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ESTHESIONEUROBLASTOMA – EXPERIENCE AT A TERTIARY CARE CENTRE, A PROSPECTIVE STUDY ON QUALITY-OF-LIFE AND SURVIVAL FUNCTION

Otolaryngology

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ABSTRACT

Introduction – Esthesioneuroblastoma (ENB) is an uncommon, rapidly growing tumour that apparently originates from the roof of the nasal cavity or the olfactory fossa. It is otherwise referred to as "olfactory neuroblastoma" due to its neuroepithelium component. This tumour, when leaving the confines of the olfactory fossa, often involves the cribriform plate, skull base and the lymph nodes of the neck. These are commonly are treated with surgery and radiotherapy if they are in the early stage at initial presentation. Advanced tumours are treated multi-modally using chemotherapy, radiotherapy and surgery. It is imperative that patients undergo early biopsy of nasal mass on Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) to establish prompt diagnosis. Here, we are describing a case series of ENB from the Dept. of ENT - Head & Neck Surgery, with different modes of presentation, course of disease, outcomes, prognostic factors and quality-of-life (QOL) measures.

Objectives - To compare Quality-of-Life measures in patients diagnosed with olfactory neuroblastoma and to study survival functions

Methods – Prospective cohort comparative study. Duration – 7 years (from 2011 – 2018). Data collected from the hospital tumour board registry and by questionnaire.

Results – Recorded data shows poor Quality of Life soon after diagnosis. Same worsened if the presenting stage was advanced. Survival statistics calculated.

Conclusion – Case series data from our tertiary care centre was compared with other similar studies and certain merits and demerits are highlighted. Esthesioneuroblastoma, though rare, has great effect on QOL of the patient and his/her care-givers / relatives. Early detection and radio-imaging, avoidance of risk factors go a long way in making life better in those diagnosed with such malignant pathology. Further palliative measures, combination treatment options have to be explored to definitely improve QOL.

KEYWORDS

Esthesioneuroblastoma; neoplasm; questionnaire; quality-of-life; survival.

Introduction:

Esthesioneuroblastoma (ENB) is a rare malignant neoplasm of the olfactory fossa, presumed to originate from the olfactory epithelium. In 1924, Berger et al first described the lesion and named it "esthésioneuroépithéliome olfactif" [1]. The two common terms used in recent publications are esthesioneuroblastoma and olfactory neuroblastoma. There are myriad opinions about its origin, diagnosis, and management as it has some peculiar qualities such as varying biological activity and quite easily mistaken for other nasal neoplasms. Kadish et al were the first to propose a staging classification, of three categories, for ENB[2].The simplicity of this staging system led to few controversies which were duly noted and addressed by Morita et al [3] in the modified Kadish staging system and later on incorporated into the more elaborate TNM system[4]. The clinical and radiological staging can be done easily now-a-days with computed tomography (CT) and magnetic resonance imaging (MRI), making it effective in assessing the anatomical extent of disease.

ENB constitutes around 3% of all intranasal neoplasms [5]. It manifests across all ages with peaks of presentation around the 2nd or 6th decade of life [6]. As the lesion has a lot of space to expand (within nasal cavities and paranasal sinuses), it usually presents at various stages of advancement. This makes monotherapies such as surgery / radiotherapy / chemotherapy very ineffective in curing the disease.

Leaving the controversies aside, looking primarily into the natural course of the neoplasm, there have not been many studies looking into the impact it has on the quality-of-life of the affected individual. This study aims to define the disease in terms of prognostic factors and quality-of-life parameters.

Aims & Objectives:

1. To study and compare Quality-of-Life measures in patients diagnosed with olfactory neuroblastoma.
2. To study survival functions.

Materials and methods:

Patient characteristics - A total number of 23 cases treated at our hospital from Jan 2011 to Jan 2018, were included in our study. Demographics tabulated. They underwent a thorough pre-treatment examination and were enrolled if they had conclusive tissue diagnosis of Esthesioneuroblastoma (ENB). The cohort comprised of 13 females and 10 males. The age range was 17 to 52 years. 6 patients presented with neck nodes. 1 patient with skull-base metastases was observed at initial referral.

