

SUPPLEMENTARY MATERIALS

**Towards early and broad evaluation of innovative surgical devices:
integrating evidence synthesis, stakeholder involvement and health economic modelling into
the clinical research stages of the IDEAL framework**

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An empirical example: sentinel lymph node biopsy in the management of oral cavity squamous cell carcinoma

This empirical example aims to demonstrate what the proposed approach looks like in clinical practice. It comprises a description of one of our previous projects about sentinel lymph node biopsy in oral cavity squamous cell carcinoma, which was a novel procedure at that time. Although this case does not present the development of a *surgical device*, but the innovation of a *procedure*, we believe the evaluation undertaken in this case can be applied to surgical devices in the same way. Our approach was still under development at that time. That is, the separate steps of our approach – evidence synthesis, qualitative exploration, modelling studies and clinical studies – were followed, but these were mainly considered separate studies, and not integrated as proposed in our approach. Here, we will first briefly introduce the clinical example followed by a description of each step. Then, we will illustrate what our approach has contributed, and what could be improved by integrating the different elements.

The role of sentinel lymph node biopsy in oral cavity squamous cell carcinoma

In 2012, our research group started a project on the role of sentinel lymph node biopsy in the management of oral cavity squamous cell carcinoma. By that time, standard treatment of oral cavity cancer in patients with a clinically negative neck (cN0) consisted of dissection of the tumour with mostly elective neck dissection to treat potential lymph node metastases or sometimes watchful waiting to monitor potential lymph node metastases. Approximately 30% of patients have occult lymph node metastases, which implicated that a large proportion of patients were subjected to a treatment they might not have needed and which is associated with morbidity.[1–4] Watchful waiting, on the other hand, could have resulted in lower survival when occult metastases were present.[5–7] Sentinel lymph node biopsy was a novel and promising treatment approach in which a biopsy is taken from the first lymph node draining a tumour. The procedure provided an intermediate approach between elective neck dissection and watchful waiting, allowing for the selection truly positive patients for further treatment. It could thereby reduce both over- and undertreatment. Nevertheless, strong evidence for the clinical effectiveness or cost-effectiveness of sentinel lymph node biopsy, compared to elective neck dissection or watchful waiting was lacking. It was neither qualitatively explored whether there was a clinical need for sentinel lymph node biopsy, and related wishes and expectations. Our aim therefore was to inform decisions in the management of oral cavity squamous cell carcinoma patients with a clinically negative neck in an evidence-based manner. In the following paragraphs, our findings for each element – evidence synthesis, stakeholder involvement, decision modelling and clinical studies – are described.

Evidence synthesis

A comparison of international guidelines for the treatment of oral cavity squamous cell carcinoma concluded that there was high variation in the management of the neck and that there seemed to be a need to establish more evidence-based management and more uniform practice patterns.[8] Also, a diagnostic meta-analysis was performed to systematically assess the accuracy of a sentinel lymph node biopsy in oral cavity squamous cell carcinoma patients with a clinically negative neck. The pooled data showed high sensitivity of 0.93 and suggested a role for sentinel lymph node biopsy in the management of oral cavity cancer.[9] This evidence synthesis was performed in line with our recommendations as described in the main text, but could have been applied more broadly to map other innovations.

Stakeholder involvement

The qualitative exploration was aimed at identifying ways in which oral cavity squamous cell carcinoma care could be improved. A pilot interactive evaluation method was used including 9 healthcare professionals and 3 patients. Results showed that participants had diverging opinions about the safety and effectiveness of sentinel lymph node biopsy and whether sentinel lymph node biopsy ought to be used in clinical practice. In hindsight, stakeholder involvement should have been integrated more thoroughly to establish factors that should be taken into account in the cost-effectiveness studies, in or determining the outcome measures for prospective clinical studies. Moreover, policy makers or family members of the patients should also have been included as to involve all relevant stakeholders as suggested in the integrated approach.

Health economic modelling

A health economic model was conducted where five strategies for diagnosing and treating lymph node metastases in N0 patients were evaluated by means of a Markov model.[10] The evaluated strategies consisted of existing and novel techniques: elective neck dissection, watchful waiting, gene expression profiling followed by neck dissection or watchful waiting, sentinel lymph node biopsy followed by neck dissection or watchful waiting and gene expression profiling in combination with sentinel lymph node biopsy followed by neck dissection or watchful waiting. The model showed that the sentinel lymph node biopsy followed by neck dissection or watchful waiting was most (cost-)effective. An uncertainty analysis showed that the model was sensitive to changes in assumed incidence of occult metastases and utility values. A second model was created in which individual patient characteristics were included to weigh risks, benefits and costs for individual patients.[11] This model showed that a personalized treatment approach resulted in improved health outcomes and cost savings compared to a population approach, but available prediction models should be improved before implementation in clinical practice is possible. Both models meet the requirements of the element as described in our main text, as they help to map the magnitude of the problem, uncertainties and conditions for added value.

Clinical studies

To determine quality of life of oral cavity squamous cell carcinoma patients, a cross-sectional study was set up to inform decision modelling.[12] Furthermore, a prospective clinical study was initiated to measure patient quality of life over time. At the same time several, mostly retrospective, cohort studies about the performance of sentinel lymph node biopsy were published by other research groups.[13–15] In 2020, a large cohort study of 878 patients was published comparing sentinel lymph node biopsy to elective neck dissection.[16] Results showed that sentinel lymph node biopsy is as accurate as elective neck dissection, except for floor of mouth tumours where elective neck dissection seems more accurate. More recently, a randomized clinical trial was published which confirmed that sentinel lymph node biopsy is oncologically equivalent to elective neck dissection, and results in lower morbidity.[17] The results of a prospective longitudinal study regarding the quality of life demonstrated benefit in short-term shoulder function, whereas no significant differences for shoulder morbidity, or health-related quality of life were found at 6 weeks, 6 months, and 12 months between the groups.[18] These results therefore confirm our earlier modelling findings that elective neck dissection is the most (cost-) effective management option. The clinical research phases did not adhere to all stages of the IDEAL framework. We are currently not able to conclude whether a better adherence to these stages would have led to an earlier adoption of the procedure. We do, however, believe that adherence to the IDEAL framework will in the end lead to less research waste.

The merits of an integrated approach

Since the start of this project, standard clinical practice in the Netherlands has slowly shifted towards the use of sentinel lymph node biopsy. It is difficult to determine what exactly has caused this shift, but based on conversations with involved clinicians it seemed that accumulating evidence of the added value of sentinel lymph node biopsy, including the evidence gained through our project, was a major contributor.

All elements of our approach were followed in this case. But in retrospect, we believe that the research into sentinel lymph node biopsy should have started earlier and in a more coordinated way by using the IDEAL framework. The research by individual groups, including ours, could have been better coordinated and integrated. For example, multiple retrospective cohort studies with comparable aims were performed simultaneously. If the different clinical stakeholders involved in these studies would have collaborated, fewer studies would have sufficed. This saves time, money and, perhaps most importantly, lowers the burden of patients. In addition, a staged and more coordinated approach would have allowed to design studies in line with the views of a wider variety of stakeholders, such as patients and relatives. A more integrated research approach would thus have led to a better alignment of the different elements, which can lead to more efficient research practices, and perhaps an accelerated uptake of the innovation.

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