Original research article

ETIOLOGICAL, CLINICAL AND PATHOLOGICAL PROGNOSTIC MARKERS IN HEAD AND NECK CANCERS TREATED WITH CONCURRENT CHEMO-RADIATION

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Publication Info

Paper Submission Date
10-05-2017

Paper Acceptance Date
31-05-2017

Paper Publication Date
July 2017

DOI
10.21761/jms.v2i01.10842

Abstract

Introduction: Advanced squamous cell carcinoma of head and neck are usually treated with surgery and/or radiotherapy. Integration of chemotherapy also plays an important role for improving organ preservation. Various prognostic factors help in selecting the appropriate treatment regimen for the individual patient. The present study was conducted to identify the prognostic factors in head and neck cancers.

Material and Methods: Previously untreated 33 patients of squamous cell carcinoma were selected. They were treated with concurrent chemotherapy and radiotherapy. The response assessment was analyzed in terms of various patient, tumor and treatment related factors. Statistical analysis was done using chi square test.

Results: Etiological factors tobacco & alcohol, non-vegetarean diet were associated with a poor outcome but were not statistically significant. Clinical factors- like higher N-stage (p=0.04) and AJCC stage (p=0.03) were found to be significant predictors of poor prognosis while T-stage was not found significant, probably due to short follow-up. Patients receiving less than 5 cycles of concurrent chemotherapy had a significantly worse prognosis (p=0.04). Among the pathological factors that were studied, high mitotic index (Grade III or more) were associated with a significantly poorer prognosis (p=0.04).

Conclusion: Many clinico pathological factors have been correlated with locoregional control in head and neck cancers. These can be used to individualize the treatment by different surgical techniques, various radiotherapy dose & fractionation schedules and chemotherapy protocols.

Keywords: head and neck cancer, chemoradiation, prognostic markers

INTRODUCTION

The standard treatment for advanced squamous cell carcinoma of the head and neck (SCCHN) has been surgery and/or radiotherapy (RT) for patients with resectable tumors and RT for unresectable patients. Integration of chemotherapy into the treatment of advanced SCCHN has been shown to be useful for improving organ preservation in resectable cases with squamous cell carcinoma (SCC) of the larynx and hypopharynx,[1-3] and for improving survival in unresectable SCCHN patients treated with concurrent chemoradiotherapy (CCR).[4,5]

Prognostic factors can guide the physician in selecting the appropriate treatment regimen for the individual patient. The patient related prognostic factors such as gender, age, tobacco & alcohol intake, co morbid conditions and Human Papilloma Virus (HPV) status are studied. Further, tumor characteristics such as anatomic site, disease staging, nodal metastasis, extra capsular spread, histological differentiation, perineural invasion, mitotic index and molecular characteristics such as p53, VEGF, EGFR, Ki-67 also have shown to play prognostic role.[6-10]

The goal of our study is to identify various tumor, patient and treatment related prognostic factors in our population.

MATERIAL AND METHODS

For the present study, previously untreated 33 patients of histologically proven locally advanced malignancies of head and neck region were selected.

The inclusion criteria were age ≥ 18 years; Karnofsky Performance Status (KPS) >70 with normal hemogram, renal function tests, liver function tests and ECHO. The exclusion criteria were patients with prior or synchronous malignancy; distant metastasis present; previously partially

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treated patients (in terms of surgery, radiotherapy and chemotherapy); patients with compromised renal or cardiac functions, pregnancy and lactating mothers.

All the patients underwent pretreatment evaluation by complete history taking, general physical examination, local examination, hemotological and biochemical tests (complete haemogram, renal function tests, liver function tests), radiological investigations (Chest X-ray, USG abdomen, CECT neck) and 2D ECHO.

All the patients were treated with concurrent radiotherapy (70 Gy in 35 fractions in 7 weeks) and chemotherapy (Cisplatin 35 mg/m2 weekly).

