Healthcare resource use and medical costs for the management of oesophageal cancer

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Background: This study examined the interaction between natural history, current practice patterns in diagnosis, monitoring and treatment of oesophageal cancer, and associated health resource utilization and costs.

Methods: A cost analysis of a prospective population-based cohort of 1100 patients with a primary diagnosis of oesophageal cancer was performed using chart review from the Australian Cancer Study Clinical Follow-Up Study. The analysis enabled estimation of healthcare resources and associated costs in 2009 euros by stage of disease and treatment pathway.

Results: Most patients (88.5 per cent) presented with stage II, III or IV cancer; 61.1 per cent (672 of 1100) were treated surgically. Overall mean costs were €37 195 (median €29 114) for patients undergoing surgery and €17 281 (median €13 066) for those treated without surgery. Surgery contributed 66.4 per cent of the total costs (mean €24 697 per patient) in the surgical group. In the non-surgical group, use of chemotherapy was more prevalent (81.9 per cent of patients) and contributed 61.1 per cent of the total costs. Other important cost determinants were gastro-oesophageal junction tumours, treatment location and tumour stage. Mean costs of those monitored for Barrett's oesophagus (7.3 per cent of patients) were lower, although about one-third still presented with advanced-stage cancer.

Conclusion: Overall costs for managing oesophageal cancer were high and dominated by surgery costs in patients treated surgically and by chemotherapy costs in patients treated without surgery; radiotherapy, treatment location and cancer subtype were also important. Monitoring for Barrett's oesophagus and earlier stage detection were associated with lower management costs, but the potential net benefit from surveillance strategies needs further investigation.

+A: Introduction

The incidence of oesophageal adenocarcinoma in Western nations has grown four- to fivefold over the past 30 years^{1,2}, with a parallel increase in the number of deaths from this cancer of 4–7 per cent annually¹. Less than 20 per cent of people currently diagnosed with oesophageal cancer can expect to survive beyond 5 years¹, although there is much scope for improving survival given that early detection of oesophageal adenocarcinoma is associated with a 5-year survival rate of 70–95 per cent³.

The mainstay of treatment for earlier stage cancer is oesophagectomy. Chemotherapy and radiotherapy are used before surgery in patients undergoing resection of more advanced disease, and are the principal treatment in patients unwilling or unfit for surgery, as well as in those with disseminated disease. The clinical course of the cancer can vary markedly, with a low proportion of at-risk patients currently proceeding straight to diagnosis and surgery⁴. A detailed understanding of resource utilization for the treatment of this disease remains elusive. Compared with many other cancer populations, healthcare resource use and costs in patients diagnosed with oesophageal cancer may potentially be high owing to a protracted disease process, frequent treatment-related complications, and the high number and frequency of monitoring and diagnostic investigations^{4–6}.

Considering the relatively poor survival outlook for patients with advanced disease, there is a strong incentive to develop health technologies that will either detect cancer earlier or treat patients more effectively, while containing healthcare costs. Management options have expanded over the past decade, with new ablative therapies, enhanced imaging, endoscopic mucosal resection, and calls for standardized surveillance of Barrett's oesophagus^{7–9}. However, these strategies are suitable only for early-stage disease, and most patients still present with advanced cancer.

Only one previous study has attempted to track healthcare resources and costs in treating oesophageal cancer at the patient level. That study was conducted a decade ago, before many of the current management and therapy alternatives were available, and it analysed a sample of only 29 patients from one centre⁴. It was not large enough to allow practice patterns to be explored. Hence, studies assessing the cost-effectiveness of alternative oesophageal cancer treatments^{10,11} in jurisdictions of interest have relied on assumptions, rather than patient data, to inform treatment pathways and associated base-level probabilities, outcomes and their interaction with treatment effects^{12,13}. The absence of evidence to inform practice patterns, and the interaction of practice patterns with natural history, reduce the validity of the findings of all of these modelling studies^{10,11,14}. In view of these gaps in the evidence, the present authors sought to identify treatment patterns and their interaction with natural history, to quantify the type and extent of resources used to treat actual patients with oesophageal cancer in Australia, and to analyse the attendant healthcare costs.

+A: Methods

Patient-level clinical practice, healthcare and medical outcome data were collected during the Australian Cancer Study Clinical Follow-Up (ACS CFU) Study for a cohort of 1100 patients with oesophageal cancer. These patients were previously enrolled in the ACS, a nationwide case-control study. The study was approved by the Human Research Ethics Committees of the Queensland Institute of Medical Research and participating hospitals. Eligible persons were aged 18–79 years, had a primary diagnosis of invasive adenocarcinoma, squamous cell carcinoma of the oesophagus or adenocarcinoma of the gastro-oesophageal junction, were English-speaking and provided consent for the investigators to undergo medical chart review. Full details have been published previously¹⁵. Briefly, study participants were recruited through their treating doctors or state-based cancer registries in the mainland Australian states between 1 July 2002 and 30 June 2005 (registration of cancer is mandatory in all states and territories of Australia). A total of 1577 patients received an invitation to participate in the study, of whom 1102 patients (858 via clinics and 244 through cancer registries) consented (69.9 per cent of all invited; 35.0 per cent of all living and deceased persons in mainland Australia who had been diagnosed with incident oesophageal cancer). Two patients were removed from analysis because of unclear diagnosis. Participants were asked to complete a survey providing information on

sociodemographics, disease symptoms and health behaviours. A total of 44 consenting participants did not return these surveys but remained eligible for clinical follow-up.

+B: Cost perspective, data collection of resources used, and duration of follow-up

Following recommended guidelines¹⁶, costs associated with oesophageal cancer treatment were estimated from a health provider (government) perspective. Data were abstracted from medical charts on to standard case-report forms by trained research nurses. Information was collected on each patient's investigations by point of incidence at diagnosis, before and after treatment (endoscopy, computed tomography (CT)/positron emission tomography (PET), X-rays, etc.), operative treatment and related adverse events, endoscopic therapies (argon beam, laser, photodynamic therapy, stenting), chemotherapy and radiotherapy. Resource data were collected from date of diagnosis (including peridiagnostic tests) to date of death or last date of follow-up. The mean duration of follow-up for the sample was 4.3 years. The Australian National Death Index was searched periodically during the study to monitor mortality for the cohort. Survival was calculated in days from the date of diagnosis to the date of death, or administratively censored at 31 January 2008.

