

PET-NECK: a multicentre randomised Phase III non-inferiority trial comparing a positron emission tomography-computerised tomography-guided watch-and-wait policy with planned neck dissection in the management of locally advanced (N2/N3) nodal metastases in patients with squamous cell head and neck cancer

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Scientific summary

PET-CT-guided watch-and-wait versus planned neck dissection

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Scientific summary

Background

Chemoradiotherapy (CRT) has become the preferred method of treatment for patients with advanced head and neck squamous cell carcinoma (HNSCC). The traditional standard care in the UK for these patients included undertaking a neck dissection (ND) (surgery to remove the lymph nodes in the neck) before or after CRT. However, there is considerable debate about whether or not ND is actually needed or whether or not CRT alone is sufficient to treat the disease without the need for surgery and its added complications. The standard imaging technology for assessing response to CRT has been computerised tomography (CT) and/or magnetic resonance imaging (MRI). However, more advanced functional modalities [especially positron emission tomography (PET) scans] have in recent decades been shown to have a high negative predictive value for assessing response. Using a combination of PET with CT, for example, has been shown in retrospective studies to have a higher predictive value than CT or MRI combined, making it possible to perform a ND only if the nodal response to treatment is incomplete. There is, however, a lack of multicentre high-quality evidence.

Objectives

- To compare the efficacy of a PET–CT-guided active surveillance (watch-and-wait) policy with the current practice of planned ND on overall survival (OS), disease-specific survival, recurrence, quality of life and cost-effectiveness in the management of advanced (N2 or N3) nodal metastasis in patients treated with CRT for their HNSCC primary.
- To assess the predictive value of PET–CT scanning in detecting persistent/residual disease in the primary site of patients with HNSCC treated with primary CRT.

End points

Primary end point

- Overall survival at 2 years.
- Cost-effectiveness [incremental cost per incremental quality-adjusted life-year (QALY)].

Secondary end points

- Disease-specific survival.
- Recurrence in the neck.
- Quality of life.
- Complication rates.
- Accuracy of PET–CT scanning for assessing the primary tumour.

Study design and methodology

A two-arm pragmatic multicentre randomised non-inferiority trial was performed to compare a PET–CT-guided watch-and-wait policy (experimental arm) with the current planned ND policy (control arm) in HNSCC patients with advanced neck metastasis treated by radical CRT. A total of 564 patients were randomised in a 1 : 1 ratio.

Stratification was performed according to centre, timing of ND (before vs. after CRT), chemotherapy schedule [concomitant platinum, concomitant cetuximab Erbitax® (Merck Biopharma, Darmstadt, Germany), neoadjuvant platinum, neoadjuvant docetaxel Taxotere® (Sanofi-Aventis, Gentilly, France), platinum and 5-fluorouracil (TPF)], disease site (oropharyngeal, laryngeal, oral, hypopharyngeal or occult), tumour (T) stage (T1–T2 vs. T3–T4 vs. occult) and nodal (N) stage (N2a–N2b vs. N2c–N3).

Treatment and investigations, radiotherapy and chemotherapy protocols

For each patient, the participating centre decided on the CRT schedule, which was chosen from an approved list of schedules. All approved schedules were standard normal schedules used in the UK. All were supported by a strong evidence base, and all were considered biologically equivalent.

Post-chemoradiotherapy assessment

This was performed at 12 (9–13) weeks after completion of CRT.

Patients were assessed for response to the CRT by:

- control arm – a single CT/MRI scan and examination (clinical or under anaesthetic)
- experimental arm – a single PET–CT scan followed by examination (clinical or under anaesthetic).

Diagnostic criteria and reporting protocols for PET–CT scanning

Standardised criteria for reporting of PET–CT scans were disseminated to all participating centres. A core laboratory facility was set up in the Paul Strickland Scanner Centre, Mount Vernon Hospital, to read scans for units that had the equipment and ability to perform PET–CT but did not have the expertise to read them. The laboratory also performed second-stage quality assurance on all PET–CT scans performed for study patients.