Response & Toxicity Assessment:

WHO Response criteria- Complete response (CR): Disappearance of all known disease determined by two observations not less than 4 weeks apart. Partial response (PR): Sum of products of all lesions decreased by >/= 50% for at least 4 weeks; no new lesions; no progression of any lesion. Stable disease (SD): Sum of product of lesions decreased by 50% or increased by ≤ 25% in the size of one or more lesions. Progressive disease (PD): a single lesion increased by ≥ 25% or the appearance of new lesions.

Complete blood counts and kidney function tests and liver function tests were repeated in all patients every week before each chemotherapy cycle. Late Radiation toxicity was assessed by Common Toxicity Criteria (CTC) late morbidity scoring.

Prognostic factors documented:

A) Etiological factors: Lifestyle factors (smoking, alcohol & food habits); hematological & biochemical parameters (hemoglobin, serum creatinine).

B) Clinical factors: ♦Patient related: age, gender, BMI, performance status and co-morbid conditions (diabetes mellitus, hypertension, tuberculosis) ♦Tumor related: tumor size, stage, nodal status and AJCC stage. ♦Treatment related: overall treatment time (OTT), radiotherapy and chemotherapy dose received.

C) Pathological: Histopathology: (squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma); Grading (well / moderately / poorly differentiated), mitotic index (low, medium and high), necrosis (present / absent), keratinization (keratinizing or non keratinizing), inflammation (type and density).

Data was analyzed using chi square test.

RESULTS

In the present study of 33 patients, more than 90% of the patients were in the habit of consuming tobacco products like cigarette, beedi, gutka, khaini, zarda etc. Almost 80% (26/33) were beedi smokers of which 15% were consuming more than 20 beedis/day. Fourteen patients (42%) did not consume alcohol while almost 58% (19/33) patients were in the habit of alcohol consumption. Ten patients (30%) consumed alcohol daily, 5 patients (15%) took alcohol weekly while 4 (12%) were ocassional consumers. Greater than 50% of patients (18/33) were consuming both tobacco products and alcohol while the other 15 (45.5%) were not taking both together. The patients enrolled in the trial mostly consumed mixed vegetarian / non vegetarian diet.

Patient, tumor and treatment related characteristics are shown in Table 1, 2 and 3.

Presence of comorbidity was observed in 7 (18%) patients- 12% (4 patients) were hypertensive and 6% (2 patients) were diabetic. None of the patients had a history of T.B. or cardiac illness.

No significant Grade III/ IV haematological toxicities and radiotherapy reactions (acute and late) were seen in the present study.

Complete response after 6 months in terms of tumor and nodal response was 91% and 93% respectively. Overall complete response was seen in 91% (30/33)of patients with no evidence of disease at six months, 9% patient (3/33) had disease presence of which two patients had residual disease and one patient had recurrence.

Table-1: Patient Characteristics

Characteristics	n (%)
Gender	
Male	31 (93.9)
Female	2 (6.1)
Age (years)	
≤ 50	9 (27.2)
> 50	24 (72.8)
Hemoglobin*	
Grade 0	14 (42.4)
Grade I/II	19 (57.6)
BMI	
< 18.5 (Underweight)	14 (42.4)
18.5-24.9 (Normal)	16 (48.5)
25.0-29.9 (Overweight)	3 (9.1)

*According to WHO criteria

Table-2: Tumor Characteristics

Characteristics	n (%)
T Stage	
T1/T2	13 (39.4)
T3/T4	20 (60.6)
Node Status	
Node Present	27 (81.8)
Node Absent	6 (18.2)
AJCC Stage	
I/II	2 (6.0)
III/IV	31 (94.0)
Tumor Grade	
Well Differentiated	9 (27.3)
Moderately Differentiated	23 (69.7)
Poorly Differentiated	1 (3.0)
Mitotic Activity	
Grade I	21 (63.6)
Grade II/III	12 (36.4)
Necrosis	
Present	13 (39.4)
Absent	20 (60.6)
Inflammation	
Mild	4 (12.1)
Moderate	12 (36.4)
Marked	17 (51.5)
Keratinization	
Non Keratinizing SCC	12 (36.4)
Focally Keratinizing SCC	8 (24.2)
SCC with Keratin pearls	13 (39.4)

*Grade I (0-1/HPF), Grade II (2-3/HPF), Grade III (4-5/HPF)

Table-3: Treatment Characteristics

Characteristics	n (%)
Cisplatin cycles (Weekly)	
5-7 Cycles	28 (84.8)
<5 Cycles	5 (15.2)
Radiotherapy dose	
≥ 66Gy	28 (84.8)
< 66 Gy	5 (15.2)
Overall Treatment Time	
Mean	51 Days
Median	50 Days

Table 4 show the correlation of prognostic factors with clinical response.