+B: Estimating costs from resource use

Costs for the primary surgical treatment were derived from the clinical costing department of a large metropolitan hospital (Royal Brisbane and Women's Hospital) where a separate and recent sample of 40 participants had been treated surgically for oesophageal cancer. Cost per hospital inpatient separation by number of hospital days admitted was modelled for the three most common Australian Refined Diagnosis-Related Groups¹⁷: G03A, 'Stomach, oesophageal and duodenal procedures for malignancy'; G42A, 'Other gastroscopy for a major digestive disease'; and G60A, 'Digestive malignancy with complications'. Costs for chemotherapeutic agents were estimated from the 2008 Chemotherapy Pharmaceuticals Access Program¹⁸. Unit prices for imaging tests, radiotherapy, clinic consultations and all other outpatient investigations were obtained from the hospital clinical costing department, where available, or from the Australian Medicare Benefits Schedule¹⁹. Costs associated with the resource implications of any complications while on chemotherapy or any supportive care medications were not collected and were omitted from the analyses. Resources relating to palliative care provided by community health services were omitted but all in-hospital palliative treatments such as endoscopic dilatation or stenting, and palliative chemotherapy were included.

+B: Analysis

All analyses were stratified into patients who underwent surgical resection (surgical group) *versus* patients who did not undergo surgical resection (non-surgical group). The non-surgical group included patients who were unfit for surgery, had metastatic disease at presentation, or had declined surgical resection. Stratification was undertaken because of the different disease presentation and treatment implications across the two groups.

Cancer staging data were not reported routinely for all participants at diagnosis and were missing for 48.7 per cent of patients. To address this, stage data were imputed by fitting an ordered logit regression model with stage as the dependent variable and generating predicted values for each stage category for each patient. To allow for uncertainty in modelling, a random variable was generated from the uniform distribution on 0–1 interval and these values were compared with the predictions in order to assign a stage category for the missing cases. The random variable was necessary so that the variance in the subsequent regression models was not overestimated²⁰.

Costs were updated to 2009 Australian dollars (AUD) using the Consumer Price Index²¹ and converted to euros where 1 AUD = €0.519²². Descriptive statistics were generated for medical costs by the major resource categories. Bootstrapping was employed to estimate distributions around mean costs per participant and associated 95 per cent confidence intervals (c.i.), allowing for right-skewing of cost data²³. One thousand bootstrapped samples from the original skewed distribution, with replacement, were run using the bias-corrected and accelerated approach²⁴. The Wald test was used to assess subgroup differences^{24,25}. Tests were two-sided and results were considered statistically significant when $P < 0.050$.

To account for the right-censored data, mean costs by surgical *versus* non-surgical groups were assessed for variation in baseline clinical or patient factors using the three-part model of Basu and Manning²⁶. First, an accelerated failure-time generalized gamma regression model provided the survival and hazard functions. Second, for patients whose costs were fully observed, a gamma generalized linear model with square-root link was undertaken. Third, for patients in whom censoring occurred, an extended estimating equation using a flexible Box-Cox link function and power variance function was performed (using STATA command ‘PGLM’)²⁷. Goodness-of-fit and model specification were assessed with normality tests, Pearson’s correlation, Pregibon’s link test, and visual assessment for systematic bias in the residuals across

deciles of linear predictors and for v-fold cross-validation with the Copas test for overfitting²⁸.

Data were analysed using STATA[®] SE 11.0 (StataCorp, College Station, Texas, USA).

+A: Results

The mean age of participants was 64 years at diagnosis; 79.6 per cent were men, and most were partnered (77.4 per cent) (*Table S1*, supporting information). Adenocarcinoma of the oesophagus was present in 33.4 per cent of participants, 38.6 per cent had adenocarcinoma of the gastro-oesophageal junction and 27.7 per cent had squamous cell carcinoma of the oesophagus. Of patients with a known cancer stage, 11.5 per cent had stage I cancer, 34.8 per cent stage II, 28.7 per cent stage III and 25.0 per cent stage IV. A total of 79 (7.3 per cent) of 1081 participants were being monitored for Barrett's oesophagus: stage I cancer, 16.3 per cent (23 of 141); stage II, 8.0 per cent (33 of 413); stage III, 5.5 per cent (19 of 348); stage IV, 2.2 per cent (4 of 179). Of the patients under surveillance for Barrett's oesophagus, 29 per cent (23 of 79) presented with stage III or IV oesophageal cancer, and 17 of these 23 patients were treated surgically. Overall median survival was 23.5 (interquartile range (i.q.r.) 1.5–78.1) months and was longer for patients treated surgically (median 33.0, 1.8–78.1) than for those not treated surgically (13.2, 2.1–72.6). Patients receiving routine surveillance for Barrett's oesophagus had a median survival of 47 (range 5–84) months, compared with 22 (2–84) months for all other patients.

+B: Resources used

A total of 3679 staging investigations were performed before treatment in 1098 participants (mean 3.3 per participant) with CT representing 28.0 per cent and PET 13.6 per cent of all tests (*Tables 1* and *2*). Radiotherapy was given to 43.9 per cent (295 of 672) of surgical patients and 81.5 per cent (347 of 426) of non-surgical patients. Of patients with stage IV cancer who were treated surgically, a higher proportion received chemotherapy and radiotherapy (70 and 75 per cent respectively) compared with those with stage I–III cancers (32.3 and 59.6 per cent respectively) (*Table 1*). Of patients with stage IV cancer who were not treated surgically, 66.2 per cent underwent diagnostic PET *versus* 35.3–43.6 per cent of those with stage I–III cancers (*Table 2*). Of participants with squamous cell carcinoma, 66.9 per cent received both radiation and chemotherapy, compared with 52 per cent of patients with adenocarcinoma of the oesophagus and 37.6 per cent of those with adenocarcinoma of the gastro-oesophageal junction. The four most commonly used chemotherapy agents were 5-fluorouracil, cisplatin, epirubicin

hydrochloride and carboplatin. These accounted for 93.6 per cent of all administrations; a total of 25 agents was used in the sample overall.

