

# **The use of intensive radiological assessments in routine surveillance after treatment for head and neck cancer: an economic evaluation**

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## ABSTRACT

*Background.* There is uncertainty around the optimal surveillance of head and neck cancer patients following primary curative treatment. This study aims at assessing the cost-effectiveness of a post-treatment program of frequent radiological assessments (maximal approach) compared to a symptom-driven surveillance (minimal approach).

*Materials and Methods.* A decision-analytic Markov model is developed to assess the cost-utility of two alternative follow-up programs with a lifetime horizon. The two interventions differ in the number of radiological assessments (i.e. magnetic resonance imaging, computed tomography, and positron emission tomography) performed over a 5-year period. Clinical and utility parameters are derived from published and unpublished literature and expert opinion. The cost analysis is conducted from the perspective of a major Italian region's healthcare system. Cost-effectiveness results are expressed as incremental cost per life year gained (LYG) and per quality-adjusted life year (QALY) and checked against a cost-effectiveness threshold of €25,000-40,000 per QALY. One-way, two-way, and probabilistic sensitivity analyses are carried out.

*Results:* In the base-case analysis, an intensive program of radiological investigations leads to 0.10 additional QALYs (0.15 LYG) and an increase in costs of €1,903 per patient compared to a minimal option, resulting in an incremental cost of €19,951/QALY gained (€13,123/LYG). In probabilistic sensitivity analysis, 72% of the results lie below the €40,000 threshold (55% below €25,000).

*Conclusions:* An intensive post-treatment follow-up with scheduled radiological assessments over time might be cost-effective compared to symptom-driven surveillance in head and neck cancer patients. Further research is needed to check these results in empirical studies or real-world settings.

*Keywords:* head and neck cancer; follow-up; radiological assessments; Markov model; cost-utility analysis.

## 1. Introduction

Head and neck cancer (HNC) is the sixth most common cancer worldwide; in Europe alone, around 143,000 people are diagnosed and more than 68,000 die each year because of the disease [1]. The incidence in Italy is about 16 cases per 100,000 [2]. Despite the routine introduction of combined-modality treatment, the 5-year overall survival rate is 40% to 60% [2-4] and up to 50% of patients relapse with loco-regional or metastatic recurrences [4-6]; additionally, a constant rate of 2-3% per year of second primaries is observed [7].

A few patients with loco-regional recurrences or second primaries can be salvaged by a potentially curative treatment (i.e. surgery or re-irradiation) [1, 4], while most are only suitable for palliative treatment usually including a combination of chemotherapeutics and anti-epidermal growth factor receptor drugs [8]. The prognosis for patients with recurrent or metastatic disease not eligible for curative treatment is very poor, with a median overall survival of around 10 months under the standard scheme of platinum-based chemotherapy plus cetuximab [9].

A post-treatment follow-up program is essential in the first few years after primary treatment to identify potentially curable relapses, as well as monitoring long-term therapy-related side effects. However, there is no consensus in the medical community around the optimal strategy. Published recommendations are mostly based on retrospective studies and expert opinions, whilst the added value of intensive radiological assessment over a scheme based on self-reported symptoms (e.g. pain, dysphagia, hoarseness) has not yet been confirmed in any prospective study.

This study evaluates the cost-effectiveness of an intensive follow-up strategy (maximal approach) versus a symptom-driven surveillance (minimal approach) using a modeling framework.

## **2. Materials and methods**

A decision-analytic Markov model is developed to assess the long-term health and economic consequences of two different surveillance schemes. A randomized controlled trial (HETeCo, [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02262221) identifier NCT02262221) is currently being conducted in Italy and Switzerland to compare an intensive versus a non-intensive follow-up program of equal length (i.e. 5 years). The trial started in 2014 and is expected to be completed by 2020; thus, it is mainly used to generate a research question, while most of the data are obtained from other sources.

