MANAGEMENT STRATEGY FOR RECURRENT HEAD AND NECK CANCER FOLLOWING CHEMORADIATION AND CHALLENGES IN DECISION MAKING FOR SURGICAL SALVAGE OF LOCO-REGIONAL DISEASE

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ABSTRACT
Background: Advanced head and neck cancers are often treated with Chemo-radiation (CT-RT) in an attempt for organ preservation. Loco regional failure following CT-RT is a major challenge for surgical salvage especially in the neck which constitutes bulk of the cases.

Aim: To determine the salvage strategy for the management of post CT-RT recurrent squamous cell carcinoma of head and neck region with emphasis on the role of salvage neck dissection with its complications.

Methods: This is a retrospective analysis of 105 cases with post CT-RT recurrent cancer of head and neck from 2005 to 2014. Patients were divided into three groups based on the site of recurrence; primary only (I), primary with neck (II) and only neck (III). Imaging was done in all cases. Surgical salvage was performed in all patients. The specimens were assessed for any perineural, peri-vascular, dermal and muscle spread. 3 patients received re-irradiation after 1 year.

Results: 36 cases in group I, 28 cases in group II and 41 cases in group III. 1 year disease specific survival rate was calculated using Kaplan Meier and data analyzed with STATA 13. It was 83.84% for group-I, 56.25% for group II and 60.8% for group III. Patients in group II and III performed poorly. Extra-capsular spread, muscle invasion, peri-vascular involvement, peri-neural spread and dermal spread was assessed after salvage surgery.

Conclusions: Post CT-RT patients always have a poor prognosis and especially when associated with neck recurrence.

Keywords: chemo-radiation, salvage surgery, neck dissection.
The neck is usually tackled in 3 ways:

1. Observation and strict follow up in patients who show a complete or near-complete response to treatment and have a negative positron emission tomography (PET) scan.

2. Planned neck dissection within 6 weeks of CT-RT

3. Salvage neck dissection in all clinically and radiologically positive neck cases.

The site of the primary tumor and its extent is also an important factor influencing therapeutic decision-making. Metastatic nodal disease from tumors of certain sites like the nasopharynx, tongue base, tonsil are said to be exclusively sensitive to radiation therapy with good locoregional control rates. A planned neck dissection following complete response to CT-RT may not be particularly beneficial in these patients with these tumors. Hence, a salvage neck dissection in those with recurrence is a better accepted approach.

The response of the primary tumor to CT-RT also varies depending on the site of involvement. Decision making for the treatment of primary and neck plays a pivotal role in the overall survival of patient, quality of life and early rehabilitation and return to normal activities.

**MATERIALS AND METHODS:**

We have enrolled 105 patients with squamous cell carcinoma of various sites of head and neck (Table-1) for a retrospective observational study spanning over a period of 9 years from January 2005 to December 2014. All the patients had received concurrent CT-RT as the primary modality of treatment. The patients were divided into three groups based on the site of recurrence: primary site only, primary site with neck recurrence and cases with only neck recurrence during their follow up period. Average follow up period for each group was about 22, 13 and 15 months respectively.

Amongst the 105 cases, 36 cases (34.20%) had recurrence only at primary site, 28 cases (24.76%) were with recurrence at primary site along with neck nodes and 41 cases (39.04%) showed only neck disease. All the patients were examined thoroughly with rigid/flexible endoscopy and biopsy along with CT/MRI. Ultrasound guided FNAC for suspected neck disease. PET-CT was performed by only 17 cases (Fig-1) due to financial constraints among the patients under study. Distant metastasis was also evaluated pre operatively and during their follow up. 13 patients showed radiological evidence of distant spread during their post operation period.

