ORIGINAL ARTICLE

Septic patients with cancer: Do prehospital antibiotics improve survival?

A sub-analysis of the PHANTASi trial

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ABSTRACT

Background: Sepsis in patients with cancer is increasingly common and associated with high mortality. To date, no studies have examined the effectiveness of prehospital antibiotics in septic patients with cancer. This study aimed to compare survival of septic patients with cancer to those without and to evaluate the effect of prehospital antibiotics in septic patients with cancer.

Methods: We conducted a post-hoc sub-analysis of the PHANTASi (PreHospital ANTibioitcs Against Sepsis) trial database: a randomised controlled trial which enrolled patients with suspected sepsis who were transported to the emergency department by ambulance. Patients in the intervention group were administered prehospital intravenous antibiotics while those in the control group received usual care. We compared patients who had cancer to those who did not. Primary outcome was 28-day mortality; among the secondary outcomes, we included in-hospital mortality and 90-day mortality.

Results: 357(13.4%) of the 2658 included patients had cancer in the past five years, of which, 209 (58.5%) were included in the intervention and 148 (41.5%) usual care groups; 28-day mortality was significantly higher in patients who were diagnosed with cancer in the past five years than those without cancer in the past five years: 15.2% vs. 7.1%, respectively ($p < 0.001$).

Prehospital antibiotics in the group of patients with cancer in the last five years yielded no significant effect on survival. There were however, significantly fewer 30-day readmissions ($p = 0.031$) in the intervention group of cancer patients (12.2% vs 5.7%).

Conclusion: Prehospital antibiotics did not improve overall survival. However, there was a significant reduction in 30-day readmissions.

KEYWORDS

Cancer, mortality, prehospital antibiotics, readmission, sepsis

INTRODUCTION

Sepsis is a syndrome which often leads to high morbidity and mortality.[1-3] Although absolute mortality has decreased in recent years, incidence is still rising. Several factors are associated with increased mortality in septic patients, including age, gender, presence of organ dysfunction, and active cancer.

Retrospective studies in the last decade have found that early treatment with antibiotics is associated with better outcomes in sepsis patients,[4,5] although a recent prospective study found no benefit of prehospital antibiotics on overall survival (PHANTASi). The Surviving Sepsis Campaign currently recommends antibiotic treatment within one hour after arrival at the hospital.[6] However, whether early antibiotics administration lead to better outcomes in all sepsis patients is a matter of debate.[7,8]

Several studies have investigated the epidemiology of sepsis in patients with cancer.[9-12] The diagnosis of infection in this cohort is difficult as its early signs and symptoms are mimicked by non-infective causes, including the cancer

itself and responses to systemic anti-cancer treatment (SACT).[13,14] Retrospective studies in this sub-group of patients have shown that this population may benefit from early treatment with antibiotics.[15-17] Multiple studies have been conducted in septic cancer patients with neutropenia and shown that delay in administration of the first dose of antibiotics, as well as pneumonia and thrombocytopenia, were risk factors for severe complications.[12]

The aim of this study was to evaluate whether septic patients with cancer have a different survival rate compared to non-cancer patients, who have reached the emergency department (ED) by ambulance. In addition, we investigated the effect of early antibiotics administration in these two sub-groups on patient outcomes.

MATERIALS AND METHODS

Design and setting

A sub-analysis was conducted using the PHANTASi (PreHospital ANTibioitcs Against Sepsis) trial database.[7,18,] In this randomised controlled, open-labelled trial, we investigated whether improved recognition of sepsis and administration of antibiotics in the ambulance led to increased survival when compared to usual care (fluid resuscitation and supplementary oxygen). Patients under usual care received their first dose of antibiotics at the ED. Between June 2014 and June 2016, eligible patients who were transported to one of the 34 participating hospitals in the Netherlands were enrolled.

Sepsis was defined as: a diagnosed or suspected infection, a temperature of > 38°C or < 36°C, and a minimum of one other Severe Inflammatory Response Syndrome (SIRS) criterion (heart rate > 90 beats per minute or a respiratory rate > 20 per minute). Due to the lack of prehospital leucocyte test, this was not used as an inclusion criterion.

Sepsis severity was categorised into three groups according to the 2001 SSCM/ ESCIM/ ACCP/ ATS/ SIS International Sepsis definitions Conference guidelines:[19] uncomplicated (non-severe) sepsis, severe sepsis, and septic shock.

Data collection methods have been described elsewhere.[7] In short, data were collected by emergency medical services (EMS) personnel and the PHANTASi trial investigators. Variables collected included patient demographics, comorbidities, sepsis severity, mortality, and length of stay, among others. Infection site and microbiological data was also retrieved. The case record form has been published elsewhere.[7]

Methodology

A total of 2,658 patients were included in the PHANTASi trial. In this post-hoc review, we compared patients who had any type of cancer in the past five years to those who were cancer free. Patients who had benign neoplasms in the past five years were categorised into the latter group.

Cancers in our study were categorised into 18 categories: (1) bladder cancer, (2) breast cancer, (3) renal cancer, (4) prostate cancer, (5) leukaemia, (6) colorectal cancer, (7) hepatobiliary cancer, (8) melanoma, (9) lymphoma, (10) upper gastrointestinal cancer, (11) lung cancer, (12) pancreatic cancer, (13) head and neck cancer, including thyroid cancer, (14) myeloma, (15) gynaecological cancer, (16) sarcoma, (17) primary central nervous system (CNS) cancer, and (18) cancer of unknown primary origin.

An overview of cancer types that were included in each category can be found in the appendix (supplementary table 1)*.

Statistical analysis

The primary outcome of this study was 28-day mortality. Secondary outcomes included in-hospital mortality, 90-day mortality, focus of infection, time to antibiotics before arrival at the ED, time to antibiotics after arrival at the ED, 30-day readmission, intensive care unit (ICU) admission, length of hospital stay (LOS), temperature in the ambulance and at the ED, systolic blood pressure in the ambulance and at the ED, thrombocyte count at the ED, positive blood cultures, and ceftriaxone resistance. These clinical parameters were chosen as they have been described in the literature as being associated with mortality in septic patients with and without cancer.[1,12,15,20-28]

Descriptive statistics were used to describe patient characteristics, presented as frequency (proportion), mean ± standard deviation (SD), or as median (interquartile range (IQR)). Comparisons between the groups of patients with and without cancer were performed using the Pearson Chi-square. Confounders were identified and corrected for through logistic regression analyses. Power calculation showed that we were able to detect at least a 3.9% difference in 28-day mortality by using our sample size of 2,658 patients with a power of 80% (two-sided testing). All analyses were performed in IBM SPSS Statistics 22.0 (Chicago, USA), with $p < 0.05$ considered significant.

Ethics

The study protocol of the PHANTASi trial was approved by the medical ethical committee of the Amsterdam University Medical Centre, Location VU University Medical Centre, the coordinating centre, and all ethical committees of each participating hospital. Due to the complexity of the PHANTASi trial, the ethics committees granted approval to obtain deferred consent when necessary. Informed consent before study enrolment or deferred consent was obtained from all patients or their legal representatives or surrogates. All efforts were made by EMS personnel to obtain informed consent before study inclusion.

