateral part of orbit (including globe) and underlying maxillary bone were spared. A decision was taken to consider the case as olfactory neuroblastoma.

![Figure 1. Pre-radiotherapy patient photograph](image)

buccal sulcus and up to level of first molar. However underlying maxillary bone was normal. Histopathology reported mass as a neuroblastoma invading soft tissue and skeletal muscle with immunocytochemistry positive for CD99, S-100 (focally), PAS (focally) and chromogranin (focally).

<table>
<thead>
<tr>
<th>Age / sex</th>
<th>Kadish stage</th>
<th>Dose of RT</th>
<th>BED3</th>
<th>BED10</th>
<th>Response</th>
<th>Recurr. site</th>
<th>Time to recur.</th>
<th>FU period</th>
<th>Late toxicity</th>
<th>Present status</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 / M</td>
<td>B</td>
<td>60 Gy / 30 fractions</td>
<td>100.2 Gy</td>
<td>72 Gy</td>
<td>CR</td>
<td>none</td>
<td>none</td>
<td>14 m</td>
<td>none</td>
<td>CR</td>
</tr>
</tbody>
</table>

Table 1: Patient characteristics, treatment and follow up

(Definition of terms: BED: Biological equivalent dose; CR: complete remission; Gy: Gray / unit of radiation dose delivered; BED3: Biological equivalent dose for α / β ratio of 3 i.e. late toxicities; BED10: Biological equivalent dose for α / β ratio of 10 i.e. acute toxicities)

<table>
<thead>
<tr>
<th>Structure</th>
<th>Doses to PTV and Organ at risk (in eGy)</th>
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<tbody>
<tr>
<td></td>
<td>D95 (for PTV)</td>
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<tr>
<td>--------------------------------</td>
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</tr>
<tr>
<td>PTV Phase 1 (40 Gy)</td>
<td>3600</td>
</tr>
<tr>
<td>PTV Phase 2 (60 Gy)</td>
<td>2050</td>
</tr>
<tr>
<td>Brainstem</td>
<td>-</td>
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<tr>
<td>Optic Chiasma</td>
<td>-</td>
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<tr>
<td>Rt Optic Nerve</td>
<td>-</td>
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<tr>
<td>Lt Optic Nerve (involved side)</td>
<td>-</td>
</tr>
<tr>
<td>Lt Eye (involved side)</td>
<td>-</td>
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<tr>
<td>Rt Eye</td>
<td>-</td>
</tr>
<tr>
<td>Left parotid</td>
<td>-</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2: Dose obtained for target and various critical structure volumes.
and offer conformal radiotherapy. Counseling regarding high risk of permanent vision loss in left eye and associated complications was given to the parents and consent for radiotherapy taken. Patient was treated by 3D-CRT to a dose of 60 Gy, completed in November 2011. Since the tumor volume was encasing left eye and optic nerve, these structures also received tumoricidal doses. Post radiotherapy, patient was in complete clinical remission and had grade 2 left conjunctival hyperemia and photophobia which were temporary (Tables 1, 2).

Patient was kept on close follow up. An MRI done in March 2012 showed no evidence of disease (Figure 2). We also closely followed up for any left eye sequelae as mean dose there could not be limited below 55 Gy. At follow-ups in January, April, August and December 2012, patient did not have any conjunctival or corneal damage and both pupillary reflexes were normal. Retinoscopy and Fluorescein staining did not reveal any late radiation damage. Fundoscopy was also normal.

Discussion

Olfactory neuroblastomas (ENB) are rare malignancies of the neuroepithelium and less than 1000 cases have been reported in literature. Prospective studies are difficult to conduct because of low incidence rates. ENB has long natural history and five-year survival rates are estimated at 82% (1). Poor prognostic factors include: age > 50 years at presentation, female gender, extent of disease and recurrent disease (2).

