

Institution: University of Birmingham		
Unit of Assessment: UoA 1, Clinical Medicine		
Title of case study: Transforming the treatment of Head and Neck cancer by dramatically reducing the need for invasive surgery		
Period when the underpinning research was undertaken: 2007–2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Professor Hisham Mehanna	Professor of Head and Neck Surgery	2012–present
Dr Sally Roberts	Senior Lecturer, Institute of Cancer and Genomic Sciences	1989–present
The late Professor Ciaran Woodman	Professor of Cancer Virology	1988–2015
Period when the claimed impact occurred: June 2016–December 2020		
Is this case study continued from a case study submitted in 2014? No		
<p>1. Summary of the impact</p> <p>Chemoradiotherapy is now the standard first line treatment for patients with head and neck cancer (HNC) who have advanced lymph node disease. For many years, this has been followed by neck dissection surgery but only a minority of patients are subsequently found to have had residual tumour and as such many undergo unnecessary painful, disfiguring and debilitating surgery. Professor Mehanna has demonstrated that the use of advanced imaging, positron emission tomography (PET-CT) eliminates the need for invasive surgery in over 80% of these patients, thereby reducing operative complications from 31% to 8%. The specific impacts which follow from this are:</p> <ul style="list-style-type: none"> • Improved outcomes for patients, as surgery is no longer necessary and hospital stay and surgery-associated complications are therefore reduced. • New National and International recommendations for the treatment of patients with HNC (including UK, Europe, Japan and USA) have been introduced. • Widespread change in clinical practice as neck dissections for HNC patients are no longer performed, leading to reduction in surgical activity in the UK, Europe and Australia. • Reduced costs of treatment both nationally and internationally; for example, the NHS saves approximately £3 million each year as a result of reduced hospital stays for ~2,000 patients. 		
<p>2. Underpinning research</p> <p>Head and neck cancer (HNC) is the sixth most common cancer globally, affecting more than 5.5 million people, with 600,000 new cases a year, and causing over 379,000 deaths in 2015. Average 5-year survival following diagnosis in the developed world is 42–64%.</p> <p>For many years, surgical neck dissection has been used after initial chemoradiotherapy in patients with locally advanced disease. However, this is a 2–3 hour operation and requires a 4–7 day hospital stay. It can result in life-changing complications such as life-threatening bleeding, pain and life-long paralysis of mouth movement, prominent scarring and disfigurement, and permanently reduced shoulder movement and infection.</p> <p>Previous work carried out by Mehanna (Isles et al 2008) showed that PET-CT scanning had a high negative predictive value (97.5%) for persistent cancer in the neck following chemoradiotherapy (i.e. a negative scan indicates high confidence that there is no tumour). However, this evidence was from small retrospective studies, supporting the need for a definitive trial. Mehanna then</p>		

designed the PET-NECK study which compared PET-CT guided surveillance policy to planned neck dissection. The study was run in conjunction with Professor Janet Dunn (lead cancer statistician) at Warwick Clinical Trials Unit.

During trial recruitment, early evidence emerged of the potential importance of a coincident viral infection, Human Papillomavirus (HPV), which appeared to drive many cases of HNC. HPV-positive head and neck cancer (HPV+HNC) responds much better to chemoradiotherapy treatment than HPV- cases (HPV-HNC) with consequent improved survival. Importantly, HPV+HNC is the fastest-rising subgroup of HNC in the UK and incidence doubled between 1996 and 2006, and then again between 2006 and 2010. It was therefore critical to understand both the global prevalence of HPV+HNC and the effects of HPV status on the outcomes of the treatments being assessed in the PET-NECK trial.

Working with Dr Sally Roberts and Professor Ciaran Woodman, Mehanna carried out a systematic review of the global prevalence of HPV+HNC, which confirmed significantly rising trends, especially in the USA and Europe (R1). These results led to a critical 2-year extension of the trial, enabling assessment of subjects' HPV status, and investigation of this on the outcomes of imaging versus surgery.

PET-NECK, published in 2016, recruited 564 patients and is the largest UK HNC trial in the last 2 decades, (R2, R3). 282 patients were in the 'neck dissection' arm and 215 neck dissections were performed in this cohort, with patients experiencing a total of 85 (30%) complications. In contrast, the 282 patients in the 'PET-CT surveillance' arm underwent 56 neck dissections, experiencing a total of 22 (8%) complications. Importantly, survival and tumour control were the same in both groups.

These research findings provided clear evidence that 'PET-CT surveillance' treatment was as effective as 'routine neck dissection', providing the same tumour control rate, whilst sparing an invasive neck dissection operation in 80% of patients who received PET-CT surveillance. This equated to 214 patients being spared surgery in this study alone.

Full health economic analysis, including modelling of long-term health economic benefit, was undertaken in 2016–2017 in collaboration with Claire Hulme and Peter Hall, Leeds University (R4).