A total of 672 participants (61.2 per cent) underwent surgery; of these, 124 (18.5 per cent) had preoperative chemotherapy and radiotherapy. Hospitalization for the surgical treatment of oesophageal cancer resulted in approximately 12 600 (mean 18.8; median 15) inpatient days. Hospital days were right-skewed with the fifth and 95th percentiles being 9 and 43 days respectively. A further 2244 postoperative investigations were performed to assess surgical outcomes. Postoperative adverse events were most frequently attributed to pneumonia (18.2 per cent), arrhythmia (10.8 per cent), anastomotic leak (10.1 per cent) and wound infection (8.3 per cent) (*Table 3*). The length of hospital stay was generally longer for those with than those without operative complications (mean 23.0 *versus* 13.7 days; $P < 0.001$). However, some 25.0 per cent of individuals who experienced complications had a shorter than average stay (14 days or less) and, conversely, 25.0 per cent of patients with no complications stayed longer than average (15 days or more). This was unlikely to have been influenced by the in-hospital mortality rate of 1.3 per cent (9 of 672). Endoscopic therapy constituted a small proportion of the resources used for the sample, with 220 procedures in total with the majority of these for endoscopic stent placement (*Tables 1 and 2*).

+B: Costs

Applying unit costs for each resource type (*Table S2*, supporting information), overall mean costs were estimated as €17 281 (median €13 066) for the non-surgical group and €37 195 (median €29 114) for patients who underwent surgical management (*Table 4*), of which €24 697 was for the actual surgical episode. Total costs related to the overall patient cohort with a mean survival of 28.9 (i.q.r. 11.5–44.9) months. Among patients who had surgical management, primary surgical costs represented the highest share (66.4 per cent) of total costs followed by chemotherapy (20.8 per cent) and radiation therapy (3.5 per cent). Among patients who underwent non-surgical management, chemotherapy comprised 61.1 per cent of costs followed by radiation (15.8 per cent) and investigations after initial adjuvant therapies (8.1 per cent). For both surgical and non-surgical cases, costs rose sharply during the first 3 months and increased gradually thereafter.

+B: Univariable analysis

+C: Non-surgical group

For non-surgical patients, mean costs were higher for individuals with gastro-oesophageal junction tumours (€24 762 *versus* €16 169 for oesophageal adenocarcinoma; $P=0.007$), for those who received any chemotherapy (€20 030 *versus* €4626 for no chemotherapy; $P<0.001$), for any radiotherapy (€18 107 *versus* €13 657 for no radiation; $P=0.024$) and for patients aged less than 65 years (€18 986 *versus* €15 922 for those aged 65 years or more; $P=0.053$). Costs were not significantly associated with sex, cancer stage, smoking status, being monitored for Barrett's oesophagus, co-morbidity or household income (*Table S3*, supporting information).

+C: Surgical group

For individuals who underwent surgery, higher costs were incurred for patients with stage III disease (€40 935 *versus* €32 660 in those with stage I disease; $P=0.002$). Costs for stages II and IV were not significantly different from those for stage I. Similar to costs for non-surgical cases, costs were also higher for those who received chemotherapy (€42 507 *versus* €30 686 with no chemotherapy; $P<0.001$) or radiotherapy (€40 736 *versus* €34 423 with no radiation; $P<0.001$). Costs were significantly lower for those who had endoscopic surveillance for Barrett's oesophagus (€27 667 *versus* €38 209 with no surveillance; $P<0.001$), and for those living in remote *versus* metropolitan locations (€28 907 *versus* €37 650 respectively; $P=0.001$) (*Table S4*, supporting information).

In both surgical and non-surgical subgroups, mixed results were found for costs by rurality, with no significant differences found between participants living in inner or outer regional areas compared with metropolitan locations. As numbers were very small in the remote and very remote categories, cost figures were unstable, as indicated by the 95 per cent c.i. (*Tables S3 and S4*, supporting information).

+B: Multivariable analyses

In multivariable regression analyses, extended survival (in months) was significantly associated with having an oesophagectomy, as well as endoscopic surveillance of Barrett's oesophagus, whereas shorter survival was associated with more advanced tumour stage and tumour location at the gastro-oesophageal junction (*Table S5*, supporting information). Where costs for individuals were fully observed (uncensored), mean costs were significantly higher for surgical intervention (€41 244), gastro-oesophageal junction tumour location (€37 398), chemotherapy (€31 095) and treatment delivered in Victoria (€37 821). When costs were censored, mean costs were significantly higher for surgical intervention (€32 143), chemotherapy (€32 942) and stage

III tumours (€47 680), and lower for those undergoing endoscopic surveillance for Barrett's oesophagus (€24 553) ($P=0.082$). Considering these two cost regression models together, after taking into account the high cost of surgical intervention, chemotherapy, tumour location and treatment location remained strong influences on medical costs in this cohort. The three-part regression model performed well according to standard statistical checks (*Table S5*, supporting information).

+A: Discussion

A comprehensive overview has been provided of the major practice patterns, interactions between the natural history and management of oesophageal cancer, and associated healthcare resources employed in a large patient cohort from multiple settings. Overall, the majority of patients with oesophageal cancer presented with stage II, III or IV disease, and 61.1 per cent (672 of 1100) of patients had surgical treatment. The main determinants of costs were the resources involved in the surgical episode for surgically treated patients, and chemotherapy for patients not undergoing surgery. Other important determinants of high costs were gastro-oesophageal junction tumours, treatment location, tumour stage and radiotherapy. Costs were substantially lower for the 7.3 per cent of patients who had endoscopic surveillance for Barrett's oesophagus.

