Original Article

Concurrent chemoradiotherapy for head and neck cancers in older patients: Outcomes and their determinants

Vijay K Srinivasalu, Narayana Subramaniam[1], Deepak Balasubramanian[1], Narender Kumar[2], Arun Philip, Annu Susan, Pushpaja KU[3], Anoop R Nair[3], Krishnakumar Thankappan[1], Wesley Jose, Subramania Iyer[1], Pavithran Keechilat

Departments of Medical Oncology, [1]Head and Neck Oncology and [3]Radiation Oncology, Amrita Institute of Medical Sciences, Kochi, Kerala, India, [2]Marie Skłodowska-Curie Fellow, Institute of Experimental Endocrinology and Oncology, Naples, Italy

Correspondence to: Deepak Balasubramanian, E-mail: dr.deepak.b@gmail.com

Abstract

INTRODUCTION: Meta-analyses have shown concurrent chemoradiotherapy (CCRT) provides no survival benefit over radiotherapy in patients of head and neck squamous cell carcinoma (HNSCC) aged over 70 years. This study was performed to determine the adverse-effect profile, compliance, functional and oncological outcomes in patients of HNSCC over 70 years of age treated with CCRT.

MATERIALS AND METHODS: Retrospective analysis of stage III/IV HNSCC in patients above 70 years of age who received CCRT at our institution ($n = 57$). Cox-proportional hazards regression model was used for statistical analysis.

RESULTS: There were 57 patients of stage III/IV HNSCC who underwent curative CCRT. 61% completed chemotherapy with no deaths and acceptable toxicity. The predictors of recurrence were poorer performance status ($P = 0.031$) and treatment breaks ($P = 0.04$). Tube dependence was associated with 2.7 times higher risk of mortality ($P = 0.005$).

CONCLUSION: CCRT should be considered standard of care in those over seventy with good performance status. Patients with tube dependence have a higher risk of persistent disease or treatment related mortality.

Key Words: Chemoradiotherapy, elderly, head and neck squamous cell carcinoma, organ preservation, tube dependence

Introduction

Head and neck squamous cell carcinomas (HNSCC) are a heterogeneous group of cancers and are the fifth most common cancer worldwide, with an estimated annual global incidence of over half a million.[1] Head and neck cancers account for a major percentage of the cancer burden in India, and it has been estimated that around 10% of these patients are aged over 70 years.[2] In the background of an aging population and improved life expectancy, this percentage is expected to expand rapidly.[3] It has been noted that due to a higher number of co-morbid illnesses and poorer performance status, elderly patients are often subjected to substandard or inadequate treatment for head and neck cancers in spite of being suitable for radical therapies.[4]

The definition of 'elderly' in literature has been variable. About 70 years of age has been a commonly described cut-off due to observed alterations in physiological status and increased cancer treatment-related toxicity.[5] Other studies have used the term 'elderly' for those above 65, 70 or 80.[6] Clinically, however, it is important to distinguish chronological age from physiological age, where depending on the performance status and presence of co-morbid illness, the toxicity profile of patients may resemble either patients of an older or younger age group; hence denying elderly but fit patients curative intent therapy may not be justified.

The use of concurrent chemoradiotherapy (CCRT) for head and neck cancers has been shown to be effective and safe in the older patients with cancer. A meta-analysis by Pignon *et al.* showed an improvement in overall survival by 4.5% at 5 years and an absolute benefit for concurrent CCRT of 6.5% when compared to radiation alone, however this benefit was only in patients below 70 years of age.[7] Data from the Indian subcontinent on CCRT in the elderly is scanty. This may be relevant as compared to patients in the West, Indian patients have been shown to have poor compliance to cancer therapy,[8] a lower life expectancy of around 68 years,[9] and are much more likely to incur out-of-pocket expenditure for cancer therapy due to the lack of universal healthcare,[10] which may all significantly impact treatment decisions.

