





Population-based study of treatment and outcome of recurrent oesophageal or junctional cancer

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Abstract

Background: Patients with cancer of the oesophagus or gastro-oesophageal junction have a high risk of recurrence after treatment with curative intent. The aim of this study was to analyse the site of recurrence, treatment, and survival in patients with recurrent disease.

Methods: Patients with non-metastatic oesophageal or junctional carcinoma treated with curative intent between January 2015 and December 2016 were selected from the Netherlands Cancer Registry. Data on recurrence were collected in the second half of 2019. Overall survival (OS) was assessed by Kaplan–Meier methods.

Results: In total, 862 of 1909 patients (45.2 per cent) for whom information on follow-up was available had disease recurrence, and 858 patients were included. Some 161 of 858 patients (18.8 per cent) had locoregional recurrence only, 415 (48.4 per cent) had distant recurrence only, and 282 (32.9 per cent) had combined locoregional and distant recurrence. In all, 518 of 858 patients (60.4 per cent) received best supportive care only and 315 (39.6 per cent) underwent tumour-directed therapy. Patients with locoregional recurrence alone more often received chemoradiotherapy than those with distant or combined locoregional and distant recurrence (19.3 per cent *versus* 0.7 and 2.8 per cent), and less often received systemic therapy (11.2 per cent *versus* 30.1 and 35.8 per cent). Median OS was 7.6, 4.2, and 3.3 months for patients with locoregional, distant, and combined locoregional and distant recurrence respectively ($P < 0.001$).

Conclusion: Disease recurred after curative treatment in 45.2 per cent of patients. Locoregional recurrence developed in only 18.8 per cent. The vast majority of patients presented with distant or combined locoregional and distant recurrence, and received best supportive care.

Introduction

Neoadjuvant chemoradiotherapy followed by surgery is standard of care for patients with locally advanced oesophageal or gastro-oesophageal cancer^{1,2}. Definitive chemoradiation is another curative treatment, most often indicated for patients with advanced disease (T4b) or for those with poor functional status or who are unwilling to undergo surgery^{1,3}. In the Netherlands, follow-up focuses on quality of life and symptom control⁴. Diagnostic tests including CT and endoscopy are recommended only when patients experience disease symptoms. After treatment with curative intent, disease recurs in more than 50 per cent of patients within 3 years^{5,6}. Distant recurrences are seen more often

after surgery, and locoregional recurrence is more common after definitive chemoradiation^{6–8}.

Median survival of patients with recurrent oesophageal cancer is 3–6 months^{9–12}. This is similar to that of patients with synchronous metastatic disease, who have a median survival of 4.2 months¹³. In patients with distant recurrence at multiples sites, palliative systemic treatment or best supportive care is indicated. In those who present with limited and localized recurrence, surgical resection, definitive chemoradiation or stereotactic body radiation therapy (SBRT) may achieve long-term survival in some patients^{12,14–19}.

Single-centre cohort studies^{9–12,20} have shown that patients with recurrent disease represent a diverse population in terms

Received: February 08, 2022. Revised: April 21, 2022. Accepted: July 26, 2022

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of treatment and survival. Such studies are prone to selection bias and have limited generalizability. A large population-based cohort study could help to better characterize treatment and survival of patients with recurrent disease in routine clinical practice. The aim of this nationwide population-based study was to assess the site of recurrence, treatment, and survival in patients with recurrent oesophageal or junctional cancer.

Methods

Study population

The Netherlands Cancer Registry (NCR) is a nationwide population-based cancer registry. It is based on notification of all newly diagnosed malignancies by the national automated pathology archive. Specially trained data managers routinely extract information on diagnosis, tumour stage, and treatment from medical records. Patients with adenocarcinoma or squamous cell carcinoma of the oesophagus (C15.0–C15.9) or gastro-oesophageal junction/cardia (C16.0) with recurrent disease after the diagnosis of non-metastatic disease (cT1–4A, X cN1 cM0) between January 2015 and December 2016 were selected from the NCR (Fig. S1)²¹.

Recurrent disease was defined as outgrowth of residual disease or recurrence of previous disease after treatment with curative intent. Treatment with curative intent included resection of the tumour (oesophagectomy or (sub)total gastrectomy with or without (neo)adjuvant treatment) or definitive chemoradiation (chemotherapy with concurrent radiotherapy consisting of at least 28 fractions and/or a total radiation dose of 50 Gy or more). Metastases diagnosed during treatment with curative intent (neoadjuvant treatment or definitive chemoradiation) were considered as interval metastases, as they were diagnosed after clinical staging²². As not all patients underwent neoadjuvant treatment, metastases detected at or within 5 days after surgery were also considered as interval metastases.

Data on recurrence were collected in the second half of 2019. Information on vital status was available through linkage of the NCR with the Dutch Personal Records Database and updated until 1 February 2021. According to the Central Committee on Research Involving Human Subjects, this type of study does not require approval from an ethics committee in the Netherlands. This study was approved by the Privacy Review Board of the NCR and the scientific committee of the Dutch Upper Gastrointestinal Cancer Group.

Recurrence patterns

Patients were categorized according to type of recurrence (locoregional, distant, combined). Locoregional recurrence included recurrence at the site of the primary tumour or regional lymph nodes. If locoregional and distant recurrence were diagnosed within 6 weeks of each other (as treatment generally starts within 6 weeks), they were grouped as combined locoregional and distant recurrences. Time to disease recurrence was calculated from date of resection or last day of definitive chemoradiation. A subgroup analysis was undertaken in patients with recurrent oligometastatic disease. Oligometastatic disease was defined as disease limited to one organ with up to three metastases or one non-regional lymph node station²³. Information on number of metastases per organ was available for patients with metastases limited to one organ or to the non-regional lymph nodes.

Treatment definitions

Postrecurrence treatment was classified as resection (surgical resection of locoregional or distant recurrence), chemoradiotherapy (chemotherapy with concurrent radiotherapy independent of dose and maximum dose per fraction 2.2 Gy), SBRT for metastases (at least 10 Gy per fraction if 1 or more fractions, at least 7 Gy per fraction if 5 or more fractions, or at least 5 Gy per fraction if 12 or more fractions), systemic therapy, or best supportive care. Patients could be classified into more than one treatment group, with the exception of best supportive care which was mutually exclusive from all other treatment groups. A systemic treatment regimen comprised all chemotherapy and targeted agents that started within 3 days apart and were given until suspension²⁴.

