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Cost-effectiveness analysis of PET-CT guided management for locally advanced head and neck cancer

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ABSTRACT

Purpose: A recent large UK clinical trial demonstrated that positron-emission tomography–computed tomography (PET-CT)- guided administration of neck dissection in patients with advanced head and neck cancer after primary chemo-radiotherapy treatment produces similar survival outcomes to planned neck dissection (standard care) and is cost-effective over a short-term horizon. Further assessment of long-term outcomes is required in order to inform a robust adoption decision. Here we present results of a lifetime cost-effectiveness analysis of PET-CT guided management from a UK National Health Service (NHS) secondary care perspective.

Methods: Initial 6-month cost and health outcomes were derived from trial data; subsequent incidence of recurrence events and mortality was simulated using a *de novo* Markov model. Health benefit was measured in quality adjusted life years (QALYs) and costs reported in 2015 British pounds. Model transition probabilities, costs and utilities were derived from trial data and published literature. Sensitivity analyses were conducted to assess the impact of uncertainty and broader NHS & personal social services (PSS) costs on the results.

Results: PET-CT management produced an average lifetime NHS secondary care cost saving of £1,485 [$2,133] (95% CI: -2,815 to 159) and an additional 0.13 QALYs (95% CI: -0.49 to 0.79). At a £20,000 [$28,736] willingness-to-pay per additional QALY threshold there was a 75% probability that PET-CT was cost-effective, and the results remained cost-effective over the majority of sensitivity analyses. When adopting a broader NHS & PSS perspective, PET-CT management produced an average saving of £700 [$1,005] (95% CI: -6,190 to 5,362) and had an 81% probability of being cost-effective.

Conclusions: This analysis indicates that PET-CT guided management is cost-effective in the long-term and supports the case for adoption.

1. INTRODUCTION

Chemo-radiotherapy has become a mainstay of primary treatment for many patients with squamous-cell carcinoma of the head and neck. However, for patients with advanced nodal disease (stage N2 or N3) there remains variation in subsequent treatment management. Evidence of persistent disease in nodes after neck dissection in up to 40% of patients, combined with some evidence of a survival advantage resulting from surgery, has led to many centres maintaining neck dissection as the preferred treatment strategy [1-3]. However, in the 30-45% of patients exhibiting complete response on imaging after chemo-radiotherapy, less than 10% go on to experience disease recurrence [4, 5]; combined with recent improvements in imaging technology, this has led to the sporadic adoption of image-guided treatment strategies in some countries as a means of sparing low-risk patients from the morbidity and expense of unnecessary surgery.

A recent UK clinical trial (PET-Neck) was conducted to assess the clinical utility and cost-effectiveness of a combined 18F-fluorodeoxyglucose (FDG) positron-emission tomography and computed tomography (PET-CT) guided management for patients with advanced squamous cell carcinoma [6]. The study found that, over the trial 2-year follow-up period, overall survival was similar among patients in the PET-CT arm compared to those who underwent planned neck dissection (84.9% vs. 81.5% respectively). In addition, mainly as a result of fewer operations (54 vs. 221), the intervention was associated with a 2-year cost-saving of £1,492. Combined with a small increase (+0.08) in quality-adjusted life years (QALY), PET-CT guided management was found to be cost-effective over the 2-year trial horizon.

Uncertainty remains over the long-term cost-effectiveness of image-guided management. Initial cost-savings associated with PET-CT (largely attributable to the lower procedural cost compared to neck dissection; currently £649 vs. £3,548 respectively in the UK [7]) may not translate into long term cost savings if surgery is merely delayed or if the rate of late-stage recurrence events requiring more aggressive treatments is increased. Wide-scale adoption of new and potentially expensive technologies requires robust evidence on both long term clinical effectiveness and cost-effectiveness, and local decision makers need to have a clear idea of financial implications. Full consideration of the downstream cost consequences of PET-CT, as well as the impact on patient mortality and quality of life, therefore needs to be addressed.

Here we report results of the PET-Neck study lifetime cost-effectiveness analysis, which, together with previously published clinical outcomes and short-term cost-effectiveness [6], provides vital evidence for the viability of a PET-CT guided management strategy for this patient group.

2. METHODS

Clinical trial

The PET-Neck study was a UK pragmatic multi-centre phase III randomised non-inferiority trial (ISRCTN 13735240). Full details of the trial have been previously published [6]. Briefly, between October 2007 and August 2012, 564 adult patients with head and neck (including oropharyngeal, laryngeal, oral, hypopharyngeal or occult) squamous cell carcinoma with nodal stage N2 or N3 and no distant metastasis (stage M0) disease were recruited across 43 UK National Health Service (NHS) hospitals. Patients were randomised 1:1 to receive either (a) standard care, consisting of planned neck dissection either before (within 4-weeks of randomisation) or after (within 4-8 weeks of chemo-radiotherapy completion) primary chemo-radiotherapy treatment, or (b) PET-CT management, consisting of chemo-radiotherapy followed by PET-CT scan after 10-12 weeks, with neck dissection administered within 4 weeks of a positive or equivocal PET-CT scan. No surgery was undertaken if patients did not have evidence of residual disease. All patients received subsequent ongoing follow-up including regular clinical examinations. The primary outcomes of the trial were overall survival and cost-effectiveness, and all patients were followed up for a minimum of 2 years post randomisation. Requests for survival and recurrence status at the end of the trial provided additional follow-up up to 5 years. Ethical approval for this trial was provided by the Oxfordshire Multi-Research Ethics Committee in May 2007 (Ref No: 07/Q1604/35).

Health economic analysis

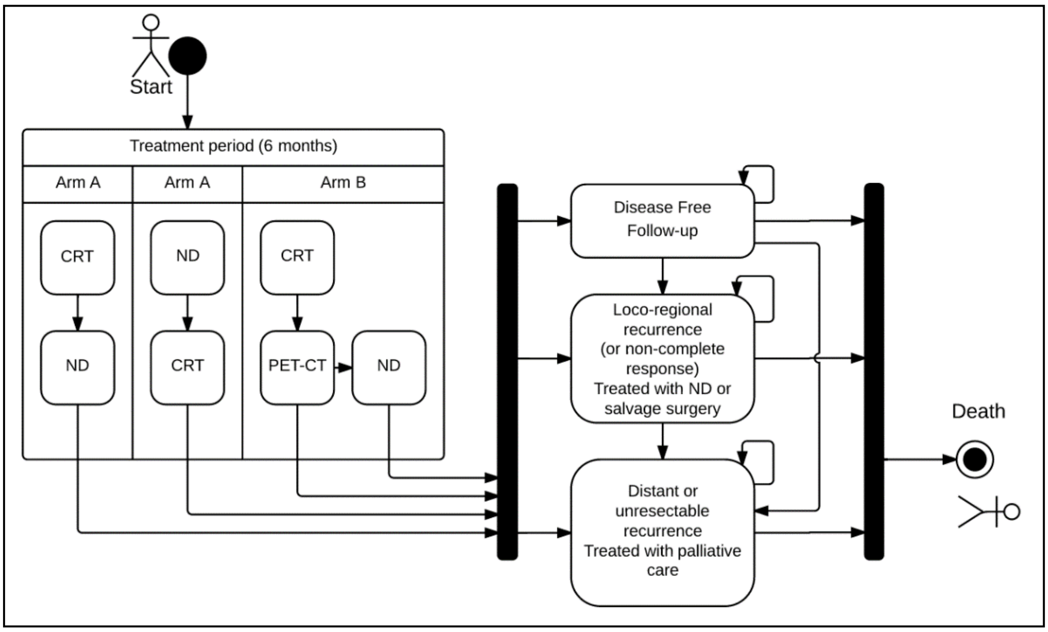
The PET-Neck health economic evaluation consisted of two components: (i) a previously reported within trial (2-year) analysis [6]; and (ii) a lifetime analysis (the focus of this paper), in which the cost-effectiveness of PET-CT management versus planned neck dissection is assessed over a lifetime horizon using a modified Markov model.