DISCUSSION

Many clinicopathological variables that are of prognostic value have been identified in HNSCC but wide heterogeneity in clinical outcomes is seen. The ability to predict the probability of successful treatment would allow for more individualised treatment in the hope of reducing toxic side effects and treatment failure.

Table-4: Etiological, clinical and pathological factors & their p value

Prognostic Factors	Statistical Significance (p value)
Etiological Factors	
Tobacco	NS
Alcohol	NS
Tobacco & Alcohol	NS
Diet	
Non Veg	NS
Clinical Factors	
Patient Related	
Age (≤ 50 years)	NS
Gender	NS
Co morbid conditions (Diabetes Mellitus + Hypertension)	**p= 0.05**
Nutritional Status	NS
Anemia	NS
Tumor Related	
Tumor Stage	NS
Nodal Status	**p= 0.04**
AJCC Stage	**p= 0.03**
Treatment Related	
Radiotherapy Dose	NS
Chemotherapy cycles	**p= 0.04**
Overall Treatment time	NS
Pathological Factors	
Grade	NS
Mitotic Index	**p= 0.04**
Necrosis	NS
Inflammation	NS
Keratinization	NS

NS = Non Significant

Etiological Factors

Tobacco & Alcohol: In present study among the patients who had residual disease at 6 months, 67% patients were bidi smokers, and consumed >20 bidi /day. Consumption of >20 bidi/day was found to be a poor prognostic factor though it was not statistically significant (p=0.62).

The most rigorous exploration of the relationship between alcohol consumption and outcome in head and neck cancer patients resulted from a prospective study of 649 patients who received in-depth questioning near the time of diagnosis regarding alcohol consumption and alcohol-related health problems.[11] Patients who consumed regular alcohol were associated with a poor prognosis but daily intake was not found to be a significant factor (p=0.88).

Concurrent use of alcohol and tobacco has been associated

with a high rate of nonspecific mutations in the tumor suppressor gene p53.[12] Perhaps as a result of these deleterious mutations, prior or continued use of alcohol and tobacco in patients with head and neck cancer is a risk factor for poor outcome. Furthermore, use of these substances has been associated with immunosuppression, malnutrition, and impaired tissue oxygenation resulting in hypoxic radioresistance.

Within the patient population, 67% patients with residual disease were in the habit of taking both tobacco products and alcohol. Intake of concurrent tobacco and alcohol associated with poor prognosis, but was not statistically significant(p=0.48). The reason for the above findings with tobacco & alcohol could be explained by the incidence of HNC in non-smokers & the small sample size under study.

Diet: The recent World Cancer Research Fund (WCRF) report into diet and cancer summarized that the evidence was strong enough to support a probable causal relationship for a decreased HNC risk with non-starchy vegetables, fruits, and food containing carotenoids.[13] All (100%) patients with residual disease were consuming a non-vegetarian diet rich in animal fat/protein, yet the above findings did not show diet to be a statistically significant prognostic factor (p=0.93).as even though meat consumption was suggested to be a risk factor for several cancers & higher intake of several meat products showed an increased risk of HNC, this needs further exploration with a more quantified diet data analysis.

Clinical Factors

Age: Siegelman-Danieli et al examined a retrospective cohort of oral tongue SCC patients, 30 of whom were 45 years of age or younger at the time of diagnosis.[14] In this study, age did not influence relapse rates, cancer-free survival, or overall survival in both univariate and multivariate analysis.

Similarly, Verschuur et al[15] conducted a retrospective case-control study on 185 previously untreated HNSCC patients. Age did not influence cause-specific survival in univariate or multivariate analysis. However, older patients were twice as likely to develop second primary SCCs of the upper aerodigestive tract (14% vs. 7%), possibly due to their increased use of tobacco products.

