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A Cost Utility Analysis Comparing CT Surveillance, PET-CT Surveillance, and Planned Post-Radiation Neck Dissection for Advanced Nodal HPV-Positive Oropharyngeal Cancer

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Abstract

Background: We compared the cost-utility of image-guided surveillance using computed tomography (CT) and positron emission-computed tomography (PET-CT) to planned post-radiation neck dissection (PRND) for the management of advanced nodal HPV-positive oropharyngeal cancer following chemoradiation (CRT).

Methods: A universal payer perspective was adopted. A Markov model was designed to simulate four treatment approaches with 3-month cycles over a lifetime horizon: (1) CT surveillance, (2) standard PET-CT surveillance, (3) a novel PET-CT approach with repeat PET at 6 months post-CRT for equivocal responders, and (4) PRND. Parameters including probabilities of CT nodal progression/resolution, PET-avidity, recurrence, and survival were obtained from the literature. Costs were reported in 2019 Canadian dollars and utilities were expressed in quality-adjusted life years (QALYs). Deterministic and probabilistic sensitivity analyses were performed to evaluate model uncertainty.

Results: PET-CT surveillance dominated CT surveillance and PRND in the base case scenario, and the novel PET-CT approach was the most cost-effective strategy across a wide range of variables tested in one-way sensitivity analysis. On probabilistic sensitivity analysis, novel PET-CT surveillance was the most cost-effective strategy in 78.1% of model iterations at a willingness-to-pay of $50,000/QALY. Novel PET-CT surveillance resulted in a 49% lower rate of neck dissection compared to traditional PET-CT, and yielded an incremental benefit of 0.14 QALY with average cost-savings of $1,309.

Conclusion: Image-guided surveillance including PET-CT and CT are cost-effective over PRND. The novel PET-CT approach with repeat PET for equivocal responders was the dominant strategy and yielded both higher benefit and lower costs compared to standard PET-CT surveillance.

Introduction

Despite advancements in chemoradiotherapy (CRT) for the treatment of advanced nodal oropharyngeal cancer (OPC), a significant proportion of patients demonstrate residual post-treatment nodal disease. This is particularly common in HPV-positive (HPV+) disease, which tends to present with a large cystic lymph node burden that can result in significant post-treatment inflammation and a prolonged involution period.[1-3]

The management of residual nodal disease has evolved from traditional planned post radiation neck dissection (PRND) to more recent imaging-guided surveillance approaches, in order to spare patients the morbidity of unnecessary surgery.[1,4] In a phase III randomized-controlled trial of 564 head and neck cancer patients with N2 or N3 disease, Mehanna et al.[1] demonstrated that patients with a complete response on ^{18}Fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) scan at 12 weeks could be spared neck dissection with no detriment to overall survival, disease specific survival, or locoregional control.

CT-guided surveillance has emerged as a safe and effective modality for detecting residual nodal disease and avoid unnecessary neck dissection.[3,5] A recent study showed that the rate of incomplete radiographic response was 51% among 257 patients with HPV+ OPC post-CRT, but many of these did not contain viable tumor and the positive predictive value was only 3% in HPV+ OPC.[3] Furthermore, there was a 90% likelihood of nodal regression within 36 weeks based on imaging surveillance and there was no significant difference in five-year regional control rates between patients with and without complete radiographic response (95% vs. 92%, p=0.14).

Some authors have advocated for the use of interval PET-CT re-imaging (i.e. repeat PET-CT after 6 months) for select patients with incomplete or equivocal responses on initial scan.[6-8] These studies have reported a 60% to 74% rate of conversion to complete response with repeat PET-CT 12 to 16 weeks after the initial scan, without detriment to survival or regional control.[6,7] These contemporary data have not been previously evaluated in cost-effectiveness analysis.

The goal of this study was to compare the long-term cost-utility of CT surveillance, PET-CT guided surveillance, and PRND for the management of advanced nodal HPV+ OPC. We also evaluated the cost-effectiveness of a novel PET-CT approach with six-month repeat PET-CT for initial equivocal responders.