The primary analysis was conducted from an UK NHS secondary care perspective (i.e. including hospital costs only); sensitivity analyses were conducted including wider NHS and personal social services (PSS) costs. Patient health benefit was measured in quality adjusted life years (QALYs): a composite measure of patient health-related quality of life - ranging from perfect health (1) to death (0) - and patient life-years. Costs are reported in 2015 British pounds (£) and future cost and health outcomes (beyond one year) were discounted at an annual rate of 3.5% as per the National Institute of Health and Care Excellence (NICE) guidance [8]. All analyses were conducted in R (version 3.1.2) [9].

Lifetime decision model

A *de novo* decision analytical model was constructed to estimate cost-effectiveness over a lifetime horizon (truncated at 100 years). The model is split into two phases (see Figure 1). In the initial 6-month treatment phase, patients in the standard care arm (arm A) receive planned neck dissection (ND) either before or after chemo-radiotherapy (CRT), whilst patients in the PET-CT management arm (arm B) receive chemo-radiotherapy followed by a PET-CT scan at 10-12 weeks post-chemo-radiotherapy which dictates whether or not patients go on to receive neck dissection. Costs and QALYs for the treatment period of the model were derived using individual participant data from the first 6 months of the trial. After 6 months, a Markov model was used to capture the health and cost implications of disease recurrence, for which the trial provided limited data.

Figure 1. Simplified lifetime decision model structure



Treatment period

Over the initial 6-month treatment period, patient health-related quality of life was measured using patient responses to the EQ-5D-3L questionnaire (collected at baseline, 2 weeks post chemo-radiotherapy and at 3, 6, 12, and 24 months post-randomisation). Multiple imputation was used to impute missing EQ-5D values, and patient utility scores were assigned to each of the EQ-5D defined health states using standard UK tariffs [10]. QALYs were calculated by combining utility values with overall survival data, using the Kaplan-Meier method to account for loss to follow-up.

Patients' use of hospital resources (e.g. surgical procedures, radiotherapy, chemotherapy, severe adverse events, patient follow-up assessments and recurrence events) was determined using the trial case report forms. National unit costs (reported in the supplementary material) were applied to each of the resource items and any costs reported in 2014 prices were inflated to year 2015 using a consumer price index inflation value of 1.005 [7] [11-13]. Bootstrap analysis (i.e. data sampling with replacement) was conducted to assess the impact of sampling uncertainty around the 6-month cost and QALY results.

Markov model

Outcomes beyond the 6-month treatment period were simulated using a cohort Markov-model. The model consisted of four health states: Disease Free (DF), Local Recurrence (LR), Distant (or unresectable) Recurrence (DR), or Death. Patients could transition between each of the model health states over monthly model cycles.

Model parameters were derived directly from trial data or from the literature using targeted searches where necessary (see Table 1). The proportion of patients beginning in each state of the model was taken directly from the trial data on overall survival and recurrences after 6 months. The cost and utility of the disease free state was based on the average monthly cost and utility values for patients who remained disease-free over the trial follow-up period (6-24 months), and the cost of initial treatment for recurrences was based on trial data on treatments administered upon recurrence. For patients who recovered from local recurrences, ongoing costs were assumed to be equal to those in the disease free state, whilst for patients remaining in the distant recurrence state an ongoing cancer supportive care cost was applied, derived from the literature [14]. Utilities for local and distant recurrence states were similarly taken from the literature [15]. Mortality within the disease free and local recurrence states were assumed equal to general population mortality (taken from Office of National Statistics [16]), multiplied by a factor of 20% derived from the literature [17]. Mortality within the distant recurrence state was determined by calibrating the model survival curve against the Kaplan Meier overall survival curve from the trial.

A key parameter in the model concerns the rate of primary recurrence over time. In the base case analysis, recurrence data from the trial extended follow-up was used to directly inform recurrence rates up to year five, with subsequent recurrence assumed to drop to zero in both arms (since recurrence at 5 years was observed to be approaching zero in both arms of the trial; see supplementary material for figures). Uncertainty around the rate of recurrence was captured by simulating 10,000 bootstrap data samples from the trial Kaplan Meier survival data. In addition, a sensitivity analysis was conducted to explore the impact of allowing recurrences beyond year 5 by fitting parametric survival curves to the within-trial Kaplan Meier recurrence survival plots (full details in supplementary material). Subsequent recurrence rates (i.e. secondary recurrence onwards) were derived from the literature [18].

Analysis

Cost-effectiveness was determined using the Incremental Cost-Effectiveness Ratio (ICER), which represents the additional cost required to be spent on a new intervention in order to gain an additional unit of health (i.e. QALY). Treatments are considered cost-effective if the mean ICER falls below a given decision-makers willingness-to-pay per additional health unit; here we adopt NICE's lower willingness-to-pay per additional QALY threshold of £20,000 per QALY. An intervention that is more effective and less costly than standard care is considered dominant and in such cases the ICER is meaningless (as there is no trade-off between additional costs and health benefits to consider) and is therefore not reported.

All primary analyses used probabilistic sensitivity analysis to capture the impact of joint parameter uncertainty on the results, based on 10,000 Monte-Carlo simulations. Model parameters were represented by appropriate probability distributions, with a different set of parameter values randomly selected within each model simulation to produce a distribution of 10,000 cost and QALY results. A series of one-way sensitivity analyses (altering individual model parameters by $^{+}$/- 25% of their base case mean value) were also conducted.

A further sensitivity analysis was conducted adopting a broader NHS and PSS perspective. This analysis used data on patients' use of secondary care outside of their enrolled hospital, as well as primary and community care, and was derived from patient reported resource-use forms used within the trial on a subset (n=42) of participants (full details in supplementary data). Since this analysis relied on data from a small subset of patients it is considered as exploratory only.

Table 1. Markov model parameters

Parameter	Mean	Standard Deviation	Distribution	Source
Global parameters				
Discount rate	0.035	-	Fixed	NICE guidance [8]
Start Age	57	-	Fixed	PET-Neck trial data [this study]
Proportion Male	0.82	-	Fixed	
Markov model health state starting distributions (end of trial 6 month treatment period)				
Planned ND: Recurrence	0.06	0.015	Beta	PET-Neck trial data [this study]
Planned ND: Proportion of recurrences local vs. distant	0.35	0.069	Beta	
Planned ND: Dead	0.03	0.01	Beta	
PET-CT: Recurrence	0.05	0.013	Beta	
PET-CT: Proportion of recurrences local vs. distant	0.41	0.066	Beta	
PET-CT: Dead	0.02	0.008	Beta	
Monthly health state costs				
DF	£71	£106	Gamma	PET-Neck trial data [this study] on DF (n=439) and LR (n=39) patients
LR initial treatment	£4,080	£4,386	Gamma	
DF after LR	£71	£106	Gamma	Assumed equivalent to DF cost
DR initial treatment	£3,726	£3,205	Gamma	PET-Neck trial data [this study] on DR patients (n=63)
DR ongoing care	£140	£32	Gamma	Hall *et al.* 2014. [14]
Terminal-month cost	£1,051	£115	Gamma	
Health state utilities				
DF	0.70	0.03	Beta	PET-Neck trial data [this study]
LR decrement	-0.11	0.12	Beta	Almeida et al. 2008 [15]
DF after LR	0.70	0.03	Beta	Assumed equivalent to DF utility
DR decrement	-0.47	0.2	Beta	Almeida et al. 2008 [15]
Dead	0	-	Fixed	-
Transition probabilities/ effects				
Recurrence over first 5 years	10,000 bootstrap simulations of Kaplan Meier recurrence-free survival curves, in each arm			PET-Neck trial data [this study]
Planned ND: proportion of recurrences local vs. distant	0.35	0.069	Beta	Assumed equivalent to rate observed within PET-Neck trial
PET-CT: proportion of recurrences local vs. distant	0.41	0.066	Beta	
Probability of LR from DF after LR	0.02	0.002	Beta	Matoscevic *et al.* 2014 [18]
Probability of DR from LR/ DF after LR	0.02	0.003	Beta	

