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Impact of fraction size on locally advanced oropharyngeal and nasopharyngeal cancers treated with chemoradiation ☆

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ABSTRACT

Objectives: Although chemoradiation regimens have used various fraction sizes, it remains unclear how differences in fraction size impact outcomes.
Materials and methods: Using the National Cancer Database, we identified patients with nasopharynx or oropharynx cancers treated between 2004 and 2012 with chemoradiation using fraction sizes of 1.8 Gy (n = 1612), 2 Gy (n = 8092) or 2.12 Gy (n = 1660). Comparisons between fraction sizes were made in the entire cohort and in a propensity matched cohort.
Results: Median follow-up was 38.1 m. Patients receiving 2.12 Gy per fraction were more likely to be treated from 2007 to 2012, to be treated at an academic center, to have T3-T4 tumors and to have oropharyngeal primaries. The 3 year overall survival for patients treated with 1.8 Gy, 2 Gy and 2.12 Gy fraction sizes was 72.9%, 77.8% and 83.3%, respectively (P < 0.0001). 2.12 Gy fraction size was associated with improved survival in patients with nasopharynx cancer (P = 0.03), base of tongue cancer (P < 0.0001) and tonsil cancer (P = 0.0002). On multivariate analysis, improved survival was associated with 2.12 Gy fraction sizes compared to 2 Gy (HR 1.23, 95% CI 1.09–1.40, P = 0.001) or 1.8 Gy (HR 1.36, 95% CI 1.17–1.58; P < 0.0001) fractions sizes.
Conclusion: Chemoradiation regimens using 2.12 Gy fraction sizes likely have a potential advantage in select nasopharynx and oropharynx cancer patients based on age, treatment facility and radiotherapy technique. However, it remains unclear if this survival advantage reflected improved disease control due to lack of locoregional control data.

Introduction

In locally advanced head and neck squamous cell carcinomas, the addition of chemotherapy given concurrently with radiation has improved locoregional control and/or overall survival [1,2]. Classically, chemoradiation has used fraction sizes of 1.8–2 Gy to a total dose of approximately 70 Gy [1–3]. The National Comprehensive Cancer Network recommendations do not currently agree on the optimal fraction size to use with concurrent chemoradiation [4]. Given the benefit of altered fractionation radiotherapy regimens in the absence of chemotherapy [5–8], several groups have incorporated slightly hypofractionated regimens in which the predominant fraction size of 2.12 Gy has been used. In particular, slightly hypofractionated regimens where the gross tumor volume is treated to 69.96 Gy in 2.12 Gy per fraction have been used with concurrent chemotherapy in three RTOG protocols for nasopharyngeal primaries and in multiple retrospective studies treating oropharyngeal cancers [9–13].

However, the results of RTOG 0234 casted doubt to the benefit for altered radiotherapy regimens to improve outcomes when administered with concurrent chemotherapy [14]. Compared to conventional fractionated regimens of 70 Gy in 2 Gy fractions, altered fractions did not increase disease control or survival. Nevertheless, RTOG 0234 used a delayed concomitant boost regimen that is different from slightly hypofractionated regimens, which, by incorporating simultaneous integrated boost techniques, treat the elective nodal regions using smaller fraction sizes. This delivery

Abbreviations: Gy, Gray; RTOG, Radiation Therapy Oncology Group; NCDB, National Cancer Database; CoC, Committee on Cancer; cSG, clinical Stage Grouping; cT, clinical T-stage; cN, clinical N-stage; HR, hazard ratio; OR, odds ratio; CI, confidence interval; OS, overall survival.

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of smaller fraction sizes to the elective nodal regions may improve treatment tolerability by causing less toxicity [15]. Furthermore, 40% of the patients in the RTOG 0129 had cancers involving the larynx, oral cavity or hypopharynx that have worse prognoses and may mask small differences in outcomes due to differences in fraction sizes. Therefore, the extent to which slightly hypofractionated regimens impact outcomes in patients with other head and neck cancers remains unclear.

Here, we used the National Cancer Database to compare outcomes in patients treated with conventional or slightly hypofractionated chemoradiation schemes in nasopharyngeal and oropharyngeal cancers.

Material and methods

Data sources

This study utilized the National Cancer Data Base (NCDB), which is a hospital based registry and is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors. The NCDB has set criteria to ensure the data submission by each cancer center meets pre-specified quality benchmarks.