Management of cancer in the older population has often been under-represented in clinical trials and most of the trials have had arbitrary upper age limits. A majority of elderly cancer patients are less likely to receive definitive or adequate cancer-directed therapy. But for the healthiest patients who are generally considered good surgical candidates, CCRT offers the potential for organ preservation with no detriment to overall survival. Our institutional policy has always been to offer curative intent treatment to all patients with a good performance status irrespective of age; chemotherapy with cisplatin or carboplatin has been our standard regimen for concurrent CCRT in HNSCC. This retrospective study is a review of our experience administering curative intent CCRT in patients aged over 70 years with concurrent cisplatin or carboplatin. The objective was to review the efficacy of these regimes, the treatment response, patient compliance, toxicities, and outcomes of the treatment. We also investigated the prognostic determinants in this cohort.

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Materials and Methods

Patient population

After approval for the project from the institutional ethical committee, 57 patients of HNSCC aged over 70 years who received definitive primary CCRT over a period of nine years (January 2006–December 2014) were identified from our department database. As this was a retrospective review, we included all consecutive patients treated in our institution during this period to avoid bias. The subsites of HNSCC included were oropharynx (n = 15), larynx (n = 18) and hypopharynx (n = 24). All of these patients received 3D conformal radical CCRT with a dose equivalent to 70Gy in conventional fractionation. Patients over 70 years of age who received curative intent CCRT had either stage III (n = 14) or stage IV (n = 43) disease and a good performance status (Eastern Cooperative Oncology Group 1-2); this was in accordance with our general treatment policy for locally advanced HNSCC.

Pre-treatment evaluation

All patients underwent pre-treatment evaluation with thorough clinical evaluation, baseline biochemical evaluation (complete blood count, renal function tests and serum electrolytes), loco-regional cross sectional imaging, and a metastatic workup (contrast enhanced computerized tomography of the thorax or whole-body positron emission tomography scans), and biopsy. The treatment decisions were taken for each patient individually after discussion in the multidisciplinary tumour board based on clinical staging, comorbidities, treatment morbidity, and patient's choice.

Chemotherapy

Cisplatin was administered weekly at 40 mg/m^2 (n = 21) or at 100 mg/m^2 if used three weekly (n = 14). The maximum dose of weekly cisplatin was 70 mg. Carboplatin was administered (n = 22) after calculating the creatinine clearance, with an area under curve (AUC) of 2. Patients received a pre- and post-hydration of 1000 mL of 0.9% sodium chloride. Ten mmol of magnesium sulfate and twenty mmol of potassium chloride were added in the post-hydration saline for patients with cisplatin. Patients who received a cumulative dose of 200 mg/m^2 of cisplatin and 6 weekly doses of carboplatin at AUC 2 were considered as having completed chemotherapy. The standard prophylactic anti-emetic protocol used was a combination of 5-hydroxytryptamine-3 ($5HT_3$) – antagonists (ondansetron) and dexamethasone.

Radiotherapy schedule

Radiotherapy was delivered by 3D conformal radiotherapy (3DCRT). Planning was by CT simulation from vertex to mid-thorax (level of T6 vertebra) with 3 mm slice thickness. Contouring was as per RTOG guidelines[11] with contouring of the Gross tumour volume (GTV) and the Clinical target volume (CTV), which was the GTV plus areas at risk for microscopic disease spread. A standard fractionation of 70Gy in 35 fractions was used for all patients. Radiotherapy was delivered using linear accelerators, and treatment was administered on five days a week (Monday to Friday, with a planned break on Saturday and Sunday).

Toxicity evaluation

All patients on treatment were assessed on a weekly basis in our medical oncology and radiation oncology outpatient departments. The toxicities were graded according to the Radiation Therapy Oncology Group (RTOG) and common toxicity criteria (CTCAE) guidelines.[12] Serial weekly monitoring of performance status, mucositis, skin reaction, full blood count, urea, creatinine and electrolytes were performed. Patients were considered unfit for further chemotherapy when there was deterioration of performance status, kidney function (GFR <50 mL/min), or blood counts (absolute neutrophil count <1500 cells and platelets <100,000); the cycle was first delayed and these patients were reassessed, however if the derangements persisted no further chemotherapy was administered. Chemotherapy was also discontinued if grade IV toxicity occurred.

