The impact of institutional clinical trial recruitment versus hospital volume on survival outcomes of patients with head and neck cancer

Lin, Daniel J.; McConkey, Christopher C.; Nankivell, Paul; Dunn, Janet; Mehanna, Hisham

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Title

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.

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 to 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.

Keywords

Clinical Trial; Patient Recruitment; High-Volume Hospitals; Low-Volume Hospitals; Outcomes Research; Survival Analysis; Head and Neck Cancer

Conflict of interest statement

None declared.

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 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 to 59 per year, and high throughput hospitals an average of 60 or more HNC patients per year (Supplementary 1: Figure 1).

Recruitment to interventional head and neck cancer clinical trials

A total of 96 HNC clinical trials were conducted in England from 2008 – 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: Figure 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: Figure 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 (less than 60) and high throughput (>60 cases per year) hospitals (p=0.33) (Figure 1 and Supplementary 4: Figure 1) and DSS (p=0.09) (Supplementary 4: Figures 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) (Figure 2). If a cut-off of 5 or less was applied, OS was significantly worse for low-recruiters (log-rank *p*=0.0442, Supplementary 5: Figure 1), with a 2-year OS of 66.0% (95% C.I. 45.5, 86.6) for centres recruiting between 1 and 5 patients, and a 2-year OS of 83.6%, (95% C.I. 80.1, 87.0) for centres recruiting 6 or more patients, with a hazard ratio of 2.07 (*p*=0.05). No significant difference was found between disease specific survival and recruitment volume (Supplementary 5: Figure 2).

Multivariate analysis

When multivariate analysis was performed, there was a statistically significant association between low trial recruitment volume (1-5 patients) and lower overall survival (HR=2.236, 95%CI=1.052 – 4.754, *p*=0.0365). Low nodal stage (HR=0.6, *p*=0.02), never smokers (HR=0.36, *p*=0.0085), and p16 negative status (HR=2.91, *p*<0.0001) were also significantly associated with overall survival. All other variables including hospital throughput, age, sex, T-stage, and ECOG did not show a statistically significant effect on survival (Table 1).

Potential causes for differences in survival

The only statistically significant difference in the characteristics of the three recruitment groups was in the chemotherapy schedules used to treat patients (~~Supplementary 6:~~ Table 2~~1~~), with a greater proportion of patients in low recruiting hospitals (50%, n=13) receiving neoadjuvant chemotherapy (TPF) (*p*=0.003). In the low-recruiter group, 6 out of 13 (46.2%) given docetaxel, platinum, and 5-fluorouracil (TPF) died; compared to 2 out of 8 (25%) on other chemotherapy regimens (mainly concomitant cisplatin) died. In the high-recruiter group, 25 out of 109 (22.9%) given TPF died; and 73 out of 335 (21.8%) on other chemotherapy regimens died. There were no other significant differences in variables across the groups.

Discussion

There have been several studies establishing positive associations between outcomes and patient throughput or trial recruitment. Our study, however, is the first to analyse the relationship of *both* throughput and recruitment into clinical trials with survival, enabling us to explore whether these are related or independent predictors of outcome. It confirms the recent finding of a positive association between recruitment to interventional studies and improved survival outcomes of HNC patients. According to our data, low recruiting centres have a 90% increased risk of death (HR 1.90, *p*=0.05) which is similar to that reported by Wuthrick et al. (HR 1.91). Our study demonstrated however that this association appears to be related to the activity of recruiting into clinical trials itself, and was not a surrogate for patient throughput of the treating centre, as previously thought by Wuthrick et al[7].

Our findings that outcome is related to academic engagement are further supported by the findings of Chen et al. that patients treated for advanced stage laryngeal cancer at academic high-volume centres had the highest survival rates, more than high-volume non-academic centres[6]. The differences in survival demonstrated in our study between high and low recruiting centres appear to reflect potential differences in decision-making and in quality of care, and not differences in case mix. Patients in low recruitment centres had similar or even slightly more favourable, baseline characteristics (e.g. p16+ and ECOG status) than patients in high recruitment centres. Yet, a higher proportion of patients in the lower recruitment centres received the more aggressive (TPF) treatment regimen, possibly reflecting differences in the quality of decision-making. Clinicians in the PET-NECK trial selected chemotherapy schedules from a pre-determined, approved list which included neoadjuvant TPF with concomitant chemotherapy. The chemotherapy regimens were selected pre-randomisation to the PET-NECK trial and the treatment decisions were made through a centralised UK regional multidisciplinary team meeting. More importantly, lower recruitment centres had a higher mortality (46% vs 23%) from the more toxic treatment regimen (TPF). This may in part be due to lower recruitment centres having less experience, ability or provision to support patients through complex interventions and/or to deal with the complications associated with their use. These differences may also be a reflection of the nature of clinicians engaging in academic trials, and/or of the positive impact of academic engagement on the overall institutional delivery of care to patients with HNC[12,13]. Process of care factors at academic institutions need to be further investigated to clarify the personnel and resource characteristics of high recruitment centres that may have a positive impact on the quality of care delivered at those institutions.

The reasons for the often-cited relationship between high hospital throughput and better patient outcomes have been postulated to be due to differences in the quality and process of care which patients receive at high throughput centres, including quality of surgery[1,3,14,15], radiotherapy planning and delivery[16], and multi-disciplinary care[17]. Our study demonstrated that after adjustment for other factors, there was no independent association between patient throughput and survival. However, our study demonstrated a correlation between high throughput and higher recruitment into clinical trials, which may explain why previous studies found positive associations between patient throughput and outcome.[2,3,6,7,18]

Limitations

There is a potential for selection bias in that all institutions studied were involved in recruiting patients to the PET-NECK trial. By definition, we could not include hospitals with no trial activity at all ('non-recruiters') or comment on their outcomes.