Analysis population

This analysis included patients age ≥18 years old who had head and neck squamous cell cancers involving the nasopharynx, base of tongue or tonsil that received at least part of the initial treatment at the reporting facility and received chemotherapy and radiation (Fig. 1). Patients were excluded if they had evidence of *in situ* disease, distant metastatic disease, were treated with palliative intent or were treated to a total radiation dose <64 Gy or >75 Gy. Patients were treated between 2004 and 2012 because 2004 was the first year the National Cancer Database began collecting detailed information on radiation treatment and 2012 was the last year in the database with survival information. The cohort composition as derived from the whole database is shown in Fig. 1.

Variables

Demographic variables included age, sex, comorbidity, year of diagnosis, distance from treating facility and facility type. Age was grouped into four categories: ≤50 years, 51–60 years, 61–70 years and >70 years. Comorbidity index was based on Charlson/Deyo comorbidity score representing 0 comorbid conditions, 1 comorbid condition or ≥2 comorbid conditions. Year of diagnosis was grouped into 3 categories: 2004–2006, 2007–2009 and 2010–2012. Distance from treating facility was calculated based on the patients and treating facilities zip codes and grouped into 5 categories: <10 miles, 10–19 miles, 20–21 miles, ≥30 miles or unknown. Facility type was grouped into 4 categories: Academic/Research program (Academic), Comprehensive Community Cancer Program (Com Cancer), Community Cancer Program or Integrated Network Cancer Program (Com Other) and Unknown. Clinical variables included stage grouping clinical Stage Grouping 1–2 (cSG1-2 vs. cSG3-4), clinical tumor stage (cT1-2 vs. cT3-4), clinical N-stage (cN0-1 vs. cN2-3). Total radiation dose was calculated by adding the regional and boost doses. Fraction sizes were calculated by dividing the total radiation dose by the total number of treatment fractions. Fraction sizes were initially divided into ≤2 Gy or >2 Gy, respectively. Fraction sizes resulting in the whole numbers of 180, 200 or 212 were included in 1.8, 2 and 2.12 Gy groups. Fraction sizes not meeting these criteria were defined as other. Elapsed radiation days were defined as >65 d or ≤65 d in order to account for delays greater than one week for a 70.2 Gy regimen given in 1.8 Gy fractions. Treatment delays were categorized as ≥7 d or <7 d and calculated according to the expected number of days each fraction size was required to complete treatment in the following regimens: 70.2 Gy in 1.8 Gy/fraction, 70 Gy in 2 Gy/fraction or 69.96 Gy in 2.12 Gy/fraction. The Biologically Effective Dose (BED10) was calculated according the linear quadratic model: $nd\,[1 + d/(a/b)]$ where d = fraction size, n = number of fractions and

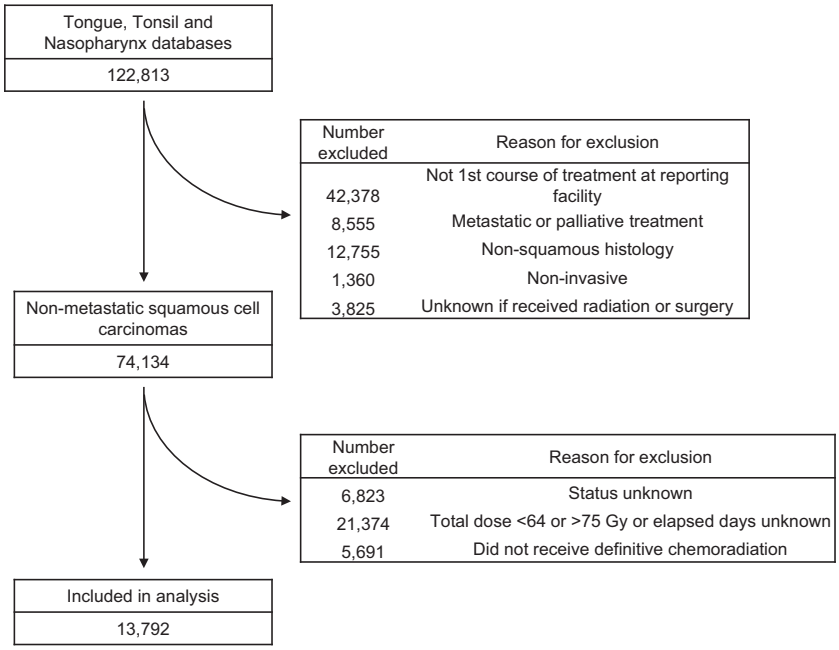

Fig. 1. Scheme to define the study cohort.