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Sixty-day all-cause mortality rates in patients treated for gastrointestinal cancers, in randomised trials, at the Royal Marsden Hospital

Ourania Katopodis [a], Paul Ross [a], Andrew R. Norman [b], Jacqui Oates [a], David Cunningham [a,*]

[a] *Gastrointestinal Unit, Royal Marsden Hospital, Downs Road, Sutton SM2 5PT, UK*
[b] *Department of Computing and Information, Royal Marsden Hospital, Downs Road, Sutton SM2 5PT, UK*

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Abstract

The aim of this study was to determine the 60-day all-cause mortality rate, during chemotherapy, for patients with oesophagogastric, pancreatic, and colorectal cancer. We analysed 1720 patients that were treated within randomised trials. The minimum follow-up period was >60 days. Sixty-day mortality and 95% Confidence Intervals (CI) were calculated from the Kaplan–Meier survival curves. Causes of death were classified as treatment-related, disease-related or vascular syndrome-induced deaths. Patients with oesophagogastric cancer that could not tolerate a *cis*-platinum-containing regimens were treated with infused 5-fluorouracil (5FU) ± mitomycin-C (MMC). The 60-day mortality rate depends upon the site of the primary tumour and the disease status (adjuvant *versus* advanced). The rate of treatment- and vascular syndrome-induced deaths was ⩽1.8%. For patients with advanced disease, most of the early deaths were disease-related. In adjuvant colorectal cancer, one patient died within 60 days (myocardial infarction). This study provides a benchmark for assessing the safety of regimens used in these disease settings.

Keywords: Gastrointestinal cancer; Oesophagogastric cancer; Pancreatic cancer; Colorectal cancer; Sixty-day mortality; Chemotherapy-related deaths; Vascular syndrome-related mortality

1. Introduction

Treatment for gastrointestinal (GI) cancers has evolved rapidly in the last decade. Clinical trials are powerful tools for collecting information to provide an evidence base for implementing change in medical practice, and to determine the efficacy and safety of new drugs or drug schedules. Early mortality detected in a clinical trial is one of the most important parameters for assessing the safety of a chemotherapy regimen.

In 1999, the results of two large randomised studies were reported indicating that the addition of irinotecan to 5-fluorouracil (5FU) and leucovorin (LV) improved survival in patients with advanced stage colorectal cancer [1,2]. The first one [1] demonstrated a higher response rate and longer time to progression with the combination of infused 5FU/LV plus irinotecan compared with infused 5FU/LV alone. The second one compared irinotecan with weekly bolus 5FU/LV, with irinotecan plus bolus 5FU/LV (IFL), and resulted in significantly longer progression-free and overall survival for the IFL regimen [2].

In 1999, the North Central Cancer Treatment Group (NCCTG) designed a randomised phase III trial (N9741) for patients with advanced colorectal cancer comparing various schedules of irinotecan or oxaliplatin + 5FU/LV and irinotecan/oxaliplatin (IOx) with 5FU/LV alone (Fig. 1). The use of a real-time toxicity monitoring programme, previously established by the NCCTG, detected an excessive toxicity rate. In the irinotecan plus 5FU/LV

* Corresponding author. Tel.: +44-208-661-3156; fax: +44-208-643-9414.
E-mail address: dcunn@icr.ac.uk (D. Cunningham).

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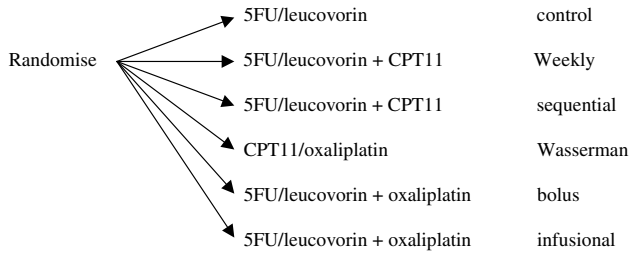

Fig. 1. Initial N9741 trial (1999). 5FU, 5-fluorouracil; CPT11, irinotecan.