<table>
<thead>
<tr>
<th>PRIMARY SITES</th>
<th>NUMBER OF CASES (%)</th>
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<tbody>
<tr>
<td>Supra glottis</td>
<td>18 (17.1%)</td>
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<tr>
<td>Glottis</td>
<td>16 (15.2%)</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>24 (22.8%)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>19 (18.1%)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>16 (15.2%)</td>
</tr>
<tr>
<td>MUP</td>
<td>07 (0.6%)</td>
</tr>
<tr>
<td>Nose and paranasal sinus</td>
<td>05 (0.3%)</td>
</tr>
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Table-2: Showing the primary sites.
treatment follow up period. Neck recurrences were detected in all ‘N’ stages and were managed appropriately. Patients presented as unilateral (62.3%) or bilateral (37.7%) neck disease in the following manner.

A comprehensive neck dissection was performed in all the patients depending on the primary site and extent of neck recurrence with relation to pre-treatment findings (Table-3). Modified/Radical neck dissection was performed in all N positive cases. The management of neck is illustrated in (Table-4).

Figur2: Showing N staging of pre-treatment neck.

The resected specimens were assessed meticulously for any perineural, perivascular, dermal and myogenic invasion which had a direct impact on the survival of the patient. Primary sites of recurrence were surgically resected with a healthy margin to provide R0 clearance. It comprised of different approaches to surgical resection which included Trans-oral laser assisted resection (TOLR), hemi-mandibulectomy with partial maxillectomy (HAPMX), near-total laryngectomy (NTL) total laryngectomy with partial pharyngectomy (TL + PP), total laryngo-pharyngo-esophagectomy (TLPE) with gastric transposition (GT) and craniofacial resection (CFR). (Fig-2)

Table 5: shows the number of cases in each group

<table>
<thead>
<tr>
<th>SURGERY PERFORMED AT PRIMARY</th>
<th>NUMBER OF CASES</th>
</tr>
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<tbody>
<tr>
<td>TOLR</td>
<td>22</td>
</tr>
<tr>
<td>HAPMX</td>
<td>9</td>
</tr>
<tr>
<td>NTL</td>
<td>2</td>
</tr>
<tr>
<td>TL + PP</td>
<td>18</td>
</tr>
<tr>
<td>TLPE + GT</td>
<td>8</td>
</tr>
<tr>
<td>CFR</td>
<td>1</td>
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</tbody>
</table>

Patients with Kornofsky score of >80 and ECOG score >3 are said to better tolerate the treatment modalities. 3 of our patients were having Kornofsky grade of <80 while rest were in the above 80 group. 2 cases were above 70 years of age. 4 cases were found to continue smoking and 3 with persistent gutka chewing during their follow up. 3 patients with suspicious positive margin received re-irradiation at 14 months, 16 months and 19 months post primary radiation following the recent guidelines. Patients with oncologically unresectable primary, pre operative distant metastasis, those unfit or unwilling for surgery were excluded from the study and treated with palliative chemotherapy and supportive care. The cases are being followed up in a regular manner to assess the quality of life and re-recurrences.

RESULTS

In our retrospective study, we analyzed 105 clinically and radiologically proven cases of post CT-RT recurrent head and neck squamous cell carcinoma and found 36 cases (34.20%) with recurrence only at primary, 28 cases (24.76%) with recurrence at primary site along with neck nodes and 41 cases (39.04%) with only neck nodal disease. Average follow up period for each group was about 22, 13 and 15 months respectively. Surgical salvage was performed in all patients the extent
of which depended on the post-treatment status of primary and neck disease.

All the cases which were followed up for 1 year were considered separately to calculate the 1 year disease specific survival rate. It was found to be 83.84% for isolated primary recurrence, 56.25% for primary and neck recurrence and 60.8% for neck disease using Kaplan Meier scale. Patients with neck nodal recurrence performed poorly than those with only primary recurrence with respect to survival and quality of life. The mean survival time obtained for group I: 44.87 months, group II: 20 months, group III: 25 months. Using the combined graph, there is difference in survival functions between the 3 groups. Log rank test was performed p = 0.0017 (figure 3).

Table 6: Histopathological analysis of resected specimens.