Our hospital volume thresholds were selected post hoc. We accept that this could be criticised as arbitrary and that especially the hospitals performing near each threshold boundary may be performing at slightly different rates resulting in re-classification to different tertile groups. In the absence of a definition of performance thresholds, this approach was necessary to fully explore the general trends in performance. However, when analysing by groupings into low versus high performers we do not anticipate individual hospitals moving between the two groups to affect our final analysis.

Due to the lack of a defined threshold for low versus high recruitment and hospital throughput, we modelled this relationship using Cox's proportional hazards regression analysis to find the optimal

cut-point. Therefore, the arbitrary cut-off between high and low-recruiters set at 5 is unique to our data set and requires future studies with matched outcomes to validate this threshold.

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REFERENCES

[1] Birkmeyer JD, Siewers AE, Finlayson EVA, Stukel TA, Lucas FL, Batista I, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346:1128–37. doi:10.1056/NEJMsa012337.

[2] Finlayson EVA, Birkmeyer JD. Effects of hospital volume on life expectancy after selected cancer operations in older adults: a decision analysis. J Am Coll Surg 2003;196:410–7. doi:10.1016/S1072-7515(02)01753-2.

[3] Birkmeyer JD, Sun Y, Wong SL, Stukel TA. Hospital volume and late survival after cancer surgery. Ann Surg 2007;245:777–83. doi:10.1097/01.sla.0000252402.33814.dd.

[4] Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. N Engl J Med 2011;364:2128–37. doi:10.1056/NEJMsa1010705.

[5] Reames BN, Ghaferi AA, Birkmeyer JD, Dimick JB. Hospital volume and operative mortality in the modern era. Ann Surg 2014;260:244–51. doi:10.1097/SLA.0000000000000375.

[6] Chen AY, Fedewa S, Pavluck A, Ward EM. Improved survival is associated with treatment at high-volume teaching facilities for patients with advanced stage laryngeal cancer. Cancer 2010;116:4744–52. doi:10.1002/cncr.25364.

[7] Wuthrick EJ, Zhang Q, Machtay M, Rosenthal DI, Nguyen-Tan PF, Fortin A, et al. Institutional Clinical Trial Accrual Volume and Survival of Patients With Head and Neck Cancer. J Clin Oncol 2015;33:156–64. doi:10.1200/JCO.2014.56.5218.

[8] Health and Social Care Information Centre 1 Trevelyan Square, Boar Lane, Leeds, LS1 6AE, United Kingdom. Hospital Episode Statistics n.d.

[9] Profile of Head and Neck Cancers in England: Incidence, Mortality and Survival n.d. file:///C:/Users/lind/Downloads/100504_OCIU_Head_and_Neck_Profiles.pdf (accessed May 27, 2016).

[10] National Institute for Health Research: Clinical Research Network. The Clinical Research Network 2016. https://www.crn.nihr.ac.uk/ (accessed July 21, 2016).

[11] Mehanna H, Wong W-L, McConkey CC, Rahman JK, Robinson M, Hartley AGJ, et al. PET-CT Surveillance versus Neck Dissection in Advanced Head and Neck Cancer. N Engl J Med 2016:1–11. doi:10.1056/NEJMoa1514493.

[12] Benasso M, Lionetto R, Corvò R, Ponzanelli A, Vitale V, Rosso R. Impact of the treating institution on the survival of patients with head and neck cancer treated with concomitant alternating chemotherapy and radiation. Eur J Cancer 2003;39:1895–8. doi:10.1016/S0959-8049(03)00487-8.

[13] Lassig AAD, Joseph AM, Lindgren BR, Fernandes P, Cooper S, Schotzko C, et al. The Effect of Treating Institution on Outcomes in Head and Neck Cancer. Otolaryngol - Head Neck Surg 2017;147:1083–92. doi:10.1177/0194599812457324.

[14] Begg CB, Cramer LD, Hoskins WJ, Brennan MF. Impact of Hospital Volume on Operative Mortality for Major Cancer Surgery. JAMA 1998;280:1747–51.

[15] Cheung MC, Koniaris LG, Perez EA, Molina MA, Goodwin WJ, Salloum RM. Impact of Hospital Volume on Surgical Outcome for Head and Neck Cancer. Ann Surg Oncol 2009;16:1001–9. doi:10.1245/s10434-008-0191-9.

[16] Chen Y, Mahal BA, Muralidhar V, Nezolosky M, Beard CJ, Den RB, et al. Association Between Treatment at a High-Volume Facility and Improved Survival for Radiation-Treated Men With High-Risk Prostate Cancer. Int J Radiat Oncol Biol Phys 2016;94:683–90. doi:10.1016/j.ijrobp.2015.12.008.

[17] Ziabari Y, Wigmore T, Kasivisvanathan R. The multidisciplinary team approach for high-risk and major cancer surgery. Br J Anaesth Educ 2017;17:255–61. doi:10.1093/bjaed/mkx003.

[18] Sharma A, Schwartz SM, Méndez E. Hospital volume is associated with survival but not multimodality therapy in Medicare patients with advanced head and neck cancer. Cancer 2013;119:1845–52. doi:10.1002/cncr.27976.