Methods

Institutional research ethics board approval was obtained. This manuscript was prepared in accordance to ISPOR guidelines using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.[9,10]

Model

A Markov model was designed to simulate the treatment of advanced nodal classification (cN2-N3, UICC/AJCC 7th edition TNM) HPV+ OPC presenting three months after completion of CRT

(Figure 1). The model was designed with 3-month cycles and half-cycle correction over a lifetime horizon, assuming a starting age of 50.

We compared four treatment arms: (1) CT surveillance, (2) PET-CT surveillance, (3) PRND, and (4) a novel PET-CT strategy with repeat PET at 6 months for patients with initial incomplete/equivocal radiographic response. The decision tree and state-transition diagram are shown in Figures 1a and 1b, respectively.

In the CT arm, nodes could either regress, progress, or remain unchanged. Nodal regression was defined as the involution of previous gross lymphadenopathy to 1.0 cm or less without adverse radiologic features or with a fibrotic response considered to be inert at least 6 months after radiation.[1,3] In the case of nodal regression, patients entered into a disease-free state from which they could remain disease-free, recur, or die. In the case of nodal progression, patients underwent neck dissection and then entered a disease-free state. Patients with stable nodal disease underwent serial CT scans every three months for one year before transitioning into a disease-free state.

In the standard PET-CT arm, patients with an incomplete/equivocal radiographic response underwent neck dissection prior to transitioning into a disease-free state, and patients with a complete response entered the disease-free state directly. A novel PET surveillance strategy was also modelled with repeat PET-CT at six months post-CRT for patients with initial equivocal response. Patients with a complete response on repeat PET-CT entered a disease-free state while patients with residual nodal disease underwent neck dissection. In the PRND arm, all patients underwent neck dissection and entered a disease-free state.

The costs and disutility of recurrences and subsequent treatment were factored into the model. Local recurrences were treated with salvage surgery and free flap reconstruction. Regional recurrences were treated with neck dissection. Local and regional salvage operations were considered curative. Patients with distant recurrence or a second locoregional recurrence entered a palliative state, in which they remained for three cycles (9 months) before dying. We assumed that patients recurred within the first five years due to lack of long-term data and studies demonstrating that most locoregional and distant recurrences occur within the initial three-year period.[11-13]

Model parameters

Model parameters for the base case analysis, including estimates of probabilities of PET-avidity, nodal progression/resolution, and salvage surgery were determined from the literature and institutional chart review (Table 1).[1,3,6,14] The rate of PET-avidity and locoregional recurrence in the PET-CT and PRND arms were calibrated to the phase III randomized-controlled trial (RCT) comparing PET-CT and PRND, and internal validation performed through comparison of oncologic outcomes.[1]

In the CT arm, parameters including nodal progression, nodal regression, and locoregional recurrence were derived from the study by Huang et al.[3] Their study included 27% of patients who underwent PRND; subgroup analysis was performed to obtain parameters for patients managed

with image-guided surveillance alone. Survival was modeled using life tables from Statistics Canada[15].

Costs

A universal payer perspective was adopted. Costs of treatment, complications, and salvage surgery were derived using institutional costs, gathered from the Princess Margaret Cancer Center (PMCC) and University Health Network in Toronto, Ontario. Costs encompassed direct and indirect in-hospital expenditures, including operating room costs, perioperative care, ICU, nursing, pharmacy, allied health (i.e. physical therapy, occupational therapy, speech language pathology, respiratory therapy, social work), laboratory investigations, and imaging. Overhead/support costs such as administration, finance, and depreciation were also recorded. The cost of professional fees, outpatient visits, and diagnostic imaging were obtained from the Ontario Schedule of Benefits.[16] Palliative care costs was derived from a Canadian study of patients receiving hospice care for terminal cancer.[17] All costs were inflated to 2019 Canadian dollars using the Consumer Price Index for health and personal care.[18] Costs and utilities were discounted at a rate of 1.5%.[19]

Utilities

Health state utilities were derived from literature review for all relevant treatment, complication, disease free and recurrence states.[13] Utility weights were multiplied by the time spent in a specific health state and weighted according to the probability of that particular health state in order to derive an estimate of quality-adjusted life expectancy for each treatment.

Cost-Effectiveness Analysis

Incremental costs and utilities were computed from the difference in costs and utilities between strategies. An incremental cost-utility ratio (ICER) was derived by calculating the quotient of the incremental cost and the incremental utility as measured in quality adjusted life-years (QALYs). Acceptability curves were plotted for the base case analysis. All cost-utility analyses were performed using TreeAge Pro software (Version 18.2.0, Williamstown, MA, 2018).

