NICE National Institute for Health and Care Excellence

2022 exceptional surveillance of oesophago-gastric cancer: assessment and management in adults (NICE guideline NG83)

Surveillance report

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Surveillance decision

We will update the section on palliative management in the NICE guideline on oesophago-gastric cancer. The update will focus on recommendation 1.5.11 on combination therapy of self-expanding metal stents (SEMS) and external beam radiotherapy (EBRT) for luminal obstruction in palliative management.

Exceptional surveillance review summary

Reason for the exceptional review

The purpose of this exceptional review was to examine any impact on NICE's guideline on oesophago-gastric cancer following the publication of the National Institute for Health Research's report on palliative radiotherapy combined with stent insertion to reduce recurrent dysphagia in oesophageal cancer patients: the ROCS (radiotherapy after oesophageal cancer stenting) RCT (randomised control trial).

Methods

The exceptional surveillance process consisted of:

- Considering the new evidence that triggered the exceptional review.
- Literature searches to identify relevant evidence.
- Considering the evidence used to develop the guideline in 2018.
- Feedback from topic experts.
- Examining the NICE event tracker for relevant ongoing and published events.
- Assessing the new evidence and topic expert feedback against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.

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 ROCS study is a UK-based, pragmatic, multicentre RCT that examines the effect of palliative EBRT following SEMS insertion compared with SEMS alone, for the relief of dysphagia in people with oesophageal cancer who present with incurable disease. The ROCS study also examines the impact on quality of life (due to ability to swallow), bleeding events, overall survival and cost effectiveness.

Methods

Participants (n=220) were recruited from 23 cancer centres and acute hospitals across England, Scotland and Wales. Participants were included if they:

- had oesophageal cancer with histological confirmation or clinical or radiological evidence of invasive tumour
- were not suitable for radical oesophagectomy or radical chemoradiotherapy
- had a clinical need for stent insertion to treat dysphagia
- were aged over 16 years
- had a treatment decision made for stent insertion
- were deemed suitable for radiotherapy
- had an expected survival of at least 12 weeks
- could provide written consent
- had completed the baseline quality of life (QoL) questionnaires.

Both arms of the study received SEMS for primary treatment of dysphagia related to oesophageal cancer, and randomisation post stenting was permitted following the initial study pilot. The intervention arm of the study also received EBRT, the protocol for which stated that EBRT should begin within 4 weeks, but preferably 2 weeks following stent insertion. The intervention arm had 2 treatment doses, either 20 Gy in 5 fractions over

1 week or 30 Gy in 10 fractions over 2 weeks using daily fractionation. The choice of treatment dose was determined by the patient's clinical oncologist. If patients missed 7 consecutive calendar days of radiotherapy, they were withdrawn from the trial.

All patients were followed up at 1 week after stent insertion, where QoL data was collected using the World Health Organization (WHO) performance status, questionnaires including EORTC QLQ-C30, EORTC QLQ-OG25, EQ-5D-3L, and toxicity assessment (CTCAE). Following the 1-week check, all patients were followed up 4-weekly for up to 1 year, until all participants had completed 12 weeks of follow up. Data on serious adverse events was monitored throughout.

The primary outcome for the ROCS study was measure of dysphagia symptoms, which was patient reported at each follow up, and also included death up to the 12-week time point. The dysphagia score taken at 1 week post-SEMS insertion was taken as time zero, as some relief in dysphagia was expected in all patients. Cost effectiveness was assessed using cost–utility analysis with a time horizon of 12 weeks in the base case as well as 12 months in the sensitivity analysis. There was also an embedded qualitative study designed to explore patient experience and feasibility of recruitment to the study, and also to understand patient experience of living with advanced oesophageal cancer and dysphagia.

