Symptoms, investigations and management of patients with cancer of the oesophagus and gastro-oesophageal junction in Australia

Bernard M Smithers, Paul P Fahey, Tracie Corish, David C Gotley, Gregory L Falk, Garett S Smith, George K Kiroff, Andrew D Clouston, David I Watson and David C Whiteman

ABSTRACT

Objective: To document presenting symptoms, investigations and management for Australian patients with oesophageal adenocarcinoma (OAC), gastro-oesophageal junction adenocarcinoma (GOJAC) and oesophageal squamous cell carcinoma (OSCC).


Main outcome measures: Prevalence of primary symptoms, and staging investigations and treatment modalities used.

Results: The primary presenting symptom was dysphagia, which was self-reported by 41%, 39% and 48% of patients with OAC, GOJAC and OSCC, respectively. Less common symptoms were reflux, chest pain, bleeding and weight loss. All patients underwent endoscopy, most had a staging computed tomography scan (OAC 93%, GOJAC 95% and OSCC 93%), and about half had positron emission tomography scans (OAC 51%, GOJAC 44% and OSCC 42%). Pretreatment tumour stage was reported in 25% of records, and could be derived from results of investigations in a further 23%, but the remaining half lacked sufficient information to ascribe a pretreatment stage. Curative treatments were attempted for 60% of OAC, 88% of GOJAC and 65% of OSCC patients. Surgery was performed on 52% of OAC, 83% of GOJAC and 41% of OSCC patients. About two-thirds of surgical patients received additional therapies.

Conclusions: With anticipated increases in oesophageal cancer incidence, the resources required to diagnose and manage patients with oesophageal cancer are also likely to rise. Our data provide a baseline from which to plan for the future care of patients with cancers of the oesophagus.

METHODS

Our study was based on a cohort of patients previously enrolled in the Australian Cancer Study (ACS), a population-based, case–control study undertaken to investigate risk factors for oesophageal cancer. For our study (the ACS Clinical Follow-up Study), we collected clinical information and outcome data on ACS patients. We collected data on the presenting symptoms of patients, investigations and treatment pathways.

Patients

For the ACS, all patients aged 18–79 years with a histologically confirmed primary invasive cancer of the oesophagus or gastro-oesophageal junction diagnosed between 1 July 2002 (1 July 2001 in Queensland) and 30 June 2005 in mainland Australia were identified. Full details of recruitment of patients into the ACS have been described elsewhere. Briefly, patients were ascertained principally via systematic review of admissions and clinic registers at major treatment centres throughout Australia; additional cases were identified by cancer registries (cancer notification is mandatory in all states). Histological details were abstracted from pathology reports. Anatomical sites of adenocarcinoma tumours were categorised according to the World Health Organization classification into “oesophageal” and “oesophago-gastric junction” tumours. For analysis, we compared patients with OAC, GOJAC and OSCC.

Our study was approved by the Human Research Ethics Committee of the Queensland Institute of Medical Research and the ethics committees of participating hospitals. All participants gave their informed consent to take part.
Data collection
Two sources of data were used: prediagnostic symptom information self-reported by patients at the time of their recruitment into the ACS, and clinical and treatment information obtained from each patient’s medical records.

Thus, patients self-completed a questionnaire on recruitment into the ACS (2002–2005), followed shortly after by a standardised interview to elicit details of symptom history, presentation, and pathway to diagnosis. Case-control analyses to identify risk factors for oesophageal cancer have been reported separately.3–7

Clinical data were abstracted from each patient’s medical records by trained nurses in 2006–2007 and entered on standardised case report forms. Medical records included hospital files and reports from private practitioners and pathology, radiology, and other imaging services. Information was collected on presenting symptoms, diagnostic and staging investigations, clinical stage of disease, and management. For the latter, details were recorded regarding chemotherapy, radiotherapy, other endoscopic treatments and surgery that the patient received. Outcome information was also collected, including details of dates of admission, discharge (or death) for each episode of treatment, date of last recorded outpatient attendance, and disease status.