Table 1. *Type of cancer and mortality*

	n	In-hospital mortality (%)	28-day mortality (%)	90-day mortality (%)
Type of Cancer				
Bladder cancer	34	3 (8.2%)	3 (8.2%)	8 (23.5%)
Breast cancer	22	3 (13.6%)	4 (18.2%)	4 (18.2%)
Renal cancer	5	0 (0%)	0 (0%)	1 (20%)
Prostate cancer	44	5 (11.4%)	7 (15.9%)	8 (18.2%)
Leukaemia	12	2 (16.7%)	5 (41.7%)	5 (41.7%)
Colorectal cancer	43	1 (23.2%)	2 (4.7%)	4 (9.3%)
Hepatobiliary cancer	5	0 (0%)	1 (20%)	2 (40%)
Melanoma	5	0 (0%)	0 (0%)	0 (0%)
Lymphoma	18	2 (11.1%)	3 (16.7%)	4 (22.2%)
Upper gastrointestinal cancer	14	3 (21.4%)	5 (35.7%)	8 (57.1%)
Lung cancer	48	3 (6.3%)	9 (18.8%)	14 (29.1%)
Pancreatic cancer	10	1 (10%)	1 (10%)	2 (20%)
Head and neck cancer (including thyroid)	7	1 (14.2%)	1 (14.2%)	1 (14.2%)
Myeloma	10	2 (20%)	3 (30%)	3 (30%)
Gynaecological cancer	5	0 (0%)	0 (0%)	1 (20%)
Sarcoma	0	0 (0%)	0 (0%)	0 (0%)
Primary CNS cancer	0	0 (0%)	0 (0%)	0 (0%)
Cancer of unknown primary origin	75	7 (9.3%)	10 (13.3%)	17 (22.7%)

CNS = central nervous system; n = number of patients

Table 2. *Sepsis severity and mortality all patients*

	Cancer	No cancer	p-value
In-hospital mortality, n (%)*			
Sepsis	2 (1.5)	7 (0.8)	0.911
Severe sepsis	22 (11.1)	96 (7.3)	0.266
Septic shock	7 (38.9)	21 (25.9)	0.524
Other diagnosis	2 (25.0)	2 (4.8)	0.144
28-day mortality, n (%)*			
Sepsis	7 (5.3)	13 (1.5)	0.278
Severe sepsis	36 (18.2)	125 (9.5)	0.125
Septic shock	9 (50.0)	19 (23.5)	0.349
Other diagnosis	2 (28.6)	5 (12.8)	0.824
90-day mortality, n (%)*			
Sepsis	18 (13.5)	30 (3.5)	0.047
Severe sepsis	51 (25.8)	173 (13.2)	0.044
Septic shock	9 (50.0)	25 (30.9)	0.941
Other diagnosis	4 (50.0)	6 (14.0)	0.303

*Percentage mortality per sepsis category
n = number of patients

RESULTS

Among all included subjects in PHANTASi trial, 357 (13.4%) were diagnosed with cancer within five years prior to their inclusion in the study, while the remaining 2,301 (86.6%) patients did not. The most common types of cancer were colorectal, prostate, and lung cancer. Table 1 provides an overview of the mortality rates per cancer type. In the group of patients with cancer, 148 patients (41.5%) were in the usual care group and 209 patients (58.5%) were in the intervention group with a mean age of 74.8 ± 9.4 years and 74.7 ± 9.7 years, respectively. See table 2 and 3 for more details on sepsis severity and mortality.

Mortality

Difference between patients with and without cancer in the total population

Overall, in patients with and without cancer there was a significantly higher age-adjusted in-hospital mortality (9.2% vs. 5.5%, respectively; p = 0.008), 28-day mortality (15.2% vs. 7.1%, respectively; p < 0.001) and 90-day mortality (23.0% vs. 10.2%, respectively; p < 0.001) (table 4).

Usual care group

Among patients in the usual care group, the age-adjusted in-hospital mortality between patients with and without cancer did not differ significantly (6.8% vs. 5.8%, respectively; p = 0.715). However, those with cancer had a significantly higher age-adjusted 28-day mortality (15.5% vs. 7.5%, respectively; p = 0.002) and 90-day mortality (26.4% vs. 10.1%, respectively; p < 0.001) than those without cancer (table 4).

Intervention group

Among subjects in the intervention group, patients with cancer had a significantly higher age-adjusted mortality than patients without cancer in all outcomes: in-hospital mortality (11.0% vs 5.2%, respectively; p = 0.002), 28-mortality (14.9% vs 6.8%, respectively; p < 0.001) and 90-day mortality (20.6% vs 10.3%, respectively; p < 0.001) (table 4).

Patients with cancer < 5 years

In the group of patients with cancer, there were no significant differences between the usual care compared to the intervention group for age-adjusted in-hospital (6.8% vs 11.0%, respectively; p = 0.173), 28-day (15.5% vs 14.9%, respectively; p = 0.203) and 90-day (26.4% vs 20.6%, respectively; p = 0.870) mortality (table 5). See supplementary figures 1-3 and supplementary tables 21-24 for more details on mortality.

Table 3. *Sepsis severity and mortality in patients with cancer < 5 years*

	Intervention	Usual care	p-value
In-hospital mortality, n (%)*			
Sepsis	2 (2.6)	0	0.336
Severe sepsis	14 (11.8)	8 (10.1)	0.284
Septic shock	5 (50)	2 (25.0)	0.911
Other diagnosis	2 (50)	0	0.336
28-day mortality, n (%)*			
Sepsis	5 (6.6)	2 (3.5)	0.421
Severe sepsis	19 (16.0)	17 (21.5)	0.331
Septic shock	6 (60.0)	3 (37.5)	0.538
Other diagnosis	1 (33.3)	1 (25.0)	0.829
90-day mortality, n (%)*			
Sepsis	9 (11.8)	9 (15.8)	0.815
Severe sepsis	27 (22.7)	24 (30.4)	0.907
Septic shock	6 (60.0)	3 (37.5)	0.365
Other diagnosis	1 (25.0)	3 (75.0)	0.260

*Percentage mortality per sepsis category
n = number of patients

Table 4. *Mortality between patients with and without cancer < 5 years*

	Cancer < 5 years (%)	No cancer (%)	p-value	p-value, age-adjusted
All patients				
In-hospital mortality	33 (9.2)	126 (5.5)	0.005	0.008
28-day mortality	54 (15.2)	162 (7.1)	< 0.001	< 0.001
90-day mortality	82 (23.0)	234 (10.2)	< 0.001	< 0.001
Intervention group				
In-hospital mortality	23 (11.0)	69 (5.2)	0.001	0.002
28-day mortality	31 (14.9)	89 (6.8)	< 0.001	< 0.001
90-day mortality	43 (20.6)	135 (10.3)	< 0.001	< 0.001
Usual care group				
In-hospital mortality	10 (6.8)	57 (5.8)	0.643	0.715
28-day mortality	23 (15.5)	73 (7.5)	0.001	0.002
90-day mortality	39 (26.4)	99 (10.1)	< 0.001	< 0.001

Table 5. *Mortality patients with cancer < 5 years*

	Intervention (%)	Usual care (%)	p-value	p-value, age-adjusted
In-hospital mortality	23 (11.0)	10 (6.8)	0.172	0.173
28-day mortality	31 (14.9)	23 (15.5)	0.869	0.870
90-day mortality	43 (20.6)	39 (26.4)	0.201	0.203

Secondary outcomes

Difference between patients with and without cancer

No significant difference was observed for LOS between subjects with and without cancer (8.1 vs. 8.0 days, p = 0.867). An overview of vital parameters and laboratory findings of both groups can be found in the supplementary tables 2 and supplementary tables 11-21.