Type of neck dissection

Modified radical ND involving nodal levels I to V or selective NDs were acceptable provided that involved nodal groups were included.

Timing of neck dissection

Neck dissection before CRT had to be performed within 4 weeks of randomisation. ND after CRT had to be performed 4–8 weeks after completion of CRT.

Sample size determination

The study was planned to randomise 560 patients (280 to PET–CT surveillance and 280 to planned ND), which would allow for the demonstration of non-inferiority of the PET–CT arm, with a 5% one-sided significance and 90% power, defining non-inferiority as no worse than 10% below the estimated 75% 2-year OS of the control arm, that is, having a hazard ratio (HR) no higher than 1.50. This allowed for a 3% loss to follow-up.

Follow-up

Follow-up was at 6, 12 and 24 months post randomisation and continued until at least 24 months after randomisation. Long-term health status data on death and recurrence were collected for patients until the end of the study. Patients were flagged with the Office for National Statistics and copies of their death certificates were requested for long-term follow-up. This will be reported in a long-term follow-up paper.

Key inclusion/exclusion criteria

Inclusion criteria

Patients with *all* of the criteria listed below were eligible:

- histological diagnosis of oropharyngeal, laryngeal, oral, hypopharyngeal or occult HNSCC
- clinical and CT/MRI imaging evidence of nodal metastases staged N2 (a, b or c) or N3

- indication to receive curative radical concurrent CRT for primary
- fitness for ND surgery
- ND was technically feasible to perform and to remove nodal disease (e.g. no carotid encasement, no direct extension between tumour and nodal disease)
- aged 18 years old or more
- able to give informed consent
- receiving one of the CRT regimens approved by the study.

Exclusion criteria

Patients with *any* of the criteria listed below were ineligible:

- undergoing resection for their primary tumour, for example resection of the tonsil or base of tongue with flap reconstruction (diagnostic tonsillectomy was not considered an exclusion criteria)
- distant metastases to chest, liver, bones or other sites
- previous treatment for HNSCC
- pregnant
- had had another cancer diagnosis in the past 5 years (except basal cell carcinoma or carcinoma of the cervix in situ).

Patients with N2 or N3 histologically and/or cytologically proven squamous cell carcinoma and an occult primary (after examination under anaesthetic and PET-CT scan) were eligible for the PET-NECK trial if they were going to be treated with CRT.

Patients undergoing neoadjuvant chemotherapy followed by concomitant CRT were eligible for the PET-NECK trial. If these patients were randomised to the ND (control) arm, it was recommended that they have a ND after, not before, CRT. Patients with recurrence remained in the trial for the purposes of follow-up and data collection.

Results

In total, 564 patients were recruited (ND arm, $n = 282$ and surveillance arm, $n = 282$; 17% N2a, 61% N2b, 18% N2c and 3% N3). Eighty-four per cent had oropharyngeal cancer. Seventy-five per cent of tested cases were p16 positive. The median length of follow-up was 36 months.

The HR for OS was 0.92 [95% confidence interval (CI) 0.65 to 1.32] indicating non-inferiority. The upper limit of the non-inferiority HR margin of 1.50, which was informed by patient advisors to the project, lies at the 99.6 percentile of this estimate ($p = 0.004$). There were no differences in this result by p16 status. There were 54 NDs performed in the surveillance arm, with 22 surgical complications, and 221 NDs in the ND arm, with 85 complications. Quality-of-life scores were slightly better in the surveillance arm. Compared with planned ND, PET-CT surveillance produced an incremental net health benefit of 0.16 QALYs (95% CI 0.03 to 0.28 QALYs) over the trial period, and 0.21 QALYs (95% CI to 0.41 to 0.85 QALYs) over the modelled lifetime horizon.

Conclusions

Positron emission tomography-computerised tomography-guided active surveillance showed similar survival outcomes to the ND arm, but resulted in considerably fewer NDs, fewer complications and, probably, lower costs. Further exploration of the significance of persistent nodal enlargement but no PET uptake is required.

Trial registration

This trial is registered as ISRCTN13735240.

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