(sequential) and in the oxaliplatin plus 5FU/LV bolus arms, a lethal toxicity rate of 8% and 16%, respectively, was identified. Therefore, the trial was revised into a three-arm study comparing oxaliplatin + infusional 5FU/LV (FOLFOX4), and IOx, with IFL, the new control arm [3]. A review of the treatment-related mortality rate reported in large, selected, advanced colorectal cancer chemotherapy trials, showed a treatment-related death rate of approximately 1% [1,2,6–8], and this was adopted as a threshold that would trigger intervention. In April 2001, the treatment-related mortality rate in the IFL arm reached 3.1% (95% Confidence Interval (CI: 1.4–5.8)). Eight of the nine deaths occurred within the first cycle of chemotherapy, due to several consistent toxicities [4].

Contemporaneously, the Cancer and Leukaemia Group B (CALGB) was co-ordinating a trial of adjuvant chemotherapy, comparing IFL with 5FU and LV (Roswell Park schedule [9]), in patients with resected, stage III colon cancer (C89803 trial). A review of data from this trial indicated an imbalance of the 60-day all-cause mortality rate between the two treatment groups.

An independent review of 60-day mortality, in both the N9741 and C89803 trials, demonstrated that most of the early deaths in patients treated with IFL were treatment-induced [5], due to an increase in GI syndrome-induced deaths, with a smaller increase in vascular syndrome-induced deaths.

We aimed to determine the 60-day all-cause mortality rate in patients who have undergone treatment for oesophagogastric, pancreatic or colorectal cancer in the adjuvant or metastatic setting. In addition, we wanted to investigate the cause of death, including disease-related, vascular syndrome and treatment-related deaths. Finally, we aimed to provide a benchmark for assessing the safety of any future chemotherapy regimens used in these diseases.

2. Patients and methods

The 60-day mortality rate was defined as one minus the probability of survival from all causes at 60 days.

Causes of mortality that were used for this study were classified (Fig. 2) as follows:

Treatment-related deaths: death clearly caused by protocol treatment.

Disease-related deaths: death clearly caused by the disease or disease progression.

Vascular syndrome-induced death: death clearly caused by myocardial infarction (MI), cerebrovascular accident (CVA) or pulmonary embolism (PE). This was not associated with chemotherapy-induced toxicities.

Patient population: Patients treated within randomised trials between 1992 and 2001 at the Royal Marsden Hospital.

2.1. Oesophagogastric cancer

Patients with advanced, previously untreated oesophagogastric cancer included in this analysis had participated in three previously published randomised studies [12–14].

The first compared epirubicin, cisplatin and protracted venous infusion (PVI) 5FU (ECF) *versus* 5FU, doxorubicin and methotrexate (FAMTX) [12]. Patients treated with FAMTX were not included, as this is no longer a reference regimen for oesophagogastric cancer.

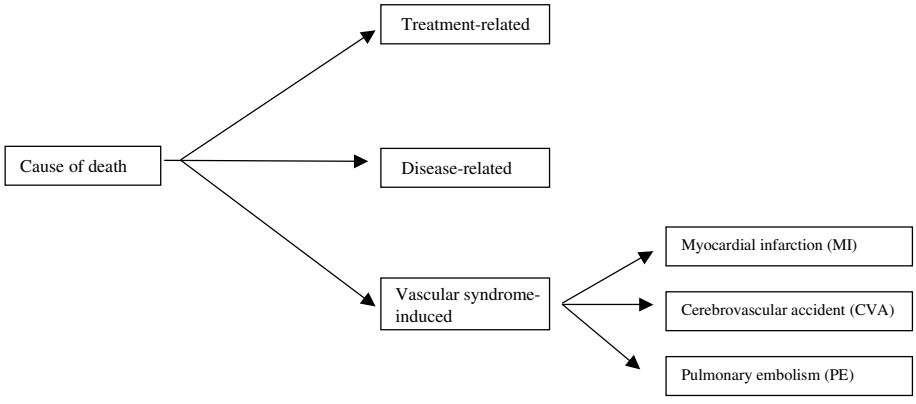

Fig. 2. Cause of death.

The second trial compared ECF with mitomycin-C (MMC), cisplatin and PVI 5FU (MCF) [13].

In addition, patients with other co-morbidity factors, precluding treatment with platinum-based therapy received PVI 5FU ± MMC [14].

All patients were separated into two groups: patients treated with a platinum-based chemotherapy regimen (ECF or MCF) and patients treated with a non-platinum-based regimen (5FU alone or 5FU/MMC).