Statistical analysis

Patient and tumour characteristics were summarized with numbers and percentages, or median (range) values, and were compared using χ^2 test, Kurskal-Wallis test or Fisher's exact test, as appropriate. Kaplan–Meier methods and log rank tests were used to evaluate overall survival (OS). OS was assessed from diagnosis of recurrent disease until date of death or end of follow-up. Deaths were included until 1 February 2021. $P < 0.050$ was considered statistically significant. All analyses were conducted using SAS[®] version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patients

In total, 2063 of 2587 patients (79.7 per cent) had treatment with curative intent, and information on follow-up was available for 1909 of 2063 patients (92.5 per cent). Patient and treatment characteristics of this population are shown in Table S1. Some 862 of 1909 patients were diagnosed with recurrent disease, of whom 858 were included in the study (Fig. S1). Median time to disease recurrence was 10.5 months (Table 1). Median OS after disease recurrence was 4.4 (i.q.r. 1.6–10.5) months. Recurrence according to treatment of the primary tumour is shown in Table 2.

Pattern and timing of recurrence

Locoregional recurrence alone was observed in 161 of 858 patients (18.8 per cent), 415 patients (48.3 per cent) had distant recurrence only, and 282 (32.9 per cent) had combined locoregional and distant recurrence (Table 1). The sites of locoregional recurrence, combined locoregional and distant recurrence, and distant recurrence only are shown in Fig. 1. Median time to disease recurrence in patients with locoregional recurrence, distant recurrence, and combined locoregional and distant recurrence was 13.6 (i.q.r. 8.0–20.2), 9.4 (5.2–17.2), and 10.2 (5.5–16.6) months respectively ($P < 0.001$).

Locoregional recurrence

Of patients with locoregional recurrence, 5.0 per cent underwent surgery, 19.3 per cent were treated with chemoradiotherapy, 11.2 per cent had systemic therapy, and 64.6 per cent received best supportive care only after recurrence (Fig. 2a). Among those who received best supportive care, 27.9 per cent had radiotherapy for symptom control and 42.3 per cent received a stent for dysphagia. Nearly all patients who underwent chemoradiotherapy had a total dose of at least 50.4 Gy (90 per cent) and received carboplatin plus paclitaxel (97 per cent) (Table S2).

At the time of locoregional recurrence, patients who were previously treated with definitive chemoradiation were older

Table 1. Characteristics of patients with disease recurrence

| | All patients (n = 858) | Recurrence | | | P* |
|---|---------------------------|---------------------------|----------------------|--|---------|
| | | Locoregional (n = 161) | Distant (n = 415) | Locoregional and distant (n = 282) | |
| Sex | | | | | 0.070 |
| M | 677 (78.9%) | 117 (72.7) | 329 (79.3) | 231 (81.9) | |
| F | 181 (21.1) | 44 (27.3) | 86 (20.7) | 51 (18.1) | |
| Age (years), median (i.q.r.) | 68.0 (62.0–73.0) | 72.0 (66.0–79.0) | 67.0 (61.0–72.0) | 67.0 (61.0–72.0) | <0.001† |
| No. of co-morbidities | | | | | 0.029 |
| 0 | 388 (45.2) | 56 (34.8) | 204 (49.2) | 128 (45.4) | |
| 1 | 302 (35.2) | 61 (37.9) | 144 (34.7) | 97 (34.4) | |
| ≥ 2 | 148 (17.2) | 38 (23.6) | 58 (14.0) | 52 (18.4) | |
| Unknown | 20 (2.3) | 6 (3.7) | 9 (2.2) | 5 (1.8) | |
| Performance status | | | | | 0.596 |
| 0–1 | 325 (37.9) | 70 (43.5) | 152 (36.6) | 103 (36.5) | |
| ≥ 2 | 161 (18.8) | 26 (16.1) | 80 (19.3) | 55 (19.5) | |
| Unknown | 372 (43.4) | 65 (40.4) | 183 (44.1) | 124 (44.0) | |
| Time to disease recurrence (months), median (i.q.r.) | 10.5 (5.7–17.5) | 13.6 (8.0–20.2) | 9.4 (5.2–17.2) | 10.2 (5.5–16.6) | <0.001† |
| Reason for diagnosis | | | | | 0.030‡ |
| Symptoms | 677 (78.9) | 119 (73.9) | 320 (77.1) | 238 (84.4) | |
| Follow-up visit | 159 (18.5) | 39 (24.2) | 82 (19.8) | 38 (13.5) | |
| Coincidental | 10 (1.2) | 1 (0.6) | 8 (1.9) | 1 (0.4) | |
| Other or unknown | 12 (1.4) | 2 (1.2) | 5 (1.2) | 5 (1.8) | |
| Histology | | | | | <0.001 |
| Adenocarcinoma | 659 (76.8) | 101 (62.7) | 343 (82.7) | 215 (76.2) | |
| Squamous cell carcinoma | 199 (23.2) | 60 (37.3) | 72 (17.3) | 67 (23.8) | |
| Treatment at primary diagnosis | | | | | <0.001 |
| Definitive chemoradiation | 213 (24.8) | 100 (62.1) | 58 (14.0) | 55 (19.5) | |
| Surgical resection with or without (neo)adjuvant treatment | 645 (75.2) | 61 (37.9) | 357 (86.0) | 227 (80.5) | |
| Neoadjuvant therapy at primary diagnosis | | | | | 0.747‡ |
| No neoadjuvant therapy | 36 (6) | 5 (8) | 21 (6) | 10 (4) | |
| Chemotherapy | 55 (9) | 6 (10) | 30 (8) | 19 (8) | |
| Chemoradiotherapy | 554 (86) | 50 (82) | 306 (86) | 198 (87) | |
| Adjuvant therapy at primary diagnosis | | | | | 0.713‡ |
| No adjuvant therapy | 612 (95) | 58 (95) | 336 (94) | 218 (96) | |
| Chemotherapy | 30 (5) | 3 (5) | 18 (5) | 9 (4) | |
| Chemoradiotherapy | 3 (0) | 0 (0) | 3 (1) | 0 (0) | |
| Radicality of resection | | | | | 0.448‡ |
| R0 | 573 (89) | 52 (85) | 317 (89) | 204 (90) | |
| R1 | 64 (10) | 7 (11) | 37 (10) | 20 (9) | |
| Unknown | 8 (1) | 2 (3) | 3 (1) | 3 (1) | |
| Tumour location at primary diagnosis | | | | | 0.006‡ |
| Cervical oesophagus | 3 (0.3) | 1 (0.6) | 1 (0.2) | 1 (0.4) | |
| Proximal third oesophageal | 33 (3.8) | 12 (7.5) | 11 (2.7) | 10 (3.5) | |
| Middle third oesophageal | 100 (11.7) | 30 (18.6) | 36 (8.7) | 34 (12.1) | |
| Distal third oesophageal | 590 (68.8) | 97 (60.2) | 294 (70.8) | 199 (70.6) | |
| Overlapping/unknown oesophageal | 31 (3.6) | 7 (4.3) | 15 (3.6) | 9 (3.2) | |
| Gastro-oesophageal junction/cardia | 101 (11.8) | 14 (8.7) | 58 (14.0) | 29 (10.3) | |
| cT category at primary diagnosis | | | | | 0.078‡ |
| cT1 | 11 (1.3) | 4 (2.5) | 6 (1.4) | 1 (0.4) | |
| cT2 | 236 (27.5) | 46 (28.6) | 102 (24.6) | 88 (31.2) | |
| cT3 | 554 (64.6) | 99 (61.5) | 278 (67.0) | 177 (62.8) | |
| cT4 | 14 (1.6) | 0 (0) | 9 (2.2) | 5 (1.8) | |
| cTX | 43 (5.0) | 12 (7.5) | 20 (4.8) | 11 (3.9) | |
| cN status at primary diagnosis | | | | | 0.069‡ |
| cN0 | 303 (35.3) | 69 (42.9) | 135 (32.5) | 99 (35.1) | |
| cN1 | 326 (38.0) | 65 (40.4) | 163 (39.3) | 98 (34.8) | |
| cN2 | 186 (21.7) | 21 (13.0) | 95 (22.9) | 70 (24.8) | |
| cN3 | 32 (3.7) | 5 (3.1) | 15 (3.6) | 12 (4.3) | |
| cNX | 11 (1.3) | 1 (0.6) | 7 (1.7) | 3 (1.1) | |
| Tumour differentiation at primary diagnosis | | | | | 0.075 |
| Well/moderately differentiated | 343 (40.0) | 72 (44.7) | 166 (40.0) | 105 (37.2) | |
| Poorly differentiated/undifferentiated | 352 (41.0) | 51 (31.7) | 179 (43.1) | 122 (43.3) | |
| Unknown | 163 (19.0) | 38 (23.6) | 70 (16.9) | 55 (19.5) | |
| No. of sites with distant recurrence | | | | | <0.001 |
| 0 | 161 (18.8) | 161 (100) | – | – | |
| 1 | 330 (38.5) | – | 228 (54.9) | 102 (36.2) | |
| ≥ 2 | 367 (42.8) | – | 187 (45.1) | 180 (63.8) | |