Extension of primary tumor based on the Kadish staging system has been identified as the most important determinant of treatment outcome (2). Kadish et al (2) in a review of 17 patients, suggested limited surgery, followed by radiation therapy, in stage A ENB. For stage B, pre-operative radiation therapy and limited surgery was advised; and for stage C, high-dose radiation therapy of 60-65 Gy followed by surgical resection of residual disease, if operable. The local control rates were 100% for stage A, 80% for stage B and 49% for stage C.

The staging system, presented by Kadish et al (2) in 1976, has been widely accepted though shortcomings were pointed out by Dulguerov et al (4) being: incidence of Stage A disease is very low as more patients are diagnosed with involvement of ethmoid sinuses with modern imaging upstaging the disease; lack of a clear prognostic significance of stage A and Stage B disease as sinus involvement does not adversely impact surgical resectability and is not an adverse prognostic factor. Regional disease was also not included in the staging system in view of its rarity. Recently, Morita et al suggested a modified classification by inserting stage D tumors, presenting as distal or nodal metastases (3). But despite its inadequacies (4) Kadish system is still the most commonly used.

Craniofacial surgery (CFR) is the mainstay of treatment in ENB followed by adjuvant radiation in high grade and locally advanced tumors (5). But in spite of aggressive surgery, local recurrence after surgery alone happens in 20–60% of cases. Hence adjuvant radiation therapy in advanced (stages B or C) disease even after complete resection is advocated to improve local control (5, 6, 7). Biller et al (5) in a review of literature found higher incidence of regional and distant failures after combined surgery and radiation therapy compared with surgery alone. But this finding...
could have been affected by a selection bias in which advanced disease, with known increased risk of regional metastases, were often treated with radiation. Foote et al (8) reported improved local control (87% versus 41%) after post-op radiation compared with surgery alone.

Chemotherapy as part of combined modality in treatment of ENB is still investigational, though studies have shown promising results(9-11). Kim et al (11) have reported the use of neoadjuvant etoposide, ifosfamide and cisplatin for the treatment of olfactory neuroblastoma. Median survival was 18 months and three year survival rate was 40%. Only two patients out of 11 achieved CR, while after subsequent treatment with radiotherapy four more patients achieved CR. Another study by Mishima et al (12) using cyclophosphamide, doxorubicin and vincristine chemotherapy and continuous infusion cisplatin and etoposide with peripheral blood stem cell transplantation showed good complete response rate of 66.7%. Radiotherapy was a part of this protocol.

Theilgaard et al (13) reported on a Danish demographic study comprising 40 patients registered between 1978 and 2000. Patients were treated as: stage A patients: surgical tumor resection and RT; stage B: surgical tumor resection and RT; stage C, surgical tumor resection via craniofacial resection and RT combined with chemo. The five year disease-free survival was 75% for stage A patients, 67% for stage B, and 32% for stage C. Thus combined modality treatment with surgery and radiation therapy is increasingly being considered part of management protocol.

3D-CRT is capable of improving dose coverage of the tumor volume and decreasing the risk of normal tissue complications and so allows tumor dose escalation (14). Roa et al (14) showed that CT-based 3D radiotherapy is beneficial in minimizing the risk of eye complications in the management of advanced paranasal sinus malignancies. But better dose conformity and reduction of non-target doses could be achieved with IMRT. Zabel et al (15) showed that target coverage using IMRT was equal to 3D-CRT, while maximum dose delivered to organs at risk (OAR) was lower with IMRT, with dose conformity to the target volume using IMRT better than 3D-CRT. IMRT was superior in larger treatment volumes whereas 3DCRT was equivalent to IMRT in smaller treatment volumes. In our report also we were able to get significant sparing with 3DCRT alone as IMRT facility was not available at that time in our Institute.

Conclusion

It is evident from literature that patient survival has increased due to a combination of different treatment approaches and use of new technologies. Combined therapy increases patients’ survival but an early diagnosis is important in the prognosis.

Patients in developing countries present in advanced stages and for better outcomes it is necessary to combine surgery, radiation and chemotherapy. 3D-CRT permits increased dose to the tumor with sparing surrounding critical areas and can be considered in centers without IMRT.

References