2.2. Colorectal cancer

Patients with advanced colorectal cancer were divided into those treated with 5FU alone and those treated with 5FU and MMC. These patients had participated in one of the three randomised trials:

1. The first trial compared PVI 5FU ± interferon α-2b (IFN) [15].
2. The second trial compared PVI 5FU ± MMC [16].
3. The final trial included patients treated with PVI 5FU/MMC or circardian-timed 5FU/MMC [17].

Patients receiving adjuvant chemotherapy for stage II or III colorectal cancer had participated in a randomised trial comparing bolus 5FU/LV, days 1–5 monthly for 6 months, with 3 months PVI 5FU [18].

2.3. Pancreatic cancer

Patients with inoperable pancreatic cancer were treated within a phase III randomised trial comparing PVI 5FU ± MMC [23].

Details of the eligibility criteria, chemotherapy regimens and outcomes have all been described in detail in the relevant publications [12–23].

2.4. Statistics

The Kaplan–Meier method was used to calculate all-cause mortality and its 95% CI from the survival curves. Events were defined as death from any cause. The baseline was the date of randomisation. Association between 60-day mortality and categorical variables was assessed using the χ^2-test and Fisher's-exact test, where appropriate. Logistic regression was used to assess the impact of age, performance status (PS) (0–1 *versus* 2–3) and gender.

3. Results

One thousand seven hundred and twenty patients that received treatment within randomised clinical trials were used included in this study (Fig. 3). The minimum follow-up was 60 days from randomisation.

3.1. Oesophagogastric cancer

Three hundred and sixty three patients had oesophagogastric cancer. Two hundred and fifty four patients received a platinum-based regimen (ECF or MCF), and had median age of 59 years (30–79 years). One hundered and nine patients were treated with PVI 5FU ± MMC and had a median age of 73 years (52–84 years) (Table 1).

In the platinum-based group of patients ($n = 254$), 16 deaths were reported within 60 days from randomization (6.3%) (95% CI: 3.9–10.1) (Table 2 and Fig. 4). One toxic death was noted (0.4%), (grade III stomatitis, Hickman line septicaemia and PS deterioration). The

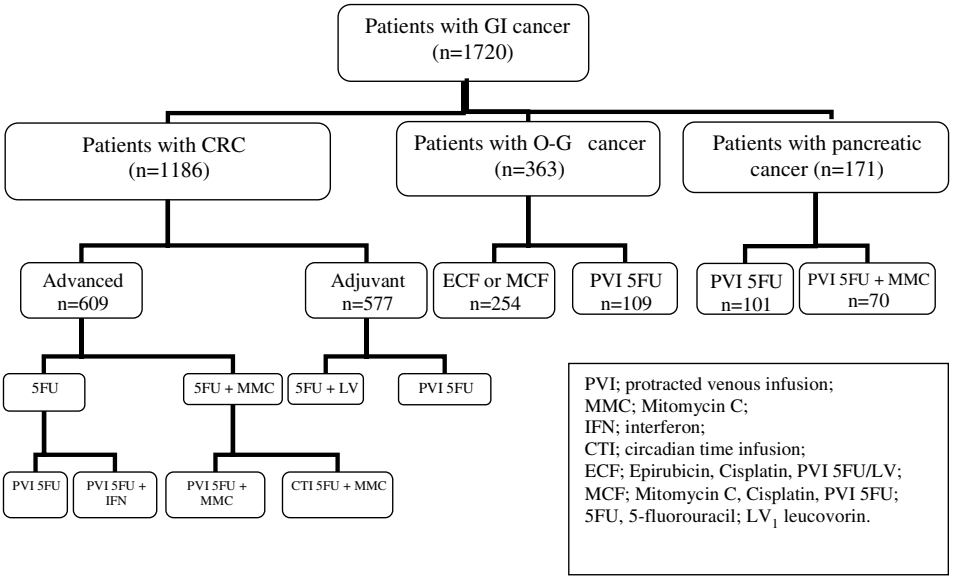

Fig. 3. Chemotherapy regimens that were used for the study (*GI: gastrointestinal, CRC: colorectal cancer, O-G: oesophagogastric).