Figure 1. Kaplan-Meier survival curve of the relationship between hospital throughput and OS

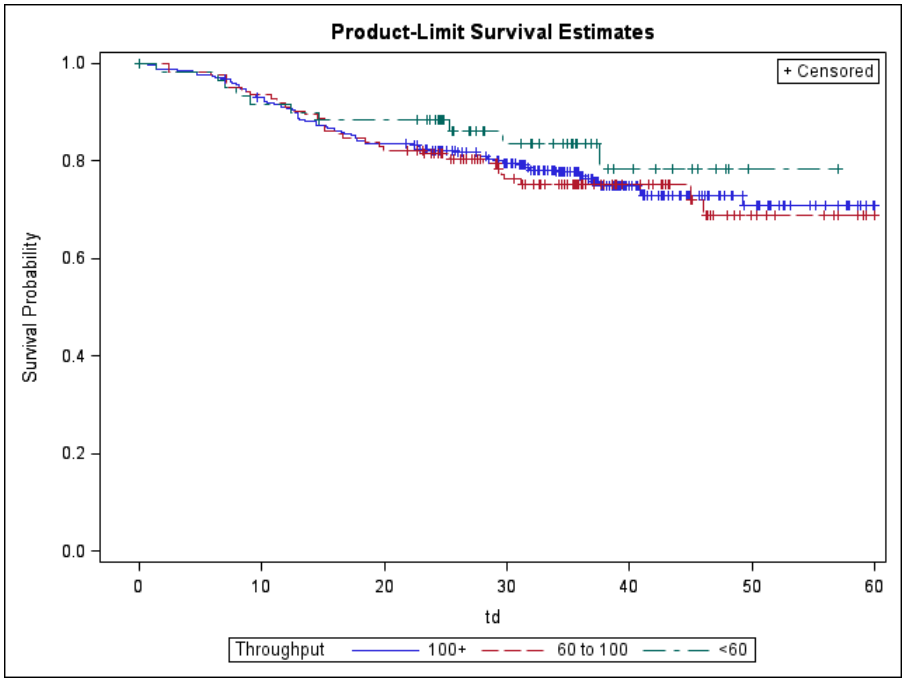

Figure 2. Kaplan-Meier survival curve of the relationship between recruitment and OS. (106 events)

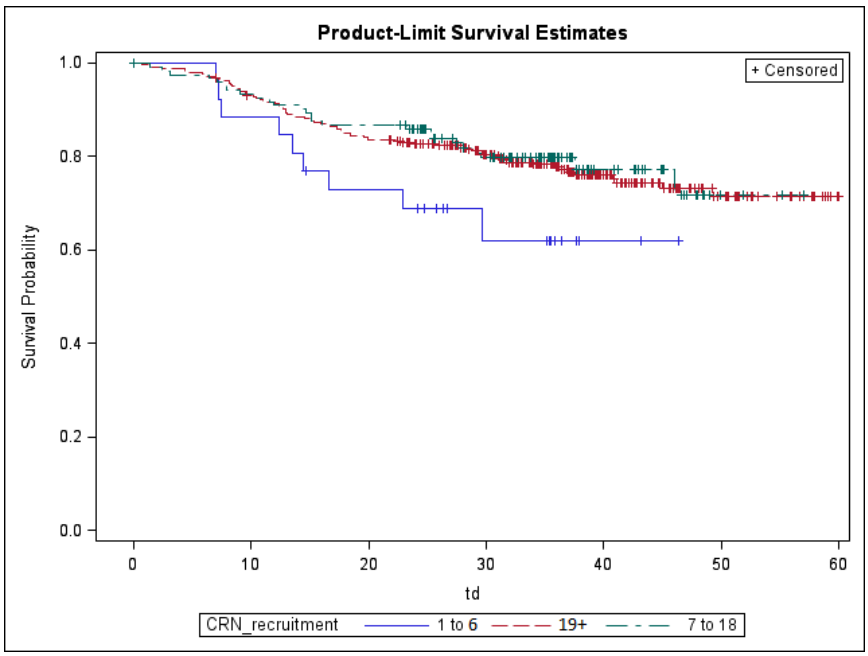

Table 1. Multivariate analysis

Parameter		HR	95% C.I. Lower limit	95% C.I. Upper limit	*p*-value
N-stage	Low N-stage (1-2)~~1~~	0.601	0.393	0.917	0.0182
T-stage	Low T-stage (1-2)~~1~~	0.820	0.190	3.546	0.7910
T-stage	High T-stage (3-4)~~2~~	1.198	0.280	5.125	0.8071
Sex	Female	1.366	0.785	2.375	0.2695
Age		1.023	0.996	1.050	0.0917
p16	Negative	2.912	1.789	4.739	<.0001
p16	Not known	1.635	0.942	2.838	0.0808
Throughput	100+	1.142	0.577	2.260	0.7028
Throughput	60-100	1.380	0.663	2.871	0.3887
ECOG		1.450	0.975	2.157	0.0664
Recruit	1-5	2.236	1.052	4.754	0.0365
Smoking	Current	1.328	0.843	2.091	0.2211
Smoking	Never	0.357	0.166	0.769	0.0085