Analysis of the ACS CFU data provides a better understanding of the current patterns of care and their interaction with natural history over the course of oesophageal cancer. In doing so, this study has provided a foundation for modelling comparative outcomes, resource use and cost-effectiveness of alternative technologies, management pathways and strategies relative to current practice⁷⁻⁹. For example, any treatments that can substitute for oesophagectomy with equal efficacy in the treatment of oesophageal cancer, or eliminate adverse events and reduce length of hospital stay, are likely to reduce initial resource outlays significantly. Conversely, with late-stage care, new chemotherapeutic agents are unlikely to be cost-effective unless they are inexpensive and have substantial health gains, especially as the main chemotherapeutic agents used for the treatment of oesophageal cancer, 5-fluorouracil and cisplatin, are relatively inexpensive. Patients with stage I disease had significantly lower costs compared with patients presenting with more advanced disease, suggesting that detection strategies that allow earlier treatment of oesophageal cancer might extend survival prospects and reduce overall treatment

costs. It is important to note that the treatment costs were estimated with the full range of presentations of patients with oesophageal cancer. Although this study found that patients in surveillance programmes presented with earlier stage tumours and incurred fewer treatment costs, this does not lead to the conclusion that surveillance is a cost-effective strategy. To make such a claim, it would be necessary to assess the total costs of surveillance, including the costs of following up all of the people who did not develop cancer. The main value of the present study is its detailed assessment of a wide range of resources employed throughout the disease course; by this means it has provided an accurate view of healthcare costs and the main cost determinants for oesophageal cancer.

Several other studies have examined resource utilization and costs among individuals with oesophageal cancer^{4,29,30}. In a 2001 cross-sectional study from the USA by Soni and Sonnenberg⁴, analysis was undertaken on resource utilization and costs for 29 patients with oesophageal adenocarcinoma from a single centre. The present study verifies these findings by also showing that very high costs were incurred overall but with wide variation. A Taiwanese study by Hsieh and Chien²⁹ in 2009 assessed costs by disease stage over a long time interval and concluded that surgery and stage were the most influential factors in predicting high costs. In 2009, Polinder *et al.*³⁰ studied the costs of nursing follow-up care over 12 months and concluded that nurse-led care achieved cost savings compared with standard follow-up, although the differences in this study were not statistically significant. The present data are likely to be more robust, for several reasons. First, a much larger patient cohort was incorporated and this enabled three cancer subtypes to be evaluated with sufficient power for multivariable regression analysis. Second, a wide range of resources throughout the disease course was covered. Third, methods addressing right-skewed and right-censored data were used.

The present study has some limitations in coverage of all potential treatments and resource use. Treatments and resources used for side-effects from chemotherapy or radiation treatment were not collected, and neither were data on family practitioner visits, proton pump inhibitor medications or costs relating to end-of-life healthcare where they were incurred outside hospital. These additional costs are likely to be orders of magnitude lower than those for surgery, radiotherapy and chemotherapy, although the present study did not address this. A recent Australian study estimated the costs of ovarian cancer treatment in a cohort of 85 women over 2.5 years and found additional mean costs of \$23 040 (AUD 2008) per patient treated for

complications while receiving chemotherapy³¹. Overall, with the exception of stage data, the proportion of missing data was negligible. Tumour stage was not recorded in the case notes for nearly half of the patients; however, American Joint Committee on Cancer stage was imputed using regression methods to minimize the potential bias of this on study findings. Some data gaps are inevitable because the study depended on the quality of clinical records for each participant. However, every effort was made to reduce these errors with case-form auditing and training of research nurses before and during the study. None of the participants with early-stage cancers had endoscopic mucosal resection, a relatively new procedure that is a less invasive alternative to oesophagectomy. Endoscopic treatment of early-stage intramucosal disease was not allowed. If endoscopic treatments were to become routine for the very early stage of these cancers, total costs would be expected to be lower in these populations if the duration of hospital stay were shortened and/or fewer postoperative complications arose. However, this assumption is currently untested.

The profile of study participants matched closely that of other Western populations with oesophageal cancer – predominantly male Caucasians aged in their mid-sixties¹. However, in generalizing results to the total patient population, it should be noted that recruitment was largely via notifications from upper gastrointestinal surgeons and gastroenterologists, and patients aged over 80 years were excluded. Patients over 80 years of age are usually managed by non-surgical treatment, and some patients referred directly to medical oncologists and radiotherapists for palliative treatment may have been missed. Hence, the proportion of patients who were relatively well and had earlier stage cancers was probably higher than in the overall population. Nevertheless, the present assessment of specific costs of surgical *versus* non-surgical treatment is still likely to be valid and representative of these treatment pathways. In addition, resource use has been presented separately before applying unit prices, allowing costs to be estimated in other jurisdictions that apply their own pricing schedules. The evidence of relative treatment cost from Australia should translate well to the UK and mainland Europe, given similar publicly funded universal healthcare systems, populations and relative prices (for example, the cost of endoscopy will be significantly higher than that of chest X-ray in both settings), and the use of purchasing power parities in exchange rate conversion. Ultimately, the data and analysis presented will be most useful in economic modelling studies of new technologies for managing oesophageal cancer where detailed cost and resource estimates are required.

