OXFORD

Short Report

BJS Open, 2023, zrad159
https://doi.org/10.1093/bjsopen/zrad159
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Economic cost-utility analysis of stage-directed oesophageal cancer treatment

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Presented to a meeting of the Association of Surgeons of Great Britain and Ireland, Harrogate, UK, May 2023

Introduction

Oesophageal cancer (OC) treatment is guided by radiological diagnostic stage[1], with prognosis worsening as stage advances[2]. Potentially curative treatment is possible in 30–40% of patients[2,3]. Treatments include definitive chemoradiotherapy or surgery, with or without neoadjuvant therapy[4], and patients not considered suitable for curative treatment receive palliative treatments or Best Supportive Care (BSC)[2,5]. Clinical effectiveness of treatments can be estimated in terms of Quality-Adjusted Life Years (QALYs) to price a treatment's cost-effectiveness[6].

The aim of this study was to estimate the cost-utility of curative treatment related to OC stage compared with BSC. The primary hypothesis was that OCs of earlier stage would prove cheaper to treat in fiscal terms than OCs of more advanced later stage.

Methods

Consecutive patients undergoing surgical treatment for OC diagnosed according to established protocols with curative intent within a regional cancer network from 2010 to 2020 were included in the analysis. The cost of 1-year's treatment from referral was calculated based on current management standards. Primary outcome was overall survival (OS). Detailed methods can be found in *Supplementary methods*.

Results

365 patients (median age 65 years (range 38–80), 308 male, 57 female, 263 neoadjuvant therapy) who underwent surgical treatment with curative intent for OC were included. Based on pathological and intraoperative assessment, 111 (30.4%) were stage I, 65 (17.8%) stage II, 118 (32.3%) stage III and 71 (19.5%) were analysed as stage IV. Of these, 331 had adenocarcinoma, 32 squamous cell carcinoma and two high-grade dysplasia. Median follow-up was 36 (interquartile range (i.q.r.) 34.9–39.0) months and median OS was 42.9 (95% c.i. 35.6 to 53.2) months with an average cost of the first year's treatment of €30 916. This resulted in a QALY-adjusted survival of 34.3 months, with cost per QALY of €10 817.

In patients who underwent curatively intended surgery, median survival in the patients receiving neoadjuvant chemotherapy followed by surgery (CS) was 35.8 (95% c.i. 26.5 to 45.1) months compared with 45.6 (95% c.i. 37.7 to 46.7) months in the patients receiving neoadjuvant chemoradiotherapy followed by surgery (CRS) and 50.8 (95% c.i. 39.4 to 47.2) months in patients receiving surgery (S) alone. The QALY-adjusted survival was 28.6 months in the CS cohort, compared with 36.5 in the CRS cohort and 40.6 in the S cohort. The cost per QALY for CS was €14 448, CRS €13 040 and S €5276. The CS cohort had a significantly lower proportion of patients with pTNM stage I and II disease (28.6%) compared with the CRS and S cohorts (66.7 and 69.6% respectively, $P < 0.001$).

Data relating to QALY-adjusted survival and the cost per QALY, stratified by tumour stage, can be found in *Table 1*. The cost analysis of treating OC related to TNM stage and treatment modality can be found in *Fig. 1*. Median OS for patients receiving BSC reported in the literature is around 4 months[7], with a Health State Utility Value (HSUV) of 0.56, equating to a QALY-adjusted survival of 2.24 months and a cost per QALY of €70 463.

In patients undergoing CS, CRS and S, the QALY OS gains were 26.4, 34.3 and 38.4 months, with an associated increased cost of €20 110, €26 510 and €4694 respectively. This equates to an Incremental Cost-Effectiveness Ratio (ICER) of €9672/QALY for CS, €9275/QALY for CRS and €1467/QALY for S.