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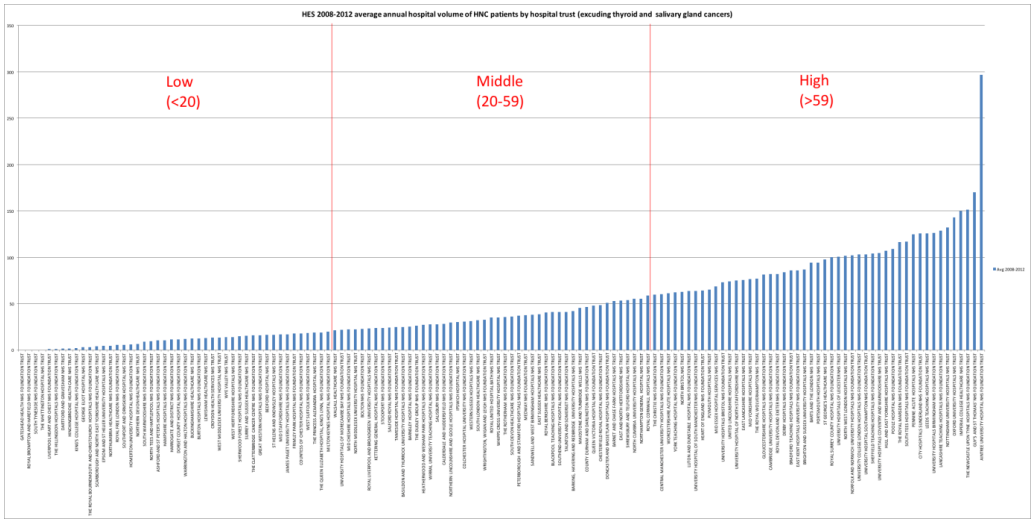
Supplementary 1: Figure 1. HES data on average annual hospital throughput of HNC patients* by hospital trust from 2008 through 2012



**excluding thyroid and salivary gland cancers*

Supplementary 2: Table 1. UKCRN Head and Neck Cancer Clinical Trials (2008-2012) and inclusion/exclusion categories