Sensitivity analysis

Deterministic one-way sensitivity analysis was performed for key model parameters, including the probability of nodal progression in CT surveillance, probability of neck dissection in PET-CT surveillance, and cost of neck dissection. An ICER was calculated for each iteration of the sensitivity analysis. Parameters with uncertainty, including age, costs, utilities, and probabilities of complications, survival, and recurrence, were varied in probabilistic sensitivity analysis. Probabilistic sensitivity analysis was performed using second-order Monte-Carlo methods with 10,000 simulations. A willingness-to-pay threshold (WTP) of $50,000/QALY was adopted for all sensitivity analysis. Standard deviations were obtained from the literature where available, and otherwise assumed to represent 20% of the mean.[20] ICERs were plotted for probabilistic sensitivity analyses with 95% confidence ellipsoids.

Results

Model Validity

Our model predicted a 2-year overall survival of 92% for PET-CT surveillance and 90% for PRND, which were slightly higher than rates reported in the phase III trial by Mehanna et al.[1] (84.9% and 81.5%; Supplemental Figure 1a). This is compatible with the proportionality of HPV+ patients in this trial which contained a mixed HPV+ and HPV- population. Our model also estimated a 2-year locoregional control of 90% and 92% for PET-CT and PRND respectively, comparable with reported rates of 91.9% and 90.4% in the aforementioned trial (Supplemental Figure 1b).[1] The comparability of these oncologic outcomes supports the assumptions and parameters adopted in our model.

Base case analysis

In the base case analysis over a lifetime horizon, the average costs of the treatment arms were $21,249 for CT surveillance, $23,625 for standard PET-CT surveillance, $22,316 for novel PET-CT surveillance, and $25,483 for PRND. CT surveillance yielded incremental cost-savings of $1,067, $2,376, and $4,234 compared to novel PET-CT, standard PET-CT, and PRND, respectively. The novel PET-CT approach resulted in cost-savings of $1,309 and $3,167 compared to traditional PET-CT and PRND.

The average quality adjusted life expectancies measured in QALYs were 12.45 for CT surveillance, 12.74 for PET-CT surveillance, 12.88 for the novel PET-CT approach, and 11.61 for PRND. Compared to CT and PRND, PET-CT yielded an incremental effectiveness of 0.29 and 1.13 QALY, respectively. The novel PET-CT approach resulted in an additional incremental benefit of 0.14 QALY over traditional PET-CT surveillance.

A summary of cost-effectiveness comparisons between strategies is shown in Table 2. In the base case scenario, all three image-guided surveillance strategies dominated PRND, demonstrating both greater effectiveness and lower costs. Both traditional and novel PET-CT strategies were cost-effective compared to CT surveillance with an ICER of $8,193 and $2,481 per QALY, respectively. When comparing traditional and novel PET-CT strategies, novel PET-CT dominated traditional PET-CT with both higher effectiveness and lower cost.

The lifetime rate of neck dissection (including those for regional recurrences) was lowest for CT surveillance (10.6%), followed by 13.5% for novel PET-CT, 26.8% for traditional PET-CT, and 101% for PRND. The rate of regional recurrence was lowest for PRND (2.0%), followed by 4.8% for PET-CT, 5.1% for novel PET-CT, and 9.3% for CT surveillance.

One-Way Sensitivity

One-way sensitivity analyses were performed varying the probability of PET avidity, utility of neck dissection, cost of neck dissection, regional recurrence post-neck dissection, and regional recurrence with PET-CT surveillance. All image-guided approaches were cost-effective over PRND in one-way analysis, and the novel PET-CT approach remained the most cost-effective strategy throughout the range of variables tested at a WTP of $50,000/QALY (Supplemental

Figures 2-3). The two PET-CT surveillance strategies demonstrated equivalent costs and effectiveness when the PET-avidity rate was reduced to zero (Supplemental Figure 2a).