Statistical analysis

Overall survival (OS) was defined as the time from the date of diagnosis of malignancy to the date of death or last follow-up in clinic. Disease free survival (DFS) was defined as the time from date of diagnosis of malignancy to date of proven recurrence. Kaplan-Meier curves were plotted to calculate OS. The compliance to chemotherapy treatments were measured as numbers of cycles completed. The parameters studied as potential determinants of OS or PFS were treatment breaks while on chemotherapy, average weight loss and tube dependence (requirement of nasogastric or gastrostomy tube for maintenance of nutrition), 3 months post-treatment. Survival curves were generated using the Kaplan Meier method and log rank test was used for univariate analysis. Multivariable analysis was performed using the Cox proportional hazards model. All statistics were 2-sided, and $P < 0.05$ was considered statistically significant. Data analysis was performed using STATA 13 software.

Results

Overall characteristics

Patient and disease characteristics are shown in Table 1. The mean age in our cohort was 75.18 years (range 70-86 years), with a predominance of males (91%). Major co-morbidities were documented, which included type 2 diabetes, coronary artery disease, cerebrovascular disease, chronic obstructive pulmonary disease, hypertension, chronic kidney disease, chronic liver disease and others. Less than half (46%) had no co-morbidities, nearly a third (31%) had a single co-morbidity and the remaining had two or more. The median follow-up in this cohort was 23 months (range 6-108 months). Stage of disease was III (25%) or IVA/B (75%). Hypopharynx was the commonest subsite involved by cancer (n = 24), followed by larynx (n = 18) and oropharynx (n = 15). Patients received either cisplatin (n = 35) or carboplatin (n = 22) as chemotherapy along with radiation as part of radical CCRT. Only 61% of patients completed chemotherapy (defined as cumulative dose of 200 mg/m^2 of cisplatin and 5 weekly dose of carboplatin at AUC 2). All but one patient (98%) completed radiation, with no treatment related death. The mean weight loss was 3.53 kg (range 0-10 kg).

Table 1: Patient and disease characteristics

Patient and disease characteristics	
Age (years)	Median (SD): 75 (±3.97) years, range 70-86 years
70-79 years	48 (84%)
≥80 years	9 (16%)
Sex (%)	
Male	52 (91%)
Female	5 (9%)
Performance status (%)	
ECOG 1	31 (54%)
ECOG 2	26 (46%)
Site (%)	
Larynx	18 (32%)
Hypopharynx	24 (42%)
Oropharynx	15 (26%)
Smoking (%)	
Yes	22 (39%)
Co-morbidities	
No co-morbidities	26 (46%)
One co-morbidity	18 (31%)
Two co-morbidities	7 (12%)
Three co-morbidities	6 (11%)
TNM Stage (%)	
III	14 (25%)
IV	43 (75%)
Chemotherapy	
Cisplatin	35 (61%)
Carboplatin	22 (39%)

Table 2: Treatment characteristics

Treatment characteristics		
Radiotherapy completed (%)		56 (98%)
Treatment breaks (%)		5 (9%)
Toxicities		
Skin reactions	Grade I	8 (14%)
	Grade II	12 (21%)
	Grade III	15 (26%)
	Grade IV	9 (16%)
Mucositis	Grade I	8 (14%)
	Grade II	5 (9%)
	Grade III	11 (19%)
	Grade IV	5 (9%)
Dysphagia	Grade I	12 (21%)
	Grade II	7 (12%)
	Grade III	8 (14%)
	Grade IV	13 (23%)
Hyponatremia	Grade I	8 (14%)
	Grade II	5 (9%)
	Grade III	11 (19%)
	Grade IV	4 (7%)
Thrombocytopenia	Grade I	2 (4%)
	Grade II	1 (2%)
	Grade III	6 (11%)
	Grade IV	1 (2%)
Neutropenia	Grade I	8 (14%)
	Grade II	4 (7%)
	Grade III	15 (26%)
	Grade IV	3 (5%)
Hypercreatinemia	Grade I	2 (4%)
	Grade II	1 (2%)
	Grade III	5 (9%)
	Grade IV	1 (2%)
Fatigue	Minor	3 (5%)
	Major	9 (16%)
Post-treatment residual disease		0
Recurrence		20 (35%)
Tracheostomy dependence at 3 months		4 (10%)
Feeding tube dependence at 3 months		14 (32%)
Feeding tube and tracheostomy dependence at 3 months		4 (10%)
Chemotherapy completed		35 (61%)

