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The impact of institutional clinical trial recruitment versus hospital volume on survival outcomes of patients with head and neck cancer: An analysis of the PET-NECK trial outcomes, UKCRN portfolio, and Hospital Episode Statistics (HES) in England

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ABSTRACT

Objectives: High institutional clinical trial recruitment and high hospital volume are reported to be independent indicators of better patient outcomes following cancer treatment. However, their relationship in head and neck cancers (HNC) remains less clear.

Methods: We aimed to assess the relationship between institutional clinical trial recruitment, hospital throughput of HNC cases, and survival of patients with advanced HNC treated with primary chemoradiotherapy at hospitals which recruited to the PET-NECK trial (2008–2012). The impact on outcome was assessed using Cox's proportional hazards regression analysis and multivariate analysis.

Results: HNC RCT recruitment positively correlated with hospital throughput ($r = 0.57$, $p < 0.0001$). Low-recruiters (1–5 patients) had a 107% increased risk of death when compared to high-recruiters (> 5 patients) (HR = 2.07, $p = 0.05$). There was no significant impact of hospital throughput on overall or disease-specific HNC survival. Multivariate analysis identified p16 status, N-stage, smoking, and RCT recruitment volume as the only significant predictors of survival. There was a significant difference in chemotherapy regimen between low and high-recruiters ($p = 0.003$) where a higher proportion of patients (50%, n = 13) in low-recruiting compared to high-recruiting hospitals (29%, n = 92) received neoadjuvant chemotherapy. A higher proportion of these patients died at low-recruiting hospitals (46% versus 23%).

Discussion: A significant association exists between high recruitment and better OS for patients with HNC. However, no significance was found between hospital throughput and outcomes. The significance of individual centre differences in chemotherapy regimen needs further investigation. Future studies need a greater number of patient outcome events to support the trends found in this study.

Introduction

Studies have attempted to identify institutional factors that influence the outcome of patients undergoing treatment for cancer. The inverse relationship between high hospital volume and lower mortality for cancer treatment has been well documented in head and neck (HNC) and other cancers [1–6]. More recently, positive outcomes from cancer treatment have also been associated with institutional recruitment into clinical trials [7]. Wuthrick et al. demonstrated that institutions with high recruitment to clinical trials had a better 5-year overall survival

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compared to low recruitment centres [7]. Patients with HNC who were treated at low recruitment centres had a 91% increased risk of death (hazard ratio 1.91) [7]. To date however, the mechanisms underlying better outcomes at high volume hospitals and high recruitment centres have yet to be elucidated, especially whether the association of clinical trials with better outcomes is simply a surrogate for centre throughput or is an independent factor.

We hypothesised that outcomes for HNC are independently associated with recruitment to clinical trials, a marker of academic engagement, and not simply a surrogate for institutional patient throughput.

Methods

Subjects and databases

HES data for hospital throughput volume of head and neck cancers

The number of new patients with HNC treated at hospitals in England from 2007 through 2012 was obtained from the NHS England Hospital Episodes Statistics (HES) [8] database using the following International Classification of Diseases (ICD-10) codes for head and neck cancers: oral cavity cancer excluding inner part of lip and hard palate (C02, C03, C04, C06), oropharynx cancer excluding soft palate (C01, C09, C10), nasopharynx cancer (C11), hypopharynx cancer (C12, C13), larynx cancer (C32), and palate cancer (C05) [9]. The data was reported as the total number of HNC patients seen per year at each hospital in England, and an average annual hospital throughput of HNC patients was then calculated for 2007–2012.

Recruitment to head and neck cancer interventional clinical trials

Data on recruitment to head and neck clinical trials at all hospitals in England was obtained from the UK Clinical Research Network (UKCRN) [10] clinical trials portfolio database for the years 2008–2012, the period of recruitment of the PET-NECK trial. Recruitment data for the years prior to 2008 were aggregated, and therefore were excluded from the study. Only data on interventional trials was included in the statistical analysis. Only data for English hospitals was available, and no data was available for hospitals in Scotland, Wales, and Northern Ireland.