Selection Criteria – Histopathology proven ENB with no previous intervention, no history of previous malignancy, and no history of 2nd primary tumor. Study type – Prospective, cohort study, single-blinded. Institutional Review board and Ethical committee clearance obtained (SMC/IEC/2011/037). All candidates were counselled by psychiatrist and nutritionist. Written informed consent was obtained from participants acknowledging the state of the disease and treatment options available.

Clinical features - Ranged from slow indolent growth to a very highly aggressive neoplasm with rapid widespread metastasis resulting in variable prognosis. Common symptoms include unilateral nasal obstruction, epistaxis, and change in sense of smell, anosmia, headache, facial distortion, visual changes and neck swelling. Local spread of tumor via skull base foramen can present as proptosis, cranial nerve palsies, seizures, etc. Overall denominator for the symptoms which was cause for OPD presentation was epistaxis.

Using radiological assessment, Modified Kadish [3] and TNM staging [4] systems were used for patient classification. Follow up period planned was for 5 years or the survival of the patient from primary treatment till demise - monthly once for first 6 months; once every 2 months for next 6 months; once every 3 months for next 12 months and once every 6 months for next 36 months. Survival rates were calculated accordingly. Hyam's histological grading was used in all patients.

Patients were on age-dependent treatment regime / care / diet. All patients had surgical debulking with neurosurgical supervision and post-operative chemo-radiotherapy. Radiotherapy was intensity-modulated. Node positive patients underwent neck dissection. The radiation dose was maintained on an average of 63 – 66 Grays. Chemotherapy regimen were standard [7,8].

Pre-Treatment and 1 year post-treatment follow-up questionnaire - EORTC QLQ-C30 (version 3) [9]was used for assessment of quality-of-life.Proforma with EORTC-CLC-Q30 (version 3) questionnaire was attached to each patient's file for data reference during follow up. The questionnaire was filled by the patient themselves or proxy-filled by the care givers. The values were auto-downgraded if the patient succumbed to the disease. Statistical analyses used – paired t-test and Kaplan-Meier test. Data were tabulated in a spreadsheet for basic calculations and averages. Categorical data and continuous data were expressed as number (percent %) and mean (± standard deviation) respectively. IBM SPSS (SPSS for Windows, v22, SPSS Inc., Chicago, Illinois) was the software used for statistical analysis. p value <0.05 was considered statistically significant.

Observation and Results:

Demographics:

Sample size (n) = 23. Age distribution (**Fig. 1**) shows a range from 17 to 52 years (mean 36.5 ± 7.69 years).The cohort comprised of 13 females and 10 males, (M: F-1: 1.3). The common clinical presentation requiring referral to ENT OPD was epistaxis. Neck node and metastasis status are also depicted (**Fig, 2**).

Modified Kadish staging was Stage A - 0, Stage B – 13 (56.5%), Stage C – 9 (39.12%) and Stage D – 1 (4.35%) (**Fig. 3**). TNM staging was T1 – 13 (56.5%), T2 – 9 (39.12%), T3 – 1 (4.35%) and T4 – 0; N0 – 17 (73.91%), N1 – 6 (26.09%); M0 – 22 (95.65%), M1 – 1 (4.35%) (**Fig. 3**). Hyam's histological grading was Grade I – 2 (8.7%), Grade II – 10 (43.48%), Grade III – 11 (47.83%) and Grade IV – 0 (**Fig. 4**).

