Recruitment, response rates and characteristics of 5511 people enrolled in a prospective clinical cohort study: head and neck 5000

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Dear Editor,

Head and neck cancer is an important cause of ill health with rapidly changing aetiology and approaches to treatment.\(^1\)\(^,\)\(^\,\)\(^2\) Survival appears to have improved, but the reasons for this are unclear.\(^3\) There is no large population-based comprehensive longitudinal biomedical resource of people with head and neck cancer. Several registries exist, such as the US National Cancer Institute surveillance epidemiology and end results programme, but these lack individual consent and biological samples.\(^4\) Large retrospective aetiological case-control studies with consent, clinical and socio-demographic information and biological samples, such as the International Head and Neck Cancer Epidemiology Consortium, have limited follow-up data, focus on past rather than current exposures and recruited people at different stages of treatment.\(^5\) Existing prospective studies have fewer than 1000 participants and are often based on follow-up of randomised trials (a potentially unrepresentative group).\(^6\)

The importance of adequately powered, population-based, comprehensive, longitudinal biomedical resources in healthy populations is accepted. The value of similar biomedical resources for clinical conditions is increasingly appreciated. We report here on recruitment, response rates and characteristics of 5511 people enrolled in a prospective clinical cohort study: head and neck 5000.\(^7\)

**Methods**

**Ethical considerations**

The study was approved by the National Research Ethics Committee (South West Frenchay Ethics Committee, reference 10/H0107/57, 5th November 2010) and approved by the research and development departments for participating NHS Trusts.

**Recruitment to the study**

We have described the study methods in detail previously.\(^7\) Briefly, all people with a new diagnosis of head and neck cancer were eligible. People were recruited before their treatment started, unless their treatment was their diagnostic procedure. Participants offered palliative support were recruited as soon after diagnosis as possible. A research nurse obtained a wide-ranging consent. The teams kept logs of the number of eligible people who were approached and the reason they were not recruited.

**Baseline data and sample collection**

The research nurse gave participants three questionnaires. The first enquired about social and economic circumstances, overall health and lifestyle behaviours. The second enquired about physical and psychological health, well-being and quality of life. The third enquired about past sexual behaviours.\(^7\) The nurse abstracted information from the hospital medical records about diagnosis, treatment and...
comorbidity onto a data capture form and asked participants to provide a blood sample and a saliva sample. The nurse posted the samples to the study laboratory. We asked local pathologists to send paraffin embedded tumour blocks along with an anonymised copy of the participant’s histopathology report.7

**Study follow-up**

We have not collected any further biological samples. We sent out follow-up questionnaires at 4 and 12 months after the person joined the study. We added questions about fear of recurrence in the 4- and 12-month questionnaires. A separate questionnaire asking about late radio-toxicity was sent to people at 12 months who had a course of radiotherapy as part of their initial treatment plan. The research nurses abstracted updated clinical information from the hospital medical records at 4 and 12 months. We have flagged participants with the UK Health and Social Care Information Centre to obtain data on date and cause of death.

**Statistical analysis**

Age was calculated from the date on the consent form and the date of birth on the data capture form. Gender, diagnosis and stage were recorded on the data capture form. We coded diagnosis using the International Classification of Diseases (ICD) version 10.8 We derived the clinical staging of the tumour from T (characteristics of the tumour site), N (degree of lymph node involvement) and M (the absence or presence of metastases) based on the American Head and Neck Society TNM staging of head and neck cancer.9 We present numbers and percentages overall and for different diagnostic groups.

**Results**

**Recruitment**

We started recruiting in April 2011 and closed to recruitment at the end of December 2014. We opened the study in a few centres to ensure the protocol was running smoothly before rolling it out elsewhere. The study was open in 78 UK centres (two centres did not enrol any participants). We enrolled 5511 people into the study.

**Baseline response rates**

At baseline, we have received 5474 (99%) data capture forms, 4099 (74%) health and lifestyle questionnaires, 4115 (75%) quality of life questionnaires and 3470 (63%) sexual history questionnaires. We have obtained 4986 saliva samples (90%), 4676 blood samples (85%) and 2301 tissue samples (42%). Twenty-three people withdrew from completing baseline questionnaires.