Case report forms were returned to the Queensland Institute of Medical Research for data coding and checking. Summary variables were derived from primary variables for analysis. We used the American Joint Committee on Cancer (AJCC) tumour stage classification for oesophageal cancer, when reported. For cases with missing stage data, we attempted to impute the stage using available information.

We assigned each participant an index of remoteness and accessibility to services based on their residential postcode using the 2006 Accessibility/Remoteness Index of Australia codes from the Australian Government Department of Health and Ageing (http://www9.health.gov.au/aria/ariainpt.cfm).

Data analysis
We compared age distributions across subtypes using one-way analysis of variance. For categorical variables, we used the $\chi^2$ test. Analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC, USA), statistical significance was assumed at the 5% level, and no adjustments were made for multiple comparisons.

RESULTS
We identified 3273 potentially eligible patients with oesophageal cancer, of whom 1618 were excluded for various reasons and 385 declined to participate (Box 1). Of the remaining 1270, 1140 patients had histologically confirmed oesophageal cancer and gave consent for access to their medical records. Completed case report forms were available for 1100 patients (370 OAC, 425 GOJAC and 305 OSCC) and linked questionnaire data were available for 1056 patients.

Patient demographics are shown in Box 2. Notably, age distributions were similar for the three patient groups, whereas sex distributions were markedly different for OSCC patients compared with OAC and GOJAC patients. Eighty-seven per cent of patients resided in cities and towns, 11% lived in moderately accessible regional locations, and 2% were from remote or very remote locations.

Presenting symptoms
Interview data describing medical presentation and symptom history were available for 831 patients. The primary symptom for which the patient sought medical attention, the prevalence of all symptoms volunteered by the patient, and the prevalence of symptoms as elicited and recorded by the doctor are shown in Box 3. Dysphagia, the most frequent primary symptom, was self-reported by 41%–48% of patients. Gastro-oesophageal acid reflux was self-reported by 7%–9% of patients as the primary reason for presentation but elicited by a doctor in 46% of OAC and 44% of GOJAC patients. As recorded by the doctor, OSCC patients had a higher prevalence of odynophagia than OAC or GOJAC patients, but less reflux. Odynophagia, epigastric pain, chest pain and weight loss were all uncommon reasons for presentation, but were commonly found to be present on direct questioning. Eight per cent and 3% of OAC and GOJAC patients, respectively, were diagnosed through Barrett’s oesophagus surveillance programs, and 2%–4% of OAC, GOJAC and OSCC diagnoses were incidental findings from routine health checks.

Investigations
All patients had undergone upper gastrointestinal endoscopy as an eligibility criterion for our study (Box 4). A computed tomography (CT) scan was performed in 93%–95% of patients, a fluorodeoxyglucose positron emission tomography (FDG-PET) scan in 42%–51% of patients, and endoscopic ultrasound (EUS) in 20%–21% of patients. Laparoscopy was more commonly performed in the GOJAC group than the OAC and OSCC groups.

Pretreatment staging
An AJCC stage was reported in 7% of patient records (range, 5%–10%) (Box 5); converting tumour–node–metastasis (TNM) codes into AJCC tumour stages increased the overall proportion of patients with stage data to 25% (range, 23%–27%). Imputation using the FDG-PET scan result for M status and EUS for T and N status increased the overall proportion of patients with stage data to...
apy (CRT) was used more commonly than and OSCC. Preoperative chemoradiotherapy was performed on similar proportions of patients with OAC, GOJAC, and 65% (197/305) of OSCC (222/370) of OAC, 88% (372/425) of ACS, and a dispersed population, the issue of access is important. Reassuringly, we found the geographical distribution of this cohort was similar to that of the 2001 census.