### ***2.1 HETeCo trial***

The full trial protocol is available at [clinicaltrials.gov](https://clinicaltrials.gov). Briefly, patients with a diagnosis of clinical or pathological stage III-IV squamous HNC in the oral cavity, oropharynx, larynx, or hypopharynx and without evidence of disease six months after having received radiotherapy with curative intent (alone or with systemic therapy or in postoperative setting) are randomly allocated to one of two follow-up programs.

The non-intensive follow-up (arm A, minimal approach), designed according to National Comprehensive Cancer Network (NCCN) guidelines [10], comprises several outpatient visits during which patients receive both physical and fiber optic endoscopic examinations; laboratory tests are performed once a year. Radiological assessment through magnetic resonance imaging (MRI) or computed tomography (CT) is performed within six months of completion of treatment and then only at the occurrence of new signs or symptoms. Patients are contacted by phone between visits to monitor any health changes and instructed how to recognize them.

The alternative strategy (arm B) is a more intensive follow-up (maximal approach) where outpatient visits and laboratory tests are performed similarly to arm A. Imaging tests are scheduled for all patients twice a year in the first two years and annually in the third and fourth years; MRI is preferred over CT for all sub-sites except for laryngeal cancer. Positron emission tomography (PET) scans are performed annually in the first three years in high-risk patients.

## ***2.2 Model structure***

The Markov state-transition model (Figure 1) simulates the experience of a hypothetical cohort of 1,000 patients after being treated for primary stage III-IV HNC; mean age and gender ratio are representative of the patients enrolled in the trial (until May 2016). All patients enter the model free of disease and move through the different health states according to a set of transition probabilities. Recurrent patients are divided based on the intent of the treatment received (i.e. potentially curative or palliative); patients treated with curative intent are assigned to either ‘surgery’ or ‘re-irradiation’ states. Patients without progression remain in the ‘no evidence of disease’ states; the final, absorbing state is ‘death’.

The cycle length of the model is one month with a lifetime horizon. Utility weights ranging from 0 (death) to 1 (perfect health) and costs are applied to the time spent in each health state. The model is run until the whole cohort (i.e. >99%) dies to estimate differences in life years gained (LYG), quality-adjusted life years (QALYs) and long-term costs associated with the two follow-up schemes under investigation in the HETeCo trial.

### ***2.3 Clinical and utility parameters***

Transition probabilities between states are mainly derived from a combination of clinical parameters (Tables 1-2). The proportion of potentially salvageable recurrences in the study arm A (25%) is derived from the literature [11], while the percentage in group B (50%) is a clinical assumption of the study, which is intended to test whether a more intensive radiological assessment could detect a higher rate of salvageable relapses. The ‘potentially curative treatment’ state is assumed temporary, meaning that each patient can only remain in it for one cycle; surgery is considered the only potentially curative treatment for second primaries. The risk of relapsing after secondary treatment is estimated at 3% monthly, based on published studies [12-14]; this parameter is also consistent with the 0.009 weekly (i.e. 0.034 monthly) adopted by a previous cost-effectiveness model in Italy [15]. Any recurrence (or second primary) beyond the first is assumed to be treated with palliative intent only. Patients receiving palliative chemotherapy are assumed to have a median survival of 10 months, corresponding to a 1-year overall survival of around 43% (i.e. 6.6% monthly mortality) [9, 16]. In each health state patients also experience a general risk of dying for reasons other than HNC; mortality rates for 5-year age groups are obtained from official statistics [17]. Annual probability values reported in the literature are transformed into monthly probabilities using the formula:  $p = 1 - \exp(-r \cdot t)$  where  $p$  is probability,  $r$  is rate and  $t$  is the time expressed in months [18].

The utility parameters are summarized in Table 3. An average utility value for the ‘no evidence of disease’ state (i.e. at recruitment) is calculated from the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) trial data using the English tariff set. The same value (i.e. 0.85) is confirmed by a cross-sectional study recruiting a comparable population [19]. Utility values for all other states are identified by a systematic literature review [20].