The sample size for this study was originally calculated to detect patient deterioration and increased dysphagia at 4 weeks. This was revised to include dysphagia deteriorations at the 12-week time point. The authors highlight that missing data increased significantly after 12 weeks of participation, thought to be due to the increasing frailty of the study population by this stage in their disease. The revised calculations required 220 participants to be randomised, to allow for a 25% loss to follow up, and achieve 80% power to detect an increase in median time to self-reported dysphagia deterioration. An increase in time to dysphagia deterioration of 4 weeks was determined to be clinically meaningful. The authors state this was based on similar studies, expert multidisciplinary clinical and service user opinion, as median survival in this patient group was approximately 4 months.

Results

Baseline characteristics were similar and well-balanced following randomisation for both the usual care group (SEMS, n=112) and intervention group (SEMS plus EBRT, n=108).

For the primary outcome, the modified intention-to-treat population included 108 patients

from the usual care group and 97 patients from the SEMS plus EBRT group, of which 74 and 75 patients respectively had complete data at the primary end point of 12 weeks post-stent insertion. No between-group differences were seen for the dysphagia-free survival up to week 12 post stent for usual care versus SEMS plus EBRT respectively (36/74 [48.6%] versus 34/75 [45.3%]; adjusted odds ratio [OR] 0.82; 95% confidence interval [CI] 0.40 to 1.68; p=0.587). The best (p=0.612) and worst (p=0.345) case scenario for missing data also showed no between-group differences for the primary end point.

This finding was also seen when the per-protocol population was considered, with 66 (usual care) versus 64 (SEMS plus EBRT) patients having a complete data set at 12 weeks post stent (28/66 in the usual care group [42.4%] versus 26/64 in the SEMS plus EBRT group [40.6%]; adjusted OR 0.99; 95% CI 0.45 to 2.14; p=0.972). No evidence of between-group difference was seen when the sensitivity analysis was performed, treating death by week 12 as no event (19/66 usual care [28.8%] versus 19/64 SEMS plus EBRT [29.7%]; adjusted OR 1.20; 95% CI 0.53 to 2.71; p=0.666).

A secondary analysis of dysphagia deterioration-free survival found the median time to dysphagia event or death was 13.1 weeks (95% CI 10.0 to 17.9 weeks) in the usual care arm (SEMS only) and 14.7 weeks (95% CI 12.1 to 17.4 weeks) in the SEMS plus EBRT arm, with an overall median time to dysphagia for the whole study population of 14.6 weeks (95% CI 12.1 to 17.4 weeks).

No evidence of a between-group difference was seen in the secondary outcome of overall survival (19.7 weeks for the usual care group [95% CI 14.4 to 27.7 weeks] versus 18.9 weeks for the EBRT group [95% CI 14.7 to 25.6 weeks], p=0.700).

No evidence of time versus treatment interactions was seen for the subscales of the EORTC QLQ-C30 and EORTC QLQ-OG25 questionnaires scales and WHO performance status (global health, odynophagia, pain/discomfort, eating restrictions) with all p values above 0.05. A time to treatment interaction however was seen for dysphagia at week 4 where it was higher in the SEMS plus EBRT group, but by week 8, there were no longer any between-group differences. The authors stated previously that initial increase in discomfort is expected from radiotherapy treatment and as such, this finding was not unexpected. The mean pain score was also higher in the SEMS plus EBRT group compared with the usual care group (p=0.005) at weeks 8, 12 and 16; similarly, interactions for constipation (p=0.009) were also seen at those time points for the SEMS plus EBRT group.

Higher median scores for cognitive function at weeks 12 and 16 (p=0.007), body image at

weeks 8 and 16 (p=0.011), anxiety at weeks 12 and 16 (p=0.002) and trouble swallowing saliva at week 16 (p=0.025) were seen in the SEMS plus EBRT group. However, no evidence for time-treatment interactions for fatigue (p=0.522), weight loss (p=0.053) or WHO performance status (p=0.565) were seen.