The PET-NECK trial collected data on clinical efficacy, treatment complications, NHS resource use and societal costs allowing comprehensive assessment of impact on people's lives and on healthcare costs. Careful comparison of implementation costs of surgery versus PET-CT imaging established a reduction in cost of treatment of £1,492 per patient and supported wide-scale adoption.

The analysis of HPV-status was crucial as it showed similarly good outcomes in HPV+ patients between the two arms, demonstrating that PET-CT surveillance was equally effective for patients with HPV-HNC and HPV+HNC and could therefore be used with confidence to treat both patient groups (R2 and R3).

Key findings (KF):

- i. 'PET-CT surveillance' is as effective as 'routine neck dissection' in rate of tumour control and can be used to manage both HPV- and HPV+ HNC.
- ii. Patients can be spared neck dissection using PET-CT surveillance.
- iii. PET-CT demonstrates long-term cost effectiveness to healthcare providers.

3. References to the research

1. Mehanna H, Beech T, Nicholson T, El-Hariry I, McConkey C, Paleri V, Roberts S. Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer--systematic review and meta-analysis of trends by time and region. *Head Neck*. 2013 May;35(5):747-55. DOI: 10.1002/hed.22015.

2. Mehanna HM, Wong WL, McConkey CC, Rahman JK, Robinson M, Hartley AGJ et al. PET-NECK – a multi-centre randomized phase III controlled trial (RCT) comparing PETCT guided active surveillance with planned neck dissection (ND) for locally advanced (N2/N3) nodal metastases (LANM) in patients with head and neck squamous cell cancer (HNSCC) treated with primary radical chemoradiotherapy (CRT). N Engl J Med 2016;374:1444–54. DOI: [10.1056/NEJMoa1514493](https://doi.org/10.1056/NEJMoa1514493).
3. Mehanna H, McConkey CC, Rahman JK, Wong WL, Smith AF, Nutting C, Hartley AG, Hall P, Hulme C, Patel DK, Zeidler SV, Robinson M, Sanghera B, Fresco L, Dunn JA. 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. Health Technol Assess. 2017 Apr;21(17):1-122. DOI: [10.3310/hta21170](https://doi.org/10.3310/hta21170).
4. Smith AF, Hall PS, Hulme CT, Dunn JA, McConkey CC, Rahman JK, McCabe C, Mehanna H. Cost-effectiveness analysis of PET-CT-guided management for locally advanced head and neck cancer. Eur J Cancer. 2017 Nov; 85:6-14. DOI: [10.1016/j.ejca.2017.07.054](https://doi.org/10.1016/j.ejca.2017.07.054).

Extension grant: Mehanna, Dunn, Nutting, Fisher, Wong, MacLennan, MacKenzie, McCabe. Positron Emission Tomography-Computerised Tomography scan (PET-CT) guided watch and wait policy versus planned neck dissection for the management of locally advanced (N2/N3) nodal metastases in patients with head neck squamous carcinoma treated with radical chemoradiotherapy (CRT) – extension. Dept. of Health National Coordinating Centre Health Technology Assessment Unit, December 2012.

4. Details of the impact

We have fundamentally transformed the treatment of HNC globally, thereby **improving patient outcomes and reducing costs**. This has been achieved by **directly informing professional standards and guidelines which has resulted in** the adoption of **new clinical practice**.

1. Improved patient outcomes by reduction in invasive neck surgery

Significant patient benefits are demonstrated by **reductions** in both **the need for major surgery and in surgery-associated complications** (which significantly affect quality of life [R2, R3]). This is evidenced by results of the PET-NECK study (R2, R3; KFii) and reflected by the fact that the number of **neck dissections** carried out for HNC patients receiving chemoradiotherapy in the UK has **reduced by over 50%** from 25.8% in 2007 (before PET-NECK trial started) to 12.2% in 2018 (Hospital Episode Statistics (HES) data) [S1(i-ii)]. As a result, it is projected that 12,000 patients have been spared neck dissection in the UK since 2014 and 2,760 patients have avoided complications in the UK alone. To illustrate, the Beatson Oncology centre (Glasgow), which delivers CRT for whole of the West of Scotland Cancer network, reported **a 95% reduction in neck dissections** between 2013–2016 (presented ICHNO 2019, in publication [S2i]). **Only 5% of 187 patients assessed by PET-CT required a neck dissection thus 177 patients were spared the pain, complications and hospital stay** (on average 935 in-patient hospital days) associated with surgery.

This patient benefit has been repeated internationally. For example, at the Princess Alexandra Hospital, the main cancer centre in Queensland, Australia, the number of patients receiving PET-CT after **CRT increased from 8 in 2005–2006 to 83 in 2017–2018** with only 4 (5%) patients needing neck dissection [S2ii]. Similarly, at the University Hospitals of Cologne and Leipzig (major HNC centres in Germany) the number of **PET-CTs after CRT rose from 7 in 2010 to 89 in 2019** and from **11 in 2005–2006 to 102 in 2018–2019** respectively, after the German Joint Federal Committee approved PET-CT in 2017 [S2iii].