Baseline mortality in DF/ LR	Life Table	-	Fixed	Office for National Statistics, 2013 age- and sex- standardized rates [16]
Excess mortality factor for DF and LR	1.2	-	Fixed	Van der Schroeff *et al*. 2010 [17]
DR mortality	0.3	0.3	Beta	Calibration of model survival curve against PET-Neck trial survival data

ND= Neck Dissection; PET-CT= positron-emission tomography and computed tomography; DF= Disease Free; LR= Local Recurrence; DR= Distant Recurrence.

3. RESULTS

PET-CT guided management was associated with a per-patient lifetime NHS secondary care cost saving of £1,485 [$2,133] (95% CI: -2,815 to 159) and a health gain of 0.13 (95% CI: -0.49 to 0.79) QALYs compared to planned neck dissection (see Table 2 and Figure 2). At a £20,000 [$28,736] per QALY threshold PET-CT was cost-saving 96% of the time, more effective than planned neck dissection 66% of the time, and the most cost-effective strategy 75% of the time.

Table 2. Lifetime cost-effectiveness results

Strategy	Total Cost (95% CI)	Total QALY (95% CI)	Incremental Cost (95% CI)	Incremental QALY (95% CI)	ICER	Probability cost-effective
NHS secondary care perspective (base case)						
Planned ND	£24,074 (12,947 – 63,200)	9.01 (7.87 – 10.46)	-	-	-	-
PET-CT	£22,589 (11,319 – 62,155)	9.14 (8.05 – 10.55)	-£1,485 (-2,815 – 159)	0.13 (-0.49 – 0.79)	Dominant	75%
NHS & PSS perspective (sensitivity analysis)						
Planned ND	£99,898 (68,360 – 139,654)	9.01 (7.87 – 10.46)	-	-	-	-
PET-CT	£99,198 (67,304 – 139,049)	9.13 (8.05 – 10.54)	-£700 (-6,190 – 5,362)	0.13 (-0.49 – 0.79)	Dominant	81%

CI = confidence interval; QALY= quality adjusted life year; ICER= incremental cost-effectiveness ratio; ND= neck dissection; PET-CT= positron-emission tomography and computed tomography; NHS= National Health Service; Dominant= more effective and less costly than standard care (ICER not reported in these cases).

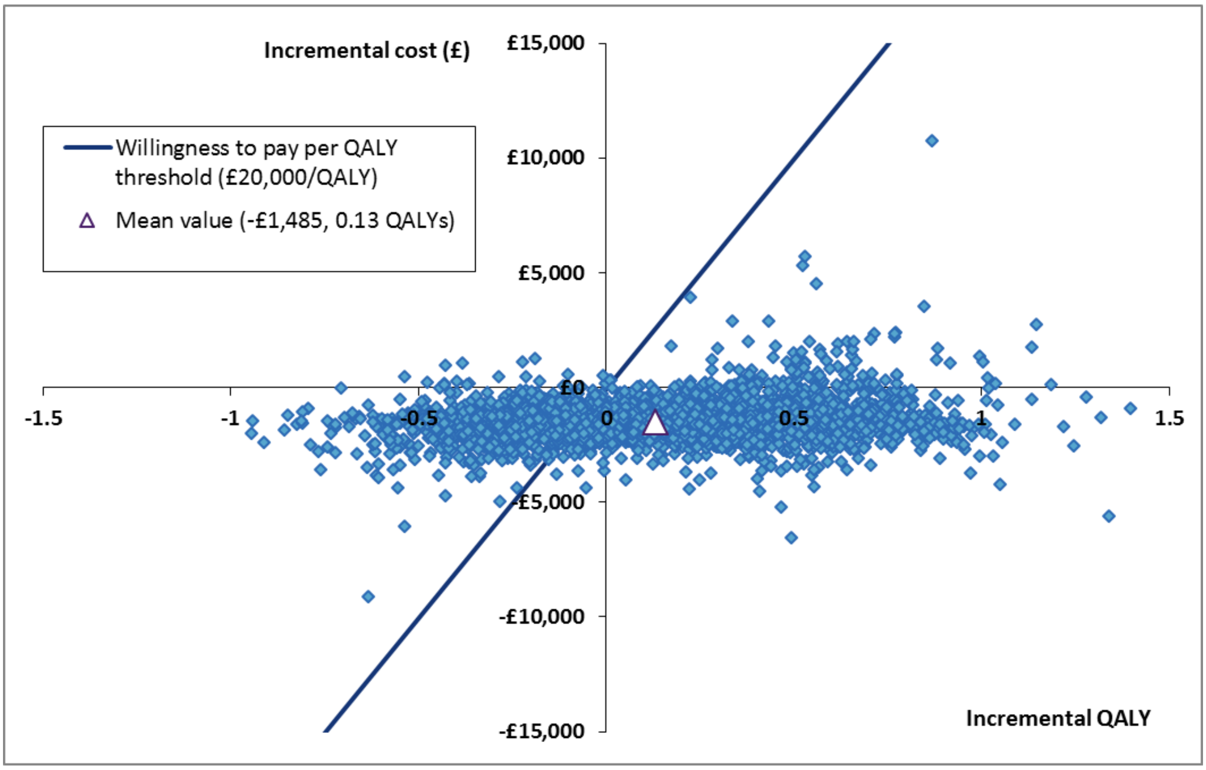


Figure 2. Scatter plot of lifetime cost-effectiveness results using an NHS secondary care perspective (base case). This plot shows the incremental cost and quality adjusted life year (QALY) results for PET-CT management versus standard care for each of the 10,000 model simulations (i.e. the blue dots). The diagonal line represents a willingness-to-pay per additional QALY threshold of £20,000 per QALY. Points below this line are considered cost-effective; points above this line are not considered cost-effective. The triangle indicates the mean incremental cost and QALY result.

The level of uncertainty around the cost-effectiveness of PET-CT management over different willingness-to-pay per additional QALY thresholds is illustrated in the cost-effectiveness acceptability curve shown in Figure 3. The probability that the PET-CT management strategy is cost-effective remains above 67% up to a £150,000 [$215,517] per QALY threshold.