The most common presenting symptom was dysphagia, which on direct questioning was found to be present in over 70% of patients, a proportion similar to that found in other studies.16,17 Dysphagia occurs when the oesophageal circumference has been reduced by two-thirds,18 which is sufficient to compromise the lumen. The United Kingdom guidelines for managing oesophageal cancer outline a number of “alarm symptoms”, of which dysphagia is the first, and for which referral for endoscopy is recommended within 2 weeks of presentation.19 Our data suggest most patients do not recognise the importance of dysphagia as an alarm symptom. Only 7%–9% of patients reported reflux as their primary symptom, a similar proportion to that reported in a

### DISCUSSION

Our study provides the first comprehensive description of the presentation and management of Australian patients with oesophageal cancer. The cohort is not entirely representative, as enrolment into the study was not fully representative, as enrolment into the study was considered to be too low for patients with GOJAC followed by patients with OSCC and those with OAC.

The most common palliative therapy was CRT. Stents were used for 168 patients (for 98 patients as immediate palliative treatment, and for 70 patients after initial attempts at curative treatment). No patient who had a resection had a stent inserted.

### 3 ACS Clinical Follow-up Study: reasons for presentation self-reported by patient* and recorded by doctor in clinical files

<table>
<thead>
<tr>
<th>Symptom</th>
<th>OAC (n = 291)</th>
<th>GOJAC (n = 317)</th>
<th>OSCC (n = 223)</th>
<th>OAC (n = 291)</th>
<th>GOJAC (n = 317)</th>
<th>OSCC (n = 223)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odynophagia</td>
<td>11 (4%)</td>
<td>16 (5%)</td>
<td>12 (5%)</td>
<td>29 (10%)</td>
<td>31 (10%)</td>
<td>26 (12%)</td>
<td>0.752</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>119 (41%)</td>
<td>125 (39%)</td>
<td>106 (48%)</td>
<td>156 (54%)</td>
<td>169 (53%)</td>
<td>138 (62%)</td>
<td>0.095</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>9 (3%)</td>
<td>6 (2%)</td>
<td>5 (2%)</td>
<td>15 (5%)</td>
<td>12 (4%)</td>
<td>10 (4%)</td>
<td>0.716</td>
</tr>
<tr>
<td>Reflux†</td>
<td>23 (8%)</td>
<td>30 (9%)</td>
<td>16 (7%)</td>
<td>36 (12%)</td>
<td>45 (14%)</td>
<td>28 (13%)</td>
<td>0.768</td>
</tr>
<tr>
<td>Weight loss</td>
<td>3 (1%)</td>
<td>7 (2%)</td>
<td>7 (3%)</td>
<td>17 (6%)</td>
<td>24 (8%)</td>
<td>22 (10%)</td>
<td>0.233</td>
</tr>
<tr>
<td>Bleeding</td>
<td>15 (5%)</td>
<td>9 (3%)</td>
<td>3 (1%)</td>
<td>18 (6%)</td>
<td>14 (4%)</td>
<td>6 (3%)</td>
<td>0.168</td>
</tr>
<tr>
<td>Chest pain</td>
<td>13 (4%)</td>
<td>15 (5%)</td>
<td>8 (4%)</td>
<td>27 (9%)</td>
<td>23 (7%)</td>
<td>15 (7%)</td>
<td>0.505</td>
</tr>
<tr>
<td>Other</td>
<td>64 (22%)</td>
<td>81 (26%)</td>
<td>52 (23%)</td>
<td>85 (29%)</td>
<td>128 (40%)</td>
<td>80 (36%)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

ACS = Australian Cancer Study. GOJAC = gastro-oesophageal junction adenocarcinoma. OAC = oesophageal adenocarcinoma. OSCC = oesophageal squamous cell carcinoma. * Symptoms self-reported by patient at telephone interview. † Number of patients with missing data in each category: odynophagia (26), dysphagia (25), epigastric pain (27), reflux (28) and weight loss (25). ‡ Gastro-oesophageal acid reflux.
4 ACS Clinical Follow-up Study: investigations

