Oral Hybrid Verrucous Carcinoma: A Clinical Study

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Received: 19 May 2014 / Accepted: 28 July 2014 / Published online: 28 August 2014
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Abstract Hybrid Verrucous Carcinoma is an uncommon tumour wherein Verrucous Carcinoma (VC) is coexisting with conventional Squamous Cell Carcinoma (SCC) within same maternal field. The heterogeneous nature, infrequency of occurrence and the difficulties associated with diagnosis and management of this tumor is discussed through a retrospective study. Patients of primary hybrid VC treated from Jan 2010 to May 2013 at a tertiary institute were analyzed on multivariate cox regression model. During the above mentioned period; 37 patients of hybrid VC were reported; 18(48.6 %) were male and 19(51.3 %) were female. Age ranged between 33 years to 78 years. Median follow up period was 32 months. T stage status and Stage grouping was not statistically significant for mortality (p value: 0.338). In the multivariate cox-regression model, the presence of second primary oral cancer was significantly associated with mortality, adjusted HR; 23.10 (95 % CI: 1.73, 307.65) ($p=0.017$). Tumour staging is often unreliable in predicting prognosis of hybrid VC, occurrence of second primary oral cancer and recurrence appears to be significant factors effecting prognosis.

Keywords Hybrid verrucous carcinoma · Verrucous carcinoma · Oral cancer

Introduction

A Hybrid Verrucous Carcinoma (HVC) is defined as a neoplasm in which there is histological diagnostic verrucous carcinoma (VC) and a non- verrucous squamous cell carcinoma(SCC) arising synchronously from the same maternal field [1, 2].

The published literature suggests that 20 % of initially diagnosed VC patients contained hybrid variety [2]; these foci of less differentiated carcinoma were attributed to so called “anaplastic transformation” of VC treated by radiotherapy in previous literature, currently there is no sufficient evidence to attribute anaplastic transformation of hybrid VC to radiotherapy [3], rather; surgery is the treatment of choice owing to the better disease control of surgically treated patients to patients treated by primary radiotherapy [4]. Unlike VC, hybrid VC is managed similar to conventional SCC [3], further; hybrid VC is staged and graded similar to SCC. Current study describes the difficulties of conventional methods to understand this tumour.

Patients and Methods

Historical cohorts of patients diagnosed as hybrid VC from January 2010 to May 2013 at a tertiary cancer centre were analysed; Primary oral cancer cases with final histology diagnosis of VC with synchronous areas of SCC were only selected.

Patients were staged and grouped depending on UICC TNM staging; patients in whom neck dissection was not done initially were observed for minimum period of 12 months and

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stage grouped accordingly (patients without neck recurrence within 12 months were considered as N0 for the purpose of stage grouping).

Margin status of ≤ 5 mm in histology was considered as “close margin”. Patients with margin status < 1 mm or with microscopic tumour at the margin were considered as “involved”, however; all of the involved margin patients were later revised. Patients with presence or development of another oral cancer 20 mm farther from the primary cancer were considered as second primary.

Patients received adjuvant therapy depending upon presence of other risk factors.

Multivariate analysis and Cox regression was done for age, sex, T staging, stage grouping, locoregional recurrence, second primary oral cancer.

Statistical Methods

Variables were first tested for association with death in bivariate analysis using the Log-rank test as appropriate, associated variables were further tested in a multivariable Cox regression model adjusting for potential confounders. The Kaplan-Meier graphs were drawn to indicate the survival probability. The software SPSS version 17.0 for Windows (SPSS, Chicago, IL, USA) was used for statistical analysis. A two-tailed *P*-value of less than 0.05 was considered statistically significant.

Results

A total of 40 patients were reported with oral hybrid VC in the given period, among them three patients did not return for follow up thus remaining 37 patients were selected for the study. median period of follow up was 32 months.

Among 37 patients, 18(48.6 %) were males and 19(51.3 %) were females. Age ranged between 33 years to 78 years, median age of presentation was 50 years. Grade of conventional SCC component was well differentiated in 32(86.4 %) patients, moderately differentiated in 5(13.5 %) patients.

Eight patients presented tumour over tongue, 24 patients over buccal mucosa, five over gingiva.