Usual care group

In the usual care group, no significant difference was observed between patients with and without cancer in terms of the frequency of ICU admissions (p = 0.589) and 30-day readmissions (p = 0.076). The average LOS in patients with vs. without cancer were 9 days (IQR 3.25-9.0) and 7.8 days (IQR 3.0-9.0), respectively (p = 0.922).

Intervention group

In the intervention group, there was no significant difference in frequency of ICU admissions or 30-day readmissions between patients with and without cancer (p = 0.155 vs. p = 0.290, respectively). Mean LOS in patients with vs. without cancer were 8.3 days (IQR 3.25-9.0) and 8.2 days (IQR 3.0-9.0), respectively (p = 0.898).

Patients with cancer < 5 years: usual care group vs. intervention group

Patients with cancer had a median time to antibiotics of 26 minutes (IQR 19-34) prior to arrival at the ED in the intervention group; in the usual care group, patients had a median time to antibiotics of 76 minutes (IQR 36-134.5) after arriving at the ED, leading to a mean time advantage of 102 minutes for the intervention group.

In patients with cancer, there was no significant difference in ICU admissions (p = 0.947) between the intervention group and the usual care group. The average LOS in the intervention group and usual care group was 8.3 ± 8.1 days and 7.9 ± 10.7 days, respectively (p = 0.714). However, 30-day readmission was significantly lower in the intervention group (p < 0.031).

Chemotherapy one month prior to ED was not significantly correlated with increased in-hospital, 28-day, or 90-day

mortality (supplementary tables 3 and 4). Information on micriobiological data can be found in supplementary tables 5-10.

DISCUSSION

To the best of our knowledge, this is the first study to compare the effect of prehospital antibiotics in septic patients with and without cancer. In the complete patient population included in the PHANTASi trial, when comparing patients with and without cancer, we found a significantly higher in-hospital (9.2% vs. 5.5%, respectively), 28-day (15.2% vs. 7.1%, respectively) and 90-day (23.0% vs. 10.2%, respectively) mortality rates. Despite receiving their first dose of intravenous antibiotics 102 minutes earlier, septic patients with cancer in the intervention group did not have significantly different mortality rates to those receiving usual care. However, septic patients with cancer in the intervention group did have a significantly lower readmission rate.

Previous studies compared clinical outcomes of patients with and without sepsis. However, these studies only included non-ED patients or patients without prehospital intravenous antibiotics.[20] Nurse-led protocols for sepsis and cancer patients have been shown to be an effective, safe, and sustainable method for early antibiotic administration but have not demonstrated a significant decrease in mortality.[29] Similarly, in the PHANTASi trial, EMS personnel were trained in the recognition of sepsis, which lead to an improvement in the recognition of sepsis as well as time to antibiotics.

Following SACT, cancer patients may produce vasoactive pro-inflammatory cytokines such as interleukin (IL)-2, IL-6, and tumor necrosis factor. This, together with the ability of the malignancy itself to mimic an infective driver of SIRS, can give a false impression that a cancer patient has sepsis.[30] This alternative pathway is responsible for a proportion of sepsis presentations in patients with cancer and may partially explain the ineffective prehospital antibiotics on clinical outcomes in these patients.

Our study has a number of strengths. First, this study had a large sample size of septic patients of whom 357 had cancer. Previous studies in similar populations had significantly smaller sample sizes.[20,31] Second, this is the first study to compare the effect of prehospital intravenous antibiotics by EMS personnel in septic patients with and without cancer. Other studies have investigated either septic patients[1-3,32] or cancer patients with febrile neutropenia.[11,12] Third, a retrospective chart analysis was conducted on PHANTASi trial data by two acute physicians and an infectious diseases specialist, which allowed us to efficiently include patients with sepsis. In addition, in the PHANTASi trial, sepsis severity was classified by reviewing available information such as admission letters, vital parameters, lab results, and discharge papers available in electronic patient charts.[7] These thorough reviews ensured high-quality samples and data. Fourth, this study investigated several factors associated with mortality in septic patients with and without cancer, described in literature, including time to antibiotics, systolic blood pressure, temperature, thrombocyte count, haemoglobin levels, C-reactive protein levels, leucocyte count, neutrophil count, gram-negative and gram-positive bacteraemia, type of cancer, and chemotherapy prior to ED admission.[1,12,15,20-28]

Septic patients have an increased risk of readmission and unplanned admissions after discharge. This risk is higher in septic patients with cancer.[23] Interestingly, we found a lower 30-day readmission in cancer patients who received prehospital antibiotics compared to those who did not. This same trend was found in the PHANTASi trial.[7] A possible explanation has been suggested for this effect that early antibiotics administration prevents the development of organ failure during the initial hospital admission which, in turn prevents readmission.[33]

Despite the smaller sample size of studies mentioned and minor differences in categorising cancer types, the main groups of cancer are similar in our study compared to others.[15,20]

Despite these strengths, our study also has a few limitations. First, our study was a sub-analysis of the PHANTASi trial, which inevitably leads to limitations. Although we did not apply stratified randomisation on the basis of cancer, we had a relatively large sample size compared to other studies on septic patients with cancer. Second, we had relatively limited amount of data on the cause of death as we did not have long-term follow-up. We could only retrieve data on in-hospital mortality and documented mortality by family members. Third, we included all patients with cancer in the past five years rather than only those with a currently an active form of malignancy due to absence of data. Despite these limitations, we did find a significantly higher mortality rate in septic patients with cancer (five years prior to the ED admission) compared to those who are cancer free.

Early antibiotic administration remains a paradigm of care for cancer patients presenting with sepsis and many studies have demonstrated the challenges of achieving this through routine care. This study shows that paramedic administration of intravenous antibiotics is a safe and effective strategy for decreasing the time to intravenous antibiotics in septic patients. However, in this unselected group of cancer patients with sepsis, this did not improve mortality and further studies are required to determine markers of high-risk patients who will benefit from this intervention.

CONCLUSION

Septic patients with cancer had higher in-hospital, 28-day, and 90-day mortalities compared to those without. Prehospital antibiotics did not lead to a decrease in mortality in patients with cancer, but did reduce 30-day readmission rate. Future studies should focus on optimisation of the treatment of septic patients with active malignancy.

* For supplementary tables and figures, see njmonline.nl

DISCLOSURES

All authors declare no conflict of interest.