2. Transforming global professional standards and guidelines for HNC treatment

Globally, **changes have been made to national clinical guidelines** including the USA, Italy, Japan, Germany [S3(i-vi)] and the UK [S3(v-vii)]; as well as a recommendation for implementation by NICE guidelines in 2018 [S3(vii)], based on our findings [KFi–KFiii].

Citing Mehanna and the PET-NECK (R2) study as primary evidence, the following **national guidelines** have changed to include the use of PET-CT for HNC:

- The UK's National Institute for Clinical Excellence (NICE) updated its guidelines (2018) for cancers of the upper aerodigestive tract referencing the PET-NECK trial (R2) as evidence (Recommendation 1.5) [S3v].
- The UK National Head and Neck Management Guidelines (2016) [S3vi] were changed (based on KFi–KFii) to recommend the use of PET-CT scan-guided surveillance in management of advanced nodal disease instead of planned neck dissection. This has translated to changes in many local and regional guidelines across the UK, for instance the West of Scotland Regional head and neck cancer guidelines [S3vii].
- **US** National Comprehensive Cancer Network (NCCN) Head and Neck Guidelines, 2018 [S3i].
- **Italian** Medical Oncology Society (AIOM) Guidelines for H&N cancer, 2016 [S3ii].
- **Japanese** head and neck cancer guidelines, 2018 [S3iii].
- **German** Joint Federal Committee, part of the Federal Ministry of Health (2017) [S3vi].

3. Transforming professional clinical practice around the world in the treatment of HNC

Prior to the PET-NECK study, no clinical units in the UK offered PET-CT scans to patients for HNC. In 2018, 82% of the 21 centres in CompARE indicated **they would assess patients by PET-CT 3 months after treatment**. This is supported by participation in the national multi-centre CompARE trial looking at different treatments for people with oropharyngeal cancer (2017–ongoing) [S4i–iii].

The number of PET-CT scans now administered to HNC patients receiving **chemoradiotherapy in the UK has increased from no scans in 2007 to 685 in 2018** as verified by the latest data available from HES [S1(i-ii)].

International change in practice is reflected by reduced surgeries carried out at International centres as detailed above.

That our work led to change is further attested to by the American Society for Clinical Oncology (ASCO, the world's largest cancer society), which described PET-NECK as one of the “most notable advances in cancer treatment” in ASCO's 2016 and 2017 reports on the advances in cancer treatment [S5].

4. Reduced treatment costs for HNC surgery

Our health economic study measured per-person lifetime cost-saving and quality-adjusted life years savings of £1,492 per patient, on an average treatment cost of £24,047 (R4; KFiii). This translates to a saving of approximately £3 million each year to the NHS. In the UK alone, we calculate a reduction of 12,000 operations between 2014 and 2020, saving £18 million for the NHS. As international practice has changed, major cost-savings would be anticipated worldwide.

5. Sources to corroborate the impact

S1. (i) [Health episodes statistics analysis 2007–2018](#) supporting (ii) increased numbers of PET-CT scans and reduced numbers of Neck Dissections for patients with HNC.

S2. (i) UK (Beatson): Abstract - [PET CT Surveillance post radiotherapy in advanced head and neck cancer](#), **(ii)** Australia (Queensland): Howard YL Utility of a repeat PET/CT scan in HPV-associated Oropharyngeal Cancer following incomplete nodal response from (chemo)radiotherapy, et al, Oral Oncology 88 (2019) 153–159 [DOI:10.1016/j.oraloncology.2018.11.033](#), **(iii)** Germany: Confirmation of hospital data, **(a)** Department of Otorhinolaryngology, University Hosp Cologne, **(b)** Department of Head and Neck Surgery, University of Leipzig Hospital.

S3. Changes to HNC Management guidelines: including **(i)** USA, **(ii)** Italy, **(iii)** Japan, **(vi)** Germany, **(v)** NICE, **(vi)** UK National Head and Neck Guidelines 2016, **(vii)** West of Scotland Network: *all guidelines cite the PET neck trial as the evidence underpinning their recommendations.*

S4. CompARE trial protocol (NCT04116047): **(i)** Summary on Cancer Research UK website, [Summary on Cancer Research UK website](#), **(ii)** CompARE trial summary protocol on: [clinicaltrials.gov international database](#): **(iii)** [Imaging sites involved in CompARE trial](#).

S5. Commendation of PET neck trial by international cancer societies **(i)** Featured as one of the most important advances of the year in the treatment of cancer: Clinical Cancer Advances 2016: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology [DOI:10.1200/JCO.2015.65.8427](#), **(ii)** Referenced again as one of the most notable advances in cancer treatment: ASCO annual report on Clinical cancer advances 2017 [DOI:10.1200/JCO.2016.71.5292](#)