Values are n (%) unless otherwise indicated. * χ^2 test, †Kruskal–Wallis test, and ‡Fisher's exact test.

(75.5 versus 67.0 years) and more often had co-morbidities (72.0 versus 44 per cent) than those who had surgical resection of the primary tumour. After diagnosis of locoregional recurrence, patients who had definitive chemoradiation for the primary

tumour less often had chemoradiotherapy (3.0 versus 46 per cent; $P < 0.001$) and more often received best supportive care (81.0 versus 38 per cent; $P < 0.001$) than patients who underwent oesophagectomy or gastrectomy for the primary tumour

Table 2 Recurrence according to treatment of primary tumour for all patients of whom information on follow-up was available ($n = 1909$)

| Treatment at primary diagnosis | No. of patients | Recurrence | | | |
|--|-----------------|--------------|------------|--------------------------|------------|
| | | Locoregional | Distant | Locoregional and distant | None |
| Neoadjuvant chemoradiotherapy followed by surgery (without adjuvant treatment) | 1251 | 50 (4.0) | 300 (24.0) | 194 (15.5) | 707 (56.5) |
| Surgery alone (without (neo)adjuvant treatment) | 110 | 5 (4.5) | 21 (19.1) | 10 (9.1) | 74 (67.3) |
| Definitive chemoradiation | 404 | 101 (25.0) | 59 (14.6) | 55 (13.6) | 189 (46.8) |
| Other treatments* | 144 | 7 (4.9) | 37 (25.7) | 23 (16.0) | 77 (53.5) |

Values are n (%). *Surgery with (neo)adjuvant chemotherapy or surgery with neoadjuvant chemoradiotherapy and adjuvant chemo(radio)therapy.

