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Original Article

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Abstract

Objective: To evaluate the prognostic significance of computerized tomography derived tumour volume for squamous cell cancers of the head and neck, treated primarily by surgery.

Methods: The retrospective review study comprised 72 patients with head and neck malignancies who were treated primarily by surgery at Aga Khan University Hospital, Karachi, with/without adjuvant. It was done from May 2007 to November 2008. Each patient was followed up for a minimum of one year to check for recurrence. For statistical analysis SPSS 17 was used. Frequencies, cross-tabulations with chi square tests to find associations, binary logistic regression analysis, Cox regression analysis and receiver operating characteristic curve tests were run on the data.

Results: Overall, the median tumour volume for patients with recurrent disease was 52cm³ compared to 22cm³ for those who did not have a recurrence. It was found that large tumour volume was associated with a significantly higher chance of recurrence ($p = 0.009$). Laryngeal cancers with volumes greater than 46cm³ and oral cancers with volumes greater than 23.1cm³ were associated with poor prognosis.

Conclusions: The primary tumour volume can represent an important prognostic factor for treatment outcome. Patients with larger primary tumour volumes should be treated more aggressively.

Keywords: Tumour volume, Head and neck Neoplasms, Cancer, Recurrence. (JPMA 62: 1129; 2012)

Introduction

Squamous cell cancer of the head and neck is common worldwide with a prevalence of 4% and 5% in USA and UK respectively.[1] In Pakistan it is the second most common malignancy in both males and females, after breast cancer in females and lung cancer in males.[2]

Smoking tobacco, drinking alcohol and having a poor diet are important known risk factors in the West. In the subcontinent, chewing betel or areca nuts, smoking bidis, and taking snuff are important risk factors.[1]

The prognosis of head and neck cancer depends largely on the stage of presentation, with the single most important factor being the presence of neck node metastases, which reduces long-term survival by 50%.[1] Recently, however, concerns have been expressed about the weakness of the TNM classification for several head and neck cancer sites, as the cure rates reported in the literature vary and prognosis is not sufficiently related to the TNM values.[3] Several later studies reported the primary tumour volume to be the important factor in determining the outcome of treatment in head and neck carcinomas.[4-8]

In this study we explored the prognostic significance of tumour volume on the outcome of patients with squamous cell carcinoma of the head and neck.

Methodology

The retrospective review was conducted from May 2007 to November 2008. All patients had to have biopsy-proven, previously untreated, squamous cell carcinoma of the oral cavity, hypopharynx or larynx; measurable or assessable disease; no synchronous primary tumours; and age > 18 years. Initially, 130 patients with head and neck squamous cell carcinoma (HNSCC) treated at Aga Khan University Hospital (AKUH), Karachi, Pakistan, were selected. Of them 40 (30.76%) patients were excluded because of the unavailability of a pre-operative three dimensional CT scan for our review (not done at AKUH). Another 18 (13.85%) patients were surgically treated for recurrent disease (locally or regionally) who were also excluded. The remaining 72 (55.38%) patients were selected and their pre-op CT scans (within one month) were reviewed by a radiologist. The history of the patients was reviewed from their medical records.

The research tool was a questionnaire designed by the reviewers to encompass all details of the patients. It

consisted of three parts. The first part included demographic information, including age, gender and presence of any identifiable risk factors for developing head and neck malignancies; such as smoking, betel nut chewing or family history of any malignancies. The second part consisted of details of the primary tumour which were obtained both by review of the pre-surgery CT scan as well as the patients' files. The tumour volume consisted of CT-derived volume of the primary tumour and volume of positive lymph nodes (>1cm along the longest dimension). The surgical procedure, histopathology details of the excised tumour as well as the use of neo-adjuvant or adjunct radiotherapy and chemotherapy were also noted. The third part dealt with prognosis, and details of recurrence, if any, were noted. Date of recurrence was also noted to calculate disease-free interval. Files were reviewed until November 2009 to have at least 1-year follow-up for all the patients.