Contributors

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Baseline sociodemographic and disease characteristics of surgical and non-surgical patients (Word document)

Table S2 Resource unit costs (€2009) and sources (Word document)

Table S3 Bootstrapped mean total costs (€2009) by subgroups for 426 patients managed without surgery (Word document)

Table S4 Bootstrapped mean total costs (€2009) by subgroups for 672 patients managed by surgery (Word document)

Table S5 Results of three-part multivariable regression analysis (Word document)

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Table S1 Baseline sociodemographic and disease characteristics of surgical and non-surgical patients

	Non-surgical patients (n=426)	Surgical patients (n=672)
Mean(s.d.) age (years)	65.0 (9.6)	62.9 (9.5)
Age category (years)†		
≥ 65	237 (55.6)	313 (46.6)
< 65	189 (44.4)	359 (53.4)
Sex		
F	93 (21.8)	130 (19.3)
M	333 (78.2)	541 (80.5)
missing		1 (0.1)
Educational level		
School	199 (46.7)	299 (44.5)
Trade/certificate/diploma	163 (38.3)	302 (44.9)
Bachelor degree	39 (9.2)	52 (7.7)
Missing	25 (5.9)	19 (2.8)
Marital status†		
Never married	28 (6.6)	20 (3.0)
Married/living together	284 (66.7)	523 (77.8)
Separated/divorced/widowed	82 (19.2)	106 (15.8)
Missing	32 (7.5)	23 (3.4)
Rurality		
Major city	255 (59.9)	399 (59.4)
Inner regional	94 (22.1)	167 (24.9)
Outer regional	48 (11.3)	71 (10.6)
Remote or very remote	13 (3.1)	10 (1.5)
Missing	16 (3.8)	25 (3.7)
State		
New South Wales	102 (23.9)	199 (29.6)
Queensland	136 (31.9)	218 (32.4)
South Australia	49 (11.5)	80 (12.0)
Victoria	86 (20.2)	121 (18.0)
Western Australia	52 (12.2)	54 (8.0)
Missing	1 (0.2)	
Ethnicity		
Caucasian	387 (90.8)	640 (95.2)
Other	13 (3.1)	13 (1.9)
Missing	26 (6.1)	19 (2.8)
Employment status (1 year earlier)		
Full-time	110 (25.8)	209 (31.1)
Part-time	29 (6.8)	58 (8.6)
Disability pension	16 (3.8)	18 (2.7)
Not working	230 (56.3)	350 (51.8)
Unemployed	7 (1.6)	7 (1.0)
Missing	34 (8.0)	30 (4.5)
Gross annual household income (AUD)		
Not stated	39 (9.2)	68 (10.1)
< 45 000	243 (57.0)	384 (57.1)
45 000–79 000	71 (16.7)	138 (20.5)
≥ 80 000	48 (11.3)	63 (9.4)
Missing	25 (5.9)	19 (2.8)
Smoking status†		
Current smoker	116 (27.2)	153 (22.8)
Ex-smoker	199 (46.7)	319 (47.5)
Never smoked	83 (19.5)	178 (26.5)
Missing	28 (6.6)	22 (3.3)

Co-morbid conditions*		
None	50 (11.7)	52 (7.7)
1	135 (31.7)	187 (27.8)
≥ 2	241 (56.6)	433 (64.4)
Cancer type†		
Squamous cell cancer of oesophagus	180 (42.3)	125 (18.6)
Gastro-oesophageal junction adenocarcinoma	72 (16.9)	353 (52.5)
Oesophageal adenocarcinoma	173 (40.6)	194 (28.9)
Missing	1 (0.2)	0 (0)
AJCC stage†		
I	11 (2.6)	54 (8.0)
II	44 (10.3)	152 (22.6)
III	39 (9.2)	123 (18.3)
IV	115 (27.0)	26 (3.9)
Unknown	217 (50.9)	317 (47.2)
Monitored for Barrett's oesophagus†		
No	405 (95.1)	597 (88.8)
Yes	15 (3.5)	64 (9.5)
Missing	6 (1.4)	11 (1.6)

Values in parentheses are percentages. AUD, Australian dollars; AJCC, American Joint Committee on Cancer. *Co-morbid conditions included diabetes mellitus type I or II, Barrett's oesophagus, oesophagitis, gastritis, pancreatitis, ulcer, hernia, irritable bowel syndrome, diverticulitis, gallstones, bulimia, and breast, ovarian, stomach and colonic cancer. † $P < 0.050$ (non-surgical *versus* surgical patients, Wald test).

Table S2 Resource unit costs (€2009) and sources

	Unit	Unit cost (€)	Source
Endoscopic therapy			
Argon plasma coagulation	Per procedure	204	Shenfine 2009
Photodynamic therapy		113	RBWH
Endoscopic laser therapy		204	Shenfine 2009
Endoscopic stent placement		2761	Flinders Medical Centre
Surgery			
Median length of stay 15.5 days	Sample mean(s.d.) of mean per episode	1318(877)	Based on RBWH sample with AR-DRGs G03A, G42A, G60A
Median (range) \$2429 (649–8203)			
Chemotherapy agents (5 most common)			
5-Fluorouracil	Per mg	0.0060	Chemotherapy Pharmaceuticals Access Program
Cisplatin		0.3160	
Epirubicin hydrochloride		2.4985	
Carboplatin		0.1419	
Chemotherapy delivery/administration	Per day	433	RBWH
Radiotherapy	Per day	125	Flinders Medical Centre
Investigations			
Endoscopy (60 min)	Per procedure	485	RBWH
Endoscopic ultrasonography		562	RBWH
Computed tomography		276	RBWH
Abdominal X-ray		36	RBWH
Barium meal		64	RBWH
Blood test		9	RBWH
Whole-body bone scan/PET		482	RBWH
Bronchoscopy (60 min)		182	RBWH
Chest X-ray		38	RBWH
Electrocardiography		13	RBWH
Fine-needle aspiration		362	RBWH
Laparoscopy		203	MBS 30391 + 20706
Magnetic resonance imaging		232	MBS 63204
Other X-ray		36	RBWH
Biopsy		337	RBWH
Ultrasonography		68	RBWH
Other concurrent investigations			
Electrocardiography		59	MBS 11000
Intravenous pyelography		443	RBWH
ERCP		79	RBWH

Angiography	365	RBWH
Colonoscopy (60 min)	464	RBWH
Echocardiography	167	RBWH
<hr/>		
Other procedures		
Pleurodesis	459	MBS 38424
Drainage tap of collection	362	RBWH
<hr/>		

RBWH, Royal Brisbane and Women's Hospital; AR-DRG, Australian refined diagnosis-related group; PET, positron emission tomography; MBS, Medicare Benefits Schedule; ERCP, endoscopic retrograde cholangiopancreatography.