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APPENDIX

Supplementary tables and figures

Supplementary table 1. *Categories of cancer*

Category	Included cancers
Bladder cancer	Bladder cancer
Breast cancer	Breast cancer
Renal Cancer	Kidney cancer
Prostate cancer	Prostate cancer
Leukaemia	Chronic lymphocytic leukaemia Acute myeloid leukaemia Chronic myeloid leukaemia
Colorectal cancer	Rectal cancer Sigmoid cancer Colon cancer Caecum cancer Duodenal cancer
Hepatobiliary cancer	Biliary duct cancer Gallbladder cancer
Melanoma	Melanoma
Lymphoma	Lymphoma T-cell lymphoma B-cell lymphoma Mantel cell lymphoma Follicular lymphoma Hodgkin lymphoma
Upper gastrointestinal cancer	Oesophageal cancer Gastric cancer
Lung cancer	Lung cancer
Pancreatic cancer	Pancreatic cancer
Head and neck cancer (including thyroid)	Larynx cancer Oral cancer Papillary thyroid cancer Thyroid cancer
Myeloma	Multiple myeloma
Gynaecological cancer	Vulvar cancer Cervix cancer Endometrium cancer Uterus cancer Ovarian cancer
Sarcoma	Sarcoma
Primary CNS cancer	Primary CNS cancer
Cancer of unknown primary	Unknown origin of cancer

CNS = central nervous system

Supplementary table 2. *Characteristics of all patients at baseline*

Characteristic	Cancer (n = 357)	No cancer (n = 2301)
Age, year	74.7 ± 9.6	72.5 ± 14.3
Male, n (%)	245 (68.6)	1283 (55.8)
Method of referral, n (%)		
General practitioner	246 (68.9)	1685 (73.2)
Other specialist	11 (3.1)	47 (2.0)
Self-referral	95 (26.6)	526 (22.9)
Unknown	5 (1.4)	43 (1.9)
Charlson comorbidity score (median/IQR)	4 (3-6)	1 (0-2)
Corrected Charlson comorbidity score (median/IQR)*	1 (0-3)	1 (0-2)
Underlying chronic conditions		
Hypertension	132 (37.0)	848 (36.9)
Chronic pulmonary disease	93 (26.1)	700 (30.4)
Diabetes	81 (22.7)	559 (24.3)
Atrial fibrillation	51 (14.3)	353 (15.3)
Cerebrovascular disease	49 (13.7)	365 (15.9)
Peripheral vascular disease	39 (10.9)	269 (11.7)
Congestive heart disease	30 (8.4)	251 (10.9)
Myocardial infarction	27 (7.6)	251 (10.9)
Renal disease	38 (10.6)	207 (9.0)
Smoking	33 (9.2)	237 (10.3)
Dementia	7 (2.0)	128 (5.6)
Liver disease	10 (2.8)	52 (2.3)
Peptic ulcer disease	8 (2.2)	47 (2.0)
AIDS or HIV	0	8 (0.3)
DNR policy at admission, n (%)	55 (25.3)	273 (16.5)
Severity of sepsis		
Sepsis	133 (37.3)	861 (37.4)
Severe sepsis	198 (55.5)	1316 (57.2)
Septic shock	18 (5.0)	81 (3.5)
Other diagnosis	8 (2.2)	43 (1.9)
Organ dysfunction		
Respiratory	114 (32.2)	800 (35.1)
Tissue perfusion	81 (22.9)	471 (20.6)
Neurologic	83 (23.5)	493 (21.7)
Cardiovascular	48 (13.6)	249 (10.9)
Renal	29 (8.2)	168 (7.4)
Hypotension	30 (8.5)	150 (6.6)
Liver	12 (3.4)	69 (3.0)
Haematologic	9 (2.6)	31 (1.4)
Ileus	2 (0.6)	10 (0.4)
TTA before arriving at the ED (IQR)	26 (19-34)	26 (19-34)
TTA after arriving at the ED (IQR)	76 (36-134.5)	67 (36-127)

* Corrected Charlson comorbidity score is the Charlson score without points for cancer or metastasis
AIDS = acquired immune deficiency syndrome; DNR = do not resuscitate; ED = emergency department; HIV = human immunodeficiency virus; IQR = interquartile range; n = number of patients; TTA = trauma team activation

Supplementary table 3. *Characteristics of the patients with cancer at baseline (total n = 357)*

Characteristic	Usual care (n = 148)	Intervention group (n = 209)
Age, year	74.8 ± 9.4	74.7 ± 9.7
Male, n (%)	108 (73.0)	137 (65.6)
Method of referral, n (%)		
General practitioner	102 (68.9)	144 (68.9)
Other specialist	5 (3.4)	6 (2.9)
Self-referral	38 (25.7)	57 (27.3)
Unknown	3 (2.0)	2 (1.0)
Charlson comorbidity score (median/IQR)	5 (3-6)	4 (3-6)
Corrected Charlson comorbidity score (median/IQR)*	1 (0-3)	2 (0-3)
Underlying chronic conditions		
Hypertension	57 (38.5)	75 (35.9)
Chronic pulmonary disease	36 (24.3)	57 (27.3)
Diabetes	29 (19.6)	52 (24.9)
Atrial fibrillation	18 (12.2)	33 (15.8)
Cerebrovascular disease	19 (12.8)	30 (14.4)
Peripheral vascular disease	12 (8.1)	27 (12.9)
Congestive heart disease	10 (6.8)	20 (9.6)
Myocardial infarction	8 (5.4)	19 (9.1)
Renal disease	13 (8.8)	25 (12.0)
Smoking	17 (11.5)	16 (7.7)
Dementia	2 (1.4)	5 (2.4)
Liver disease	4 (2.7)	6 (2.9)
Peptic ulcer disease	2 (1.4)	6 (2.9)
AIDS or HIV	0	0
DNR policy at admission, n (%)	19 (21.6)	36 (27.9)
Severity of sepsis		
Sepsis	57 (38.5)	76 (36.4)
Severe sepsis	79 (53.4)	119 (56.9)
Septic shock	8 (5.4)	10 (4.8)
Other diagnosis	4 (2.7)	4 (1.9)
Organ dysfunction		
Respiratory	39 (26.7)	75 (36.1)
Tissue perfusion	38 (26.0)	43 (20.8)
Neurologic	32 (21.8)	51 (24.8)
Cardiovascular	22 (15.1)	26 (12.6)
Renal	11 (7.5)	18 (8.7)
Hematologic	2 (1.4)	7 (3.4)
TTA before arriving at the ED (IQR)		26 (19-34)
TTA after arriving at the ED (IQR)	76 (36-134.5)	
Type of cancer		
Bladder cancer	15 (10.1)	19 (9.1)
Breast cancer	6 (4.0)	16 (7.6)
Renal cancer	1 (0.7)	4 (1.9)
Prostate cancer	24 (16.2)	20 (9.6)
Leukaemia	4 (2.7)	8 (3.8)
Colorectal cancer	22 (14.9)	21 (10.0)
Hepatobiliary cancer	3 (2.1)	2 (0.9)
Melanoma	0 (0)	5 (2.4)
Lymphoma	5 (3.3)	13 (6.3)
Upper gastrointestinal cancer	6 (4.0)	8 (3.8)
Lung cancer	20 (13.5)	28 (13.4)
Pancreatic cancer	5 (3.4)	5 (2.4)
Head and neck cancer (including thyroid)	3 (2.0)	4 (1.9)
Myeloma	4 (2.7)	6 (2.8)
Gynaecological cancer	2 (1.3)	3 (1.4)
Sarcoma	0 (0)	0 (0)
Primary CNS cancer	0 (0)	0 (0)
Cancer of unknown primary	28 (18.9)	47 (22.6)
Metastases	52 (42.3)	52 (32.1)
Chemotherapy		
< 1 month	24 (20.5)	33 (21.4)