<table>
<thead>
<tr>
<th>HPE STATUS OF PRIMARY + NODES</th>
<th>NO. OF CASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>No capsular involvement</td>
<td>17 (24.6%)</td>
</tr>
<tr>
<td>Extra-capsular</td>
<td>34 (49.2%)</td>
</tr>
<tr>
<td>Muscular</td>
<td>08 (11.5%)</td>
</tr>
<tr>
<td>Perivascular</td>
<td>06 (8.6%)</td>
</tr>
<tr>
<td>Perineural</td>
<td>09 (13%)</td>
</tr>
<tr>
<td>Dermal</td>
<td>02 (2.9%)</td>
</tr>
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During follow up, careful clinical examination, biochemical and radiologic investigations were performed keeping the probable sites of metastasis in mind. Distant metastasis to lungs (7 cases), bone (3 cases), Skin (1 Case), spine and liver (2 cases each) were found during the follow up period. Neck recurrences were
carefully evaluated and staged as per UICC 2010 guide lines and were managed with comprehensive neck dissection. The surgical complications include carotid blow out (1 case) during the first week after surgery, mucositis and dysphagia (12 cases), skin hyper pigmentation (7 cases), neck swelling/hematoma (4 cases), chyle leak (4 cases) and 3 cases of pharyngo-cutaneous fistula and 2 cases of osteoradionecrosis of mandible. 3 deaths were noted, one due to carotid blowout and 2 due to non-cancer causes and details were not available. Viable tumor was higher in patients who had a less-than-complete response to CT-RT compared with those who had a complete response. Better survival rates were observed in cases with negative neck disease. The cases are being followed up and the survival rates and prognosis of the patients are being further contemplated.

**DISCUSSION:**

The management of post CT-RT recurrence depends on the early detection by vigilant diagnostic methods and keen methodical clinical judgment. There is no universally accepted diagnostic technique which has high sensitivity and specificity for detection of persistent nodal disease after concurrent chemoradiation. Post-treatment changes obscure accurate clinical judgment. Anatomical diagnostic imaging techniques such as CT, MRI, and Ultrasonography, all fall short of consistently and accurately demonstrating persistent or recurrent tumor following chemotherapy and radiation. One has to be precise in taking biopsy specimens in a previously treated area since large number of false negative cases result due to sampling error owing to lack of a proper demarcation between normal and tumor tissue. The benefit with less invasive biopsy techniques such as fine-needle aspiration may be even more doubtful since a specimen interpreted as negative for malignancy may still harbour viable tumor. Previous studies by Wang et al, Lavertu et al have demonstrated the inadequacy in evaluation of tumor response by clinical examination and other diagnostic techniques. The discrepancy existing between observed clinical response and histological assessment of tumor persistence is mainly due to our present inability to distinguish viable tumor cells from tumor tissue by routine sectioning and hematoxylin-and-eosin staining. Hence, a better way of identifying patients with residual disease who would benefit from a neck dissection is the need of the hour.

PET-CT is a recent diagnostic modality with better sensitivity for the detection of recurrence. It involves assessment by functional imaging with 18-Fluorodeoxyglucose (FDG) whose uptake is a detrimental in differentiating tumor from viable tissue. It has been shown to correlate with clinical response to concurrent CT-RT before, during, and after therapy. Wong et al reviewed 143 patients with previously treated head and neck squamous cell carcinoma who underwent FDG-PET scan to detect recurrent disease and found this to be a highly sensitive method with a 96% and 72% sensitivity and specificity, respectively. However, the specificity of PET-CT is low and number of false positive cases would be more during the immediate post-CT-RT period. Greven et al evaluated 45 patients with head and neck cancer by FDG-PET scan before radiotherapy and serially after radiotherapy at 1, 4, 12, and 24 months after radiotherapy and concluded that at 1 month post-radiotherapy, the false-negative rate was 28%. The ideal time to perform FDG-PET scans for the evaluation of residual disease has yet to be determined, but seems to be between 1 and 4 months. Further prospective studies are necessary prior to the adoption of PET scanning as the gold standard evaluation of the neck following CT-RT. Owing to financial constraints; PET-CT was done for only 17 cases with the rest undergoing CT or MRI scan in this study.