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>OAC (n = 370)</th>
<th>GOJAC (n = 425)</th>
<th>OSCC (n = 305)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopy</td>
<td>370 (100%)</td>
<td>425 (100%)</td>
<td>305 (100%)</td>
<td></td>
</tr>
<tr>
<td>CT scan</td>
<td>344 (93%)</td>
<td>402 (95%)</td>
<td>284 (93%)</td>
<td>0.589</td>
</tr>
<tr>
<td>FDG-PET scan</td>
<td>187 (51%)</td>
<td>187 (44%)</td>
<td>127 (42%)</td>
<td>0.050</td>
</tr>
<tr>
<td>EUS</td>
<td>74 (20%)</td>
<td>91 (21%)</td>
<td>61 (20%)</td>
<td>0.853</td>
</tr>
<tr>
<td>Laparoscopy</td>
<td>57 (15%)</td>
<td>123 (29%)</td>
<td>31 (10%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Barium swallow</td>
<td>46 (12%)</td>
<td>50 (12%)</td>
<td>55 (18%)</td>
<td>0.035</td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td>4 (1%)</td>
<td>6 (1%)</td>
<td>24 (8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other investigation</td>
<td>151 (41%)</td>
<td>169 (40%)</td>
<td>130 (43%)</td>
<td>0.740</td>
</tr>
</tbody>
</table>

ACS = Australian Cancer Study. CT = computed tomography. EUS = endoscopic ultrasound. FDG-PET = fluorodeoxyglucose positron emission tomography. GOJAC = gastro-oesophageal junction adenocarcinoma. OAC = oesophageal adenocarcinoma. OSCC = oesophageal squamous cell carcinoma. ◆

5 ACS Clinical Follow-up Study: pretreatment staging

<table>
<thead>
<tr>
<th>Pretreatment AJCC tumour stage</th>
<th>OAC (n = 370)</th>
<th>GOJAC (n = 425)</th>
<th>OSCC (n = 305)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recorded by doctor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total available*</td>
<td>36 (10%)</td>
<td>21 (5%)</td>
<td>19 (6%)</td>
</tr>
<tr>
<td>Imputed from doctor’s record of TNM codes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-stage (T1, T2, T3, T4) recorded by doctor</td>
<td>105 (28%)</td>
<td>129 (30%)</td>
<td>100 (33%)</td>
</tr>
<tr>
<td>N-stage (N0, N1) recorded by doctor</td>
<td>106 (29%)</td>
<td>126 (30%)</td>
<td>102 (33%)</td>
</tr>
<tr>
<td>M-stage (M0, M1) recorded by doctor</td>
<td>83 (22%)</td>
<td>99 (23%)</td>
<td>83 (27%)</td>
</tr>
<tr>
<td>Total available†</td>
<td>99 (27%)</td>
<td>99 (23%)</td>
<td>80 (26%)</td>
</tr>
<tr>
<td>Imputed from doctor’s record of TNM codes and clinical test results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-score from EUS</td>
<td>67 (18%)</td>
<td>84 (20%)</td>
<td>54 (18%)</td>
</tr>
<tr>
<td>N-score from EUS</td>
<td>68 (18%)</td>
<td>81 (19%)</td>
<td>53 (17%)</td>
</tr>
<tr>
<td>M-score from FDG-PET scan</td>
<td>178 (48%)</td>
<td>177 (42%)</td>
<td>123 (40%)</td>
</tr>
<tr>
<td>Total available‡</td>
<td>186 (50%)</td>
<td>208 (49%)</td>
<td>142 (47%)</td>
</tr>
<tr>
<td>Stage</td>
<td>(n = 186)</td>
<td>(n = 208)</td>
<td>(n = 142)</td>
</tr>
<tr>
<td>I</td>
<td>20 (11%)</td>
<td>26 (13%)</td>
<td>15 (11%)</td>
</tr>
<tr>
<td>II</td>
<td>53 (28%)</td>
<td>79 (38%)</td>
<td>51 (35%)</td>
</tr>
<tr>
<td>III</td>
<td>43 (23%)</td>
<td>74 (36%)</td>
<td>43 (30%)</td>
</tr>
<tr>
<td>IV</td>
<td>70 (38%)</td>
<td>29 (14%)</td>
<td>33 (23%)</td>
</tr>
<tr>
<td>Total</td>
<td>186 (100%)</td>
<td>208 (100%)</td>
<td>142 (100%)</td>
</tr>
</tbody>
</table>