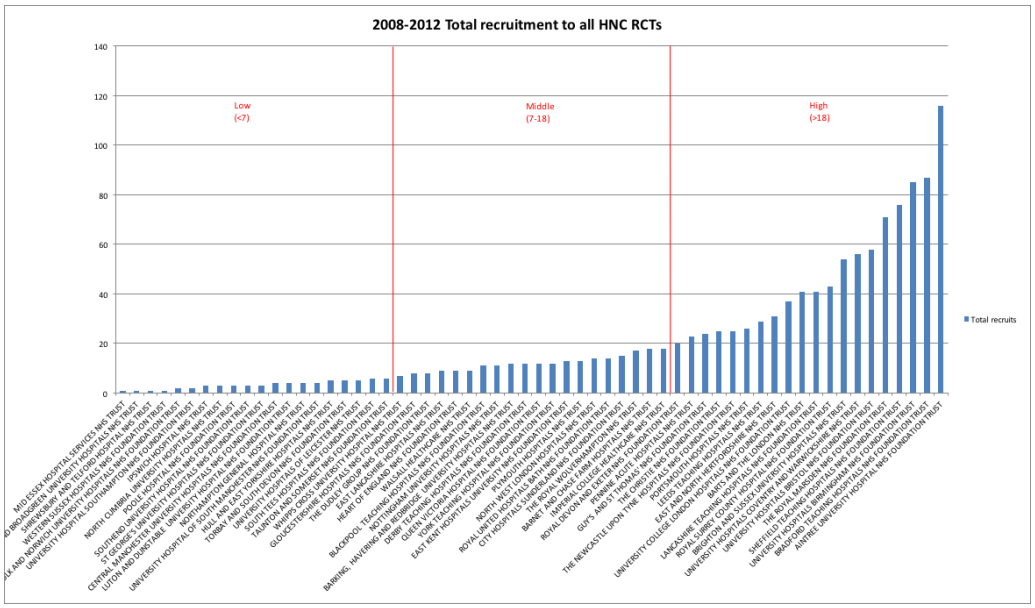
	UKCRN HNC trials in England (2008-2015)	UKCRN ID	Included (Y/N)	RCT (Y/N)	Trial design	RCT recruiting '08-'12
1	DORA	3832	Yes	Yes	Randomised	Yes
2	NCRN007 Zalute - BSC+/- zalatumumab in SSCHN pts failing platinum chemo	2484	Yes	Yes	Randomised	Yes
3	NCRN013 - SPECTRUM	2675	Yes	Yes	Randomised	Yes
4	NCRN468 MEGHAN - MEHD7945A vs cetuximab in recurrent/metastatic head & neck SCC	13085	Yes	Yes	Randomised	Yes
5	Trismus RfPB trial	13415	Yes	Yes	Randomised	Yes
6	De-ESCALaTE HPV	11723	Yes	Yes	Randomised	Yes
7	HOPON	4550	Yes	Yes	Randomised	Yes
8	Lugol's Iodine in Head and Neck Cancer Surgery	9621	Yes	Yes	Randomised	Yes
9	NCRN153 - EMD 1201081 +Cetuximab in 2nd line, recurrent / metastatic SCCHN	8153	Yes	Yes	Randomised	Yes
10	SEND	2069	Yes	Yes	Randomised	Yes
11	ART DECO	9562	Yes	Yes	Randomised multicentre	Yes
12	COSTAR	5265	Yes	Yes	Randomised multicentre	Yes
13	NCRN291- E7050 +/- Cetuximab in platinum resistant SCCHN	10728	Yes	Yes	Randomised multicentre	Yes
14	PET-NECK study	3799	Yes	Yes	Randomised multicentre	Yes
15	TITAN	10000	Yes	Yes	Randomised multicentre	Yes
16	COAST - Cisplatin Ototoxicity attenuated by Aspirin Trial	13400	Yes	Yes	Randomised, double-blind, placebo-controlled	Yes
17	NCRN206 - LUX-adjuvant Afatinib after chemoradiation in primary unresectable HNC	11522	Yes	Yes	Randomised, double-blind, placebo-controlled	Yes
18	The LEONIDAS2 study	10229	Yes	Yes	Randomised, double-blind, placebo-controlled	Yes
19	NCRN002 - lapatinib and concurrent radiotherapy / cisplatin in stage III, IV SCCHN	2604	Yes	Yes	Randomised, double-blind, placebo-controlled, multicentre	Yes
20	NCRN006 - aadjuvant / maintenance Lapatinib in resected SCCHN	2658	Yes	Yes	Randomised, double-blind, placebo-controlled, multicentre	Yes
21	ARTFORCE Head & Neck (2-arm study)	18545	No	Yes	Randomised	No
22	CANC - 3417 Phase III Study of MK3475 vs standard treatment in recurrent or metastatic HNC	17352	No	Yes	Randomised	No
23	CHARTWEL	663	No	Yes	Randomised	No
24	CompARE Trial	18621	No	Yes	Randomised	No
25	DAHANCA 21	13565	No	Yes	Randomised	No
26	NCRN - 3173 CheckMate 141: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 141	16460	No	Yes	Randomised	No
27	TUBE Trial	16822	No	Yes	Randomised	No
28	PARSPORT	1283	No	Yes	Randomised multicentre	No
29	PATHOS	18645	No	Yes	Randomised multicentre	No
30	AMG 319 in HPV negative HNSCC	19161	No	Yes	Randomised, double-blind, placebo-controlled	No
31	NCRN583 BKM120 + paclitaxel vs. paclitaxel + placebo	14907	No	Yes	Randomised, double-blind, placebo-controlled, multicentre	No
32	NIMRAD (NIMorazole/placebo plus RADiotherapy in head and neck cancer)	16203	No	Yes	Randomised, placebo-controlled	No
33	EaStER Feasibility Study	1503	No	Yes	Randomised, closed early (incomplete)	No
34	IoN	10876	No	Yes	Thyroid cancer	No
35	NCRN131-Sorafenib vs placebo in Locally Advanced/Metastatic RAI-Refractory Differentiated Thyroid Ca	7698	No	Yes	Thyroid cancer	No
36	NCRN319 - E7080 in refractory thyroid cancer	10831	No	Yes	Thyroid cancer	No
37	ElaTION	17373	No	Yes	Thyroid cancer	No
38	'HiLo'	1718	No	Yes	Thyroid cancer	No
39	NCRN087 - XL184 vs placebo in unresectable/metastatic thyroid Ca	7069	No	Yes	Thyroid cancer	No
40	NCRN363: Vandetanib in metastatic medullary thyroid carcinoma	12051	No	Yes	Thyroid cancer	No
41	SIP SMART: Swallowing Intervention package - Self Monitoring, Assessment & Rehabilitation Training	17043	No	No	Qualitative	-
42	Resources for Living (R4L) Pilot	16705	No	No	Qualitative	-
43	Pain: screen and treat	8883	No	No	Questionnaire study	-
44	Quality of life driven consultations in head and neck cancer follow up	8079	No	No	Questionnaire study	-
45	DeteQT	10323	No	No	Questionnaire study	-
46	Determination of Quality of Life Instrument	6082	No	No	Questionnaire study	-
47	Alternative Splicing of Raf Kinases in Cancer	9055	No	No	Observational	-
48	GRAD	19140	No	No	Observational	-
49	HeadandNeck5000	9894	No	No	Observational	-
50	MSCC	9450	No	No	Observational	-
51	NCRN - 2376 Caprelsa in MTC	15014	No	No	Observational	-
52	Do genetic tests help specialists to detect cancer cells?	7493	No	No	Observational	-
53	EORTC Quality of Life Head and Neck Module v4	12850	No	No	Observational	-
54	Exome and protein analysis in HPV associated cancer / pre-cancer	11945	No	No	Observational	-
55	FLAIRE	13992	No	No	Observational	-
56	Head and Neck Cancer: molecular, cellular and immunological mechanisms	8130	No	No	Observational	-
57	A study of biomarkers of senescence in neoplasms of the oral cavity	9854	No	No	Observational, case-controlled	-
58	Genetic factors involved in eyelid mBCC and SGC	14687	No	No	Observational, case-controlled	-
59	After treatment is over: what matters most?	11124	No	No	Observational, cohort study	-
60	Assessing dysphagia and voice in laryngectomy	8600	No	No	Observational, cohort study	-
61	INSIGHT	13860	No	No	Observational, cohort study	-
62	Long-term swallowing outcomes in head and neck cancer	15131	No	No	Observational, cohort study	-
63	PREDICTR-HNC	11317	No	No	Observational, cohort study	-
64	Survivorship in people with oral cancer and their partners	12430	No	No	Observational, cohort study	-
65	Developing a core information set for consent to oral cancer surgery	15348	No	No	Observational, qualitative	-
66	Development of a CBT intervention for dysphagia	15151	No	No	Observational, qualitative	-
67	Home but not Alone	5207	No	No	Observational, qualitative	-
68	Pilot study of CTCAE Toxicity Questionnaires	5995	No	No	Observational, qualitative	-
69	PSQ;H&N	1746	No	No	Observational, qualitative	-
70	SIP2	20259	No	No	Observational, qualitative	-
71	The CONSENSUS Study	13823	No	No	Observational, qualitative	-
72	Imaging Hypoxia in Head & Neck Cancer - A pilot study	14487	No	No	Safety study	-
73	Monitoring of Oral Cancer Patients Using Novel Lab-On-A-Chip Ensembles	7654	No	No	Safety study	-
74	NCRN054 - Zalatumumab+ radiotherapy in locally adv SSCHN not suitable for platinum based chemo	6081	No	No	Safety study	-
75	NCRN362 - Safety of PC-A11 with laser light application in recurrent head & neck SCC	11926	No	No	Safety study	-
76	REALISTIC	11160	No	No	Safety study	-
77	Dielectrophoresis in oral cancer	7073	No	No	Safety study	-
78	ASPOD	6070	No	No	Safety study	-
79	NCRN123 - pemetrexed,cisplatin+ cetuximab in metastatic SSCHN	7695	No	No	Safety study	-
80	A Phase Ib trial of MVAEBNA1/LMP2 vaccine in nasopharyngeal carcinoma	13732	No	No	Safety study	-
81	BoHEMIaN Study	13125	No	No	Safety study	-
82	OCTiLarynx (Optical Coherence Tomography in Larynx)	8939	No	No	Safety study	-
83	QUITS 1.0	13212	No	No	Safety study	-
84	RECaD Larynx	1274	No	No	Safety study	-
85	T4 immunotherapy of head and neck cancer	19183	No	No	Safety study	-
86	VortigERn	7341	No	No	Safety study	-
87	MVA Vaccine Study	5100	No	No	Safety study	-
88	NCRN110 - zalutmumab in non curable SCCHN	8287	No	No	Safety study	-
89	FLT PET to assess tumour proliferation during radical radiotherapy	8495	No	No	Safety study	-
90	PANDORA	13475	No	No	Safety study	-
91	PATRIOT	17568	No	No	Safety study	-
92	TCUK IN	7070	No	No	Thyroid cancer	-
93	EORTC 1209EnTF	18682	No	No	Thyroid cancer	-
94	Assessment of Quality of Life Tools in Medullary Thyroid Cancer (QaLM)	20272	No	No	Thyroid cancer	-
95	Diagnosing thyroid cancer using a blood test	9847	No	No	Thyroid cancer	-
96	THRIFT	15036	No	No	Thyroid cancer	-