Table 1
Patients' characteristics

	CRC advanced	CRC adjuvant	O-G platinum	O-G non-platinum	Pancreatic cancer
n	609	577	254	109	171
Median age (in years) (range)	63 (16–82)	63 (26–83)	59 (30–79)	73 (52–84)	62.5 (28–86)
Gender					
Male	370 (60.8%)	296 (51.3%)	205 (80.7%)	76 (69.7%)	105 (61.4%)
Female	239 (39.2%)	281 (48.7%)	49 (19.3%)	33 (30.3%)	66 (38.4%)
Performance status (PS)					
0	135 (22.2%)	273 (47.3%)	39 (15.4%)	3 (2.7%)	24 (14.0%)
1	335 (55%)	266 (46.2%)	156 (61.4%)	60 (55%)	96 (56.1%)
2	119 (19.5%)	37 (6.6%)	59 (23.2%)	46 (42.2%)	49 (28.7%)
3	2 (3.3%)	0 (0%)	0 (0%)	0 (0%)	2 (1.2%)

CRC, colorectal cancer; O-G, oesophagogastric cancer.

Table 2
Sixty-day mortality in patients with GI cancer – results

Group	*n* of deaths within 60 days	Sixty-day mortality (%)	95% CI	Cause of death (%)		
				Treatment	Disease	Vascular syndrome
CRC advanced	609	21	3.4 (2.3–5.2)	2.3–5.2	0.2	3.3	0
CRC adjuvant	577	1	0.2 (0.0–1.2)	0.0–1.2	0	0	0.2
O-G platinum	254	16	6.3 (3.9–10.1)	3.9–10.1	0.4	4.7	1.2
O-G non-platinum	109	9	8.3 (4.4–15.3)	4.4–15.3	0	7.4	0.9
Pancreatic cancer	171	22	12.9 (8.7–18.9)	8.7–18.9	1.2	11.1	0.6

CRC, colorectal cancer; O-G, oesophagogastric cancer; GI, gastrointestinal; CI, Confidence Interval.

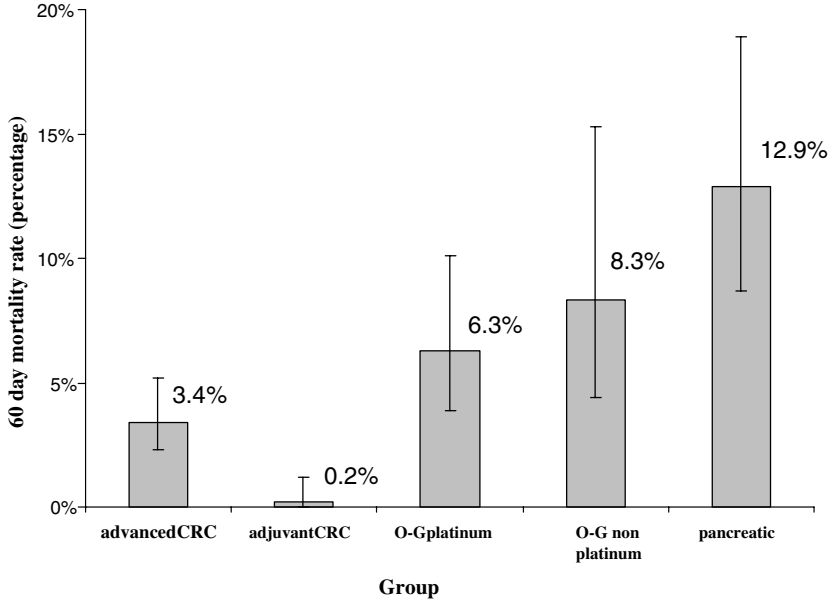

Fig. 4. Sixty day mortality of patients with GI cancer. CRC: colorectal cancer, O-G: oesophagogastric cancer.

4.7% of deaths were disease-related (12 patients). Three vascular syndrome deaths (1.2%) were noted (2 CVAs and 1 PE). Gender and age did not have a significant impact on 60-day mortality ($P = 0.552$ and $P = 0.122$, respectively). Comparison of patients in the PS 2/3 group with those in the with PS 0/1 group showed the relative risk of mortality in $\leqslant 60$ days to be significantly increased by 12.191 times ($P < 0.001$, 95% CI: 3.76–39.51).

In the non-platinum-treated patients with oesophagogastric cancer ($n = 109$), 9 deaths were reported within 60 days (8.3%) (95% CI: 4.4–15.3) (Table 2 and Fig. 4).

