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Assessing cumulative acute toxicity of chemoradiotherapy in head and neck cancer with or without induction chemotherapy☆,☆☆

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ABSTRACT

Background: To compare cumulative acute toxicity in head and neck cancer patients treated with concurrent chemoradiotherapy alone (CCRT) versus induction chemotherapy (IC) followed by CCRT (I/CCRT).
Methods: 77 patients underwent definitive CCRT (30 I/CCRT and 47 CCRT). Toxicity was graded using the Common Terminology Criteria for Adverse Events version 4.0. Using the TAME adverse event reporting system, short-term toxicity (T) scores were generated for IC (T_{IC}), CCRT (T_{CCRT}), total treatment duration (T_{Rx}), post-treatment period (T_{PT}) and an overall score ($T_{overall}$) from treatment start to post treatment period.
Results: Acute toxicity other than dysphagia, odynophagia, or dermatitis was reported in 90.0% and 66.0% of I/CCRT and CCRT patients, respectively ($P = 0.02$). Compared to CCRT group, I/CCRT patients reported greater mean T_{Rx} (T_{Rx}: 2.11 vs. 2.87, $P = 0.01$) and $T_{overall}$ ($T_{overall}$: 2.60 vs. 3.70, $P = 0.003$).
Conclusion: I/CCRT patients reported more cumulative acute toxicity during treatment compared to CCRT patients using the TAME reporting system.

1. Introduction

In 2015, head and neck cancers (HNC) comprised an estimated 3.6% of all newly diagnosed cancers and approximately 2.1% of all cancer-related deaths in the US, with major risk factors being smoking, alcohol consumption, and human papilloma virus infection (HPV) [1]. HNC treatment is targeted towards locoregional control (LRC), a determining factor for long-term outcome [2]. The current standard of care for locally advanced HNC is concurrent chemoradiotherapy (CCRT) [3], which improves LRC and survival compared to radiotherapy (RT) alone through the radiosensitizing effect of chemotherapy [4].

Induction chemotherapy (IC) is a part of the treatment strategy for some solid tumors, with aims to cytoreduce the primary allowing for more effective and less toxic locoregional treatment while eradicating micrometastases. Induction chemotherapy regimens of docetaxel, cisplatin, and 5-fluorouracil (TPF) showed promising results in phase I–II trials [5]. This was followed by randomized trials which showed improved survival among patients treated with TPF regimen compared to patient receiving cisplatin, and 5-fluorouracil (PF) regimen. However, recently phase III randomized trials evaluating IC followed by CCRT compared to CCRT have failed to demonstrate a survival benefit to the addition of IC [6–8]. Criticisms include the lack of stratification for HPV status for oropharyngeal carcinoma and not sufficiently advanced overall stage distribution. Despite these data, IC still remains a treatment intensification consideration for locally advanced HNC. However, acute toxicities from this paradigm may delay the start of definitive CCRT and offset any potential gains IC.

The objective of this study was to compare the cumulative acute treatment-related toxicity, disease control and survival outcome in HNC patients treated with I/CCRT versus CCRT alone in an urban tertiary academic medical center. We employed the acute toxicity "T" score metric from a relatively new adverse event reporting method to concisely and uniformly assess the cumulative acute side-effects of treatment [9].

2. Materials and methods

2.1. Patient selection

The study was performed as a retrospective review approved by the institutional review board with a waiver of informed consent. From

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December 2005 to January 2012, 77 patients with biopsy confirmed HNC underwent definitive concurrent chemoradiotherapy therapy at our institution. Patients with recurrent disease or history of malignancy within the previous 5 years were excluded. All patients were staged according to the 2002 American Joint Committee on Cancer (AJCC) classification with history, physical examination, focused head and neck evaluation, panendoscopy with biopsy, and positron emission tomography (PET) [10]. The final study population consisted of 30 patients who received I/CCRT, and 47 patients who received CCRT alone.

2.2. Demographics and tumor characteristics

Patient demographic data was obtained from hospital registration records and included age at diagnosis (years), gender, race/ethnicity (white, black, other), primary language spoken (English or other), marital status (married or unmarried). Patients were classified into smokers if they were current smokers or had a past smoking history. For smokers, pack-year smoking history was collected if available. Tumor staging including AJCC and TNM stage were ascertained from clinical records. Oropharyngeal tumors comprised 36.4% ($n = 28$) of all patients. Non-oropharyngeal tumors included those of the oral cavity ($n = 7$), larynx ($n = 15$), hypopharynx ($n = 12$), nasopharynx ($n = 10$), unknown primary ($n = 3$) and other ($n = 2$). Primary (GTV-P) and nodal (GTV-N) GTVs were derived from planning dose volume histograms (Philips Pinnacle® software suite), and are detailed in the Supplemental Materials section.