Biologic markers such as NEU, HSP27, p53, ki-67, and GST may be useful in predicting nodal failure after chemoradiation. Given that anatomic imaging techniques are inferior in identifying residual neck disease, and that FDGPET is promising but lacks specificity in the post-treatment setting, new molecular diagnostic methods represent the future of optimal patient assessment. Biologic markers such as NEU, HSP27, p53, ki-67, and GST may be useful in predicting nodal failure after radical radiotherapy or CT-RT. Fortin et al found that the presence of NEU oncoprotein and the absence of HSP27 expression were associated with an increased rate of neck failure in patients treated with radiotherapy. These markers may predict the subgroup of patients who require post-treatment neck dissection. The combination of molecular markers with functional imaging would
expand the horizons in view of early clinical detection and thereby allowing significantly improved assessment of the post treated neck.

Neck dissection in a post-irradiated neck is challenging and the ultimate aim is to maximize the probability of achieving regional control. Patients with low-volume (N1) neck disease have very high rates of control in the neck. Risk of neck failure is steadily associated with increasing neck node stage and tumor burden. Parson et al reported better neck control rates in patients with N2 and N3 disease treated with radiotherapy followed by neck dissection than radiotherapy alone. With other studies as done by Dubrey et al, One can conclude that planned neck dissection contributes to neck control in unselected N2 and N3 patients treated with radiation or chemoradiation. Recurrent (rN1) disease has better prognostic outcome. Recurrent Neck staging (rN2-rN3 status) is an important prognostic indicator of poor survival with propensity for distant metastasis. Performance scale of patients is also detrimental to the overall wellbeing of the patient. Patients with Kornofsky score of >80 and ECOG score >3 are said to better tolerate the treatment modality. 3 of our patients were having Kornofsky grade of <80 while rest were in the above 80 group.

Several studies like the one by McHamm et al have shown that patients with a complete response to CT-RT clinically and radiologically may have microscopic residual disease in the neck which makes planned neck dissection a viable option. Similarly, Stenson et al analyzed 69 patients with advanced-stage head and neck cancer that underwent a neck dissection within 5 to 17 weeks of primary concurrent CT-RT of which 35% had microscopic residual disease that was not correlated with clinical or radiological response. Only one patient had recurrent disease in the neck after neck dissection, emphasizing the importance of neck dissection after CT-RT to remove residual viable tumor. Wanebo et al reported a series of 43 patients treated with concurrent CT-RT for advanced stage head and neck squamous cell carcinoma. A planned neck dissection was performed 3 to 4 weeks after the completion of CT-RT among patients with clinically N1-3 nodes prior to therapy, 9 (31%) of 29 had residual node involvement at neck dissection and none of these patients had failure in the neck. These studies suggested that neck dissection plays a vital role in optimizing tumor control in such group of cases. The presence of clinically positive nodal disease in neck dissection specimens after concurrent CT-RT has been found to correlate with neck recurrence and survival probability. Lavertu et al evaluated 53 patients with N2/3 necks who had planned neck dissections after concurrent CT-RT. He concluded that pathologically positive neck disease was associated with a worse survival in most of the studies. Some studies like Strasser et al suggested that many of the pathologically positive necks did not contain viable cancer cells and that continued cell kill occurs for several weeks or months after CT-RT. These findings reiterated the importance of timing of neck dissection and the interval between chemo-radiation and neck dissection because cell death continues to occur for many weeks following completion of treatment.