Supplementary 2: Table 2. Grouping of hospitals into tertiles for throughput versus recruitment

Recruited (2008-12)	Hospital throughput (/yr)		
	Low (<60)	Middle (60-100)	High (>100)
Low (≤ 6)	9	5	6
Middle (7-18)	8	8	4
High (19+)	2	6	12

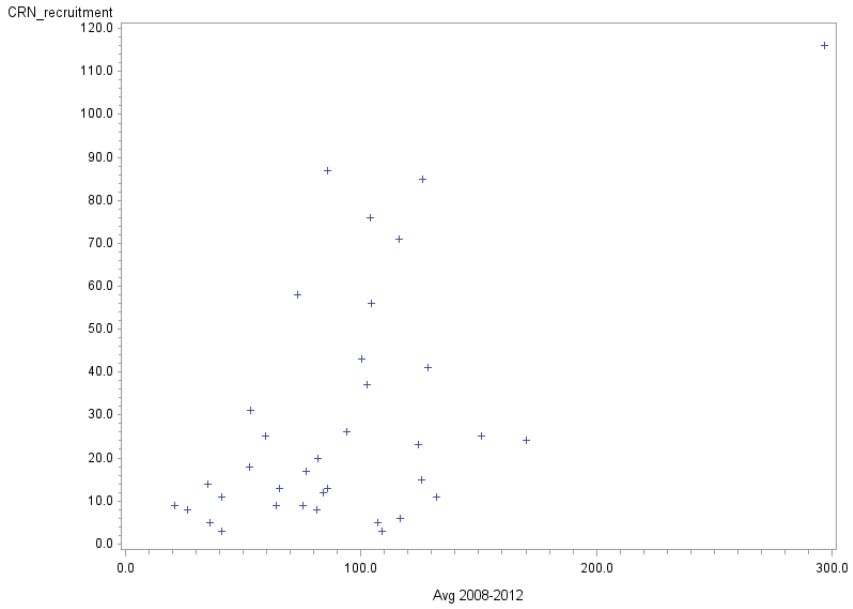
p=0.006 for trend

Supplementary 2: Figure 1. Total recruitment to all HNC interventional trials from 2008 through 2012 for hospital trusts in England



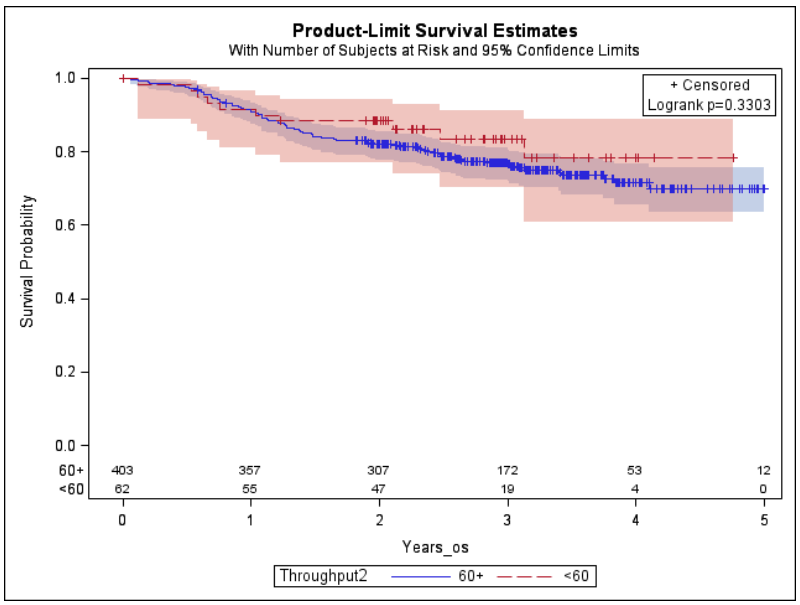
Total recruitment to all HNC RCTs ranged from 1 to 116 with a mean of 21.27 HNC patients recruited in the period from 2008 through 2012.