* Corrected Charlson comorbidity score is the Charlson score without points for cancer or metastasis

AIDS = acquired immune deficiency syndrome; DNR = do not resuscitate; ED = emergency department; HIV = human immunodeficiency virus; IQR = interquartile range; n = number of patients; TTA = trauma team activation

Supplementary table 4. *Chemotherapy < 1 month and mortality*

	Chemotherapy < 1 month (n = 57)	No Chemotherapy < 1 month (n = 214)	p-value
In-hospital mortality	7 (12.3)	19 (8.9)	0.438
28-day mortality	12 (21.1)	28 (13.1)	0.136
90-day mortality	17 (29.8)	43 (20.1)	0.116

n = number of patients

Supplementary table 5. *Microbiology all patients*

	Cancer (n = 357)	No cancer (n = 2301)	p-value
Site of infection/focus of sepsis, n (%)			
Respiratory tract	181 (50.7)	1285 (55.8)	0.069
Urinary tract	83 (23.2)	490 (21.3)	0.403
Abdomen	33 (9.2)	144 (6.3)	0.035
Soft tissue/skin	13 (3.6)	131 (5.7)	0.111
Central nervous system	11 (0.5)	0 (0.0)	0.191
Catheter-related infection	3 (0.8)	1 (0.0)	< 0.001
Other	10 (2.8)	70 (3.0)	0.804
Unknown	28 (7.8)	134 (5.8)	0.138
No infection	6 (1.6)	35 (1.5)	-

n = number of patients

Supplementary table 6. *Microbiology patients with cancer < 5 years*

	Usual care group (n = 148)	Intervention group (n = 209)	p-value
Site of infection/focus of sepsis, n (%)			
Respiratory tract	74 (50.0)	107 (51.2)	0.824
Urinary tract	43 (29.1)	40 (19.1)	0.029
Abdomen	15 (10.1)	18 (8.6)	0.625
Soft tissue/skin	1 (0.7)	12 (5.7)	0.012
Catheter-related infection	2 (1.4)	1 (0.5)	0.373
Other	0	10 (4.8)	0.007
Unknown	10 (6.8)	18 (8.6)	0.521
No infection	3 (2.0)	3 (1.4)	-

n = number of patients

Supplementary table 7. *Cause of death*

Cause of death, n (%)	Usual care (n = 16)	Intervention (n = 14)
Sepsis*	11 (68.8)	8 (57.1)
Cancer	2 (12.5)	2 (14.3)
Cardiac arrhythmia	2 (12.5)	1 (7.1)
Cerebrovascular accident	0 (0)	1 (7.1)
Multiple organ failure	1 (6.3)	0 (0)
Refractory haemodynamic shock	0 (0)	1 (7.1)
Euthanasia	0 (0)	1 (7.1)

*Includes sepsis, urosepsis, pneumosepsis, and pneumonia.
n = number of patients

Supplementary table 8. *Mortality and ceftriaxone resistance in patients with cancer*

	Intervention (n = 74)	Usual care (n = 37)
In-hospital mortality, n (%)		
Ceftriaxone resistant	0 (0)	0 (0)
Resistant to other antibiotics	3 (13.6)	1 (10.0)
No resistance	5 (25.0)	3 (21.4)
Contamination in blood culture	2 (7.1)	0 (0)
28-day mortality, n (%)		
Ceftriaxone resistant	1 (25.0)	0 (0)
Resistant to other antibiotics	5 (22.7)	2 (20.0)
No resistance	6 (31.6)	4 (28.6)
Contamination in blood culture	2 (7.1)	2 (25.0)
90-day mortality, (%)		
Ceftriaxone resistant	2 (50.0)	1 (20.0)
Resistant to other antibiotics	6 (27.3)	6 (60.0)
No resistance	7 (35.0)	5 (35.7)
Contamination in blood culture	5 (17.9)	2 (25.0)

n = number of patients

Supplementary table 9. *Mortality and blood cultures in all patients*

All Patients (n = 2657)	No	Yes	p-value
In-hospital mortality, n (%)			
Gram positive	96 (5.1)	63 (8.2)	0.002
Gram negative	106 (5.4)	52 (7.3)	0.067
28-day mortality, n (%)			
Gram positive	137 (7.3)	79 (10.3)	0.011
Gram negative	156 (8.0)	60 (8.5)	0.701
90-day mortality, n (%)			
Gram positive	201 (10.6)	115 (15.0)	0.002
Gram negative	219 (11.2)	96 (13.6)	0.102
Cancer (n = 357)	**No**	**Yes**	**p-value**
In-hospital mortality, n (%)			
Gram positive	22 (8.3)	11 (11.8)	0.317
Gram negative	20 (8.1)	13 (11.7)	0.279
28-day mortality, n (%)			
Gram positive	38 (14.4)	16 (17.2)	0.524
Gram negative	34 (13.8)	20 (18.2)	0.289
90-day mortality, n (%)			
Gram positive	55 (20.8)	27 (29.0)	0.106
Gram negative	53 (21.5)	29 (26.1)	0.341
No cancer (n = 2300)	**No**	**Yes**	**p-value**
In-hospital mortality, n (%)			
Gram positive	74 (4.6)	52 (7.7)	0.003
Gram negative	86 (5.1)	39 (6.5)	0.171
28-day mortality, n (%)			
Gram positive	99 (6.1)	63 (9.3)	0.006
Gram negative	122 (7.2)	40 (6.7)	0.691
90-day mortality, n (%)			
Gram positive	146 (9.0)	88 (13.0)	0.004
Gram negative	166 (9.8)	67 (11.2)	0.306

n = number of patients

Supplementary table 10. *Mortality and blood cultures in patients with cancer < 5 years*