Patient characteristics and outcome data from the PET-NECK trial

The primary and secondary outcomes for this study were overall survival and disease specific survival of all patients recruited to the PET-NECK trial (UKCRN ID 3799) [11] at each participating hospital respectively. Additional demographic data and characteristics of these patients were also obtained and used in the multivariate analysis, including age, gender, smoking status, T-stage, N-stage, tumour p16 status, and Eastern Cooperative Oncology Group (ECOG) performance status.

Statistical analysis

Categorisation of hospital throughput

Cut-offs for recruitment and hospital throughput volumes were determined by identifying the tertiles of the whole hospital data. Kaplan-Meier survival curves of low and intermediate versus high recruiting hospitals, and conversely low versus intermediate and high hospital throughput groups were compared using log-rank tests. Correlation between institutional recruitment and hospital throughput was assessed. Multivariate analysis of the determinants of survival was then performed by adjusting for age, sex, p16 status, smoking, T-stage, N-stage, ECOG performance status, hospital throughput, and institutional recruitment. Proportions of each variable: N-stage, T-stage, oropharyngeal, chemotherapy regimen, age, sex, p16 status, ECOG status, and smoking status were compared across tertiles for recruitment and hospital throughput to assess for significant differences between groups.

Survival curves were produced using the Kaplan-Meier method. Adjusted analysis of survival and multivariate models used Cox's proportional hazards regression analysis. Tests of differences between groups based on count data were by Pearson's chi-square and where this is for a trend the Mantel-Haenszel chi-square was used. Analyses were performed using SAS version 9.3.

Results

Hospital throughput volumes

A total of 142 hospitals in England submitted HES data on the number of patients with head and neck cancers who were treated from 2008 through 2012. The average annual individual hospital throughput volume of HNC patients ranged from 0 to 297, with a mean of 49 HNC patients. Low throughput hospitals treated an average of less than 20 patients per year, intermediate throughput hospitals an average of 20–59 per year, and high throughput hospitals an average of 60 or more HNC patients per year (Supplementary 1: Fig. 1).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.oraloncology.2018.08.006.

Recruitment to interventional head and neck cancer clinical trials

A total of 96 HNC clinical trials were conducted in England from 2008 to 2012. Of those, 20 were interventional trials that completed recruitment between 2008 through 2012. A list of HNC clinical trials and reasons for inclusion or exclusion in this study are described in Supplementary 2: Table 1.

A total of 60 hospitals recruited to the 20 HNC interventional trials from 2008 through 2012. Total recruitment per hospital ranged from 1 to 116, with a mean of 21 HNC patients recruited during that period. The recruiting hospitals were classified into low, middle, and high-recruiter tertiles with 20 hospitals in each group (Supplementary 2: Table 2): low-recruiter centres recruited 6 patients or less in total between 2008 and 2012, intermediate-recruiters recruited between 7 and 18 patients, and high-recruiters recruited 19 or more patients to HNC interventional studies during the specified time period (Supplementary 2: Fig. 1).

Relationship between hospital throughput and recruitment

Amongst the hospitals that recruited to the PET-NECK trial, there was a positive association between hospital throughput and clinical trial recruitment, where high throughput hospitals tended to have higher recruitment to HNC interventional trials, with a Pearson's correlation of $r = 0.42$ ($p < 0.0001$) (Supplementary 3: Fig. 1).

Relationship between hospital throughput and survival

Using the higher tertile cut-off (60 per annum) for hospital throughput, there was no significant difference in OS between low (< 60) and high throughput (> 60 cases per year) hospitals ($p = 0.33$) (Fig. 1 and Supplementary 4: Fig. 1) and DSS ($p = 0.09$) (Supplementary 4: Figs. 2 and 3). However, the comparisons appeared to suggest that lower-throughput hospitals had marginally better outcomes than higher-throughput hospitals.

Relationship between recruitment and survival

The association between different thresholds of recruitment with OS was then examined using a Cox's proportional hazard model. Patients treated at the lowest tertile of recruiting hospitals (1–6 patients) appeared to show a trend towards worse OS (HR = 1.90, $p = 0.07$, 2-yr OS 69% low vs 86% medium and 83% high-recruiters) (Fig. 2). If a cut-