NICE National Institute for Health and Care Excellence

2020 exceptional surveillance of cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over (NICE guideline NG36)

Surveillance report

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Surveillance decision

We will not update the NICE guideline on cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over.

Reason for the exceptional review

This exceptional review examined the impact of the Selective Neck Dissection study (SEND study) on the NICE guideline.

Methods

The exceptional surveillance process consisted of:

- Considering the new evidence that triggered the exceptional review.
- Considering the evidence used to develop the guideline in 2016.
- Assessing the new evidence against current recommendations to determine whether the guideline needs updating.

We decided that full updated literature searches were not needed because the information from the original guideline and the new study was enough to establish whether an update to the guideline was needed.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Information considered in this exceptional surveillance review

The SEND study is a multicentre randomised controlled trial (RCT) that compared the resection of oral squamous cell carcinoma (OSCC) with or without elective neck dissection (END) in people in an early stage of the disease in the UK (Hutchison et al. 2019).

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Adults with a histopathological diagnosis of OSCC stage T1/T2 without evidence of nodal involvement (N0) or other oral cancers (such as lip cancer or pharyngeal squamous cell carcinoma) were included in the study. Participants were stratified by age, tumour stage and surgeon. They were randomised to receive a resection of the primary tumour with or without END. Participants who declined to participate in the study were invited to be part of a 'real-world' cohort of patients so potential selection bias could be further assessed. In case of recurrence of the disease, participants could be treated following local protocols based on national guidelines, including further resection, neck dissection, radiotherapy and chemotherapy. All participants were followed up every 2 months during the first 2 years, every 3 months in the third year, and every 6 months until 5 years. The primary outcome assessed was overall survival (OS) at the end of the follow up period (5 years). Secondary outcomes included disease-free survival (DFS), loco-regional recurrence, adverse events at 6 months (mild, moderate, severe or life threatening/disabling), quality of life (QoL), and NHS resource use. Recruitment was stopped early after preliminary analyses demonstrated benefits of END.

The authors also updated a previous meta-analysis published in the area (Ren et al. 2015) with the results of the SEND study (per-protocol analysis) and presented the pooled estimates for the main outcomes assessed.

From a total of 776 eligible participants, 255 were included in the RCT (124 in resection only and 126 END) or 346 in the cohort study (234 in resection only and 112 END). Five patients were ineligible and excluded from the analysis.

Randomised controlled trial

In an intention to treat analysis, there were no differences between groups for OS (5-year hazard rate [HR] 0.71; 95% confidence interval [CI] 0.43 to 1.17; overall HR 0.86; 95% CI 0.55 to 1.34) or for local-regional recurrence (5-year HR 0.61; 95% CI 0.36 to 1.02; overall HR 0.61; 95% CI 0.36 to 1.02). For DFS, the 5-year HR was better in the END group (5-year HR 0.66; 95% CI 0.44 to 0.98), but no differences were identified for DFS overall HR (overall HR 0.71; 95% CI 0.48 to 1.04). These results contrasted with the per-protocol analysis, where significant differences were observed in most of the outcomes: OS 5-year HR 0.59 (95% CI 0.35 to 1.01), OS HR 0.73 (95% CI 0.45 to 1.17), DFS 5-year HR 0.56 (95% CI 0.37 to 0.86), DFS overall HR 0.61 (95% CI 0.41 to 0.92), local-regional recurrence 5-year HR 0.48 (95% CI 0.28 to 0.84) and loco-regional overall HR 0.48 (95% CI 0.28 to 0.84). Most loco-regional disease events occurred within 2 years of surgery (57/60); only 3 were seen after this time.

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The END group had a greater number of adverse events (60.5% resection only; 77.8% END; p=0.003) compared with the resection only group. Neck sensory and motor nerve abnormalities, and swallowing problems were also most frequent in the END group. Most of the adverse events were low grade and there were no differences between groups in the number of severe or severe or life threatening/disabling adverse events.

There was no difference in the use of additional surgery between the resection only and the END group. Most participants in the resection only group received chemoradiotherapy after a recurrence (19.4% resection only group compared with the 10.3% in the END group).

At 6 months, there were no differences between groups in most of the QoL measures. Occurrences of dry mouth were worse in the END group and nausea were worse in the resection only group.

Initially, participants in the END group spent more days in hospital than participants in the resection only group. However, after 2 years, there were no differences between the groups for the number of inpatient days, the number of outpatient visits or GP visits.