**Follow-up response rates**

To date, 827 people enrolled by 24 July 2015 have died and 74 have withdrawn from the study. We have 4-month data capture forms for 5232 (95%) and 4-month questionnaires from 3357 (63%) participants and 12-month data capture forms for 3906 (86%) and 12-month questionnaires from 2353 (57%) participants. These follow-up response percentages are the number received against the number for which we are expecting forms, that is those who provided baseline data and remain in the study. They do not include participants who have not yet reached, or died before, the relevant 12-month window.

**Recruitment and response rate by centres**

Centres varied in size and joined the study at different times. The mean number of people recruited per centre was 40 (range from 0 to >300). Similarly, there were large variations in response rates by centres. Percentage recruitment to the study varied from less than 20% to greater than 90% of those eligible, response rate to the health and lifestyle questionnaire varied from less than 30% to greater than 90% and the percentage of participants providing a blood sample varied from less than 50% to greater than 90%. These differences are shown in Fig. 1.
Characteristics of participants

The percentage of people enrolled in the study was 5511 from 11,158 people who were identified as potentially eligible (49%). The mean age of the people recruited was 61 years, and the range was 18–96 years. The percentage of female participants was 27%. The most common cancers were oropharyngeal (37%), oral (26%) and laryngeal (21%). The number and percentage of people with different diagnoses and stage of disease is summarised in Table 1. The number of people with complete data (defined as valid diagnosis, stage, blood sample and baseline health and lifestyle questionnaire) was 3336 of the 5511 (61%). The number of people with complete data to date is shown in Fig. 2.

Discussion

We have successfully recruited 5511 people with head and neck cancer from across the UK. We recruited people before treatment started and obtained wide-ranging consent, clinical information, self-reported socio-demographic, lifestyle and quality of life data and biological samples.

We took time to build a clinical consensus and opened to recruitment gradually. This delayed recruitment but meant we encountered few local problems. One clinician initially refused to allow people under his care to complete the sexual behaviour questionnaire. The response rates to this questionnaire are slightly lower, but we have had no complaints about these questions.

We recruited fewer people with salivary, thyroid and laryngeal cancers than we expected. The lower number of people with salivary tumours may reflect the coding of some minor salivary gland cancers as oral cancer. The lower number of people with thyroid cancers reflects the fact that many are not treated by the head and neck multidisciplinary team. The lower number of laryngeal cancers may reflect the case mix in the study centres.

Table 1. Disease category and stage of disease in people recruited to head and neck 5000

| Category                  | Diagnosis    | Grouped staging |
|---------------------------|--------------|-----------------|
|                           |              | I   | II   | III  | IV   | Total |
| Upper aerodigestive tract | Oropharynx   | 101  | 189  | 274  | 1317 | 1881  |
|                           |              | 5.4% | 10.1% | 14.6% | 70.0% |        |
|                           | Oral cavity  | 427  | 300  | 101  | 467  | 1295  |
|                           |              | 33.0%| 23.2% | 7.8%  | 36.1% |        |
|                           | Larynx       | 435  | 276  | 174  | 186  | 1071  |
|                           |              | 40.6%| 25.8% | 16.3% | 17.4% |        |
|                           | Hypopharynx  | 10   | 33   | 35   | 150  | 228   |
|                           |              | 4.4% | 14.5% | 15.4% | 65.8% |        |
|                           | Nasopharynx  | 11   | 32   | 43   | 42   | 128   |
|                           |              | 8.6% | 25.0% | 33.6% | 32.8% |        |
|                           | Sinuses      | 3    | 2    | 7    | 43   | 55    |
|                           |              | 5.5% | 3.6%  | 12.7% | 78.2% |        |
|                           | Nasal cavity | 12   | 15   | 6    | 16   | 49    |
|                           |              | 24.5%| 30.6% | 12.2% | 32.7% |        |
|                           | Thyroid      | 119  | 31   | 73   | 18   | 241   |
|                           |              | 49.4%| 12.9% | 30.1% | 7.5%  |        |
|                           | Salivary glands | 33  | 21   | 22   | 55   | 131   |
|                           |              | 25.2%| 16.0% | 16.8% | 42.0% |        |
|                           | Total        | 1151 | 899  | 735  | 2294 | 5079  |
|                           |              | 22.7%| 17.7% | 14.5% | 45.2% |        |