When varying the rate of nodal recurrence after neck dissection, the novel PET-CT strategy remained the cost-effective strategy through a wide range of variables tested, and PRND did not emerge as the cost-effective strategy even at a zero nodal recurrence rate. CT surveillance became more cost-effective over traditional PET-CT when the post-neck dissection nodal recurrence exceeded 7.3% (Supplemental Figure 3a). When varying the rate of nodal recurrence associated with PET-CT surveillance, traditional and novel PET-CT surveillance were cost-effective over CT when the nodal recurrence rates were less than 7.2% and 11.6%, respectively (Supplemental Figure 3b).

Probabilistic Sensitivity

Probabilistic sensitivity analysis was conducted over 10,000 iterations varying all probabilities, costs, and utilities simultaneously. Novel PET-CT surveillance was the most cost-effective strategy in 78.1% of model iterations at a WTP of $50,000/QALY (Figure 2). Furthermore, individual comparison of novel PET-CT surveillance to other strategies showed that it was cost-effective to other strategies in the majority of iterations: CT in 97.5% of iterations, traditional PET-CT in 79.6% of iterations, and PRND in 81.5% of iterations (Figure 3). Traditional PET-CT surveillance was cost-effective over CT in 73.1% of iterations and PRND in 78.4% of iterations (Supplemental Figure 3). CT surveillance was also cost-effective over PRND in 71.9% of iterations (Supplemental Figure 4).

Discussion

The management of residual nodal disease following CRT for HPV+ OPC has evolved from traditional planned neck dissection to image-guided surveillance using CT or PET-CT. This paradigm shift was predicated on the low likelihood of persistent disease found in patients undergoing planned neck dissection, particularly in those with complete radiographic response.[8,21-23]

We constructed a lifetime Markov model to compare the cost-utility of CT surveillance, PET-CT surveillance, and PRND for the management of N2-N3 HPV OPC following CRT. We also evaluated a novel PET-CT strategy with interval PET-CT at 6 months for patients with initial equivocal PET-CT findings. In our modelling, novel PET-CT surveillance remained the dominant strategy in the base case and across a wide range of variables tested in one-way sensitivity analysis. On probabilistic sensitivity analysis, novel PET-CT surveillance was the most cost-effective strategy in 78.1% of model iterations at a willingness-to-pay of $50,000/QALY. Standard PET-CT surveillance was also cost-effective over CT and PRND in the base case scenario.

Our findings are consistent with the two published studies comparing the cost-effectiveness of PET-CT and PRND.[14,15] Mehanna et al.[12] compared the cost-utility of PET-CT and PRND using data from their multicenter phase III RCT and found that PET-CT yielded an incremental benefit of 0.21 QALY (95% CI -0.41-0.85 QALY) and average cost-savings of £1485 over a lifetime

horizon. At a £20,000 WTP, PET-CT surveillance was associated with a 75% probability of being cost-effective compared with PRND. They also reported similar overall survival (HR 0.92, 95% CI 0.65-1.32) with significantly fewer neck dissections and lower costs.

PET-CT is associated with a low positive predictive value (PPV) in the post-CRT setting among patients with HPV+ OPC, with recent meta-analyses reported values as low as 52%.[21,23] Consequently, newer studies have advocated for the use of interval PET-CT scan to improve the diagnostic performance of PET-CT and reduce the rate of false positives leading to unnecessary neck dissection. Prestwich et al.[7] evaluated patients with head and neck squamous cell carcinoma who underwent an interval PET-CT performed roughly 3 months after the initial three-month post-treatment scan on patients with an incomplete/equivocal response. On interval PET-CT, they found that 74% patients with initial incomplete/equivocal response converted to a complete nodal response. In another study, Rulach et al.[6] demonstrated that 67% of patients with HPV+ OPC who have an equivocal response after initial PET-CT, will convert to complete response on PET-CT at six months. They also found similar survival between complete responders and equivocal responders. This emerging body of literature supports the use of interval PET-CT to reduce the number of neck dissections resulting associated with initial false positive scans.

In our cost-utility model, novel PET-CT surveillance was the dominant strategy across a wide range of variables compared to traditional PET-CT, likely as a result of a 40% lower neck dissection rate. Novel and standard PET-CT strategies demonstrated similar survival and locoregional control, consistent with the findings of other studies.[6-8] Our findings corroborate the value of a step-wise approach with a second PET-CT in equivocal responders. This approach may reduce the likelihood of neck dissection without compromising oncologic control, thus affording longer quality adjusted life years and avoiding the disutility of a neck dissection with associated sequelae such as shoulder dysfunction.

