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OUTCOMES OF LOCALLY ADVANCED RETROMOLAR TRIGONE CANCERS TREATED WITH A MULTIMODALITY APPROACH.

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Abstract: Our objective is to review the current articles pertaining to multimodality treatment that surround the management of retromolar trigone (RMT) cancer patients. RMT tumors constitute a small minority of all oral cancers. Majority of these patients present with locally advanced stage and its treatment is challenging. Good oncologic outcomes can be achieved by advocating an aggressive surgical approach in combination with post operative radiation therapy. In this literature review we intend to discuss locally advanced trigone cancer and its outcome after the completion of the multimodality treatment.

INTRODUCTION

The retromolar trigone (RMT) is a small but complex sub-site of the oral cavity surrounded by vital anatomical areas. RMT is a relatively rare sub-site for oral cancer. The most frequent type of RMT tumor is squamous cell carcinoma. RMT Cancers have an aggressive biologic behavior due to predilection for early bone invasion, perineural and lymphatic spread and infratemporal fossa (ITF) invasion. In view of the rarity of the tumor and heterogeneity of treatment, there is limited literature available pertaining to RMT tumors. Various treatment

modalities have been tried in the past including surgery, radiotherapy and combination therapy using chemoradiation.¹⁻⁴

There is limited literature of the use of systematic combination therapy (surgery and radiation therapy) in the treatment of locally advanced RMT cancer. Moreover, there is controversy regarding the extent of surgery. Some advocate a radical surgical approach for every patient where as some groups advocated a more limited surgical approach. Our objective is to review the literature, discuss the current controversies and the present recent trends of

systematic combination therapy in the management of locally advanced RMT cancer.

METHODS AND MATERIALS

According to pubmed article abstracts published from 1959 to June 2015, a search with these key-words was done-

- a- “squamous cell carcinoma” (medical subject heading, or MeSH), “retromolar trigone”
- b- “oral” (MeSH), “survival” (MeSH)
- c- “retrospective studies” (MeSH)
- d- “treatment”(MeSH), “surgery” (MeSH), “radiotherapy” (MeSH),
- e- “combined modality therapy(MeSH).

Among these, articles with the below inclusion criteria were selected:

- 1- Randomized clinical studies, series and reviews
- 2- Histologic findings of squamous cell carcinoma as the major diagnostic factor
- 3- Tumor origin in the retromolar trigone area
- 4- Locally advanced tumors with no distant metastasis

RESULTS

There were 388 articles which could be identified from the initial search criteria. After reading and evaluating the abstracts, articles not fulfilling the inclusion criteria were ignored. Finally, just fifteen articles pertaining to retromolar trigone cancers were available for review.

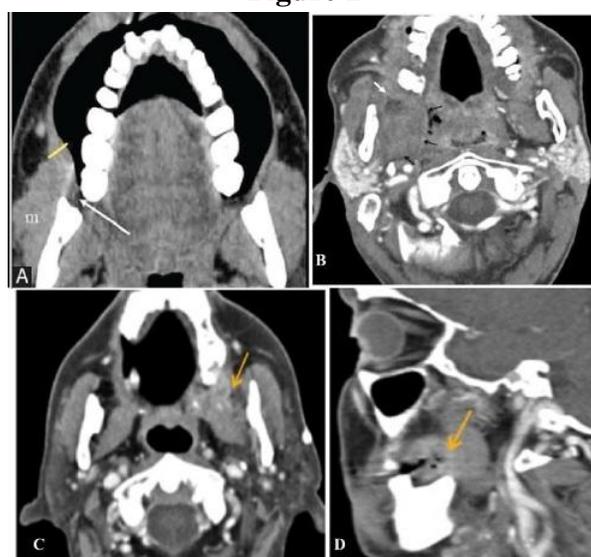
DISCUSSION

Retromolar trigone cancer is rare, aggressive malignancy with an incidence varying between 15% to 26% of all squamous cell carcinoma involving the oral cavity.¹⁻³ RMT is a relatively small anatomical sub-site in the oral cavity and some series have also included patients with secondary involvement of RMT from tumors arising from adjoining areas like tonsillar pillar and buccal mucosa.³⁻⁶ As there are petite reports of the disease in literature, most previously published studies have included both

early and locally advanced tumors together for survival analysis.^{2,7-9} In the current review, only cancers arising from RMT were included. In addition only patients with stage III & IVa were included in the current review and the results compared only in the patients having received combination therapy.