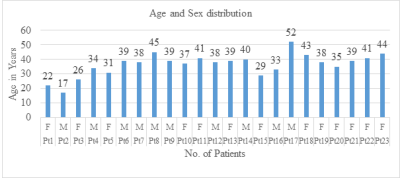

Figure 1. Age and sex distribution

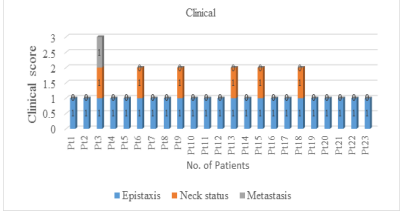

Figure 2. Clinical presentation

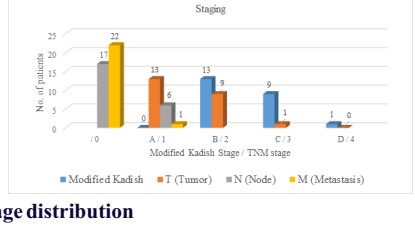

Figure 3. Stage distribution

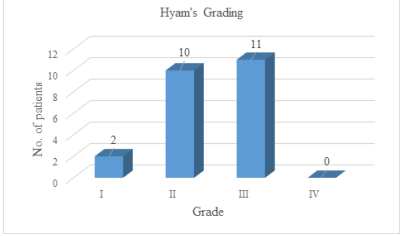

Figure 4. Hyam's grading

EORTC

Overall quality of life measures assessed at 1 year post-treatment follow-up showed a definite and statistically significant improvement over initial presentation. The QOL values were below significance for 4 patients (p = 0.546, 0.163, 0.536, and 0.463) (Fig. 5). This change between overall and individual QOL analysis was largely due to psychiatric affect once the patients became aware of the lesion/diagnosis. Other contributing factors are later discussed. It was observed during the course of our study that though much effort was put into counselling, the initial diagnosis of ENB had a huge bearing on the individual's QOL. The Total pre- and post- treatment EORTC values were 1908 and 1367 respectively. The average pre- and post-treatment EORTC values were 82.96 and 59.43 respectively.

Paired Samples Test							
Patient data expressed as Patient No. _ Pre-treatment – Post-treatment [(PTn_PRE – PTn_POST), n = Patient No.		Paired Differences					Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		
					Lower	Upper	
PT 3	PT3_PRE - PT3_POST	.133	1.196	.218	-.313	.580	.546
PT 13	PT13_PRE - PT3_POST	-.300	1.149	.210	-.729	.129	.163
PT 18	PT18_PRE - PT18_POST	.133	1.167	.213	-.302	.569	.536
PT 22	PT23_PRE - PT23_POST	.200	1.472	.269	-.349	.749	.463
Others	PRE – POST	.882	1.636	.299	.271	1.494	< 0.05

Figure 5. Paired t-test

Kaplan-Meier survival analysis was done (Fig. 6and Fig. 7). Figure 6 shows time of loco-regional recurrence / distant metastasis. 8 patients developed local/skull base (n=5, 21.74%) or distant metastasis (n=3, 13.04%) during follow-up period (after 1 year of treatment completion). The timeline of metastasis development and progression of disease was within 15 – 29 months with an average period of 22 months after completion of primary treatment. Recurrence rate was 34.78%. 5 patients (21.74%) underwent salvage surgery. However, 4 patients succumbed to the disease. Mortality rate was 17.39%. Figure 7 shows occurrence of events / post-treatment morbidities which required admission along with survival characteristics.

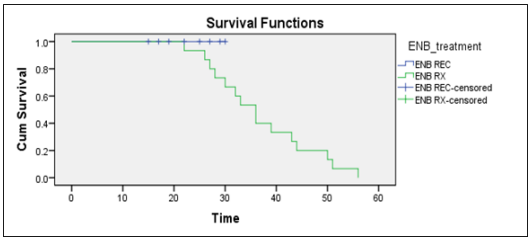

Figure 6 . Survival outcome of 23 Esthesioneuroblastoma patients. ENB - Esthesioneuroblastoma. REC - recurrence. RX - no recurrence.