Supplementary 3: Figure 1. Scatterplot of average annual hospital throughput versus clinical trial recruitment (2008-2012)



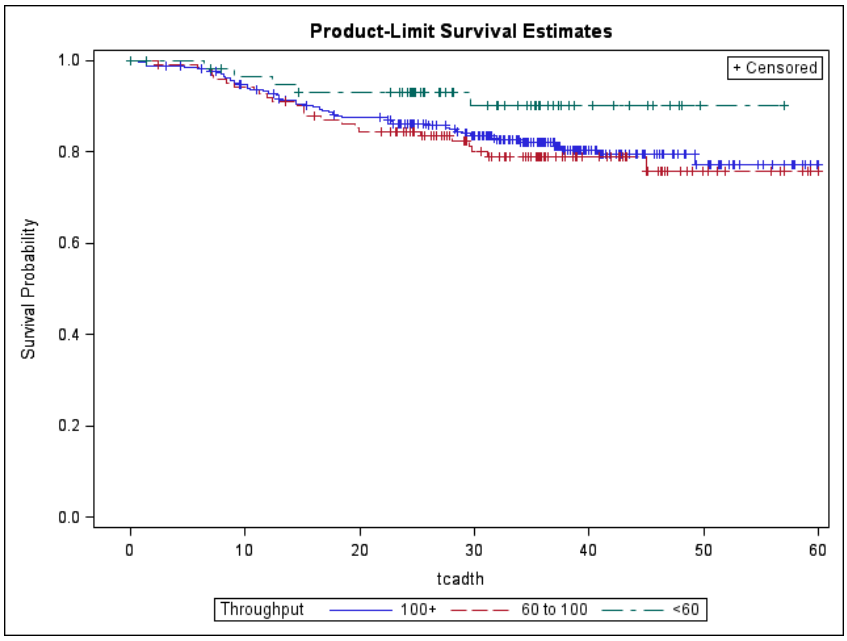
Pearson's correlation for this association is r=0.42 (p<0.0001)

Supplementary 4: Figure 1. Low versus high hospital throughput and OS

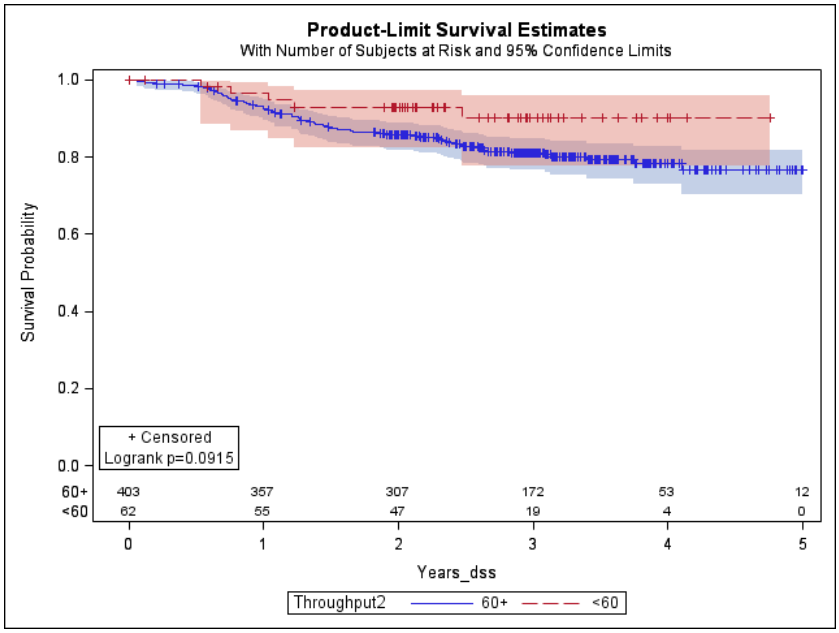


<60 recruited, 2-year OS: 88.3%, 95% CL (80.2, 96.4); 60+ recruited 2-year OS: 81.9%, 95% CL (78.1, 85.7).