The whole procedure of the CT review, tumour delineation, digitisation of images and tumour volumetric calculations were coordinated by an experienced head-and-neck radiologist who was unaware of the patients' outcome. For calculation of the tumour volume, dimensions were taken in the cranoicaudal, anteroposterior and transverse dimensions and then multiplied to get the tumour volume. Lymph nodes of at least 1cm in the longest dimension were considered involved and their volume was also calculated and added to the primary tumour volume to obtain the total tumour volume. Measurements were done twice. If these values varied by l0% or less, an average of the two readings was used as the measured volume. If the variation exceeded l0%, another two measurements were made and an average of the four readings was used as the measured volume.

For statistical analysis, SPSS version 17 was used. Besides, chi square test, binary logistic regression analysis, Cox regression analysis and receiver operating characteristic (ROC) curve tests were run on the data.

Results

Of the 72 patients in the study, 53 (73.61%) were male and 19 (26.38%) were female, with an average age of 52±13 years. The study group was divided according to the site of tumour (American Joint Committee on Cancers [AJCC] 2002 classification)[9] with 49 (68.1%) being oral cancers, 16 (22.2%) laryngeal cancers and 6 (8.3%) being hypopharyngeal cancers and 1 (1.38%) case was that of periauricular tumour.

Of all the patients, 47 (65.3%) were betel nut chewers, 26 (36.1%) were smokers and 8 (11.1%) had a positive family history of malignancies. Besides, 40 of the 49 (81.63%) oral cavity cancer patients were betel nut chewers, showing a significant association between developing oral cavity cancer and betel nut chewing (p = 0.001) (Figure-1).

Smoking status, positive family history or betel nut chewing did not show significant correlation with the increasing tumour volume.

The bulk of the tumours in our sample - 55 (76.4%) - were moderately differentiated squamous cell carcinomas; 10 (13.9%) had well-differentiated squamous carcinomas; and 2 (2.8%) were poorly-differentiated squamous cell carcinomas. Another 3 (4.2%) cases were described as moderate to poorly differentiated squamous cell carcinomas and 2 (2.8%) were described as moderate to well differentiated squamous cell carcinomas.

Eight (11.1%) had infiltrating and keratinising cancers; 21 (29.2%) had only keratinizing; and 14 (19.2%)

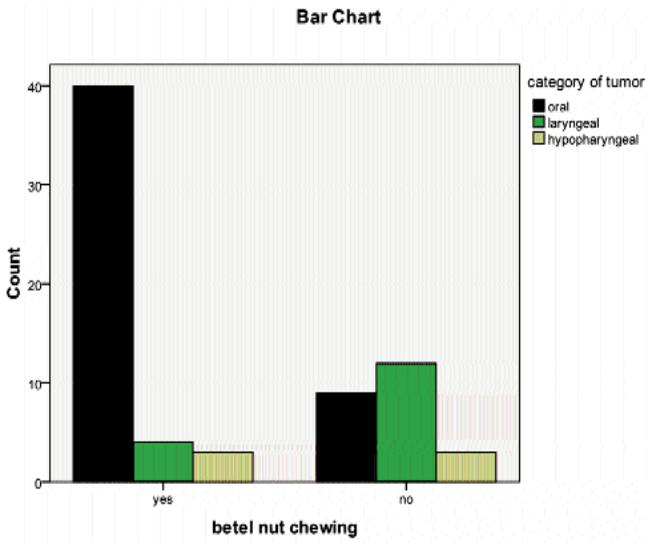

Figure-1: Category of tumours.

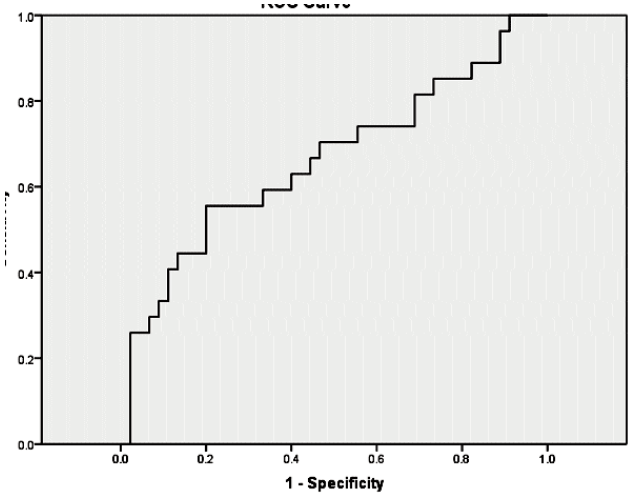

Figure-2: Receiver Operating Characteristic (ROC) curve of oral cancer recurrence.