2.3. Treatment

Seventy one patients were treated with IMRT (29 I/CCRT and 42 CCRT) and 6 patients were treated with 3D-CRT (1 I/CCRT and 5 CCRT). All patients were treated to a median dose of 70.0 Gy (range 67.8–72.0) over a mean of 50 days. Choice of chemotherapy regimen was at the discretion of the medical oncologist, as detailed in the Supplemental Materials section. During CCRT, all patients received weekly chemotherapy. CCRT duration and change in dose or agent were also recorded for all patients. Lastly, differences in missed treatment weeks were also analyzed.

2.4. Toxicity assessment

Toxicity (adverse event) is a standard defined variable, which includes any unfavorable and unintended sign, symptom, or disease temporally associated with treatment. Acute toxicities were assessed retrospectively by a single author who categorized and graded each toxicity on a severity scale using the using the (CTCAE), version 4.0. The CTCAE is organized into system organ class (SOC) groups within which adverse events and their severity scale are listed. The incidence of toxicity Common Terminology Criteria for Adverse Events was recorded separately for three phases: a) induction chemotherapy, b) concurrent chemoradiotherapy and c) post treatment period (3 months following treatment completion). Cumulative acute toxicities for all phases of treatment (start of induction to end of CCRT for I/CCRT patients and duration of concurrent chemoradiotherapy for CCRT patients) were also calculated. Toxicities with grade ≥ 3 were recorded and compared.

2.5. Short-term (acute) toxicity score (T-score)

TAME is a summary reporting system of adverse events which was designed to address deficiencies in the established models of adverse event data reporting [9]. It is suggested as a supplement to more detailed reporting of adverse events associated with a toxicity profile. It consists of following domains: short-term (acute) toxicity (T), adverse long-term (late) events (A), treatment-related mortality (M), end-results (E) summary format.

The calculation of short-term (acute) toxicity, T-score, is described in detail first [9]. Briefly, grade 3 and grade 4 adverse events are combined into one clinically important high-grade [3,4] category. For each patient, one high-grade event per adverse reporting category is then counted. An individual patient data (IPD) T score is then generated for each patient by summing the number of high-grade events reported for that patient during a defined treatment interval period. Mean T-score is then calculated by taking mean of IPD T scores during each interval.

Using this methodology, T-scores were calculated for induction chemotherapy (T_{IC}), concurrent chemoradiotherapy (T_{CCRT}), total treatment duration (T_{Rx}) (induction and concurrent chemoradiotherapy period for I/CCRT and concurrent chemoradiotherapy period for CCRT group) and post treatment (T_{PT}) period. T-scores from different time periods were then added to generate an overall T-score ($T_{overall}$) for I/CCRT ($T_{overall} = T_{IC} + T_{CCRT} + T_{PT}$) and CCRT ($T_{overall} = T_{CCRT} + T_{PT}$) groups.

2.6. Other data collection

Information on G-tube placement before, during and post treatment was collected along with any further treatment received during the 3-month follow-up period post CCRT. In addition, the number of hospitalizations during induction chemotherapy, the interval following induction, concurrent chemoradiotherapy, and post treatment were recorded. Patient weight was recorded at the beginning of induction chemotherapy (for I/CCRT patients), start of concurrent chemoradiotherapy and at the end of the treatment period. Percent change in weight was calculated for total treatment duration and concurrent chemotherapy alone.

2.7. Follow-up

Patients were followed after the conclusion of treatment and continuing until analysis or patient death. Follow-up consisted of serial clinical examinations every 3 months, including fiberoptic examination, a PET/CT at approximately 12 weeks after completion of RT, and then annually for patients who obtained a complete response as part of routine clinical care. Disease recurrence was defined as site of failure including local failure, nodal failure or distant failure. All failures were confirmed by biopsy.

2.8. Statistical analysis

Differences in normally distributed continuous variables were evaluated using a two-tailed Student's *t*-test. Non-parametric Wilcoxon-Mann-Whitney test was used to assess differences in median values. For categorical variables and comparisons of incidence of acute toxicities between I/CCRT and CCRT patients, Chi-square or Fisher's exact test was performed when appropriate.

Two-year actuarial rates were estimated for local control (LC), nodal control (NC), distant control (DC), overall survival (OS) (death due to any cause), and disease-free survival (DFS) using the Kaplan-Meier method [11]. All endpoints were measured from the end of RT until relapse or death with censorship at last follow-up or death. A probability value of <0.05 was considered statistically significant for all analyses. All statistical computations were performed on SAS 9.1 system (SAS Institute, Cary, NC).

3. Results

3.1. Patients, tumor and treatment characteristics

The mean age of the patient population was 58.4 years with males comprising 72.7% of patient cohort. Sixty five patients (84.4%) reported a current or past smoking history with mean of 39.1 pack-years. There were no significant differences between the groups with respect to their demographics. I/CCRT patients were diagnosed with more

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