Sixty seven percent were aged >50 years while 33 % were <50 years in the patients who had residual disease at follow up. The study did not find a significant difference in prognosis with age >50 years (p=0.51).

Gender: Most large series have failed to find a significant difference in outcome with respect to sex.[12,16-20] In contrast, one relatively large study conducted on[21] patients with stage I to IV laryngeal cancer found that female patients experienced a 76% 3-year overall survival, compared to 63% in male patients. However, the disease-free interval was nearly identical, 60.4 months in women and 59.7 months in men.

In the current study, there were 33 patients included, out of which 31 were male patients (approx 94%), and only 2 female patients, making them 6% of the total study population. This skewered male to female ratio can be explained by the very low incidence of tobacco products intake in the women of the region. Out of the patients with residual at 6 months, almost 70% were male. Male gender was associated with worse prognosis but this finding was not statistically significant (p=0.79).

Co-morbidity: In a prospective study of 1,086 patients with primary head and neck cancer, the presence of comorbidity was a significant, independent predictor of 2-year survival, even after controlling for age, sex, race, and stage.[22] As compared to patients without comorbidity, the mortality HR was 1.9 for patients with moderate comorbidity and 2.5 for patients with severe comorbidity. Similar results were reported in a study of 9,386 elderly Medicare beneficiaries with HNSCC.[23] Out of all patients with residual, 67% patients had co-morbidities (diabetes mellitus) while one (33%) had both diabetes and hypertension. Statistically, presence of comorbidity was found to have a significant impact (p=0.05) on prognosis.

Nutritional Status: A pooled analysis by Mia M. Gaudet et al, of case–control studies reported a 50% lower risk for overweight and obesity and a 2-fold higher risk for leanness in overall analyses.[24] BMI and HNC mortality have been examined in a pooled analysis of prospective data from 57 cohort studies.[25] In the study, 100% of the residual disease was observed in patients who were less than 25kg/m2 (100%). This indicates a better prognosis in overweight patients but this finding was not found to be significant statistically (p=0.096).

Tumor Stage: The correlation between tumor size and risk of poor prognosis or teatment failure has been confirmed in multiple studies.[26,27]

Of the total 33 patients included in the trial, 2 patients (6%) had T1 lesion, 11 patients (33%) had T2 lesion, 12 (36%) had T3 lesion and 8 (24%) had T4a lesion. The patients

with the T1 lesion were included because they had positive nodal status. Out of 3 patients with residual disease, 1 was T4a pre treatment, 2 were T3. In our current study was not significant (p=0.083).This can be explained by the short period of follow-up.

Nodal Status: The number of positive nodes clearly predicts risk of distant metastatic disease for all sites of HNSCC.207,[28-30] Number of positive nodes predicts both regional recurrence and distant recurrence[30] even after controlling for other prognostic variables in multivariate analysis. It also consistently correlates with survival in univariate analysis for all major sites of HNSCC.[8,10,31,32]

In a review of 250 radical neck dissection specimens, Carter et al. found that pathologic nodal size > 2 cm correlated with increased risk for regional recurrence.[21] Furthermore, in a multivariate analysis of clinical parameters, node size was a significant predictor of poor overall survival.

In the current study, advanced N stage was found to be a significant prognostic marker (p=0.04) with all residual observed in patients in higher (N2b & N2c stage). Residual disease was seen in 3 patients, all of whom were N2 stage, (N2b-two case and, N2c-one case).

AJCC Stage: For decades, the Tumour, Node, Metastasis classification (TNM), based on tumour size (T), regional lymph node metastasis status (N) and distant metastasis status (M) has been used to estimate the prognosis in HNSCC. Higher AJCC stage was found to be a significant prognostic factor (P=0.03). Out of the patients in stage II or III, none had residual disease at 6 months of follow-up. Residual disease was seen in only stage IV patients.