The 7.4% were disease-related (8 patients). One patient (0.9%) developed MI. Gender and age did not have a significant impact on the 60-day mortality rate ($P = 0.586$ and $P = 0.343$, respectively). When patients in the PS 2/3 group were compared with patients in the PS 0/1 group, the relative risk of mortality in $\leqslant 60$ days was increased by 5.474 times ($P = 0.04$, 95% CI: 1.1–27.7).

3.2. Colorectal cancer

One thousand one hundred and eighty-six patients had colorectal cancer. Six hundred and nine patients with advanced disease received 5FU ± MMC. The median age was 63 years (16–82 years). Five hundred and seventy seven patients received adjuvant chemotherapy with bolus 5FU/LV or PVI 5FU. The median age was 63 years (26–83 years) (Table 1).

In patients with advanced disease ($n = 609$), the 60-day mortality rate was 3.4% (21 patients) (95% CI: 2.3–5.2) (Table 2 and Fig. 4). Treatment-related deaths were 0.2% (one patient died of neutropenic sepsis). Disease-related deaths were 3.3% (20 patients). There were no vascular syndrome-induced deaths (Table 2).

Gender and age had no impact on the 60-day mortality rate ($P = 0.149$ and $P = 0.172$, respectively). Patients in the PS 2 and 3 group were compared with patients in the PS 0 and 1group and the relative risk of mortality in $\leqslant 60$ days was found to be significantly increased by 5.958 times ($P < 0.001$, 95% CI: 2.42–14.7).

In the adjuvant setting ($n = 577$), there was only 1 death occurring within 60 days (0.2%) (95% CI: 0.0–1.2) (Table 2 and Fig. 4), and this was caused by a MI. Gender, age or PS had no significant effect on the 60-day mortality rate in these patients ($P = 0.995$, $P = 0.222$ and $P = 0.992$, respectively).

3.3. Pancreatic cancer

One hundred and seventy one patients had pancreatic cancer and received treatment with PVI 5FU ± MMC. Their median age was 63 years (28–86 years) (Table 1).

The 60-day mortality rate was 12.9% (22 patients) (95% CI: 8.7–18.9) (Table 2 and Fig. 4). Two toxic deaths (1.2%) were noted, both associated with GI toxicities (grade III stomatitis and diarrhoea) and one also developed neutropenic sepsis. 11.1% (19 patients) were disease-related deaths. There was 1 vascular syndrome-induced death (due to PE) (0.6%). The age and gender of these patients had no impact on the 60-day mortality rate ($P = 0.287$ and $P = 0.486$, respectively). The relative risk of mortality in $\leqslant 60$ days was increased by 3.385 times when patients in the PS 2/3 group were compared with patients in the PS 0/1 group ($P = 0.009$, 95% CI 1.36–8.45).

The incidence of vascular syndrome-induced deaths in patients with oesophagogastric (1.2% – platinum; 0.9% – non-platinum) and pancreatic cancer (0.6%) was significantly higher than those with advanced colorectal cancer (0%) ($P = 0.02$ – Fisher's exact test). This difference remained, even if after controlling for age, PS and gender of the patients.

4. Discussion

Sixty-day all-cause mortality rates have been used to assess the safety of chemotherapy only recently. The main advantages for the use of this parameter are: 1. It is simple to estimate (it requires no assessment of the cause of death) and 2. It is applicable to completed and on-going trials [10]. Critically, the time-period includes the first two cycles of treatment when fatal toxicities occur most frequently.

The highest rate of treatment- and vascular syndrome-induced deaths was 1.8% (pancreatic cancer group). The lowest rate (0.1%) was seen in colorectal cancer patients.

In patients with advanced gastrointestinal malignancies, most early deaths were disease-related, irrespective of the primary site. However, the all-cause 60-day mortality rate was strongly influenced by the site of primary disease (highest in the pancreatic cancer group (12.9%) and lowest in the advanced colorectal cancer (3.4%) group). Predictably, there was a significantly lower rate for patients receiving adjuvant chemotherapy for colorectal cancer (0.2%).

In a review of IFL-associated 60-day mortality within the N9741 and C89803 trials, deaths were classified as treatment-related, treatment-unrelated or treatment-exacerbated [5]. Treatment-induced and treatment-exacerbated deaths were sub-divided into two syndromes based on toxicities: GI syndrome comprising diarrhoea, nausea, vomiting, anorexia and abdominal cramping, and vascular syndrome comprising acute, fatal MI, PE or CVA.