Recurrence at the primary site needs separate mention in management since the role of conservative laser assisted surgery is still controversial and is much dependent on the surgical expertise and accurate assessment of the extent of lesion. Radical procedures like hemi-mandibulectomy with partial maxillectomy, total laryngectomy with partial pharyngectomy, near total laryngectomy, total-laryngo-pharyngo-

Table 7: Guidelines for selection of patients

<table>
<thead>
<tr>
<th>CRITERIA FOR RESECTABILITY</th>
<th>CRITERIA FOR UNRESECTABILITY</th>
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<tr>
<td>Complete resection of tumor with negative margins</td>
<td>Unresectable disease extension</td>
</tr>
<tr>
<td>Patient fitness for major surgery and recovery</td>
<td>N3 fixed nodes to internal carotid artery and Vagus nerve</td>
</tr>
<tr>
<td>Good surgical expertise</td>
<td>Reconstruction is very morbid</td>
</tr>
<tr>
<td>Speech and swallowing morbidities acceptable to patient</td>
<td>Extensive infratemporal fossa involvement</td>
</tr>
<tr>
<td>Reconstruction with least morbidities</td>
<td>Patient not medically fit</td>
</tr>
<tr>
<td>Post-operative caretaker and counseling</td>
<td>Post-operative morbidity might reduce quality of life</td>
</tr>
<tr>
<td>No metastasis</td>
<td>Metastasis</td>
</tr>
</tbody>
</table>
esophagectomy with gastric transposition have all stood the test of time for recurrent primary tumors. We have performed laser assisted function preserving surgery in a total of 22 cases for malignancy glottis, supraglottis, oropharynx and hypopharynx with negative margins. Steiner et al provides literature on good results following laser assisted excision of primary in selected cases with better compliance.

Patients treated with CT-RT are at high risk of developing complications after neck dissection owing to poor local tissue healing capacity in irradiated neck, poor vascularity, prior positive node with extracapsular spread, adhesions to surrounding tissues, difficulty in detecting viable tissue from tumor tissue, pre-treatment micro-metastasis, CT-RT resistant clones. Common complication encountered after neck dissection in these patients are wound infection and dehiscence with fistula formation, bleeding and hematoma, chyle leak, sialadenitis, injury to major vessels and Spinal accessory nerve, Greater auricular nerve, Vagus nerve and cervical and brachial plexus with comorbidities. Early recognition with adequate conservative management techniques before surgical intervention should be routinely followed.

Re-irradiation as an additional modality of treatment is gaining grounds in recent times. We had 3 cases with positive margin on resection which were re-irradiated with 50 Gray (5 fractions per week) for 4-6 weeks at 14 weeks, 16 weeks and 19 weeks post-primary radiation respectively in accordance to the principle of not re-irradiating within 1 year of primary radiotherapy. The dosage of radiation depends on the tumor volume, type and amount of primary radiation exposure. The performance status of the host and comorbidities along with tumor factors play an important role in overall survival and response to treatment. It is generally advised to undertake re-irradiation at the center where initial radiation therapy was undertaken. IMRT has enabled use of higher targeted dosages while reducing the complications at the same time. Mucositis, hyper-pigmentation of skin and dysphagia are noted in 2 cases. No major complication noted in any of the 3 patients after re-irradiation.

CONCLUSION

The management of the clinically positive recurrence at primary and neck following CT-RT is a surgical challenge and requires adequate training and experience. Treatment of recurrent primary site lesion remains controversial, especially with high-volume nodal metastases. The role of imaging techniques such as FDG-PET scan, biomarkers and stringent follow up with a curious eye is mandatory in this setting. It is noted that cases with nodal recurrence with or without primary involvement have poorer survival rates and response to treatment than those with only primary recurrence. Re-irradiation +/- chemotherapy following salvage resection may improve disease free survival and locoregional control but not the overall survival. Considerable progress needs to be made in developing more reliable means of detecting recurrent disease in the treated neck and more reliable biologic markers of response to CT-RT are under research. Until our ability to predict and detect recurrence in the treated neck improves, it seems prudent to recommend a planned neck dissection for all patients treated with CT-RT for high-volume neck disease. Surgical resection of the recurrent primary site and neck disease needs expertise and vigilant post-operative care to identify the potential complications as early management can prevent a catastrophe.

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