One surprising finding in our model was the relative difference in cost-effectiveness when comparing novel PET-CT surveillance with the CT and PRND arms. On probabilistic analysis, CT was cost-effective over PRND in approximately 70% of iterations. However, novel PET-CT was overwhelmingly more cost-effective over CT (in 97.5% of iterations) while only cost-effective over PRND in 81.5% of iterations. This may be explained by the lower rate of regional recurrences in the PRND arm compared to CT (2.0% vs. 9.3%) and the range of parameters tested on sensitivity analysis.

Our study findings must be interpreted in the context of certain limitations. There were several potential sources of variability which we attempted to mitigate using sensitivity analysis by varying parameters across their plausible ranges. The costs in our model were obtained predominantly from a single institution and may not be generalizable to other jurisdictions, countries, or health systems. While treatment and diagnostic costs are relatively similar across our Canadian universal health care system, these costs may vary drastically in other countries. Furthermore, our model did not include home care costs or out-of-pocket costs. Parameters in the PET-CT and PRND arms were largely derived from phase III RCT data; however, data in the CT arm were extracted from cross sectional and single institution studies. While these represent the best available data, they are subject to the biases of retrospective study design. Probabilities of CT nodal progression and regression were derived from a study by Huang et al.[3], which adopted

imaging-guided surveillance using both CT and MRI. In addition, PET-CT was also used in approximately 34% of cases.[3] This could have inflated CT performance and underestimated the costs associated in the CT surveillance arm. Nevertheless, our study showed that both the standard and novel PET-CT approaches were cost-effective over CT surveillance. Finally, this study evaluated patients with HPV-positive OPC and did not include patients with HPV-negative disease, which is associated with more persistent nodal disease and a higher rate of locoregional recurrence.[3,6,7,12] Inclusion of HPV-negative OPC would increase the rate of positive imaging findings and subsequent neck dissection, resulting in increased cost and decreased effectiveness of image-guided surveillance approaches.

While model simulation is an invaluable tool for evaluating complex questions, it does not perfectly replicate real world scenarios. Additional prospective studies with larger, homogenous patient populations, randomized treatment arms, and long-term follow up are needed to obtain better parameter estimates of survival and recurrence. Furthermore, the base case and parameters included all comers with both complete and incomplete radiographic response in accordance to the RCT design developed by Mehanna et al.[1] More data is also needed to determine the incidence of an equivocal radiographic primary tumor response and evaluate its impact on cost-effectiveness modelling. Further research is needed to generate outcomes for a subgroup of patients with incomplete radiographic response, which represents a more clinically salient scenario for the comparison of surveillance versus upfront neck dissection. Further research is also needed to establish standardized criteria and protocols to guide the selection of patients, timing, and interpretation of serial PET-CT imaging.

Conclusion

Our lifetime cost-utility model found that image-guided surveillance using CT or PET-CT were cost-effective over planned neck dissection for patients with advanced nodal HPV-positive OPC following chemoradiation. In our model, the most cost-effective strategy was the novel PET-CT approach which involved repeat PET-CT at 6 months for radiographic equivocal responders. Novel PET-CT resulted in a lower neck dissection rate than traditional PET-CT surveillance, and yielded both incremental benefit and cost-savings compared to the standard approach. The findings of this study are particularly important in the setting of constrained health care systems with limited resources. Future prospective studies are needed to corroborate the findings in our study and directly compare oncologic outcomes and cost-effectiveness between strategies.