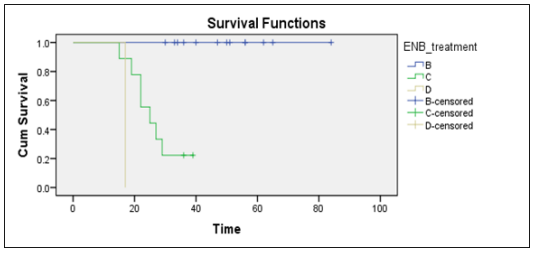

Figure 7. Survival curve with events for each Modified Kadish stage (B, C, D). ENB - Esthesioneuroblastoma.

Discussion:

Sample size (n) = 23. Other studies conducted on ENB had a sample size from n = 9[10] to n = 187[11]. Age distribution (**Fig. 1**) shows a range from 17 to 52 years (mean 36.5 years). Study by Wade et al [12] also showed a bimodal distribution whereas a study by Jethanamest et al [13]

showed a unimodal distribution. The cohort comprised of 13 females and 10 males, (F: M-1.3:1) showing a female preponderance. Similar study showed a ratio of F: M-1.5:1. The common clinical presentation requiring referral to ENT OPD were epistaxis and unilateral nasal block which were documented in most other studies [14,15].

6 patients (26.09%) had significant level II and level V neck nodes at initial presentation. Study by Tajudeen et al [16] documented that node positive skull base lesions had poor prognosis. Similar conclusions were derived from this study. Of the 6 patients, 1 patient had both positive neck status and skull base metastasis at initial presentation. All six had advanced clinical presentations with poor general condition. These patients were on intense nutritional care and were also advised chemo-radiotherapy. A study of 5 recurrent olfactory neuroblastoma by Wade et al [12] showed intermediate response to chemotherapy. The responses in our cohort were similar.

Modified Kadish staging and TNM staging was done (**Fig. 3**). The higher the staging, poorer was the individual outcome. Study by Sakata et al documented 3 cases with metastasis [17]. Hyam's histological grading was done (**Fig. 4**) which again echoed the findings of staging systems – higher the grade, poorer was the prognosis [7].

Currently, plan for treatment were done on an observed survival advantage with multimodality therapy [18]. Surgery to the primary site was favoured as the first line treatment with adjuvant radiation next in line [19]. The reported incidence of neck recurrence in ENB patients varies widely in the literature with reports ranging from 15–33% [14–17].

These rates may vary based on patient cohort and analysis methodology. Studies not using the Kaplan-Meier method to quantify recurrence rate will tend to underestimate the true incidence. In our series, the incidence of neck node at presentation was low (n=1, 4.3%), as anticipated. The incidence of subsequent recurrence in the initially N0 neck was 21.47% (n=5).

EORTC – QLQ C30 (version 3) [9]Quality-of-Life questionnaire scores were computed. Comparison between pre- and post- treatment showed mean pre-score was 2.87 (± 0.263), post-score was 2.14 (± 0.57). Paired t-test provided a p-value of **< 0.05** in 19 patients which showed that QOL improvement was statistically significant. The p-value **(>0.05)** in other 4 patients showed no statistically significant improvement – possibly due to skull base metastasis, poor nutritional status, reduced general care.

Loss of dentition, xerosis, mucositis, alopecia, nausea, vomiting, myalgia, gastro-intestinal upset, visual disturbances, dyspnoea, and dysphagia were common complaints encountered. Morbidity rate was high (n=18, 78.26%). Survival Analysis showed Overall Disease-free survival rate to be 82.61% at 5 years. This rate was in moderation as compared to other centres [10,18]. 19 patients were long term survivors.
Limitations:

A larger sample size would definitely help in better assessment of QOL. Comparison of treatment with / without prophylactic neck dissection can help in deciding on better loco-regional control of the disease.

Conclusion:

Best QOL noted in patients presenting at early stages. Survival rates may enhance if aggressive initial intervention is done. Psychological and nutritional assessment of the patient and counselling to the patient and their care-givers are a must. Disease surveillance in post-treatment candidates will likely identify recurrences early. Standardised staging and grading will tremendously help in comparing outcomes across global centres.

Declaration of interest: None
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