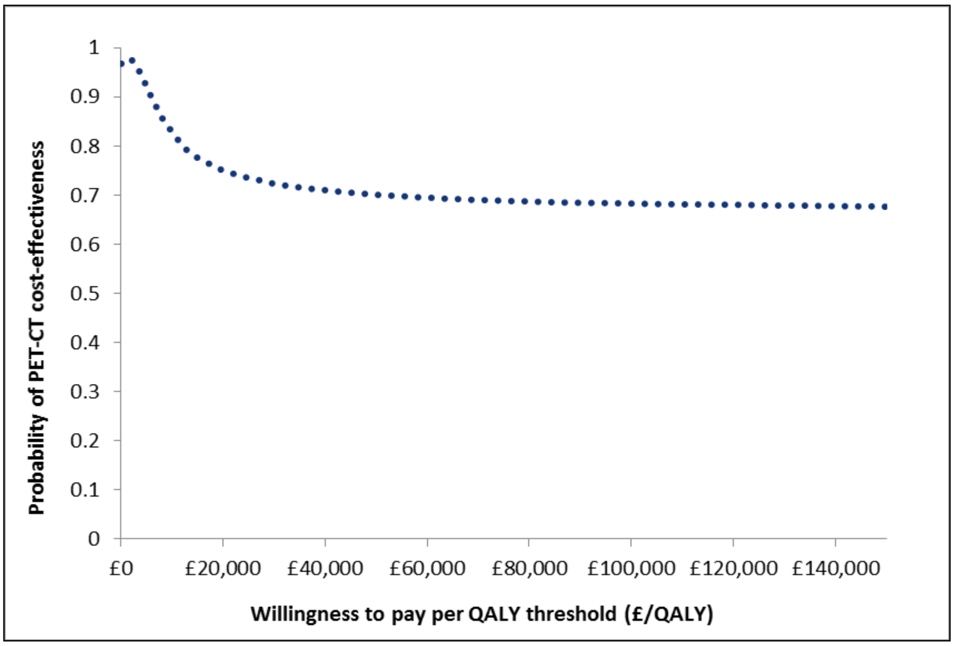


Figure 3. Cost-effectiveness acceptability frontier (CEAF) for the lifetime cost-effectiveness results using an NHS secondary care perspective (base case). This plot shows the probability that PET-CT management is cost-effective versus standard care (i.e. the proportion of points lying under the willingness-to-pay per additional QALY threshold in figure 2) over alternative threshold values.

Broadening the analysis to an NHS and PSS perspective resulted in substantial increases in the overall costs in both arms, with an average saving of £700 in favour of PET-CT, and an 81% probability that PET-CT management is cost-effective at a £20,000 per QALY threshold (see Table 2). Allowing secondary and subsequent recurrences to occur beyond 5 years in the model led to a slight reduction in the expected additional QALYs to +0.10 (95% CI:-0.56 to 0.80), but PET-CT remained dominant with a 71% probability of being cost-effective (results presented in supplementary material).

One-way sensitivity analysis

Results of the one-way sensitivity analysis are presented in Figure 4 (note: only parameters with the highest impact are shown). The results are most sensitive to changes in relative rate of primary recurrences in each arm.

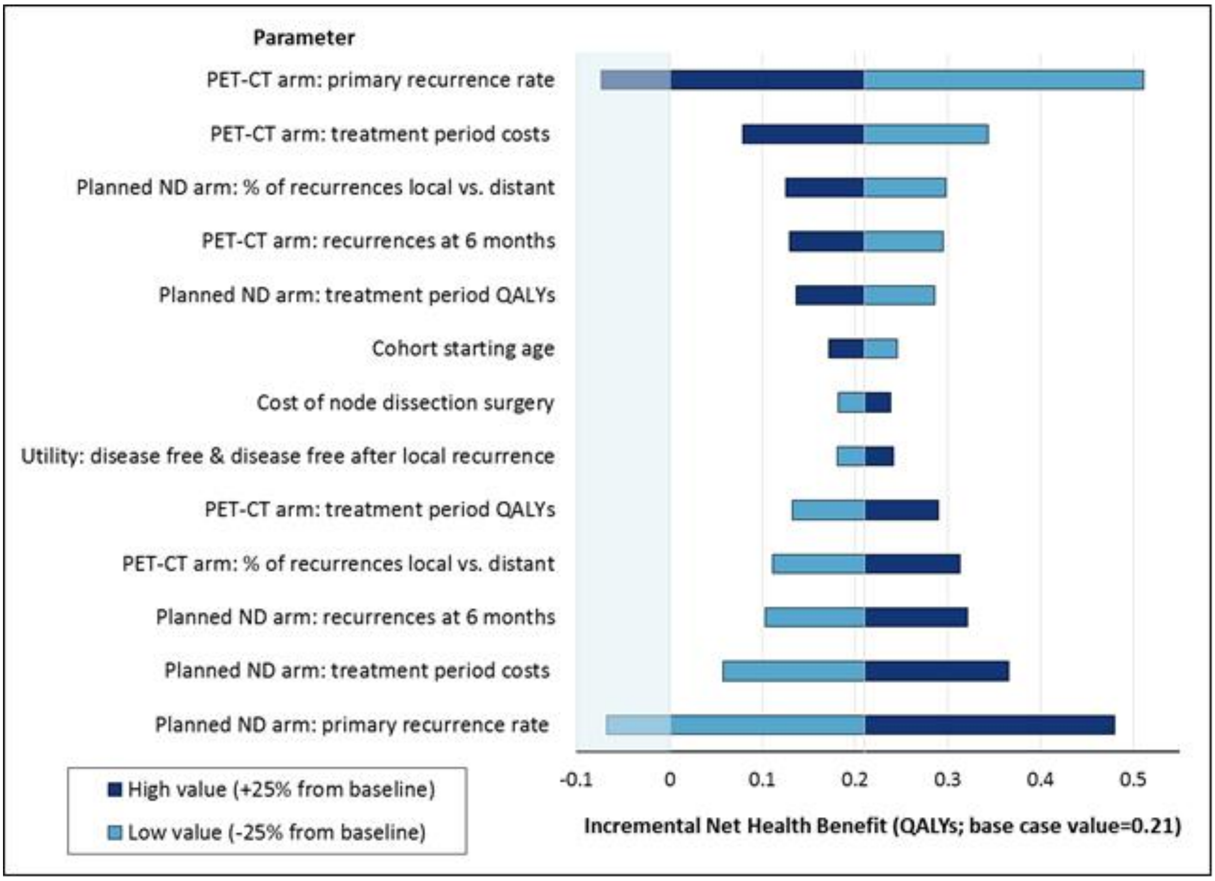


Figure 4. One-way sensitivity analysis for lifetime cost-effectiveness results using an NHS secondary care perspective. This plot shows the change in the base case model results when changing individual model parameters by +/- 25%. The cost-effectiveness of PET-CT management is presented in terms of the overall Incremental Net Health Benefit (INHB), which is a composite measure of incremental cost and quality adjusted life years (QALYs): additional costs are converted into lost QALYs by dividing by the willingness-to-pay per additional QALY threshold (£20,000), and this is subtracted from the additional QALYs associated with PET-CT management. INHB values above zero are considered to be cost-effective, whilst values below zero (indicated by the shaded region) are not considered to be cost-effective.

4. DISCUSSION

In addition to verifying the effects on survival and recurrence rates, research into long-term health economic implications is critical in order to determine the overall value of treatment strategies by weighing up both cost and health outcomes at all points along the patient pathway. This current evaluation provides the first confirmation that PET-CT guided management is likely to provide a cost-effective alternative to planned neck dissection within a randomised setting in the longer term, and from a UK healthcare perspective. This adds support to the previous body of studies in favour of adopting PET-CT into routine clinical practice.

We found that, on average, PET-CT guided management is expected to produce long-term cost savings and improve patient outcomes, similar to results of the previously reported within-trial analysis [6]. The main difference is an increased level of uncertainty (with the probability that PET-CT management is cost-effective dropping from 99% to 75%), which is an expected consequence of any model attempting to extrapolate from short-term to long-term outcomes. The findings are also in line with previous economic evaluations undertaken in non-randomised studies: in a recent study Pryor *et al.* found that a similar PET-CT guided strategy was a safe and significantly less costly alternative strategy to planned surgery from an Australian health service perspective [19], and three studies have demonstrated cost-effectiveness from a United States health care perspective [20-22].