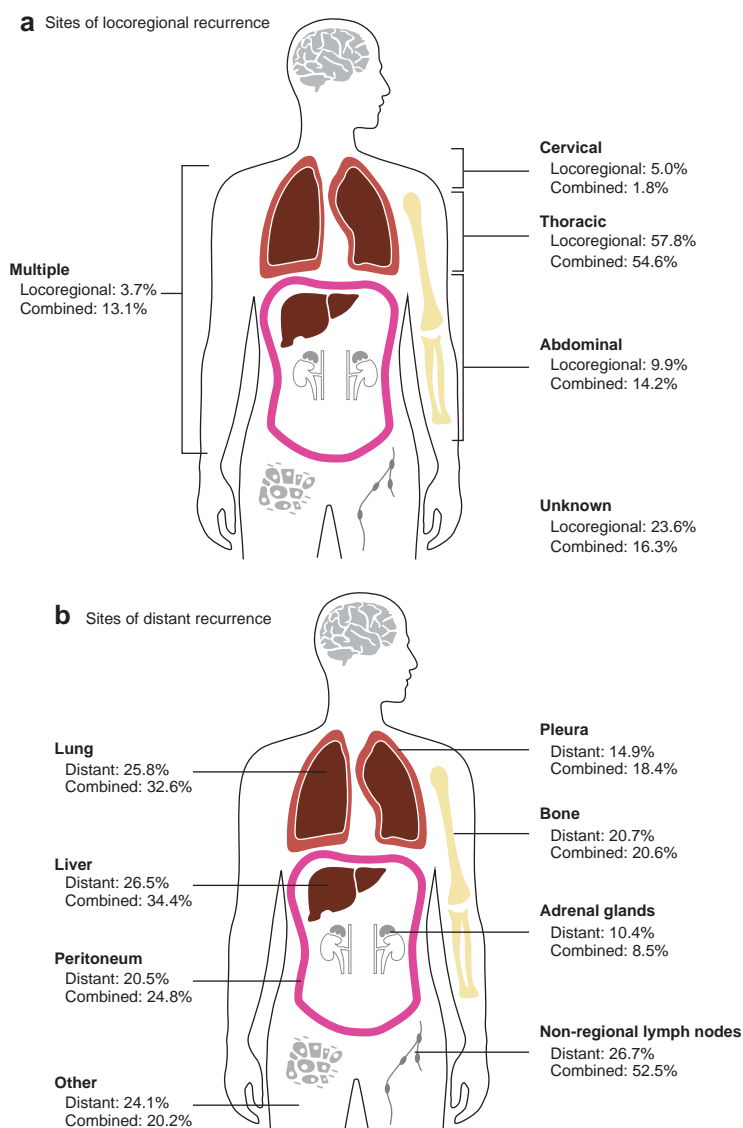


Fig. 1 Sites of recurrence

a Sites of locoregional recurrence in patients with locoregional recurrence or combined locoregional and distant recurrence, and **b** sites of distant recurrence in patients with distant recurrence or combined locoregional and distant recurrence.

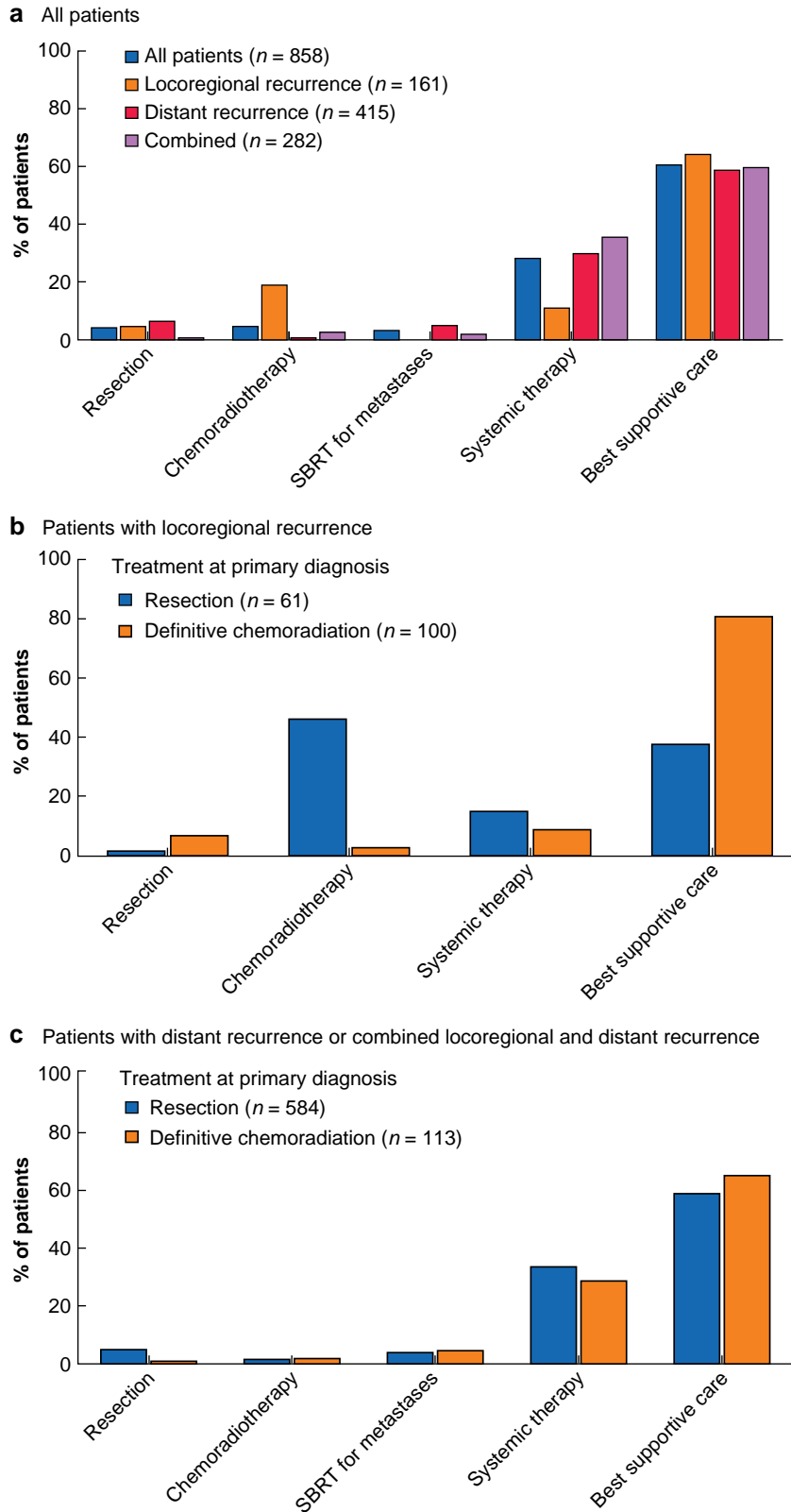


Fig. 2 Treatment after diagnosis of recurrent disease

a For all patients and by type of recurrence, **b** in patients with locoregional recurrence stratified by type of treatment after primary diagnosis (resection (oesophagectomy or gastrectomy) or definitive chemoradiation), and **c** in patients with distant recurrence or combined locoregional and distant recurrence stratified by type of treatment after primary diagnosis. SBRT, stereotactic body radiation therapy.

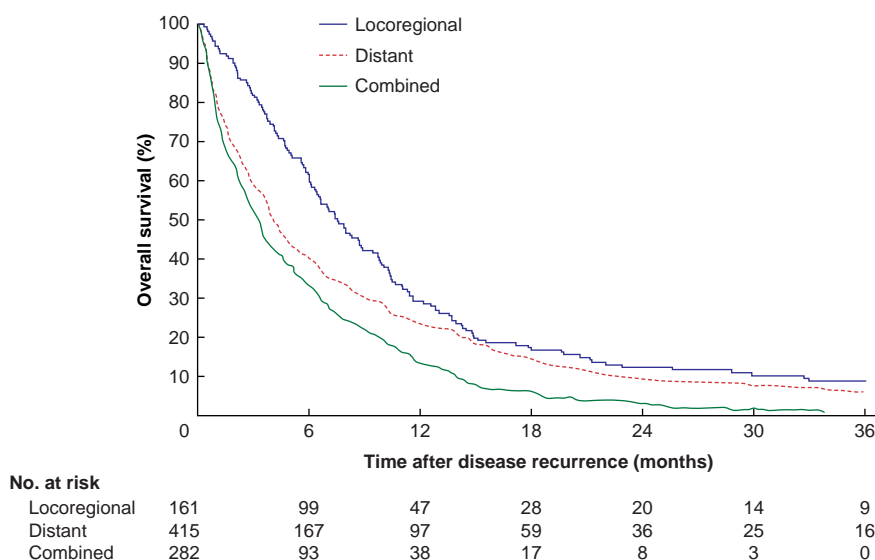


Fig. 3 Overall survival of patients with locoregional recurrence, distant recurrence or locoregional and distant recurrence

$P < 0.001$ (log rank test).