Shenfine J, McNamee P, Steen N, Bond J, Griffin SM. A randomized controlled clinical trial of palliative therapies for patients with inoperable esophageal cancer. *Am J Gastroenterol*. 2009 Jul;104(7):1674-85.

Table S3 Bootstrapped mean total costs (€2009) by subgroups for 426 patients managed without surgery

	Mean total cost (€)	Wald statistic	<i>P</i> *
AJCC stage			
I	16 102 (10 662, 21 542)	Reference	
II	17 885 (15 175, 20 596)	0.33	0.566
III	15 349 (13 203, 17 494)	0.06	0.803
IV	18 820 (15 604, 22 037)	0.70	0.404
Monitored for Barrett's oesophagus			
No	17 344 (15 785, 18 903)	Reference	
Yes	14 691 (8812, 20 569)	0.73	0.394
Cancer subtype			
Oesophageal adenocarcinoma	16 169 (13 833, 18 506)	Reference	
Gastro-oesophageal junction adenocarcinoma	24 762 (18 953, 30 571)	7.24	0.007
Squamous cell carcinoma	15 398 (13 842, 16 954)	0.28	0.594
Radiotherapy			
No	13 657 (10 098, 17 216)	Reference	
Yes	18 107 (16 406, 19 807)	5.07	0.024
Chemotherapy			
No	4626 (4037, 5215)	Reference	
Yes	20 030 (18 257, 21 803)	258.06	< 0.001
State			
New South Wales	15 627 (12 648, 18 606)	Reference	
Queensland	15 684 (13 506, 17 862)	0.00	0.976
South Australia	13 749 (11 284, 16 214)	0.93	0.335
Victoria	22 409 (17 540, 27 278)	5.16	0.023
Western Australia	19 691 (15 862, 23 521)	2.73	0.098
Sex			
F	15 929 (13 197, 18 659)	Reference	
M	18 012 (16 046, 19 978)	1.44	0.231
Age category (years)			
≥ 65	15 922 (13 819, 18 025)	Reference	
< 65	18 986 (16 654, 21 318)	3.76	0.053
Smoking status			
Current smoker	16 348 (13 790, 18 905)	Reference	
Ex-smoker	18 127 (15 567, 20 686)	0.95	0.330
Non-smoker	17 342 (13 744, 20 940)	0.12	0.730
Household income (AUD)			
Not stated	19 587 (14 261, 24 913)		
< 45 000	16 677 (14 570, 18 783)	Reference	
45 000–79 000	18 340 (14 770, 21 909)	0.62	0.430
≥ 80 000	19 320 (14 088, 24 552)	0.89	0.346
No. of co-morbidities			

0	16 214 (12 409, 20 020)	Reference	
1	16 882 (14 349, 19 416)	0.08	0.779
≥ 2	17 726 (15 519, 19 934)	0.45	0.502
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Rurality			
Major city	17 065 (15 162, 18 979)	Reference	
Inner regional	19 608 (15 539, 23 677)	1.21	0.272
Outer regional	13 616 (10 575, 16 658)	3.52	0.061
Remote	15 263 (10 902, 19 624)	0.57	0.451
Very remote	28 748 (18 346, 39 149)	4.68	0.031

Values in parentheses are 95 per cent confidence intervals. AJCC, American Joint Committee on Cancer; AUD, Australian dollars. Wald test.

Table S4 Bootstrapped mean total costs (€2009) by subgroups for 672 patients managed by surgery

	Mean total cost (€)	Wald statistic	<i>P</i> *
AJCC stage			
I	32 660 (28 518, 36 802)	Reference	
II	35 621 (33 141, 38 103)	1.41	0.234
III	40 935 (37 693, 44 177)	9.79	0.002
IV	37 537 (32 755, 42 319)	2.29	0.130
Monitored for Barrett's oesophagus			
No	38 209 (36 322, 40 096)	Reference	
Yes	27 667 (24 133, 31 201)	24.92	< 0.001
Cancer subtype			
Oesophageal adenocarcinoma	36 695 (33 803, 39 589)	Reference	
Gastro-oesophageal junction adenocarcinoma	38 039 (35 475, 40 604)	0.50	0.450
Squamous cell carcinoma	35 582 (32 016, 39 149)	0.22	0.637
Radiotherapy			
No	34 423 (32 084, 36 762)	Reference	
Yes	40 736 (38 137, 43 335)	12.87	< 0.001
Chemotherapy			
No	30 686 (28 226, 33 146)	Reference	
Yes	42 507 (40 228, 44 786)	47.81	< 0.001
State			
New South Wales	35 321 (32 446, 38 198)	Reference	
Queensland	32 582 (30 214, 34 951)	2.19	0.139
South Australia	39 969 (34 348, 45 590)	2.12	0.146
Victoria	45 328 (40 251, 50 405)	11.81	< 0.001
Western Australia	40 377 (33 826, 46 928)	1.94	0.164
Sex			
F	36 872 (32 898, 40 846)	Reference	
M	37 029 (35 045, 39 012)	0.00	0.945
Age category (years)			
≥ 65	36 183 (33 701, 38 667)	Reference	
< 65	38 076 (35 748, 40 404)	1.18	0.277
Smoking status			
Current smoker	38 117 (34 723, 41 510)	Reference	
Ex-smoker	37 245 (34 766, 39 724)	0.17	0.680
Non-smoker	35 777 (32 296, 39 258)	0.87	0.352
Household income (AUD)			
Not stated	33 429 (29 634, 37 223)		
< 45 000	37 353 (35 050, 39 655)	Reference	
45 000–79 000	36 403 (31 971, 40 835)	0.14	0.707
≥ 80 000	39 992 (35 063, 44 920)	0.91	0.340
No. of co-morbidities			

0	38 817 (33 665, 43 968)	Reference	
1	39 307 (36 038, 42 576)	0.03	0.870
≥ 2	36 087 (33 971, 38 203)	0.91	0.340
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Rurality			
Major city	37 650 (35 467, 39 832)	Reference	
Inner regional	36 380 (33 031, 39 728)	0.40	0.527
Outer regional	36 348 (30 014, 42 682)	0.15	0.701
Remote	28 907 (24 461, 33 352)	12.58	0.001
Very remote	54 007 (22 984, 85 030)	1.06	0.304

Values in parentheses are 95 per cent confidence intervals. AJCC, American Joint Committee on Cancer; AUD, Australian dollars. Wald test.