## 2.4 Cost data

The cost analysis is conducted from the perspective of a major Italian region (i.e. Lombardy) healthcare system. Unit costs for hospital admissions, specialist visits, radiological exams, laboratory tests and outpatient treatment regimens are from diagnosis-related groups (DRGs) and other regional tariffs (year 2016) (Table 4). The cost of each follow-up program (A or B) performed in the ‘no evidence of disease’ state is calculated for 5 years (i.e. standard length of follow-up) and reported in Table 5, according to the description provided in the trial protocol. Patients surviving the ‘potentially curative treatment’ states are assumed to be monitored within a program resembling the less intensive scheme (arm A). Re-irradiation is assumed to involve a cycle of intensity modulated radiation therapy (IMRT) sessions based on current practice. Standard platinum-based chemotherapy supplemented with 5-fluorouracil (5FU) and cetuximab until one month before death is assumed for the ‘palliatively treated recurrence’ state; additionally, an average cost of dying for HNC is assigned to each patient entering this state based on the estimated consumption of formal end-of-life care (i.e. home-based assistance and hospital care). A synthesis of monthly cost values for all health states is reported in Table 6.

## 2.5 Cost-effectiveness analysis

Health outcomes (i.e. LYG, QALYs gained) and total costs are combined into an incremental cost-effectiveness ratio ( $ICER = \frac{Cost_B - Cost_A}{LYS_B - LYS_A}$ ) and cost-utility ratio ( $ICUR = \frac{Cost_B - Cost_A}{QALYS_B - QALYS_A}$ ) to represent the incremental cost of achieving one unit of health outcome when an intensive follow-up strategy (arm B) replaces a less intensive one (arm A). The ICUR obtained is compared with the range of €25,000-€40,000 recommended by the Italian Health Economics Association [21]. All costs and outcomes are discounted at 3% (converted to 0.247% monthly) and expressed in Euro (€) 2016.

## ***2.6 Sensitivity analyses***

One-way sensitivity analyses explore the robustness of the base-case results by varying some key model parameters one at a time. For example, the risk of overall relapse during follow-up is varied between 20% and 50%. The impact of different risks of dying because of toxicities following re-irradiation is explored using values from a systematic review [8]. We also examine the alternative that patients surviving the ‘potentially salvageable recurrence’ states have the same follow-up intervention (A or B) received in the ‘no evidence of disease’ state after primary treatment.

Additionally, a two-way sensitivity analysis is performed to assess the simultaneous effect of varying the proportion of salvageable recurrences in the two arms, with all else unchanged in the model. This analysis is performed because of the uncertainty surrounding this parameter based on clinical opinion and not yet confirmed within the ongoing trial.

Finally, a probabilistic sensitivity analysis is performed using Monte Carlo simulation with 5,000 random iterations from the distributions assigned to the model parameters. A beta distribution is chosen for probabilities and utilities, and a gamma distribution for costs (except for official tariffs, which are fixed in the model). A cost-effectiveness scatterplot illustrates the uncertainty surrounding the base-case ICUR, while cost-effectiveness acceptability curves (CEAC) quantify the probability of the intensive follow-up being cost-effective at different thresholds.

The decision model is implemented in Microsoft Excel 2013 with the support of @RISK software (Palisade Corp) for the sensitivity analyses.



### **3. Results**

The baseline cost-effectiveness results yield an ICUR of €19,951 per QALY gained and an ICER of €13,123 per LYG (Table 7). In univariate sensitivity analysis (Table 8), the recurrence risk over the 5-year follow-up is inversely proportional to the ICUR. Other variables including re-treatment-related mortality, cost of head and neck surgery and discounting have a limited effect on the results. In Figure 2, the cost-effectiveness of the intensive follow-up (arm B) increases with the positive difference between the “curability” of arm B and arm A, reaching a maximum value of €6,330/QALY (€4,163/LYG) when this parameter is equal to 0.7 in arm B and 0.1 in arm A and a minimum value of €113,354/QALY (€74,561/LYG) when the difference between the two “curability” rates is only 0.05.

