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Predictive factors of survival and treatment tolerance in older patients treated with chemotherapy and radiotherapy for locally advanced head and neck cancer

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SUMMARY

Purpose: To report outcomes and predictive factors of overall survival, hospitalization and treatment completion rates in elderly patients with locally advanced head and neck cancer treated with concurrent chemoradiotherapy (CRT).

Material and methods: A retrospective analysis of patients aged 70 years or older treated with concurrent CRT for locally advanced head and neck cancer was conducted. Univariate and multivariate analysis as well as competing risk survival analysis were used to determine predictors of mortality. Logistic regression was used to predict for hospitalization and treatment completion rates.

Results: In total, 129 patients were included. Median follow-up was 27 months (range: 1.7–125 months). Completion rate of combined CRT was 84%. Actuarial OS and DSS at 4 years were 56% and 75%. Hospitalization rate was 36%. On multivariate analysis, a Karnofsky performance status (KPS) $\leqslant$80 was predictive of mortality. Using competing risks, KPS $\leqslant$80 and weight loss >5% were predictive of cancer mortality whereas Charlson score $\geqslant$3 was predictive of mortality due to other causes. On logistic regression, patients with abnormal renal function and lower body mass index were more likely to be hospitalized during their treatment course. Charlson score and chemotherapy regimen were predictive of treatment completion.

Conclusion: Concurrent CRT may be a feasible treatment option for healthier older patients at the cost of high hospitalization rates. Pre-treatment factors linked to physiological age such as KPS $\leqslant$80, Charlson score $\geqslant$3, abnormal renal function should be considered at the time of treatment decision.

Introduction

The incidence of head and neck cancers (HNC) in the elderly population continues to increase. In fact, it is estimated that between 24 and 40% of head and neck cancers occur in patients over 70 years of age [1,2]. Concurrent chemoradiotherapy (CRT) has been established as the standard treatment for locally advanced head and neck cancer (LA-HNC)[1] [3], yet clinical trials evaluating the role of concurrent CRT rarely include elderly patients. Consequently, there are limited evidence-based guidelines on the adequate management of LA-HNC in the elderly population, which is believed to be at greater risk of exaggerated toxicities [4,5]. In fact, a pooled analysis of 230 patients with HNC treated with concurrent CRT from 3 RTOG studies showed that age was a strong independent risk factor for the development of severe late toxicities [6]. A meta-analysis has shown that patients over 70 years of age with HNC cancers had lower tolerance and compliance to treatment and increased rates of death not related to cancer [3]. As a result, clinicians have traditionally been reluctant to expose elderly patients to serious treatment toxicity and

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in current practices, patients with advanced age will often receive less aggressive substandard treatments based solely on their chronological age even when they have limited co-morbidities [7–10]. Recent data rather emphasizes the importance of functional age and defines the elderly patient as an individual who's health status could interfere with oncological treatment guidelines [11]. In fact, the elderly population is constituted of a broad spectrum of patients: from healthy and totally independent patients to fragile patients at higher risk of functional decline or even death [12–14]. Treatment prejudice against elderly cancer patients has been challenged recently as some small single center series reported treatment tolerance in these patients to be comparable to that of younger patients if they received adequate management and support [15]. Furthermore, new radiotherapy treatment techniques such as intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) have improved patient tolerance to irradiation because of the sharp dose fall off which significantly decreases radiation to the normal tissues [16–18]. Clinical uncertainty in determining the best management in the elderly can lead to suboptimal or exaggeratedly toxic treatment; for this reason, it becomes important to properly select patients for aggressive therapy and to anticipate their functional response. The purpose of this study was to report outcomes and predictive factors of overall survival (OS), hospitalization and treatment completion rates in elderly patients with LA-HNC treated with concurrent CRT at our institution.