Final histology revealed nine (24.3 %) patients with pT1, 20(54 %) patients with pT2, one (2.7 %) patient with pT3 and seven (18.9 %) patients with pT4 respectively. 32(86.4 %) patients underwent neck dissection along with resection of primary tumour and five (13.5 %) patients did not undergo neck dissection.

Neck status on histology showed 28 patients with N0, three patients with N1, and one patient with N2b neck staging. five patients did not undergo neck dissection; these five patients were under observation, one patient reported with neck recurrence and died on seventh month post surgery, this patient was

stage grouped as IV stage, and rest four patients were considered as N0 and stage grouped depending on primary tumor status.

Restaging the sample after 12 months of surgery revealed: 32 patients with N0, three patients with N1 and two patients with N2b. Thus, nine patients were stage I, 17 patients were stage II, three patients were stage III and eight patients were stage IV.

None of the patients were positive for lymph vascular emboli or perineural spread on histological examination.

Adjuvant radiotherapy was given in 21(56.7 %) patients.

During follow up, three (8.1 %) patients reported with second primary oral cancer. One with metachronous tumour on contra lateral site to primary on fifteenth post operative month, this patient underwent surgical excision of second tumour and is currently alive without disease. another patient initially presented with synchronous ipsilateral lesions each in T1 stage; this patient presented with neck recurrence and died on tenth post operative month, third patient presented with metachronous tumour in a site ipsilateral to primary tumour and died on 30th month of follow up.

Two patients developed Locoregional recurrence (one local and one neck).

Three (8.1 %) patients died and 34(91.89 %) survived by the end of study period. One patient died of locoregional advanced second primary oral cancer, one of locally advanced recurrence and one of neck recurrence (this patient had synchronous second primary oral cancer).

Statistical analysis revealed the following results.

Risk of death was high for patients with primary tumour presented on tongue compared to buccal mucosa in this study (25 % vs 4.2 %; $p=0.135$). However, this difference was not statistically significant.

T stage and stage grouping was not reliable in predicting risk of death (*p* value: 0.338) (Table 1) and (*p* value: 0.223) (Table 2).

Patients with locoregional recurrence died often when compared to patients without locoregional recurrence in this studied sample (100 vs 6.7 %; $p=0.005$). This difference was statistically significant (Table 3).

Patients without second primary oral cancer had better survival to patients with second primary oral cancer (2.9 vs 66.7 %; $p=0.013$). This difference was statistically significant (Table 4).

Table 1 Association between T-stage and mortality in the studied sample

T stage	Alive	Dead	P value
T1	7	2	0.338
T2	19	1	
T3	1	0	
T4a	7	0	

Table 2 Association between stage of the cancer and death in the studied sample

Stage	Alive	Dead	P value
I	7	2	0.223
II	17	0	
III	3	0	
IV	7	1	

Close margin status was a risk factor for occurrence of death, HR, 1.09 (95 % CI: 0.09, 12.74) ($p=0.947$). However, it was not significant.

Adjuvant therapy was not beneficial in preventing loco regional recurrence in current study. (Table 5).

In the univariate cox-regression model revealed that female patients had better survival to male patients, hazard ratio (HR): 2.04; 95 %

In the univariate cox-model, it was found that patients with second primary oral cancer had 19.5 fold increase in the risk of death at 5 years to patients without second primary oral cancer, HR, 19.48 (95 % CI: 1.76, 215.46) ($p=0.015$). the multivariate cox-regression model, adjusted with margin status, revealed significant risk associated with occurrence of second primary oral cancer to death, adjusted HR; 23.10 (95 % CI: 1.73, 307.65) ($p=0.017$) (Table 5).

Discussion

First report of oral hybrid carcinoma was described by Jesus E et al [2], in their study of 104 cases; authors reported 20 % of lesions with coexistent less differentiated carcinomas, the recurrence of verrucous carcinoma into less differentiated carcinomas were observed in the follow up of these patients.

Initial biopsy of 21(56.7 %) patients in the current study failed to diagnose SCC component of hybrid VC, although universally accepted protocols for incision biopsy were routinely followed at our institute. Incision biopsy specimen consisted of deeper connective tissues and adjacent normal mucosa in every case. Biopsies were frequently repeated if tissue obtained did not represent the above mentioned criteria.