In the cost-effectiveness plane (Figure 3), most ICURs (72%) are to the right of the €40,000 willingness-to-pay for Italy; even considering the lowest threshold (i.e. €25,000), the maximal approach is cost-effective in more than 50% of simulations. None of the simulations fell in the left side of the graph implying a negative difference in QALYs. In Figure 4, the CEAC shows that at a willingness-to-pay equal to zero almost 5% of the simulations report a cost-saving result.

### **4. Discussion**

There is no agreement on a common follow-up strategy in HNC across clinical guidelines worldwide. Among them, the NCCN guidelines do not recommend routine imaging in the absence of symptoms [10], while clinical practice in Italy is heterogeneous and sometimes involves more intensive programs. The addition of routine MRI, CT and PET scans to the scheduled clinical examinations might increase the detection accuracy of recurrent HNC in patients, especially the asymptomatic ones. However, the

effectiveness (and cost-effectiveness) of more intensive follow-up schemes has never been shown with rigorous methods.

The current model predicts costs and outcomes in terms of QALYs and survival gains of two alternative follow-up programs in HNC, corresponding to the arms of an ongoing clinical study. In this model, more intensive follow-up (maximal approach) appears cost-effective with a cost per QALY gained of €19,951, and more than two-thirds of the Monte Carlo simulations falling below the willingness-to-pay of €40,000. Moreover, the two-way sensitivity analysis shows that a difference in the proportion of potentially salvageable recurrence of about 0.15 between the two programs is sufficient to obtain an acceptable ICUR for arm B. The intermediate findings are comparable with data reported in the literature. For example, the 5-year survival is equal to 58% and 60.5% in arm A and arm B, respectively, which is consistent with the epidemiological data [2-4]. Moreover, the average stay of 13-14 months in the palliative treatment state is aligned with the median overall survival (i.e. 10 months) reported by Vermorken [9], since survival times are positively skewed.

A recent study [22] systematically reviewed economic evaluations comparing alternative follow-up programs in cancer. Since no study considered HNC, and the incremental costs per QALY or LYG were rarely reported, comparisons with our results are not straightforward. However, we calculated an incremental cost per salvageable recurrence of €20,249, which coincides with the value reported (i.e. £18,077) by a modeling study comparing intensive versus standard surveillance for colorectal cancer in UK [23].

As a modeling study, the analysis inevitably represents a simplification of the real world. First, we assume that cancer-related deaths occur only during the active disease and patients without any cancer relapse experience the same risk of dying as the general population at the same age. However, previous

studies have reported an extra-mortality risk for HNC survivors [24], that may lead to lower ICER/ICUR if this information is incorporated into the model. Second, we do not consider second primary tumors not in the head and neck region and reported by previous studies [25-27] in the lung, esophagus, and colon. Third, the possibility of combined salvage treatment (e.g. surgery followed by re-irradiation) [28] and the use of radiotherapy with palliative intent [29] are disregarded, as well as any re-treatment failures other than death, such as non-fatal toxicities [8] or residual disease after salvage surgery. Fourth, this study does not account for patient's anxiety and discomfort, nor for potential toxicities related to the use of PET and CT, and the risk of false-positive imaging leading to further costly investigations or unnecessary treatments [25, 30]. Fifth, the costs of follow-up are spread out over a 5-year period, thus the monthly cost represents an average value; however, we derive two different estimates for follow-up B, since most radiological assessments are performed during the first three years. Finally, the analysis is limited to direct healthcare costs, thus ignoring patient's out-of-pocket costs and productivity losses due to frequent travels to the hospital; moreover, the cost of informal care may be substantial during the terminal disease stages, when 91% of patients are estimated to be cared for at home [31].

This study is the first to investigate strategies of different intensity for monitoring patients after completion of treatments for primary HNC from a health economics perspective. Although a definite answer awaits the completion of the trial, the model shows that an intensive surveillance scheme may well be cost-effective in Italy. The trial protocol is currently under review, with a low-dose chest CT being included annually in heavy smokers according to the lung cancer screening NCCN guidelines [32]. Different results might be obtained by using alternative cost data, thus similar evaluations in other countries are valuable. Further research evaluating the benefits of a risk-adapted follow-up according to demographic, clinical or biomolecular factors is also warranted.

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