Material and methods

Patients' characteristics

A retrospective analysis of patients aged 70 years or older treated with concurrent CRT for locally advanced HNC between May 2000 and December 2012 was conducted. Inclusion criteria were: (1) histology proven squamous cell carcinoma of the head and neck; (2) stage III, IVa or IVb (T1-4, N0-2c and N3M0) as per the American Joint Committee on Cancer 7th edition; (3) treatment with curative intent; (4) treatment with concurrent CRT. Patients with neoadjuvant chemotherapy followed by concurrent CRT and patients with post-operative CRT were included in this study. Patients with recurrent or metastatic disease were excluded from the study. Initial work-up at diagnosis included for all patients: complete blood count and biochemistries, a computed tomography (CT) scan of the neck, a chest X-ray or a CT scan of the thorax and a histological confirmation of squamous cell cancer. Thirty-five percent of patients had fluoro-2-deoxy-D-glucose-positron emission tomographic (FDG-PET) scan as part of their initial investigations. Treatment decision was determined in a joint committee formed by radiation oncologists, medical oncologists, head and neck surgeons and diagnostic radiologists. Patients underwent pre-treatment evaluation by a multidisciplinary team including nutrition, speech therapy and maxillofacial surgery. Reasons to begin nasogastric tube feeding during treatment included: weight loss of >10% from pre-treatment baseline, uncontrolled pain with swallowing or risk of aspiration as demonstrated by modified barium swallow examination after assessment by a speech therapist. When it was estimated that a feeding tube would be required for longer than 3 months (ex: In patients with symptoms of aspiration at the beginning of their treatment course or patients with low potential of recovery of their normal swallowing function), a percutaneous gastrostomy was installed. Institutional ethics review board approval was obtained for this study.

Radiotherapy

All patients had a 1.5 mm slice thickness planning computed tomography (CT) scan from the vertex to the carina with and without intravenous contrast injection in supine position. Immobilisation device included a thermoplastic mask of the head and shoulder fixed to the treatment table. When available, positron tomography (PET)-CT scan and magnetic resonance imaging for tumor imaging were fused with planning CT. Patients were treated using 6-MV photons, and treatment was given in 5 daily fractions per week. Patients undergoing definitive CRT were planned to receive a dose of 70 Gy in 33 fractions with a simultaneous integrated boost when treated with intensity modulated radiotherapy (IMRT) or a dose of 70 in 35 fractions when treated with 3D-conformal radiotherapy. Patients undergoing postoperative CRT were treated to 60–66 Gy in 30–33 fractions. Indications for postoperative CRT were positive margins and/or extra-capsular lymph node invasion. Treatment plans were normalised so that the prescription dose covered at least 95% of the PTV volume. Treatment techniques included sliding window IMRT, Helical Tomotherapy™, RapidArc™ and 3D-conformal radiotherapy.

Chemotherapy

Chemotherapy regimen was one of the following: (1) carboplatin 70 mg/m^2/day in bolus for 4 days, with 5-fluorouracil (FU) 600 mg/m^2/day as a continuous infusion for 4 days every 3 weeks for 2–3 cycles, (2) high dose cisplatin (100 mg/m^2) every 3 weeks for 2–3 cycles, (3) weekly low dose cisplatin (30–35 mg/m^2/day) for the duration of the radiation (4) weekly cetuximab at an initial dose of 400 mg/m^2/day followed by 250 mg/m^2 for the following doses for the duration of the radiation (6–8 weeks). Chemotherapy started on the first day of radiotherapy.

Complementary neck dissection

A CT scan of the head and neck area was done 6–8 weeks after completion of CRT. If residual disease was observed on the CT scan (defined as reduction in lymph node diameter of less than 80% [19]) or at the clinical examination, a complementary neck dissection was offered to patients.

Follow-up and statistics

Standard follow-up for all patients typically included: (1) weekly visits after treatment at a multidisciplinary clinic involving the treating radiation oncologist, oncology nurse, nutritionist and speech therapist for 4–6 weeks or as needed, (2) alternating otolaryngology and radiotherapy follow-ups every 2 months for the first 2 years, every 4 months for the following 3 years and annually thereafter. Every patient had a follow-up CT scan 6–8 weeks after treatment and periodically during the first 2 years if symptoms and/or results on physical examination were suspicious for recurrence. A chest radiograph was done annually. Local failure was detected based on clinical examination and/or CT scan (± TEP scan) and confirmed histologically. Treatment toxicities were graded per treatment, by the treating physician. Toxicities were graded as per Common Toxicity Criteria for Adverse Events (CTCAE) version 2.0.

Follow-up duration was defined as the time from the date of diagnosis to the date of last follow-up or death. Reported outcomes included disease-specific survival, overall survival, treatment completion, hospitalization, cause of mortality as well as grade $\geqslant 3$ toxicity rates. Cause of mortality was based on one of the following: hospital admission records, palliative care team follow-up notes or treating physician follow-up notes. Incomplete treatment was defined as a radiation dose inferior to the prescribed dose and/or <2 cycles carboplatin/5-FU or high dose cisplatin, <6 cycles of cetuximab, or <6 cycles of weekly cisplatin.

Kaplan–Meier method was used for estimation of overall survival (OS) and disease specific survival (DSS). Logistic regression