Verrucous hyperplasia may be differentiated from VC through adopting specific protocols in performing initial biopsy, Shear et al [5] described that verrucous hyperplasia can be best differentiated from VC in biopsies taken from margins of the lesion. They described that, the verrucous processes and the greater part of the hyperplastic epithelium are superficial to

Table 3 Association between locoregional recurrence and death in the studied sample

Loco regional recurrence	Alive	Dead	P value
Absent	34	1	$P=0.005$
Present	0	2	

Table 4 Association between occurrence of second primary and death

Second primary	Alive	Dead	P value
No	33	1	$P=0.013$
Yes	1	2	

adjacent normal epithelium in verrucous hyperplasia, whereas; VC shows superficial verrucous processes, however; broad rete processes extend into the connective tissue deeper than adjacent normal epithelium.

In cases of hybrid VC, there is no such specific region to sample for biopsy which could probably help to arrive at best diagnosis on initial biopsy. Possibly these are the clinical scenarios where devices such as spectrometer [6] might be helpful to locate best possible location to perform incision biopsy.

Odds of Incision biopsy in the identification of invasive component of hybrid VC entirely depends on sampling by the operator; multiple biopsies from entire lesion may be helpful in sampling different areas of the tumour but does not preclude missing out of invasive component until resection specimen is evaluated after definitive surgery.

Hybrid VC is graded and staged similar to SCC [7] but within hybrid VC, the proportion of conventional SCC component may vary, since prognosis of VC is better than SCC it may be assumed that cases with the major proportion of VC would more likely have better prognosis. However, clinician wouldn't know actual quantity of conventional SCC in the given tumour, unless pathologist makes an attempt to quantify and specify the proportion of conventional SCC, this might be the reason that staging and stage grouping did not impact on outcome of patients in the current study (Tables 1 and 2).

Survival in the current study was 91.9 % ($n=34$), disease free survival was 91.9 % ($n=34$), Locoregional recurrence was 5.4 % ($n=2$), three patients developed second primary; of them two died and one is alive without recurrence after second surgery.

Occult metastasis to neck in our cases was 13.5 % in contrast to conventional SCC cases which shows minimum of 30 % occult metastasis even in early cases [8–10].

Initial reports of neck metastasis in the literature of VC were later attributed to presence of hybrid VC on re-evaluation, classic VC did not metastasise [11, 12]. Since occult metastasis is often associated with decreased survival, Prognosis of hybrid carcinoma appears to be better than conventional SCC.

It is interesting to note that lower T stage was associated with second primary in our study. Among patients with second primary; two patients had pT1 tumour, and one pT2. Neck status was N0 in all of them, despite favourable staging two of the patients with second primary died of advanced disease associated with either recurrence or second primary oral

Table 5 Univariate and multivariate associations between various factors and risk of death in the studied population

Factors	Total sample N	Dead n (%)	Unadjusted HR (95 % CI)	P value	Adjusted HR (95 % CI) [§]	P value
Gender						
Male	18	2 (11.1)	2.04 (0.19, 22.46)	0.561	–	–
Female	19	1 (5.3)	1.00			
Grade						
Mdscc	5	0 (0.0)	1.00			
Wdscc	32	3 (9.4)	26.87 (0.0, 1382901.9)	0.624	–	–
Stage						
I	9	2 (22.2)	1.00			
II	17	0	–			
III	3	0	–			
IV	8	1 (12.5)	0.83 (0.07, 9.58)	0.884	–	–
Margin status						
Clear	10	1 (10.0)				
Close	24	2 (8.3)	1.00	0.947	–	–
Involved revised	3	0	1.09 (0.09, 12.74)			
Locoregional recurrence						
Absent	35	1 (2.9)	1.00			
Present	2	2 (100)	1.01 (0.001, 887.72)	1.000	–	–
Adjuvant therapy						
Not given	16	1 (6.3)	1.00			
Given	21	2 (9.5)	1.28 (0.11, 14.33)	0.843	–	–
Second primary						
No	34	1 (2.9)	1.00		1.00	
Yes	3	2 (66.7)	19.48 (1.76, 215.46)	0.015	21.67 (1.92, 245.08)	0.013