Table S5 Results of three-part multivariable regression analysis

	Coefficient for survival (<i>n</i> = 1037) (gamma regression accelerated failure-time)	Coefficient for uncensored costs (<i>n</i> = 685) (gamma GLM square-root link)	Coefficient for censored costs (<i>n</i> = 352) (extended estimating equation)
Oesophagectomy	0.73 (0.6, 0.9)	121.9 (109.2, 134.6)	0.57 (0.4, 0.7)
AJCC stage II	−0.16 (−0.4, 0.1)	8.5 (−9.8, 26.8)	0.07 (−0.0, 0.2)
AJCC stage III	−0.38 (−0.6, −0.2)	1.5 (−16.4, 19.4)	0.07 (−0.0, 0.2)
AJCC stage IV	−0.71 (−1.0, −0.5)	5.5 (−13.7, 24.7)	0.08 (−0.1, 0.2)
Gastro-oesophageal junction adenocarcinoma	−0.23 (−0.4, −0.1)	29.6 (13.8, 45.4)	0.01 (−0.0, 0.1)
Age at diagnosis	0.00 (0.0, 0.0)	0.05 (−0.64, 0.73)	0.00 (0.0, 0.0)
Any chemotherapy	0.04 (−0.1, 0.2)	72.9 (60.8, 85.0)	0.37 (0.2, 0.5)
Any radiotherapy	−0.09 (−0.3, 0.1)	11.8 (−1.4, 25.0)	−0.08 (−0.2, 0.0)
Monitored for Barrett's oesophagus	1.19 (0.9, 1.5)	12.4 (−17.3, 42.0)	−0.06 (−0.1, 0.0)
Co-morbidity ≥ 2	0.10 (0.0, 0.2)	6.9 (−3.5, 17.3)	−0.03 (−0.1, 0.0)
Employed	0.08 (−0.1, 0.3)	7.8 (−6.5, 22.1)	0.01 (−0.1, 0.1)
State – Queensland	0.02 (−0.2, 0.2)	−1.4 (−13.7, 11.0)	−0.03 (−0.1, 0.0)
State – South Australia	0.02 (−0.2, 0.3)	−5.5 (−24.2, 13.3)	−0.07 (−0.2, 0.1)
State – Victoria	0.17 (−0.0, 0.4)	28.5 (6.7, 50.2)	0.03 (−0.1, 0.1)
State – Western Australia	0.04 (−0.2, 0.3)	3.7 (−14.3, 21.8)	0.02 (0.0, 0.1)

Values in parentheses are 95 per cent confidence intervals. Uncensored refers to data that have been captured for the full duration until the individual's death, whereas censored data are those cut short administratively because the end of the study collection period (31 January 2008) was reached and therefore involve unknown cost data. GLM, generalized linear model; AJCC, American Joint Committee on Cancer. Overall, the regression model for total uncensored costs performed well with a low Akaike Information Criterion (23.7), link test ($P < 0.001$), Pearson's test ($P = 0.559$) and Copas test (coefficient 0.84, $P = 0.096$), indicating no overfitting. Performing just as well, the corresponding results for the censored cost model were Pearson's test ($P = 0.288$), Copas test (coefficient 0.74, $P = 0.093$), and there were no systematic patterns in residuals across the deciles of linear predictors.

Table 1 Resources used in the diagnosis and management of patients treated surgically for oesophageal cancer by American Joint Committee on Cancer stage*

	Stage I (n=99)		Stage II (n=285)		Stage III (n=235)		Stage IV (n=53)		Total (n=672)	
	n	% patients	n	% patients	n	% patients	n	% patients	n	% patients
Diagnostic investigations										
Endoscopies†	99	100	285	100	235	100	53	100	672	100
CT	93	94	267	93.7	214	91.1	49	92	623	92.7
Endoscopic ultrasonography	28	28	57	20.0	68	28.9	8	15	161	24.0
PET	39	39	126	44.2	109	46.4	25	47	299	44.5
Bronchoscopy	4	4	6	2.1	6	2.6	1	2	17	2.5
Laparoscopy	18	18	57	20.0	59	25.1	14	26	148	22.0
Other test/procedure‡	43	43	138	48.4	98	41.7	29	55	308	45.8
Total	324		936		789		179		2228	
Chemotherapy§										
Fluorouracil	856	36	4582	41.1	4454	40.0	1071	41	10 963	54.0
Cisplatin	166	35	914	35.1	597	31.9	242	32	1919	44.9
Epirubicin hydrochloride	61	8	417	9.1	266	8.9	185	8	929	11.0
Carboplatin	15	2	145	1.1	70	1.3	27	2	257	1.9
Other	133	15	176	8.0	436	14.0	47	17	792	23.1
Total	1231	38	6234	54.0	5823	60.0	1572	70	14 860	54.6
Radiotherapy¶	145	32	503	35.1	663	51.9	175	75	1486	43.9
Initial investigations after adjuvant therapy	51	21	188	31.9	218	36.2	41	30	498	32.0
Surgical inpatient days	1791	15#	5139	15#	4724	15#	934	15#	12 588	15#
Postsurgical investigations	367	87	929	80.0	815	82.1	133	87	2244	82.0
Subsequent investigations	94	21	278	26.0	289	28.9	70	38	731	27.0