We decided to formulate the vascular syndrome-induced deaths as a separate category that may occur during or shortly after starting chemotherapy, and they could either be an isolated event or in association with GI or other drug-induced toxicities. By including these deaths as a separate category, a more objective picture of the aetiology of 60-day mortality will be established, as the investigator does not assign such deaths as being either treatment- or disease-related. This method of classifying the cause of 60-day mortality also permits an accurate comparison of the rate of vascular syndrome-induced deaths between patients with different diseases.

As shown, the incidence of such deaths in patients with oesophagogastric (1.2% – platinum; 0.9% – non-platinum) and pancreatic cancer (0.6%) was significantly higher then in patients with advanced colorectal cancer

(0) and this difference remained even after controlling for age, PS and gender.

In patients with oesophagogastric cancer, the all-cause 60-day mortality was higher in the group treated with non-platinum chemotherapy schedules (8.3% *versus* 6.3%). These patients were treated either with platinum [11–13] or non-platinum-containing chemotherapy [14], based upon co-morbidities and PS. Consequently, patients treated with a non-platinum regimen had a higher median age (73 years *versus* 59 years) and poorer PS (42.2% PS 2 *versus* 23.2% PS 2) than patients treated with a platinum regimen. These demographic differences between the two groups are further reflected by the higher 60-day disease-related mortality observed for patients treated with non-platinum-containing therapy (7.4% *versus* 4.7%). In the platinum-based chemotherapy group, the relative risk of mortality in $\leqslant 60$ days was 12.191 times more for patients with a poor PS. This risk reduced to 5.474 times for those patients with a poor PS receiving a non-platinum based regimen. However, it is not possible to draw definite conclusions about the relative impact of the ECF regimen compared with PVI 5FU monotherapy on 60-day disease-related mortality rate. ECF is an established reference regimen for oesophagogastric cancer, with response rates of above 40% being observed [11–13]. PVI 5FU monotherapy is a suitable regimen for palliation, of patients unfit for ECF, with response rates of 16.1% and a median overall survival rate of 6.3 months [14].

The all-cause, 60-day mortality rate was lower in the adjuvant (0.2%) compared with the advanced (3.4%) colorectal cancer group. A literature review reported by the NCCTG committee showed a 60-day treatment-related mortality rate for advanced colorectal cancer patients of 1% [1,2,6–8]. No vascular syndrome-induced deaths were reported in our advanced patient group. PS was important with regard to the 60-day mortality rate in these advanced colorectal cancer causes. Patients with a poorer PS had of 5.958 times more risk compared with those with a better PS. The current reference regimen for adjuvant treatment of colorectal cancer is 5FU/LV [18–21]. PS had no impact in this group.Treatment-related deaths are less acceptable in these patients and so it is important that new poly-chemotherapy regimens, and possibly immuno-chemotherapy regimens, are shown to have no excess 60-day mortality prior to acceptance as a 'standard of care'.

Most of patients with adenocarcinoma of the pancreas present with inoperable disease and an extremely poor prognosis [22]. The all-cause 60-day mortality rate was worst for this group (12.9%), with disease-related mortality rate of 11.1%. The CI was very high for this group (8.7–18.9), due to the small number of patients and more studies need to be performed to evaluate the 60-day mortality rate more accurately. The treatment-related death rate was also higher in these patients, (1.2%; three patients). All three patients had a PS of 2. Most of patients (approximately 70%) had a PS of 0 or 1. PS has been demonstrated (by multivariate Cox analysis) in previous studies to be an independent prognostic factor for the outcome of these patients [23]. Thus, a poor PS could contribute to a poor tolerance of treatment. The relative risk of mortality for patients with a poorer PS was found to be 3.385 times more than for patients with a better PS.

Until now, the 60-day mortality rates have only been compared between different chemotherapy regimens in recently completed randomised trials. This parameter has never before been related to the site of disease. This study has established a benchmark for all-cause 60-day mortality rates against which new chemotherapy or immuno-chemotherapy schedules evaluated in oesophagogastric, pancreatic or colorectal cancers can be compared.

Conflict of interest statement

None.

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