(Fig. 2b). In the subgroup of patients with locoregional recurrence who received best supportive care, those who had definitive chemoradiation for the primary tumour less often underwent radiotherapy for symptom control (15 per cent), but more often received a stent (52 per cent) compared with patients who had surgery for the primary tumour (radiotherapy for symptom control 74 per cent, stent 9 per cent).

Median OS for patients with locoregional recurrence was 7.6 (i.q.r. 3.9–13.7) months (Fig. 3). It was 17.2 (10.4–44.9) and 5.6 (2.9–9.9) months after receiving radical treatment (chemoradiotherapy, resection, and/or SBRT for metastases) and best supportive care respectively ($P < 0.001$) (Fig. 4a). In patients with locoregional recurrence, median survival was longer for those who had surgery for the primary tumour than for patients who had definitive chemoradiation: 11.1 (7.1–19.8) versus 5.9 (3.1–9.9) months ($P < 0.001$) (Fig. S2).

Distant recurrence or combined locoregional and distant recurrence

Of patients with distant recurrence, 6.5 per cent underwent resection of the distant metastasis, 0.7 per cent had chemoradiotherapy, 5.3 per cent received SBRT for metastases, 30.1 per cent underwent systemic therapy, and 59.0 per cent received best supportive care only after recurrence (Fig. 2a). Among patients with combined locoregional and distant recurrence, 0.7 per cent underwent resection, 2.8 per cent received chemoradiotherapy, 2.1 per cent had SBRT for metastases, 35.8 per cent underwent systemic therapy, and 59.9 per cent received best supportive care only after recurrence. The majority of patients who had systemic therapy received doublet therapy (73.5 per cent), most commonly capecitabine and oxaliplatin (47.8 per cent) followed by carboplatin and paclitaxel (18.1 per cent) (Table S2). There were no differences in the treatment of recurrence (distant only or combined locoregional and distant) between patients who at primary diagnosis underwent resection of the primary tumour and those who had definitive chemoradiation after diagnosis

and developed distant or combined locoregional and distant recurrence (Fig. 2c).

Median OS was 4.2 (i.q.r. 1.4–11.1) and 3.3 (1.1–7.7) months for patients with distant or combined locoregional and distant recurrence respectively (Fig. 3). As similar treatment patterns were observed for patients with distant recurrence or combined locoregional and distant recurrence, these patients were combined for the following survival analysis. Among patients with distant recurrence or combined locoregional and distant recurrence, median OS was 13.7 (7.1–25.2), 8.3 (4.5–14.2), and 1.8 (0.8–3.9) months for those receiving radical treatment, systemic therapy, and best supportive care respectively ($P < 0.001$) (Fig. 4b).

Oligometastatic disease

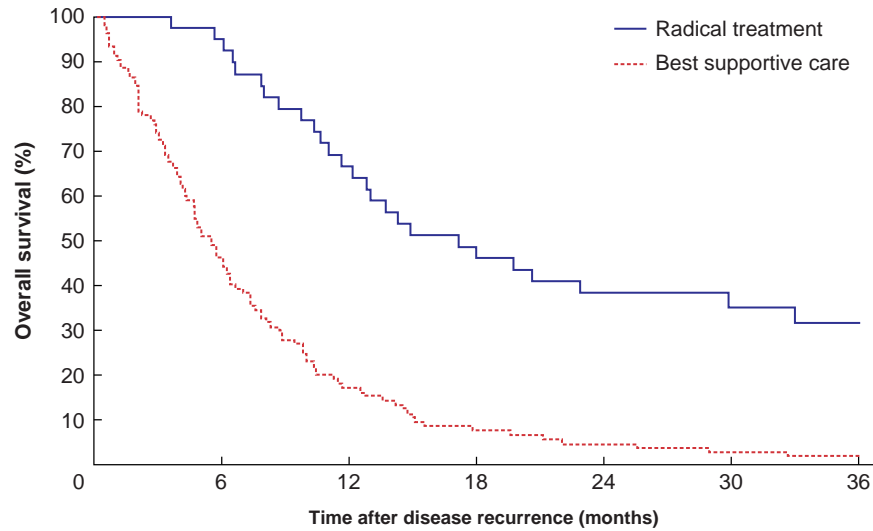
Of the 697 patients with distant or combined locoregional and distant recurrence, metastases were limited to a single site in 330 (47.3 per cent) (Table 1). The number of metastases was known in 181 of these patients (54.9 per cent), and 143 (79.0 per cent) were considered to have oligometastatic disease. Most common sites were brain (28 patients), lung (24 patients), bone (24 patients), liver (22 patients), and non-regional lymph nodes (19 patients). Among patients with oligometastatic disease, 110 (76.9 per cent) had distant recurrence, and 33 (23.1 per cent) had combined locoregional and distant recurrence.

Some 16.8 per cent of patients with oligometastatic disease underwent metastasectomy, 4.2 per cent had chemoradiotherapy, 14.7 per cent received SBRT for metastases, 28.0 per cent underwent systemic therapy, and 39.9 per cent received best supportive care only (Table S3). Median OS of patients with oligometastatic disease was 10.2 (i.q.r. 4.5–21.0) months overall. It was 15.8 (8.9–29.7), 12.1 (7.1–22.9), and 4.7 (2.3–11.7) months for patients receiving radical treatment, systemic therapy, and best supportive care respectively.