The results remained cost-effective over a range of sensitivity analyses. The notable exception is when considering changes to the rate of primary recurrence. In the base case analysis, as a result of non-significantly different recurrence-free survival observed between treatment arms in the trial and zero primary recurrences assumed beyond five years, there was no resulting long-term negative consequences from averting surgery. Artificially raising the rate of recurrence in the intervention arm, however, has a predictably detrimental impact on the expected cost-effectiveness, with PET-CT management no longer being cost-effective when the rate of recurrence is increased by 25% in that arm.

A key limitation of our analysis concerns the limited NHS secondary care perspective adopted in the base case analysis. For patients with advanced nodal disease, it is highly probable that subsequent treatment management will take place in hospital, and we therefore expect this analysis to capture the key cost elements; it is preferable however that cost-effectiveness assessments should account for all resources which will be consumed as a result of implementing the new intervention. This restricted perspective was adopted as a result of a lack of sufficient data within the trial upon which to derive full NHS or societal costs and is a frequent problem encountered in cancer trials. We conducted a sensitivity analysis looking at potential impact on broader NHS costs using data on a subset of patients in whom additional resource use data was collected. It is encouraging that these exploratory results support the main findings; however these results need to be interpreted with caution due to the small sample size.

Further limitations of the analysis relate to the quality of evidence from the literature used to inform several of the model parameters. As with any model, uncertainty is introduced when using disparate sources to inform model inputs, and finding quality sources to inform post-recurrence outcomes is a particular issue in such analyses due to the paucity of data in this area. We conducted a range of sensitivity analyses in order to identify any key uncertain parameters. As discussed, the results were found to be largely robust.

In conclusion, our study indicates that the use of PET-CT guided management for patients with advanced head and neck cancer after primary chemo-radiotherapy reduces lifetime costs and improves patient health outcomes. These findings are likely to be generalizable to other countries where clinical pathways and procedural costs are similar.

Supplementary Material

Contents:

1. Unit Costs applied to trial resource use data

Table 3 reports unit costs applied to trial resource use data in the analysis. Note: prices are reported as given in the original source i.e. non-inflated.

Table 3. Table of unit costs

Resource Item	Unit cost	Source	Details/ assumptions
Secondary care costs (relating to trial case report form items)			
Inpatient "hotel cost" (per night cost)	£200	East and North Hertfordshire NHS Trust Performance Report. [23]	
Oncology assessment	£181	NHS Ref costs 2013/14. [7]	Medical oncology first face-to-face attendance.
Cardiology assessment	£160		Cardiology first face-to-face attendance.
Respiratory assessment	£186		Respiratory Medicine first face-to-face attendance.
Other assessment	£196		General Medicine first face-to-face attendance.
Dental assessment	£126		Dental Medicine first face-to-face attendance.
Nasopharyngoscopy	£114		Diagnostic Nasopharyngoscopy, 19 years and over.
Fine needle aspiration	£164		Minor Maxillofacial Procedures.
Surgery assessment	£150		General surgery first face-to-face attendance.
CT scan	£147		Computerised Tomography Scan, more than three areas.
PET-CT Scan	£649		Nuclear Medicine, Category 8 (PET-CT).
MRI Scan	£145		Magnetic Resonance Imaging Scan, one area, post contrast only, 19 years and over.
X-ray	£40	Personal communication with Leeds Teaching Hospitals Trust.	
Ultrasound	£76	NHS Ref costs 2013/14. [7]	Ultrasound Mobile Scan or Intraoperative Procedures, less than 20 minutes.
Other radiography assessment	£88		Clinical Oncology (Previously Radiotherapy) first attendance.

Nurse assessment	£100	PSSRU 2014. [12]	Assume an assessment is equivalent to 1 hour of contact time.
Palliative care assessment	£97		
Social other	£37		Assume equivalent to speech/diet assessment.
Speech assessment	£37		Assume an assessment is equivalent to 1 hour of contact time.
Dietician assessment	£37		As above.
Rehabilitation assessment	£36		Assume equivalent to 1 hour of occupational therapist contact time.
Psychology assessment	£138		Assume hospital assessment cost equivalent to community visit cost.
Counselling assessment	£50		As above.
Pegswab	£7	NHS Ref costs 2013/14. [7]	Directly Accessed - Pathology Services. Microbiology.
Bloods- haematology	£3		Directly Accessed - Pathology Services. Haematology
Bloods- biochemistry	£1		Directly Accessed - Pathology Services. Clinical Biochemistry.
Bloods- microbiology	£7		Directly Accessed - Pathology Services. Microbiology.
Bloods- other	£8		Directly Accessed - Pathology Services. Other.
Secondary care costs (relating to trial patient-reported items)			
Short stay (≤2 days) inpatient cost	£611	p111 2014 PSSRU. [12]	
Long stay (>2 days) inpatient cost	£2716		
Hospital day centre	£119	NHS Ref Costs 2013/14. [7]	Inpatient Specialist Palliative Care, Same Day, 19 years and over.
Outpatient visit	£109	2014 PSSRU. [12]	
Accident and Emergency visit	£135	NHS Ref Costs 2013/14. [7]	Total Outpatient Attendances.
Nursing/ convalescent home	£82	2014 PSSRU. [12]	Assume cost for 1 day and night equals the reported private sector nursing home cost per week / 7.
Primary and community care service costs (relating to trial patient-reported items)			
GP surgery visit (phone call)	£46 (28)	2014 PSSRU. [12]	
GP home visit	£67		Assume equal to reported cost for 17 min surgery visit.
District nurse home visit (phone call)	£66 (11)		Assume each visit equal to 1 hour contact time and a call is equivalent to 10 mins of contact time.

Social worker visit (phone call)	£79 (13)		As above.
Physiotherapist visit (phone call)	£36 (6)		As above.
Occupational therapist visit (phone call)	£36 (6)		As above.
Counsellor visit (phone call)	£50 (8)		As above.
Home help service	£24 (4)		Assume a visit is equal to 1 hr of weekday contact and a call is equivalent to 10 mins of this time.
Psychiatrist	£138		Assume a visit is equal to 1 hr contact time and a call is equivalent to 10 mins of contact time.
Day centre	£24		Assume equivalent to home help service visit.
Chemotherapy drug costs			
5FU	£3.47	eMIT 2015. [11]	5g/100ml vial, 5%, size 1.
Cisplatin	£16.69		100mg/100ml vial.
Carboplatin	£28.89		600mg/60ml vial.
Cetuximab	£890.50		5mg/ml, 100ml vial.
Docetaxel	£29.78		160mg/8ml vial.
Delivery cost	£328	NHS Ref costs 2013/14. [7]	Deliver subsequent elements of a chemotherapy cycle.
Radiotherapy costs			
Radiotherapy delivery	£149	NHS Ref costs 2013/14. [7]	Deliver a fraction of complex treatment on a megavoltage machine.
Radiotherapy planning visit	£1587		Prep for Intensity Modulated Radiation Therapy, with Tech Support.
Surgery costs			
Node dissection	£3548	NHS Ref costs 2013/14. [7]	Elective inpatient. Intermediate Maxillofacial Procedures.
Salvage surgery	£7722		Elective inpatient. Major Maxillofacial Procedures, 19 years and over, with CC Score 1+.
Follow-up visit assessment costs			
Anaesthetic examination	£85	NHS Ref costs 2013/14. [7]	Anaesthetics: Diagnostic, Laryngoscopy or Pharyngoscopy, 19 years and over.
Biopsy	£164		Maxillo-Facial Surgery: Minor Maxillofacial Procedures.
Clinical exam	£109		Maxillo-Facial Surgery: Diagnostic, Laryngoscopy or Pharyngoscopy, 19 years and over.