ACS = Australian Cancer Study. AJCC = American Joint Committee on Cancer. EUS = endoscopic ultrasound. FDG-PET = fluorodeoxyglucose positron emission tomography. GOJAC = gastro-oesophageal junction adenocarcinoma. OAC = oesophageal adenocarcinoma. OSCC = oesophageal squamous cell carcinoma. TNM = tumour–node–metastasis. * At least AJCC stage I, II, III or IV. † Doctor’s record of AJCC stage augmented by doctor’s record of TNM code and endoscopic ultrasound and FDG-PET findings where available. ◆

previous study. The underlying precipitant for these patients may have been a change, likely worsening, of previous reflux symptoms or the development of new symptoms.

A key finding was the infrequent recording of AJCC pretreatment tumour stage (7%), and although stage could be imputed for a further 42%, for about half of the patients it was impossible to determine the extent of their cancer. Of the staging investigations employed, CT scans were the most common, being used in more than 90% of patients in our study. The major benefit of CT is the ability to rapidly identify patients with distant metastases. Staging information is improved by also performing an EUS to assess local infiltration and local nodal status. Relatively few Australian centres were performing EUS at the time of our study, hence the low usage of this investigation. Compared with conventional staging modalities, FDG-PET scanning has been shown to detect distant metastases in 42%–51% of the patients. Thus, despite limited availability, both FDG-PET scanning and EUS were performed on sizeable numbers of patients, suggesting rapid uptake for these modalities.

Putting aside the extent of incomplete reporting, our study differs from others in having relatively fewer patients with stage IV cancers. For example, a United States study reported stage IV disease in 48% of OAC patients and 52% of GOJAC patients — considerably higher than the proportions we observed. Reporting of cancer stage is not mandatory in Australia, hence there are no reliable population-based data for comparison. Instead, estimates of the distribution of cancer stage must be derived from chart reviews. As the use of chart reviews requires patient consent, and because consent is less likely among patients with late-stage disease, it is likely that all studies based on chart review will underestimate the incidence of late-stage disease. We identified apparent differences in the surgical management of OAC and GOJAC.

Specifically, our data suggest that patients with GOJAC are more likely to undergo surgery alone than OAC or OSCC patients. A similar finding was reported in an Irish study. Information bias may partly explain these differences, as the location of a tumour can be identified more precisely from surgical resection specimens than from endoscopy. Thus, patients who have undergone surgery are more likely to have the anatomical location of their tumour classed as gastro-oesophageal junction than patients who have not received surgery.

The proportion of surgical patients undergoing neoadjuvant therapy in our study was lower than the proportion in the US study but higher than that found in the Irish study. At the time that the patients in our study were being treated, there had been one international report of benefit from neoadjuvant CRT in patients with OAC, and one account of benefit from preoperatively chemoradiotherapy in both OAC and OSCC patients. An Australian phase II study assessing the role of neoadjuvant CRT and CRT alone for cure and palliation of OAC and OSCC had
It is likely that these publications, along with an active Australian trial of preoperative CRT,26 raised awareness among Australian clinicians who treat such patients. This could explain the high prevalence of neoadjuvant therapy for OAC and OSCC, and may also explain why 10% of patients in our study were also enrolled in trials. While there is no evidence from trials that routine postoperative therapy improves survival, we observed reasonably high proportions of patients undergoing postoperative therapy. The reasons for this were not clear from the records.

We found that use of definitive CRT in our study was markedly higher for patients with OSCC (37%) than for patients with OAC (13%) or GOJAC (5%). In comparison, the Irish study observed proportions of patients undergoing definitive CRT as 12% for OAC, 6% for GOJAC and 12% for OSCC.22 A possible explanation for the difference may be a widespread perception among clinicians that adenocarcinomas are less sensitive to radiation than squamous cell carcinomas. There are limited data to determine the validity of this perception; however, there are more publications reporting benefits for CRT as an alternative to resection for OSCC27,28 than as a treatment for OAC.