Treatment-related toxicities

Treatment characteristics are shown in Table 2. The most common hematological toxicities with cisplatin were neutropenia (grade III in 26% and grade IV in 7%) and thrombocytopenia (grade III in 11% and grade IV in 2%). Carboplatin was associated with higher grades of hypercreatinemia (grade III in 9% and grade IV in 2%). Interestingly, all the patients who developed hyponatremia were on cisplatin chemotherapy; none in the carboplatin arm developed hyponatremia. Mucositis was a common occurrence (grade III in 19% and grade IV in 9%). Feeding tube dependence was noted in 32%, tracheostomy dependence was noted in 10% and both feeding and tracheostomy tube dependence were noted in 10% of patients of larynx/hypopharynx cancer at 3 months following completion of treatment. Of these, only 3 patients (7%) underwent tracheostomy prior to commencement of CCRT.

Determinants of survival

Factors predicting good disease free survival (DFS) were ECOG status (1 vs 2) (P = 0.031) [Figure 1] and completion of treatment without any breaks while on CCRT (P = 0.04) [Table 3]. Based on the age distribution, we divided the cohort into those below or equal to 75 years of age and those older; patients older than 75 years had a negative trend in DFS compared to their younger counterparts (P = 0.08). Factors that were not statistically significant predictors of DFS but were associated with a higher risk of recurrence were hyponatremia (HR = 1.11), hypercreatinemia (HR = 1.22) and weight loss of more than 3 kgs from baseline while on treatment (HR = 1.20). There was no difference in DFS or OS between the weekly or three-weekly administered cisplatin groups. DFS in patients who received CCRT was 22 months and 15.53 months for stage III and IV respectively. The only factor that was found to impact treatment or disease related death was tube dependence; dependence on a tracheostomy or feeding tube at three months following completion of chemoradiotherapy was associated with a 2.7-fold increase in risk of death in patients with hypopharynx or larynx cancer, HR = 2.7 (95% CI 1.880-3.833 P = 0.005) [Table 4].

Discussion

Definitive CCRT is considered standard of care for locoregionally advanced head and neck squamous cell carcinomas of the larynx, hypopharynx and oropharynx. But in older patients, physicians are often not keen adding

chemotherapy to radiotherapy fearing issues with tolerance and adverse events. Chemotherapeutic agents when used in combination with radiotherapy have been shown to improve locoregional control and survival. They act as radio-sensitizers, causing potential damage by forming DNA adducts and cell cycle arrest in G2 phase.[13]

Elderly patients with good performance status tolerated CCRT in our study with a few adverse events; 61% of the patients completed chemotherapy and 98% completed the proposed schedule of radiation therapy. The dose of cisplatin used was 100 mg/m² three-weekly or 40 mg/m² weekly for a total of 6 doses, as used in a large number of trials.[14-16] With the median age in the study group being 75 years and the oldest treated patient being 86 years old, this study demonstrates the reasonable tolerance of the elderly to CCRT; elderly patients should not be denied the option of CCRT based only on chronological age. In the context of the recent trial that showed three-weekly cisplatin is clearly advantageous over weekly cisplatin for locally advanced head and neck squamous cell carcinoma,[17] it was relevant to note that there was no difference in survival between these groups in our study. Although our samples size is small, this may suggest that the less toxic weekly dosing may be sufficient for locoregional control in these patients. It also demonstrates that age is not a proxy for functional status and may not adequately determine which patients are most likely to tolerate and complete a full course of CCRT.