Recurrence treatment costs			
Brachytherapy	£2,393	NHS Ref costs 2013/14. [7]	1 x Preparation for interstitial brachytherapy (£1,196). 1 x Deliver a Fraction of Intraluminal Brachytherapy (£1,197).
Chemotherapy course	£4,753		6 x Procure chemotherapy drugs for regimens in Band 2 (£323). 1 x Deliver more complex Parenteral Chemotherapy at first attendance (£317). 5 x Deliver subsequent elements of a chemotherapy cycle (£328). 6 x Medical Oncology Follow-up
Radiotherapy course	£1,744		Assumes 1 radiotherapy planning visit and 1 delivery.
Annual supportive care cost post distant recurrence	£1,682	P.Hall et al. 2014. [14]	
Terminal month palliative care cost post distant recurrence	£1,051		
Resection/ Free Flap Reconstruction	£7722	NHS Ref costs 2013/14. [7]	Elective inpatient. Major Maxillofacial Procedures, 19 years and over, with CC Score 1+.
CC= Currency code; SC= Service code			

2. PET-Neck within-trial time to recurrence plots

Time to recurrence by treatment arm within the extended 5-year PET-Neck trial follow-up period is shown in Figure 5. For Kaplan-Meier analysis of recurrence, the time of recurrence was taken as the time from completion of radiotherapy to reported recurrence or to cancer death if there was no reported recurrence.

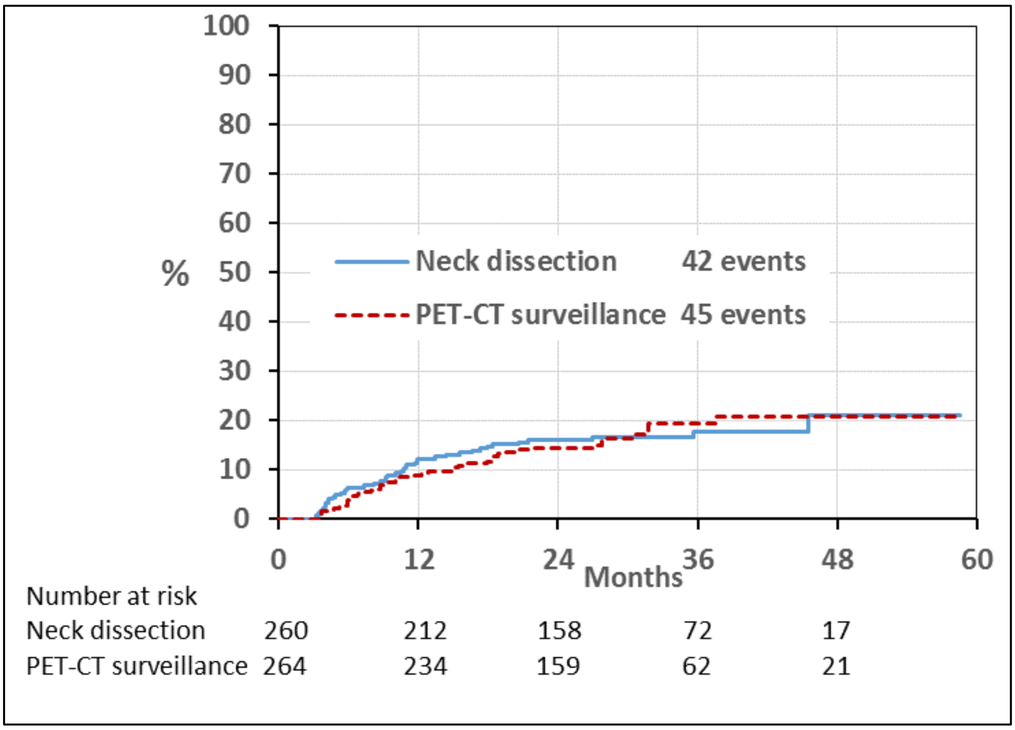


Figure 5. Time to recurrence by treatment arm in the PET-Neck trial

3. Sensitivity analysis: NHS & PSS perspective

Methods

In the base case analysis, costs were calculated using data from the trial case report forms which provided information on a range of secondary care resource usage for the total trial population (n=564). Additional data on primary and community care resource usage, as well as additional secondary care resource usage (outside of the enrolled oncology department), was collected for a subgroup of the trial population (n=42) enrolled at the two main recruiting centres. These patients were asked to recall their use of NHS and PSS services over the past 3 months (or since completion of the last form where appropriate) at baseline, during treatment (2 weeks post CRT), and at 3, 6, 12 and 24 months post randomisation. A sensitivity analysis was conducted to assess the potential impact of including this additional cost data, by imputing the mean reported values for the additional resource use items collected in the patient-reported forms to the total trial population. Mean values were calculated using a complete case analysis of the patient- reported data. Due to the small sample size it was deemed inappropriate to attempt to conduct multiple imputation for missing data.

Within the patient-reported questionnaires, patients were asked to report any additional visits to hospital (inpatient, day centre, outpatient, A&E or nursing home visits), not including visits to their enrolled oncology department; this was in order to capture additional secondary care resource usage not already captured in the case report forms routinely completed at the patient's enrolled oncology department. However, where additional hospital visits were reported, patients were asked to give the name of the hospital they visited, and a significant number of patients identified the hospital as the same as that to which they were enrolled in the trial. In such cases it was assumed that this data would already have been captured in the trial case report forms and these events were therefore excluded from the analysis.

Results

Results of the sensitivity analysis using an NHS and PSS perspective are presented in Figure 6 and Figure 7 (note: the results table for this analysis is reported in Table 2 in the main article text).