When stratified by tumour stage, the ICER for TNM stage I was €3960/QALY, for stage II it was €11 365/QALY, for stage III it was

Received: June 23, 2023. **Revised:** November 14, 2023. **Accepted:** December 01, 2023

Table 1 Cost-utility analysis of treatment of oesophageal cancer related to disease stage

Tumour stage	Median survival (months)	Average treatment costs (€)	QALY-adjusted survival (months)	Cost per QALY (€)
Stage I	60 (46.8,52.8)	28 257	48	7064
Stage II	38.2 (34.2,43.7)	39 909	30.6	15 692
Stage III	28.7 (25.8,31.6)	32 753	23	17 089
Stage IV	16.3 (11.9,20.6)	31 788	13	23 402

Values in parentheses are 95% confidence intervals. QALY, quality-adjusted life year.

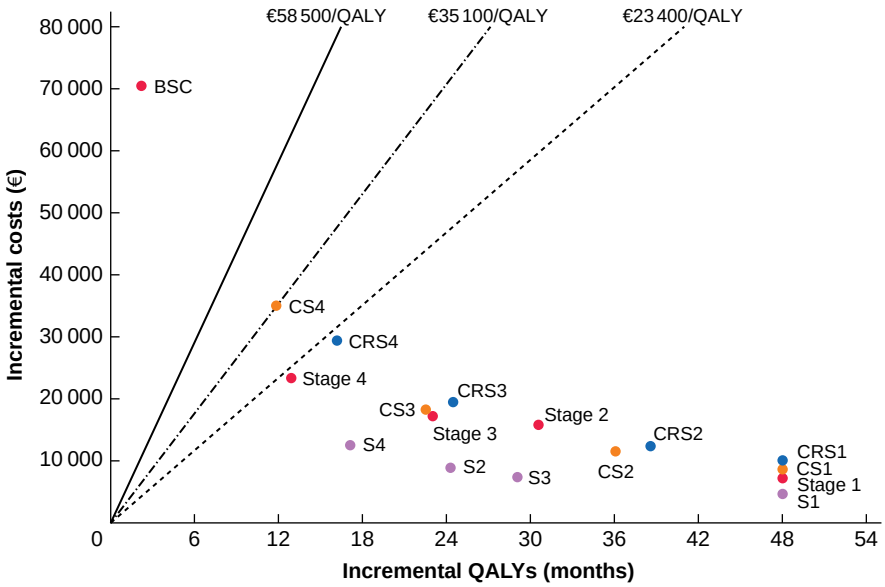

Fig. 1 Cost-effectiveness of oesophageal cancer treatment stratified by stage and treatment modality
BSC, best supportive care; stage 1, pathology tumour node and metastasis (pTNM) stage I; stage 2, pTNM stage II; stage 3, pTNM stage III; stage 4, pTNM stage IV; S1, CS1 and CRS1, pTNM stage I oesophageal cancer (OC) treated with surgery alone, perioperative chemotherapy and perioperative chemoradiotherapy respectively; S2, CS2 and CRS2, pTNM stage II OC treated with surgery alone, perioperative chemotherapy and perioperative chemoradiotherapy respectively; S3, CS3 and CRS3, pTNM stage III OC treated with surgery alone, perioperative chemotherapy and perioperative chemoradiotherapy respectively; S4, CS4 and CRS4, pTNM stage IV OC treated with surgery alone, perioperative chemotherapy and perioperative chemoradiotherapy respectively (intention to treat). CRS, chemoradiotherapy followed by surgery; CS, chemotherapy followed by surgery; S, surgery alone; QALY, quality-adjusted life years.

€10 226/QALY and for stage IV it was €20 783/QALY. When further stratified by tumour stage and treatment modality, the ICER for TNM stage I S, CS and CRS was €1231/QALY, €5581/QALY and €6952/QALY respectively. The ICER for stage II S, CS and CRS was €2553/QALY, €7542/QALY and €8749/QALY respectively. The ICER for stage III S, CS and CRS was €2097/QALY, €12 604/QALY and €14 292/QALY respectively. The ICER for stage IV was €3765/QALY, €26 435/QALY and €22 789/QALY respectively. Further results can be found in *Supplementary results*.