Intervention (n = 209)	No	Yes	p-value
In-hospital mortality, n (%)			
Gram positive	14 (9.9)	9 (13.4)	0.441
Gram negative	13 (8.4)	10 (18.2)	0.048
28-day mortality, n (%)			
Gram positive	21 (14.9)	10 (14.9)	0.995
Gram negative	18 (11.7)	13 (24.1)	0.028
90-day mortality, n (%)			
Gram positive	27 (19.0)	16 (23.9)	0.417
Gram negative	27 (17.5)	16 (29.1)	0.069
Usual care (n = 148)	**No**	**Yes**	**p-value**
In-hospital mortality, n (%)			
Gram positive	8 (6.6)	2 (7.7)	0.834
Gram negative	7 (7.6)	3 (5.4)	0.597
28-day mortality, n (%)			
Gram positive	17 (13.9)	6 (23.1)	0.243
Gram negative	16 (17.4)	7 (12.5)	0.426
90-day mortality, n (%)			
Gram positive	28 (23.0)	11 (42.3)	0.042
Gram negative	26 (28.3)	13 (23.2)	0.499

n = number of patients

Supplementary table 11. *Haemoglobin and mortality of all patients*

	n	In-hospital mortality	p-value	28-day mortality	p-value	90-day mortality	p-value
Hb ≤ 5	54	8 (14.8)	0.006	9 (17.0)	0.018	17 (31.5)	< 0.001
Hb ≤ 6	208	35 (16.8)	< 0.001	41 (19.8)	< 0.001	64 (30.8)	< 0.001
Hb ≤ 7	624	59 (9.4)	< 0.001	79 (12.7)	< 0.001	126 (20.1)	< 0.001
Hb ≤ 8	1341	97 (7.2)	0.006	131 (9.8)	0.002	198 (14.8)	< 0.001
Hb ≤ 9	327	142 (6.6)	0.007	193 (9.0)	0.001	280 (13.0)	< 0.001

Hb = haemoglobin; n = number of patients

Supplementary table 12. *CRP and mortality of all patients*

	n	In-hospital mortality	p-value	28-day mortality	p-value	90-day mortality	p-value
CRP > 5	2554	155 (6.1)	0.370	208 (8.2)	0.956	305 (11.9)	0.723
CRP > 50	1698	109 (6.4)	0.211	148 (8.7)	0.144	218 (12.8)	0.046
CRP > 100	1134	85 (7.5)	0.005	105 (9.3)	0.071	152 (13.4)	0.038
CRP > 200	2085	47 (8.2)	0.011	55 (9.6)	0.143	77 (13.5)	0.186

CRP = C-reactive protein; n = number of patients

Supplementary table 13. *Leucocytes and mortality of all patients*

	n	In-hospital mortality	p-value	28-day mortality	p-value	90-day mortality	p-value
L ≤ 2.0	43	9 (20.9)	< 0.001	11 (25.6)	< 0.001	16 (37.2)	< 0.001
L ≤ 3.9	107	15 (14.0)	< 0.001	19 (17.8)	< 0.001	26 (24.3)	< 0.001
L 4.0 - 12.0	1177	65 (5.5)	0.369	95 (8.1)	0.925	131 (11.1)	0.279
L ≥ 12.1	1373	79 (5.8)	0.608	102 (7.4)	0.171	159 (11.6)	0.607
L ≥ 25.0	186	23 (12.4)	< 0.001	25 (13.4)	0.006	38 (20.4)	< 0.001

L = leucocyte count

Supplementary table 14. *Temperature and mortality of patients with cancer < 5 years*

	In the ambulance			At the Emergency Department		
	Temperature < 36ºC	Temperature > 36ºC	p-value	Temperature < 36ºC	Temperature > 36ºC	p-value
In-hospital mortality	2 (20.0)	31 (8.9)	0.234	2 (28.6)	31 (8.9)	0.075
28-day mortality	3 (30.0)	51 (14.7)	0.185	2 (28.6)	52 (14.9)	0.318
90-day mortality	3 (30.0)	79 (22.8)	0.592	2 (28.6)	80 (22.9)	0.722

Supplementary table 15. *Temperature and mortality of patients with cancer < 5 years*

	In the ambulance			At the Emergency Department		
	Temperature < 38ºC	Temperature > 38ºC	p-value	Temperature < 38ºC	Temperature > 38ºC	p-value
In-hospital mortality	3 (17.6)	30 (8.8)	0.222	8 (12.9)	24 (8.3)	0.250
28-day mortality	4 (23.5)	50 (14.8)	0.328	10 (16.4)	43 (14.8)	0.756
90-day mortality	4 (23.5)	78 (23.0)	0.960	13 (21.0)	68 (23.4)	0.674

Supplementary table 16. *Haemoglobin and mortality of patients with cancer < 5 years*

	n	In-hospital mortality	p-value	28-day mortality	p-value	90-day mortality	p-value
Hb ≤ 5	19	4 (21.1)	0.068	5 (26.3)	0.164	8 (42.1)	0.042
Hb ≤ 6	65	10 (15.4)	0.059	17 (26.2)	0.006	25 (38.5)	0.001
Hb ≤ 7	160	18 (11.3)	0.238	31 (19.5)	0.041	49 (30.6)	0.002
Hb ≤ 8	244	24 (9.8)	0.570	38 (15.6)	0.717	62 (25.4)	0.107
Hb ≤ 9	319	32 (10.0)	0.137	52 (16.4)	0.072	79 (24.8)	0.019

Hb = haemoglobin

Supplementary table 17. *CRP and mortality of patients with cancer < 5 years*

	n	In-hospital mortality	p-value	28-day mortality	p-value	90-day mortality	p-value
CRP > 5	343	32 (9.3)	0.782	52 (15.2)	0.925	80 (23.3)	0.431
CRP > 50	244	26 (10.7)	0.176	41 (16.9)	0.189	66 (27.0)	0.007
CRP > 100	170	18 (10.6)	0.403	29 (17.1)	0.342	50 (29.4)	0.006
CRP > 200	74	9 (12.7)	0.265	16 (22.5)	0.053	26 (36.6)	0.002

CRP = C-reactive protein

Supplementary table 18. *Leucocytes and mortality of patients with cancer < 5 years*

	n	In-hospital mortality	p-value	28-day mortality	p-value	90-day mortality	p-value
L ≤ 2.0	27	3 (11.1)	0.728	5 (18.5)	0.614	7 (25.9)	0.704
L ≤ 3.9	42	6 (14.3)	0.230	8 (19.0)	0.456	10 (23.8)	0.890
L 4.0-12.0	131	11 (8.4)	0.674	22 (16.8)	0.514	32 (24.4)	0.618
L ≥ 12.1	184	16 (8.7)	0.712	24 (13.1)	0.267	40 (21.7)	0.569
L ≥ 25.0	38	6 (15.8)	0.141	10 (26.3)	0.043	14 (36.8)	0.031

L = leucocyte count

Supplementary table 19. *Neutrophils and mortality of patients with cancer < 5 years*

	n	In-hospital mortality	p-value	28-day mortality	p-value	90-day mortality	p-value
N < 1.0	18	4 (22.2)	0.004	5 (27.7)	0.002	7 (38.9)	< 0.001
N < 1.5	20	4 (20.0)	0.008	5 (25.0)	0.006	7 (35.0)	0.001
N 1.5-9.0	466	27 (5.8)	0.847	40 (8.6)	0.705	59 (12.7)	0.573
N > 9.0	2172	127 (5.8)	0.521	170 (6.5)	0.228	249 (11.5)	0.143

N = neutrophil count

Supplementary table 20. *Physiological and laboratory variables of patients with cancer < 5 years*