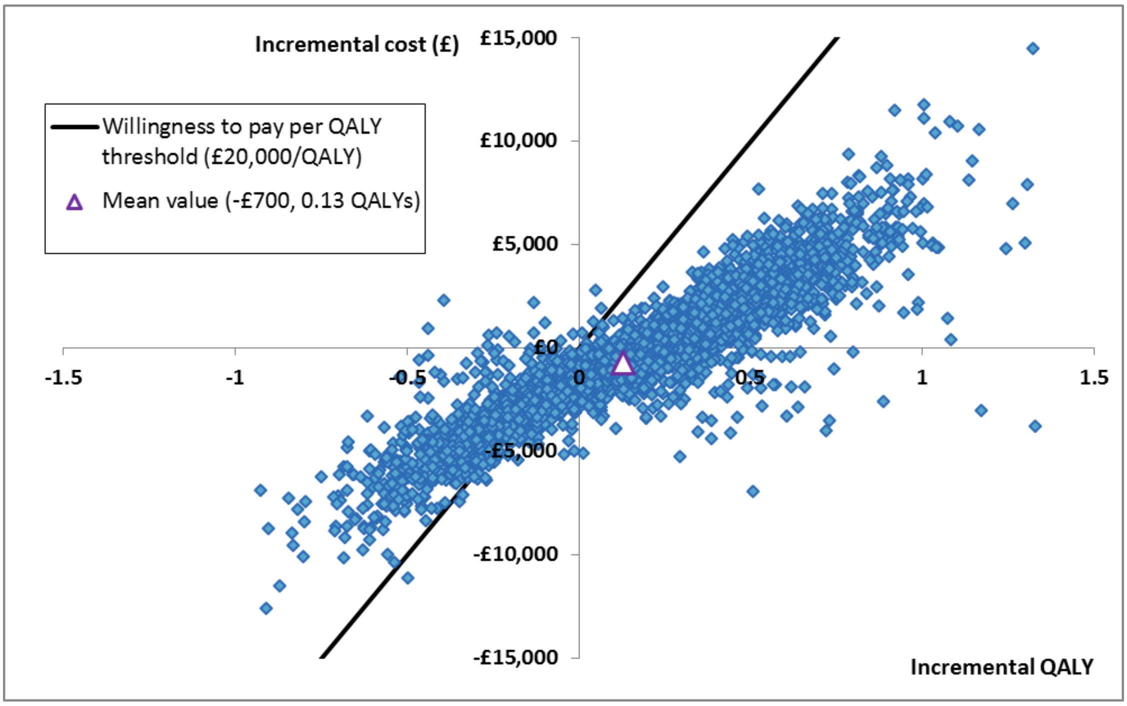


Figure 6. Scatter plot of lifetime cost-effectiveness results using an NHS and PSS perspective. This plot shows the incremental cost and quality adjusted life year (QALY) results for PET-CT management versus standard care for each of the 10,000 model simulations (i.e. the blue dots). The diagonal line represents a willingness-to-pay per additional QALY threshold of £20,000 per QALY. All points below this threshold line are considered cost-effective; points above this line are not considered cost-effective. The triangle indicates the mean incremental cost and QALY result.

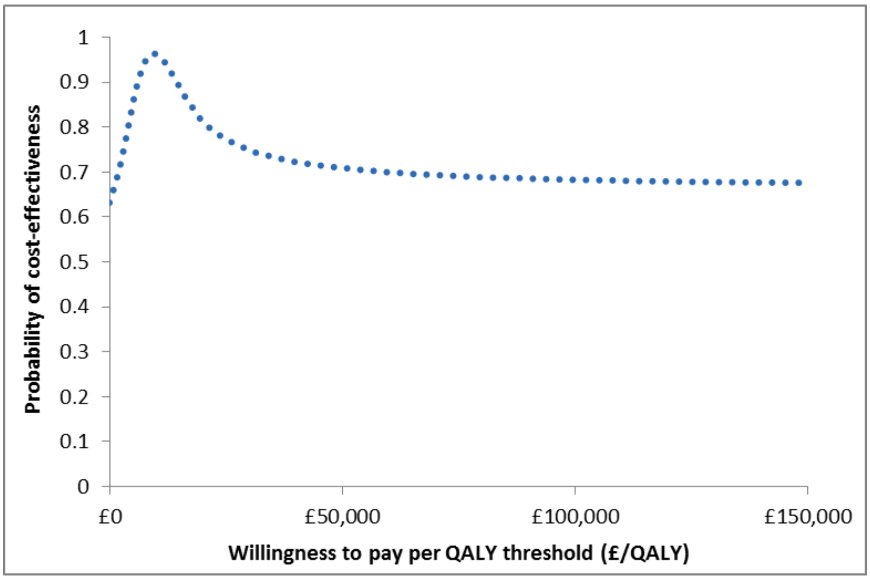


Figure 7. Cost-effectiveness acceptability frontier (CEAF) for the lifetime cost-effectiveness results using an NHS and PSS perspective. This plot shows the probability that PET-CT management is cost-effective versus standard care (i.e. the proportion of points lying under the willingness-to-pay per additional QALY threshold) over alternative threshold values.

4. Sensitivity analysis methods and results: primary recurrence beyond year five

Methods

In the base case analysis no recurrence events were assumed to occur beyond year five in the model. A sensitivity analysis was conducted assuming recurrences could occur beyond year five by fitting parametric survival curves to the within-trial recurrence free survival Kaplan Meier plots. Long term recurrence probabilities for the planned neck dissection arm were estimated using a Gompertz parametric survival curve fitted to the trial baseline Kaplan Meier data; a hazard ratio (HR) was then applied to this curve in order to derive survival within the PET-CT management arm (using the HR observed across the trial follow-up period= 1.008) as outlined in Briggs et al. 2006 [24].

The Gompertz distribution was identified as the best fitting curve to estimate long term recurrence events (compared to the Exponential, Weibull, Gamma and Lognormal distributions), based on an analysis of AIC and BIC criteria (see Table 4; better fitting curves are indicated by lower AIC and BIC values) and a visual inspection of the curve fits (see Figure 8).

Table 4. AIC and BIC criteria to estimate the goodness of fit of alternative parametric survival curve model specifications for the estimation of long term recurrences

Model specification	AIC	BIC
Planned ND arm		
Exponential	679.50	683.14
Gamma	674.96	682.96
Weibull	673.83	681.11
Lognormal	665.86	673.14
Gompertz	659.03	666.31
PET-CT surveillance arm		
Exponential	734.08	737.72
Gamma	735.58	742.86
Weibull	735.16	742.44
Gompertz	727.89	735.17
Lognormal	726.19	733.48

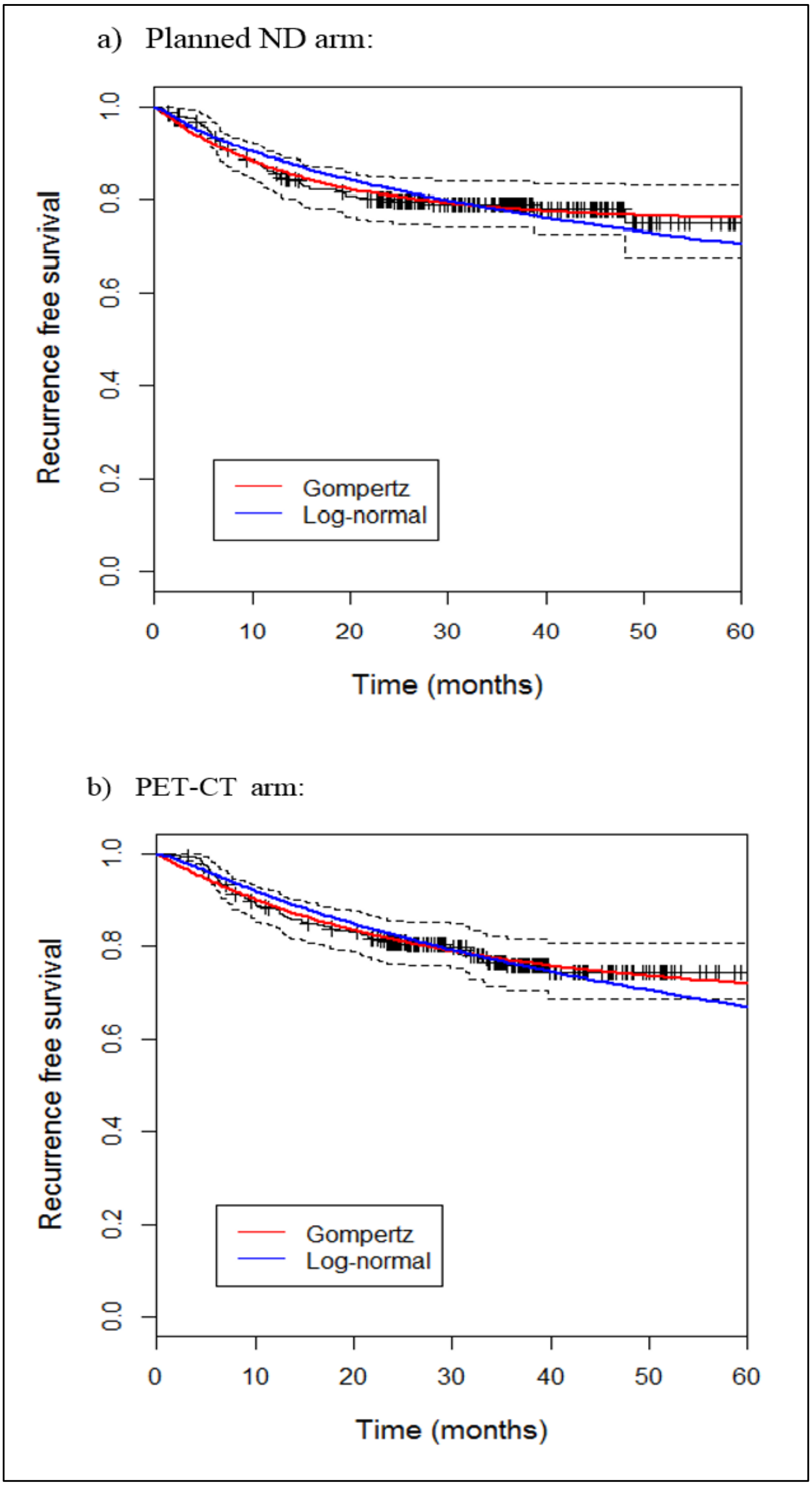


Figure 8. Plot of parametric survival curves (using Gompertz and Log-normal model specifications*) against trial data on patient recurrence free survival.