Discussion

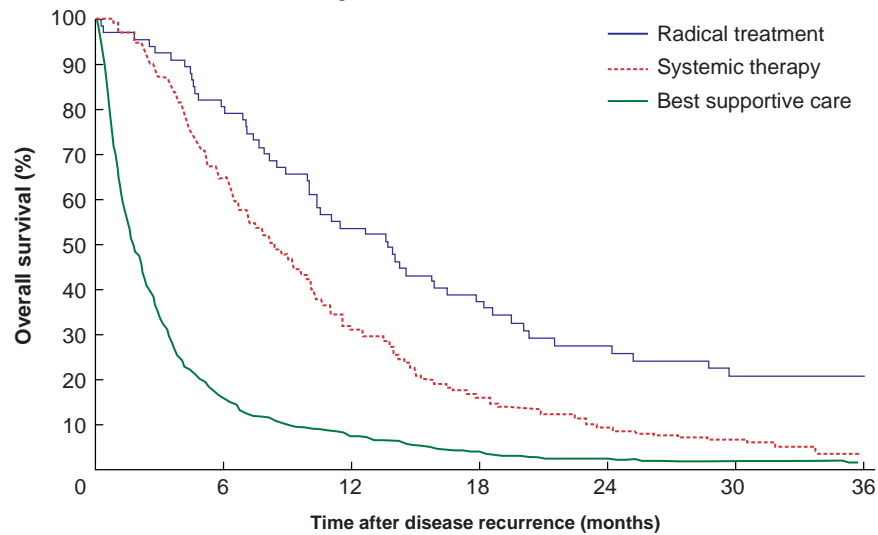
The present study has shown that patients who develop disease recurrence after curative treatment have a poor prognosis. More

a Patients with locoregional recurrence



| No. at risk | | 0 | 6 | 12 | 18 | 24 | 30 | 36 |
|----------------------|--|-----|----|----|----|----|----|----|
| Radical treatment | | 39 | 37 | 26 | 19 | 15 | 11 | 7 |
| Best supportive care | | 104 | 48 | 18 | 8 | 5 | 3 | 2 |

b Patients with distant recurrence or combined locoregional and distant recurrence



| No. at risk | | 0 | 6 | 12 | 18 | 24 | 30 | 36 |
|----------------------|--|-----|-----|----|----|----|----|----|
| Radical treatment | | 67 | 54 | 36 | 25 | 17 | 12 | 9 |
| Systemic therapy | | 216 | 140 | 68 | 35 | 18 | 11 | 3 |
| Best supportive care | | 414 | 66 | 31 | 16 | 9 | 5 | 4 |

Fig. 4 Overall survival of patients with locoregional recurrence, or combined locoregional and distant recurrence by type of treatment after recurrence **a** Locoregional recurrence and **b** combined locoregional and distant recurrence, **a,b** $P < 0.001$ (log rank test).

than half of all patients received best supportive care and long-term survival was limited to a few patients.

A previous Dutch study¹⁰ of patients with recurrent oesophageal cancer after surgery between 1993 and 2010 reported a median survival of 3.0 months. Median survival was 4.4 months in the present study, indicating a marginal improvement since 2010. This may be explained by the higher proportion of patients with locoregional recurrence and tumour-directed therapy in the present study.

In the Netherlands, follow-up after treatment with curative intent is recommended 3 weeks after treatment, every 3 months in the first year, and half yearly thereafter until 5 years after

treatment⁴. Radiological tests or endoscopies to detect recurrent disease are recommended only when patients experience disease symptoms. This strategy may have an effect on the proportion of patients diagnosed with locoregional versus distant recurrence. Diagnosis is delayed compared with routine diagnostic testing during follow-up, which could result in lead time bias in survival time after recurrence. Recently, an international multicentre study²⁵ reported that radiological follow-up (defined as minimum annual CT for 3 years after surgery) was associated with improved survival for patients with localized disease and those who underwent surgery only. Additionally, radiological follow-up was associated with a higher

proportion of patients receiving systemic therapy after recurrence²⁵. Whether more intensive surveillance strategies, for example radiological tests and/or endoscopies, would have an impact on the type of recurrence (locoregional versus distant), and consequently on treatment and survival, after recurrent disease in the Netherlands is unknown.

In the present study, patients with distant or combined locoregional and distant recurrence treated with systemic therapy had similar survival (8.3 months) to patients with synchronous metastatic disease (7.5 months)²⁴. First-line chemotherapy combined with anti-programmed cell death protein 1 (anti-PD-1) therapy is a new standard of care, and expected to improve survival of patients with human epidermal growth factor receptor 2-negative oesophagogastric carcinoma and high programmed death-ligand 1 (PD-L1) expression^{26,27}. Additionally, anti-PD-1 therapy is indicated in the adjuvant setting in a subset of patients after neoadjuvant chemoradiotherapy and surgery, based on the results of the CheckMate 577 study²⁸. However, it remains uncertain whether anti-PD-1 therapy is of benefit in patients with recurrent disease as these patients might have already received anti-PD-1 therapy in the adjuvant setting.

Survival of patients receiving best supportive care was very poor. Reasons for refraining from systemic therapy were unknown, but it could be that the physical state of patients precluded this treatment, or because of patient preference and perceived short life expectancy. Currently, systemic therapy is not advised for patients near the end of life as it is associated with poorer quality of life²⁹⁻³¹. Therefore, it could be speculated that not giving systemic therapy was the right decision. The results of the present study emphasize the importance of high-quality palliative care for patients with recurrent disease.

Patients who received radical treatment, for both locoregional and distant recurrence, survived for longer than those who received a different type of treatment. Salvage oesophagectomy is an option for a well selected subgroup of patients after definitive chemoradiation (7 per cent among patients with locoregional recurrence in the present study). Although long-term survival can be achieved, salvage oesophagectomy is associated an increased risk of postoperative morbidity and mortality^{32,33}.

Radical treatment was more common among patients with oligometastatic disease than those with distant recurrence. This is supported by data from recent cohort studies¹⁷⁻¹⁹ on oligometastatic disease that reported improved survival for these patients. However, a randomized study has not been performed. In the present study, 39.9 per cent of patients with oligometastatic disease received best supportive care only, and the number of patients who received both systemic and local treatment was limited (2.8 per cent).