	In ambulance			At the Emergency Department		
Variable	**Usual Care (n = 148)**	**Intervention group (n = 209)**	**p-value**	**Usual Care (n = 148)**	**Intervention group (n = 209)**	**p-value**
SIRS criteria						
Temperature, °C	38.9 ± 9.9	38.9 ± 10.2	0.984	38.8 ± 1.0	38.6 ± 1.0	0.188
Respiratory rate, per minute	25.9 ± 7.2	26.2 ± 6.8	0.673	24.8 ± 7.1	24.5 ± 6.8	0.805
Heart rate, per minute	113.7 ± 21.4	113.0 ± 20.0	0.735	107.3 ± 21.1	104.9 ± 20.3	0.295
White cell count, *10^9/l median (IQR)	-	-	-	11.7 (8.4-16.8)	12.9 (7.5-17.1)	0.260
Systolic blood pressure (SBP)	132.8 ± 27.2	130.5 ± 27.1	0.439	124.6 ± 25.3	126.5 ± 28.0	0.510
Other variables						
Glasgow Coma Score	14.6 ± 1.2	14.7 ± 0.8	0.456	14.4 ± 1.6	14.6 ± 1.2	0.304
C-reactive protein	-	-	-	111.5 ± 94.2	123.8 ± 107.8	0.271
Haemoglobin	-	-	-	7.4 ± 1.3	7.2 ± 1.4	0.109
Platelet count, *10^9/l	-	-	-	240.8 ± 124.0	214.9 ± 121.9	0.056
Bilirubin µmol/l median (IQR)	-	-	-	12.0 (8.0-15.0)	8.0 (6.0-12.5)	0.008
Glucose, mmol/l	-	-	-	8.4 ± 4.1	8.0 ± 3.2	0.358
Albumin	-	-	-	30.0 ± 6.7	30.9 ± 5.8	0.303
Creatinine, µmol/l median (IQR)	-	-	-	95.0 (74.0-129.0)	99 (74.5-126)	0.457
Urea, mmol/l	-	-	-	8.8 ± 4.9	9.5 ± 8.5	0.405
International normalised ratio	-	-	-	2.8 ± 2.6	2.3 ± 1.9	0.245
Arterial pH	-	-	-	7.44 ± 0.06	7.45 ± 0.05	0.599
PaCO2, mmHg	-	-	-	32.0 ± 16.8	35.7 ± 9.8	0.220
Bicarbonate, mmol/l	-	-	-	23.1 ± 4.9	23.5 ± 4.4	0.535
Lactate, mmol/l	-	-	-	2.6 ± 2.6	1.9 ± 1.0	0.009
Neutrophil count *10^9/l median (IQR)	-	-	-	9.3 (5.95-14.10)	8.8 (5.90-13.44)	0.459

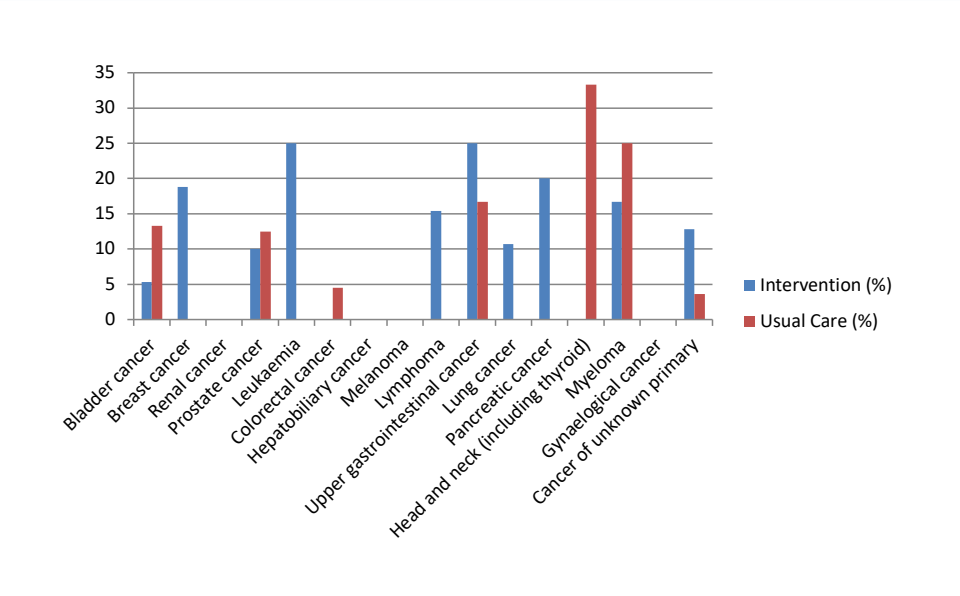
IQR = interquartile range; PaCO2 = partial pressure of carbon dioxide; SIRS = systemic inflammatory response syndrome

Supplementary table 21. *Physiological and laboratory variables all patients*

	In ambulance			At the Emergency Department		
Variable	**Cancer (n = 357)**	**No Cancer (n = 2301)**	**p-value**	**Cancer (n = 357)**	**No Cancer (n = 2301)**	**p-value**
SIRS criteria						
Temperature, ^{0}C	38.9 ± 1.0	38.9 ± 0.9	0.684	38.7 ± 1.0	38.7 ± 0.9	0.997
Respiratory rate, per minute	26.1 ± 7.0	26.6 ± 7.3	0.196	24.6 ± 7.0	24.7 ± 6.9	0.906
Heart rate, per minute	113.3 ± 20.5	111.0 ± 19.3	0.037	105.9 ± 20.6	104.0 ± 19.7	0.089
White cell count, *10^9/l median (IQR)	-	-	-	12.4 (8.1-16.9)	12.2 (8.6-16.6)	0.003
Systolic blood pressure (SBP)	131.5 ± 27.1	134.5 ± 27.4	0.048	125.7 ± 26.9	132.0 ± 26.3	< 0.001
Other variables						
Glasgow Coma Score	14.7 ± 1.0	14.6 ± 1.3	0.115	14.5 ± 1.4	14.6 ± 1.3	0.287
C-reactive protein	-	-	-	118.7 ± 102.5	111.8 ± 107.0	0.259
Haemoglobin	-	-	-	7.3 ± 1.4	8.0 ± 1.2	< 0.001
Platelet count *10^9/l	-	-	-	225.8 ± 123.3	225.3 ± 96.3	0.929
Bilirubin, µmol/l median (IQR)	-	-	-	90 (60-140)	100 (70-160)	0.524
Glucose, mmol/l	-	-	-	8.2 ± 3.6	8.2 ± 3.7	0.968
Albumin	-	-	-	30.5 ± 6.2	33.3 ± 14.0	0.002
Creatinine, µmol/l median (IQR)	-	-	-	97 (74-128.5)	90 (71-119)	0.133
Urea, mmol/l	-	-	-	9.2 ± 7.2	8.6 ± 6.1	0.102
International normalised ratio	-	-	-	2.4 ± 2.2	2.3 ± 1.9	0.446
Arterial pH	-	-	-	7.44 ± 0.05	7.44 ± 0.07	0.064
PaCO2, mmHg	-	-	-	34.4 ± 12.8	35.0 ± 11.6	0.647
Bicarbonate, mmol/l	-	-	-	23.3 ± 4.6	24.0 ± 8.8	0.285
Lactate, mmol/l	-	-	-	2.2 ± 1.9	2.1 ± 2.0	0.756
Neutrophil count, *10^9/l median (IQR)	-	-	-	8.9 (5.9-13.6)	10.0 (6.9-13.9)	0.422