Endoscopic therapy										
Argon plasma coagulation	1	1	5	1.8	3	1.3	1	2	10	1.5
Photodynamic therapy	2	2	3	1.1	0	0	0	0	5	0.7
Endoscopic stent placement	7	7	20	7.0	14	6.0	3	6	44	6.5
Endoscopic laser therapy	0	0	0	0	7	3.0	2	4	9	1.3
Total	10	10	28	9.8	24	10.2	6	11	68	10.1

*Cancer stage was imputed using regression methods for half the sample where data were missing. †Endoscopy was a condition of entry into the study. ‡Includes additional positron emission tomography (PET) or computed tomography (CT) in the diagnostic phase. §Values denote the number of administrations for the four most commonly employed agents; some patients received more than one agent. ¶Values denote number of weeks of radiotherapy. #Median number of inpatient days.

Table 2 Resources used in the diagnosis and management of patients not treated surgically for oesophageal cancer by cancer stage*

	Stage I (n=46)		Stage II (n=133)		Stage III (n=117)		Stage IV (n=130)		Total (n=426)	
	n	% patients	n	% patients	n	% patients	n	% patients	n	% patients
Diagnostic investigations										
Endoscopy†	46	100	133	100	117	100	130	100	426	100
CT	42	91	124	93.2	112	95.7	129	99.2	407	95.5
Endoscopic ultrasonography	3	7	21	15.8	23	19.7	18	13.8	65	15.3
PET	17	37	47	35.3	51	43.6	86	66.2	201	47.2
Bronchoscopy	1	2	6	4.5	4	3.4	7	5.4	18	4.2
Laparoscopy	4	9	21	15.8	17	14.5	21	16.2	63	14.8
Other test/procedure‡	32	70	81	60.9	81	69.2	77	59.2	271	63.6
Total	145		433		405		468		1451	
Chemotherapy§										
Fluorouracil	924	43	2930	45.9	1898	43.6	3019	40.0	8771	79.1
Cisplatin	100	37	411	33.1	349	36.8	333	27.7	1193	60.1
Epirubicin hydrochloride	32	5	53	3.0	38	4.3	147	7.7	270	10.1
Carboplatin	112	1	126	0.8	84	0.0	470	2.3	792	2.1
Other	71	11	201	14.3	238	12.8	416	19.2	926	33.1
Total	1239	72	3721	82.7	2607	84.6	4385	82.3	11952	81.9
Radiotherapy¶	214	80	679	85.0	564	82.9	481	76.9	1938	80.9
Initial investigations after adjuvant therapy	213	85	617	91.7	565	88.9	391	82.3	1782	87.1
Subsequent investigations	48	24	117	23.3	111	29.1	188	30.8	464	27.0
Endoscopic therapy										
Argon plasma coagulation	0	0	4	3.0	2	1.7	3	2.3	9	2.1
Photodynamic therapy	1	2	0	0	2	1.7	0	0	3	0.7
Endoscopic stent placement	12	26	30	22.6	41	35.0	30	23.1	125#	29.3

Endoscopic laser therapy	1	2	3	2.3	5	4.3	6	4.6	15	3.3
Total	14	30	37	27.8	50	42.7	39	30.0	140	32.9

*Cancer stage was imputed using regression methods for half the sample where data were missing. †Endoscopy was a condition of entry into the study. ‡Includes additional positron emission tomography (PET) or computed tomography (CT) in the diagnostic phase. §Values denote the number of administrations for the four most commonly employed agents; some patients received more than one agent. ¶Values denote number of weeks of radiotherapy. #Some patients had more than one stent placement.

Table 3 Frequency of adverse events after oesophagectomy (*n*=665)

	<i>n</i>	% patients
Pneumonia	121	18.2
Arrhythmia	72	10.8
Anastomotic leak	67	10.1
Wound infection	55	8.3
Respiratory failure	29	4.4
Chyle leak	27	4.1
Septic shock	23	3.5
DVT/PE	22	3.3
Bleeding	16	2.4
Renal failure	7	1.1
Postop. multiorgan failure	2	0.3
Other	163	24.5
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Total	355*	53.4

*No. of patients with at least one adverse event. Seven surgical patients had missing data for adverse events. DVT/PE, deep vein thrombosis/pulmonary embolism.

Table 4 Unadjusted costs by resource categories by non-surgical and surgical cases*

	Non-surgical patients (n=426)		Surgical patients (n=672)	
	No. affected	Cost (€)†	No. affected	Cost (€)†
Peridiagnostic investigations	426	507 153 (6.9)	672	825 800 (3.3)
Endoscopic therapy (any)	141	350 341 (4.8)	62	125 918 (0.5)
Chemotherapy				
Drugs (all)	350	298 581 (4.1)	370	384 951 (1.5)
Clinical cost/admin	350	4 198 184 (57.0)	370	4 804 299 (19.2)
Radiotherapy	347	1 164 709 (15.8)	295	884 982 (3.5)
Investigations (initial)	371	593 345 (8.1)	213	168 400 (0.7)
Surgery	0	0 (0)	672	16 596 620 (66.4)
Postop. investigations	0	0 (0)	553	755 339 (3.0)
Investigations (subsequent)	116	156 618 (2.1)	185	225 754 (0.9)
Doctor consultations	426	92 956 (1.3)	672	222 532 (0.9)
<hr/>				
Total cost (€)		7 361 887 (100)		24 994 595 (100)
Mean(s.d.)		17 281(16 299)		37 195(22 763)
Median		13 066		29 114
95th percentile		49 850		83 324

Values in parentheses are percentages of the total cost. *Two patients with no data on surgical intervention were excluded. †Currency conversion used was 2009 Australian dollars (AUD): 1 AUD = €0.519 (Organisation for Economic Co-operation and Development purchasing power parity).