In contrast to previous single-centre cohort studies^{11,12,34}, the present analysis included patients who developed recurrence after either surgical resection or definitive chemoradiation. Definitive chemoradiation is considered a treatment with curative intent as this is an alternative to surgical resection^{1,35}. Systemic therapy is not the preferred method for palliation of dysphagia in patients with locoregional recurrence, and reirradiation or resection of a locoregional recurrence is often not possible in patients who received definitive chemoradiation^{36,37}. Of these patients, a higher proportion received best supportive care for recurrent disease, and survival was poorer than that among patients who underwent surgery. The shorter postrecurrence survival may be explained by poorer physical functioning of patients who received definitive chemoradiation

compared with patients who underwent surgery for the primary tumour. At the time of disease recurrence, patients who had undergone definitive chemoradiation for the primary tumour were older and had more co-morbidities.

A strength of the present study is that a nationwide cohort was included with information on current practice for recurrent disease. However, some variables were reported incompletely, for example performance status. It was also unknown whether patients presented with solitary locoregional recurrence or had oligometastatic recurrence. For patients with locoregional recurrence, it was unknown whether the recurrence developed at the anastomotic site. Finally, no subgroup analyses according to type of recurrence and treatment were undertaken owing to the limited sample size.

This population-based study has shown that patients with recurrent disease after treatment for oesophageal or gastro-oesophageal junctional cancer have a poor prognosis, especially in the setting of distant or combined locoregional and distant recurrence. Patients who underwent radical treatment had the longest survival, and future research should assess whether more patients may benefit from tumour-directed therapy. In addition, there is a need for novel treatments for patients with poor performance status to improve their outcome.

Funding

This work was supported by Bristol Myers Squibb (BMS) (CA209-77E). The funder financed part of the data collection and two employees of the funder have contributed as co-authors to the article.

Acknowledgements

The authors thank the registration team of the Netherlands Comprehensive Cancer Organization (IKNL) for the collection of data for the Netherlands Cancer Registry. The authors thank all participating hospitals in the Netherlands. The data underlying this article are available at the IKNL upon justified request. No preregistration exists for the studies reported in this article. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Disclosure

D.B. is employee of BMS, and holds stock in BMS and GlaxoSmithKline (GSK). L.M. is employee of, and holds stock in, BMS. N.H.M. reports personal fees (consultancy) from BMS, Eli Lilly, Astra Zeneca, Servier, and Merck Sharp & Dohme (MSD). M.I.v.B.H. reports unrestricted research grants from Stryker and Olympus with fees paid to the institution, and an advisory role for Johnson and Johnson, Bbraun, Alesi Surgical, Mylan, and Medtronic, all consultancy fees paid to institution. H.W.M.v.L. reports grants from Roche, has served as a consultant for BMS, Celgene, Lilly, and Nordic, and has received unrestricted research funding from Bayer, BMS, Celgene, Lilly, Merck, Serono, MSD, Nordic, Philips, and Roche. R.H.A.V. reports grants from BMS and Roche. The authors declare no other conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

References

- Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D, Committee EG. Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016;**27**:v50–v57
- van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;**366**:2074–2084
- Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Corvera C, Das P et al. Esophageal and esophagogastric junction cancers, version 2.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2019;**17**:855–883
- Federatie Medisch Specialisten.** Dutch Clinical Practice Guidelines for Esophageal Carcinoma—Follow-up. 01-12-2010. <https://www.richtlijnen database.nl> (accessed 1 March 2021)
- Meguid RA, Hooker CM, Taylor JT, Kleinberg LR, Cattaneo SM II, Sussman MS et al. Recurrence after neoadjuvant chemoradiation and surgery for esophageal cancer: does the pattern of recurrence differ for patients with complete response and those with partial or no response? *J Thorac Cardiovasc Surg* 2009;**138**:1309–1317
- Oppedijk V, van der Gaast A, van Lanschot JJ, van Hagen P, van Os R, van Rij CM et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. *J Clin Oncol* 2014;**32**:385–391
- Jeene PM, van Laarhoven HWM, Hulshof M. The role of definitive chemoradiation in patients with non-metastatic oesophageal cancer. *Best Pract Res Clin Gastroenterol* 2018;**36–37**:53–59
- Lou F, Sima CS, Adusumilli PS, Bains MS, Sarkaria IS, Rusch VW et al. Esophageal cancer recurrence patterns and implications for surveillance. *J Thorac Oncol* 2013;**8**:1558–1562
- Hsu PK, Wang BY, Huang CS, Wu YC, Hsu WH. Prognostic factors for post-recurrence survival in esophageal squamous cell carcinoma patients with recurrence after resection. *J Gastrointest Surg* 2011;**15**:558–565
- Blom RL, Lagarde SM, van Oudenaarde K, Klinkenbijl JH, Hulshof MC, van Laarhoven HW et al. Survival after recurrent esophageal carcinoma has not improved over the past 18 years. *Ann Surg Oncol* 2013;**20**:2693–2698
- Butter R, Lagarde SM, van Oijen MGH, Anderegg MCJ, Gisbertz SS, Meijer SL et al. Treatment strategies in recurrent esophageal or junctional cancer. *Dis Esophagus* 2017;**30**:1–9
- Parry K, Visser E, van Rossum PS, Mohammad NH, Ruurda JP, van Hillegersberg R. Prognosis and treatment after diagnosis of recurrent esophageal carcinoma following esophagectomy with curative intent. *Ann Surg Oncol* 2015;**22**:S1292–S1300
- Pape M, Vissers PAJ, Bertwistle D, McDonald L, Slingerland M, Mohammad NH et al. A population-based study in synchronous versus metachronous metastatic esophagogastric adenocarcinoma. *Ther Adv Med Oncol* 2022;**14**:1–14
- Hiyoshi Y, Morita M, Kawano H, Otsu H, Ando K, Ito S et al. Clinical significance of surgical resection for the recurrence of esophageal cancer after radical esophagectomy. *Ann Surg Oncol* 2015;**22**:240–246
- Kato F, Monma S, Koyanagi K, Kanamori J, Daiko H, Igaki H et al. Long-term outcome after resection for recurrent oesophageal cancer. *J Thorac Dis* 2018;**10**:2691–2699
- Jeene PM, Versteijne E, van Berge Henegouwen MI, Bergmann JJ, Geijssen ED, Muller K et al. Definitive chemoradiation for locoregional recurrences of esophageal cancer after primary curative treatment. *Dis Esophagus* 2017;**30**:1–5
- Seyedin SN, Gannon MK, Plichta KA, Abushahin L, Berg DJ, Arshava EV et al. Safety and efficacy of stereotactic body radiation therapy for locoregional recurrences after prior chemoradiation for advanced esophageal carcinoma. *Front Oncol* 2020;**10**:1311
- Yamamoto T, Niibe Y, Matsumoto Y, Dekura Y, Oh RJ, Yamashita H et al. Stereotactic body radiotherapy for pulmonary oligometastases from esophageal cancer: results and prognostic factors. *Anticancer Res* 2020;**40**:2065–2072
- Yeung R, Hamm J, Liu M, Schellenberg D. Institutional analysis of stereotactic body radiotherapy (SBRT) for oligometastatic lymph node metastases. *Radiat Oncol* 2017;**12**:105
- Mariette C, Balon JM, Piessen G, Fabre S, Van Seuning I, Triboulet JP. Pattern of recurrence following complete resection of esophageal carcinoma and factors predictive of recurrent disease. *Cancer* 2003;**97**:1616–1623
- Fritz A, Percy C, Jack A, Shanmugarathan S, Sobin L, Parkin DM et al. *International Classification of Diseases For Oncology: ICD-O (3rd edn)*. World Health Organization, 2000
- Kroese TE, Dijksterhuis WPM, van Rossum PSN, Verhoeven RHA, Mook S, Haj Mohammad N et al. Prognosis of interval distant metastases after neoadjuvant chemoradiotherapy for esophageal cancer. *Ann Thorac Surg* 2022;**113**:482–490
- Kroese TE, van Laarhoven HWM, Nilsson M, Lordick F, Guckenberger M, Ruurda JP et al. Definition of oligometastatic esophagogastric cancer and impact of local oligometastasis-directed treatment: a systematic review and meta-analysis. *Eur J Cancer* 2022;**166**:254–269
- Dijksterhuis WPM, Verhoeven RHA, Slingerland M, Haj Mohammad N, de Vos-Geelen J, Beerepoot LV et al. Heterogeneity of first-line palliative systemic treatment in synchronous metastatic esophagogastric cancer patients: a real-world evidence study. *Int J Cancer* 2020;**146**:1889–1901
- Elliott JA, Markar SR, Klevebro F, Johar A, Goense L, Lagergren P et al. An international multicenter study exploring whether surveillance after esophageal cancer surgery impacts oncological and quality of life outcomes (ENSURE). *Ann Surg* 2022
- Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet* 2021;**398**:27–40
- Sun JM, Shen L, Shah MA, Enzinger P, Adenis A, Doi T et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *Lancet* 2021;**398**:759–771
- Kelly RJ, Ajani JA, Kuzdzal J, Zander T, Van Cutsem E, Piessen G et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. *N Engl J Med* 2021;**384**:1191–1203
- Besseling J, Reitsma J, Van Erkelens JA, Schepens MHJ, Siroen MPC, Ziedses des Plantes CMP et al. Use of palliative chemotherapy and ICU admissions in gastric and esophageal cancer patients in the last phase of life: a nationwide observational study. *Cancers (Basel)* 2021;**13**:145
- Earle CC, Landrum MB, Souza JM, Neville BA, Weeks JC, Ayanian JZ. Aggressiveness of cancer care near the end of life: is it a quality-of-care issue? *J Clin Oncol* 2008;**26**:3860–3866
- Wright AA, Zhang B, Ray A, Mack JW, Trice E, Balboni T et al. Associations between end-of-life discussions, patient mental