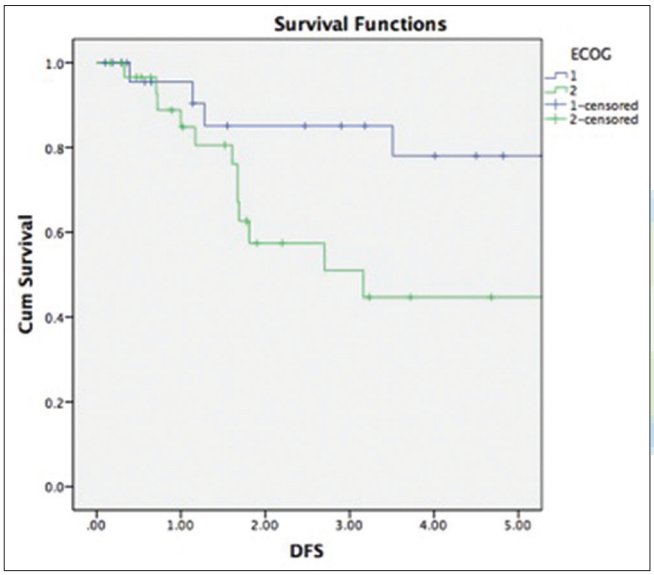

Figure 1: Disease free survival (DFS) of cohort based on European Cooperative Oncology Group (ECOG) functional status: (1) ECOG 1 (2) ECOG 2. *P* = 0.04

While hematologic complications are chemotherapy-specific, both chemotherapy and radiotherapy contribute to oral complications, and their combination results in an additive effect.[18] The rate of severe mucositis in patients who received CCRT in our study was 28%, which was lower than other studies that were in the range of 43-45%.[19-20] Another consideration in administering chemotherapy to the elderly is a reduced hematopoietic reserve, predisposing them chemotherapy-induced myelotoxicity.[21] The hematologic toxicities in our study were grade III/IV neutropenia in 33% and grade III/IV thrombocytopenia in 13%, with no treatment-related mortality. This was in contrast to a recent study by Strom *et al*.,[22] who showed that patients over seventy years, who predominantly received three-weekly cisplatin had five times the risk of mortality at three months following therapy compared to their younger counterparts.

Based on predictors of disease free survival and overall survival, our data suggests that patients over seventy who are most likely to benefit from chemotherapy are patients under seventy five years with a good performance status, those having no pre-treatment indicators of tube dependence (pre-treatment dysphagia, laryngeal dysfunction or tube dependence), and those likely to complete treatment without breaks.

These findings concur with those in a recent analysis of the National Cancer Data Base by Amini *et al*.,[23] who evaluated survival outcomes in elderly patients with locally advanced head and neck cancer treated with CCRT. Their study included over four thousand patients, and found a survival benefit with addition of chemotherapy

Table 3: Multivariate analysis for determinants of disease free survival

Characteristic	Category	Confidence interval	Hazard ratio	*P*
Treatment breaks	Yes	1.02-6.32	2.54	0.04*
	No			
Performance status	ECOG 1	0.09-0.70	4	0.031*
	ECOG 2			
Age	70-75 years	1.01-1.20	1.09	0.08
	>75 years			
Hyponatremia	Yes	0.78-1.58	1.11	0.549
	No			
Hypercreatinemia	Yes	0.75-1.99	1.22	0.421
	No			
Weight loss ≥3 kg on treatment	Yes	0.35-1.95	1.20	0.670
	No			
Chemotherapy	Cisplatin	0.08-3.35	1.08	0.419
	Carboplatin			
Completion of chemotherapy	Yes	4.34-6.46	0.98	0.987
	No			

*$p<0.05$ is significant

Table 4: Multivariate analysis for determinants of disease or treatment related death

Characteristic	Category	Confidence interval	Hazard ratio	*P*
Treatment breaks	Yes	0.31-9.28	1.14	0.43
	No			
Performance status	ECOG 1	0.29-10.5	1.2	0.420
	ECOG 2			
Age	70-75 years	0.61-4.93	1.17	0.110
	>75 years			
Hyponatremia	Yes	0.06-5.98	1.21	0.565
	No			
Hypercreatinemia	Yes	0.35-1.90	1.09	0.379
	No			
Weight loss ≥3 kg on treatment	Yes	0.64-12.8	1.12	0.513
	No			
Tube dependence (tracheostomy or feeding tube)	Yes	1.88-3.83	2.70	0.005*
	No			
Chemotherapy	Cisplatin	0.98-5.32	0.90	0.350
	Carboplatin			
Completion of chemotherapy	Yes	2.68-4.83	1.04	0.480
	No			