The categories comprised the following ICD codes:

Oropharynx = C01, C05 and C09 (including all subcategories) and C10.0 2, C10.3, C10.8 and C10.9.
Oral cavity = C00, C02, C03, C04, C05 and C06 (including all subcategories except C06.9).
Larynx = C10.1, C32 (including all subcategories).
Hypopharynx = C12 and C13 (including all subcategories).
Nasopharynx = C11 (including all subcategories).
Sinuses = C31 (including all subcategories).
Nasal cavity = C30 (including all subcategories).
Thyroid = C73.
Salivary glands = C06.9, C07 and C08 (including all subcategories).
Overall, around 49% of eligible people consented to join the study and of these 61% have provided us with complete baseline data. Therefore, we have data on around 30% of people eligible to join the study. Our baseline response rates were lower than we anticipated. There are several reasons for this. We tried to obtain consent and collect data from people in the short period between diagnosis and treatment. Clinics were busy with limited space or time to see people. We faced practical issues with people moving between centres for treatment or not being discussed at the multidisciplinary team meetings. There were also times when research nurses were not available.

Some of the missing data may be unrelated to care or outcome, for example, where a research nurse was unavailable. However, much of the data will not be missing at random and could result in bias. We may be able reduce the impact of bias in recruitment and response to follow-up by improving the completeness of our clinical data and exploring the clinical characteristics of those who did not consent to join the study by linking to national audit data.10

Our ability to study the impact of centralisation (which was a primary aim of our study) is limited by the low recruitment rate, the fact that centres, although varied in size, were self-selected and that not all centres contributing to a multidisciplinary team recruited people to the study.

We have shown it is possible to recruit a large DNA-backed clinical cohort in people with head and neck cancer in the UK. This cohort is a comprehensive resource, and we welcome collaboration.

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Keypoints

• Head and neck cancer is an important cause of ill health with rapidly changing aetiology.
• Survival appears to have improved but the reasons for this are unclear.
• Adequately powered, longitudinal studies in people with head and neck cancer are required.
• We recruited 5511 people with head and neck cancer to a large DNA-backed clinical cohort.
• Multicentre clinical cohort studies in head and neck cancer are feasible in the UK.

Conflict of interest

None declared.

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The role of pectoralis major flap in reducing the incidence of pharyngocutaneous fistula following total laryngectomy: a single-centre experience with 102 patients

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Dear Editor,

Concomitant chemoradiotherapy (CRT) is commonly advocated for advanced laryngeal cancer to achieve cure together with an allegedly organ-function preservation. This widely applied treatment strategy has led to a paradigm shift in the management of laryngeal cancer during the past three decades. For those who are unfortunate and fail CRT, salvage total laryngectomy (TL) may be offered as a second line. However, post-CRT surgery encompasses intra- and postoperative challenges, which result in increased morbidity and postoperative complications. Moreover, with primary CRT disease-free survival rates ranging between 60% and 80% at 5 years, the number of patients who need to be salvaged is considerably high. In addition, patients, who were cured with laryngeal organ preservation but have no function preservation, retain their unserviceable larynx and remain tracheostomy and/or gastrostomy dependent. These patients may also benefit from TL.

Numerous studies have shown higher complication rate for patients who undergo salvage TL. The most significant complication in this regard is the formation of pharyngocutaneous fistula (PCF), which delays postoperative recovery and function acquisition, increases hospital stay and adversely affects patient’s quality of life. Rarely, a salivary leak can erode into cervical or mediastinal blood vessels causing potentially life-threatening complications.

The incidence of PCT following CRT is markedly increased, with some estimates as high as 65%. These fistulas tend to be more severe and of a longer duration. Previous studies showed reduced incidence and even prevention of PCF with the use of vascularized flaps such as the pectoralis major flap (PMF) and free vascular flaps.

This data first raise the question whether vascularized flaps should be routinely employed in every salvage surgery or only after careful patient selection. Second, have vascularized flaps become the standard of care in the organ preservation era? And if so, how does it affect the individual surgeon’s decision-making process?

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