- health, medical care near death, and caregiver bereavement adjustment. *JAMA* 2008;**300**:1665–1773
32. Faiz Z, Dijksterhuis WPM, Burgerhof JGM, Muijs CT, Mul VEM, Wijnhoven BPL et al. A meta-analysis on salvage surgery as a potentially curative procedure in patients with isolated local recurrent or persistent esophageal cancer after chemoradiotherapy. *Eur J Surg Oncol* 2019;**45**:931–940
 33. Fajardo R, Abbas AE, Petrov RV, Bakhos CT. Salvage esophagectomy. *Surg Clin North Am* 2021;**101**:467–482
 34. Yamashita K, Watanabe M, Mine S, Kuroguchi T, Okamura A, Hayami M et al. Patterns and outcomes of recurrent esophageal cancer after curative esophagectomy. *World J Surg* 2017;**41**:2337–2344
 35. Hulshof M, Geijsen ED, Rozema T, Oppedijk V, Buijsen J, Neelis KJ et al. Randomized study on dose escalation in definitive chemoradiation for patients with locally advanced esophageal cancer (ARTDECO study). *J Clin Oncol* 2021;**39**:2816–2824
 36. Ramakrishnaiah VP, Malage S, Sreenath GS, Kotlapati S, Cyriac S. Palliation of dysphagia in carcinoma esophagus. *Clin Med Insights Gastroenterol* 2016;**9**:11–23
 37. Touchefeu Y, Archambeaud I, Landi B, Lievre A, Lepere C, Rougier P et al. Chemotherapy versus self-expanding metal stent as primary treatment of severe dysphagia from unresectable oesophageal or gastro-oesophageal junction cancer. *Dig Liver Dis* 2014;**46**:283–286

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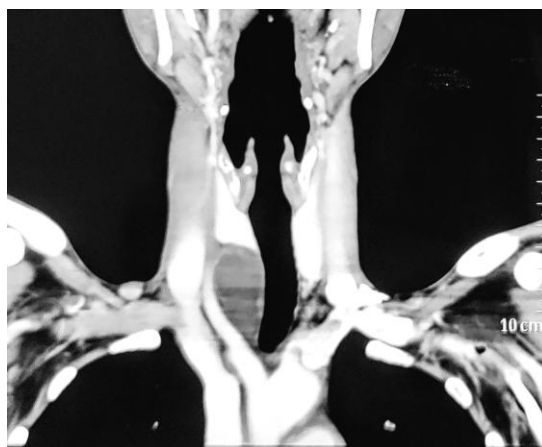
Parathyroid cyst: enigma

<https://doi.org/10.1093/bjs/znac206>

Advance Access Publication Date: 17 June 2022

Surgical Snapshots

A 25-year-old gentleman, with chronic calcific pancreatitis and bilateral medullary nephrocalcinosis caused by hypercalcaemia, was found to have a 3.2×3.6 cm right inferior parathyroid adenoma. Contrast-enhanced computed tomography of the neck showed an enlarged well-defined cystic right inferior parathyroid gland located posterior to the right lobe of the thyroid with retrosternal extension. He underwent focused parathyroidectomy under the cervical block with the removal of a brown coloured cyst.



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