Various imaging modalities can be used for mandibular assessment in oral cancer. CT scan (Figure 1) is one of the commonest modalities used and variable results of accuracy have been reported in literature.^{3,10-12}

Figure 1



Weisberger et al, found that 33% of the patients with histologically proven bone infiltration showed no radiological signs of bone invasion.¹⁰ In the review by Tsue et al, 34% (11 of 32) mandibular specimen demonstrated cancerous involvement which was not detected radiologically.¹¹ Lane et al, in his series of 26 patients reported 50% sensitivity, 91% specificity and 61.1% negative predictive value of CT detecting mandibular invasion.¹² In the series by Deo et al, three of 20 histologically bone involvement showed no radiological signs of bone involvement.¹³ Deo et al reported 50% sensitivity, 61.4% specificity and 76.7% negative predictive value of CT for bone involvement in

RMT cancers. The low sensitivity and negative predictive value of CT for bone involvement in RMT cancers predicts that half of the patients can still present with histologic bone invasion despite no radiologic sign of bone invasion. The possible explanation of these suboptimal results may be - the thick section studies (>5mm) and the deficiency of high resolution bone algorithm on the retromolar trigone region.¹²

Magnetic Resonance Imaging (MRI) is relatively expensive but important tool in assessing surrounding structures including mandible. In a retrospective study by Crecco et al, the results of MRI and pathological data were compared for 22 patients with RMT cancers.¹⁴ MRI appeared to be highly accurate in assessing the infratemporal involvement. In assessing the involvement of the surrounding structures, MRI showed high accuracy, specificity and sensitivity (>90%). In assessing bone marrow invasion, the sensitivity was 100% but the specificity was 77%. But pertaining to cortical bone involvement, accuracy of MRI was similar to that seen by CT scan.

As far as bone involvement is concerned, Kowalsky et al reported pathological mandibular involvement in 14% of 114 patients undergoing hemimandibulectomy.⁷ Hao et al documented maxillary and mandibular involvement in 22% and 18% of RMT tumor patients undergoing mandibular resection.¹⁵ Deo et al documented pathologically mandibular and maxillary involvement of 47.6 % and 11.9% respectively, probably due to a large number of locally advanced patients included in their analysis.¹³

To date, no clear uniform guidelines have been proposed for the treatment of RMT cancers because of the rarity of RMT tumors and the retrospective nature of majority of the studies. We found only 15 studies on RMT cancer treatment published in the English-language literature between 1959 and 2013. Ayad et al in

his major review showed that there was a significant heterogeneity as far as treatment policies were concerned.³ Some of the studies favored surgery^{1,16} whereas others have tried radiation therapy as primary treatment.^{4,17} Combination treatment (surgery with adjuvant radiotherapy) was also tried in some RMT series.^{2,7-9,13,15-16} Since, the patient & tumor characteristics and the treatment modalities used in most of these studies were not uniform, the reported outcomes were not comparable. Only in the study by Deo et al, there was uniformity in patient population and treatment protocols.¹³ The cause specific survival was not mentioned in 5 of these studies^{1,6,7,18-19} whereas in other studies the cause specific survival was not comparable because analysis was done using the T stage in few studies and stage grouping in others.^{2,7-9,15} The present work reviews all the studies with locally advanced RMT cancer patients receiving combination therapy (surgery with adjuvant radiotherapy).

There is great debate pertaining to the extent of surgery in RMT tumors. This is mainly due to the low sensitivity of radiological tests for detecting bone involvement. Because RMT cancers lie directly on the anterior ramus of the mandible, bone resection must be routinely considered even if there is no gross bone invasion. Some groups have advocated limited mandibular resection including marginal²⁰ and segmental mandibulectomy^{9,15} whereas others have advocated radical resections like hemimandibulectomy.^{7,13,16} In advanced RMT cancers, extensive resection such as hemimandibulectomy with en-bloc infratemporal clearance (Figure 2) is crucial in achieving oncologically clearance.

Figure 2

In 1959, Barbosa reported “the retromolar operation” an original procedure consisting of a hemimandibulectomy with “en bloc” infratemoral clearance that includes resection of the pterygoid and masseter muscles and ipsilateral radical neck dissection.¹⁶ His initial study compared 10 patients surgically treated to 11 treated by radiation therapy. Even though surgery was favored as the most adequate treatment for RMT cancer, one must hold back from finalizing the study results. In his study the fact that the patients had short duration of follow-up (less than 2 years), the small number of patients in each group and the evolution of radiation therapy since 1959 restrained in arriving at a definitive conclusions. Still, Barbosa has the merit to be the first to specifically assess the effectiveness of different treatment modalities for this small subsite of the oral cavity and emphasize the importance of the retromolar operation.¹⁶ In both the series, Barbosa concluded that surgery is superior to radiation therapy.^{16,21}

Kowalski et al reviewed their experience on hemimandibulectomy with ITF clearance in

114 patients with RMT tumors and documented a local control of 72.8%. Thereby the author concluded that a more extensive resection is appropriate in patients with RMT tumors to achieve an oncological cure.⁷

Contrary to Kowalski, Hao et al emphasized on conservative bone resection. Marginal mandibulectomy was performed in patients having tumor abutting the mandible clinically; whereas segmental mandibulectomy was done in cases whose mandible was found involved radiologically. Mandible bone infiltration was seen in 2 of 18 patients who underwent marginal mandibulectomy and 7 of 12 patients who underwent segmental mandibulectomy in his series. The local control was achieved in 82% of the patients.¹⁵

Deo et al had used the standard retromolar operation in all their 42 patients of locally advanced retromolar cancer. Margin negative resection despite the ablative surgery was achieved in 93% patients. The local control after median follow-up of twenty months was achieved in 90.5% of the patients.¹³