*Note: lognormal and Gompertz specifications are shown here as these were the two models identified as having the best fit via an analysis of AIC and BIC criteria. The Gompertz curve was used in the sensitivity analysis as this had the best overall fit when taking into account AIC and BIC criteria and a visual inspection of the goodness of fit.

Results

Results of the sensitivity analysis allowing primary recurrences beyond year five are presented in Table 5, Figure 9 and Figure 10.

Table 5. Results of sensitivity analysis: primary recurrence beyond year five (lifetime horizon, NHS secondary care perspective)

Strategy	Total Cost (95% CI)	Total QALY (95% CI)	Incremental Cost (95% CI)	Incremental QALY (95% CI)	ICER	Probability cost-effective
Planned ND	£24,313 (13,149 – 63,642)	8.76 (7.60 – 10.32)	-	-	-	
PET-CT	£22,841 (11,492 – 62,359)	8.86 (7.73 – 10.40)	-£1,472 (-2,934 – 381)	0.10 (-0.56 – 0.80)	Dominant	71%

CI = confidence interval; QALY= quality adjusted life year; ICER= incremental cost-effectiveness ratio; ND= neck dissection; PET-CT= positron-emission tomography and computed tomography; Dominant= more effective and less costly than standard care (ICER not reported in these cases).

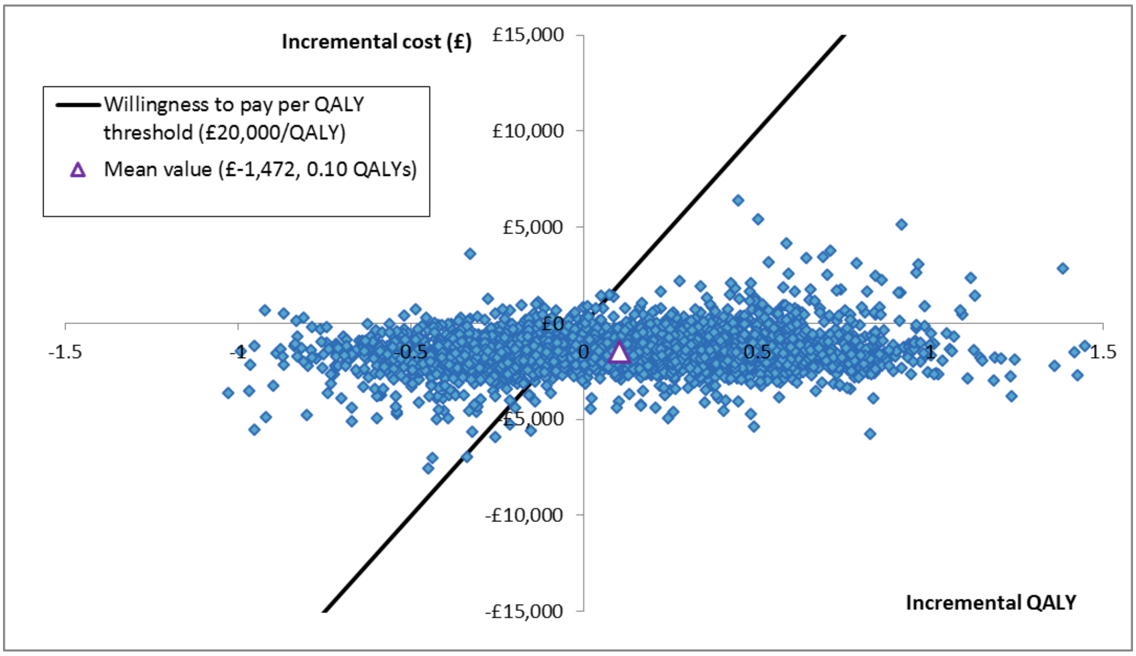


Figure 9. Scatter plot of lifetime cost-effectiveness results using an NHS secondary care perspective allowing primary recurrence beyond year five. This plot shows the incremental cost and quality adjusted life year (QALY) results for PET-CT management versus standard care for each of the 10,000 model simulations (i.e. the blue dots). The diagonal line represents a willingness-to-pay per additional QALY threshold of £20,000 per QALY. All points below this threshold line are considered cost-effective; points above this line are not considered cost-effective. The triangle indicates the mean incremental cost and QALY result.

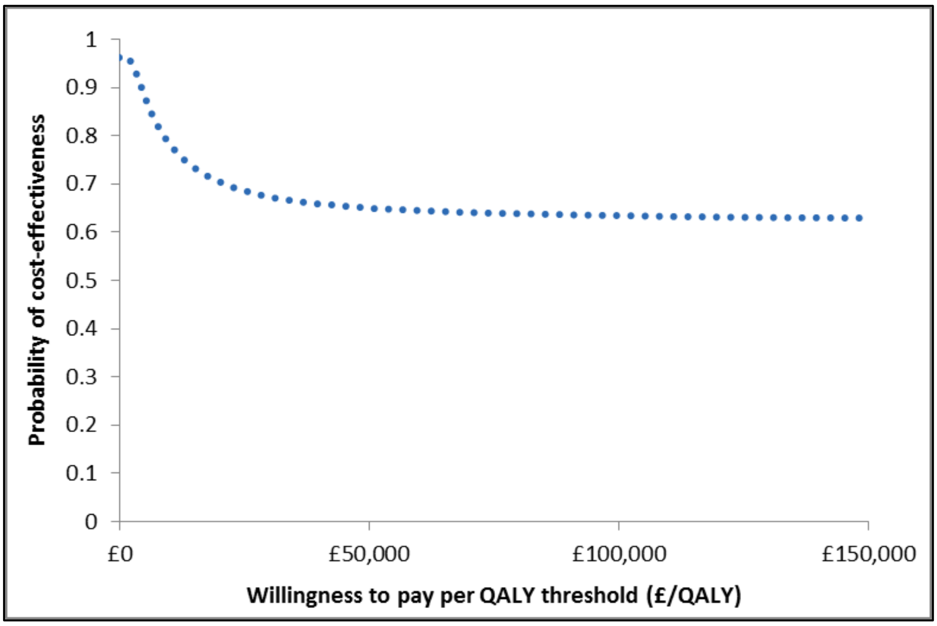


Figure 10. Cost-effectiveness acceptability frontier (CEAF) for the lifetime cost-effectiveness results using an NHS secondary care perspective allowing primary recurrence beyond year 5. This plot shows the probability that PET-CT management is cost-effective versus standard care (i.e. the proportion of points lying under the willingness-to-pay per additional QALY threshold) over alternative threshold values.

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