Gastrointestinal (GI)-related bleeding events were observed initially up to week 16, where 19 patients (18.6%) versus 10 patients (10.3%) had an upper GI-related bleed event (SEMS alone versus SEMS plus EBRT). At week 52, upper GI-related bleed events were seen in 28.4% and 16.5% of patients in the usual care and SEMS plus EBRT groups respectively, up to week 52, giving a number needed to treat of 8.4. Median time to first bleeding event (upper GI-related bleed event or upper GI-related hospital admission) was 49.0 weeks (95% CI 33.3 to not reached weeks) in the SEMS alone arm versus 65.9 weeks (95% CI 52.7 to not reached weeks) in the SEMS plus EBRT arm. In a post-hoc subgroup analysis, no evidence of an interaction between group allocation, tumour length and time to first bleed was found (p=0.947). The treatment effect was consistent in both the less than 6 cm (p=0.216) and more than 6 cm (p=0.265) baseline tumour length subgroups indicating that SEMS plus EBRT had a positive impact on bleeding events.

Analysis of toxicity found the SEMS plus EBRT group experienced more vomiting at week 4, and more fatigue at week 12, more nausea, anorexia and stent-related pain compared with the usual care group; however, the SEMS plus EBRT group had less anaemia and upper GI haemorrhage. Additionally, 29 patients received palliative radiotherapy outside of the study protocol, 20 in the SEMS alone group and 9 in the SEMS plus EBRT group.

Discussion

This study was a well-designed RCT that is directly relevant to the UK population. Limitations were seen in consistent guidance on the trial itself from a patient perspective, with patients also raising that although stenting is commonly used to relieve symptoms of advanced disease such as dysphagia, it does not address the likely course of the disease. Difficulties in recruitment were also noted, with 1,252 people being assessed for eligibility, of whom 546 were eligible to enter the trial. The additional symptoms patients live with that may affect their QoL may have been improved by additional interventions such as dietary advice and pain relief information. The authors also highlight that the assumption that stent insertion addresses all issues of food intake and nutrition may inadvertently obstruct additional treatment options. The study found no evidence that SEMS plus EBRT was beneficial compared with SEMS plus usual care for any outcome except for upper GI bleeding events, which were fewer in the SEMS plus EBRT group. No significant difference

was found between groups for the primary outcome of dysphagia-free survival. This finding is not consistent with recommendation 1.5.11 in the NICE guideline, which states 'Consider external beam radiotherapy after stenting for people with oesophageal and gastro-oesophageal junctional cancer, for long-term disease control'.

Health economics evaluation

A cost–utility analysis, using a combined decision tree and Markov model, was performed to assess the cost effectiveness of SEMS plus EBRT on patient-reported dysphagia, and dysphagia-related events at 12 weeks in the base case and at 12 months in sensitivity analysis, following stent insertion. The key model assumptions are:

- Adverse events were not included as separate states within the model (to avoid potential double-counting as adverse events would be reflected in health-related quality of life and healthcare resource use data collected throughout the trial).
- If a patient underwent stent reinsertion during the first 12 weeks, this would be accounted for by the individual costs and utilities calculated in the respective 4-week period.
- Base-case analysis was based on the modified intention-to-treat population of 199 patients.

The cost–utility analysis produced incremental cost-effectiveness ratios (ICERs) expressed as cost per quality-adjusted life year (QALY) gained, following a UK NHS and personal social services perspective for analysis of health outcomes. The implementation cost of EBRT and cost of subsequent healthcare use were included for all patients where 4 follow-up points were available for data collection. These implementation costs were added to determine a total mean cost per patient at the 12-week and 12-month time points.

Intervention implementation costs for planning EBRT was costed at £377.15, with a cost per fraction of radiotherapy delivered of £155.58 (mean fractions per patient 6.06). Based on all available cases, the mean EBRT cost per patient was £1,304.42.

Total healthcare costs (including the cost of all primary, secondary and social care, and any medications prescribed) at the 12-week period were not significant between groups despite the SEMS plus EBRT group having higher healthcare costs in the first 8 weeks, and lower costs in the remaining 4 weeks. After adding the intervention implementation costs, the SEMS plus EBRT arm accrued a mean cost of £5,854.10 (standard deviation [SD]

£4,768.79), compared with £5,699.02 (SD £5,024.49) in the SEM alone arm.