Cohort study results

Differences in the stage of the disease and tumour diameter were observed (and expected) between the groups, as participants with larger tumours were more likely to receive END. Differences favouring END were identified in the DFS (adjusted HR 0.64; 95% CI 0.41 to 0.98), local-regional recurrence (adjusted HR 0.36 95% CI 0.19 to 0.69) but not in the OS (adjusted HR 0.81; 95% CI 0.51 to 1.28). The incidences of adverse events and further neck resections in the cohort study were similar to those in the RCT. Total number of adverse events were higher in the END group (no differences for grade 3 to grade 4 events) and more participants in the resection only group had further neck dissections compared with the END group.

Meta-analysis results

The authors updated the searches of a systematic review previously published in the area, and no new additional studies beyond the SEND study were identified. The results showed that END reduces the risk of death by 31% (HR 0.69, 95% CI 0.55 to 0.87) and the risk of recurrence/death by 33% (HR 0.67, 95% CI 0.46 to 0.98) in people in an early stage of the disease.

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The study has some limitations, importantly, recruitment was stopped early because preliminary data showed that END was more effective than resection only. However, the authors stated that the study had the statistical power to show differences in important outcomes assessed. The results of the study were influenced by non-adherence to treatment allocation for 20 patients. Seven patients who were allocated to the resection only group had an END. These 7 patients were all disease-free at the end of follow up. In 1 further patient, the procedure received was unreported. Finally, 12 patients allocated to the END group had a resection only; 5 had a cancer occurrence in the neck, 1 developed a new oral tumour, and all of them died. The per-protocol analysis excluded all 20 patients and showed statistical differences favouring the END in most of the outcomes assessed (except in the OS though not statistically significant, the results were positive).

Information considered when developing the guideline

The guideline development committee noted that the optimal management of the patients with a clinically and radiologically N0 neck was controversial. The END reveals occult metastases in up to 26% of cases, raising concerns about overtreatment of these patients.

The guideline recommends surgical treatment of the neck to all people with early oral cavity cancer (T1-T2, N0). It also recommends sentinel lymph node biopsy (SLNB) to people with early oral cavity cancer (T1-T2, N0), unless they need cervical access at the same time.

When developing the guideline, different comparisons were assessed including END versus observation/therapeutic neck dissection, radical neck versus selective neck dissection, SLNB, surgery plus radiotherapy versus surgery alone, and chemotherapy plus locoregional therapy versus locoregional therapy alone. The primary outcomes were overall mortality, locoregional recurrence, DFS, and treatment-related mortality. Evidence from 5 studies informed the comparison of END versus observation/therapeutic neck dissection (all are included in the meta-analysis presented by Hutchison et. al 2019). END reduced the risk of locoregional evidence (pooled RR 0.49; 95% CI 0.39 to 0.60), and DFS (HR 0.45; 95% CI 0.34 to 0.59) compared with observation/therapeutic neck dissection. There was no difference in OS between the interventions assessed (pooled RR 0.76; 95% CI 0.47 to 1.23). The economic analysis developed in the guideline evaluated the cost effectiveness of END, watchful waiting, and SLNB then neck dissection or watchful waiting for the treatment of the early stage OSCC. END and SLNB were cost-effective strategies

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compared with watchful waiting, but SLNB was less costly and more effective than END. The Committee considered that for patients not needing a neck operation for reconstruction, most multidisciplinary teams would offer SLNB (which would have an impact on the number of END performed). If reconstruction were needed, then an END would be offered rather than an SLNB.

Topic expert feedback

We contacted 6 topic experts to seek their views on the SEND study and current clinical practice around management of the N0 neck in T1-T2 squamous cell carcinoma of the oral cavity. Two oncologists, 1 surgeon and 1 radiographer replied, all except 1 were members of the guideline development committee. Most mentioned that different factors are considered when deciding whether to select SLNB or END for the management of N0 neck in T1-T2 squamous cell carcinoma of the oral cavity, including the expectation of invasive squamous cell carcinoma, risk of loss to follow up, and location of the main lesion. Nationwide variation in capacity for SLNB was also mentioned, as well as the impact of the COVID pandemic on resource availability (for example ICU/anaesthetic time). More research is needed comparing END with SLNB for the treatment of N0 neck in T1-T2 squamous cell carcinoma of the oral cavity. The results of the SEND trial were considered to support current guideline recommendations.

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

Results of the clinical evidence review conducted in the original guideline showed that END lowered the risk of locoregional recurrences and improved DFS compared to observation, without affecting the OS. The SEND study showed similar results, improving the DFS and reducing the locoregional recurrences without affecting the OS of the patients. Results from the SEND study updated a meta-analysis of the relevant published studies (all included in the original guideline). The pooled estimates showed an improvement of the previous estimates in all the main outcomes assessed. After reviewing the new evidence identified, we considered that it does not have an impact on the current recommendations.

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