Supplementary 4: Figure 2. Kaplan-Meier survival curve of the relationship between hospital throughput and DSS

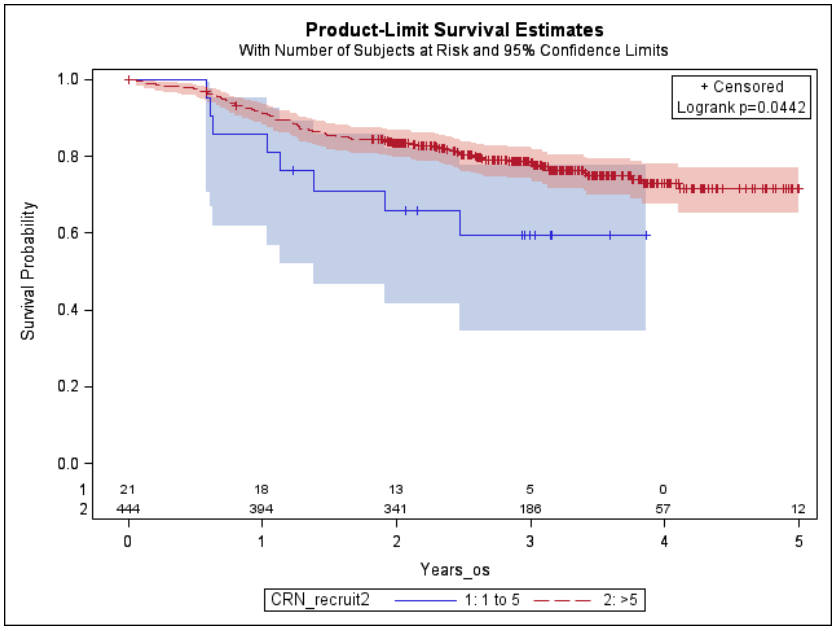


Supplementary 4: Figure 3. Low versus high hospital throughput and DSS



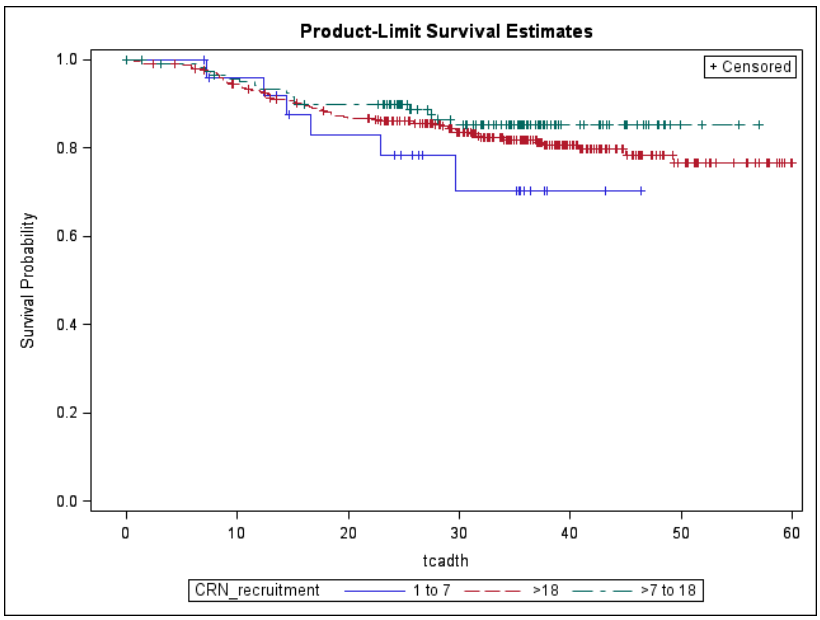
<60 recruited (5 deaths), 2-year OS: 93.0%, 95% CL (86.5, 99.6); 60+ recruited (74 deaths), 2-year OS: 85.7%, 95% CL (82.2, 89.2).

Supplementary 5: Figure 1. Low versus high recruitment and OS



1 to 5 recruited 2-year OS: 66.0%, 95% C.I. (45.5, 86.6); >5 recruited, 2-year OS: 83.6%, 95% C.I. (80.1, 87.0).

Supplementary 5: Figure 2. Kaplan-Meier survival curve of the relationship between recruitment and DSS. (79 events)



~~Supplementary 6:~~ Table 2~~1~~. Comparison of variables across hospital recruitment tertiles

	Low (1 to 6) n (%)	Middle (7 to 18) n (%)	High (19+) n (%)
N-stage 1-2	20 (76.9)	100 (81.3)	242 (76.6)
N-stage 3-4	6 (23.1)	23 (18.7)	74 (23.4)
T-stage 1-2	16 (61.5)	68 (55.3)	184 (58.2)
T-stage 3-4	10 (38.5)	49 (39.8)	128 (40.5)
T-stage (occult)	0 (0)	6 (4.9)	4 (1.3)
Oropharyngeal	26 (100)	106 (86.2)	267 (84.5)
Concomitant cisplatin	13 (50.0)	90 (73.2)	185 (58.5)
TPF	13 (50.0) †	17 (13.8)	92 (29.1)
Cetuximab	0 (0)	10 (8.1)	17 (5.4)
Other	0 (0)	6 (4.9)	22 (7.0)
Female	4 (15.4)	24 (19.5)	59 (18.9)
p16 positive	14 (77.8)	69 (70.4)	181 (74.8)
ECOG 0	21 (80.8)	93 (75.6)	251 (79.4)
ECOG 1	5 (19.2)	29 (23.6)	63 (19.9)
ECOG 2	0 (0)	1 (0.8)	2 (0.6)
Never smoked	8 (30.8)	32 (26.0)	81 (25.6)
Past smoker	8 (30.8)	56 (45.5)	149 (47.2)
Current smoker	10 (38.5)	35 (28.5)	86 (27.2)
Mean age	55.9	59.0	57.8

Each tertile group is comprised of cases aggregated from 20 hospitals.

† The proportion of patients in low recruiting hospitals (50%, n=13) receiving neoadjuvant chemotherapy (TPF) was significantly different from the other tertiles (p=0.003). There were no other significant differences in variables across the groups.