*$p<0.05$ is significant

to radiotherapy in the 71 to 81 year age group, except in poor performance status and advanced TNM stage of disease. Their criticism of MACH-NC study[7] was that the exclusion of elderly patients from trial settings resulted in an underrepresentation of the elderly in this meta-analysis (only 4% of the 17,346 patients were over seventy years of age), and that the study included data from the 1960s and 1970s, where radiotherapy and chemotherapy were more morbid. Another publication from the National Cancer Data Base by Giacalone *et al*.[24] showed similar improvement in OS when CCRT was compared with radiotherapy, adjusted for co-morbidity, stage, age and primary site.

An earlier study from the Surveillance, Epidemiology and End Results (SEER) database by VanderWalde *et al*.,[25] however, showed conflicting results in their cohort of over ten thousand patients. Their finding was that addition of chemotherapy was associated with a 13% higher risk of mortality in patients over seventy. However it must be noted that unlike the study by Amini *et al*., this cohort included patients receiving induction chemotherapy as well; patients undergoing induction chemotherapy have been shown to be less likely to completely concurrent chemoradiotherapy, impacting survival. They also included surgical subsites where CCRT is not the standard of care (oral cavity, salivary glands, middle ear) and had incomplete data on nodal and overall TNM staging.

Our findings of elderly patients with a performance status ECOG 1 having a better survival than those with a worse performance status were reflected in another recent study published by der Grun *et al*.;[26] elderly patients with ECOG status 2 or 3 in their study had worse progression free and overall survival. They did not note a difference in survival between the age groups ≥65 years, ≥70 year and ≥75 years, whereas our results showed a negative trend in survival for those over 75 years of age. Lai *et al*.[27] also found performance status to be a key predictor of survival in elderly patients receiving CCRT; they also found T-stage and total dose of radiotherapy to be significant determinants of outcome.

There were, however, three unique findings in our study, which to our knowledge, have not been demonstrated in this age group. Firstly, completion of chemotherapy (defined by number of cycles or area under the curve) was not found to impact recurrence or survival. This is important to note since only 61% of our cohort successfully completed chemotherapy. The benefit of chemotherapy in the elderly *may* exist even at a suboptimal dose, however this needs to be verified in a larger cohort of patients. Secondly, choice of chemotherapeutic agent (cisplatin or carboplatin) was not associated with a difference in recurrence or survival. Thirdly, tube dependence in laryngeal/hypopharyngeal cancers persisting beyond three months after completion of chemotherapy was associated with a significantly higher risk of mortality in the elderly. These deaths were due to disease or aspiration pneumonia, which is considered late sequelae of chemoradiotherapy toxicity. From an oncological standpoint, tube dependence may represent a persistence or recurrence of the underlying disease process, but mortality from aspiration pneumonia in this age group is likely to be lethal; patients in this age group are unlikely to tolerate laryngeal dysfunction.

Contrasting data and a lack of consensus makes a definitive recommendation difficult. Based on our findings, it is to be noted that for a subset of patients over seventy, chemotherapy is well tolerated and improves survival. This makes it difficult to support the notion that age be used as a contraindication to the current standard of care for locally advanced HNSCC. In our cohort, 61% completed chemotherapy, 98% completed radiotherapy and no patients had residual disease after treatment. The treatment response was good; the 2-year DFS of patients with stage III disease was 80% and stage IV disease was 55%. It is our recommendation that patients between seventy and

seventy-five years of age with a good performance status, who are motivated and likely to complete treatment be offered concurrent chemoradiotherapy as the standard of care. Whether aggressive swallowing rehabilitation improves survival by preventing aspiration pneumonia in this age is a question that needs to be answered by prospective study.

Conclusion

Curative intent chemoradiotherapy should be considered as standard of care even in patients above 70 years with good ECOG status. Both cisplatin and carboplatin were well tolerated and associated with good oncological and functional outcomes. Factors that predicted good disease free survival were patients with ECOG 1, age between 70-75 years and completion of treatment without breaks. Tube dependence was associated with a significantly higher risk of mortality due to disease or aspiration pneumonia.

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Conflicts of interest

There are no conflicts of interest.

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