Anemia: One of the first studies to illustrate the impact of anemia on locoregional tumor control in head and neck cancer patients came from the Danish Head and Neck Cancer II Study (DAHANCA II).[33] This study showed a strong correlation between the pretreatment hemoglobin levels and local control was noted in male patients with pharyngeal tumors. Male patients with pharynx cancer who had pretreatment hemoglobin levels of 14.5 g/dl had five year local tumor control rate of 61% as compared with only 14% in the patients with pretreatment hemoglobin values <14.5 g/dl.[34]

Grade II Anemia was observed in 67% patients with residual disease, which was not significant statistically as a prognostic factor (p=0.42).

Treatment Parameters

Radiotherapy dose: For head and neck malignancies, a radiation dose of ≥ 66 Gy is considered radical/curative. Patients recieving less than the above desired dose are at a risk of having higher incidence of residual disease and are associated with poor prognosis. Hence, RT dose of less than 66Gy was found to be associated with worse prognosis though it was not found to be a statistically significant prognostic factor(p=0.28).

Chemotherapy cycles: Clinical data suggests that patients recieving lesser than 5 cycles of concurrent chemotherapy have a significantly higher incidence of tumor residual even after curative dose of radiation is received by patient. This leads to poorer prognosis compared to those recieveing 6-7 cycles of concurrent chemotherapy. In the current study, out of the patients who recieved less than 5 cycles, 60% of the patients had residual disease. Less than 5 cycles of chemotherapy was associated with poorer prognosis and this finding was significant (p=0.04).

Overall Treatment Time: Patients who are unable to receive the prescribed treatment in its designated course of time have a higher risk of residual disease. The ideal overall treatment time in patients receiving conventional R.T. is 7 weeks (49 days) whereas the study arm showed Mean OTT of 51 days. No significant prognostic benefit of lesser/greater OTT observed(p=0.42).

Pathological Factors

Grade: Broders proposed a four-tiered grading system for lip cancer that, based on the proportion of the neoplasm resembling normal squamous epithelium.[35] This grading system roughly correlates with prognosis, as poorly differentiated tumors are more likely to recur and reduce survival.[12,34-36]

In the present study 27% patients had well differentiated tumour out of which one 3% residual at 6 months. Seventy percent patients had moderately differentiated tumors out of which 9% had residual at 6 months. Three percent had poorly differentiated tumour, none of whom had residual at 6 months. Hence, pathological grade was not found to be a significant prognostic factor (p=1.10).

Mitotic Index: Anneroth et al combined mitotic index with multiple parameters to predict tumor prognosis. He graded it into 4 categories (Grade I-IV) according to number of mitotic figures per single High Power Fields (HPF) (0-1,2-3,4-5,>5). This grading system is internationally used for

grading purpose.[37] All 3 patients with residual tumor was associated with Grad III mitotic index (100% patients). High Grade mitotic activity was a significant prognostic factor predicting poor prognosis (p=0.04).

Necrosis: There is some evidence that the presence of necrosis or poor tumor perfusion might also be predictive factors for outcome. It is believed that the presence of visible necrosis is an important factor for cure by radiotherapy in squamous cell cancers of the head and neck.[38] In the current study, 66% patients with residual at 6 months had tumor necrosis, while 34% patient with residual at 6 months were without tumor necrosis. Presence of necrosis was associated with poorer prognosis but was approaching significance (p=0.08). This parameter needs further exploration with larger sample size.

Inflammation: Intra-tumoral Inflammation has been associated with a better prognosis and has been included in various pathological systems as one of the parameters. Marked or dense prognosis has been associated with a better response to treatment while low or absent inflammation is a poor prognosis indicator.[39] Possible good prognostic marker, but not found to be statistically significant (p=1.67).

Keratinization: Jakobsson et al[40] and Willen et al[41] also corroborated the above data in their pathological grading system where they depicted presence of keratinization in tumor tissue to be associated with better prognosis. Keratinisation was not found to be a significant prognostic factor (p=0.28) in concordance with research literature.

CONCLUSION

In the present study comorbid conditions, nodal status, AJCC stage, chemotherapy cycles and mitotic index were found to affect clinical response which was statistically significant.

Prognostic markers should be extensively researched to develop optimum treatment regimens for individual patients so that treatment failure rates in terms of local and distant disease could be decreased.

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