IQR = interquartile range; PaCO2 = partial pressure of carbon dioxide; SIRS = systemic inflammatory response syndrome

Supplementary figure 1. *In-hospital mortality: intervention vs. usual care*

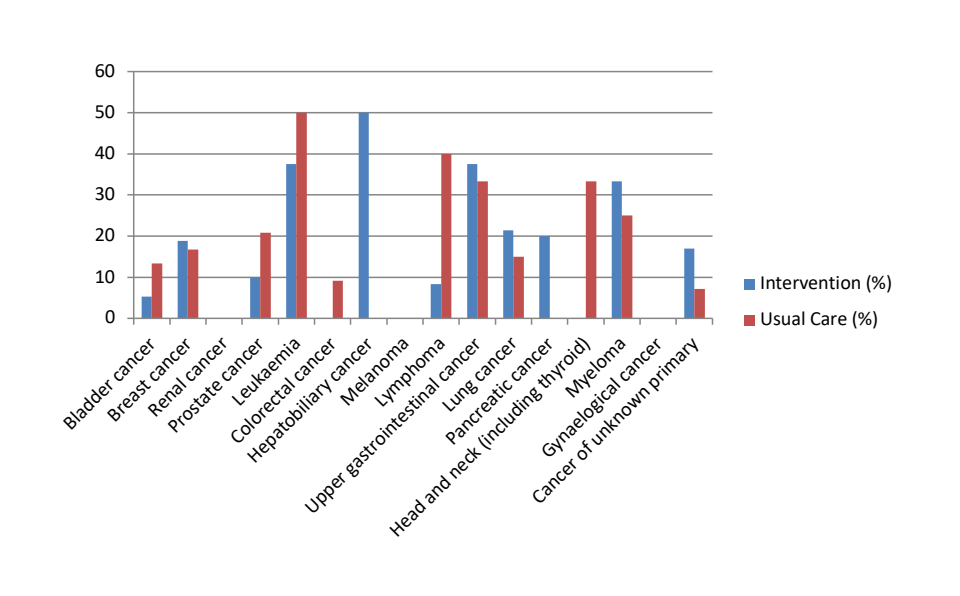


*Unknown patients only in Usual care group

Supplementary table 22. *In-hospital mortality cancer patients: intervention vs. usual care*

	Intervention (n = 209)	Usual Care (n = 148)
Type of Cancer, %		
Bladder cancer	5.3	13.3
Breast cancer	18.8	0
Renal cancer	0	0
Prostate cancer	10.0	12.5
Leukaemia	25	0
Colorectal cancer	0	4.5
Hepatobiliary cancer	0	0
Melanoma	0	0
Lymphoma	15.4	0
Upper gastrointestinal cancer	25.0	16.7
Lung cancer	10.7	0
Pancreatic cancer	20.0	0
Head and neck (including thyroid)	0	33.3
Myeloma	16.7	25.0
Gynaecological cancer	0	0
Cancer of unknown primary origin	12.8	3.6

Supplementary figure 2. *28-day mortality: intervention vs. usual care*

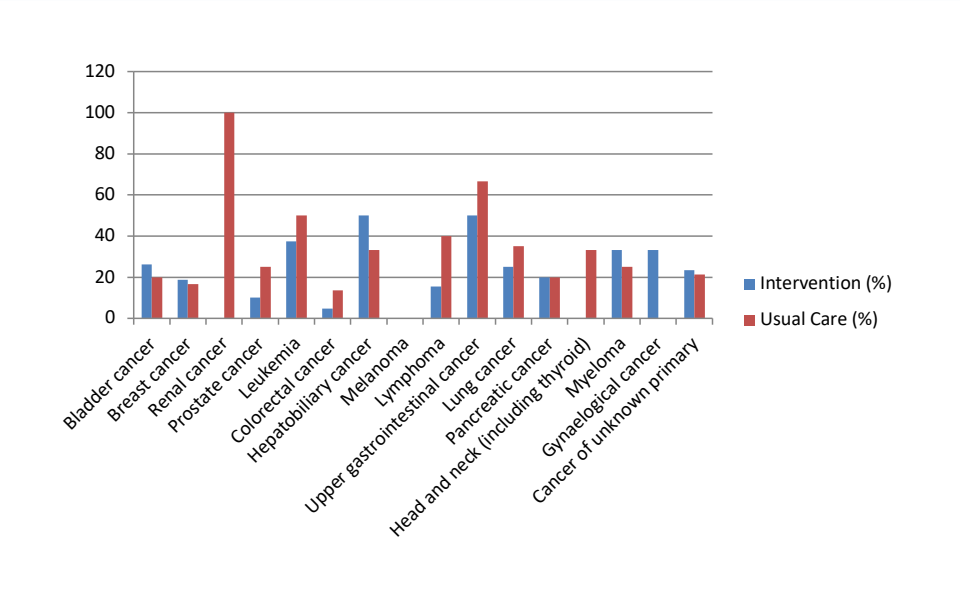


*Unknown patients only in Usual care group

Supplementary table 23. *28-day mortality cancer patients: intervention vs. usual care*

	Intervention (n = 209)	Usual Care (n = 148)
Type of Cancer, %		
Bladder cancer	5.3	13.3
Breast cancer	18.8	16.7
Renal cancer	0	0
Prostate cancer	10	20.8
Leukaemia	37.5	50.0
Colorectal cancer	0	9.1
Hepatobiliary cancer	50.0	0
Melanoma	0	0
Lymphoma	8.3	40.0
Upper gastrointestinal cancer	37.5	33.3
Lung cancer	21.4	15.0
Pancreatic cancer	20.0	0
Head and neck (including thyroid)	0	33.3
Myeloma	33.3	25.0
Gynaecological cancer	0	0
Cancer of unknown primary origin	17.0	7.1

Supplementary figure 3. *90-day mortality: intervention vs. usual care*



*Unknown patients only in Usual care group

Supplementary table 24. *90-day mortality cancer patients: intervention vs. usual care*

	Intervention (n = 209)	Usual Care (n = 148)
Type of Cancer, %		
Bladder cancer	26.3	20.0
Breast cancer	18.8	16.7
Renal cancer	0	100.0
Prostate cancer	10.0	25.0
Leukaemia	37.5	50.0
Colorectal cancer	4.8	13.6
Hepatobiliary cancer	50.0	33.3
Melanoma	0	0
Lymphoma	15.4	40.0
Upper gastrointestinal cancer	50.0	66.7
Lung cancer	25.0	35.0
Pancreatic cancer	20.0	20.0
Head and neck (including thyroid)	0	33.3
Myeloma	33.3	25.0
Gynaecological cancer	33.3	0
Cancer of unknown primary origin	23.4	21.4