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Table 1. Model Parameters

Parameter	Value	95% CI	Reference
Probabilities			
Nodal Progression under Surveillance (1-year)	0.04	0.037 - 0.043	Huang et al.[3]
Nodal Regression under Surveillance (1-year)	0.93	0.88 - 0.98	Huang et al. [3]
PET Avid (Incomplete) or Equivocal Response at 3 months	0.25	0.20 - 0.30	Mehanna et al. [1]
Proportion of PET Equivocal Response at 3 months	0.68	0.54 - 0.82	Rulach et al.[6]
Unresectable Disease post-CRT	0.14	0.11 - 0.17	Huang et al.[3]
Repeat PET at 6 months with Complete Response	0.67	0.54 - 0.80	Rulach et al.[6]
Local Recurrence (3-year)	0.04	0.03 - 0.05	Mehanna et al.[1]
Regional Recurrence with Neck Dissection (5-year)	0.007	0.005 - 0.009	Mehanna et al.[12]
Regional Recurrence with PET surveillance (5-year)	0.021	0.017 - 0.025	Mehanna et al.[12]
Regional Recurrence with CT surveillance (5-year)	0.05	0.04 - 0.06	Huang et al.[3]
Distant Recurrence (3-year)	0.06	0.04 - 0.07	Mehanna et al.[1]
Death	age-dependent	stage-dependent	Statistics Canada[15]
Salvageability of Local Recurrence	0.24	0.19 - 0.29	Patel et al.[14]
Salvageability of Regional Recurrence	0.90	0.82 - 0.98	Patel et al.[14]
Costs*			
Follow up visit	$91.84	$81 - $101	OHIP Schedule of Benefits[16]
CT-scan	$199.69	$184 - $215	OHIP Schedule of Benefits[16]
PET-CT	$802.49	$721 - $985	OHIP Schedule of Benefits[16]
PRND	$6,464.22	$5,494 - $7,757	OHIP Schedule of Benefits[16], PMCC Institutional Review
Regional Salvage	$9,111.39	$7,471 - $10,751	OHIP Schedule of Benefits[16], PMCC Institutional Review
Local Salvage	$32,290.63	$24,863 - $36,488	OHIP Schedule of Benefits[16], PMCC Institutional Review
Palliative care	$10,643.02 (per cycle)	$8,814 - $12,772	Kyeremanteng et al.[17]
Utilities			
Disease Free	1.0	-	De Almeida et al.[13]
Disease Free Post Neck Dissection	0.94	0.91 - 0.97	De Almeida et al.[13]
Local Recurrence post Salvage Surgery	0.82	0.77 - 0.87	De Almeida et al.[13]
Regional Recurrence post Salvage Neck Dissection	0.88	0.85 - 0.91	De Almeida et al.[13]
Distant Recurrence	0.57	0.50 - 0.64	De Almeida et al.[13]
Palliative	0.42	0.34 - 0.50	De Almeida et al.[13]
Death	0	-	De Almeida et al.[13]

Abbreviations: CI, confidence interval; PET, positron emission-computed tomography; CT, computed tomography; CRT, chemoradiotherapy; OHIP, Ontario Health Insurance Plan; PMCC, Princess Margaret Cancer Centre.

* Costs reported in 2019 Canadian dollars.

Table 2. Cost-effectiveness comparison between strategies.

	Incremental Cost	Incremental Effectiveness	ICER (cost/QALY)
CT vs. PRND	-$ 4,234	0.84	CT dominates
PET vs. PRND	-$ 1,858	1.13	PET dominates
PET vs. CT	$ 2,376	0.29	$ 8,193
Novel PET vs. PET	-$ 1,309	0.14	Novel PET dominates
Novel PET vs. PRND	-$ 3,167	1.27	Novel PET dominates
Novel PET vs. CT	$ 1,067	0.43	$ 4,807

Abbreviations: ICER, incremental cost-effectiveness ratio; PET, positron emission-computed tomography.

Table and Figure Legends

Table 1. Model Parameters

Table 2. Cost-effectiveness comparison between strategies.

Figure 1. Schematic Representation of the Model.

Figure 2. Cost-effectiveness acceptability curve.

Figure 3. Probabilistic sensitivity analysis comparing the novel PET-CT surveillance strategy to other strategies.

Supplemental Figure 1. Predicted overall survival and locoregional control demonstrating model validity.
Supplemental Figure 2. One-way sensitivity varying the (a) rate of PET avidity, (b) utility of neck dissection, and (c) cost of neck dissection.

Supplemental Figure 3. One-way sensitivity varying the 5-year nodal recurrence rate with neck dissection and PET-CT surveillance.

Supplemental Figure 4. Probabilistic sensitivity analysis comparing PET-CT vs. CT surveillance and Planned Post-Radiation Neck Dissection.

Supplemental Figure 5. Probabilistic sensitivity analysis comparing CT surveillance vs. Planned Post-Radiation Neck Dissection.