§: Adjusted Hazard Ratios were resulted after adjusting for cofounders

cancer. These observations were similar to the study by Jones et al [13] who reported the occurrence of second primaries in the patients with lower stage index tumours (T1, T2) without nodal metastasis compared to patients with higher index tumours and nodal metastasis on initial presentation (p values of ,0.0001 and 0.0003). These authors reported five year survival of 26 % in patients with second primary [13, 14]. The median time of second primary presentation was 36 months in them, although our sample is small and follow up period is not long, it appears that hybrid VC develops second primary often early in comparison to conventional SCC. The second primary rate in the study by Jones et al [13] was 9.1 % at 372 months. Parallel to their report 8.1 % of patients in current study presented with second primary, considering the limited median follow up period of 32 months in our series; this proportion might certainly increase.

Development of second primary was associated with poorer outcome in oral hybrid VC as revealed in current series, this finding were parallel to the study by Schwartz et al [15] and Hordyk, G. J., et al [16] who reported poor prognosis in head and neck carcinomas associated with second primary cancer.

All the three patients with second primary oral cancer underwent PORT (Post operative radiotherapy) within 6 weeks post surgery for primary oral cancer (all of them were N0, However; PORT was given since, two patients had close margins on final histology and one was a deeply infiltrating tongue tumor), it is not possible to interpret on impact of radiation in the current study but authors observed that the patients who developed second primary or recurrence ipsilateral to irradiated tissue had poorer outcome than the patient with contra lateral second primary. Fijuth et al [17] in his analysis of second primary tumours in oral and oropharyngeal cancers treated with radiotherapy reported poor survival in such patients.

Jones et al [13] in their study on “Second primary tumours in patients with head and neck squamous cell carcinoma” did not find association of radiotherapy for development of second primary in early cancers, whereas Cooper, Jay et al [18] based on the RTOG experience could find this risk as 10 % within 3 years, 15 % within 5 years and 23 % within 8 years respectively.

Weather second primaries in our study ware radiation induced or due to wide areas of carcinogen sensitization

Fig. 1 Overall survival status of the patients

resulting in field changes as explained by Slaughter et al [19] or extensions of a primary tumour clone, cannot be interpreted without further analysis.

Field cancerization concept put forward by Slaughter et al [19] advocated multiple separate carcinomas developing from preconditioned epithelium to carcinogenic agent, in contrast to Slaughter et al., Worsham et al [20] proposed concept of single focus spreading laterally by arborisation without disrupting adjacent normal mucosa, this theory was strengthened by research on monoclonal development of second primaries [21, 22].

Current data wasn't sufficient to evaluate second primary statistically, however it is not easy to obtain sufficient sample of this rare tumor, A systematic review by Atienza, Jonessa Ann S et al [23] reported high incidence of second primaries in head and neck sites, according to them environmental, genetic and immunological factors could explain such association.

Locoregional recurrence in hybrid VC is associated with poor outcome as in cases of conventional SCC; this is quite in contrast to VC. VC is associated with recurrence after repeated excision but seldom leads to death unless it dedifferentiates into much poor grade on recurrence. 5 year disease free survival of entire cohort of 101 patients of verrucous carcinoma in study by Rohan R Walvekar et al [14] was 77.6 %, whereas; among conventional SCC, stage I and stage II cancers correspond to similar prognosis [8–10].

Studies on prediction of second primary could be beneficial in evaluating cases of hybrid VC during the follow up period, Bongers et al [24] in their study attempted to identify the risk of second primary cancer, authors observed an increased expression of glutathione S-transferase (GST) in normal

tissues around the first tumour in comparison to matched controls.

p53 analysis for margins could be useful to predict recurrence in cases with clear tumour margin [25], but clinical applicability of any tool is still far from per operative usefulness, nevertheless such tools will be helpful to sample patients who could probably develop second primary thus caution clinician and patient during the follow up period.

Conclusion

Hybrid VC presents second primary oral cancers more often and early than conventional SCC, T Staging and Stage grouping in conventional methods do not appear to correlate with prognosis in current study, overall prognosis of Hybrid VC might be better than conventional SCC unless associated with second primary.

The patients with second primary oral cancer had 19.5 fold increased risk of death at 5 years when compared to patients without second primary oral cancer in oral hybrid VC (Fig. 1).

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