Total healthcare costs at the 12-month period were based on cases who were able to contribute 1 healthcare data set at 1 follow-up point within the trial period (n=102 SEMS, n=104 SEMS plus EBRT). The total 12-month healthcare costs in this population were £7,440.43 (SD £7,643.21) and £9,087.14 (SD £8,890.75) in the SEMS plus EBRT and SEMS alone arm respectively, with a mean difference of -£1,646.70 (95% CI -£3,922.89 to £629.49), which was not statistically significant (p=0.155). When the EBRT implementation costs were added at an individual patient level, the cost difference decreases to -£568.05 (95% CI -£2,858.80 to £1,722.71; p=0.625).

No statistically significant difference in QALYs between the SEMS alone and SEMS plus EBRT group were seen at baseline, 12-week or 12-month time points (p=0.1345).

After 1,000 simulated patients in the cost–utility analysis, the difference in QALYs between arms was minimal over 12 weeks (total QALYs, SEMS plus EBRT 53.993, SEMS alone 55.32). However, the total cost of the SEMS plus EBRT arm were over £750,000 higher compared with SEMS alone.

This resulted in an incremental cost of £549,200 per QALY gained at 12 weeks for SEMS plus EBRT compared with SEMS alone, highlighting that SEMS plus EBRT is less effective than SEMS alone and more costly. The one-way sensitivity analyses conducted at 12 months found no change to the base-case conclusion, SEMS plus EBRT was dominated and as such found to not be cost effective for end stage treatment of oesophageal cancer.

The impact of the significant reduction in bleeding events for the SEMS plus EBRT group did not result in a decrease in costs associated with hospital admission or healthcare interventions. However, the potential for EBRT to reduce bleeding in those patients who are clinically more likely to experience bleeding events could be further examined.

At a willingness to pay threshold of £20,000 per QALY gained, the use of SEMS plus EBRT for advanced oesophageal cancer is not a cost-effective option.

Search and selection strategy

We searched for new evidence related to the use of SEMS plus EBRT for palliative care in patients with advanced oesophageal cancer.

We found 516 studies in a search for all study types published between 1 January 2018 and 23 March 2022, of which 2 met the inclusion criteria.

Studies included from the literature review

A systematic review and meta-analysis by Lai et al (2018) examined 8 RCTs and 732 patients with oesophageal cancer who received palliative care for the primary outcomes of mean change in dysphagia score, QoL and overall survival. Adverse events were also examined as secondary outcomes.

Three combinations of therapy were compared, of which 1 is relevant to this review: stents alone versus stents combination therapy (combination therapy included radiotherapy). In the stents combination therapy group, improvements were seen in mean dysphagia score (particularly in those patients 3 months post insertion), overall survival, QoL, lower risk of stent migration, aspiration pneumonia and restenosis when compared with the stents alone group. However, risk of fistula formation, haemorrhage and severe pain were higher in the stent combination group compared with the stent alone group. The authors conclude that whereas there were no immediate short-term differences, for patients living longer than 3 months, there was a significant improvement in dysphagia score for the stents combination group, as well as improvements in overall survival and QoL scores.

A systematic review and meta-analysis (Tinusz et al. 2020) of 17 studies compared stents alone (control group) with stents combined with any active oncological treatment (intervention group) including radio-, chemo- or photodynamic therapy, for efficacy and safety as treatment for people with oesophageal cancer receiving palliative care. Dysphagia grade, survival, late dysphagia, medical costs and oesophageal perforation were examined by the review. There were no significant differences seen in any complications between the control group (stents only, n=629 participants) and the intervention group (stents plus active oncological treatment, n=548). Of the 13 studies that reported on survival between the 2 groups (mean or median), 8 studies showed significantly longer life expectancy in the intervention group compared with the control group; however, the remaining 5 studies found no between-group difference in survival. The authors conclude that the benefit of additional oncological treatment alongside stenting was unclear; however, it was not associated with any increase in adverse effects.