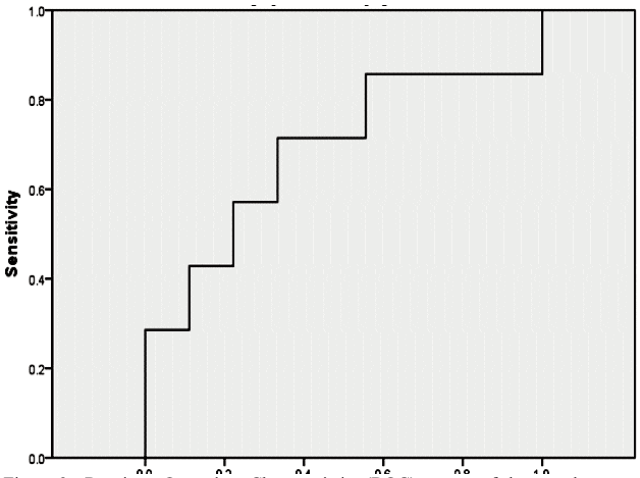

Figure-3: Receiver Operating Characteristic (ROC) curve of laryngeal cancer recurrence.

had only infiltrating cancers. The rest of the 29 (40.27%) cases were neither keratinising nor infiltrating. The tumour differentiation statistically did not predict recurrence for patients in the study.

Overall, 27 (37.5%) patients had recurrence of malignancy during the study period. Of the 49 patients with oral cancers, 19 (38%) had recurrent disease; 7 (43.8%) out of 16 laryngeal cancer patients showed recurrence; and 1 (16.7%) out of 6 hypopharyngeal malignancies recurred (Table-1).

Of the patients who had recurrence, the median recurrence time was around 4 months (mean 7±8 months). The recurrence times for tumour subtypes were similar, with the median time for oral cancers being 4 months and of laryngeal cancers being 5 months.

It was noted that tumours with the shortest surgical margin >4mm had a lesser chance of having recurrence. Only 23% of cases with margin >4mm recurred as opposed to 42% in those tumours whose margins were ≤ 4mm. However, the trend of decreasing margins with increased recurrence was not statistically significant in our study.

Overall, the median tumour volume of patients who had recurrence of disease (52cm³) was more than twice that of those who did not have recurrence (22.0cm³) (Table-2). This observation was consistent for all tumour subtypes.

Following surgery, 17 (23.6%) patients received both radiotherapy and chemotherapy; 26 (36.1%) received radiotherapy alone; 3 (4.2%) received chemotherapy alone and 26 (36.1%) received neither radiotherapy nor chemotherapy. The use of chemotherapy and radiotherapy either alone or in combination was not found to be

Table-1: Mean recurrence times.

Tumour category	Number of cases	Mean recurrence time (months) (SD*)	Median recurrence time (months)	Interquartile range
Oral	19	7.5 ± 8.8	4	5
Laryngeal	7	7.8 ± 5.2	5	10
Hypopharyngeal	1	2.0 ± 0	2	0
Total	27	7.3 ± 8.0	4	5

Only cases with positive recurrence are noted here. *SD: standard deviation.

Table-2: Radiological total tumour volume.

Category of tumour	Median volume- Positive recurrence	Interquartile Range	Median volume- negative recurrence	Interquartile range
Oral	37.0cm³	63.8	20.2cm³	33.2
Hypopharyngeal	115.0cm³	NA*	38.9cm³	23.9
Laryngeal	80.9cm³	91.1	29.0cm³	64.3
Total	52.1cm³	102.6	22.0cm³	36.5

*There was only one case of recuurence of hypopharyngeal cancer.

Table-3: Median Tumour Volume of patients who received adjuvant therapy.

	Recurrence			
Adjuvant Therapy	Yes	Interquartile range	No	Interquartile range
Both Radiotherapy and chemotherapy	80.6	80	18.6	22.9
Only chemotherapy	18.9	NA*	10.4	NA*
Only radiotherapy	67.3	95.4	29.0	40.0
No adjuvant therapy	52.1	93.2	20.2	55.8

*Only 3 patients received chemotherapy alone.

statistically significant in our study.