From our observation, most patients present with late-stage disease, although precise staging information is infrequently recorded. We encourage efforts to increase the reporting of tumour stage for these cancers, when planning for future health service needs. Finally, given the high proportion of patients with late-stage disease, and the acknowledged poor survival rates for these cancers, we need to continue to explore ways to reduce the disease burden through primary prevention and early detection.

**ACKNOWLEDGEMENTS**

Our study was supported by the Cancer Council Queensland and the National Health and Medical Research Council. David Whiteman is supported by a Future Fellowship from the Australian Research Council. The funding bodies played no role in the design or conduct of the study; the collection, management, analysis or interpretation of the data; or preparation, review or approval of the manuscript. We thank Shahram Sadeghi for assistance with pathology abstractions, and Nimma Pandeya for data cleaning and programming. The study investigators were David Whiteman, Adele Green, David Gottley, B Mark Smithers, David Watson, Gregory Falk, Garett Smith, George Kiroff, Steven Archer, Nicholas Hayward and Andrew Clouston; the project manager was Tracie Corish; the database managers were Karen Harrap and Troy Sadkowski; and the research nurses were Janine Thomas, Ellen Minehan, Deborah Roffe, Sue O’Keefe, Suzanne Lipshut, Gabby Connor, Hayley Berry, Linda Terry, Michael Connard, Leanne Bowes, MaryRose Malt and Jo White. The clinical contributors were: Australian Capital Territory — Charles Mosse and Noel Taft; New South Wales — Chris Bambach, Andrew Biankan, Roy Brancatisano, Max Coleman, Michael Cox, Stephen Deane, James Gallagher, Mike Hollands, Tom Hugh, David Hunt, John Jorgensen, Christopher Martin, Mark Richardson, Ross Smith and David Storey; Queensland — John Avramovic, John Croese, Justin D’Arcy, Stephen Fairley, John Hansen, John MASON, Ian Martin, Les Nathanson, Barry O’Loughlin, Leigh Rutherford, Richard Turner and Morgan Windsor; South Australia — Justin Blessell, Peter Devitt and Glyn Jamieson; Victoria — Stephen Blamey, Alex Boussioutas, Richard Cade, Gary Crosthwaite, Ian Faragher, John Gribbin, Geoff Hebbard, Bruce Mann, Bob Millar, Paul O’Brien, Robert Thomas and Simon Wood; Western Australia — Kingsley Faulkner and Jeff Hamdorf.

**COMPETING INTERESTS**

None identified.
AUTHOR DETAILS

Bernard M Smithers, MB BS, FRACS, FRCS, Associate Professor of Surgery
Paul Pa Fahey, BSc, MMedStat, Biostatistician
Tracie Corish, RN, Research Nurse
David C Gotley, MD, FRACS, Professor of Surgery
Gregory L Falk, FRACS, FACS, Clinical Associate Professor of Surgery
Garett S Smith, MS, FRACS, Clinical Associate Professor of Surgery
George K Kiroff, MB BS, MS, FRACS, Surgeon
Andrew D Clouston, MB BS, PhD, FRCPA, Pathologist
David I Watson, MD, FRACS, Professor
David C Whiteman, MB BS, PhD, FAFPHM, Senior Principal Research Fellow

1 Upper GI and Soft Tissue Unit, Division of Surgery, Princess Alexandra Hospital, Brisbane, QLD.
2 Queensland Institute of Medical Research, Brisbane, QLD.
3 Concord Repatriation General Hospital, Sydney, NSW.
4 University of Sydney Northern Clinical School, Royal North Shore Hospital, Sydney, NSW.
5 Geelong Hospital, Geelong, VIC.
6 Envoi Specialist Pathologists, Brisbane, QLD.
7 Department of Surgery, Flinders University, Adelaide, SA.
Correspondence: david.whiteman@qimr.edu.au

REFERENCES