Information considered when developing the guideline

Recommendation 1.5.11 states that EBRT could be considered for patients following stenting with oesophageal and gastro-oesophageal junctional cancer, for long-term disease control. The recommendation was made in 2018 as part of the full guideline, following a literature search for evidence to address the review question 'What is the optimal management of luminal obstruction for adults with oesophago-gastric cancer not amenable to treatment with curative intent?'. The search resulted in 9 studies that were suitable for inclusion, and 20 RCTs that were extracted from 1 systematic review. Of these 29 studies, 1 RCT from 2012 considered the use of SEMS compared with SEMS followed by EBRT. Full details can be found in section 9.4 on luminal obstruction in the NICE full guideline on oesophago-gastric cancer.

Moderate-quality evidence from 1 RCT (n=79) found that there may be a clinically significant harmful effect of SEMS alone compared with SEMS plus EBRT for decreasing mean dysphagia-free survival; however, uncertainty around the estimate was noted.

The committee considered that management of luminal obstruction is a palliative procedure and as such noted the critical outcomes were symptom improvements (largely dysphagia), time to recurrence of symptoms and procedure-related morbidity. The committee were also interested in patient-reported QoL; however, no studies in this area were identified for inclusion in the 2018 guideline evidence review. When considering the benefits and harms of treatments, the committee used their clinical experience to conclude that early intervention could reduce emergency admissions for dysphagia, such as proactive stenting. As such the committee concluded that stenting offered benefits to patients that outweighed any potential adverse effects. The committee felt that the immediate relief provided by stenting compared with radiotherapy which temporarily worsened dysphagia allowed SEMS to be recommended, adding that combining SEMS with EBRT improved both overall and dysphagia-free survival. Cost-effectiveness evidence was only found for the comparison between SEMS and plastic stents, and as such no health economic data was presented for SEMS plus EBRT compared with SEMS alone during the 2018 guideline evidence review.

Topic expert feedback

We contacted 8 topic experts for feedback on the use of SEMS plus EBRT. Two topic

experts (a consultant clinical oncologist and a consultant upper GI surgeon) responded. Both topic experts agreed that the ROCS study by the NIHR impacts on recommendation 1.5.11. One expert stated that the findings of this study have already been embraced by the oesophago-gastric medical community, making recommendation 1.5.11 outdated. The other expert confirmed that the study contradicted this recommendation. One topic expert agreed that there may be cases where SEMS plus EBRT could be clinically indicated, such as in those who are at greater risk of bleeding events; however, this would need to be balanced with patient experience as it would involve more hospital visits and likely more side effects.

Equalities

No equalities issues were identified during the surveillance process.

Summary

The ROCS trial demonstrated that not only is there no benefit on dysphagia-free survival for the use of SEMS plus EBRT compared with SEMS alone, but also that SEMS plus EBRT was not cost effective. The SEMS plus EBRT group had significantly less bleeding events compared with the SEMS alone group; however, this was also not cost effective. When recommendation 1.5.11 was made, there was no cost-effectiveness evidence available, with evidence coming from an RCT with a relatively small sample size. The ROCS study had a much larger sample size and provided a detailed cost–utility analysis compared with the only study included when the guideline was developed in 2018.

Two additional studies were found during a literature search for evidence relating to recommendation 1.5.11 which states: 'Consider external beam radiotherapy after stenting for people with oesophageal and gastro-oesophageal junctional cancer, for long-term disease control'.

A systematic review and meta-analysis found 8 studies that suggested SEMS plus active oncological treatment improved survival, and 5 that found no differences, resulting in an unclear effect overall. Another systematic review found stent combination therapy led to better overall survival, QoL and less stent migration compared with stents alone; however, there were increases in the risk of pain, fistula formation and haemorrhage. As such, the evidence found from the literature search regarding the use of SEMS plus EBRT is unclear.

Overall decision

We will update recommendation 1.5.11 in the NICE guideline on oesophago-gastric cancer: assessment and management in adults.

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