Discussion

This is the first cost-utility analysis of stage-directed potentially curative OC therapy. The salient findings were that surgery improved OS six-fold compared with BSC and was cost-effective at nationally accepted thresholds of readiness to pay per QALY, supporting the primary hypothesis. Costs per QALY increased incrementally and proportionately with the stage of OC so that stage I treatment cost per QALY was a fifth of that associated with BSC, and stage III treatment cost per QALY less than half that of BSC. Similarly, regarding ICER-defined cost-effectiveness comparisons, treatment of patients diagnosed with stage I cancer was between three- and four-fold cheaper than treatment of patients diagnosed with stage IV disease.

Economic cost-utility analyses regarding potentially curative treatment for cancers from other anatomical sites, namely breast[8], colorectal[8] and prostate[8] cancers, have reported similar associations between greater costs and more advanced stage at presentation[8,9]. Powell *et al.* in a related study from the same regional cancer network reported similar findings in a cost-utility analysis related to gastric cancer, with costs per QALY gained of €8335, €8952, €11 317 and €25 669 related to stages I through IV respectively[9].

The poorer survival seen in advanced disease is a major contributor to cost per QALY[10]. Current evidence suggests that only 15–20% of patients undergoing neoadjuvant therapy and surgery for OC show significant pathological tumour regression[11]. Improving response to chemotherapy might, therefore, offer the best cost benefit[11]. This study showed at least a 10-month QALY-adjusted OS benefit associated with perioperative chemotherapy in patients with stage pTNM II. However, this was not the case for stage III cancer, where perioperative chemotherapy was associated with a poorer QALY-adjusted OS. This likely reflects the differential extent of downstaging *versus* no response in these patients. These findings support a precision-medicine approach to OC. A cost-utility analysis of the Keynote 559 trial, Pembrolizumab plus 5-Fluorouracil and Cisplatin-based

chemotherapy in advanced OC, revealed differential cost-effectiveness based on the expression of PD-L1 (programmed death-ligand 1), the target antigen of Pembrolizumab[12]. Given the risk profiles and costs associated with using biological therapies to treat OC, it would seem beneficial to reserve these for patients most likely to benefit.

This study has inherent limitations in that key working assumptions were made. Operational efficiency meant excluding the added costs of deviations from the standard treatment pathway. The cost will also inflate if complications occur. To promote the relevance of these results to current clinical practice, all CS and CRS patients were assumed to have received the FLOT (fluorouracil, leucovorin, oxaliplatin, docataxel) chemotherapy regime. Treatment costs were not assessed at a patient level and did not account for the heterogeneity in durations of hospital stay, chemotherapy- and operation-related morbidity rate, which affect as many as 38% of patients[3]. Despite these limitations, the present study has several strengths, benefiting from robust follow-up data with more than 85% followed for at least 5 years or until death. Patients were included consecutively from a single UK geographical region, and treated by the same multidisciplinary team, using standardized treatment algorithms[4].

In conclusion, the five-fold increase in cost-effectiveness of surgical and oncological therapies supports strong initiatives to help early diagnosis of oesophageal cancer, with treatment aimed at curative intent being most cost-effective.

Funding

The authors have no funding to declare.

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

The data that support the findings of this study are available on request from the corresponding author, G.L.H. The data are not publicly available due to the need to preserve patient confidentiality.

Author contributions

Geraint Herbert (Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing—original draft, Writing—review & editing), David Robinson (Data curation, Formal analysis, Methodology, Supervision, Writing—review & editing), Arfon Powell (Conceptualization, Data curation, Formal analysis, Methodology, Software, Supervision, Writing—original draft, Writing—review & editing), Tarig Abdelrahman (Data curation, Methodology, Supervision, Writing—review & editing), Usman Khalid (Formal analysis, Methodology, Supervision, Writing—review & editing) and Wyn Lewis (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing—original draft, Writing—review & editing)

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