Pascoal et al compared results in stage IV tonsillar and RMT cancer patients who underwent a marginal mandibulectomy (n=20) to those who underwent segmental mandibulectomy (n=22). The patients had locally advanced disease without clinical or radiographic evidence of bone invasion. Twenty-eight patients (66.7%) were staged IVa and fourteen patients (33.3%) were staged IVb. All the patients received postoperative radiotherapy. Local and regional recurrence was observed in 35% patients of marginal mandibulectomy group, and 36.4% of segmental mandibulectomy group. Though the series has grouped RMT cancers and tonsillar cancers together, study concluded that conservative approach is not favored in locally advanced RMT cancers.²²

Presence of regional nodal metastasis to the neck is a bad prognostic factor not only in RMT tumors but also in majority of head neck squamous cell carcinomas. Different series have reported pathological lymph nodal involvement ranging between 26% to 80% in patients with RMT tumor.^{1,3,6,15} A comprehensive neck dissection is a must in all the patients of locally advanced RMT cancers. In the exclusive series of locally advanced RMT cancers by Deo et al pathological nodal metastasis was seen in only 54.7 % of the patients mostly involving level I and II nodes.¹³ Rest of the series had included both the early and advanced staged RMT cancer patients.^{1,2,7,15}

In patients with unfavourable pathological features, postoperative radiotherapy (PORT) or postoperative concurrent chemo-radiotherapy (POCRT) has been shown to improve locoregional control and survival.²³⁻²⁴ General indications for PORT include- T3 or T4 tumor, compromised surgical resection margins (<5mm inked margin), presence of lymphovascular invasion and/ or perineural invasion, positive lymph node invasion with or without extracapsular invasion.

Hitchcock et al in a series of 76 patients showed that patients who received combined

therapy (Surgery and Radiotherapy) had cause specific survival of 82% for stage I-III and 43% for stage IV.²⁵ Deo et al in 42 patients, who received postoperative external beam radiotherapy of 60-62 greys in 30-32 fractions, reported 5 year disease free survival of 64% and overall survival of 71%.¹³ Mendenhall et al concluded that the probability of cure is influenced by the extent of disease and treatment modality favoring the combined therapy. In his series radiotherapy dose was based on the margin status: 60-65 Gy for negative margins, 65-70 Gy for microscopic margins and 70-75 Gy for patient with macroscopic residual disease after surgical resection. The author reported 5 year loco-regional control of 71% albeit seventeen recurrences.⁸

As far as survival is concerned, nodal involvement has emerged as an adverse prognostic factor. Different series have reported 5-year survival of 47% to 60% in pathological node positive patients.^{2,7,9,15} Survival results (Table 1) indicate that by adopting an aggressive and uniform treatment policy good out comes can be achieved in locally advanced RMT tumors which are otherwise difficult to treat.

Table 1- Represents the survival outcome of patients of locally advanced retromolar trigone cancer reported in different series

Author	Total number patients	Number patients receiving combined therapy	Stage Distribution	Primary surgical profile	Recurrence	5 year disease free survival (DFS)	5 year Overall survival
Kowalski et al 1993[7]	114	66(All N+ and margin positive patients)	I-3 II- 20 III – 28 IV- 48 N+ 65	Hemi mandibulectomy with ITF clearance	41/114 patients with 50 recurrence	T3- 34.5% T4-65.2% N0 – 59.5% N+ 54.9%	T3- 46.5% T4-65.2% N0-62.9% N+ 58.8%
Huang et al 2001[2]	65	27	I- 10 II-9 III – 10 IV- 20 N+ - 36	Not mentioned	III – 2 IV- 8 N+-10	T3- 72% T4-54% N0- 69% N+ 56%	Not Mentioned
Mendenhall et al 2005[8]	72	53	I-2 II-9	Not mentioned	Locoregional recurrence	I-III -87% IV- 62%	I-III -72% IV – 45%

			III – 14 IV – 39 (includes one pt with IV _B)		I-III – 3/25 IV – 14/39 Local recurrence T4- 11/33		
Hao et al 2006[15]	50	23	I-6 II-13 III – 4 IV – 27 N+ 13	Segmental 12 Marginal 18	18	III -75% IV -43.6%	Not mentioned
Binahmed et al 2007[9]	41	15	I-8 II-25 III – 12 IV – 29	Segmental-22 Marginal -10	28/41	III-56% IV- 38% N0-55% N+ 47.5%	51.4%
Deo et al 2012[13]	42	42	III – 5 IV – 37 N+ 23	Hemimandibulectomy with ITF clearance	10	DFS 66% N0 – 89% N+ 60%	74%

CONCLUSION

RMT tumors constitute a small minority of all oral cancers and the available literature is limited, mostly retrospective and heterogeneous. Because of inaccessibility, great mobility and close skeletal relations, the retromolar area offers poor prospects for oncological treatment.

In sight of the complex anatomy, high propensity for mandibular invasion and difficulty in treating infra temporal fossa

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