Among patients who received adjuvant therapy, those with recurrence were found to have higher tumour volumes (Table-3). Patients who received a combination adjuvant therapy and had a positive recurrence had a median tumour volume of 80cm³. In contrast, patients with recurrence who had received no adjuvant therapy had a median tumour volume of 52.1cm³.

Binary logistic regression revealed a positive correlation between increasing tumour volume and odds of developing recurrence (p = 0.009) (95% confidence interval 1.004-1.030). The results showed that with a 1-point increase in tumour volume (i.e. 1cm³), the odds of recurrence went up by 1.7% (p = 0.009).

It was also noted that above a critical value of 23.1cm³, oral cancers had a greater chance of showing recurrence (63% sensitivity and 63.2% specificity). Besides, 26.9% tumours (7 out of 26) below the cutoff recurred as opposed to 52.1% (12 out of 23) above the cutoff (Figure-2)

Similarly, for laryngeal cancer, the cutoff was 46.0cm³, above which there was a greater chance that the tumour recurred (71.4% sensitivity and 66.7% specificity). Besides, 25% (2 out of 8) had positive recurrence below this cutoff and 62.5% (5 out of 8) had positive recurrence above it (Figure-3).

Discussion

The results demonstrated that significant association existed between tumour volume of head and neck cancers (oral and laryngeal) and prognosis of the same after surgery.

Previously, tumour volume has been shown to be a predictor for prognosis in glottic, supraglottic, nasopharyngeal and hypopharyngeal cancers treated with radiotherapy alone[10-15] or concurrent chemo-radiation.[4,6] Data from other head and neck cancers has revealed that volume of oropharyngeal cancer did not have an important impact on local control after radiotherapy[8,16] or surgery[5] although some studies do report association between the two.[6] To our knowledge, no study has investigated the prognostic impact of tumour volumetry of oral cavity cancers. Regarding the relationship of prognosis with tumour volume in patients treated primarily by surgery, limited data is available which finds a positive association between tumour volume and prognosis in supraglottic squamous cell carcinoma.[17]

Different studies show a wide range of volumetric cutoffs above which tumour recurrence becomes more likely. This may be possible due to the different modalities used in treating the patients and/or hospital/surgeon techniques and possibly due to the different ethnic groups being studied.

There is a large variation in the cutoff values for determining prognosis for laryngeal tumours treated with radiotherapy or chemo radiation ranging from 3.5cm³[18-20] up to 112cm³.[7] Several authors used the mean gross tumour volumes (GTV) as the cutoff point. For tumours treated primarily by surgery, a cutoff of 16cm³ has been reported to predict local control and survival in patients with supraglottic cancers.[17] Such cutoffs are not available for oral cavity cancers since tumour volume has not been compared to prognosis in much detail. We found that tumour volume was associated with local recurrence and control both for laryngeal and oral cavity cancers. The cutoff that we report is not the mean GTV. According to our data, tumour recurrence can be predicted with a cutoff of about 23cm³ for oral cavity cancers, and 46cm³ for laryngeal cancers.

Further analysis of our data revealed that one-point increase in tumour volume was associated with approximately 1.7% increase in risk of recurrence, indicating that even in groups in the same cutoff range, the bulkier tumour was at a higher risk of recurrence.

According to our data, tumour volume seems to be significantly correlated with prognosis for both laryngeal and oral cavity cancers with the bulkier tumours having greater chance of failure to control the disease.

Thus we recommend that in addition to AJCC TNM staging, clinicians also use tumour volume to ascertain the aggressiveness of treatment. This is because any one T stage can have a wide variety of volumes within it. As such, we recommend that subsequent high-risk and low-risk groups be made to decide what course of action to take in a patient's treatment. We also suggest larger studies with different ethnic groups represented so a clearer picture about the strength of the association between volume and prognosis can be ascertained.

Conclusion

In advanced T-staged (T3 and T4) head and neck cancers, a substantial variation of primary tumour volume is present within the same T stage and primary tumour volume can represent an important prognostic factor for treatment outcome. Volumetric measurements can help to refine the TNM staging system as they afford an even sharper view considering the wide variation of size seen within the same stage. Based on our results we recommend that patients with larger primary tumour volumes should be treated more aggressively.

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